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# SMJ

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MONTHLY

ORIGINAL ARTICLE
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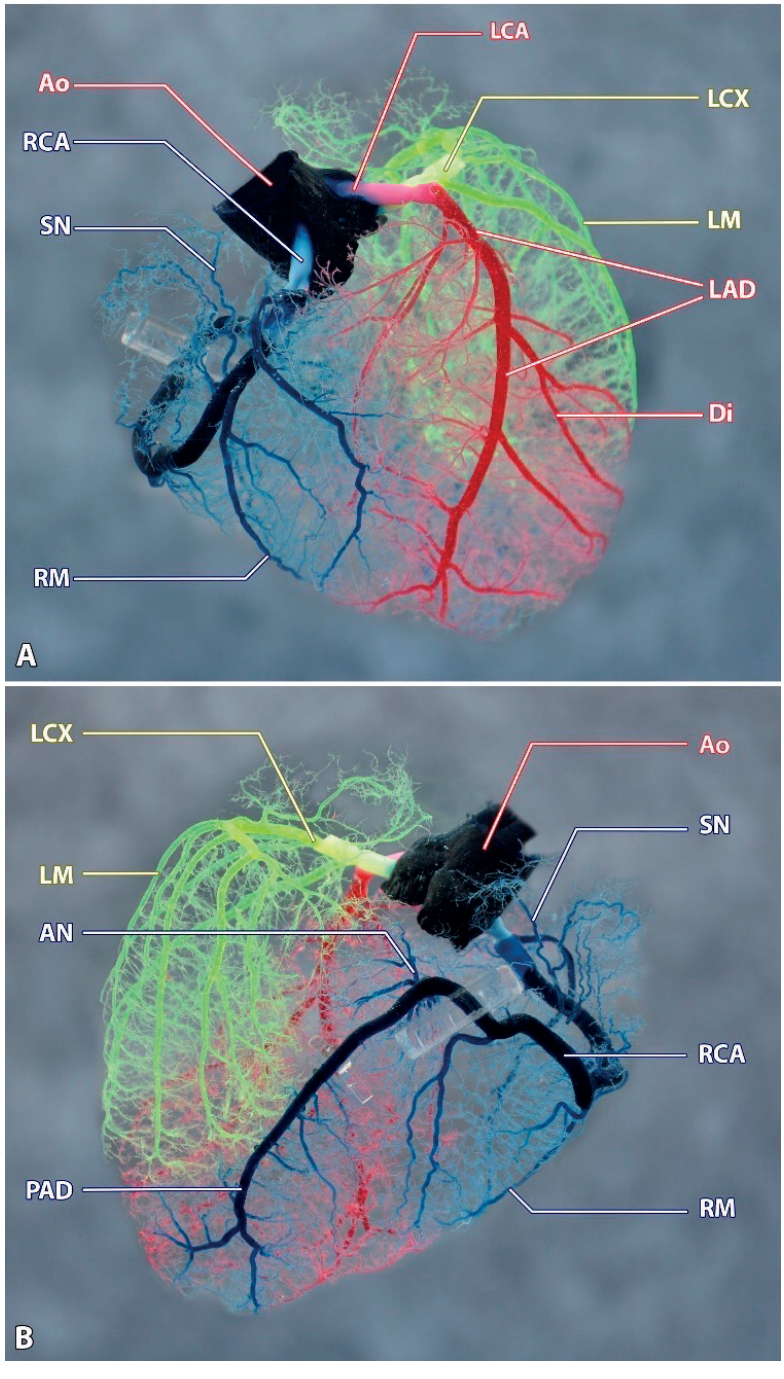


By Chanagun Tounkhrua, et al.

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# Three-dimensional Kinematic Analysis and Muscle Activation of the Upper Extremity in Ruesi Dutton Exercises

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## ABSTRACT

**Objective:** To investigate 3-D upper extremity joint angles and muscle activities in selected Ruesi-Dutton exercises.

**Material and Methods:** Twenty-six healthy participants (mean age of 25.65, mean height of 165.08 cm, and mean weight of 56.69 Kg) volunteered to take part in this study. 3-D motion analysis consisted of eight cameras synchronized with a wireless electromyography (EMG) system to collect kinematic data and muscle activity. Participants performed five postures, including the Kae Lom Kho Mue posture, Kae Puat Thong Kae Kho Thao posture, Kae Kiat posture, Kae Puat Thong Sabak Chom posture, and Kae Lom Puat Sisa. The upper extremity joint angles and range of motion (ROM) and EMG were analyzed.

**Results:** Most postures were in the normal range of motion. The percentage of MVIC was more than 1% and the Trapezius muscle is the most active in all postures.

**Conclusion:** The data in this research is useful to help select the correct posture and exercise for a specific condition.

**Keywords:** Ruesi-Dutton; Hermit Doing Body Contortion; biomechanics; upper extremity (Siriraj Med J 2022; 74: 721-730)

## INTRODUCTION

Ruesi-Dutton or Hermit Doing Body Contortion (HDBC) is an exercise that has been used for over 200 years in health care.[1] Its origin is still unclear, but it was believed to have been developed by hermits who practiced it in India.[2] "Ruesi-Dutton" is composed of two words; Ruesi, which means hermit or monk from the Buddhist era and refers to people who renounced their home, practiced Buddhist teachings, and sought peace, and "Dutton", which means an exercise.[3] Therefore, Ruesi Dutton means movement or the many postures the Ruesi used to practice Buddhist teachings and relieve pain. HDBC exercises (also known as postures) are commonly performed by moving a part of the body in a sequence or performed simultaneously for a determined posture and held for five to 10 seconds, similar to an active static exercise. Then, the body is slowly returned to the start position. Each posture is repeated three to five times.[4] HDBC consists of 80 postures, including the standing posture, sitting posture, and supine posture.[1]

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There are many benefits of HDBC exercises such as pain reduction, decreased blood pressure, increased angle of joints, increased muscle strength, and improved quality of life.[5-7]

Although HDBC is widely practiced, it is still unclear how to do this exercise correctly. This problem is the result of insufficient evidence on how to perform this exercise. For example, statues in Wat Phra Chetuphon Wimonmangkalaram or paintings only display the end posture of a contortion. Moreover, a poem in Thai scripture only describes the hermit's history, the benefits of postures, and the preliminary steps leading to variations in HDBC. In addition, research studies relating to HDBC are associated with the effectiveness of the postures. Currently, no study has comprehensively investigated movement patterns and muscle activity in HDBS. Understanding these movement patterns and how the muscles perform provides essential information to study the characteristics of the exercise. Therefore, this study aims to investigate the 3-dimensional kinematics and muscle activities of HDBC postures related to the upper extremities.

## MATERIALS AND METHODS

### Study design

This cross-sectional study was conducted at the Faculty of Medicine Siriraj Hospital, Bangkok, Thailand. The protocol of this study was approved by the Siriraj Institutional Review Board [Si 365/2016 (EC3)] and registered in the Thai Clinical Trials Registry (TCTR20211014004). The experimental protocol, risks, and benefits of the study were clearly explained to participants. All participants then signed and gave their informed consent before data collection.

### Subjects and Sample Size calculation

Healthy volunteers aged between 18-32 were recruited for this study. The inclusion criteria was a waist circumference of less than or equal to 90 cm (36 inches) in males and 80 cm (32 inches) in females. Participants were excluded if they were pregnant, had neurological diseases, had musculoskeletal diseases, or had a history of allergic reactions to alcohol and adhesive tape.

The sample size was calculated for primary objectives. A study on degrees of movement of the neck[8] was determined as follows; two-tailed test, confidence interval of 95%, standard deviation of s 11.1, and an acceptable error of 5.4. Twenty-six participants were required for this study. We enrolled participants compatible with our eligibility criteria using a convenience sampling method. A total of 26 subjects consisting of 13 males and 13 females, with a mean age of 25.65 ± 2.77, mean weight of 56.69 ± 10.54 kg, a mean height of 165.08 ± 8.50 cm, mean BMI of 20.65 ± 2.49 kg/m$^2$ (which is considered normal), mean length of right arm being 55.12 ± 4.68 cm., and a mean length of the left arm 55.12 ± 4.68 cm were enrolled.

### Ruesi Dutton exercises

The selected five postures were as follows; Kae Lom Kho Mue posture (P1), Kae Puat Thong Kae Kho Thao posture (P2), Kae Kiat posture (P3), Kae Puat Thong Sabak Chom posture (P4), and Kae Lom Puat Sisa posture (P5). The procedures for the postures were chosen from *Kaiborihan Baep Ruesi Dutton Volume 1*.[4]

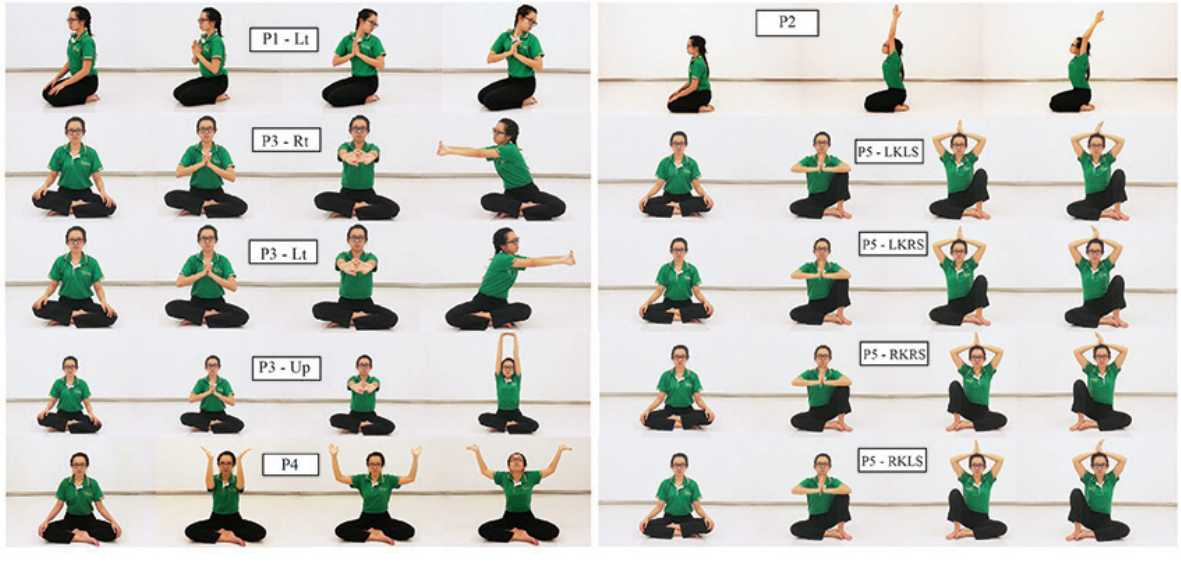


**Fig 1. Five postures of Ruesi-Dutton;** Kae Lom Kho Mue Posture (P1) consists of left (P1-Lt) directions, Kae Puat Thong Kae Kho Thao Posture (P2) has 1 direction, Kae Kiat Posture (P3) consists of 3 directions as follows, left (P3-Lt), right (P3-Rt), and upward (P3-Up). Kae Puat Thong Sabak Chom Posture (P4) has 1 direction, and Kae Lom Puat Sisa Posture (P5) consists of 4 directions as follows, left knees left side(P5-LKLS), left knee right side (LKRS), right knee right side (RKRS), and right knee left side (RKLS).

### Study Flow

Participants who passed the criteria were trained to perform the five postures using video media and were closely advised by Applied Thai Traditional practitioners while training for a total of 120 minutes. After that, participants were assessed on each posture by three expert Applied Thai Traditional practitioners with at least 10-years of experience. Following this, various areas of the participants' skin was prepared by cleaning it with alcohol and shaving skin hair to reduce interference noise when attaching an EMG to the surface. The surface Electromyography (Trigno Wireless system, Delsys Inc, Boston, MA USA) was set at a sampling rate of 1,000 Hz and placed on the Deltoid Medius muscle, the Upper Trapezius muscle, the Middle Trapezius muscle, the Lower Trapezius muscle, the Biceps muscle, and the Triceps muscle as indicated per the SENIAM protocol.[9] Maximum Voluntary Isometric Contraction (MVIC) data was collected by stimulating static muscle strength.[10] Participants were warmed up by being told to do stretching exercises for five minutes, and then begin the determined position and to slowly start increasing their force to maximum and hold it for five seconds and promptly relax. They were then asked to repeat these three times, with a pause period of 30 seconds in between tests.

Then, reflective markers were attached on the skin of participants according to the Plug-in gait protocol.[11] The markers were attached at the following positions: left and right front head, left and right back head, 7$^{th}$ cervical vertebrae, 10$^{th}$ thoracic vertebrae, clavicle, sternum, and right back, right and left shoulder, right and left upper arm, right and left elbow, right and left forearms, medial and lateral right and left wrists, right and left fingers, right and left ASIS and PSIS. Five postures were collected for three trials with a three-minute rest between each posture. The sequence of the postures was determined for 26 batches by a randomized sampling method and given to participants in sequence according to the order of enrollment. Kinematic data was collected using eight infrared cameras (Raptor-E, Motion Analysis Corporation, Santa, CA, USA) at the sampling rate of 100 Hz.

### Data processing

Data was converted from analog to digital by Cortex software, Motion Analysis Corporation, Santa, CA, USA. Kinematic data was smoothed by Butterworth low-pass filtered at a cutoff frequency of 1 Hz, and EMG data was smoothed by Butterworth high-pass filtered at a cutoff frequency of 50 Hz and Butterworth lowpass filtered at a cutoff frequency of 500 Hz. The RMS values were normalized using the averaged MVIC amplitudes of each respective muscle. Visual 3D version 2020.08.3.

### Data analysis

Descriptive statistics, mean, and standard deviations were performed using the PAWS statistics program (SPSS 18.0). Demographic data, joint kinematics, and muscle function were presented and reported.

## RESULTS

### Upper extremity joint movement in Ruesi Dutton

For cervical spine movement (Table 1), P4 was most active, followed by P3 in the left and right direction, and P2, P5. As for P1, there was very little movement on this axis. In the Y-axis (Table 2), there was lateral bending; and P3 in the right and left directions had the most movement. In the Z-axis (Table 3), P1 of the right and left rotation had the most movement, followed by the Kae Kiat posture in right and left direction, while the rest had little movement in this axis (not more than 10 degrees).

For thoracic spine movement (Table 1), the movement of P1, P3, P4, P5 was trunk flexion, and P5 had the most movement, followed by P3 in the left and right direction, P1, and P4, and P2 with movement in the form of trunk extension. In the Y-axis (Table 2), trunk movement was in the form of lateral bending and P5 had the most movement, followed by P1 and other postures without

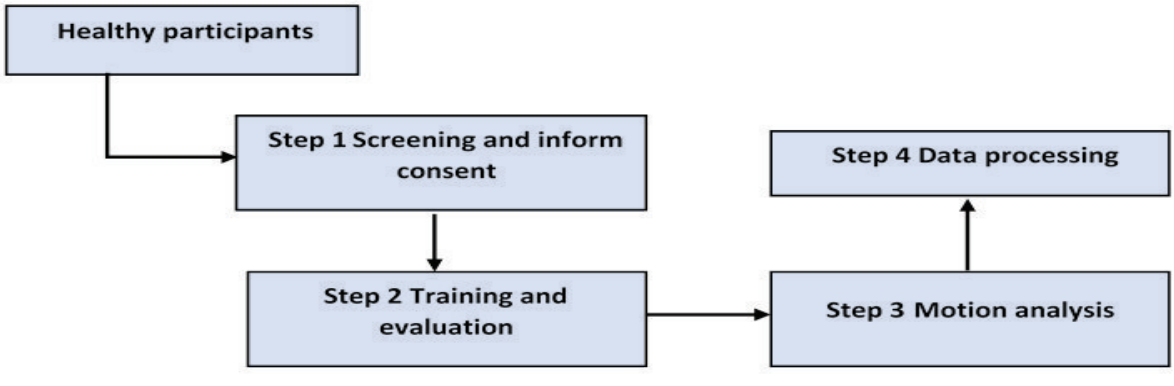


**Fig 2.** Flow chart of the study

**TABLE 1.** Sagittal plane joint angles.

| Phase | Joint angle [Degrees (Mean±SD)] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Neck | Trunk | Shoulders | | Elbows | | Wrist | |
| | | | Rt. | Lt. | Rt. | Lt. | Rt. | Lt. |
| P1 (Left) | 5.40 ± 8.67 | -14.04 ± 11.19 | 41.55 ± 10.45 | 10.29 ± 11.43 | 112.89 ± 9.49 | 129.97 ± 7.07 | -21.62 ± 25.68 | -42.83 ±38.93 |
| P1 (Right) | 2.96 ± 9.10 | -13.61 ± 10.87 | 3.24 ±11.01 | 46.5 ±9.20 | 131.95 ±7.71 | 109.18 ± 8.53 | -28.32 ±47.31 | -32.66 ±25.82 |
| P2 | 29.03 ±16.46 | 22.65 ±28.62 | 140.09 ±56.37 | 143.10 ±41.01 | 43.88 ±7.31 | 43.72 ±8.77 | -15.85 ±9.01 | -17.92 ±10.21 |
| P3 (Left) | 35.35 ±13.26 | -29.13 ±15.94 | 98.57 ±8.71 | 104.89 ±8.82 | 21.52 ±9.43 | 19.51 ±9.37 | 14.68 ±32.39 | 12.84 ±32.01 |
| P3 (Right) | 33.50 ±13.61 | -28.95 ±15.26 | 101.08 ±9.66 | 99.19 ±8.31 | 19.47 ±9.50 | 21.99 ±8.25 | 22.59 ±38.34 | 3.05 ±26.90 |
| P3 (Upward) | 14.40 ±12.81 | -6.58 ±12.47 | 147.44 ±15.78 | 151.12 ±8.57 | 26.85 ±8.34 | 26.21 ±8.43 | 6.13 ±39.43 | -8.79 ±29.26 |
| P4 | 47.93 ±14.86 | -11.76 ±13.89 | -53.26 ± 50.00 | -41.16 ± 51.99 | 88.65 ± 8.89 | 87.06 ± 8.44 | -60.1 ± 19.80 | -70.9 ± 12.94 |
| P5 (LKLS) | 15.22 ±7.88 | -37.27 ±16.96 | 148.20 ±22.51 | 144.35 ±7.75 | 118.50 ±4.62 | 118.21 ±4.62 | -57.45 ±10.20 | -56.02 ±16.00 |
| P5 (LKRS) | 16.68 ±10.12 | -37.43 ±17.16 | 139.43 ±63.26 | 144.72 ±8.29 | 121.65 ±5.09 | 116.52 ±4.87 | -62.17 ±13.75 | -51.04 ±12.78 |
| P5 (RKLS) | 16.68 ±11.61 | -37.51 ±14.63 | 146.39 ±9.37 | 148.66 ±10.87 | 119.38 ±5.15 | 119.58 ±4.14 | -55.58 ±10.61 | -49.84 ±36.85 |
| P5 (RKRS) | 15.68 ±11.45 | -38.08 ±15.02 | 142.25 ±16.77 | 147.95 ±9.58 | 121.81 ±5.16 | 117.67 ±4.86 | -57.89 ±11.11 | -52.46 ±16.08 |

Cervical and thoracic spine: X axis in (+) extension, (-) flexion, Right shoulder joint: X axis (+) forward flexion, (-) extension. Left shoulder joint: X axis (+) forward flexion, (-) extension, Right elbow joint: X axis (+) flexion, (-) extension, Left elbow joint; X axis (+) flexion, (-) extension, Right wrist: X axis (+) palmar flexion, (-) wrist dorsiflexion. Left wrist joint, X axis (+) palmar flexion, (-) wrist dorsiflexion. Kae Lom Kho Mue Posture (P1), Kae Puat Thong Kae Kho Thao Posture (P2), Kae Kiat Posture (P3), Kae Puat Thong Sabak Chom Posture (P4), and Kae Lom Puat Sisa Posture (P5)

**TABLE 2.** Frontal plane joint angles.

| Phase | Joint angle [Degrees (Mean±SD)] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Neck | Trunk | Shoulders | | Elbows | | Wrist | |
| | | | Rt. | Lt. | Rt. | Lt. | Rt. | Lt. |
| P1 (Left) | 1.59 ±6.3 | 10.97 ± 5.22 | -0.34 ± 11.05 | 30.70 ± 10.7 | 13.09 ± 8.85 | -14.12 ± 5.88 | -47.89 ±18.44 | 58.82 ±12.69 |
| P1 (Right) | -3.23 ±7.96 | -8.50 ±5.73 | -31.84 ±10.57 | -6.01 ±10.25 | 11.23 ±6.39 | -22.95 ± 8.88 | -63.47 ±16.53 | 45.99 ±12.81 |
| P2 | -1.36 ±3.37 | 1.28 ±1.70 | -13.43 ±3.71 | 13.70 ±5.23 | -6.90 ±7.19 | 4.05 ±6.23 | -12.50 ±8.77 | 12.41 ±8.00 |
| P3 (Left) | 7.47 ±8.94 | -4.23 ±7.17 | 9.81 ±8.86 | 22.27 ±11.90 | -7.44 ±5.79 | 5.16 ±6.29 | -51.06 ±14.36 | 57.25 ±15.29 |
| P3 (Right) | -8.35 ±10.99 | 2.60 ±6.88 | -23.86 ±14.49 | -11.15 ±10.60 | -8.81 ±5.64 | 2.78 ±6.95 | -56.90 ±15.68 | 47.74 ±16.89 |
| P3 (Upward) | -0.42 ±4.05 | 0.32 ±2.11 | -14.72 ±4.59 | 13.98 ±5.70 | -6.91 ±5.96 | 4.31 ±6.79 | -55.76 ±16.97 | 56.95 ±14.00 |
| P4 | -0.94 ± 3.65 | -0.83 ± 6.10 | -70.68 ± 9.26 | 73.67 ± 8.82 | -5.02 ± 7.68 | 6.7 ± 6.82 | -37.68 ± 22.00 | 33.6 ± 17.77 |
| P5 (LKLS) | -1.21 ±5.97 | -17.99 ±9.56 | -45.00 ±5.92 | 41.83 ±6.59 | 6.58 ±7.96 | -10.20 ±6.42 | -15.10 ±17.68 | 16.58 ±12.44 |
| P5 (LKRS) | 1.57 ±4.41 | -17.51 ±10.08 | -48.56 ±5.65 | 38.63 ±5.35 | 6.45 ±7.89 | -9.63 ±6.83 | -16.27 ±17.55 | 16.39 ±11.93 |
| P5 (RKLS) | -0.51 ±4.07 | 17.74 ±10.51 | -44.19 ±5.07 | 43.22 ±4.95 | 5.95± 7.93 | -9.54± 6.83 | -16.21 ±16.90 | 17.42 ±14.51 |
| P5 (RKRS) | 2.27 ±4.66 | 19.00 ±10.23 | -47.11 ±5.54 | 39.87 ±4.83 | 6.29 ±7.83 | -9.21 ±6.76 | -17.01 ±16.75 | 14.37 ±11.34 |

Cervical and thoracic spine: Y axis (+) right tilt (-) left tilt, Right shoulder joint: Y axis (+) adduction and (-) abduction. Left shoulder joint: Y axis (+) abduction, (-) adduction. Right elbow joint: Y axis (+) medial tilt, (-) lateral tilt. Left elbow joint; Y axis (+) lateral tilt, (-) medial tilt. Right wrist: Y axis (+) ulnar deviation, (-) radial deviation. Left wrist joint, Y axis (+) radial deviation, (-) ulnar deviation. Kae Lom Kho Mue Posture (P1), Kae Puat Thong Kae Kho Thao Posture (P2), Kae Kiat Posture (P3), Kae Puat Thong Sabak Chom Posture (P4), and Kae Lom Puat Sisa Posture (P5)

**TABLE 3.** Transverse plane joint angles.

| Phase | Joint angle [Degrees (Mean±SD)] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Neck | Trunk | Shoulders | | Elbows | | Wrist | |
| | | | Rt. | Lt. | Rt. | Lt. | Rt. | Lt. |
| P1 (Left) | 58.99 ± 12.61 | 34.76 ± 34.76 | 71.79 ± 11.86 | -11.48 ± 19.97 | 70.32 ± 20.05 | -70.22 ± 15.43 | 35.01 ±33.41 | -30.76 ±35.47 |
| P1 (Right) | -62.72 ± 13.81 | -31.81 ±6.59 | 5.86 ±22.19 | -65.79 ±14.02 | 67.21 ±20.93 | -71.19 ±15.97 | 37.86 ±50.17 | -24.63 ±19.34 |
| P2 | -0.40 ±5.08 | -5.98 ±35.14 | 58.21 ±18.59 | -54.72 ±13.45 | 62.72 ±16.25 | -62.32 ±14.62 | -4.97 ±15.97 | 5.88 ±12.67 |
| P3 (Left) | 10.37 ±9.79 | 26.16 ±14.06 | 72.92 ±17.52 | -75.27 ±16.22 | 98.19 ±19.19 | -110.60 ±24.74 | 90.33 ±35.34 | -80.50 ±38.78 |
| P3 (Right) | -12.73 ±12.65 | -22.18 ±18.72 | 80.12 ±16.68 | -65.56 ±17.09 | 95.33 ±22.66 | -112.95 ±24.46 | 87.22 ±44.93 | -68.76 ±32.84 |
| P3 (Upward) | -0.71 ±4.89 | 1.45 ±2.97 | 82.08 ±18.43 | -76.54 ±14.93 | 96.69 ±18.15 | -109.22 ±18.90 | 82.41 ±39.00 | -65.75 ±28.79 |
| P4 | -1.61 ± 5.43 | 1.8 ± 2.68 | -102.49 ± 79.49 | 87.19 ± 78.29 | 71.33 ± 19.13 | -70.56 ± 15.85 | 11.14 ± 21.70 | -1.04 ± 11.10 |
| P5 (LKLS) | -3.44 ±7.73 | -4.59 ±5.08 | 70.58 ±15.68 | -58.35 ±12.28 | 51.02 ±19.13 | -49.43 ±16.12 | -1.30 ±10.50 | 0.29 ±9.60 |
| P5 (LKRS) | -6.53 ±7.58 | -4.05 ±4.45 | 70.38 ±14.88 | -57.42 ±11.43 | 50.57 ±19.44 | -50.81 ±14.92 | 1.88 ±9.95 | 0.44 ±11.22 |
| P5 (RKLS) | 2.68 ±5.77 | 7.50 ±4.36 | 63.23 ±11.10 | -61.68 ±13.10 | 50.65 ±19.56 | -49.68 ±16.09 | -1.98 ±9.77 | -0.96 ±10.69 |
| P5 (RKRS) | -0.54 ±6.03 | 8.17 ±4.75 | 61.70 ±12.11 | -60.62 ±11.21 | 49.56 ±19.50 | -50.06 ±15.63 | -5.64 ±33.32 | -1.71 ±9.63 |

Cervical and thoracic spine: Z axis (+), (-) right rotation. Right shoulder joint: Z axis (+) internal rotation, (-) external rotation. Left shoulder joint: Z axis (+) external rotation, (-) internal rotation. Right elbow joint: Z axis (+) internal rotation of arm, (-) external rotation of arm. Left elbow joint; Z axis (+) external rotation of arm, (-) internal rotation of arm. Right wrist: Z axis (+) pronation, (-) supination. Left wrist joint: Z axis (+) supination, (-) pronation. Kae Lom Kho Mue Posture (P1), Kae Puat Thong Kae Kho Thao Posture (P2), Kae Kiat Posture (P3), Kae Puat Thong Sabak Chom Posture (P4), and Kae Lom Puat Sisa Posture (P5)

lateral bending. In the Z-axis (Table 3), the movement was in the form of trunk rotation and P1 and P3 in the right and left directions were very similar to those of the cervical spine.

The movement of the shoulder joint in the X-axis (Table 1) was in form of shoulder flexion in which P2, P5, and P3 in the upward direction had more than 140 - 180 degrees of movement whereas there were less than 100 degrees in other positions, and in P4 in the form of shoulder extension. In the Y-axis (Table 2), P4 and P5 saw the most extension of the arms whereas other postures had less than 40 degrees of extended arms. In the Z-axis (Table 3), most postures had an internal rotation of no more than 90 degrees, except for P4 which had an external rotation of greater than 100 degrees, which is higher than the degree of normal movement.

Elbow joint movement in the X-axis (Table 1) was elbow flexion, with the most flexion being P1, followed by P5, and other postures with no more than 90 degrees of flexion. In the Y-axis (Table 2), the medial till and lateral till, with very little movement, were no more than 15 degrees. In the Z-axis (Table 3), the medial rotation of the arm, with P3 had the most movement, whereas other postures did not move more than 70 degrees.

The movement of the wrist joints (Table 1) was in form of wrist extension, with P4 having the most movement, followed by P1, while other postures had movement of less than 50 degrees. In the Y-axis (Table 2), every posture was in form of radial deviation, and was most commonly found in P1, P3, P4 in which the degree was greater than normal, while other postures had movements less than 20 degrees. In the Z-axis (Table 3), P1, P3, P4 movement was in form of pronation wrist movement in which P3 had more than 80 degrees of movement while P2 and P5 were supinations, and not more than 20 degrees.

**Muscle activation of upper extremities in Ruesi Dutton**

P5 had the highest Biceps activity in the range of 12.54 - 14.40% MVIC, while other postures were in the range of 1.86 - 6.67% MVIC (Table 4). In the Triceps muscle, P3 had most muscle activity in the range of 19.53 – 32.67 %MVIC while other postures were in the range of 5.05-11.55% MVIC. In the Deltoids muscle, almost all postures had muscle activity in the range of 27.40 - 111.28% MVIC except for P1 which was in the range 3.94 - 10.82% MVIC. In the Lower Trapezius, P3 in the left and right directions, P5, P4, and P1 had muscle activity in the range of 78.73-121.33% MVIC while P4 and P3 in the upwards direction had muscle activities in the range of 30.01 - 48.87% MVIC. In the Middle Trapezius muscle, P4 had the greatest muscle activity in the range of 63.50 - 65.19% MVIC, followed by P1 had muscle activity in the range of 41.19 - 49.04% MVIC while other postures had muscle activity in the range of 4.56 - 32.88% MVIC. For the Upper Trapezius, P5 had the greatest muscle activity in the range of 74.93 - 83.25% MVIC, and P2 and P4 had similar muscle activity in the range of 55.26 - 59.45% MVIC, while P3 had muscle activity in the range of 32.71 - 47.13% MVIC and P1 had muscle activity in the range of 12.79 - 14.53% MVIC.

## DISCUSSION

The primary objective of this study was to investigate upper extremity joint angles and muscle activity while performing select HDBC postures. To the authors' knowledge, this is the first study to fully describe 3D kinematic motion and muscle activation in HDBC. The movement of each joint had a range of motion within that joint's normal range[12-14] and in daily activity,[15-17] but there was more radial deviation and extension in the wrists. In addition, caution was taken in people who had injuries or disease around the wrist. However, these exercises may be more suitable for carpal tunnel syndrome, as they are similar to tendon gliding exercises18 and require care in the movement of the neck and shoulders in the elderly and those who are overweight. This is because in such cases, the degree of motion is reduced[14,19] and the external rotation angle of the shoulder is greater than the degree of normal movement so caution is necessary while performing these postures. Moreover, HDBC is recommended for patients with frozen shoulders due to the shoulder movement being greater than the range of motion of the disease.[20] Therefore, further studies may be needed.

From the study of muscle function, it was found that the relationship between the posture name and its benefits could not be clearly explained because it was a study of the superficial muscle function in the upper extremities only, and it did not look at the muscles related to the name of the posture. In P1, the Lower and Middle Trapezius muscles are used more than any other bundle which can reduce wrist pain from myofascial pain syndrome which has a trigger point at the shoulder and upper back.[21] However, EMG devices should be attached to pronator teres muscle, flexor, and extensor muscle group of the forearms and brachioradialis muscle because these muscles are directly related to wrist function. The lower and upper Trapezius have the most function in P2 but the benefits do not relate to the name of posture because the protocol for placing devices is not focused on proving the relationship. Therefore, EMG devices

**TABLE 4.** Muscle activity in Ruesi Dutton of upper extremities follows as; biceps, triceps, deltoid, upper trapezius, middle trapezius, and lower trapezius.

| Posture | | % MVIC (Mean±SD) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Biceps | | Triceps | | Deltoid | | Lower trapezius | | Middle trapezius | | Upper Trapezius | |
| Name | Direction | Rt. | Lt. | Rt. | Lt. | Rt. | Lt. | Rt. | Lt. | Rt. | Lt. | Rt. | Lt. |
| P1 | Left | 3.12 ±1.99 | 4.11 ±2.71 | 11.20 ±13.35 | 4.06 ±1.60 | 8.87 ±5.15 | 4.32 ±3.07 | 7.95 ±1.44 | 88.82 ±52.10 | 4.56 ±0.96 | 30.34 ±17.40 | 14.53 ±13.87 | 12.79 ±11.21 |
| | Right | 3.90 ±2.95 | 3.20 ±2.29 | 5.40 ±4.55 | 5.65 ±3.84 | 10.82 ±7.96 | 3.94 ±1.49 | 86.92 ±49.20 | 15.15 ±30.42 | 31.67 ±17.04 | 8.41 ±12.97 | 14.16 ±12.89 | 12.80 ±15.03 |
| P2 | - | 4.13 ±2.21 | 4.31 ±2.59 | 12.04 ±6.74 | 8.71 ±3.60 | 81.01 ±42.52 | 40.32 ±19.30 | 30.01 ±32.14 | 35.0 ±34.23 | 16.93 ±12.72 | 16.72 ±11.83 | 55.26 ±37.57 | 54.57 ±36.48 |
| P3 | Left | 1.95 ±1.15 | 2.36 ±1.48 | 32.42 ±33.55 | 21.20 ±12.74 | 57.13 ±28.04 | 27.59 ±13.79 | 10.20 ±3.73 | 93.88 ±54.37 | 6.44 ±3.15 | 32.88 ±19.37 | 38.07 ±21.06 | 38.42 ±23.22 |
| | Right | 1.86 ±1.02 | 2.34 ±1.26 | 28.73 ±19.40 | 19.53 ±10.61 | 50.20 ±22.23 | 27.40 ±13.61 | 121.33 ±72.56 | 12.64 ±4.84 | 31.86 ±18.94 | 8.68 ±4.77 | 40.46 ±21.17 | 32.71 ±28.33 |
| | Up | 2.72 ±1.48 | 3.41 ±2.09 | 32.67 ±23.81 | 24.54 ±13.32 | 89.59 ±40.40 | 47.12 ±19.23 | 44.18 ±32.72 | 48.87 ±43.43 | 31.72 ±16.90 | 29.47 ±15.72 | 47.13 ±30.90 | 46.32 ±33.78 |
| P4 | Front | 4.03 ±3.39 | 6.67 ±9.44 | 11.39 ±6.86 | 11.55 ±5.68 | 78.25 ±32.03 | 45.79 ±19.04 | 87.62 ±37.53 | 102.09 ±55.64 | 65.19 ±32.10 | 63.5 ±22.61 | 58.95 ±43.45 | 59.45 ±43.76 |
| P5 | LKLS | 12.54 ±7.67 | 16.27 ±10.95 | 11.15 ±5.80 | 9.43 ±4.02 | 107.86 ±51.30 | 54.65 ±21.04 | 113.95 ±64.60 | 90.00 ±43.83 | 49.07 ±24.46 | 40.64 ±16.53 | 78.54 ±38.66 | 82.83 ±50.52 |
| | LKRS | 14.40 ±8.34 | 14.64 ±9.13 | 10.52 ±5.51 | 9.15 ±2.95 | 111.28 ±53.10 | 53.81 ±23.16 | 111.53 ±49.96 | 89.58 ±40.77 | 48.64 ±23.16 | 41.19 ±17.21 | 80.94 ±42.39 | 83.25 ±54.85 |
| | RKLS | 13.00 ±6.99 | 16.71 ±10.17 | 10.77 ±5.30 | 9.42 ±3.82 | 107.27 ±51.26 | 54.61 ±22.03 | 78.73 ±44.83 | 119.04 ±55.12 | 45.59 ±23.70 | 46.61 ±15.82 | 80.48 ±45.07 | 76.32 ±51.83 |
| | RKRS | 13.62 ±6.82 | 14.03 ±7.94 | 10.05 ±5.47 | 9.14 ±3.30 | 103.86 ±49.57 | 52.59 ±22.46 | 82.81 ±51.83 | 109.72 ±50.99 | 42.78 ±21.59 | 44.86 ±18.49 | 81.15 ±47.48 | 74.93 ±55.06 |

Kae Lom Kho Mue Posture (P1), Kae Puat Thong Kae Kho Thao Posture (P2), Kae Kiat Posture (P3), Kae Puat Thong Sabak Chom Posture (P4), and Kae Lom Puat Sisa Posture (P5)

should be attached to the abdominal muscle and lower legs. P3 can reduce tiredness and laziness[4] according to the results and all the muscles had a function in the study. In P4, the three compartments of the Trapezius muscle have the most function which corresponds to the name of posture and benefits.[4] Moreover, there is also research on the use of this posture to treat and prevent myofascial pain syndrome at the scapular and shoulder.[5] In a further study, there must be an EMG device attached to the abdomen muscle. In P5, the muscles on the neck, shoulder, and upper back have functions that can help reduce tension-type headaches or myofascial pain syndrome[21-23] but there should be a further study to prove the efficiency and mechanisms.

In addition, the muscle function was close to 15 yoga postures.[24] The movement patterns of HDBC and asana yoga were found to have similar movement characteristics: to move the body in one position and hold still in the position for a period of time.[4,25] Therefore, the function of the muscles is working similarly. Moreover, in the Triceps muscle, 1/3 of a bench press exercise had a value greater than D1 flexion and scapular exercise.[26-27]

## CONCLUSION

This study explains the pattern of joints movement and muscle activity of the Ruesi Dutton exercise which can be used as a guide in choosing appropriate postures for different conditions to ensure maximum efficacy and safety for practitioners and trainers. In addition, this data supports evidence of Thai Traditional medicine.

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## REFERENCES

1. The Fine Arts Department. Samut Phap Khlong Ruesi Datton. Bangkok: Amarin Printing and Publishing, 2551.
2. Somdet Phraborom Wong Thoe Kromphraya Damrong Ra Chanu Phap. "Ruesi Datton". Nithan Borankhadi, 10th ed. Bangkok: Khasem Ban Na Kit, 2503.
3. The Office of Royal Society. Photchananukrom Chabap Ratchabandittayasathan B.E. 2554 Chaloemphrakiat PhraBatSomdetPhrachaoyuhua Nueang Nai Okat Phraratchaphithi Maha Mongkhon Chaloemphrachonphansa anniversary 7th. Bangkok: Sirivatana Interprint, 2556.
4. Ayurved Thamrong school, Center of Applied Thai Traditional Medicine, Faculty of Siriraj Medicine Hospital, Mahidol university. Kaiborihan Baep Ruesi Datton. Vol 1. Bangkok: Suppha Wanit Publishing, 2554.
5. Butdapan P, Narajeenarone K, Apichartvorakit A, Kade S, Jansomsarit S, Jamjuntra P, et al. The Effect of the Posture of the "Hermit Doing Body Contortion" on Relief of Shoulder and Scapular Pain Caused by Chronic Myofascial Pain Syndrome: A Randomized, Parallel Group, Controlled Trial. Siriraj Med J. 2016;68:350-7.
6. Tanasugarn L, Natearpha P, Kongsakon R, Chaosaowapa M, Choatwongwachira W, Seanglaw D, et al. Physical effects and cognitive function after exercising "Rue-si-dad-ton" (Exercise using the posture of the hermit doing body contortion): A randomized controlled pilot trial. J Med Assoc Thai. 2015;98(3): 306-13.
7. Ngowsiri K, Tanmahasamut P, Sukonthasab S. Rusie Dutton traditional Thai exercise promotes health related physical fitness and quality of life in menopausal women. Complement Ther Clin Pract. 2014;20(3):164-71.
8. Inokuchi H, Tojima M, Mano H, Ishikawa Y, Ogata N, Haga N. Neck range of motion measurements using a new three-dimensional motion analysis system: validity and repeatability. Eur Spine J. 2015: 2807-15.
9. SENIAM Project [Internet]. Netherland: Roessingh Research and Development; 2006 [cited 2019 Mar 9]. Available from: http://seniam.org/
10. Konrad P. The ABC of EMG-A practical introduction to Kinesiological Electromyography. U.S.A. Noraxon Inc., 2006.
11. Vicon Motion Systems Limited. Plug-in Gait Reference Guide [Internet]. 2017 [cited 2021 Dec 29]. Available from: https://docs.vicon.com/
12. Boone DC, Azen SP. Normal range of motion of joints in male subjects. JBJS. 1979;61(5):756-9.
13. Youdas JW, Garrett TR, Suman VJ, Bogard CL, Hallman HO, Carey JR. Normal range of motion of the cervical spine: an initial goniometric study. Phys Ther. 1992;72(11):770-80.
14. Barnes CJ, Van Steyn SJ, Fischer RA. The effects of age, sex, and shoulder dominance on range of motion of the shoulder. J Shoulder Elbow Surg. 2001;10(3):242-6.
15. Rundquist PJ, Obrecht C, Woodruff L. Three-dimensional shoulder kinematics to complete activities of daily living. Am J Phys Med Rehabil. 2009;88(8):623-9.
16. Namdari S, Yagnik G, Ebaugh DD, Nagda S, Ramsey ML, Williams Jr GR, et al. Defining functional shoulder range of motion for activities of daily living. J Shoulder Elbow Surg. 2012;21(9): 1177-83.
17. Ryu J, Cooney III WP, Askew LJ, An KN, Chao EY. Functional ranges of motion of the wrist joint. J Hand Surg. 1991;16(3): 409-19.
18. Akalin E, El Ö, Peker Ö, Senocak Ö, Tamci S, Gülbahar S, et al. Treatment of carpal tunnel syndrome with nerve and tendon gliding exercises. Am J Phys Med Rehabil. 2002;81(2): 108-13.
19. Castro WH, Sautmann A, Schilgen M, Sautmann M. Noninvasive three-dimensional analysis of cervical spine motion in normal subjects in relation to age and sex: an experimental examination. Spine. 2000;25(4):443-9.
20. Rundquist PJ, Anderson DD, Guanche CA, Ludewig PM. Shoulder kinematics in subjects with frozen shoulder. Arch Phys Med Rehabil. 2003;84(10):1473-9.
21. Headaches disorder [Internet]. Switzerland: World Health Organization; 2016 [cited 2022 Jan 14]. Available from: https://www.who.int/news-room/fact-sheets/detail/headache-disorders.

22. Prateepavanich P. Myofascial pain syndrome ca. In: Prateepavanich P, Chaudakshetrin P, editors. Myofascial pain syndrome: a common problem in clinical practice. 1st ed. Bangkok: Amarin Printing and Publishing; 2542.p.273-320.
23. Prateepavanich P. Subscapularis Muscle. In: Prateepavanich P, Chaudakshetrin P, editors. Myofascial pain syndrome: a common problem in clinical practice. 1st ed. Bangkok: Amarin Printing and Publishing; 2542.p.388-91.
24. Chopp-Hurley JN, Prophet C, Thistle B, Pollice J, Maly MR. Scapular muscle activity during static yoga postures. J Orthop Sports Phys Ther. 2018;48(6):504-9.
25. Govindaraj R, Karmani S, Varambally S, Gangadhar BN. Yoga and physical exercise–a review and comparison. Int Rev Psychiatry 2016;28(3):242-53.
26. Lauver JD, Cayot TE, Scheuermann BW. Influence of bench angle on upper extremity muscular activation during bench press exercise. Eur J Sport Sci. 2016;16(3):309-16.
27. Scott R, Yang HS, James CR, Sawyer SF, Sizer Jr PS. Volitional preemptive abdominal contraction and upper extremity muscle latencies during D1 flexion and scaption shoulder exercises. J Athl Train. 2018;53(12):1181-9.

# Factors Influencing Willingness to Pay for Teledermatology among Patients with Psoriasis

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## ABSTRACT

**Objective:** To determine the proportion of patients with psoriasis prepared to pay for TD. Attitudes and factors influencing their willingness to pay (WTP) were evaluated.

**Materials and Methods:** This cross-sectional study was conducted from July 2020 to October 2021. Adult patients with psoriasis completed a 2-page self-administered questionnaire.

**Results:** Of 200 patients, 133 (66.5%) were unfamiliar with TD. However, 144 (72%) were prepared to pay for TD if it were introduced. The majority of patients answered that 300 Bath was the maximum price that they were willing to pay for TD service. Compared with traditional in-person visits, the significant positive influencing factors on WTP were TD's quicker delivery of treatment, lower costs, and non-inferiority to usual care. Multivariate analysis showed that the independent factors for WTP were higher educational levels, elimination of out-of-pocket, in-hospital visit expenses, owning a business, TD options suited to psoriasis, and no adverse effects on the patient-doctor relationship.

**Conclusion:** Knowing patients' attitudes toward TD and the factors influencing their WTP is essential for developing efficient services. Data from this study can be used to develop successful TD services for patients with psoriasis.

**Keywords:** Psoriasis; Teledermatology; Telemedicine; Willingness to pay (Siriraj Med J 2022; 74: 731-738)

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## INTRODUCTION

Psoriasis is a chronic, immune-related, inflammatory skin disease with various clinical features. It is found most frequently in 30- to 40-year-olds, and its incidence in children and adults has grown over the last 3 decades.[1,2] The prevalence of psoriasis among adults has been reported to range from 0.51% to 11.43% of the world's population.[3] In addition to the physical burden of the disease, psoriasis can create a socioeconomic burden due to its direct and indirect costs. Traditional face-to-face patient care has several indirect financial and non-financial costs, such as lost income, time missed from school or work, and travel costs. Teledermatology (TD) alone can never be better than face-to-face, in-office dermatology. However, it can decrease the number of face-to-face visits that are needed, increase access to dermatological care (the ability to obtain care), and improve the accessibility of dermatological care (the ease of obtaining care).[4]

During the COVID-19 pandemic, many countries adopted TD to provide treatment services for acne and chronic autoimmune inflammatory skin diseases.[5] The TD systems can be classified into 3 distinct formats: "store-and-forward," "real-time," and "hybrid." Store-and-forward involves the submission of digital photographs and related information. These are evaluated later to determine a diagnosis and an appropriate management

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strategy. The store-and-forward format contrasts with real-time TD (for example, the use of video conferencing and online meeting rooms), in which the consultation and diagnosis take place synchronously. The third format, hybrid TD, combines the store-and-forward and real-time formats. All 3 formats can be used for direct care, clinical counseling, triage, and follow-up treatment.[6,7] However, TD involves costs for items such as its administration and imaging support services. These extra costs are typically charged to patients by private hospitals and, for service outside standard consultation hours, by public hospitals. Private or public health insurance does not cover these additional expenses in several countries.

Due to technological advancements, TD can be as efficient as face-to-face visits.[8,9] Additionally, TD is less time-consuming for patients.[10-12] Different factors are associated with the willingness to use TD versus the willingness to pay (WPT) for TD. Werner et al studied the willingness to use telemedicine for routine care and specialized care. Their findings indicated that the participants were more willing to use telemedicine for routine care than specialized care. The patients' willingness to use telemedicine was also negatively influenced by their concerns about using new technology, attitudes toward telemedicine, and fear that the patient-physician relationship might be undermined.[13] However, the factors influencing patients' willingness to use telemedicine and their attitudes toward telemedicine may not be the same as the factors and attitudes relating to WTP for telemedicine. Moreover, only a few studies have used a WTP approach to compare the preferences for TD versus traditional in-hospital visits of patients with psoriasis.

This study investigated the attitudes of patients with psoriasis toward TD and the factors influencing their WTP for TD.

## MATERIALS AND METHODS

This cross-sectional study was conducted at the Department of Dermatology outpatient clinic, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand, from July 2020 through October 2021. Before this research began, its protocol was approved by the Siriraj Institutional Review Board (Si 490/2020). The eligibility criteria were adult patients with psoriasis who were 18 years or older. Patients were excluded if they could not read or understand the study questionnaire or had mental or psychological diseases. All participating patients provided written informed consent.

Patients individually completed a 2-page, self-administered questionnaire. It was designed to identify attitudes toward TD technology and factors influencing WTP for TD. Patients needing assistance with any aspect of the questionnaire could ask for the help of an investigator. Details of the following were collected: demographic data (age, sex, education, occupation, income, and comorbid diseases), information related to face-to-face visits to the hospital (waiting time to see a doctor, out-of-pocket expenses, type of medical insurance, and frequency of visits), attitudes toward TD, and WTP for TD. We determined the patient's WTP out-of-pocket by using the payment card model of contingent valuation methods. The patients indicated the maximum value they were WTP for a range of amounts depending on the actual out-patient dermatological care services.

The frequencies of face-to-face visits to Siriraj Hospital to receive psoriasis treatment were classified as "very often" (≥ 1 time/month), "often" (1 time/3 months–< 1 time/month), and "not often" (< 1 time/3 months). The severity of psoriasis was classified according to the nature of the treatment provided and the Self-Administered Simplified Psoriasis Index score. Patients with "moderate to severe psoriasis" were defined as those receiving at least 1 type of systemic treatment for their psoriasis. Patients with "mild psoriasis" were considered those given topical treatments only. Patients with a Self-Administered Simplified Psoriasis Index severity score of < 10 and ≥ 20 were defined as having mild and severe psoriasis, respectively.[14] In the case of patients who indicated a WTP for TD, they were asked to select 1 of 4 possible out-of-pocket costs that they would be willing to pay for the TD service: 200 Baht ($6, €5.40); 300 Baht ($9, €8.10); 400 Baht ($12, €10.80); and 500 Baht ($15, €13.50). Biding format was not used in this study. Thus, higher or lower price than that of patient's answer did not offer.

To improve our understanding of the factors influencing WTP for TD services, we also divided patients into 2 groups. "Group A" comprised patients interviewed during the first wave of the COVID-19 epidemic in Thailand (July 2020–December 15, 2020). "Group B" consisted of patients interviewed during the second wave of the COVID-19 pandemic (December 16, 2020–October 2021). These groupings were made because TD began to be increasingly used after the first wave as part of measures to reduce the spread of COVID-19 infections in Thailand. We postulated that more patients in the second wave would have had experience with or known about TD than in the first wave.

### Statistical analysis

Statistical analyses were conducted using PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL,

USA). Continuous data are presented as the mean ± standard deviation (SD) and median (interquartile range), whereas categorical data are presented as frequencies and percentages. As appropriate, group comparisons were made using the Mann–Whitney U test, the two-tailed test, the $Chi^2$ test, or Fisher's exact test. Statistical significance was defined as *P* values less than 0.05. The factors associated with WTP for TD were analyzed using multiple logistic regression. This analysis included only those variables with a *P* value of less than 0.2 in a univariate analysis.

## RESULTS

The 200 enrolled patients had a mean age of 45.38 ± 13.22 years. There were 115 women (57.50%) and 85 men (42.50%), and most of the patients lived in urban areas (69%). The majority (73.5%) also had postsecondary education (at universities, colleges, trade schools, or vocational schools; Table 1).

Although most of the patients were full- or part-time workers, 127 (63.5%) stated that they did not need to take time off from work to visit the hospital. The most common comorbid diseases were hypertension, dyslipidemia, diabetes mellitus, and psoriatic arthritis, in decreasing order of frequency. Most patients (80.5%) had had psoriasis for more than 5 years. Based on their treatments, 152 (76%) had moderate to severe psoriasis. Most patients often visited the hospital, and the waiting time to see a dermatologist was at least 30 minutes. Public and private insurance were used to cover the medical expenses of 63% and 7.5% of the patients, respectively. The additional out-of-pocket expenses associated with the in-person hospital visits (such as travel costs and the hospital's administrative charge) were more than 200 Baht ($6, €5.40) for most patients.

One hundred thirty-three patients (66.5%) were unfamiliar with TD. However, 144 patients (72%) indicated that they were willing to pay for the service if it were introduced. Most patients believed TD would provide several benefits for psoriasis treatment in terms of a more efficient and quicker service, reduced costs (by eliminating the out-of-pocket expenses for in-person hospital visits), and no adverse effects on the doctor-patient relationship (Table 2). The proportion of patients with these positive attitudes was significantly higher among patients who indicated a WTP than patients who did not. It should be noted that the proportion of patients who knew about TD was higher among the WTP group than the non-WPT group.

Furthermore, the WTP group of patients had substantially fewer concerns about TD in general than the non-WPT group ($P = 0.010$). However, there were no significant differences in the specific points of concern of the 2 groups: the use of new forms of technology, the quality of internet connections, and online privacy and safety. The patients in the WTP group had significantly higher levels of education and greater out-of-pocket expenses for their in-person hospital visits than those in the non-WTP group. Regarding the out-of-pocket costs that patients were still prepared to pay for the TD service, 43.1%, 34%, 5.6%, and 17.4% selected 200 Baht, 300 Baht, 400 Baht, and 500 Baht, respectively (data not shown).

Univariate analysis revealed that the significant factors associated with WTP were higher educational levels, reduction of in-hospital visit expenses, TD options suited to psoriasis treatment, ability to undertake routine appointments, reduction in treatment duration, cheaper than a face-to-face visit, absence of adverse effects on the doctor-patient relationship, and concerns about the use of TD for psoriasis treatment (Table 3). Using multivariate analysis, the independent factors associated with WTP were higher educational levels, elimination of out-of-pocket, in-hospital visit expenses, owning a business, TD options suited to psoriasis treatment, and no adverse effects on the doctor-patient relationship.

In a comparison between WTP for TD among patients during the first and second waves of the COVID-19 pandemic in Thailand, a significantly higher proportion of patients during the second wave knew about TD than during the first wave (49.1% vs 27.9%; $P = 0.005$). All patients in the second wave (100%) believed that TD could be used for psoriasis treatment and routine appointments. The corresponding values for the patients in the first wave were significantly lower (89.1% for psoriasis treatment [$P = 0.007$] and 91.8% for routine appointments [$P = 0.039$]; data not shown).

## DISCUSSION

Even before the COVID-19 pandemic era, the use of TD had been growing dramatically for 2 decades. This development resulted from steady advances in technology that enabled patients to easily access medical care even if they lived in usually difficult-to-reach public health locations. The effectiveness of TD was found to be comparable to that of face-to-face visits by a randomized controlled trial in 2019 (N = 592) and a systemic review in 2020 (4 randomized controlled trials, 2 prospective cohorts, and 1 case series; N = 596).[15] Even when using TD for psoriasis treatment, there were significant improvements in psychological impairment (evaluated by psychological functioning and the Dermatology Life Quality Index) and disease severity (assessed by the Psoriasis Area and

**TABLE 1.** Demographic data and related information of 200 patients with psoriasis visiting hospital from July 2020 through October 2021.

| Variables | Values |
|---|---|
| Sex, n (%) | |
| Females | 115 (57.5) |
| Age (years), mean ± SD | 45.38 ± 13.22 |
| Current address, n (%) | |
| Urban area | 138 (69) |
| Rural area | 62 (31) |
| Education level, n (%) | |
| Less than or equal to secondary school | 53 (26.5) |
| Postsecondary | 147 (73.5) |
| Occupations, n (%) | |
| Full-time worker | 115 (57.5) |
| Part-time worker | 76 (38) |
| Business owner | 9 (4.50) |
| Income (Baht/month), n (%) | |
| ≤ 5,000 | 36 (18) |
| 5,001–10,000 | 19 (9.5) |
| 10,001–20,000 | 48 (24) |
| 20,001–50,000 | 71 (35.5) |
| > 50,000 | 26 (13) |
| Underlying diseases, n (%) | 121 (60.5) |
| Hypertension | 56 (28) |
| Dyslipidemia | 38 (19) |
| Diabetes mellitus | 32 (16) |
| Psoriatic arthritis | 31 (15.50) |
| Duration of psoriasis (years), n (%) | |
| < 5 | 39 (19.5) |
| 5–10 | 53 (26.50) |
| > 10 | 108 (54) |
| Severity scores as assessed by the Self-Administered Simplified Psoriasis Index, n (%) | |
| Mild (< 10) | 135 (67.5) |
| Moderate (10 –< 20) | 52 (26) |
| Severe (≥ 20) | 13 (6.5) |
| Current treatment, n (%) | |
| Only topical treatment | 48 (24) |
| Systemic treatment | 152 (76) |
| Frequency of hospital visits due to psoriasis, n (%) | |
| Very often (≥ 1 times/month) | 15 (7.50) |
| Often (1 time/3 months–< 1 time/month) | 148 (74) |
| Not often (< 1 time/3 months) | 37 (18.50) |
| Waiting time to see a doctor, n (%) | |
| < 15 minutes | 6 (3) |
| 15–30 minutes | 58 (29) |
| 31–< 60 minutes | 57 (28.5) |
| 1–2 hours | 50 (25) |
| > 2 hours | 29 (14.5) |
| Medical insurance, n (%) | |
| Public insurance | 126 (63) |
| Private insurance | 15 (7.5) |
| Self-insured | 59 (29.5) |
| Extra expense for hospital visit (Baht), n (%) | |
| ≤ 200 Baht (≤ $6, €5.40) | 56 (28) |
| > 200 Baht (> $6, €5.40) | 144 (72) |

**Abbreviation:** SD; standard deviation

**TABLE 2.** Comparison of attitudes of patients with psoriasis who were willing and not willing to pay for teledermatology.

| Attitudes toward WTP for teledermatology of psoriatic patients | Total (N = 200) n (%) | WTP (n = 144) n (%) | Non-WTP (n = 56) n (%) | *P* |
|---|---|---|---|---|
| Awareness of teledermatology | 67 (37.5) | 54 (37.5) | 13 (23.2) | 0.055 |
| Efficiency | | | | |
| Teledermatology can be used to treat psoriatic patients | 188 (94.0) | 140 (97.2) | 44 (78.6) | < 0.001* |
| What effect does teledermatology have on psoriatic treatment? | | | | |
| Increased quality | 65 (37.5) | 54 (37.5) | 11 (19.6) | 0.011* |
| Decreased quality | 33 (16.5) | 18 (12.5) | 15 (26.8) | |
| Same quality | 102 (51.0) | 72 (50.0) | 30 (53.6) | |
| Teledermatology enables patients to complete routine appointments | 188 (94.0) | 140 (97.2) | 48 (85.7) | 0.005* |
| Quicker than face-to-face visits | | | | |
| Teledermatology can reduce the length of treatment | 193 (96.5) | 142 (98.6) | 51 (91.1) | 0.019* |
| Cheaper than face-to-face visits | | | | |
| Teledermatology has the potential to reduce the cost of treatment | 189 (94.5) | 142 (98.6) | 47 (83.9) | < 0.001* |
| Teledermatology will impair the doctor-patient relationship | 57 (28.5) | 29 (20.1) | 28 (50.0) | < 0.001* |
| Concerned about teledermatology use for psoriasis | 103 (51.5) | 66 (45.8) | 37 (66.1) | 0.010* |

*Indicates statistical significance

Severity Index, Physician Global Assessment, and body surface area). Furthermore, TD improved the patient-physician relationship as it was easier for patients to see a doctor.[15]

Attitudes toward TD differ between subgroups of populations and patients, depending on factors such as a country's economic development, socioeconomic status, and culture. A survey in the United States of the attitudes of 100 dermatology patients toward synchronous TD during the COVID-19 era reported that 88.9% were satisfied, and 81.8% had not experienced any technical difficulties. However, despite the immense satisfaction with synchronous TD, 68.7% of the patients preferred a face-to-face consultation for their next visit.[16] Another study of 168 dermatology patients from the United States reported that most of the patients liked TD due to the more efficient use of their time (81.1%), transportation not being required (74.2%), and the ability to maintain social distancing (73.6%). The 2 most common criticisms given by the minority of patients who did not like TD were lack of physical touch (26.8%) and a perception that they received inadequate assessments (15.7%). Regarding whether TD could adequately substitute for in-person visits, 55% agreed that it could, 25% disagreed, while the remaining 20% neither agreed nor disagreed.[17]

Most patients in the studies conducted in Thailand and the United States perceived TD to be more efficient and less time-consuming than traditional in-person visits. On the other hand, the patients surveyed in both countries expressed concerns about a possible deterioration of the doctor-patient relationship and the lack of physical touch. Given that Thailand and the United States are very different in terms of ethnicity, culture, and social and economic development, the commonalities between the findings suggest that those positive and negative attitudes may be widespread.

We searched the PubMed and Embase databases using the keywords "willingness to pay," "telemedicine,"

**TABLE 3.** Multiple logistic regression analysis of factors associated with willingness to pay for teledermatology for the treatment of psoriasis.

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | Crude OR (95% CI) | *P* | Adjusted OR (95% CI) | *P* |
| Higher education levels | 2.974 (1.525–5.799) | 0.001* | 4.647 (1.820–11.865) | 0.001* |
| Greater extra expenses for in-hospital visits | 2.093 (1.082–4.050) | 0.028* | 3.626 (1.488–8.837) | 0.005* |
| Occupation | | | | |
| Full-time (ref.) | 1 | | 1 | |
| Part-time | 596187144 (0.000–N/A) | 0.999 | 297481405 (0.000–N/A) | 0.999 |
| Business owner | 0.753 (0.400–1.416) | 0.378 | 3.040 (1.129–8.191) | 0.028* |
| Awareness of teledermatology | 1.985 (0.979–4.021) | 0.057 | 2.419 (0.977–5.988) | 0.056 |
| Efficiency | | | | |
| Teledermatology can be used to treat psoriatic patients | 9.545 (2.930–31.102) | < 0.001* | 7.768 (1.486–40.620) | 0.015* |
| What effect does teledermatology have on psoriatic treatment? | | | | |
| Increased quality | 2.045 (0.942–4.443) | 0.071 | 2.234 (0.896–5.575) | 0.085 |
| Decreased quality | 0.500 (0.223–1.120) | 0.092 | 1.093 (0.356–3.350) | 0.877 |
| Same quality | 1 | | 1 | |
| Teledermatology enables patients to complete routine appointments | 5.833 (1.681–20.242) | 0.005* | 1.565 (0.223–10.996) | 0.653 |
| Quicker than face-to-face visits | | | | |
| Teledermatology can reduce the length of treatment | 6.961 (1.309–37.004) | 0.023* | 0.543 (0.028–10.356) | 0.685 |
| Cheaper than face-to-face visits | | | | |
| Teledermatology has the potential to reduce the cost of treatment | 13.596 (2.836–65.172) | 0.001* | 7.624 (0.819–70.991) | 0.074 |
| Teledermatology will impair the doctor-patient relationship | 0.252 (0.130–0.490) | < 0.001* | 0.314 (0.129–0.762) | 0.011* |
| Concerned about teledermatology use for psoriasis | 0.435 (0.228–0.827) | 0.011* | 0.499 (0.220–1.136) | 0.098 |

*Indicates statistical significance

"teledermatology," and "skin diseases." Table 4 summarizes the findings of published studies evaluating factors that influence WTP for TD to treat skin diseases (psoriasis, melanoma, acne, and skin cancer).[18-22] Qureshi et al reported that 95% of patients with psoriasis and melanoma were willing to pay out of pocket for TD if it provided quicker access to care, compared to only 58% if the access times for TD and traditional in-person visits were the same. The patients also reported that they were willing to pay a median of $25 out of pocket for TD consultations.[18] Seeing specialists (dermatologists) to detect melanoma and skin cancer was a critical factor in favor of TD.[19] For patients with acne, the critical factors supporting the use of TD were a less expensive service, fewer hours away from work or school, a reduction in lost income, and lower travel costs. Mori et al studied WTP for electronic follow-up visits among acne patients on isotretinoin therapy in the United States. Sixty-four patients (61%)

**TABLE 4.** Factors associated with willingness to pay for teledermatology of patients with skin diseases.

| Year | Authors | Study design | Skin diseases | Sample size | Type of teledermatology | Factors associated with WTP for teledermatology |
|---|---|---|---|---|---|---|
| 2006 | Qureshi et al[18] | Face-to-face interview with hypothetical scenario | - Psoriasis<br>- Melanoma | 50<br>42 | N/A | - Quicker than face-to-face visits |
| 2015 | Spinks et al[19] | Discrete choice experiment questionnaire for teledermoscopy screening detecting melanoma | - Melanoma | 35 | Store-and-forward (phone camera) | - Images reviewed by dermatologist |
| 2016 | Pathipati et al[20] | One-on-one discussion regarding their experience | - Rash & acne | 10 | Store-and-forward | - Cheaper than face-to-face visits |
| 2016 | Mori et al[21] | Individual survey responses | - Acne vulgaris | 98 | N/A | - Hours of work and school missed<br>- Lost wages<br>- Travel costs |
| 2018 | Snoswell et al[22] | Discrete choice experiment questionnaire for teledermoscopy screening for detecting skin cancer | - Skin cancer | 113 | Store-and-forward (phone camera) | - Images reviewed by dermatologist |
| 2022 | Our study | Face-to-face interview | - Psoriasis | 200 | Not specific type | Independent factors<br>- Higher education levels<br>- Greater expenses of in-hospital visits<br>- Business owner<br>- Utilizable options of teledermatology<br>- Does not affect doctor-patient relationship |

N/A, not available

were willing to pay out of pocket for an e-visit, for a median cost of $25.[21] Most of the participants (64.8%) reported having no concerns about the safety of e-visits.

Our study added further information for patients with psoriasis. Specifically, it identified that the independent factors associated with WTP for TD services were higher educational levels, elimination of out-of-pocket, in-hospital visit expenses, owning a business, TD options suited to psoriasis treatment, and no adverse effects on the doctor-patient relationship. The payment card method used in this study had some limitations, including a range bias, in which participants tended to choose the lower half of the stated price, and the range of provided amounts had the potential to affect the maximum cost of TD.

## CONCLUSION

In conclusion, although TD cannot replace face-to-face visits for psoriasis treatment, its use is likely to continue to increase markedly. Understanding the attitudes of patients and the factors associated with WTP is essential for developing successful TD services and broadening their appeal to patients with psoriasis.

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### Conflicts of interest

The authors have no relevant financial or non-financial interests to disclose.

### Abbreviations

CI: confidence interval
N/A: not available
OR: odds ratio
SD: standard deviation
TD: teledermatology
WTP: willingness to pay

## REFERENCES

1. Pezzolo E, Naldi L. Epidemiology of major chronic inflammatory immune-related skin diseases in 2019. Expert Rev Clin Immunol. 2020;16(2):155-66.
2. Icen M, Crowson CS, McEvoy MT, Dann FJ, Gabriel SE, Kremes HM. Trends in incidence of adult-onset psoriasis over three decades: a population-based study. J Am Acad Dermatol. 2009; 60(3):394-401.
3. Michalek I, Loring B, John S. A systematic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol. 2017; 31(2):205-12.
4. Landow SM, Mateus A, Korgavkar K, Nightingale D, Weinstock MA. Teledermatology: key factors associated with reducing face-to-face dermatology visits. J Am Acad Dermatol. 2014;71(3): 570-6.
5. Elsner P. Teledermatology in the times of COVID-19–a systematic review. J Dtsch Dermatol Ges. 2020;18(8):841-5.
6. Coates SJ, Kvedar J, Granstein RD. Teledermatology: from historical perspective to emerging techniques of the modern era: part I: history, rationale, and current practice. J Am Acad Dermatol. 2015;72(4):563-74.
7. Pasquali P, Sonthalia S, Moreno-Ramirez D, Sharma P, Agrawa M, Gupta S, et al. Teledermatology and its current perspective. Indian Dermatol Online J. 2020;11(1):12-20.
8. Uscher-Pines L, Malsberger R, Burgette L, Mulcahy A, Mehrotra A. Effect of teledermatology on access to dermatology care among Medicaid enrollees. JAMA Dermatol. 2016;152(8): 905-12.
9. Chambers CJ, Parsi KK, Schupp C, Armstrong AW. Patient-centered online management of psoriasis: a randomized controlled equivalency trial. J Am Acad Dermatol. 2012;66(6):948-53.
10. Wang RH, Barbieri JS, Nguyen HP, Stavert R, Forman HP, Bolognia JL, et al. Clinical effectiveness and cost-effectiveness of teledermatology: Where are we now, and what are the barriers to adoption? J Am Acad Dermatol. 2020;83(1):299-307.
11. Zakaria A, Maurer T, Su G, Amerson E. Impact of teledermatology on the accessibility and efficiency of dermatology care in an urban safety-net hospital: A pre-post analysis. J Am Acad Dermatol. 2019;81(6):1446-52.
12. Warshaw EM, Hillman YJ, Greer NL, Hagel EM, MacDonald R, Rutks IR, et al. Teledermatology for diagnosis and management of skin conditions: a systematic review. J Am Acad Dermatol. 2011;64(4):759-72.
13. Werner P, Karnieli E. A model of the willingness to use telemedicine for routine and specialized care. J Telemed Telecare. 2003;9(5):264-72.
14. Chularojanamontri L, Wongpraparut C, Winayanuwattikun W, Griffiths CE, Chalmers RJ, et al. A reevaluation of the Simplified Psoriasis Index (SPI) using the Thai language version: a study examining the validity, reliability, and interpretability of SPI when used in translation. Journal of Psoriasis and Psoriatic Arthritis. 2020;5:32-9. Available from: https://doi.org/10.1177/2475530319892196
15. Dahy A, El-Qushayri AE, Mahmoud AR, Al-kelany TA, Salman S. Telemedicine approach for psoriasis management, time for application? A systematic review of published studies. Dermatol Ther. 2020;33(6):e13908.
16. Pearlman RL, Le PB, Brodell RT, Nahar VK. Evaluation of patient attitudes towards the technical experience of synchronous teledermatology in the era of COVID-19. Arch Dermatol Res. 2021;313(9):769-72.
17. Yeroushalmi S, Millan SH, Nelson K, Sparks A, Friedman AJ. Patient Perceptions and Satisfaction With Teledermatology During the COVID-19 Pandemic: A Survey-Based Study. J Drugs Dermatol. 2021;20(2):178-83.
18. Qureshi AA, Brandling-Bennett HA, Wittenberg E, Chen SC, Sober AJ, Kvedar JC. Willingness-to-pay stated preferences for telemedicine versus in-person visits in patients with a history of psoriasis or melanoma. Telemed J E Health. 2006;12(6):639-43.
19. Spinks J, Janda M, Soyer HP, Whitty JA. Consumer preferences for teledermoscopy screening to detect melanoma early. J Telemed Telecare. 2016;22(1):39-46.
20. Pathipati AS, Ko JM. Implementation and evaluation of Stanford Health Care direct-care teledermatology program. SAGE Open Med. 2016;4:2050312116659089.
21. Mori WS, Houston N, Moreau JF, Prevost N, Gehris RP, Ferris LK, et al. Personal burden of isotretinoin therapy and willingness to pay for electronic follow-up visits. JAMA Dermatol. 2016; 152(3):338-40.
22. Snoswell CL, Whitty JA, Caffery LJ, Loescher LJ, Gillespie N, Janda M. Direct-to-consumer mobile teledermoscopy for skin cancer screening: Preliminary results demonstrating willingness-to-pay in Australia. J Telemed Telecare. 2018;24(10):683-9.

# Long-term Oncologic Outcomes After Curative Surgery in Stage I–III Thai Colorectal Cancer Patients

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## ABSTRACT

**Objective:** The survival rate for colorectal cancer varies and there are limited reports regarding the long-term outcomes after curative treatment in Thai patients. This study aimed to determine the long-term oncologic results in non-metastatic Thai colorectal cancer patients after curative surgery.

**Materials and Methods:** We performed a retrospective review of a prospectively collected colorectal cancer registry. Short-term and long-term outcomes were analyzed.

**Results:** 626 patients were included in the study, 51.9% colon cancer and 48.1% rectal cancer patients. The mean age was 63.6 ± 12.7 years. The median follow-up time was 5.4 years [IQR: 2.1–7.4]. The 5-year local recurrence was 6.4%; 3.3% in colon cancer and 9.9% in rectal cancer. The 5-year overall survival (5-yr OS) in the colon cancer patients was 76.3%; 94.6% in stage I, 80.8% in stage II, and 65.3% in stage III. The 5-yr OS in the rectal cancer patients was 65.1%; 84.7% in stage I, 75% in stage II, and 51% in stage III. The 5-year disease-free survival (5-yr DFS) in the colon cancer patients was 76.5%; 91.4% in stage I, 81.3% in stage II, and 66.4% in stage III. The 5-yr DFS in the rectal cancer patients was 63.8%; 81.5% in stage I, 75.1% in stage II, and 50.1% in stage III.

**Conclusion:** The long-term oncologic outcomes after curative treatments in this study were acceptable. The prognosis of treatment depends on the disease stage. Comparing stage by stage, colon cancer has a better prognosis than rectal cancer.

**Keywords:** Colorectal cancer; long-term outcomes; overall survival; disease-free survival; Asian; Thai (Siriraj Med J 2022; 74: 739-746)

## INTRODUCTION

Colorectal cancer is one of the most common public health problems. According to the International Agency for Research on Cancer and the World Health Organization, colorectal cancer is the third-most common cancer in men and the second-most common in women worldwide.[1] When diagnosing the disease, most patients would like to know their stage of disease and prognosis. The survival rate of colorectal cancer can vary based on a variety of factors, particularly the stage of the disease. The mortality rate from colorectal cancer has declined from the past because surgeons can now diagnose it earlier and as the treatments have improved. Most of the data regarding long-term survival are reported from Western countries. While there are some publications regarding treatment in colorectal cancer reported from Asian countries, data on the long-term outcomes after curative treatment in stage I–III colorectal cancer, particularly in Thailand, are limited. We, therefore, conducted this study to determine the long-term oncologic results in stage I–III colorectal cancer patients after curative surgery.

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## MATERIALS AND METHODS

After approval by the Siriraj Institute Review Board (Si 581/2015), we performed a retrospective review of the prospectively collected colorectal cancer registry in the Colorectal Surgery Unit, Department of Surgery, Faculty of Medicine Siriraj Hospital. We retrieved data including stage I–III colorectal cancer patients who underwent curative surgery between 2007 and 2011. Patients' information was abstracted from the registry, such as patients' demographic data (age, gender, co-morbidities), preoperative carcinoembryonic antigen (CEA), location of the tumor, type of surgery, short-term outcomes (postoperative complications and mortality), pathological staging, date of the last visit, current survival, and recurrence. The 5-year local recurrence rate (5-yr LR), 5-year overall survival (5-yr OS), and 5-year disease-free survival (5-yr DFS) were analyzed.

The exclusion criteria were 1) patients who had synchronous or a history of other primary cancers or who had developed other primary cancers during the study period, 2) histology other than adenocarcinoma, 3) stage IV disease, 4) patients who did not receive curative-intent surgery, 5) hereditary colorectal cancer syndrome, such as Lynch syndrome and familial adenomatous polyposis (FAP), and 6) either synchronous or metachronous colorectal adenocarcinoma.

### *Statistical analysis*

We exported the retrieved data to SPSS version 23 statistical software for performing all the statistical analysis. We examined the baseline characteristics of the enrolled patients using descriptive statistics. We report the categorical data by number and percentage, while continuous data, such as age, preoperative CEA level, and follow-up time, were reported by the mean and standard deviation or median and interquartile range depending on the skewness of the data. We estimated the distribution of overall survival and disease-free survival through Kaplan–Meier survival analysis.

## RESULTS

### *Study population*

We retrieve the data related to 1,010 colorectal cancer patients who underwent surgery in our unit during the study period, but then excluded 384 patients according to our exclusion criteria. Therefore, the data of 626 stage I-III colorectal adenocarcinoma patients were analyzed comprising 325 colon cancer patients and 301 rectal cancer patients. The median follow-up time was 5.4 years [IQR: 2.1-7.4].

### *Patient characteristics*

The mean age ± standard deviation of the patients was 63.6 ±12.7 years old. There were 335 (53.5%) male and 291 (46.5%) female patients. The most common co-morbidity was hypertension (33.9%) followed by diabetes mellitus (17.3%), cardiovascular disease (12.6%), dyslipidemia (10.4%), neurovascular disease (8%), respiratory disease (6.5%), and renal disease (3.4%), respectively. The median preoperative CEA was 4.4 ng/mL [IQR; 2.5-12.1]. Forty-one patients (6.5%) presented with acute obstruction. Of these, 15 patients were treated with colonic stent; 10 patients with Hartmann's procedure; 12 patients with one-stage colonic resection and anastomosis; and 4 patients with subtotal colectomy and ileorectal anastomosis. Nine percent of the rectal cancer patients received preoperative neoadjuvant concurrent chemoradiation.

### *Tumor locations and operations*

Regarding colon cancer, 99 patients (30.5%) had right-sided colon cancer, including 27 cecum, 26 ascending colons, 21 hepatic flexure, and 25 transverse colons. Meanwhile, 226 patients (69.5%) had left-sided tumors, including 10 splenic flexure colons, 43 descending colons, 123 sigmoid colons, and 50 rectosigmoid colons. For the rectal cancers, 74 lesions were located above the peritoneal reflection, 62 at the peritoneal reflection, and 165 below the peritoneal reflection. Considering the surgery technique, most patients in this study (94.7%) were operated with open surgery. Only 5.3% of patients were operated with minimally invasive surgical techniques, including both laparoscopic-assisted and hand-assisted surgery. The most common type of operation in colon cancer was sigmoidectomy or anterior resection (59.7%). Overall, 212 (70.4%) of the rectal cancer patients could have had a sphincter preserving operation. Of these, 33 patients (15.6%) had a protective diverting stoma. Meanwhile, 89 patients (29.6%) underwent abdominoperineal resection.

### *Pathology and staging*

This cohort consisted of 56 (8.9%) well differentiated carcinomas, 536 (85.6%) moderately differentiated carcinomas, 24 (3.8%) poorly differentiated carcinomas, 4 (0.6%) signet ring cell carcinomas, and 3 (0.5%) mucinous carcinomas. Regarding pT staging, the tumors were 27 (4.3%) T1, 133 (21.2%) T2, 399 (63.7%) T3, 42 (6.7%) T4a, and 25 (4%) T4b. More than one-quarter of patients (27.8%) had lymphovascular invasion and 20.6% of patients had a perineural invasion. The median number of total harvested lymph nodes was 19 [IQR: 14-27]. The positive all resection margin rate in the specimens was

9.3%; comprising 8.1% positive circumferential margin (CRM) and 1.3% positive distal resection margin. As per our anticipation, there were more positive CRM cases in rectal cancer than in colon cancer (10.6% versus 5.8%), as well as more positive distal resection margin cases in rectal cancer than in colon cancer (1.9% versus 0.6%). Most patients had pathological stage II and III diseases, both for colon and rectal cancer (Fig 1).

### *Short-term outcomes*

The overall complication rate in this study was 20.8%; 7.2% medical-related complications, and 17.1% surgical-related complications. Respiratory complication was the most common medical-related complication (3.2%) followed by 2.2% urinary tract infection, 1.6% cardiac complication, and 0.5% thromboembolism complications. Meanwhile, superficial surgical site infection was the most common surgical-related complication (10.1%), followed by 7.8% stoma complication, 2.7% urinary retention, 1.9% intraabdominal collection, 0.8% wound dehiscence, and 0.5% deep surgical site infection. The overall anastomotic leakage rate was 3%; 1.7% in colon cancer operations and 5.2% in rectal cancer operations. One percent of patients had to be re-admitted within 30 days after surgery. Approximately, 12.8% of patients required postoperative ICU stay and the postoperative mortality rate was 1%.

### *Long-term outcomes*

The 5-yr OS of all the patients in this cohort (stage I–III, including both colon and rectal cancer) was 70.9%; 89.1% in stage I, 78.6% in stage II, and 57.9% in stage III; while the 5-yr DFS of all the patients in this cohort was 70.4%; 85.9% in stage I, 79% in stage II, and 57.8% in stage III. Comparing stage by stage, rectal cancer had a poorer prognosis than colon cancer, as demonstrated by the 5-yr OS and 5-yr DFS (Table 1, Fig 2, and Fig 3). Compared to the colon cancer patients, the rectal cancer patients had a higher 5-year local recurrence rate: 3.1% in colon cancer and 8.3% in rectal cancer, respectively. The overall distant recurrence rate of both the colon and rectal cancer patients in this study was approximately 24%; 20% in colon cancer patients and 28.6% in rectal cancer patients. The liver was the most common distant recurrence site in colon cancer, while the lung was the most common distant recurrence site in rectal cancer (Table 2).

### *Factors related to distant recurrences*

On multivariate analysis, the independent predictors of distant recurrence in rectal cancer patients were preoperative CEA > 5 ng/mL, (HR=1.701; 95% CI, 1.069-2.706; P = 0.025), N2 stage (HR=2.837; 95% CI, 1.779-4.524; P < 0.001), presence of tumor deposit (HR=3.567; 95% CI, 1.539-8.271; P = 0.003), positive circumferential margin (HR=2.117; 95% CI, 1.226-3.657; P= 0.007), and tumor located below peritoneal reflection (HR=2.279; 95% CI, 1.239-4.192; P=0.008). Howerever, preoperative CEA > 5 ng/mL, (HR=2.363; 95% CI, 1.399-3.989; P = 0.001) and pathological N2 staging (HR = 4.254 ; 95% CI, 2.228-8.123; p < 0.001) were related to distant recurrence in colon cancer patients.

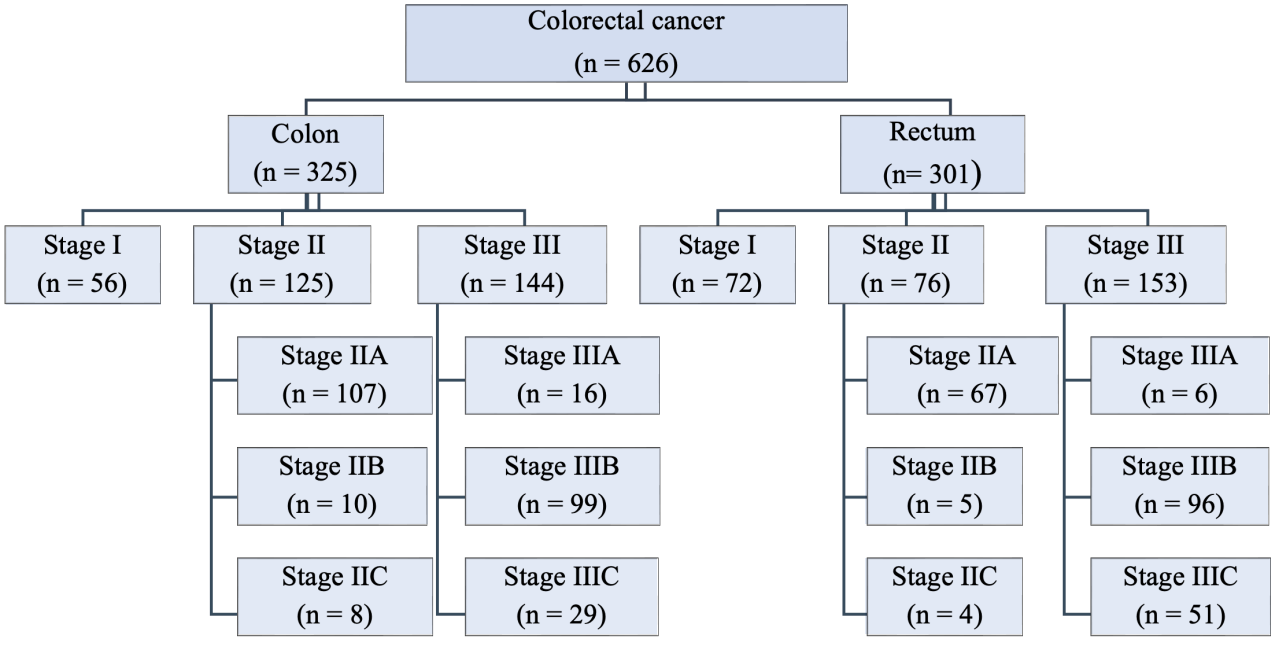


**Fig 1.** Pathological staging of the study cohort.

**TABLE 1.** Kaplan–Meier estimated 5-year overall survival and 5-year disease-free survival in stage I–III colon and rectal cancer patients.

| Stage | Colon and rectal cancer | | Colon cancer | | Rectal cancer | |
|---|---|---|---|---|---|---|
| | 5-yr OS | 5-yr DFS | 5-yr OS | 5-yr DFS | 5-yr OS | 5-yr DFS |
| **Stages I–III** | 70.9% | 70.4% | 76.3% | 76.5% | 65.1% | 63.8% |
| **Stage I** | 89.1% | 85.9% | 94.6% | 91.4% | 84.7% | 81.5% |
| **Stage II** | 78.6% | 79.0% | 80.8% | 81.3% | 75.0% | 75.1% |
| Stage IIA | 81.6% | 78.6% | 83.2% | 80.6% | 79.1% | 75.7% |
| Stage IIB | 66.7% | 84.4% | 70.0% | 88.9% | 60.0% | 80.0% |
| Stage IIC | 50.0% | 80.0% | 62.5% | 83.3% | 25.0% | 75.0% |
| **Stage III** | 57.9% | 57.8% | 65.3% | 66.4% | 51.0% | 50.1% |
| Stage IIIA | 72.7% | 79.8% | 81.3% | 86.7% | 50.0% | 55.6% |
| Stage IIIB | 65.1% | 63.1% | 71.7% | 71.4% | 58.3% | 55.1% |
| Stage IIIC | 36.3% | 37.7% | 34.5% | 33.4% | 37.3% | 39.6% |

**Abbreviations:** *5-yr OS = 5-year overall survival; 5-yr DFS = 5-year disease free survival.*

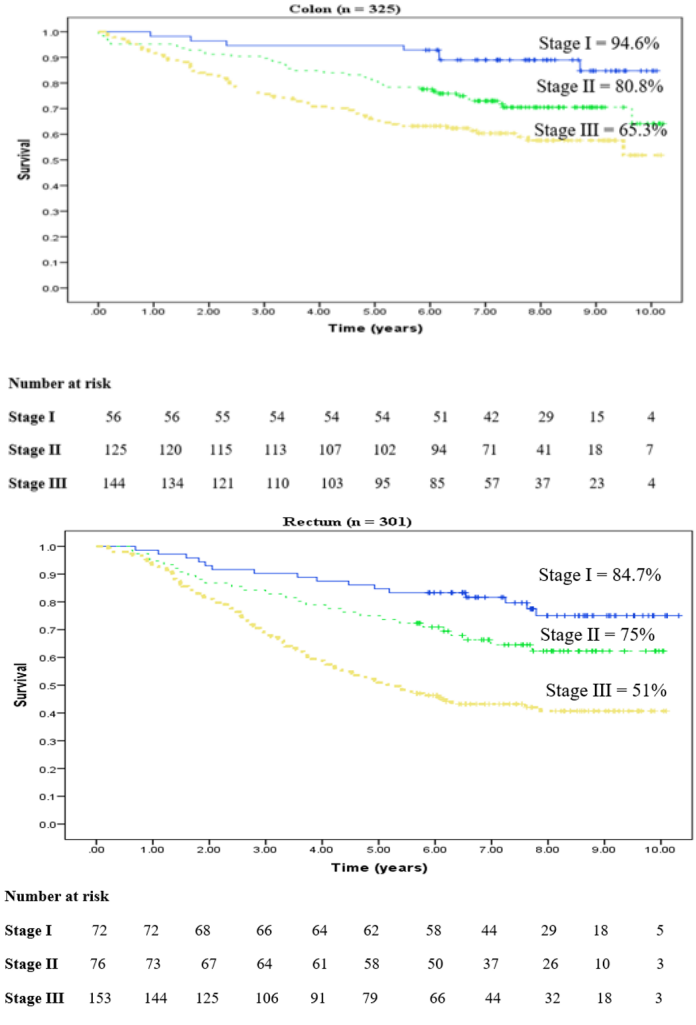


**Fig 2.** Five-year overall survival in stage I-III colon and rectal cancer patients.

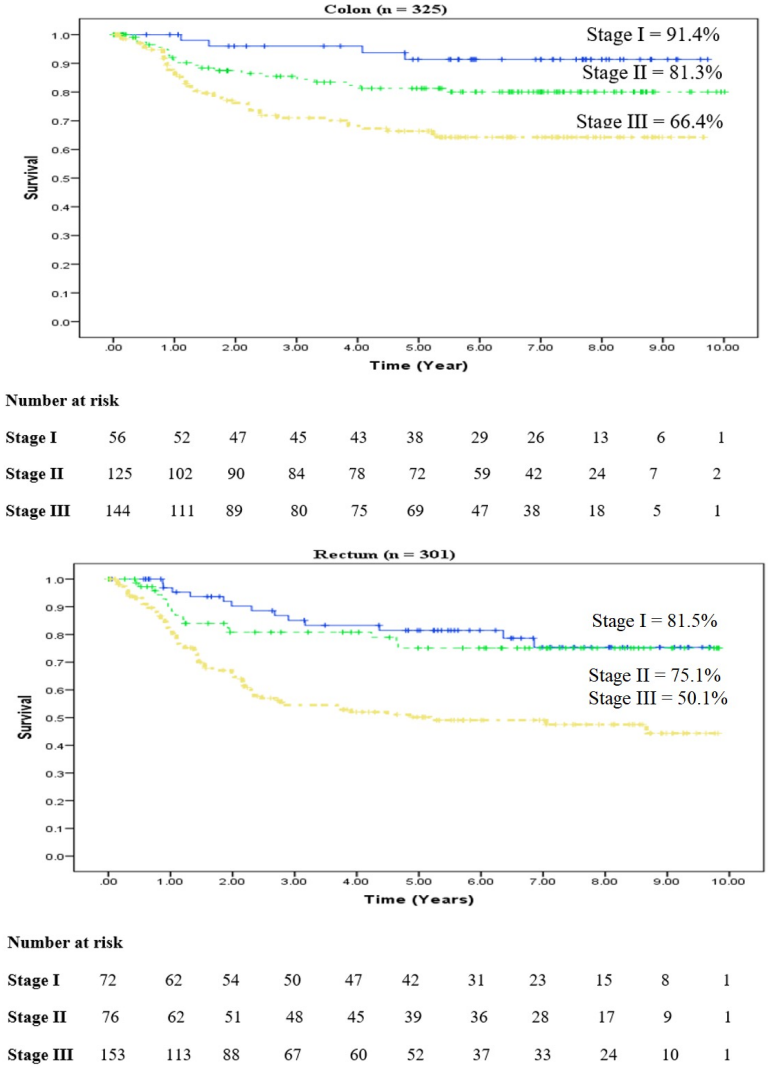


**Fig 3.** Five-year disease-free survival in stage I-III colon and rectal cancer patients

**TABLE 2.** Sites of distant recurrence in stage I–III colon and rectal cancer patients.

| | Colon cancer (n = 325) | Rectal cancer (n = 301) |
|---|---|---|
| Local | 10 (3.1%) | 25 (8.3%) |
| Distant | 65 (20%) | 86 (28.6%) |
| Liver | 39 (12%) | 32 (10.6%) |
| Lung | 24 (7.4%) | 47 (15.6%) |
| Peritoneal | 8 (2.5%) | 12 (3.9%) |
| Bone | 8 (2.5%) | 16 (5.3%) |
| Brain | 4 (1.2%) | 3 (1%) |
| Supraclavicular lymph node | 3 (0.9%) | 0 (0%) |
| Para-aortic lymph node | 6 (1.8%) | 3 (1%) |

## DISCUSSION

In our study, the age incidence of colorectal cancer was between the fifth and seventh decades of life. The incidence was higher in males than females. These patient characteristics were comparable to the previous studies reported in Western countries.[2-7] Regarding the locations of the tumors, approximately half of the patients were diagnosed with rectal cancer, which was a relatively high proportion. For the colon cancers, most were in the left-sided colon and located distal to the splenic flexure. We also noticed that most tumors were locally advanced stage. The incidence of acute obstruction was 6.5%, which was similar to previous reports. The postulated reasons to explain these results were: 1) most rectal cancer patients who needed multimodalities treatment were referred to our hospital, which is a tertiary university hospital, and 2) most patients presented with symptoms and signs of colorectal cancer rather than asymptomatic ones. This might reflect the low participation rate in colorectal

cancer screening programs and poor patient education on colorectal cancer in our country.

Concerning the treatment modalities, surgery was the primary treatment for both colon and rectal cancer. Most patients were operated with the open technique, because the long-term oncologic outcomes of minimally invasive surgery in colon cancer were just reported as an acceptable treatment and comparable to the open surgical technique during the study period. Meanwhile, minimally invasive surgery for rectal cancer was still debatable during that time. The abdominoperineal resection rate in rectal cancer in this study was 29.5%, which is acceptable for a standard colorectal cancer surgery center.[8-12] In colon cancer, postoperative adjuvant chemotherapy was given if the stage of disease was pathological stage III or high-risk pathological stage II, i.e., obstruction, perforation, poorly differentiated histology, positive lymphovascular or perineural invasion, and if the total lymph nodes harvested was less than 12 nodes. Postoperative adjuvant concurrent chemoradiation was given in most pathological stage II and stage III rectal cancer patients, while less than 10 % of rectal cancer patients in this study received preoperative neoadjuvant concurrent chemoradiation. This could be explained by the long waiting list for radiation therapy in our hospital. However, the setting up of a multidisciplinary team in our hospital among surgeons, radiation oncologists, and medical oncologists in colorectal cancer management has now resolved this problem. Previous reports have emphasized the significance of a multidisciplinary team in colorectal cancer.[13-15]

The patients in this cohort seemed to have multiple co-morbidities and a high rate of ICU admission because our hospital is a tertiary referral university hospital as previously mentioned. Nonetheless, the mortality rate and readmission rate were acceptable and quite low, as were other short-term outcomes, including medical-related complications, wound complications, and other surgical-related complications. Although approximately 15% of the rectal cancer patients who underwent low anterior resection had protective diversion of the stoma proximal to the anastomosis selectively performed, the anastomotic leakage rate was acceptable, as was the anastomotic leakage rate in colon cancer surgery. These promising short-term outcomes might result from the experience and colorectal surgery sub-specialty of the surgeons who mostly performed the operations in this study. Previous publications have underscored the association between the surgeon factor and the outcomes of colorectal cancer surgery.[16-21]

Focusing on the long-term oncologic outcomes, the pathological stage of the disease has a major impact on the 5-year survival rate. Appropriate multimodalities curative treatment in non-metastasis cases results in a good prognosis. With a median follow-up time of 5.4 years in this study, the 5-yr OS and 5-yr DFS in stage I–III both in colon and rectal cancer were 70.9% and 70.4%, respectively, which were comparable to a previous report from Thailand by Techawathanawanna et al. They reported the 5-year OS in stage I–III colorectal cancers was 83% overall and the 5-yr DFS was 72% overall. The 5-year DFS in the specific stages I–III was 90%, 85%, and 58%; while the 5-year OS in the specific stages I–III was 93%, 93%, and 73%.[22] Meanwhile, a study from another Asian country, namely one in China by Yuan et al., reported 3-year and 5-year overall survival rates of 74% and 68% respectively.[23] When looking into the long-term oncologic outcomes stage by stage, either in colon or rectal cancer, the results from our study were comparable to the results reported from Western countries; for instance, the report by O'Connell et al. in 2004. They reported 5-year cancer-specific survival rates in 119,363 colon cancer patients in sub-stages as 93.2% for stage I, 84.7% for stage II A, 72.2% for stage II B, 83.4% for stage III A, 64.1% for stage III B, and 44.3% for stage III C.[24]

Comparing stage by stage, rectal cancer had a worse prognosis than colon cancer. Local recurrence of colon and rectal cancer in our study was also acceptable and comparable to in other recent publications. Authors from the Cleveland Clinic Foundation described 5-year overall local recurrence rates in colon cancer as 5.1%; 2.2%, 5.3%, and 7.7 for stages I, II, and III respectively.[25] As reported in other studies, distant recurrence in our study was still high, particularly in locally advanced stages.[26] These reflect the current clinical practice that stage III patients receive chemotherapy, whereas stage II patients do not. To improve long-term survival and decrease distant recurrence, we should reconsider the paradigm of management in locally advanced colorectal cancer. These strategies might include: 1) postoperative adjuvant chemotherapy in high-risk patients beyond current indications directed by tissue marker, 2) preoperative neoadjuvant chemotherapy as demonstrated by preliminary studies of the FOxTROT trial in locally advanced colon cancer[27], and 3) total neoadjuvant therapy in locally advanced rectal cancer, either with induction or consolidation chemotherapy, as demonstrated by the PROSPECT trial (induction chemotherapy before a long course of concurrent chemoradiation), the Time testing trial (consolidation therapy after a long course of concurrent chemoradiation)[28,29], and the RAPIDO

trial (short-course radiation followed by consolidation chemotherapy).[30]

From our multivariate analysis, we could identify the colorectal cancer patients with high risk of distant recurrence who might have benefit if the new paradigm of preoperative treatment is given. Therefore, preoperative neoadjuvant chemotherapy should be considered particularly in colon cancer patients with high preoperative CEA or clinically multiple enlarged lymph nodes (more than 3 lymph nodes). Meanwhile, rectal cancer patients with high preoperative CEA level, N2 stage, presence of tumor deposit, threaten circumferential margin, and tumor located below the peritoneal reflection might have benefit from receiving preoperative total neoadjuvant therapy.

Our study had some limitations to note. First, it was a retrospective study design. Another was that some patients' data were missing because they were referred to receive postoperative adjuvant therapy and surveillance at their primary care hospital. This suggests we require a national colorectal cancer registry database to answer more complicated questions and should set up a guideline for the management of Thai colorectal cancer patients.

## CONCLUSION

The long-term oncologic outcomes after the curative treatments in this study were acceptable and comparable to previous publications. The prognosis of treatment depends on the disease stage. Comparing stage by stage, colon cancer has a better prognosis than rectal cancer. The new paradigm such as preoperative neoadjuvant chemotherapy in colon cancer patients or total neoadjuvant therapy in rectal cancer patients should be considered in patients with high risk of distant recurrence.

## ACKNOWLEDGMENTS

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**Conflict of interest:** All the authors declare they have no conflicts of interest for this study.

## REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5): E359-86.
2. Brenner H, Hoffmeister M, Arndt V, Haug U. Gender differences in colorectal cancer: implications for age at initiation of screening. Br J Cancer. 2007;96(5):828-31.
3. Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020;70(3):145-64.
4. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Prz Gastroenterol. 2019;14(2):89-103.
5. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683-91.
6. Abancens M, Bustos V, Harvey H, McBryan J, Harvey BJ. Sexual Dimorphism in Colon Cancer. Front Oncol. 2020;10:607909.
7. Gao RN, Neutel CI, Wai E. Gender differences in colorectal cancer incidence, mortality, hospitalizations and surgical procedures in Canada. J Public Health (Oxf). 2008;30(2):194-201.
8. Tilney HS, Heriot AG, Purkayastha S, Antoniou A, Aylin P, Darzi AW, et al. A national perspective on the decline of abdominoperineal resection for rectal cancer. Ann Surg. 2008;247(1):77-84.
9. Keller DS, Reif de Paula T, Kiran RP. Ready for the National Accreditation Programs for Rectal Cancer? Auditing rectal cancer outcomes in the United States. Colorectal Dis. 2019;21(10):1213-5.
10. Roxburgh CSD, Strombom P, Lynn P, Cercek A, Gonen M, Smith JJ, et al. Changes in the multidisciplinary management of rectal cancer from 2009 to 2015 and associated improvements in short-term outcomes. Colorectal Dis. 2019;21(10):1140-50.
11. Warschkow R, Ebinger SM, Brunner W, Schmied BM, Marti L. Survival after Abdominoperineal and Sphincter-Preserving Resection in Nonmetastatic Rectal Cancer: A Population-Based Time-Trend and Propensity Score-Matched SEER Analysis. Gastroenterol Res Pract. 2017;2017:6058907.
12. Marwan K, Staples MP, Thursfield V, Bell SW. The rate of abdominoperineal resections for rectal cancer in the state of Victoria, Australia: a population-based study. Dis Colon Rectum. 2010;53(12):1645-51.
13. Obias VJ, Reynolds HL Jr. Multidisciplinary teams in the management of rectal cancer. Clin Colon Rectal Surg. 2007; 20(3):143-7.
14. Peng D, Cheng YX, Cheng Y. Improved Overall Survival of Colorectal Cancer under Multidisciplinary Team: A Meta-Analysis. Biomed Res Int. 2021;2021:5541613.
15. Fehervari M, Hamrang-Yousefi S, Fadel MG, Mills SC, Warren OJ, Tekkis PP, et al. A systematic review of colorectal multidisciplinary team meetings: an international comparison. BJS Open. 2021; 5(3):zrab044.
16. Bhoday J, Martling A, Straßburg J, Brown G. Session 1: The surgeon as a prognostic factor in colon and rectal cancer? Colorectal Dis. 2018;20 Suppl 1:36-38.
17. Hermanek P, Mansmann U, Staimmer DS, Riedl S, Hermanek P. The German experience: the surgeon as a prognostic factor in colon and rectal cancer surgery. Surg Oncol Clin N Am. 2000; 9(1):33-49, vi.
18. Porter GA, Soskolne CL, Yakimets WW, Newman SC. Surgeon-related factors and outcome in rectal cancer. Ann Surg. 1998; 227(2):157-67.
19. van Gijn W, Gooiker GA, Wouters MW, Post PN, Tollenaar RA, van de Velde CJ. Volume and outcome in colorectal cancer surgery. Eur J Surg Oncol. 2010;36 Suppl 1:S55-63.
20. van Groningen JT, Marang-van de Mheen PJ, Henneman D, Beets GL, Wouters MWJM. Surgeon perceived most important factors to achieve the best hospital performance on colorectal

cancer surgery: a Dutch modified Delphi method. BMJ Open. 2019;9(9):e025304.
21. Renzulli P, Lowy A, Maibach R, Egeli RA, Metzger U, Laffer UT. The influence of the surgeon's and the hospital's caseload on survival and local recurrence after colorectal cancer surgery. Surgery. 2006;139(3):296-304.
22. Techawathanawanna S, Nimmannit A, Akewanlop C. Clinical characteristics and disease outcome of UICC stages I-III colorectal cancer patients at Siriraj Hospital. J Med Assoc Thai. 2012;95 Suppl 2:S189-98.
23. Yuan Y, Li MD, Hu HG, Dong CX, Chen JQ, Li XF, et al. Prognostic and survival analysis of 837 Chinese colorectal cancer patients. World J Gastroenterol. 2013; 19(17):2650-9.
24. O'Connell JB, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. J Natl Cancer Inst. 2004; 96(19):1420-5.
25. Liang J, Fazio V, Lavery I, Remzi F, Hull T, Strong S, et al. Primacy of surgery for colorectal cancer. Br J Surg. 2015;102(7): 847-52.
26. Sargent DJ, Wieand HS, Haller DG, Gray R, Benedetti JK, Buyse M, et al. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol. 2005;23(34):8664-70.
27. Foxtrot Collaborative Group. Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomized controlled trial. Lancet Oncol. 2012;13(11):1152-60.
28. Schrag D, Weiser MR, Goodman KA, Gonen M, Hollywood E, Cercek A, et al. Neoadjuvant chemotherapy without the routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol. 2014;32(6):513-8.
29. Garcia-Aguilar J, Chow OS, Smith DD, Marcet JE, Cataldo PA, Varma MG, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol. 2015;16(8):957-66.
30. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EM, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(1): 29-42.

# Medial Closing-Wedge Distal Femoral Varus Osteotomy via Lateral Approach: The Modified Technique for Treating Valgus Osteoarthritic Knee as case series

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## ABSTRACT

**Objective:** The medial closing-wedge distal femoral varus osteotomy (MCW-DFVO) was an excellent operation for painful valgus lateral unicompartmental osteoarthritic (OA) knee, especially in the young patient. Originally, it requires a medial approach that has more precarious. On top of that, releasing of the iliotibial band that is the deforming force needs added incision. Therefore, this study aims to describe the modified surgical technique of MCW-DFVO that uses a lateral approach and lateral plating to treat the valgus OA knee. Additionally, we also reveal the outcomes of our technique as the case series.

**Materials and Methods:** Ten patients (12 knees) who underwent MCW-DFVO via a lateral approach were retrospectively reviewed. The inclusion criteria were age 18-60 years, isolated lateral compartmental OA knee (Kellgren-Lawrence grade 3-4), no significant patellofemoral pain, and range of motion (ROM) > 90 degrees. We excluded the inflammatory joint disease, unstable knee (femorotibial joint subluxation > 1 cm), and prior surgical procedure. Demographic data, pre- and postoperative ROM, radiographic outcomes, complications, and survivorship were recorded.

**Results:** The mean age, body mass index, and preoperative ROM were 55.3 ± 4.0 years, 25.4 ± 3.7 kg/m$^2$ and 113.3 ± 11.5 degrees, respectively. The preoperative mechanical femorotibial angle was 162.3 ± 4.8 degrees, and the final post-operative alignment was 182.3 ± 2.6 degrees. Overall mean operative time of this technique was 92.5 ± 26.7 minutes. During the mean follow-up period of 8.3 ± 3.1 years, all osteotomy were united and the final postoperative ROM was decreased to 108.8 ± 11.7 degrees. One knee required plate removal due to hardware irritation, and another knee required subsequent total knee arthroplasty at 1 and 8.5 years after MCW-DFVO, respectively. The survivorship of this technique was 91.7% at the mean survival time of 13.8 years (95% confidence interval, 11.9 – 15.7 years).

**Conclusion:** This study proposed the modified surgical technique of MCW-DFVO via a lateral approach. This technique provided the excellent correction angle, union rate and survivorship.

**Keywords:** Distal femoral varus osteotomy; medial closing wedge; survivorship; osteoarthritis; knee (Siriraj Med J 2022; 74: 747-753)

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## INTRODUCTION

The distal femoral varus osteotomy (DFVO) was the ideal surgical treatment for fail conservative, painful valgus lateral unicompartmental osteoarthritic (OA) knee because it shifts the load from damage lateral compartment to the healthy medial compartment. In the case of valgus deformity, Matsuda et al.[1] found that the lateral femoral condyle was hypoplasia and was severely distorted compared to normal and varus OA knee. Previous investigators found that it provides better outcomes compared to the proximal tibial varus osteotomy.[2,3] Generally, DFVO is recommended for patients who have age < 60 years, isolated lateral compartmental OA knee, no significant patellofemoral pain, high demand activities, and a good range of motion (ROM).[4] The contraindications include inflammatory joint disease and unstable knee (femorotibial joint subluxation > 1 cm).[5]

The surgical techniques of this procedure can be divided into three types; medial closing-wedge (MCW-DFVO), lateral opening-wedge (LOW-DFVO), and dome DFVO (D-DFVO). MCW-DFVO is a common and widely used technique proposed by McDermott et al.[6] This technique offers a stable osteotomy site, needless to use the bone graft and good results.[5,6] However, MCW-DFVO has several limitations. Originally, it requires a medial approach that has more precarious. On top of that, releasing of the iliotibial band (ITB) that is the critical deforming force needs added incision.[7] Moreover, medial plating has not achieved a biomechanical benefit because it was applied at the adductor moment side, which cannot provide a tension band function.[5]

Therefore, this study aims to describe the modified surgical technique of MCW-DFVO that uses a lateral approach and lateral plating to treat the valgus OA knee. Additionally, we also reveal the outcomes of our technique as the case series.

## MATERIALS AND METHODS

Our institutional review board approved this study (Si 226/2014).Ten patients (12 knees) who underwent MCW-DFVO via a lateral approach were retrospectively reviewed. The inclusion criteria were age 18-60 years, isolated lateral compartmental OA knee (Kellgren-Lawrence grade 3-4), no significant patellofemoral pain, and ROM > 90 degrees. We excluded the inflammatory joint disease, unstable knee (femorotibial joint subluxation > 1 cm), and prior surgical procedure. Demographic data, pre- and post-operative ROM, radiographic outcomes, complications, and survivorship were recorded. All procedures were performed in accordance with relevant guidelines.

### *Preoperative planning*

The mechanical femorotibial angle (FTA) was measured to define the severity of valgus deformity based on bilateral full length standing alignment film. The preoperative mechanical axis was drawn from the center of the femoral head to the talus's center. It indicated where the weight passed through the knee. According to the method of Dugdale et al.[8], the final weight-bearing line was placed at a position 48-50% across the tibial plateau width from medial to lateral. The acceptable final alignment was 0-3 degree varus (180-183 degrees) of FTA.[9] The angle between the line from the center of the femoral head to the point of 48% across the tibial plateau width and the line from the center of talus to the point of 48% coordinate was measured and named radiographic correction angle. Then, the angle between the distal femoral joint line and the proximal tibial joint line was measured and called the condylar angle. This angle could be corrected by releasing ITB intraoperatively. Thus, the intended correction angle (ICA) was finally calculated from the radiographic correction angle minus the condylar angle.

The lateral and axial radiographs of the knee were also assessed for sagittal plane deformity and patellofemoral joint conditions. The Rosenberg view[10], a 45 degrees posteroanterior flexion weight-bearing radiograph at of knee, was additionally used to diagnosis the early OA in the posterior compartment of the knee.

### *Surgical technique*

This surgical technique was established and performed by the senior author (KC). The patient was placed in a supine position on the radiolucent table. This procedure could be performed with or without using the sterile thigh tourniquet. A curvilinear incision was started from Gerdy's tubercle and then along the lateral side of the femoral shaft. The incisional length was approximately 8-10 cm. ITB was identified and released from Gerdy's tubercle (Figs 1A and 1B). Vastus lateralis muscle was detached from the intermuscular septum and retracted anteromedially to visualize the distal femur.

Under fluoroscopic exam, the Kirsch wires (K-wire) were inserted to guide the osteotomy cut. The first K-wire was inserted at the metaphysodiaphyseal junction of the lateral side of the distal femur that was proximal to the trochlear groove. Its direction was aimed parallel to the distal femoral joint line. The second K-wire was then inserted with an entry point just distal to the first K-wire. Using an intraoperative goniometer assisted, the direction of the second K-wire was planned to make the angle with the first K-wire equal to ICA. The final direction

was confirmed by measuring ICA from a fluoroscopic image (Figs 2A and 2B).

The Homann's retractor was placed close to the medial cortex and retracted anteromedially to visualize the anterior cortex and protect the vascular structures. Another Homann's retractor was placed close to the posterior cortex and retracted posteriorly to identify the distal femur's posterior cortex. Then, the osteotomy was performed along the first guided wire using an oscillating saw. The plane of the saw blade was set perpendicular to the lateral femoral shaft axis. The anterior, posterior, and lateral cortices were completely cut. The medial cortex's 5 mm thickness remained to reduce the risk of vascular injury and preserve the stability of the distal femur for the second osteotomy cut. The second osteotomy cut was done along the second K-wire with the remaining 5 mm thickness of the medial cortex.

In the correction of sagittal plane deformity, the angle setting between two osteotomy planes was crucial. Flexion contracture of the knee could be improved by cutting the second osteotomy with the posterior slope while genu recurvatum could be improved by cutting with anterior slope. After that, the two osteotomies were completely cut using the osteotome, and the cut bone wedge was removed. Without the lateral hinge, the distal femoral fragment could be freely moved and adjusted the position to reduce the geometric deformity of the distal femur-the final alignment in the desired FTA of 0-3 degree varus (Figs 3A, 3B and 3C). After satisfying, two divergent temporary K-wires fixation was done from the anterolateral part of the distal fragment to the posteromedial part of the proximal fragment. The entry points of these wires had not hindered the plate placement (Fig 4A).

For the fixation technique, the 5-hole titanium distal femoral locking compression plate (DF-LCP, Synthes, Solothurn, Switzerland) was selected and bend into the contour of the distal femur. After creating the tunnel, DF-LCP was placed along the center of the lateral side of the distal femur (Fig 4B). The most distal screw hole was placed just above the intercondylar notch. At least 4 locking screws were inserted into the distal fragments, while at least 3 locking screws were inserted into the proximal fragment via the stab skin incisions. The final alignment, plate, and screw positions were rechecked (Fig 4C). At the end of the operation, a vacuum drain was placed along with the plate. The fascia sheath was then repaired. Subcutaneous tissue and skin were sutured. The non-compressive dressing was applied.

In the postoperative rehabilitation, isometric

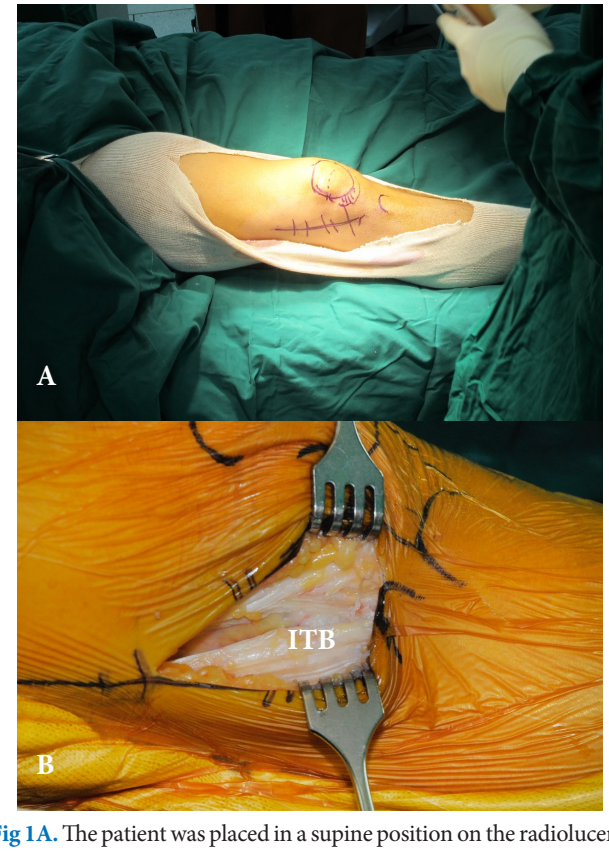


**Fig 1A.** The patient was placed in a supine position on the radiolucent table. A curvilinear incision was started from Gerdy's tubercle and then along the lateral side of the femoral shaft.
**Fig 1B.** The incisional length was approximately 8-10 cm. ITB was identified and released from Gerdy's tubercle

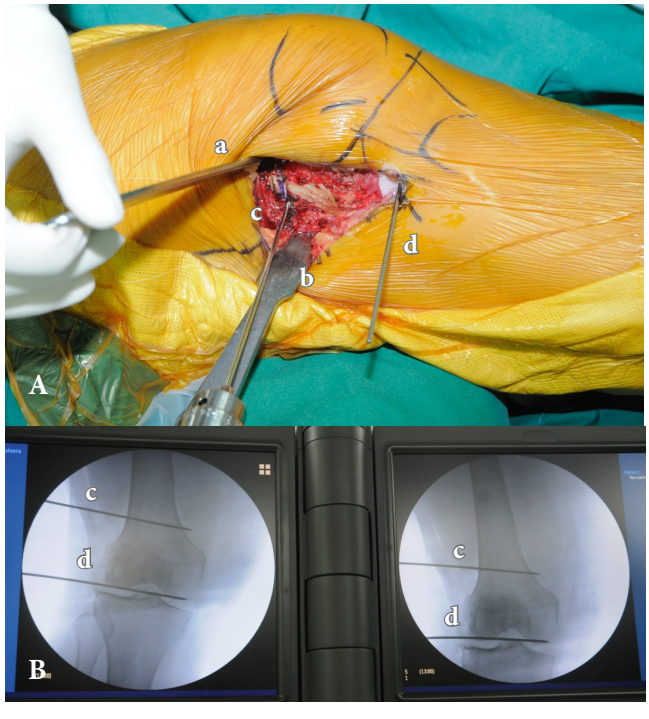


**Fig 2A.** The Homann's retractor (a) was placed close to the medial cortex. Another Homann's retractor (b) was placed close to the posterior cortex and retracted posteriorly to identify the distal femur's posterior cortex
**Fig 2B.** The fluoroscopic exam shjow the first K-wire (c) was inserted at the metaphysodiaphyseal junction of the lateral side of the distal femur that was proximal to the trochlear groove. The second K-wire (d) was then inserted with an entry point just distal to the first K-wire.

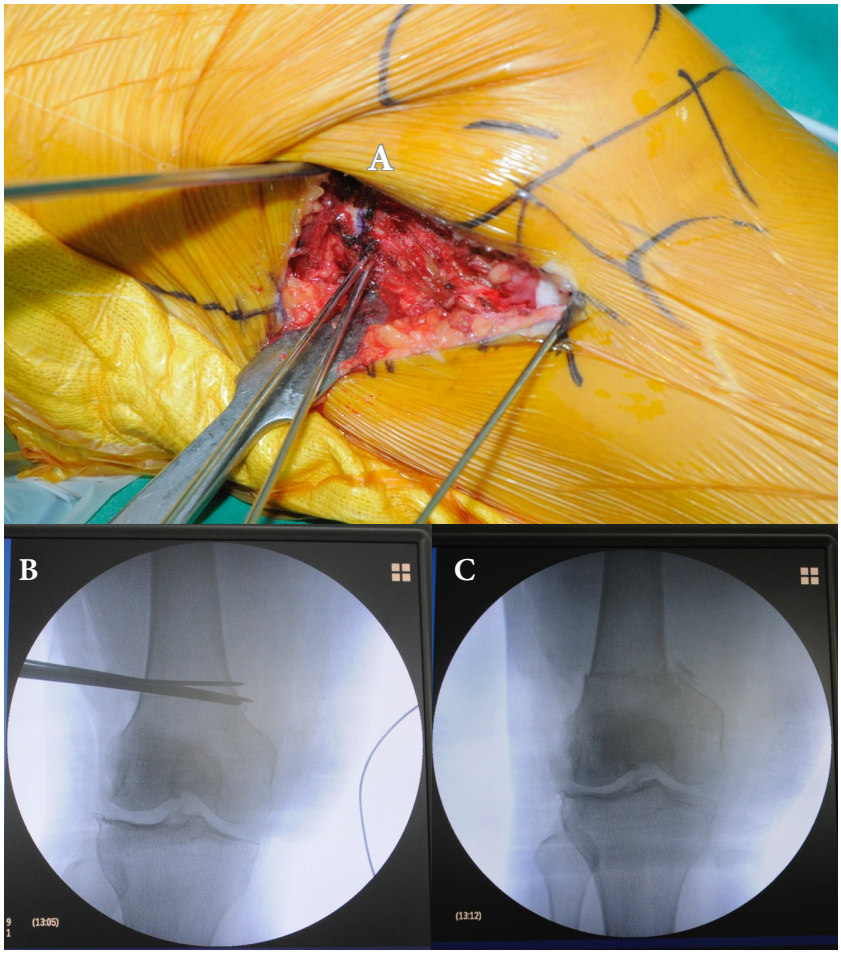


**Fig 3.** The osteotomy (A) was performed along the guided wire using an oscillating saw. After that, the two osteotomies were completely cut using the osteotome (B), and the cut bone wedge was removed. Without the lateral hinge, the distal femoral fragment could be freely moved and adjusted the position to reduce the geometric deformity of the distal femur (C).

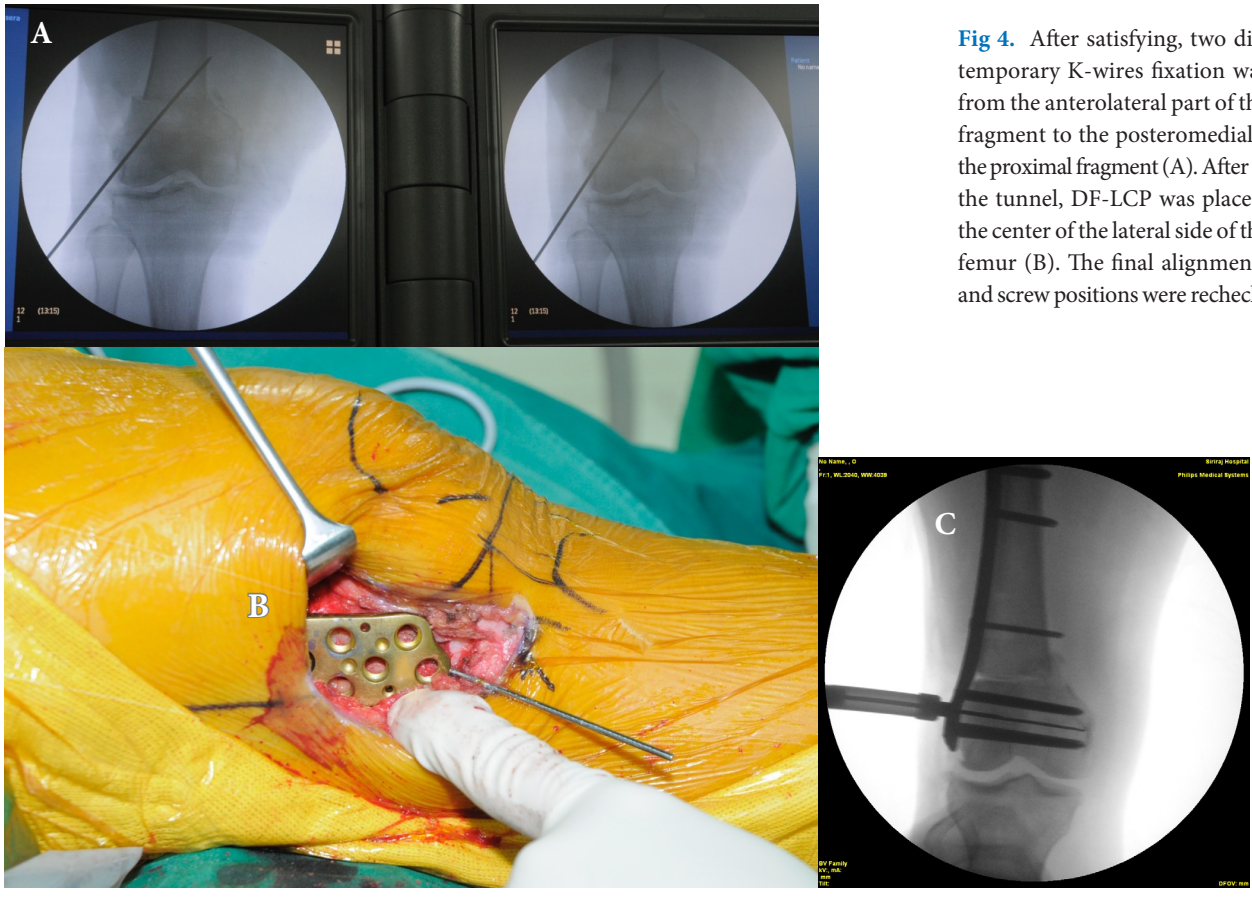


**Fig 4.** After satisfying, two divergent temporary K-wires fixation was done from the anterolateral part of the distal fragment to the posteromedial part of the proximal fragment (A). After creating the tunnel, DF-LCP was placed along the center of the lateral side of the distal femur (B). The final alignment, plate, and screw positions were rechecked (C).

quadriceps exercise and ankle pumping were started as soon as possible to prevent venous thromboembolism. The ROM exercise and walking with toe-touch weight-bearing was allowed in the first operative day. The drain was left in place for 48 hours. Partial weight-bearing was permitted beginning 2 weeks after surgery, and full weight-bearing was permitted after the radiographic union was observed.

**Declarations**

Ethical approval and consent to participate: This study included human participants. It had been approved by Siriraj Institutional (Si 226/2014 ID 221/2014 (EC2)). Informed consent was obtained from all individual participants included in the study. This study was approved by Siriraj Institutional Review Board (SIRB) and retrospectively registered at Thaiclinicaltrial. gov (TCTR202010427002).

## RESULTS

The patients' data were shown in Table 1. The mean age, body mass index, and preoperative ROM were 55.3 ± 4.0 years, 25.4 ± 3.7 kg/m$^2$ and 113.3 ± 11.5 degrees, respectively. The preoperative valgus deformity was 162.3 ± 4.8 degrees, and the final postoperative alignment was 182.3 ± 2.6 degrees. Overall mean operative time of this technique was 92.5 ± 26.7 minutes. During the mean follow-up period of 8.3 ± 3.1 years, all osteotomy were united and the final postoperative ROM was decreased to 108.8 ± 11.7 degrees. One knee required plate removal due to hardware irritation, and another knee required subsequent total knee arthroplasty (TKA) at 1 and 8.5 years after MCW-DFVO, respectively. The survivorship of this technique was 91.7% at the mean survival time of 13.8 years (95% confidence interval, 11.9 – 15.7 years). The Kaplan-Meier curve was demonstrated in Fig 5.

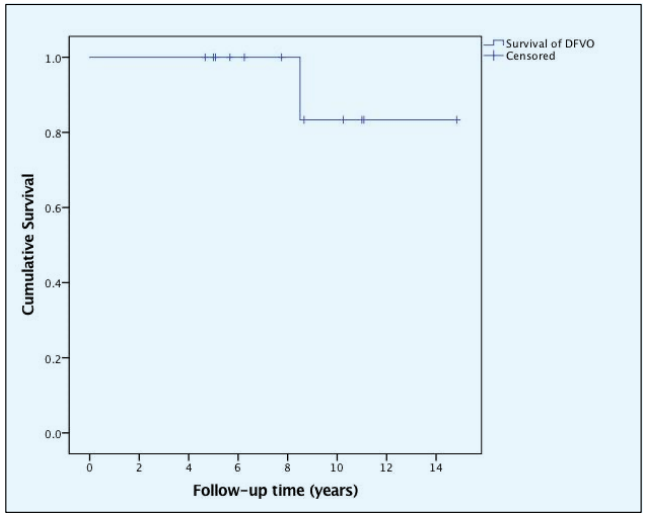


**Fig 5.** The Kaplan-Meier curve of the medial closing-wedge (MCW-DFVO) in the study.

**TABLE 1.** Data of the patients.

| No. | Gender | Age (yr) | Side (kg/m$^2$) | BMI | Range of motion (°) | | FTA (°) | | Follow-up time (yr) | Complications |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Preop | Postop | Preop | Postop | | |
| 1 | Female | 59 | Right | 27.9 | 120 | 110 | 166 | 184 | 14.8 | - |
| 2 | Male | 47 | Right | 23.4 | 120 | 100 | 168 | 180 | 11.1 | - |
| 3 | Female | 59 | Right | 31.5 | 120 | 120 | 161 | 183 | 11.0 | - |
| | Female | 60 | Left | 31.4 | 120 | 120 | 159 | 183 | 10.2 | - |
| 4 | Male | 53 | Right | 24.0 | 120 | 120 | 163 | 185 | 6.3 | - |
| 5 | Female | 58 | Right | 26.8 | 110 | 120 | 160 | 179 | 7.8 | - |
| 6 | Female | 56 | Right | 19.1 | 90 | 90 | 156 | 186 | 8.5 | Converse to TKA |
| | Female | 57 | Left | 20.9 | 120 | 105 | 169 | 183 | 8.7 | Plate removal |
| 7 | Female | 54 | Right | 25.5 | 120 | 120 | 155 | 185 | 5.0 | - |
| 8 | Male | 49 | Right | 25.1 | 110 | 90 | 169 | 178 | 5.7 | - |
| 9 | Female | 54 | Right | 24.9 | 90 | 110 | 161 | 182 | 5.1 | - |
| 10 | Female | 57 | Right | 24.2 | 120 | 100 | 161 | 180 | 5.0 | - |

**Abbreviations:** BMI; body mass index, FTA; femorotibial angle, TKA; total knee arthroplasty

## DISCUSSION

Our senior author (KC) proposed the modified surgical technique of MCW-DFVO via a lateral approach for treating isolated lateral compartmental OA knee. It contributed to good outcomes and survivorship. Our technique had the combined advantages of MCW-DFVO and lateral approach, including stable osteotomy site, unnecessary to use the bone graft, ability to release ITB for reducing the deforming and biomechanical-benefit lateral plating. Nevertheless, this technique still had technically demanded. Furthermore, complete osteotomy cut in our technique led to the loss of lateral hinge that affected in decreased stability. But the ability to adjust distal femoral fragment for reducing the geometric deformity was superseded.

Because a small number of patients were suitable for DFVO, most of the previous studies[9,12-22] were case series. In MCW-DFVO, the survivorships of 64-87% were reported at 10 years follow-up.[12-14] While, the survivorships of 79-100% were reported in LOW-DFVO during the follow-up period of 5-8 years.[18,20-22] The summary of the DFVO outcomes from previous literature review was demonstrated in Table 2. When included all techniques of DFVO, a systematic review of Saithna et al.[23] reported that the overall survivorship of DFVO was 64-84% at 10 years. For the long-term outcomes of DFVO, Kosashvili et al.[16] reported that 48.5% of patients required subsequent TKA. While 30.3% and 21.2% of patients had good and poor functional outcomes, respectively. The mean follow-up time in their series was 15.1 years. Compare to our study, the modified technique provides excellent results. The survivorship of our technique was 91.7% at the mean survival time of 13.8 years (95% confidence interval, 11.9-15.7 years).

For the complications, a previous systematic review[23] reveals that the most common complications of overall DFVO were hardware irritation that required subsequent removal of the plate. The loss of correction angle was the problem after MCW-DFVO due to inadequate fixation or poor bone quality.[13,24] While LOW-DFVO had a higher incidence of delayed union or non-union of the osteotomy site that might be needed bone graft,[9,19] our surgical technique could address these problems. However, hardware irritation still existed in our series.

**TABLE 2.** Previous studies and outcomes of distal femoral varus osteotomy (DFVO).

| Authors | Year | n | Aimed final alignment | Implant | Follow-up time (mean, range) | Survivorship |
|---|---|---|---|---|---|---|
| Medial closing-wedge DFVO | | | | | | |
| Finkelstein et al. | 1996 | 21 | 0º FTA | Blade plate | 133 (97-240) mons | 64% at 10 yrs |
| Stähelin et al. | 2000 | 21 | 1-3º varus FTA | Semitubular plate | 5 (2-12) yrs | NA |
| Wang et al. | 2005 | 30 | 0º FTA | Blade plate | 99 (61-169) mons | 87% at 10 yrs |
| Backstein et al. | 2007 | 40 | 0º FTA | Blade plate | 123 (39-245) mons | 82% at 10 yrs |
| Omidi-Kashani et al. | 2009 | 23 | 0º FTA | Blade plate | 16.3 (8-25) Mon | NA |
| Kosashvili et al. | 2010 | 33 | 0º FTA | Blade plate | 15.1 (10-25) yrs | 51.5% at 15.6 yrs |
| Lateral opening-wedge DFVO | | | | | | |
| Das et al. | 2008 | 12 | 3º valgus FTA | Puddu plate | 74 (51-89) mons | NA |
| Zarrouk et al. | 2010 | 22 | 2-3º valgus FTA | Strelitzia type blade plate | 54 (36-132) mons | 91% at 8 yrs |
| Jacobi et al. | 2011 | 14 | NA | Tomofix plate | 45 (26-64) mons | NA |
| Thein et al. | 2012 | 7 | 0º FTA | Puddu plate | 6.5 yrs | 100% at 6.5 yrs |
| Dewilde et al. | 2013 | 16 | 2º varus FTA | Puddu plate | 68 (31-127) mons | 82% at 7 yrs |
| Saithna et al. | 2014 | 21 | 0º FTA | Tomofix or Puddu plate | 4.5(1.6-9.2) yrs | 79% at 5 yrs |

There were several limitations to this study. First, the number of patients was minimal. However, we would like to demonstrate the modified surgical technique in this series. In the future, we tried to collect more number of patients and reported the outcomes. Second, because this study was retrospective design, bias and confounder were difficult to control. Furthermore, we had no data about the functional outcome or activity level of the patients after surgery.

## CONCLUSION

This study proposed the modified surgical technique of MCW-DFVO via a lateral approach. This technique provided the satisfactory outcomes including correction angle union rate and excellent survivorship. However, further study with a larger sample size was required.

## ACKNOWLEDGMENTS

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### Disclosure

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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## REFERENCES

1. Matsuda S, Miura H, Nagamine R, Mawatari T, Tokunaga M, Nabeyama R, et al. Anatomical analysis of the femoral condyle in normal and osteoarthritic knees. J Orthop Res Off Publ Orthop Res Soc. 2004;22(1):104-9.
2. Shoji H, Insall J. High tibial osteotomy for osteoarthritis of the knee with valgus deformity. J Bone Joint Surg Am. 1973;55(5):963-73.
3. Coventry MB. Proximal tibial varus osteotomy for osteoarthritis of the lateral compartment of the knee. J Bone Joint Surg Am. 1987;69(1):32-8.
4. Tírico LEP, Demange MK, Bonadio MB, Helito CP, Gobbi RG, Pécora JR. Medial Closing-Wedge Distal Femoral Osteotomy: Fixation With Proximal Tibial Locking Plate. Arthrosc Tech. 2015;4(6):e687-95.
5. Puddu G, Cipolla M, Cerullo G, Franco V, Giannì E. Which osteotomy for a valgus knee? Int Orthop. 2010;34(2):239-47.
6. McDermott AG, Finklestein JA, Farine I, Boynton EL, MacIntosh DL, Gross A. Distal femoral varus osteotomy for valgus deformity of the knee. J Bone Joint Surg Am. 1988;70(1):110-6.
7. Favorito PJ, Mihalko WM, Krackow KA. Total knee arthroplasty in the valgus knee. J Am Acad Orthop Surg. 2002;10(1):16-24.
8. Dugdale TW, Noyes FR, Styer D. Preoperative planning for high tibial osteotomy. The effect of lateral tibiofemoral separation and tibiofemoral length. Clin Orthop. 1992;(274):248-64.
9. Stähelin T, Hardegger F, Ward JC. Supracondylar osteotomy of the femur with use of compression. Osteosynthesis with a malleable implant. J Bone Joint Surg Am. 2000;82(5):712-22.
10. Rosenberg TD, Paulos LE, Parker RD, Coward DB, Scott SM. The forty-five-degree posteroanterior flexion weight-bearing radiograph of the knee. J Bone Joint Surg Am. 1988;70(10):1479-83.
11. Krettek C, Miclau T, Grün O, Schandelmaier P, Tscherne H. Intraoperative control of axes, rotation and length in femoral and tibial fractures. Technical note. Injury. 1998;29 Suppl 3: C29-39.
12. Finkelstein JA, Gross AE, Davis A. Varus osteotomy of the distal part of the femur. A survivorship analysis. J Bone Joint Surg Am. 1996;78(9):1348-52.
13. Wang J-W, Hsu C-C. Distal femoral varus osteotomy for osteoarthritis of the knee. J Bone Joint Surg Am. 2005;87(1):127-33.
14. Backstein D, Morag G, Hanna S, Safir O, Gross A. Long-term follow-up of distal femoral varus osteotomy of the knee. J Arthroplasty. 2007;22(4 Suppl 1):2-6.
15. Omidi-Kashani F, Hasankhani IG, Mazlumi M, Ebrahimzadeh MH. Varus distal femoral osteotomy in young adults with valgus knee. J Orthop Surg. 2009;4:15.
16. Kosashvili Y, Safir O, Gross A, Morag G, Lakstein D, Backstein D. Distal femoral varus osteotomy for lateral osteoarthritis of the knee: a minimum ten-year follow-up. Int Orthop. 2010;34(2): 249-54.
17. Das DH, Sijbesma T, Hoekstra H, W. van Leeuwen. Distal femoral opening-wedge osteotomy for lateral compartment osteoarthritis of the knee. Open Access Surg. 2008;1:25-9.
18. Zarrouk A, Bouzidi R, Karray B, Kammoun S, Mourali S, Kooli M. Distal femoral varus osteotomy outcome: Is associated femoropatellar osteoarthritis consequential? Orthop Traumatol Surg Res OTSR. 2010;96(6):632-6.
19. Jacobi M, Wahl P, Bouaicha S, Jakob RP, Gautier E. Distal femoral varus osteotomy: problems associated with the lateral open-wedge technique. Arch Orthop Trauma Surg. 2011;131(6): 725-8.
20. Thein R, Bronak S, Thein R, Haviv B. Distal femoral osteotomy for valgus arthritic knees. J Orthop Sci Off J Jpn Orthop Assoc. 2012;17(6):745-9.
21. Dewilde TR, Dauw J, Vandenneucker H, Bellemans J. Opening wedge distal femoral varus osteotomy using the Puddu plate and calcium phosphate bone cement. Knee Surg Sports Traumatol Arthrosc Off J ESSKA. 2013;21(1):249-54.
22. Saithna A, Kundra R, Getgood A, Spalding T. Opening wedge distal femoral varus osteotomy for lateral compartment osteoarthritis in the valgus knee. The Knee. 2014;21(1):172-5.
23. Saithna A, Kundra R, Modi CS, Getgood A, Spalding T. Distal femoral varus osteotomy for lateral compartment osteoarthritis in the valgus knee. A systematic review of the literature. Open Orthop J. 2012;6:313-9.
24. Edgerton BC, Mariani EM, Morrey BF. Distal femoral varus osteotomy for painful genu valgum. A five-to-11-year follow-up study. Clin Orthop. 1993;(288):263-9.

# Tissue Elimination of Large Vascular Corrosion Casting for Anatomy Education

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## ABSTRACT

**Objective:** Vascular corrosion casting is crucial tool for three-dimensional study. Focusing on the casting for gross anatomy, large fatty tissue reacts with corrosive agents resulting in extensive saponification. Our study aimed to prevent saponification by a) finding the optimal corrosion temperature and concentration of corrosive agent and b) comparing the flow of the agent with conventional "non-flow" setting.

**Materials and Methods:** Phase I: pig fatty tissues, weighing 10 g each, were immersed in still (non-flowing) solution containing 0.5%, 1%, and 5% sodium hydroxide. Different temperatures were set to find the minimum soap-free temperature for each concentration. Phases II, III: 6 pig hearts were injected via the coronary arteries with polymethyl methacrylate. Three hearts were immersed in non-flowing 0.5%, 1%, and 5% NaOH solution, while another three were placed in a flowing solution. The flow was set in a vertical upward fashion in a specialized chamber while the outflow residue was collected from the system. The temperature was set at the minimum soap-free temperature. The durations of the corrosion were compared.

**Results:** The minimum soap-free temperatures for the 0.5%, 1%, and 5% concentrations were 55°C, 54°C, and 47°C, respectively. The corrosion times for the non-flowing 0.5%, 1%, and 5% concentrations were 216 h, 114 h, and 24 h, respectively. Flowing of the solution reduced the corrosion time by 25%-39% compared with the non-flowing.

**Conclusion:** The most efficient condition for soap-free coronary corrosion casting is 5% NaOH solution at a minimal temperature of 47°C.

**Keywords:** Coronary artery; Angiography; Saponification; Alkaline liquefaction; *Sus scrofa domesticus* (Siriraj Med J 2022; 74: 754-759)

## INTRODUCTION

Cadaveric dissection is still the basis of anatomical education for medical students. Students' greatest challenge is understanding the complexity of the vascular system, which is hard to accomplish in a relatively limited time. To tackle this challenge, virtual 3D anatomy has been introduced to aid learning, but the lack of tactile feedback can leave kinesthetic learners behind.[1] On the other hand, the tangible model has shown better teaching outcomes than virtual dissection in the cardiovascular class.[2] This model can replicate or be derived from a real specimen (e.g., plastination or vascular corrosion casting).

Vascular corrosion casting has been utilized in vascular research for centuries.[3] However, since the 1960s, the research trend has shifted from the gross to the microscopic level in line with the rise of scanning electron microscopy (SEM). The casting technique has been developed accordingly to focus on the microscopic vessels of tiny specimens.[4-6] On the other hand, macroscopic cast production has been somewhat sidelined, with some

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technical difficulties remaining unresolved. Vascular corrosion casting consists of two steps: casting medium injection and the corrosion process. First, the medium is selected from certain polymers that have water-like fluidity in the monomeric form and rigidity in the polymeric form. Hence the medium is injected in the monomeric form and allowed to polymerize in the lumen of the blood vessel. The most popular medium is polymethyl methacrylate (pMMA). However, this polymer losses its strength at high temperature.[7] Therefore, unnecessary heat to the cast should be avoided during the whole process.

Corrosion, the second step, eliminates the surrounding tissue, typically by alkaline solution (e.g., NaOH and KOH).[4-6,8,9] Alkalis, once dissociated in water, produce hydroxide ions that react with proteins in a process called solubilization[10], which is also known as alkaline liquefaction[11] and alkaline hydrolysis.[12] Meanwhile, hydroxide ions also saponify the fat, producing an undesirable by-product as a solid soap residue.[4-6,8,9] A constant heat at 40–60°C is applied to the solution for two purposes: (a) to increase the soap solubility in water and (b) to accelerate protein solubilization. Despite the heat input, this process could take up to 7–8 days[5] and some residue (e.g., soap) is usually still nestled in the cast (Fig 1), requiring additional washing by running water.[5,6,8,9] To reduce the corrosion time and cut the washing process, the circulating laminar outflow chamber (CLOC) system was developed.[13] The CLOC system (Fig 2) consists of three parts connected in one circuit: (1) the heater, (2) the pump, and (3) the chambers. The former two generate a circulating flow of hot corrosive solution to wash the tissue and fat away. The latter part, the chambers, are composed of a specimen chamber and outflow chamber. The solution flows to the specimen chamber, then to the outflow chamber, and returns to the heat and pump unit. The wash-out residue is contained in the outflow chamber and prevented from re-circulation. A recent study[13] demonstrated the feasibility of the system for the mass production of casts. However, two questions remain: (a) what is the optimal temperature for the corrosion process? and (b) How much time efficiency does the CLOC system have for corrosion process compared to conventional corrosion process? This study approached the first question by attempting to find the "minimum soap-free temperature", defined as the lowest temperature of the corrosive solution where solid soap is not formed during the corrosion process. This temperature, on the other hand, would minimize the heat damage on pMMA cast, hence presumably an optimal temperature for the corrosion process. The second question was tackled by comparing the duration of the corrosion process (corrosion time) between the conventional, non-flowing solution and flowing solution in CLOC system.

## MATERIALS AND METHODS

Pig hearts and fatty tissues were purchased from a butcher shop in Bangkok Noi District, Bangkok. The pigs were slaughtered for commercial purposes at a registered slaughterhouse in Nakhon Pathom. The study is appoved by Siriraj Laboratory Animal Research and Care Center, Faculty of Medicine Siriraj Hospital, Mahidol University (Si 008/2022). Pig fat was cut from the subcutis into

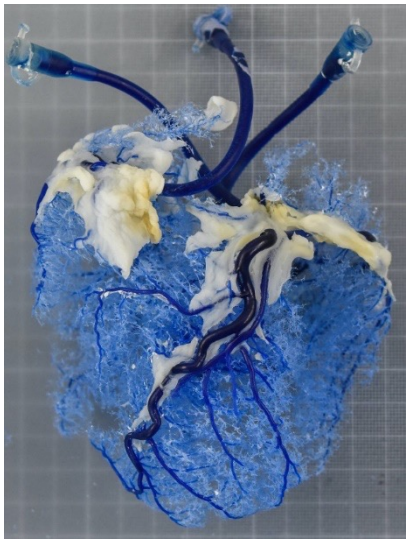

**Fig 1.** Photograph of a vascular corrosion cast that was processed via a corrosion step at too low a temperature. White solid soap residue is formed and can be seen attached to the cast.

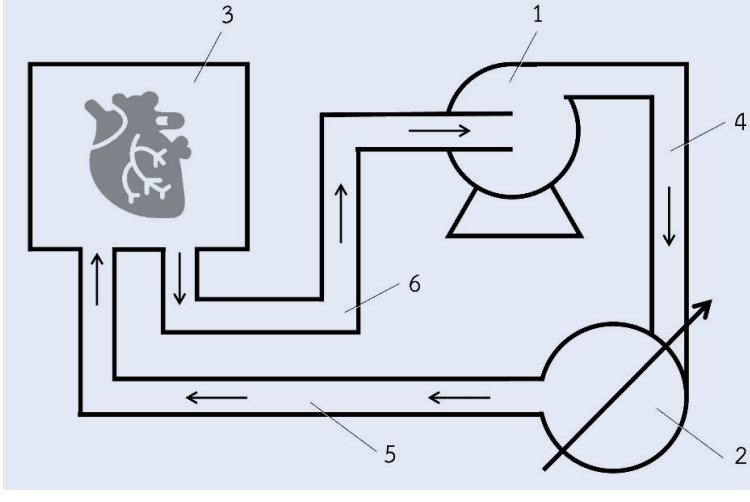


**Fig 2.** Diagram of the circulating laminar outflow chamber (CLOC) system. The system is composed of the pump (1), the heater (2) and the chamber (3) connected in a circuit (4, 5, 6). The arrows indicate the cyclic flow of the corrosive solution.

identical pieces weighing 10 g. On the other hand, the pig hearts were cannulated via the right and left coronary arteries. Then, 12 ml of polymethyl methacrylate (pMMA) (Ruthinium® group, Italy) was injected via the cannulae, 5 ml into right coronary artery and 7 ml into left coronary artery. The rate of injection was approximately 1 ml per second. The quality of the specimens, the technique, and the materials were all standardized. The specimens were allocated into three phases of experiments, as follow:

Phase I aimed to find the minimum soap-free temperatures; presumptive optimal temperature for corrosion process, at three concentrations of NaOH solution: 0.5%, 1.0%, and 5.0% (Fig 3). The volume of the solution was 3,000 ml, which, by calculation, contained an excessive amount of NaOH to complete the saponification reaction.[14] Each trial involved immersing three pieces of fat in three separate containers filled with the same NaOH concentration. The first trial started at an initial temperature of 45°C. The initial temperature was derived from the study on solubility of the tallow soap in aqueous solution.[15] After 24 h, the presence of solid soap was checked. If positive, the next trial would be repeated at a 1°C higher temperature and the presence of solid soap was checked for again. The cycle continued until the solid soap was completely absent and then the minimum soap-free temperature was declared.

Phase II aimed to measure the corrosion time (time efficiency) of the conventional corrosion process at the minimum soap-free temperature (Fig 4). The injected hearts were allocated to three concentrations of NaOH solution: 0.5% 1.0%, and 5.0%, one heart per one concentration. The temperature was set at the minimum soap-free temperature of each concentration. The corrosion process was checked regularly until tissue was eliminated completely from the cast.

Phase III aimed to compare the corrosion time (time efficiency) of the CLOC system with the conventional process (Fig 4). The CLOC system was assembled from three units: the chambers, the pump, and the heater (Fig 2).[13] The specimen chamber was fitted to contain one heart and was surrounded by an outflow chamber. The CLOC was connected to the pump and heater by a plastic tube in a circuit. The injected hearts were processed as described in phase II, but the corrosive solution was pumped at a flow rate of 600 ml/min. The temperature was set at the minimum soap-free temperature of each NaOH concentration.

## RESULTS

In phase I, the minimum soap-free temperatures for the 0.5%, 1%, and 5% NaOH concentrations were 55 °C, 54 °C, and 47 °C, respectively (Table 1).

In phase II, the minimum soap-free temperatures successfully produced residue-free corrosion casts (Fig 5). In each case, heat-induced deformity was undetectable, and the anatomy of the vessel was preserved. The corrosion times of the non-flowing 0.5%, 1%, and 5% concentrations were 216, 114, and 24 h, respectively (Table 1).

In phase III, the circulating laminar outflow chamber (CLOC) system also produced residue-free and anatomically correct casts. The CLOC reduced the corrosion time for the 0.5%, 1%, and 5% concentrations to 132, 76, and 18 h, respectively (Table 1). Compared to the non-flowing group, the reductions were 39%, 33%, and 25% for the 0.5%, 1%, and 5% concentrations, respectively.

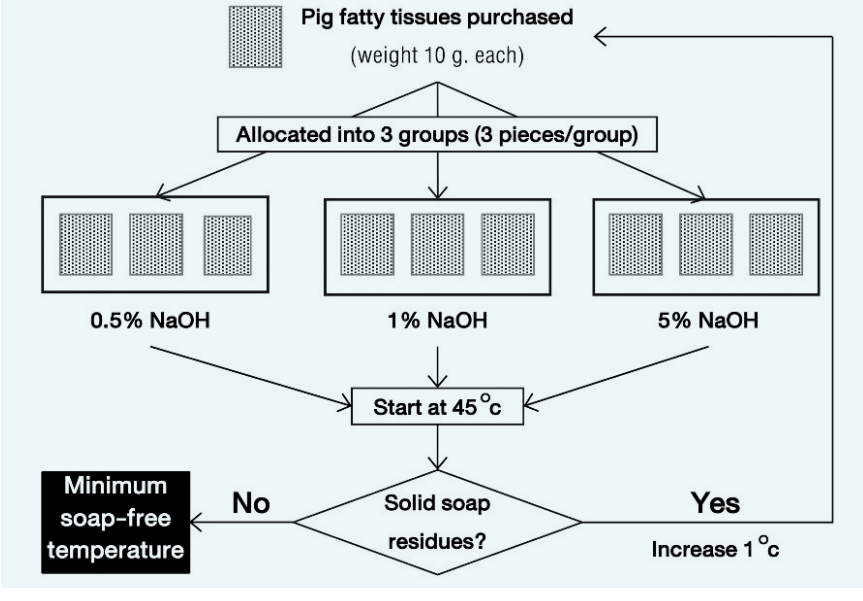


**Fig 3.** Flow chart depicting the phase I study aiming to find the minimum soap-free temperature at three concentrations of NaOH solution; 0.5%, 1%, and 5%.

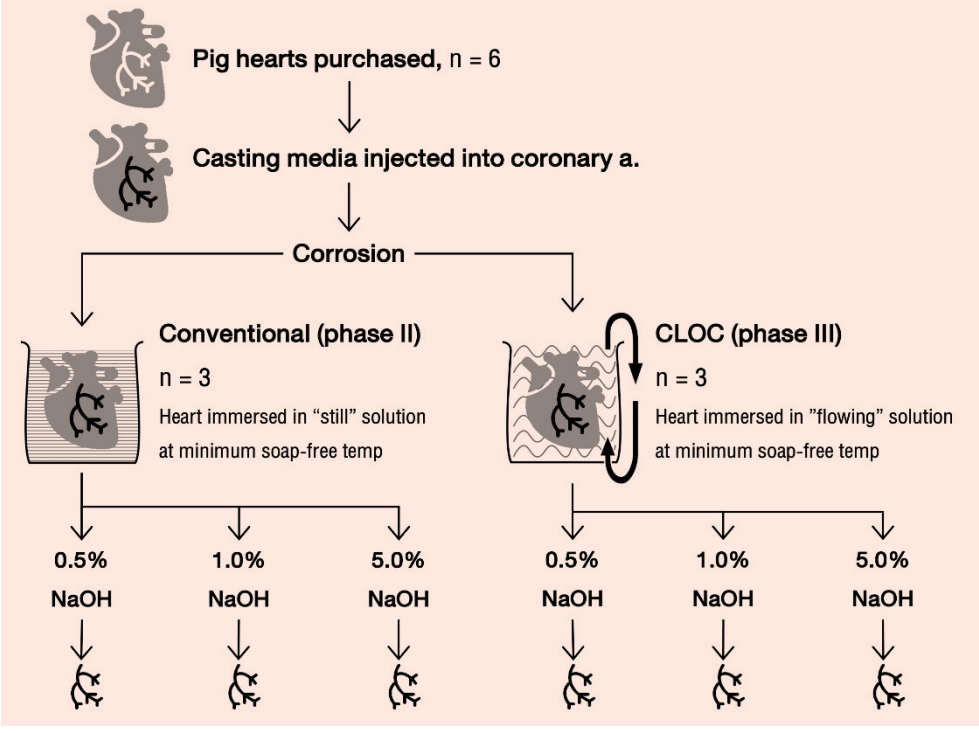


**Fig 4.** Flow chart depicting the phase II and phase III studies. Phase II aimed to measure the corrosion time of non-flowing NaOH solution at 0.5%, 1%, and 5% concentrations. The corrosion temperatures were set at the minimum soap-free temperatures. Whereas the phase III study aimed to measure the corrosion time in a flowing corrosive solution in the CLOC system.

**TABLE 1.** Minimum soap-free temperature at three concentrations of NaOH solution (phase I). Corrosion time in a non-flowing NaOH solution (phase II) and flowing NaOH solution in the CLOC system (phase III) at the minimum soap-free temperature.

| | Concentration of NaOH solution (%w/v) | | |
|---|---|---|---|
| | 0.5 | 1.0 | 5.0 |
| **Phase I**<br>Minimum soap-free temperature (ºC) | 55 | 54 | 47 |
| **Phase II**<br>Corrosion time in still solution (hours) | 216 | 114 | 24 |
| **Phase III**<br>Corrosion time in flowing solution (hours) | 132 | 76 | 18 |
| **Phase II vs III**<br>Reduction of the corrosion time | 39% | 33% | 25% |

## DISCUSSION

The solubility of soap in water depends on the composition of fatty acid in the soap[16], the temperature of the water[16], and the co-existing electrolytes.[17] To explore these issues, we introduced a new term: the "minimum soap-free temperature", despite existing terms being available, such as the clearing temperature[17] and solubility curve.[15] Our rationale was based on the instrumental limitations and practicality. First, we could not measure the concentration of all the phases that were collectively dissolved in the soap solution; micelles, hydrated crystals, and monomers.[18] Second, we needed

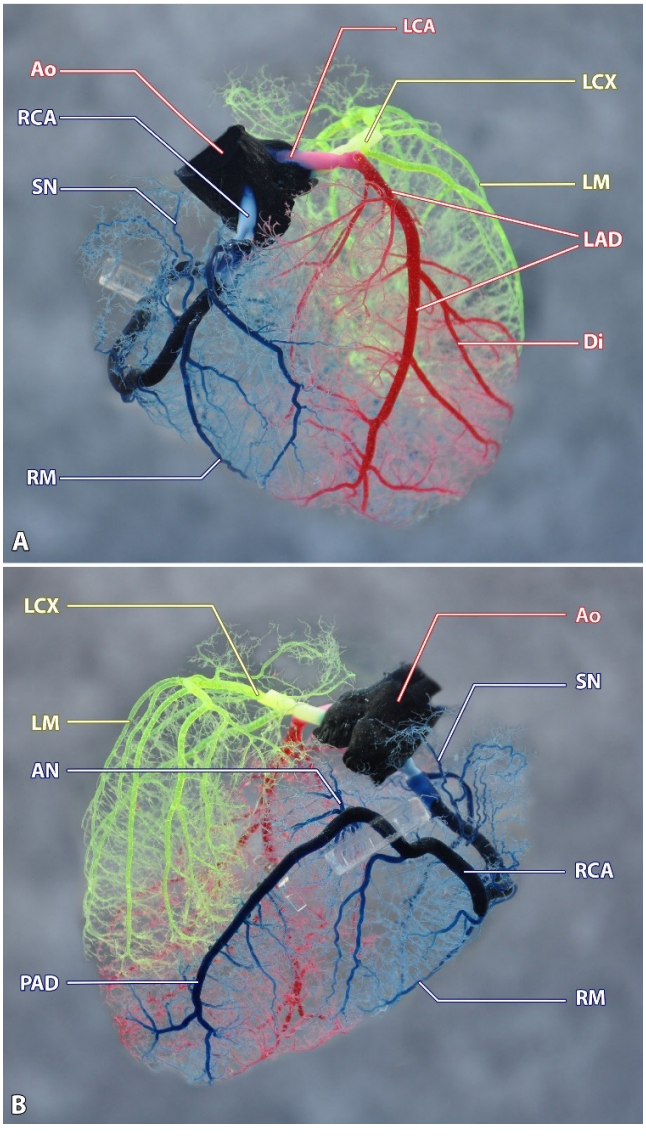


**Fig 5.** Photographs of a vascular corrosion cast produced at the minimum soap-free temperature. Three colors of pMMA were injected into three branches of coronary artery: red represents the left anterior descending artery (LAD); yellow represents the left circumflex artery (LCX); and blue represents the right coronary artery (RCA). The cast shows no heat deformity. No soap residue remained on the cast. Aorta (Ao), left coronary artery (LCA), left anterior descending artery (LAD), diagonal branch of left anterior descending artery (Di), left marginal branch of left circumflex artery (LM), sinoatrial nodal branch (SN), right marginal branch of right coronary artery (RM) and posterior descending artery (PAD)

a more specific term to describe the absence of soap residue in the corrosion casting. There was no solubility curve for lard (pig fat) soap available to be compared with our data. Fortunately, the composition of fatty acid in lard, tard (cow fat)[18], and humans[19] is similar; namely about one-half oleic acid and one-quarter palmitic acid. Therefore, the solubility curve of tallow soap should be analogous to lard and human fat soap. Our minimum soap-free temperatures corresponded to the solubility curve of tallow soap.[15] This implies the validity of the experiment and applicability of the corrosion casting for human specimens.

Focusing on the saponification reaction, the results of phase I seemed counterintuitive in suggesting that a higher NaOH concentration required a lower minimum soap-free temperature. One might think that the more NaOH is added, the more sodium soap is produced, and thus a higher temperature is required to dissolve the soap. Nevertheless, all the NaOH concentrations in phase I, i.e., 0.5%, 1%, and 5%, contained a copious amount of NaOH that would overwhelm fat in the saponification reaction. The amount of sodium soap was therefore equal in every NaOH concentration. Next, the question is why an equal amount of soap produced at different NaOH concentrations dissolved differently. The quantities of the electrolytes $Na^+$ and $OH^-$ were not actually measured, but the quantity and pH were certainly increased in the 0.5%, 1.0%, to 5% groups. Surprisingly, we could find no study in the literature describing the effect of the basicity of water on the solubility of sodium soap. On the other hand, we found one study[17] that demonstrated clearly that the more $Na^+$ is added to a solution, the lower the soap solubility is, and the higher temperature is required to completely dissolve it. If the latter concept is applied here, the highest concentration group, i.e., 5% NaOH, would be supposed to show the highest minimum soap-free temperature. However, the actual result contradicted this assumption. In practice, the data could be explained better by the protein solubilization reactions.

According to previous studies[11,12], 5% NaOH would show the highest rate of protein solubilization. By this assumption, the reaction might be so rapid that the structural proteins (e.g., collagen fiber) holding the adipocyte together would be dissolved before saponification could take place *in situ*. Therefore, the subsequent sodium soap would be produced from the free, colloidal phase of fatty tissue. In contrast to the lowest concentration group, i.e., 0.5% NaOH, the slowest solubilization might allow saponification to take place *in situ* while the structural proteins are still intact. Thus, the higher minimum soap-free temperature would be required to break the saponified tissue and dissolve it.

The success in phases II and III confirmed the validity of our minimum soap-free temperature. From these findings, we could set an appropriate temperature for the corrosion process for each NaOH concentration. Moreover, we could cut the corrosion time and subsequent washing process through the double actions of corrosion and washing in the CLOC system.

## CONCLUSION

The most efficient corrosion process to produce a coronary vascular corrosion cast was 5% NaOH via the CLOC system at 47°C, which involved the shortest corrosion time at 18 h.

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**Abbreviations:**
pMMA, polymethyl methacrylate
NaOH, sodium hydroxide
KOH, potassium hydroxide
CLOC, Circulating laminar outflow chamber
LAD, left anterior descending artery
LCX, left circumflex artery
RCA, right coronary artery

## REFERENCES

1. Johnson M. Evaluation of Learning Style for First Year Medical Students. International Journal Scholarship of Teaching & Learning. 2009;3(1). Available from: https://doi.org/10.20429/ijsotl.2009.030120
2. Lombardi SA, Hicks RE, Thompson KV, Marbach-Ad G. Are all hands-on activities equally effective? Effect of using plastic models, organ dissections, and virtual dissections on student learning and perceptions. Adv Physiol Educ. 2014;38(1):80-86.
3. Grabherr S, Cadas H, Riederer BM, Charlier P, Djonov V. Postmortem Angiography: A Historical Review. In: Grabherr S, Grimm JM, Heinemann A, editors. Atlas of Postmortem Angiography. Cham: Springer International Publishing; 2016. p.53-70.
4. Verli FD, Rossi-Schneider TR, Schneider FL, Yurgel LS, de Souza MAL. Vascular Corrosion Casting Technique Steps. Scanning. 2007;29(3):128-32.
5. Prozorowska E, Jackowiak H. The vascular corrosion casting (VCC) and scanning electron microscopy study on changes of vascular networks arrangement in the organs undergoing cyclic volume changes. Microscopy: advances in scientific research education 6th ed Badajoz, Spain: Formatex Research Center. 2014.p.112-18.
6. Walocha J, Litwin JA, Miodoński AJ. Corrosion casting technique. In: Schatten H, editor. Scanning Electron Microscopy for the Life Sciences. Cambridge: Cambridge University Press; 2012. p.16-32.
7. Abdel-Wahab AA, Ataya S, Silberschmidt VV. Temperature-dependent mechanical behaviour of PMMA: Experimental analysis and modelling. Polymer Testing. 2017;58:86-95.
8. Shanthini S, Suma HY. An innovative method in venous coronary cast technique. Anat Cell Biol. 2019;52(2):191-5.
9. Kupczyńska M, Barszcz K, Olbrych K, Polguj M, Wysiadecki G, Topol M, et al. Coronary arteries of the European bison (Bison bonasus). Acta Veterinaria Scandinavica. 2015;57:1-7.
10. Gupta PK. Chapter 23 - Toxic effects of caustics (corrosives). In: Gupta PK, editor. Fundamentals of Toxicology: Academic Press; 2016.p.267-75.
11. Zheng JL, Zhu MQ, Wu HT. Alkaline hydrothermal liquefaction of swine carcasses to bio-oil. Waste Manag. 2015;43:230-8.
12. Wang T, Wu J-H, Yi Y, Qi J-C. Optimization of Process Conditions for Infected Animal Tissues by Alkaline Hydrolysis Technology. Procedia Environmental Sciences. 2016;31:366-74.
13. Ratanalekha R. Development of Vascular Corrosion Casting for Education in Gross Anatomy. In: Laohaprasitthiphorn D, editor. Outstanding Innovation, Quality Fair, 2018, Faculty of Medicine Siriraj Hospital, Mahidol University. Bangkok, Thailand: Division of Quality Development, Faculty of Medicine Siriraj Hospital, Mahidol University; 2018.p.136-40.
14. Spitz L. Glossary. In: Spitz L, editor. Soap Manufacturing Technology. United Kingdom: Elsevier Inc; 2016.p.267-80.
15. McBain JW, Sierichs WC. The solubility of sodium and potassium soaps and the phase diagrams of aqueous potassium soaps. Journal of the American Oil Chemists Society. 1948;25(6):221-5. Available from: https://doi.org/10.1007/BF02645899
16. Hall N. Implications of Soap Structure for Formulation and User Properties. In: Spitz L, editor. Soap Manufacturing Technology. United Kingdom: Elsevier Inc; 2016.p.1-33.
17. Lin B, McCormick AV, Davis HT, Strey R. Solubility of sodium soaps in aqueous salt solutions. J Colloid Interface Sci. 2005; 291(2):543-9.
18. Hill M, Moaddel T. 2 - Soap Structure and Phase Behavior. In: Spitz L, editor. Soap Manufacturing Technology (Second Edition): AOCS Press; 2016.p.35-54.
19. Kingsbury KJ, Paul S, Crossley A, Morgan DM. The fatty acid composition of human depot fat. Biochem J. 1961;78(3):541-50.

# Psychometric Properties of Scales for Assessing Experiential Avoidance

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## ABSTRACT

**Objective:** To study and compare the psychometric properties, reliability, and validity of the Acceptance and Action Questionnaire (AAQ-II) and the Multidimensional Experiential Avoidance Questionnaire (MEAQ), which were translated into Thai.

**Materials and Methods:** This study used the AAQ-II and MEAQ, which were back translated into Thai. The Depression Anxiety Stress Scale 21 (DASS-21) and Satisfaction with Life Scale (SWLS) were used in conjunction to collect data from 35 graduate students (females 77.1%) and 462 people from the general population of Bangkok (females 74.2%).

**Result:** Item Objective Congruence (IOC) of AAQ-II and MEAQ was 0.79 and 0.87, respectively. Both had high correlation coefficients with DASS-21 and SWLS, indicating criteria-related validity. Moreover, Confirmatory Factor Analysis (CFA) was also carried out. The correlation coefficient to the original was high (0.96 for AAQ-II and MEAQ, and subscales ranging from 0.83-0.94). They also had high internal consistency, with Cronbach's alpha being 0.89 in AAQ-II and 0.92 in MEAQ, with high construct reliability (0.88 and 0.79-0.86).

**Conclusion:** The translated versions of AAQ-II and MEAQ have good psychometric properties. When comparing AAQ-II with MEAQ, it was noted that the correlation between AAQ and other scales was higher than MEAQ, which only had a moderate correlation. AAQ-II also tends to have a high association with distress variables. However, it is still possible to assess experiential avoidance. Thus, the use of each questionnaire will be depended on certain objectives.

**Keywords:** Acceptance and Action Questionnaire – II (AAQ-II); Multidimensional Experiential Avoidance Questionnaire (MEAQ); Psychometric Properties (Siriraj Med J 2022; 74: 760-768)

## INTRODUCTION

Nowadays, it is suggested that psychological problems emerge from a desire to avoid, suppress, or control an undesirable situation rather than mere thought and emotion. This desire increases the intensity of, psychological disorders and symptoms. Experiential avoidance, introduced by Steven C. Hayes, is a response by individuals to avoid undesirable events and involves attempts to evade, alter, or control experiences despite it being a part of their values or goals.[1-4] Hayes[3] defined the causes of experiential avoidance as: 1) Bidirectional nature of human language which links undesirable events and certain uses of language, possibly leading to people re-experiencing certain events and thus a desire to avoid it; 2) Inappropriate generalization of human language, which makes an individual use an ineffective coping mechanism prepared beforehand to avoid certain events; 3) Social encouragement and modeling which promotes individuals to imitate the use of experiential avoidance; and 4) Cultural support for emotions and cognitions

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in which an individual is shaped by the socio-cultural environment and perceives certain emotions and thoughts as improper and thus chooses to avoid them. All these causes lead to an inflexible coping mechanism and inability to separate one's sense of self and behavior which can have a negative impact such as the use of alcohol, drugs, or a relapse[5-7] and psychological distress.[4,8,9] It also prevents opportunities to experience valuable events. In summary, experiential avoidance is caused by human language proficiency and human nature which leads to a certain state of psychopathology.

As a response to experiential avoidance, Acceptance and Commitment Therapy (ACT) was developed under the rationale of Relational Frame Theory (RFT)[10], which focuses on language proficiency as the root cause of a person's psychological inflexibility. In ACT, the main purpose is to promote psychological flexibility and enable individuals to interact effectively in the present moment. This therapy features several questionnaires to assess the level of experiential avoidance. The most accepted and widely used questionnaire is known as the Acceptance and Action Questionnaire (AAQ). However, due to problems associated with its psychometric properties, a new version was developed, known as the Acceptance and Action Questionnaire – II (AAQ – II) to assess experiential avoidance and psychological inflexibility.[11] Concurrently, the Multidimensional Experiential Avoidance Questionnaire (MEAQ) was developed to cover elements of experiential avoidance in broader terms. However, there is still disagreement over the differences of MEAQ and AAQ – II, and on the latter's focus, which assesses the construct and is associated with neuroticism and negative affectivity rather than experiential avoidance.[12]

Experiential avoidance can be found in any population, so it is important to not only be aware, but be careful in its application. Until now, there are some studies related to Experiential Avoidance such as Thai version of the Philadelphia Mindfulness Scale (PHLMS)[13] but there has not been a study exploring experiential avoidance in the Thai population, including the psychometric property of AAQ and MEAQ due to a lack of translated questionnaires. Hence, this research translated the AAQ –II and MEAQ into Thai to study and compare their psychometric properties. This study used a sample of Bangkok residents in early adulthood (aged 18-40) as they are most likely to experience stress from inappropriate use of experiential avoidance. Thus, studying experiential avoidance as well as translating the questionnaires would lead to a better understanding in the context of the Thai population and help further develop relevant research and therapies in Thailand.

## MATERIALS AND METHODS

### Sample

Sample group 1 or the bilingual group consisted of 35 participants proficient in both Thai and English from Faculty of Medicine Siriraj Hospital, (77.1% females) aged between 22 and 29 s (M = 24.71, SD = 1.61), and with an English proficiency score (MU GRAD TEST) between 60 and 88 (M = 68.94, SD = 7.21). Sample group 2 was calculated using the W.G. Cochran formula, with a confidence interval of 95% and acceptable deviation of 5%. The sample had 462 participants (74.2% females), aged 18 to 40 years (M = 24.65, SD = 5.65). All of them resided in Bangkok.

### Instruments

#### Acceptance and Action Questionnaire – II (AAQ-II)[11]

The AAQ-II is a 7-item, 7-point Likert-type scale (7 = always, 1 = never true). It measures experiential avoidance and psychological inflexibility. The original version by Bond, Hayes[11] showed good psychometric properties (mean alpha of 0.84, 3 and 12 month test-retest reliability of 0.81 and 0.79) and one-factor structure.

#### Multidimensional Experiential Avoidance Questionnaire (MEAQ)[12]

The MEAQ is a 62-item, 6-point Likert-type scale (6 = strongly agree, 1 = strongly disagree) which measures multidimensional experiential avoidance (behavioral avoidance, distress aversion, procrastination, distraction/suppression, repression/denial, and distress endurance). The original version by Gamez, Chmielewski[12] showed good psychometric properties (mean alpha of 0.85).

#### Depression Anxiety Stress Scale 21 (DASS-21)[14]

The DASS-21 is a 21-item, 4-point Likert-type scale. It contains three subscales (depression, anxiety, and stress). The Thai version by Oei, Sawang[14] showed good psychometric properties (alpha value of depression was 0.86, anxiety was 0.81, and stress 0.70) Medium to strong positive correlations were expected between the AAQ-II and DASS-21 subscales.

#### Satisfaction with Life Scale (SWLS)[15]

The SWLS is a 5-item, 4-point Likert-type scale. It measures global cognitive judgment of satisfaction with one's life. The original version showed good psychometric properties (coefficient alpha was 0.87, test-retest reliability was 0.82).

### Design

The study procedure was approved by the Institutional

Review Board of the Faculty of Medicine Siriraj Hospital. (Si. 666/2018) Following a suggestion by Nantaga Sawasdipanich and Sujitra Tiansawad[16], the researcher chose to first translate the questionnaires into Thai and then consult with a professional translation consultant. Then, the researcher chose to back translate as suggested by the language expert. Next, the language expert and a psychology expert compared the original questionnaire to the backward translated version for revisions. Afterwards, the content was examined by three psychology experts and an Item-Objective Congruence (IOC) was obtained for every item in the questionnaire. An IOC of more than 0.5 was considered as valid.[17] The researcher improved the language as suggested by the expert to make the questionnaire more complete. As a result, two sets of questionnaires, or the Acceptance and Action Questionnaire–II: Thai version (AAQ-II), and Multidimensional Experiential Avoidance Questionnaire: Thai version (MEAQ) were delivered.

In sample group 1, the administration of the questionnaire was collective and conducted with a consent form distributed with a brief about the aim of the study, followed by an assignment to respond to AAQ-II, MEAQ, AAQ-II Thai version, MEAQ Thai version.

In sample group 2, the administration of the questionnaire was collective and conducted online with detailed information and consent provided and explained, followed by a task to respond to the AAQ-II Thai version, MEAQ Thai version, DASS-21, SWLS.

### Data analysis

The first task was to use the score to examine content validity using Item-Objective Congruence (IOC). All statistical analyses were conducted using PASW Statistics (v. 18.0; SPSS Inc., Chicago, IL, USA).

Data from sample group 1 was examined using parallel form reliability analysis. Data from sample group 2 was examined using the corrected item-total correlation (CITC), reliability: internal consistency, validity: criterion-related validity, and construct validity. Validity and, construct validity

## RESULTS

The response rate or questionnaires returned from graduate students was 35 or 100% of all samples. Meanwhile, the response rate or ordinary people who answered and returned the questionnaires was 462, which also accounted for 100% of samples. The sample size had a ratio of 25.8% males and 74.2% females. The sample age range was between 18 and 40 years (M = 24.56, SD = 5.65).

### Reliability

Table 1 shows the mean and standard deviation of both AAQ-II and MEAQ in the Thai version and original questionnaire, which were noted to be similar. Moreover, the results indicate high parallel form reliability of the Thai AAQ-II and MEAQ questionnaires, so they can be used in Thai context as well.

Table 2 shows the Cronbach's alpha coefficient for the total AAQ-II, and MEAQ scores, behavioural avoidance, distress aversion, procrastination, distraction and suppression, repression and denial, and distress endurance. Moreover, most items in both questionnaires had a CITC above 0.2[18], except some items in MEAQ which will be explained in detail in the discussion section. This indicates that those with a high score in these items also have a high total score and vice versa. These finding indicate high internal consistency of both questionnaires, and the degree of interrelationship among items on the scale along with their consistency and ability to measure the same thing.

### Validity

The results of IOC from three psychology experts verified content validity, which means the IOC of the Thai version of the AAQ-II and MEAQ were 0.79 and 0.87, respectively. The finding indicates content validity of both questionnaires was acceptable and capable of assessing the objectives of the questionnaires.

Table 3 shows the correlation between the Thai version of AAQ-II, MEAQ and DASS-21 and SWLS. According to the results, AAQ-II's score correlates with depression, anxiety, stress, and satisfaction with life score.

Moreover, the correlation coefficient between MEAQ, together with its sub-scale, and DASS-21 (depression, anxiety and stress) and SWLS significantly correlated with depression, anxiety, stress, and satisfaction with life score. Besides distraction and suppression, which only correlated with stress and distress endurance correlated with depression, anxiety, and satisfaction with life score, but not the stress scale.

Confirmatory Factor Analysis (CFA) was conducted to examine the construct validity of 462 samples. In Table 4, the results of confirmatory factor analysis found that the hypothesized measurement model of the Thai version of AAQ-II and MEAQ did not fit well with the empirical data. For the models to relate, the researcher modified them by deleting each item which had a factor load below 0.4 and/or high measurement error. The result was that the modified AAQ-II (6 items), and MEAQ (39 items) obtained construct validity with admissible fit indices.

**TABLE 1.** Parallel form reliability of AAQ-II and MEAQ (both English and Thai versions). Data was analyzed from sample group 1 (n = 35).

| Scale | ENG M (SD) | THAI M (SD) | Correlation |
|---|---|---|---|
| AAQ-II | 22.34 (8.55) | 23.88 (8.77) | .963** |
| MEAQ | 191.57 (37.05) | 189.14 (38.67) | .940** |
| BA | 36.91 (9.43) | 36.68 (9.41) | .872** |
| DA | 43.02 (11.88) | 41.71 (11.85) | .925** |
| P | 24.74 (5.71) | 24.77 (5.58) | .832** |
| DS | 24.91 (7.15) | 24.91 (8.34) | .863** |
| RD | 32.8 (9.19) | 32.14 (8.53) | .935** |
| DE | 47.82 (8.39) | 48.08 (8.7) | .882** |

**Abbreviations:** AAQ-II; Acceptance and Action Questionnaire – II, MEAQ; Multidimensional Experiential Avoidance Questionnaire, BA; Behavioral Avoidance, DA; Distress Aversion, P; Procrastination, DS; Distraction & Suppression, RD; Repression & Denial, DE, Distress Endurance, * $p < .05$, ** $p < .01$.

**TABLE 2.** Reliability and Corrected Item-Total Correlation of the AAQ-II and MEAQ translated into Thai. Data was analyzed from sample group 2 (n = 462).

| Scale | Item (N) | Cronbach's Alpha | Corrected Item-Total Correlation |
|---|---|---|---|
| AAQ-II | 7 | .892 | .610 - .756 |
| MEAQ | 62 | .921 | |
| BA | 11 | .832 | .316 - .658 |
| DA | 13 | .828 | .228 - .636 |
| P | 7 | .795 | .261 - .623 |
| DS | 7 | .825 | .491 - .638 |
| RD | 13 | .847 | .169 - .686 |
| DE | 11 | .817 | .269 - .651 |

**Abbreviations:** AAQ-II; Acceptance and Action Questionnaire – II, MEAQ; Multidimensional Experiential Avoidance Questionnaire, BA; Behavioral Avoidance, DA; Distress Aversion, P; Procrastination, DS; Distraction & Suppression, RD; Repression & Denial, DE; Distress Endurance, SWLS; Satisfaction with life Scale, * $p < .05$, ** $p < .01$.

Table 5 shows both questionnaires before model modification. Each item on the AAQ-II Thai Version had a standardized factor load between 0.65-0.82. After modification, the factor load rose from 0.70 to 0.79. For items in each domain of the Thai version of MEAQ, the standardized factor load before model modification ranged between 0.20-0.77. After modification, each domain's factor loads increased.

When considering the squared multiple correlation ($R^2$) of items or reliability of indicators for the Thai version of AAQ-II, the score ranged between 0.42-0.67. When the model was modified, the score was still similar. For the

**TABLE 3.** Criterion-Related Validity of the AAQ-II and MEAQ. Data was analyzed from sample group 2 (n = 462).

| Scale | M (SD) | D | A | S | SWLS |
|---|---|---|---|---|---|
| AAQ-II | 25.72 (9.62) | .70** | .62** | .69** | -.49** |
| MEAQ | 216.4 (34.66) | .54** | .46** | .47** | -.27** |
| BA | 41.64 (8.9) | .37** | .35** | .35** | -.14** |
| DA | 51.32 (10.95) | .35** | .29** | .31** | -.20** |
| P | 24.05 (6.84) | .52** | .39** | .42** | -.29** |
| DS | 51.32 (10.95) | .07 | .09 | .10* | -.02 |
| RD | 40.41 (11.27) | .52** | .48** | .50** | -.18** |
| DE | 46.83 (7.96) | -.19** | -.10* | -.08 | .20** |

**Abbreviations:** AAQ-II; Acceptance and Action Questionnaire – II, MEAQ; Multidimensional Experiential Avoidance Questionnaire, BA; Behavioral Avoidance, DA; Distress Aversion, P; Procrastination, DS; Distraction & Suppression, RD; Repression & Denial, DE; Distress Endurance, D; Depress from Depression Anxiety Stress Scale 21, A; Anxiety from Depression Anxiety Stress Scale 21, S; Stress from Depression Anxiety Stress Scale 21, SWLS; Satisfaction with life Scale, * $p < .05$, ** $p < .01$.

**TABLE 4.** Fit indices from of Confirmatory Factor Analysis of the Thai version of the Acceptance and Action Questionnaire - II and Thai version of the Multidimensional Experiential Avoidance Questionnaire.

| | AAQ-II | | MEAQ | |
|---|---|---|---|---|
| Fit indices | Original | Modified | Original | Modified |
| $\chi^2$ | 99.69 | 20.77 | 6892.65 | 2194.83 |
| Df | 14 | 8 | 1814 | 687 |
| P-Value | 0.000 | 0.007 | 0.000 | 0.000 |
| Relative $\chi^2$ | 7.12 | 2.596 | 3.799 | 3.194 |
| NNFI | .95 | .99 | .91 | .94 |
| SRMR | .04 | .021 | .099 | .076 |
| RMSEA | .13 | .059 | .078 | .069 |
| CFI | .97 | .99 | .91 | .94 |

**Abbreviations:** $\chi^2$; Chi-square, df; degree of freedom, RMSEA; Root Mean Square Error of Approximation, CFI; Comparative Fit Index, SRMR; Standardized Root Mean Square Residual, NNFI; Non-Normed Fit Index

Thai version of the MEAQ, the $R^2$ ranged between 0.06-0.57 before modification. Afterwards, the $R^2$ increased as follows: 1) behavioral avoidance (0.23-0.73); 2) distress aversion (0.25-0.48); 3) procrastination (0.33-0.53); 4) distraction and suppression (0.27-0.55); 5) repression and denial (0.27-0.59); and 6) distress endurance (0.28-0.57).

The construct reliability (CR) of the Thai version of AAQ-II before modification was 0.892. After modification, it was similar or 0.883. For the Thai version of MEAQ, the CR before modification was between 0.797-0.853, and was similar after or in the range of 0.792-0.862. Each domain was scored as follows: 1) behavioral avoidance (0.818); 2) distress aversion (0.802); 3) procrastination (0.810);

**TABLE 5.** Factor loading, Squared multiple correlation, Construct Reliability, Average Variance Extracted of the Thai version of the Acceptance and Action Questionnaire - II and Thai version of the Multidimensional Experiential Avoidance Questionnaire.

| | Factor loading | | $R^2$ | | CR | | AVE | |
|---|---|---|---|---|---|---|---|---|
| | Original | Modified | Original | Modified | Original | Modified | Original | Modified |
| **AAQ-II** | .65-.82 | .70-.79 | .42-.67 | .49-.62 | .892 | .883 | .543 | .557 |
| **MEAQ** | | | | | | | | |
| **BA** | .33-.72 | .53-.73 | .11-.52 | .28-.53 | .840 | .818 | .330 | .393 |
| **DA** | .25.70 | .50-.69 | .06-.48 | .25-.48 | .831 | .802 | .287 | .406 |
| **P** | .29-.72 | .58-.73 | .08-.52 | .33-.53 | .797 | .810 | .370 | .416 |
| **DS** | .52-.74 | .52-.74 | .27-.54 | .27-.55 | .827 | .827 | .409 | .409 |
| **RD** | .20-.77 | .52-.77 | .06-.56 | .27-.59 | .853 | .862 | .332 | .456 |
| **DE** | .33-.75 | .53-.76 | .13-.57 | .28-.58 | .820 | .792 | .303 | .393 |

**Abbreviations:** $R^2$; Squared multiple correlation, CR; Construct Reliability, AVE; Average Variance Extracted, AAQ-II; Acceptance and Action Questionnaire – II, MEAQ; Multidimensional Experiential Avoidance Questionnaire, BA; Behavioral Avoidance, DA; Distress Aversion, P; Procrastination, DS; Distraction & Suppression, RD; Repression & Denial, DE; Distress Endurance, * $p < .05$, ** $p < .01$

4) distraction and suppression (0.827); 5) repression and denial (0.862); and 6) distress endurance (0.792). Meanwhile, the average variance extracted (AVE) of the Thai version of AAQ-II before modification was 0.543. After modification, it increased to 0.557. For the Thai version of MEAQ, AVE ranged between 0.287-0.370 before modification. Afterwards, it increased to 0.393-0.456 and the results of each domain are as follows: 1) behavioral avoidance (0.393); 2) distress aversion (0.406); 3) procrastination (0.416); 4) distraction and suppression (0.409); 5) repression and denial (0.456); and 6) distress endurance (0.393).

## DISCUSSION

The reliability of backward translated questionnaires was equivalent to the original versions as both had statistically significant high correlation coefficients. This indicates that scores measured by the original and the backward translated version are related and consistent. In addition, by using Internal Consistency Reliability analysis, the researcher noted high internal consistency in which the alpha value of AAQ-II was 0.89 and 0.92 for MEAQ. These values are similar to the original version, in which alpha of AAQ-II and MEAQ were 0.84 and 0.85, respectively. The alpha values of other translated of other translated questionnaires or the Spanish version[19] were 0.75, and 0.93, respectively. When compared to total CITC scores, it was found that most items had a score of greater than 0.2[18], except item 23 – 'I'm in touch with my emotions'. MEAQ, which is a reversed item, had a score of 0.169. This may have been caused by a misunderstanding among participants when responding to questionnaires which had a mix of both negative and positive items. However, the reliability of translated questionnaires is consistent and equivalent to the original.

Moreover, carrying out confirmatory factor analysis after modifying the model, the squared multiple correlation ($R^2$), which signifies reliability of indicators or items in the AAQ-II, ranged between 0.49-0.62. Meanwhile, each item in the Thai version of MEAQ obtained $R^2$ in the following range: 1) behavioral avoidance (0.23-0.73); 2) distress aversion (0.25-0.48); 3) procrastination (0.33-0.53); 4) distraction and suppression (0.27-0.55); 5) repression and denial (0.27-0.59); and 6) distress endurance (0.28-0.57). After considering construct reliability (CR) to measure latent variables, it was found that after modification, the Thai version of AAQ-II was 0.883 and between 0.792-0.862 for MEAQ. The domain in each was as follows: 1) behavioral avoidance (0.818); 2) distress aversion (0.802); 3) procrastination (0.810); 4) distraction and suppression = (0.827); 5) repression and denial = (0.862); and 6) distress endurance = (0.792). For

average variance extracted (AVE) after modification, the score for the Thai version of AAQ-II: Thai Version was .557 and of between 0.393-0.456 for MEAQ. In each, the domain was as follows: 1) behavioral avoidance (0.393); 2) distress aversion = (0.406); 3) procrastination (0.416); 4) distraction and suppression (0.409); 5) repression and denial (0.456); and 6) distress endurance (0.393). Ultimately, the criteria suggests that both CR and AVE were above 0.5.[20] All domains of the Thai MEAQ had AVE below 0.5, but since *Fornell* and *Larcker* stated that if AVE is less than 0.5, but the construct reliability is higher than 0.6, we can accept convergent validity of the construct as still adequate.[21] Hence, this indicated that both the Thai version of AAQ-II and MEAQ had a good level of reliability in terms of questionnaire and in respect to each domain, including the reliability of in measuring latent variables of each construct.

Regarding validity, it was found that both questionnaires had good content validity. Each item complied with factors under consideration of the expert. In examining the relationship of scores measured using AAQ-II and MEAQ, and from DASS-21 and SWLS, statistical significance of both questionnaires' ability to measure depression, anxiety, stress, and life satisfaction scores was observed. Still, while considering each element of the MEAQ, the researcher found that subscale distraction and suppression were not related to depression, anxiety, and life satisfaction but distress. While there is no relationship between the Distress Endurance Subscale and stress, there is a negative relationship with depression and anxiety and a positive relationship with life satisfaction. This correlates with the original study.[12] Ultimately, this indicates that if an individual intentionally uses distraction and suppression to ignore certain events, it may make that individual stressed, but it does not affect depression, anxiety, or satisfaction of life. An individual with distress endurance means he/she encounters distress, but solves the problem without fear. This might result in a decrease in the individual's depression and anxiety and increases life satisfaction.

A confirmatory factor analysis examining the factors found that the hypothesized measurement model of the Thai AAQ-II and MEAQ did not fit well with empirical data. For the models to relate more, the researcher modified them based on the modification index, factor loading value, squared multiple correlations ($R^2$), and measurement error. Other factors considered were based on theory and an item's suitability.[22] The result was that the modified Thai AAQ-II and MEAQ obtained construct validity with admissible fit indices that decreased the Thai AAQ-II to six items, with a factor load between 0.70-0.79. For the Thai version of MEAQ, although there were still six component aspects, the number of items decreased to 39 with factor loading ranging from 0.5-0.89, including: 1) behavioral avoidance (0.53-0.73); 2) distress aversion (0.50-0.69); 3) procrastination (0.58-0.73); 4) distraction and suppression (0.52-0.74); 5) repression and denial (0.52-0.77); and 6) distress endurance (0.53-0.76). All had a statistical significance of .05. The result from confirmatory factor analyses of these research sample groups validated both questionnaires' ability to 'EA'. The Thai version of the AAQ-II had good constructs to measure. Also, it was a one-factor model as its first item was eliminated due to excessive difficulty of comprehension. However, the second and third items were allowed as their deviations correlated with one another. Thus, when using the Thai version of AAQ-II, one must be cautious and consider the first item. Meanwhile, the Thai version of the MEAQ had admissible levels of construct to measure before modification. Still, after modification and elimination of some items, which had factor load below 0.4[22] and/or low $R^2$, there was relatively high measurement error (the eliminated items were 1, 2, 4, 6, 7, 8, 13, 16, 18, 19, 21, 23, 24, 26, 30, 31, 34, 39, 46, 48, 53, 54, 62). This made the model more consistent with empirical data and thus confirmed that the Thai version of MEAQ was a six-factor model which correlated with the study by Gamez, Chmielewski[12] and Rochefort, Baldwin.[23] However, by eliminating 23 items, when using the MEAQ, one must be careful and modify the quality of these items for the Thai version.

In summary, the validity of both questionnaires is appropriate in terms of f content, criteria, and construct validity.

When comparing AAQ-II and MEAQ, the researcher found that the correlation between AAQ and other scales was higher compared to MEAQ, which only has a moderate correlation. This could imply that AAQ-II is associated with distress variables such as neuroticism and negative effects than experiential avoidance.[12,24] Consequently, AAQ-II is more related to scales linked to distress than MEAQ. However, this was also the limitation of this study. Thus, future research should further examine valid criteria between the Thai version of AAQ-II and MEAQ and other scales relating to avoidance. Moreover, confirmatory factor analysis to confirm structure of both hypothesized measurement models found that it was necessary to modify the model by eliminating some items so that the models are more consistent with empirical data and have the items that can explain or assess the remaining EA. Thus, the use of these two questionnaires depends on measuring objectives. For example, if one

wants to measure psychological distress, the Thai version of the AAQ-II might be more suitable. However, if one wants to measure issues involving behavioral avoidance, the Thai version of MEAQ might be better. However, the psychometric properties of these questionnaires were assessed and analyzed from a specific sample as the study population is between 18 and 40 years old and is female more than male, so the results may have gender deference, and it is not generalizable to the rest of the age, gender, and the wider context.

## CONCLUSION

This study found that the Thai versions of the AAQ-II and MEAQ have an acceptable level of psychometric properties in terms of validity and reliability since they are applicable to the Thai population aged between 18-40. Still, according to the results, there may be some items that require special attention and caution.

When comparing the Thai versions of AAQ-II and MEAQ, we can see that both questionnaires have a similar level of validity and reliability considered admissible. However, upon further investigation, the correlation between the Thai version of the AAQ-II and other scales is higher compared to MEAQ which only has a moderate correlation. This is in agreement with other reviews stating that AAQ-II tends to be associated with distress variables such as depression, anxiety, and stress. However, it is still able to assess experiential avoidance.[12,24] Hence, the use of each questionnaire will be depended on certain objectives. If one wants to measure psychological well-being or assess psychological distress such as anxiety, depression or emotional distress, the Thai version of the AAQ-II may be more suitable than its MEAQ counterpart, which concentrates on measuring behavior relating to avoidance. Still, further studies regarding the ability of both questionnaires to measure avoidance compared to other tests is required.

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**Conflicts of interest:** Ethical approval for this study was been granted by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital at Mahidol University. Sections of these findings were presented at Siriraj Graduate Forum, Bangkok, Thailand, 2019. We have no conflicts of interest to disclose.

## REFERENCES

1. Hayes SC, Strosahl KD, Wilson KG. Acceptance and commitment therapy: An experiential approach to behavior change. New York: Guilford Press; 1999.
2. Hayes SC, Wilson KG. Acceptance and commitment therapy: Altering the verbal support for experiential avoidance. Behav Anal. 1994;17(2):289-303.
3. Hayes SC, Wilson KG, Gifford EV, Follette VM, Strosahl K. Experimental avoidance and behavioral disorders: a functional dimensional approach to diagnosis and treatment. J Consult Clin Psychol. 1996;64(6):1152-68.
4. Kashdan TB, Barrios V, Forsyth JP, Steger MF. Experiential avoidance as a generalized psychological vulnerability: comparisons with coping and emotion regulation strategies. Behav Res Ther. 2006;44(9):1301-20.
5. Stewart SH, Zvolensky MJ, Eifert GH. The relations of anxiety sensitivity, experiential avoidance, and alexithymic coping to young adults' motivations for drinking. Behav Modif. 2002;26(2):274-96.
6. Westrup D. Experiential avoidance and alcohol dependence relapse (Doctoral Dissertation, West Virginia University, 1999). Dissertation Abstracts International. 1999;62:568.
7. Shorey RC, Gawrysiak MJ, Elmquist J, Brem M, Anderson S, Stuart GL. Experiential avoidance, distress tolerance, and substance use cravings among adults in residential treatment for substance use disorders. J Addict Dis. 2017;36(3):151-7.
8. Kashdan TB, Morina N, Priebe S. Post-traumatic stress disorder, social anxiety disorder, and depression in survivors of the Kosovo War: experiential avoidance as a contributor to distress and quality of life. J Anxiety Disord. 2009;23(2):185-96.
9. Spendelow JS, Joubert HE. Does Experiential Avoidance Mediate the Relationship Between Gender Role Conflict and Psychological Distress? Am J Mens Health. 2017:1557988317748123.
10. Hayes SC, Barnes-Holmes D, Roche B. Relational frame theory: a post-Skinnerian account of human language and cognition. Adv Child Dev Behav. 2001;28:101-38.
11. Bond FW, Hayes SC, Baer RA, Carpenter KM, Guenole N, Orcutt HK, et al. Preliminary psychometric properties of the Acceptance and Action Questionnaire-II: a revised measure of psychological inflexibility and experiential avoidance. Behav Ther. 2011;42(4):676-88.
12. Gamez W, Chmielewski M, Kotov R, Ruggero C, Watson D. Development of a measure of experiential avoidance: the Multidimensional Experiential Avoidance Questionnaire. Psychol Assess. 2011;23(3):692-713.
13. Silpakit O, Silpakit C. The Psychometric Property of the Short Thai Version of the Philadelphia Mindfulness Scale. Siriraj Med J. 2018;70(4):310-26.
14. Oei TP, Sawang S, Goh YW, Mukhtar F. Using the Depression Anxiety Stress Scale 21 (DASS-21) across cultures. Int J Psychol. 2013;48(6):1018-29.
15. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction with Life Scale. J Pers Assess. 1985;49(1):71-5.
16. Sawasdipanich N, Tiansawad S. Instrument Translation for Cross-Cultural Research: Technique and Issues to be Considered.

Thai Journal of Nursing Counsil. 2011;26(1):19-28.
17. Choochom O. Construction and Development of Measuring Instruments in Behavioral Science. Srinarkharinwirot University. Behavioral Science Research Institute; 2002.
18. Streiner DL, Norman GR, Cairney J. Health Measurement Scales: A practical guide to their development and use: Oxford University Press; 2014.
19. Ruiz FJ, Langer Herrera AI, Luciano C, Cangas AJ, Beltran I. Measuring experiential avoidance and psychological inflexibility: The Spanish version of the Acceptance and Action Questionnaire - II. Psicothema. 2013;25(1):123-9.
20. Joseph F. Hair, William C. Black, Babin BJ. Multivariate Data Analysis: A Global Perspective. 7th ed. Upper Saddle River: Pearson Education; 2010.
21. Fornell C, Larcker DF. Evaluating structural equation models with unobservable variables and measurement error. Journal of Marketing Research. 1981;18(1):39-50.
22. Stevens JP. Applied multivariate statistics for the social sciences, 5th ed. New York, NY, US: Routledge/Taylor & Francis Group; 2009. xii, 651-xii, p.
23. Rochefort C, Baldwin AS, Chmielewski M. Experiential Avoidance: An Examination of the Construct Validity of the AAQ-II and MEAQ. Behav Ther. 2018;49(3):435-49.
24. Wolgast M. What Does the Acceptance and Action Questionnaire (AAQ-II) Really Measure? Behav Ther. 2014;45(6):831-9.

# Surgical Outcomes of Bariatric Surgery in Siriraj Hospital for the First 100 Morbidly Obese Patients Treated

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## ABSTRACT

**Objective:** Bariatric surgery is considered the most effective treatment for morbid obesity, and is increasingly performed in Thailand and globally. We aimed to establish the outcomes of bariatric surgery performed at Siriraj Hospital, Bangkok.

**Materials and Methods:** This was a retrospective study of patients who underwent bariatric surgery between January 2012 and June 2016.

**Results:** The records of the first 100 patients who underwent bariatric surgery were reviewed, comprising 58 patients who underwent laparoscopic sleeve gastrectomy (LSG) and 42 patients who underwent laparoscopic Roux-en-Y gastric bypass (LRYGB). The median patient age, preoperative body weight, and BMI were 36 years old, 129 kg, and 46.3 kg/m$^2$. All the procedures were performed by a laparoscopic approach. The median operative times for LSG and LRYGB were 156 [85-435] and 265 [180-435] minutes. The median hospital stay was 3 days [3-14]. The major complication rate was 4%. There was no mortality in the 30-day postoperative period. The mean %excess weight loss (%EWL) of LSG was 56.8 ± 19.8%, 59.9 ± 21.7%, and 55.1 ± 21.3%, at 1, 2, and 3 years after surgery. The mean %EWL of LRYGB was 67 ± 18.3%, 66.2 ± 21.4%, and 63.6 ± 19.9%, at 1, 2, and 3 years after surgery. In the patients with type-II diabetes mellitus, 67% had complete diabetic remission at 1 year. The median FBS dropped from 127 to 99 mg/dL ($p < 0.001$) and HbA1c from 6.6% to 5.5% ($p < 0.001$). The remission rates of hypertension and dyslipidemia were 58% and 73%.

**Conclusion:** The bariatric procedures are safe with a low complication rate. The procedures also provide good outcomes in postoperative weight loss and comorbidity resolution.

**Keywords:** Bariatric surgery; laparoscopic sleeve gastrectomy; laparoscopic Roux-en-Y gastric bypass; outcomes (Siriraj Med J 2022; 74: 769-777)

## INTRODUCTION

Obesity increases the risk of many serious health problems, including diabetes mellitus (DM), hypertension, and dyslipidemia. It is also a major cause of death, particularly attributable to cardiovascular disease, stroke, and cancers. The prevalence of obesity has been increasing worldwide in recent decades, linked to the trends of excessive food intake and lack of physical activity. The most common treatment strategies are behavioral changes through healthy diet and exercise. In addition to the principle of

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behavioral changes, the three main treatment option for morbid obesity consist of lifestyle modification, medical therapy, and bariatric surgery.

Bariatric surgery has been proven to be the most effective treatment in weight loss and comorbidity resolution in the long term. Many studies have shown that bariatric surgery enables better weight reduction, comorbidity resolution, and quality of life compared to non-surgical methods. The current standard approach for bariatric surgery is the laparoscopic approach. This offers the benefits of faster recovery, a lower complication rate, and shorter hospital stay compared with open approaches.

In Thailand, the annual prevalence of obesity has been increasing dramatically over the past few decades. By 2009, the prevalence of obesity class II (BMI >30 kg/m$^2$) in Thai adults had reached 7% in men and 12% in women[1], prompting the promotion of many lifestyle modification strategies, as well as the introduction of more effective treatments in Thailand, including bariatric surgery.

Since then, bariatric procedures have been increasingly performed; however, while outcome assessment is also important it has been less reported. Consequently, in this study we aimed to establish the surgical outcomes of the initial experience of bariatric surgery in Siriraj Hospital, regarding the efficacy of weight loss, comorbidity resolution, and complications.

## MATERIALS AND METHODS

This study was approved by the Siriraj Institutional Review Board. (Si 813/2016) The first 100 patients who underwent bariatric surgery as treatment for morbid obesity between January 2012 and June 2016 in Siriraj Hospital were enrolled in the study.

The criteria for bariatric surgery in Siriraj Hospital, and according to the Asia-Pacific Bariatric Surgery society consensus 2005, are obese patients who: (1) have a BMI > 37 kg/m$^2$; (2) have a BMI > 32 kg/m$^2$ with diabetes or two significant obesity-related comorbidities; (3) have been unable to lose weight through dietary or medical treatment; and (4) are 18–65 years old.[2] Also, all the patients must be absent of any endocrine disorder causing massive obesity, psychologic instability, and alcohol or drug abuse. Revisional bariatric procedures were also excluded from this study.

The main procedures for bariatric surgery performed in Siriraj Hospital are laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB). After preoperative counseling, the patients choose the surgical procedure by themselves, providing there are no contraindications.

The patients' demographic data and clinical characteristics, including age, gender, preoperative body weight, preoperative body mass index (BMI), obesity-related comorbidities, preoperative laboratory studies, operative time, intraoperative blood loss, length of hospital stay, overall complications, and 30-day morbidity and mortality were reviewed. Concomitant cholecystectomy was performed if preoperative abdominal ultrasound showed any gallstones, regardless of the patient's symptoms.

For the patient's comorbidities, we recorded both preoperative and postoperative HbA1c, fasting blood glucose (FBG), blood pressure, serum cholesterol, triglycerides, LDL, HDL, and medications.

The outcomes of the surgery were studied in two aspects: (1) postoperative weight loss and (2) comorbidity resolution. Postoperative weight loss was reported as percent total weight loss (%TWL), and percent excess weight loss (%EWL), calculated as shown in Fig 1.

There are various definitions of successful weight loss after bariatric surgery. In our center, we use the definition of >20% TWL or >50%EWL in the first year after bariatric surgery. These are the most widely used definitions based on the evidence of comorbidities and cardiovascular risk improvement.[3]

The outcome of comorbidity resolution was reported according to the American Society of Metabolic and

$$\%\text{Total weight loss} = \frac{(\text{Initial weight}) - (\text{Postop weight})}{(\text{Initial weight})} \times 100$$

$$\%\text{Excess weight loss} = \frac{(\text{Initial weight}) - (\text{Postop weight})}{(\text{Initial weight}) - (\text{Ideal weight})} \times 100$$

**Fig 1.** Calculation of postoperative weight loss

Bariatric Surgery (ASMBS) reporting standards 2015. For type-2 diabetes mellitus (DM), complete remission was stated if HbA1c < 6% and FBG < 100 mg/dL, and partial remission was considered when HbA1c = 6.0–6.5% and FBG = 100–125 mg/dL for at least 1 year with the absence of anti-diabetic medication. Disease improvement was considered when HbA1c and FBS were significantly reduced but did not meet the criteria for remission or were decreased but with anti-diabetic medication required. Hypertension remission was documented if BP < 120/80 mmHg without medication. Dyslipidemia remission was considered when LDL < 100 mg/dL, total cholesterol < 200 mg/dL, and triglycerides < 150 mg/dL.

Postoperative complications were reported as early (<30 days) and late (>30 days postoperative) complications. Major complications, according to the ASMBS outcome reporting standards 2015, were defined as any complications that prolonged the hospital stay beyond 7 days, receiving anticoagulant therapy, reintervention, or reoperation.[3]

Before surgery, all patients must be evaluated by a multidisciplinary team, including a bariatric surgeon, nutritionist, cardiologist, pulmonologist, psychiatrist, and physical therapist. An education session covering the principles of a healthy diet and physical activity is provided for patients during the preoperative visits. Preoperative checklist, according to AACE/TOS/ASMBS Clinical Practice Guidelines 2013, was evaluated including cardiopulmonary evaluation with sleep apnea screening if indicates.[4] For the patients with severe obstructive sleep apnea (OSA), Optimizing CPAP treatment must be achieved at least 4 weeks prior to surgery. A very low calorie diet (600–800 kcal/day) is suggested to all patients 2 weeks before surgery for preoperative weight loss if there is no contraindication. We recommend 5–10 kg preoperative weight loss in every patient before surgery.

## Surgical techniques

### Laparoscopic sleeve gastrectomy

In laparoscopic sleeve gastrectomy (LSG), the patient is placed in a supine position. A 36-French orogastric tube is inserted, and 5000 units of unfractionated heparin are injected subcutaneously to prevent deep vein thrombosis. A Veress needle is inserted into the abdomen at Palmer's point for insufflation. A 12 mm camera port is placed 20 cm below the xiphoid and 4 cm to the left of the midline, using an Optiview trocar and a 10 mm zero-degree laparoscope. Then, the camera is exchanged for a 30-degree laparoscope. The patient position is changed to a reverse Trendelenburg position. Nathanson's liver retractor is applied to the left lobe of the liver via a small incision at the epigastrium. Two 5 mm ports are placed at the left anterior axillary line and right midclavicular line about 15 cm below the xyphoid process. Then, a 15 mm port is placed 20 cm inferior to the xiphoid and 2 cm to the right of the midline.

The omentum of the greater curvature of the stomach is divided using a Ligasure advanced bipolar device (Medtronic) from 4 cm proximal to the pylorus up to the angle of His. The blood supplies along the greater curvature, including the short gastric arteries, are ligated completely. Using the orogastric tube as a calibrator, a hook cautery is used to mark the resection line of the stomach. The Medtronic Autostapler (iDrive) is introduced via the 15 mm port. Then, the stomach is transected over the orogastric tube calibrator using 60 mm black cartridges at the antrum and purple cartridges at the body. The posterior wall of the gastric tube is fixed to the posterior side with interrupted 3-0 Prolene stitches in order to prevent the gastric tube from twisting. Leak tests with methylene blue dye and drain placement are performed in selected cases. Hemostasis is checked, and then the resected stomach is removed via an endobag. The 12 and 15 mm port sites are closed using 1-0 Vicryl on a suture passer, Then, the skin is closed in the standard fashion.

### Laparoscopic Roux-en-Y gastric bypass

In Laparoscopic Roux-en-Y gastric bypass (LRYGB), the patient position and preoperative preparation are similar to in LSG as mentioned above. A 12 mm camera port is placed 22 cm below the xiphoid and 2 cm to the left of midline. Nathanson's liver retractor is applied to the left lobe of the liver. A 5 mm port is placed at the left anterior axillary line as an assistant port. Three 12 mm ports are placed on the right midclavicular line, 2 cm to the right of midline and left midclavicular line.

The transverse mesocolon is retracted caudally to expose the ligament of Treitz. The jejunum is measured to 100 cm distal to the DJ junction. Then, the jejunum is transected, including its mesentery, using a 60 mm autostapler (iDrive) tan cartridge to create a 100 cm biliopancreatic limb (BP limb). Another 100 cm of the jejunum is measured. Then, by using a 45 mm tan cartridge, a stapled side-to-side jejunojejunostomy is made between the biliopancreatic limb and jejunum to create a 100 cm Roux limb. The enterotomy site is closed using a running 3-0 Vicryl and the mesenteric defect is closed to its base with a running 3-0 Prolene.

Then, the greater omentum is split in a left paramedian plane to 1 cm away from the transverse colon using a harmonic scalpel. The lesser omentum of the stomach is entered at the level of 6 cm from the EG junction to

create the gastric pouch. Then, a 3-cm horizontal firing is made across the stomach using a 45 mm autostapler purple cartridge. Sequential vertical firings by EndoGIA 60 mm purple cartridges are used to carry on the staple line upward to a point just lateral to the angle of His. This ensures the complete gastrogastric division. The blunt tip of an oral anvil of a 25 mm transoral circular stapler (EEA OrVil, Medtronic) is inserted into the distal part of the gastric pouch.

The 12 mm port at the left midclavicular line is replaced with the handle of the transoral circular stapler (EEA XL). The staple line at the end of the Roux limb is divided and the tip of the stapler handle is inserted. The Roux limb with the circular stapler is brought upward to the gastric pouch, and then the circular gastrojejunostomy anastomosis is created. The blind end including the enterotomy of the Roux limb is cut off using a 45 mm autostapler tan cartridge. A leak test is performed by instilling 50 mL of dilute methylene blue (2 mL per 100 mL of NSS) into the orogastric tube.

The Petersen's defect is closed by suturing the mesentery of the Roux limb to the mesentery of the transverse mesocolon using a running 3-0 Prolene. A 10-French JP drain is placed near the gastrojejunostomy through the LUQ port site. The 12 and 15 mm port sites are closed using a 1-0 Vicryl on a suture passer and the skin is closed in the standard fashion.

### Postoperative care

A dietary program is initiated with a clear liquid diet on postoperative day 1, and then advanced to a full liquid diet (high-protein supplement) on postoperative day 3. IV-PCA (intravenous patient-controlled analgesia) with an opioid is given to patients for postoperative pain control. A sequential compression device is used as routine for DVT prophylaxis. Then after early ambulation is initiated on postoperative day 1, the compression device can be removed.

After discharge, the patients return to the bariatric clinic for a follow-up visit at 2 weeks after surgery and will be advised on a diet comprising 3 small meals with micronutrient supplementation. A proton pump inhibitor is given to the patients for use for 3 months after surgery for marginal ulcer prevention; especially in patients who underwent LRYGB. Ursodeoxycholic acid is given to the patients for 6 months for gall stone prevention.

Follow-up appointments for clinical and nutritional assessment are scheduled at 3 months, 6 months, 9 months, 12 months, and then annually. Routine postoperative esophagogastroduodenoscopy (EGD) is performed in every patient at 1 year after surgery.

### Statistical analysis

Categorical data were reported using the number and percentage. Continuous data were expressed as the mean with the standard deviation and median value with a range of the minimum and maximum. The mean and median preoperative and postoperative parameters were compared using the paired sample t-test and Wilcoxon signed rank test, respectively. IBM SPSS Statistics version 26.0 (SPSS, Chicago, Illinois, USA) for Mac was used for all the statistical analyses. A p-value of less than 0.05 was considered as statistically significant.

## RESULTS

Among the first 100 bariatric surgery patients in Siriraj Hospital, 69% were female and 31% male. The median age was 36 years old [16-64]. The median preoperative body weight and BMI were 129 kg [88-270] and 46.3 kg/m$^2$ [34.0-83.3], respectively. For pre-existing comorbidity, 45% of patients had been diagnosed with type 2 diabetes mellitus (DM), 65% with hypertension, 38% with dyslipidemia, 4% with coronary artery disease, 35% with obstructive sleep apnea (OSA), and 10% with osteoarthritis of the knee. The patients' demographic data are summarized in Table 1.

There were 58 cases of laparoscopic sleeve gastrectomy (LSG) and 42 cases of laparoscopic Roux-en-Y gastric bypass (LRYGB). All the operations had been performed by laparoscopic approach successfully without conversion to the open approach. The median operative time for LSG

**TABLE 1.** Patients' demographic data.

| | (N = 100) |
|---|---|
| Sex (F:M) | 69:31 |
| Age, year | 36 [16–64] |
| Preoperative body weight, kg | 129 [88–270] |
| Preoperative BMI, kg/m$^2$ | 46.3 [34.0–83.3] |
| Pre-existing comorbidity | |
| DM (type 2) | 45 (45%) |
| Diet control (2/45) | |
| Oral hypoglycemic drug (37/45) | |
| Insulin therapy (6/45) | |
| Hypertension | 65 (65%) |
| Dyslipidemia | 38 (38%) |
| Coronary artery disease | 4 (4%) |
| Obstructive sleep apnea | 35 (35%) |
| Osteoarthritis of knees | 10 (10%) |

was 156 minutes [85-435] and 265 minutes [180-435] for LRYGB. The concomitant procedures generally took longer operative time than normal bariatric procedures. The longest operation of LSG (435 minutes) was firstly attempted for LRYGB but was failed due to severe adhesion from previous abdominal surgery and then was converted to LSG. The mean estimated blood loss was 20 ml and 25 ml for LSG and LRYGB, respectively. The median postoperative length of hospital stay was 3 days [3-14], as shown in Table 2.

**TABLE 2.** Operative and postoperative data of the bariatric surgery patients.

| Operative data | (N = 100) |
|---|---|
| Operative time (min) | |
| LSG | 156 [85–435] |
| LRYGB | 265 [180–435] |
| Concomitant procedure (%) | |
| Cholecystectomy | 16 |
| IPOM* | 1 |
| Adrenalectomy | 1 |
| Conversion to open approach | 0 |
| Estimated blood loss (ml) | |
| LSG | 20 [5–300] |
| LRYGB | 25 [5–400] |
| Length of hospital stay (days) | 3 [3–14] |
| Postoperative complication (case) | |
| Early (≤ 30 day) | |
| Lung atelectasis | 2 |
| Pulmonary embolism | 1 |
| Deep vein thrombosis | 1 |
| Anastomotic leakage | 0 |
| Intra-abdominal hemorrhage | 0 |
| Intra-abdominal collection | 1 |
| Surgical site infection | 3 |
| Other | 1 |
| Late (> 30 days) | |
| GERD | |
| No reflux esophagitis | 3 |
| Mild (grade A, B) | 16 |
| Severe (grade C, D) | 1 |
| Barrett's esophagus | 1 |
| Dumping syndrome | 2 |
| Marginal ulcer | 7 |
| Incisional hernia | 1 |

**Abbreviation:** IPOM; Intraperitoneal onlay mesh repair; laparoscopic hernia repair for ventral hernia

### Weight loss outcome

The follow-up rates at 1 year, 2 years, and 3 years after surgery were 76%, 57%, and 55%, respectively. The mean %TWL and mean %EWL at 3 months, 6 months, 9 months, 1 year, 2 years, and 3 years are shown in Table 3, Table 4 and Fig 2.

The mean %TWL of the patients who underwent LSG at 1 year, 2 years, and 3 years were 30.2 ± 10.4%, 30.9 ± 11.2%, and 28.4 ± 11.3%, respectively. The mean %EWL of the LSG patients at 1 year, 2 years, and 3 years were 56.8 ± 19.8%, 59.9 ± 21.7%, and 55.1 ± 21.3%, respectively. As for the patients who underwent LRYGB, the mean %TWL at 1 year, 2 years, and 3 years were 33.4 ± 7.5%, 33.2 ± 9.6%, and 31.9 ± 8.6%, respectively. The mean %EWL of the LRYGB patients at 1 year, 2 years, and 3 years were 67 ± 18.3%, 66.2 ± 21.4%, and 63.6 ± 19.9%, respectively.

### Comorbidity outcomes

For the 45 patients with pre-existing type-II diabetes, 33 patients reached the follow-up time at 1 year, comprising 9 LSG cases and 24 LRYGB cases. All 6 of the patients who had received insulin therapy had underwent LRYGB.

At 1 year after surgery, the median fasting blood glucose (FBG) dropped from 127 to 99 mg/dL ($p < 0.001$) and HbA1c also dropped from 6.6% to 5.5% ($p < 0.001$) with statistical significance. Of these 33 patients, 67% of the patients (22/33) had complete diabetic remission, while 6% of the patients (2/33) had partial remission, and 21% of the patients (7/33) showed disease improvement. Five of the six patients (5/6) who received insulin therapy prior to surgery could be successfully weaned off insulin and 4 of them achieved complete diabetic remission.

Among the 65 patients with hypertension, 38 reached the follow-up time at 1 year. The remission rate of hypertension was 58% (22/38). There were significant differences between preoperative and postoperative blood pressure. The mean systolic BP dropped from 138 ± 18 mmHg to 129 ± 13 mmHg ($p = 0.004$) and diastolic BP from 81 ± 15 mmHg to 77 ± 10 mmHg ($p = 002$).

As for the 38 patients with dyslipidemia, 22 reached the follow-up time at 1 year. The remission rate of dyslipidemia was 73% (16/22). The median serum LDL was 101 mg/dl [65-165], and the median serum triglyceride was 80 mg/dl [38-168] at 1 year after surgery, as also shown in Table 5.

### Overall complications

The overall 30-day postoperative complication rate was 9%, and the rate of major complications was 4% (Table 2). There were 2 cases of venous thromboembolic

**TABLE 3.** Weight loss outcome of laparoscopic sleeve gastrectomy (LSG).

| | 3 months (N = 54) | 6 months (N = 49) | 9 months (N = 48) | 1 year (N = 46) | 2 years (N = 31) | 3 years (N = 29) |
|---|---|---|---|---|---|---|
| %TWL | 20.2 ± 7.1 | 25.6 ± 8.9 | 29.1 ± 9.7 | 30.2 ± 10.4 | 30.9 ± 11.2 | 28.4 ± 11.3 |
| %EWL | 38.2 ± 14.5 | 48.7 ± 18.3 | 55 ± 18.7 | 56.8 ± 19.8 | 59.9 ± 21.7 | 55.1 ± 21.3 |

**TABLE 4.** Weight loss outcome of laparoscopic Roux-en-Y gastric bypass (LRYGB).

| | 3 months (N = 41) | 6 months (N = 31) | 9 months (N = 31) | 1 year (N = 30) | 2 years (N = 26) | 3 years (N = 26) |
|---|---|---|---|---|---|---|
| %TWL | 21.2 ± 5.1 | 28.1 ± 6 | 32.3 ± 7.4 | 33.4 ± 7.5 | 33.2 ± 9.6 | 31.9 ± 8.6 |
| %EWL | 42.1 ± 10.2 | 56.5 ± 13.1 | 64.5 ± 16.4 | 67 ± 18.3 | 66.2 ± 21.4 | 63.6 ± 19.9 |

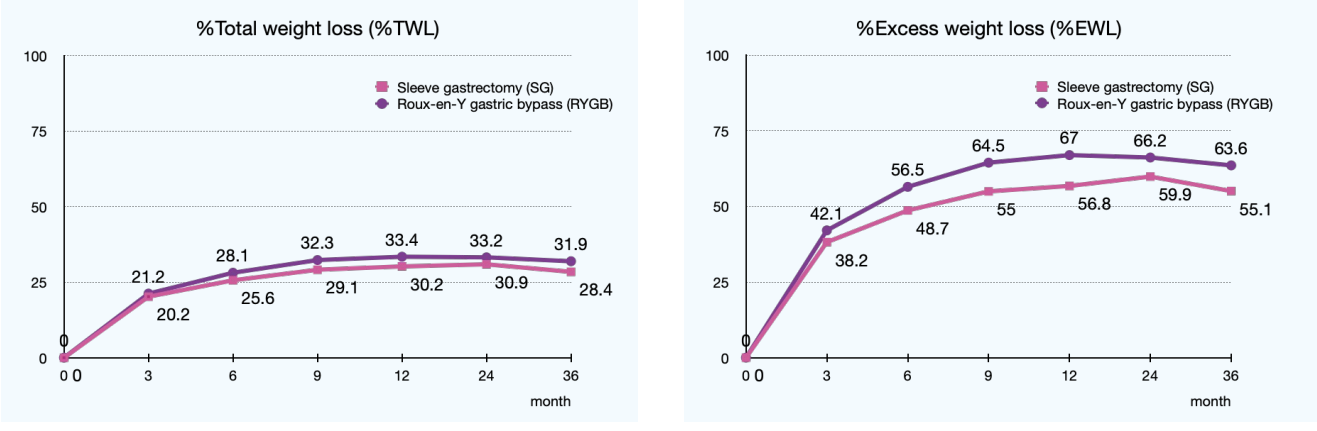


**Fig 2.** Weight loss outcome after bariatric surgery.

**TABLE 5.** Preoperative and 1-year postoperative parameters of patients in the comorbidity group.

| | Preoperative | 1-year postoperative | P-value |
|---|---|---|---|
| FBG (mg/dl) | 127 [82–379] | 99 [78–230] | < 0.001 |
| HbA1C (%) | 6.6 [5.3–15.9] | 5.5 [4.4–8.7] | < 0.001 |
| SBP (mmHg.) | 138 ± 18 | 129.1 ± 13.1 | 0.004 |
| DBP (mmHg.) | 80.6 ± 14.8 | 76.7 ± 9.9 | 0.002 |
| HDL (mg/dl) | 55 [27–191] | 65 [40–89] | 0.205 |
| LDL (mg/dl) | 112 [58–292.4] | 101 [65–165] | 0.145 |
| TG (mg/dl) | 113 [30–280] | 80 [38–168] | 0.036 |

event (comprising 1 case of pulmonary embolism and 1 case of deep vein thrombosis), where anticoagulant therapy was given to the patients. One patient who underwent LRYGB developed a small intra-abdominal collection at postoperative day 7 without anastomotic leakage, as confirmed by a contrast study. The patient was successfully treated with intravenous antibiotics. There was 1 case of reoperation, in which a patient who had underwent LRYGB developed an intestinal obstruction on postoperative day 7 due to jejunojejunostomy stenosis. Laparoscopic adhesiolysis with jejunojejunostomy revision was performed at that time. There was no mortality in the 30-day postoperative period.

Regarding late complications, among the 42 patients who underwent LRYGB, 2 patients (4.8%) developed dumping syndrome in which the symptom could be improved by dietary modification. Seven patients (16.7%) had marginal ulcer detected in surveillance endoscopy at 1 year after surgery. Proton pump inhibitor (PPI) therapy was given to those patients without endoscopic intervention or surgery required.

Among the 58 patients who underwent LSG, 21 patients (36.2%) developed gastroesophageal reflux, including 1 patient (1.7%) with severe reflux esophagitis (LA classification grade C) and 1 patient (1.7%) with Barrett's esophagus. Nine patients (15.5%) with gastroesophageal reflux complication had a concomitant sliding hiatal hernia detected by EGD at 1 year after surgery.

Moreover, 7 of the patients (12.1%) later received conversion surgery from sleeve gastrectomy to Roux-en-Y gastric bypass due to an indication of severe gastroesophageal reflux symptom (3 cases), inadequate weight loss or weight regain (3 cases), and sleeve tube stricture (1 case). The median time to conversion surgery was 3 years (ranging from 3–5 years) after the primary surgery.

## DISCUSSION

Obesity has become a global health concern as its prevalence has been rising in many countries. The impact of obesity is not only an individual health problem but also the economic burden of the treatment cost for obesity-related illnesses. The goal of treatment is to reduce the risk of developing complications related to obesity and to improve the quality of life of the patients.

In morbidly obese patients, bariatric surgery is considered to be the most effective treatment to achieve long-term outcomes both in weight loss and comorbidity resolution. Several studies have shown that bariatric surgery has significantly better outcomes for weight loss, comorbidity resolution, and quality of life compared with non-surgical methods both in the short term and long term.[5-7] A recent meta-analysis demonstrated the durable outcomes of bariatric surgery with a 10-year follow-up. The mean %EWL of sleeve gastrectomy was 58.3% in 2 studies, while Roux-en-Y gastric bypass was 56.7% in 18 studies.[8]

In this study, we demonstrated the short-term outcomes of bariatric surgery performed in Siriraj Hospital. Our center has demonstrated good weight loss outcomes with mean %EWL for LSG and LRYGB as 56.8% and 67% at 1 year after surgery, and maintenance of a mean %EWL of >50% at the follow-up time of 3 years after surgery. Other studies have reported the 1-year %EWL of LSG at between 56%–72.6%[9-11], and LRYGB at 62.6%-80.4%.[12-14] These indicate that the results of our center are comparable with the outcomes of the other studies.

Preoperative comorbidity, including type-2 DM, hypertension, and dyslipidemia, were found to be improved after surgery at our center. As for type 2 DM, our center has reported excellent outcomes, with a complete remission rate of 67% at 1 year after surgery. This result is comparable to other studies, in which the complete diabetic remission rate after bariatric surgery has been reported to be between 50.6%-67.9%.[15,16] Several studies have shown that bariatric surgery has a significant better outcome for glycemic control compared with non-surgical methods, both in the short term and long term.[6,7]

Regarding the operation safety, the complication rate of our center was considerably low. The major complication rate was reported at 4% without mortality. Ibrahim *et al.* reported the serious complication rate from 165 bariatric excellence centers in the United States ranged from 0.6%-4.9% in high-volume centers and 0.6%–10.3% in medium-volume centers.[17] Anastomotic leakage, which is the most serious complication of bariatric surgery, was not detected in our study.

Gastroesophageal reflux disease (GERD) is the most common complication after sleeve gastrectomy. The incidence was reported at 36.2% in our study. In our literature review, the incident of de novo GERD was reported at 40%–60%[18-20], based on clinical symptoms and endoscopic findings. Even so, the relationship between GERD and sleeve gastrectomy has long been controversial. Many studies have shown that the anatomical changes of LSG may worsen the existing GERD or cause GERD in some patients without pre-existing symptoms.[21] Meanwhile, some studies have also shown that LSG can improve GERD after surgery.[9,22] Some studies mentioned that the surgical technique and the shape of the gastric tube play important roles in preventing GERD after sleeve gastrectomy. Daes *et al.* proposed standardized

techniques and identified the technical errors that can lead to the development of GERD, including a narrowing at the junction of the vertical and horizontal part of the sleeve.[22] Therefore, in our center, we routinely use a 36-French bougie as the calibrator and keep the area at the incisura angularis >2 cm to make sure that the angle between the vertical and horizontal parts of the sleeve is not too narrow. Moreover, we believe that another mechanism associated with GERD is the disruption of the phrenoesophageal ligament around the esophagogastric junction (EGJ). So we only dissect the gastric fundus to the level of the left diaphragmatic crus and avoid circumferential dissection around the EGJ.

Another predisposing factor related to GERD after sleeve gastrectomy is a pre-existing hiatal hernia.[22,23] Many experts have suggested that a hiatal hernia should be repaired at the same time as sleeve gastrectomy.[24] In our center, we found that 15.5% of the patients who underwent LSG had a hiatal hernia at the endoscopy performed 1-year after surgery. The reason for this might be because the lesions were too small and may have been missed during the surgery, or the sleeve tube itself may have later migrated upward into the chest. Therefore, we think that careful identification of a hiatal hernia, both preoperatively and during surgery, and adding concomitant hiatal hernia repair would help reduce the incidence of GERD after sleeve gastrectomy in the future.

One specific complication that can occur after RYGB is a marginal ulcer. The rate of marginal ulcers varies from 7%-34%.[25-27] In our center, we found 16.7% of the RYGB patients had marginal ulcers at the routine postoperative endoscopy. Most of the patients were asymptomatic, so no early endoscopy had been performed before 1 year after surgery.

A marginal ulcer is believed to be associated with many local factors, such as inflammation, ischemia, and high acid production. A larger size of gastric pouch contains more parietal cells, causing more acidity and a greater risk of ulceration. Azagury *et al*. demonstrated that the gastric pouch length of the patients with marginal ulcers was significantly larger compared with a non-marginal ulcer group (5.6 ± 2 vs 4.9 ± 1.7, OR 1.2, p = 0.02).[28] Edholm *et al*. also showed that a smaller gastric pouch can reduce the risk of marginal ulcers.[29] So, in our center, we measure the gastric pouch length at 5–6 cm, so that the gastric pouch would not be >6 cm and <4 cm in length. We believe that a gastric pouch length of less than 4 cm might increase the tension around the gastrojejunostomy anastomosis, which could lead to acute ischemia and become a risk of leakage or the formation of a marginal ulcer afterward.

Moreover, there are multiple risk factors related to marginal ulcers, including smoking[27,28,30], chronic non-steroidal anti-inflammatory drugs (NSAIDs) use[27,30], *Helicobacter pylori* infection[30], untreated obstructive sleep apnea[30], and immunosuppression.[27] Therefore, to reduce the risk of marginal ulcer formation, we aim to ensure that all the risk modifications must be achieved before a Roux-en-Y gastric bypass procedure is performed.

This study has demonstrated safety and feasibility of bariatric procedures in Siriraj Hospital performed between 2012 and 2016 by the standard laparoscopic approach. With the good results of surgical outcomes and low complication rate in this study, we established the standard protocol of preoperative and postoperative care for bariatric procedures in our center, including the robotic bariatric procedures which was later performed in 2017.[31,32] In addition, The long-term results should be considered in a further study.

### Limitations of this study

There are some limitations in this study to note. Our follow-up rate appeared to be less than in other studies, which might be due to the ineffectiveness of the follow-up system at the time of our initial experience. Moreover, this study was conducted in the early period of our experience. Therefore, the operative time was perhaps longer compared with other centers. However, despite the longer operative time, the complication rate of our center was also considerably low. Lastly, this was a retrospective study based on a chart review, which may means of some missing data.

## CONCLUSION

Bariatric surgery, both laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass, can provide good outcomes in weight loss and comorbidity resolution. In Siriraj Hospital, the overall and major complication rates are low and comparable to other bariatric excellence centers.

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## REFERENCES

1. Aekplakorn W, Inthawong R, Kessomboon P, Sangthong R, Chariyalertsak S, Putwatana P, et al. Prevalence and trends of obesity and association with socioeconomic status in Thai adults: National Health Examination Surveys, 1991-2009. J Obes. 2014;2014:410259.
2. Lee WJ, Wang W. Bariatric surgery: Asia-Pacific perspective. Obes Surg. 2005;15:751-57.
3. Brethauer SA, Kim J, el Chaar M, Papasavas P, Eisenberg D,

Rogers A, et al. Standardized outcomes reporting in metabolic and bariatric surgery. Surg Obes Relat Dis. 2015;11(3):489-506.
4. Mechanick JI, Youdim A, Jones DB, Garvey WT, Hurley DL, McMahon MM, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. Surg Obes Relat Dis. 2013;9(2):159-91.
5. Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. BMJ. 2013;347:f5934.
6. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al. Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. N Engl J Med. 2017; 376(7):641-51.
7. Syn NL, Cummings DE, Wang LZ, Lin DJ, Zhao JJ, Loh M, et al. Association of metabolic-bariatric surgery with long-term survival in adults with and without diabetes: a one-stage meta-analysis of matched cohort and prospective controlled studies with 174 772 participants. Lancet. 2021;397(10287):1830-41.
8. O'Brien PE, Hindle A, Brennan L, Skinner S, Burton P, Smith A, et al. Long-Term Outcomes After Bariatric Surgery: a Systematic Review and Meta-analysis of Weight Loss at 10 or More Years for All Bariatric Procedures and a Single-Centre Review of 20-Year Outcomes After Adjustable Gastric Banding. Obes Surg. 2019;29(1):3-14.
9. Rawlins L, Rawlins MP, Brown CC, Schumacher DL. Sleeve gastrectomy: 5-year outcomes of a single institution. Surg Obes Relat Dis. 2013;9(1):21–5.
10. Jaruvongvanich V, Wongjarupong N, Vantanasiri K, Samakkarnthai P, Ungprasert P. Midterm Outcome of Laparoscopic Sleeve Gastrectomy in Asians: a Systematic Review and Meta-analysis. Obes Surg. 2020;30(4):1459-67.
11. Fischer L, Hildebrandt C, Bruckner T, Kenngott H, Linke GR, Gehrig T, et al. Excessive weight loss after sleeve gastrectomy: a systematic review. Obes Surg. 2012;22(5):721-31.
12. Corcelles R, Boules M, Froylich D, Hag A, Daigle CR, Aminian A, et al. Total weight loss as the outcome measure of choice after Roux-en-Y gastric bypass. Obes Surg. 2016;26(8):1794-8.
13. Garb J, Welch G, Zagarins S, Kuhn J, Romanelli J. Bariatric surgery for the treatment of morbid obesity: a meta-analysis of weight loss outcomes for laparoscopic adjustable gastric banding and laparoscopic gastric bypass. Obes Surg. 2009;19(10): 1447-55.
14. Ignat M, Vix M, Imad I, D'Urso A, Perretta S, Marescaux J, et al. Randomized trial of Roux-en-Y gastric bypass versus sleeve gastrectomy in achieving excess weight loss. Br J Surg. 2017; 104(3):248-56.
15. Lemus R, Karni D, Hong D, Gmora S, Breau R, Anvari M. The impact of bariatric surgery on insulin-treated type 2 diabetes patients. Surg Endosc. 2018;32:990-1001.
16. Peterli R, Wölnerhanssen BK, Peters T, Vetter D, Kroll D, Borbely Y, et al. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss in Patients With Morbid Obesity: The SM-BOSS Randomized Clinical Trial. JAMA. 2018;319(3):255-65.
17. Ibrahim AM, Ghaferi AA, Thumma JR, Dimick JB. Variation in Outcomes at Bariatric Surgery Centers of Excellence. JAMA Surg. 2017;152(7):629-36.
18. King K, Sudan R, Bardaro S, Soriano I, Petrick AT, Daly SC, et al. Assessment and management of gastroesophageal reflux disease following bariatric surgery. Surg Obes Relat Dis. 2021; 17(11):1919-25.
19. Soricelli E, Casella G, Baglio G, Maselli R, Ernesti I, Genco A. Lack of correlation between gastroesophageal reflux disease symptoms and esophageal lesion after sleeve gastrectomy. Surg Obes Relat Dis. 2018;14(6):751-6.
20. Oor JE, Roks DJ, Ünlü Ç, Hazebroek EJ. Laparoscopic sleeve gastrectomy and gastroesophageal reflux disease: a systematic review and meta-analysis. Am J Surg. 2016;211(1):250-67.
21. Raj PP, Bhattacharya S, Misra S, Kumar SS, Khan MJ, Gunasekaran SC, et al. Gastroesophageal reflux-related physiologic changes after sleeve gastrectomy and Roux-en-Y gastric bypass: a prospective comparative study. Surg Obes Relat Dis. 2019;15(8): 1261-9.
22. Daes J, Jimenez ME, Said N. Improvement of Gastroesophageal Reflux Symptoms After Standardized Laparoscopic Sleeve Gastrectomy. Obes Surg. 2014;24:536-540.
23. Altieri MS, Pryor AD. Gastroesophageal reflux disease after bariatric procedures. Surg Clin North Am. 2015;95(3):579-591.
24. Rosenthal RJ, International Sleeve Gastrectomy Expert Panel, Diaz AA, Arvidsson D, Baker RS, Basso N, et al. International Sleeve Gastrectomy Expert Panel Consensus Statement: best practice guidelines based on experience of >12,000 cases. Surg Obes Relat Dis. 2012;8(1):8-19.
25. Moon RC, Teixeira AF, Goldbach M, Jawad MA. Management and treatment outcomes of marginal ulcers after Roux-en-Y gastric bypass at a single high volume bariatric center. Surg Obes Relat Dis. 2014;10(2):229-234.
26. El-Hayek K, Timratana P, Shimizu H, Chand B. Marginal ulcer after Roux-en-Y gastric bypass: what have we really learned? Surg Endosc. 2012;26(10):2789-96.
27. Di Palma A, Liu B, Maeda A, Anvari M, Jackson T, Okrainec A. Marginal ulceration following Roux-en-Y gastric bypass: risk factors for ulcer development, recurrence and need for revisional surgery. Surg Endosc. 2021;35(5):2347-53.
28. Azagury DE, Abu Dayyeh BK, Greenwalt IT, Thompson CC. Marginal ulceration after Roux-en-Y gastric bypass surgery: characteristics, risk factors, treatment, and outcomes. Endoscopy. 2011;43(11):950-4.
29. Edholm D, Ottosson J, Sundbom M. Importance of pouch size in laparoscopic Roux-en-Y gastric bypass: a cohort study of 14,168 patients. Surg Endosc. 2016;30:2011-5.
30. Rodrigo DC, Jill S, Daniel M, Kimberly C, Maher EC. Which Factors Correlate with Marginal Ulcer After Surgery for Obesity? Obes Surg. 2020;30(12):4821-7.
31. Taweerutchana V, Suwatthanarak T, Srisuworanan N, Rich NC. The First Robotic Bariatric Surgery Performed in Thailand – Surgical Techniques and Review of the Literature. Siriraj Med J. 2020;72:181-7.
32. Taweerutchana V, Nimmanwudipong T, Chinswangwatanakul V, Methasate A, Akaraviputh T, Swangsri J, et al. Outcome of Robotic Approach for Bariatric Surgery: Our Initial Experience in Siriraj Hospital. J Med Assoc Thai. 2020;103:93.

# The Comparison between Frozen Elephant Trunk Technique and Conventional Total Arch Replacement, a Single-center Study

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## ABSTRACT

**Objective:** The advantage of the frozen elephant trunk technique (FET) is treating the aortic pathology extending from the aortic arch to the descending aorta in a one-stage operation. This study aimed to determine the early and long-term outcomes of total arch replacement with the frozen elephant trunk technique compared to conventional total arch replacement (cTAR).

**Materials and Methods:** This study was a single-center, retrospective cohort study. Patients who underwent aortic arch replacement between January 2009 and December 2020 were enrolled and divided into two groups. 32 patients underwent the FET and 47 patients underwent cTAR. Outcomes and survival analysis were compared.

**Results:** The 5-year survival for FET and cTAR were 87.27% and 82.55% and the aortic-related mortality was not significantly different (HR 0.97, 95%CI 0.22-0.43). Aortic re-intervention was significantly lower in the FET group accounting for 3.57%, while there was 39.1% in the cTAR group. FET significantly reduced aortic re-intervention compared with cTAR (HR 0.09, 95%CI 0.01-0.81). There were no differences in the incidence of stroke between the two groups. However, FET patients had significantly increased risks of paraplegia by 21% when compared to cTAR (Risk difference +0.21, 95%CI 0.02-0.40).

**Conclusions:** The FET technique had comparable early outcomes in terms of mortality, renal function, postoperative bleeding, and recurrent laryngeal nerve injury. Even though FET had a significant risk of postoperative paraplegia, FET reduced the aortic re-intervention rate without increasing aortic-related death.

**Keywords:** Aortic arch; Frozen elephant trunk technique; Conventional total arch replacement (Siriraj Med J 2022; 74: 778-786)

## INTRODUCTION

One advantage of aortic arch replacement with frozen elephant trunk technique (FET) over conventional total arch replacement (cTAR) is that it allows treatment of the aortic pathology extending from the aortic arch to the descending aorta in a single operation.[1,2] In some cTAR operations, the aortic pathology lies in the descending aorta or there is residual disease present after the initial operation. Thus, requiring a possible second aortic intervention to manage the remaining aortic disease.[3-6]

Another advantage is that the distal anastomosis between the native aortic tissue and prosthetic graft can be achieved more proximally than in cTAR regardless of the location of the distal diseased aorta. In FET, the

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anastomosis can be completed within Ishimaru's aortic zone 0 to zone 3.[7,8] Therefore, this technique doesn't require dissection of the para-aortic tissue toward the distal part of each zone of the aortic arch, resulting in a decrease in the circulatory arrest time and a decrease in the incidence of recurrent laryngeal nerve injury.[9,10]

Despite many advantages of using FET, the incidence of spinal cord ischemia (SCI) or post-operative paraplegia should be considered. The incidence of SCI is significantly more frequent in a patient with longer stent coverage, prolonged circulatory arrest time, and postoperative hemodynamic instability.[9]

Therefore, this study aimed to determine the early and long-term outcomes of aortic arch replacement with FET compared with cTAR. Upon the hypothesis that FET is non-inferior to a conventional technique, the outcomes were also determined in aspects of aortic-related mortality and aortic re-intervention.

## MATERIALS AND METHODS

### Patients

A retrospective cohort study was conducted at Maharaj Hospital, Faculty of Medicine, Chiang Mai University, Thailand, and was approved by the Research Ethics Committee no.4 of Faculty of Medicine, Chiang Mai University. (SUR-2021-08696, Research ID: 8696) Patients 18 years old or older who underwent aortic arch replacement between January 2009 and December 2020 were enrolled in this study. The operation included both emergency and elective surgery. The etiology of aortic disease included acute and chronic aortic dissection, dissection variants, and aneurysms. There were no differences in operative techniques in all patients even at different emergency levels or with different aortic etiology. The other aortic arch operation (hemiarch replacement, partial arch replacement) was excluded from the study. Also, patients who underwent total arch replacement via thoracotomy were excluded from the study.

The 79 cases of aortic arch replacement included in this study were divided into two groups: patients who underwent aortic arch replacement with the FET technique, FET group (n=32, 43.2%); and patients who underwent total arch replacement using a conventional technique, cTAR group (n=47, 56.8%).

### Operative technique and procedure

*Conventional total arch replacement*

The operation was performed via median sternotomy. Cardiopulmonary bypass was set up with arterial inflow via central, peripheral, or both-site cannulation. Venous drainage was obtained from a two-stage venous cannula that was inserted via the right atrial appendage. Cardiopulmonary bypass was run via a roller pump with the non-pulsatile flow. Myocardial protection was performed by selective, antegrade, and retrograde perfusion with cold Bretschneider's solution (Custodiol® Essential Pharmaceuticals, LLC). Deep hypothermia (20-24°C) concurrent with selective antegrade cerebral perfusion was used as a neuroprotective strategy during circulatory arrest with near-infrared spectroscopy (NIRS) monitoring.

All specific details of the surgical technique are defined as a total arch replacement. The distal anastomosis was performed with complete transection of the proximal descending aorta (Ishimaru's zone 3).[7] Then the distal part of the commercial or self-made quadrifurcated graft was anastomosed to the descending aorta with a 3-0 polypropylene running suture. This was followed by anastomosis of the left subclavian artery, left common carotid artery, and a brachiocephalic branch with 5-0 polypropylene. In addition, a proximal anastomosis was connected to the residual good pathological ascending aorta with 3-0 polypropylene running sutures.

*Frozen elephant trunk technique*

The initial approach and cardio-pulmonary bypass technique were similar to cTAR. The stent graft devices used for FET included the commercial hybrid stent graft (E-vita open plus (Jotec® Inc., Germany), Thoraflex™ hybrid (Vascutek Terumo, Scotland, UK)) or non-commercial stent graft. In non-commercial devices, the stent graft (Relay® plus NBS (Vascutek Terumo, Scotland, UK), Valiant™ Captivia (Medtronic, Minnesota, USA), Zenith TX2® or Zenith Alpha™ (Cook® medical, Indiana, USA) was deployed either in an antegrade or retrograde fashion. The distal anastomosis was from Ishimaru's aortic arch zone 0 to zone 3 and running continuous sutures with 3-0 polypropylene between the prosthetic graft and native aortic tissue with a stent graft inside. The aortic arch branches were debranched and reimplanted proximally to the distal anastomosis arch zones or sequence anastomosed to quadrifurcated grafts, similar to conventional total arch replacement.

*Concomitant procedures*

Concomitant procedures included aortic valve replacement in 14 patients, aortic root surgery in 16 patients, and coronary artery bypass grafting in 12 patients.

*Spinal drainage and post-operative management*

Spinal fluid drainage was selectively used in patients

that underwent FET and needed long stent coverage in the descending aorta beyond the T9 vertebra level or when the total stent graft length was longer than 200 mm. Cerebrospinal fluid (CSF) drainage was initiated when the CSF pressure was more than 10 mmHg. The spinal fluid drainage catheter was removed postoperatively on day 3 after confirmation of no existing neurological deficit. Target postoperative mean arterial pressure was 80 to 100 mmHg. If the patient developed paraplegia and spinal cord ischemia was diagnosed, spinal fluid drainage was initiated in patients without prior placement and the target means arterial pressure was raised above 100 mmHg. Intravenous corticosteroids and mannitol were used as adjunct treatments for spinal cord ischemia.

*Follow-up*

In the follow-up periods, hypertension and dyslipidemia were controlled by medical treatment. The first-line drug was beta-blockers and statins. Patients were also advised to quit smoking. Computed tomography angiography (CTA) of the aorta was the first choice for both techniques.

### Definition

Mortality was defined as aortic-related death after the operation. Aortic re-intervention was defined as any re-operation for aortic surgery (including endovascular or/and open aortic surgery) after the first operation. Stroke was defined if there was any brain lesion identified in the brain CT corresponding to the symptoms. Paraplegia was defined as a new impairment in the neurologic function of the lower extremities which occurred after the operation. Acute kidney injury was defined if the postoperative creatinine level increased > 0.5 mg/dL compared to the pre-operative level or a new post-operative renal replacement therapy. The recurrent laryngeal nerve injury was defined as a post-operative vocal cord paralysis resulting in hoarseness, aspiration, and voice change.

### Statistical analysis

Statistical analyses were performed using STATA software, version 16.1. The sample size was calculated by test-comparing two independent means based on studies in which the outcomes were similar to this study.[9]

Continuous data were analyzed by T-test analysis for normal distribution and Ranksum test for non-normal distribution. Categorical data were analyzed by Fisher's exact test. A propensity score for adjustment was calculated using the following parameters: age, sex, hypertension, current smoker, aortic etiology, emergency surgery, CSF drainage, and lowest body temp. The differences in propensity score between the two groups were shown in Table 1.

Aortic-related death and freedom from aortic re-intervention were calculated using the Kaplan–Meier method. Differences in these rates between both groups were analyzed using the log-rank test. Independent survival and aortic re-operation predictors were identified using multivariable Cox regression analysis and adjusted with propensity scores. Binary risk regression analysis was used to identify the post-op adverse outcome between the two study groups. Logistic regression analysis was used to identify the independent risk factors.

In all statistical tests, differences between the groups were considered significant at $p<0.05$.

## RESULTS

### Patient demographics

In Table 1, the comparison revealed the patients in the FET group were older than the cTAR group. However, the overall underlying diseases in both groups were comparable. Most of the aortic pathologies in cTAR were acute and chronic aortic dissection. In the FET group, aortic aneurysms represented most of the aortic pathologies. In concomitant procedures, an aortic root procedure was performed more frequently in the cTAR group.

The operative data showed no differences between the two groups' total operation time, cardiopulmonary bypass time, aortic cross-clamp time, and lower body circulatory arrest time. The mean total length of the stent graft in FET was 179.4±38.9 millimeters.

### Aortic-related mortality

The mortality was lower in the FET group accounting for 4 cases (12.5%), while there were 9 cases (19.2%) in the cTAR group. The 5-year survival for FET and cTAR was 87.27% and 82.55%. The Kaplan-Meier curves and hazard ratio (HR) showed no significant difference between the two groups (Fig 1).

### Aortic re-intervention

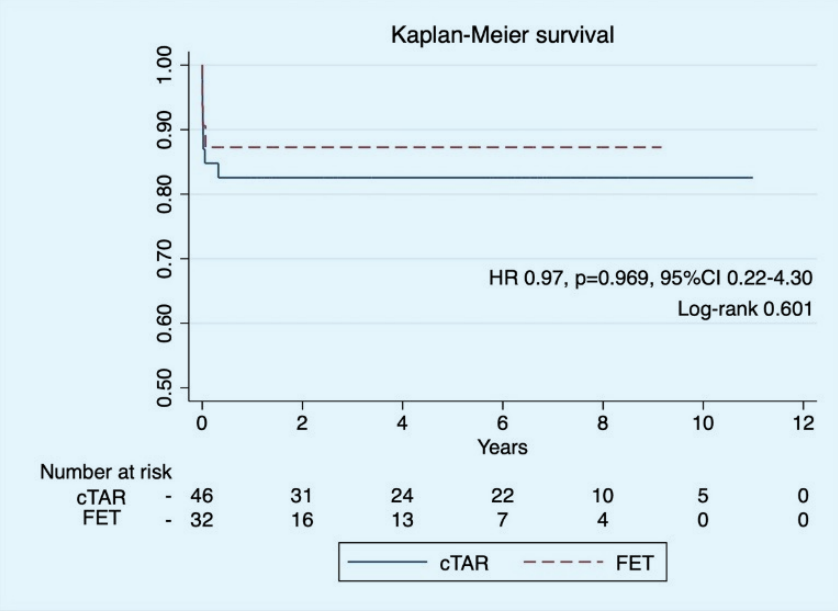
Aortic re-intervention was lower in the FET group accounting for 3.57%, while there was 39.1% in the cTAR group. 5-year re-intervention free for FET and cTAR were 93.75% and 55.61%. The median re-intervention time for cTAR was 5.42 years. The Kaplan-Meier curves and HR showed that FET had significantly reduced aortic re-intervention when compared to cTAR (Fig 2).

In the cTAR group, 9 patients underwent thoracic endovascular aortic repair (TEVAR) for re-intervention due to an aneurysmal change of the distal aorta and the

**TABLE 1.** Baseline characteristics and operative data.

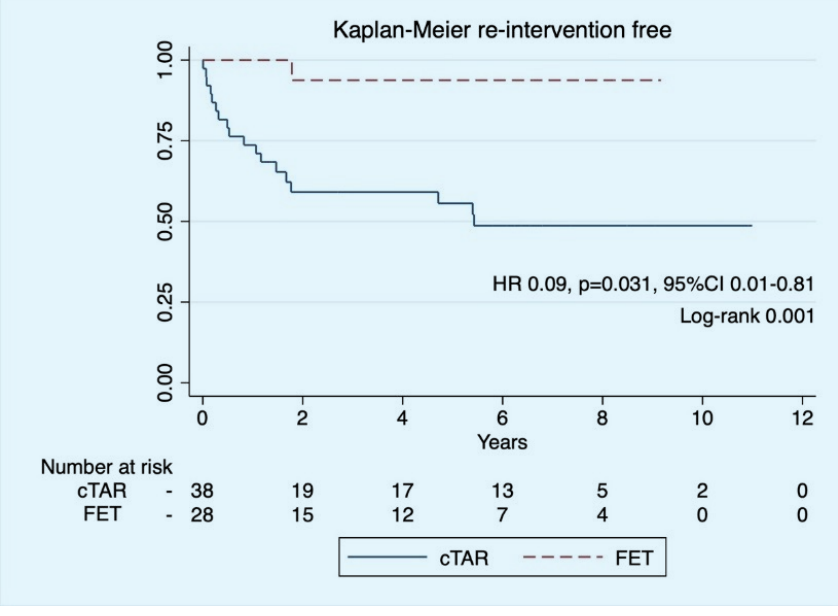
| | FET (n = 32) | cTAR (n = 47) | P |
|---|---|---|---|
| Male, n (%) | 21 (65.6) | 27 (57.5) | 0.311 |
| Age (year, mean ± SD) | 65.1±9.2 | 56.0±10.0 | <0.001 |
| Current smoker, n (%) | 22 (68.8) | 22 (46.8) | 0.044 |
| Hypertension, n (%) | 30 (93.8) | 35 (74.5) | 0.025 |
| Diabetes Mellitus, n (%) | 2 (6.3) | 3 (6.4) | 0.678 |
| CAD, n (%) | 6 (18.8) | 6 (12.8) | 0.338 |
| CVA, n (%) | 2 (6.3) | 1 (2.1) | 0.358 |
| LVEF<50%, n (%) | 3 (9.4) | 7 (14.9) | 0.359 |
| eGFR (ml/min, mean ± SD) | 65.6±15.7 | 74.5±21.6 | 0.058 |
| Renal replacement therapy, n (%) | 1 (3.2) | 0 (0) | 0.397 |
| Etiology, n (%) | | | 0.004 |
| Acute dissection | 5 (15.6) | 19 (40.4) | |
| Chronic dissection | 5 (15.6) | 15 (31.9) | |
| IMH | 2 (6.3) | 0 (0) | |
| PAU | 1 (3.1) | 0 (0) | |
| Fusiform aneurysm | 14 (43.8) | 8 (17.0) | |
| Saccular aneurysm | 5 (15.6) | 5 (10.6) | |
| Maximum aortic diameter (mm, mean ± SD) | 57.5±10.4 | 52.8±1.76 | 0.185 |
| Emergency surgery, n (%) | 4 (12.5) | 18 (38.3) | 0.010 |
| Re-sternotomy, n (%) | 4 (12.5) | 9 (19.2) | 0.323 |
| Concomitant procedure, n (%) | | | |
| CABG | 7 (21.9) | 5 (10.6) | 0.148 |
| Valve surgery | 4 (12.5) | 10 (21.3) | 0.244 |
| Aortic root surgery | 2 (6.3) | 14 (29.8) | 0.009 |
| Operation time (min, mean ± SD) | 403.4±119.4 | 379.4±118.4 | 0.382 |
| CPB time (min, mean ± SD) | 262.1±52.4 | 237.6±83.5 | 0.192 |
| Aortic cross-clamp time (min, mean ± SD) | 154.3±57.1 | 141.5±58.9 | 0.398 |
| Lower body circulatory arrest time (min, mean ± SD) | 55.1±46.4 | 44.3±26.2 | 0.233 |
| Lowest body temperature (°C, mean ± SD) | 22.3±1.9 | 23.9±2.6 | 0.007 |
| Total length of stent graft (mm, mean ± SD) | 179.4±38.9 | - | - |
| CSF drainage, n (%) | 11 (36.7) | 1 (2.2) | <0.001 |
| Propensity score* (mean ± SD) | 0.62±0.27 | 0.24±0.23 | <0.001 |

**Abbreviations:** FET, Frozen elephant trunk technique; cTAR, Conventional total arch replacement; CAD, Coronary artery disease; CVA, Cerebrovascular accident; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; IMH, Intra-mural hematoma; PAU, Penetrating aortic ulcer; CABG, Coronary artery bypass grafting; CPB, Cardio-pulmonary bypass; CSF, Cerebrospinal fluid.
*A propensity score was calculated by age, sex, hypertension, current smoker, aortic etiology, emergency surgery, CSF drainage, and lowest body temp.
Statistically significant at $p<0.05$




FET, Frozen elephant trunk technique; cTAR, Conventional total arch replacement
P < 0.05: statistically significant different.

**Fig 1.** Kaplan-Meier for freedom from aortic-related death.




FET, Frozen elephant trunk technique; cTAR, Conventional total arch replacement
P < 0.05: statistically significant different.

**Fig 2.** Kaplan-Meier for freedom from aortic re-intervention.

remaining patients underwent open surgery. One patient in the FET group underwent re-intervention upon which TEVAR was performed due to type IB endoleak.

### Postoperative outcomes

Postoperative outcomes are summarized in Table 2. The incidence of stroke was similar in both groups, but paraplegia was significantly higher in the FET group. FET patients had a significantly increased risk of paraplegia by 21% when compared to cTAR (Risk difference +0.21, p=0.029) (Table 3). Of all 5 paraplegic patients in the FET group, 3 cases were undergoing pre-operative spinal drainage. And 2 cases were undergoing spinal drainage after the patients had post-operative paraplegic symptoms. Only 1 patient was fully recovering from paraplegia within 1 year after intensive re-habitation, and other patients demonstrated varying degrees of neurological improvement. The prognostic risk factors for postoperative paraplegia in the FET technique were explored and listed in Table 4. Furthermore, the incidence rate of recurrent laryngeal nerve (RLN) injury was comparable between the two groups.

## DISCUSSION

Open surgical repair has remained the gold standard for treating aortic arch pathology since 1975, following the publication of the case series by Griepp and colleagues.[11,12] The classic elephant trunk (ET) basic principle provides a length of tubing into the descending aorta to facilitate further distal aortic procedures. ET also facilitates and

**TABLE 2.** Post-operative outcomes.

| | FET (n = 32) | cTAR (n = 47) | P |
|---|---|---|---|
| Stroke, n (%) | 4 (13.8) | 6 (13.0) | 0.593 |
| Paraplegia, n (%) | 5 (17.2) | 0 (0) | 0.007 |
| AKI, n (%) | 14 (48.3) | 16 (34.8) | 0.179 |
| Need renal replacement therapy, n (%) | 2 (6.9) | 4 (8.7) | 0.573 |
| Tracheostomy, n (%) | 2 (7.1) | 2 (4.4) | 0.589 |
| Recurrent laryngeal nerve injury, n (%) | 0 (0) | 3 (6.5) | 0.234 |
| Re-operation due to bleeding, n (%) | 4 (13.8) | 8 (17.0) | 0.487 |

**Abbreviations:** FET, Frozen elephant trunk technique; cTAR, Conventional total arch replacement; AKI, Acute kidney injury.
Statistically significant at p<0.05

**TABLE 3.** Binomial (Risk) regression adjusted with propensity score for the adverse outcome of Frozen elephant trunk technique versus total arch replacement.

| | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | RD | p | 95% CI | RD | p | 95% CI |
| Stoke | -0.01 | 0.926 | -0.15, 0.16 | 0.11 | 0.350 | -0.12, 0.33 |
| **Paraplegia** | **0.17** | **0.015** | **0.03, 0.31** | **0.21** | **0.029** | **0.02, 0.40** |
| Re-op bleeding | -0.03 | 0.702 | -0.19, 0.13 | 0.12 | 0.432 | -0.18, 0.43 |
| New AKI | 0.13 | 0.246 | -0.09, 0.36 | 0.18 | 0.258 | -0.13, 0.50 |
| New RRT | -0.02 | 0.744 | -0.14, 0.11 | 0.07 | 0.596 | -0.19, 0.34 |
| Prolong ventilator | -0.09 | 0.371 | -0.29, 0.11 | -0.18 | 0.306 | -0.52, 0.16 |
| Tracheostomy | 0.03 | 0.625 | -0.08, 0.14 | 0.01 | 0.971 | -0.18, 0.19 |
| RLN injury | -0.06 | 0.075 | -0.13, 0.01 | -0.01 | 0.371 | -0.04, 0.02 |
| | **RR** | **p** | **95% CI** | **RR** | **p** | **95% CI** |
| Stoke | 1.05 | 0.926 | 0.32, 3.43 | 1.97 | 0.356 | 0.45, 8.41 |
| Paraplegia | - | - | - | - | - | - |
| Re-op bleeding | 0.81 | 0.710 | 0.26, 2.45 | 1.57 | 0.512 | 0.41, 6,09 |
| New AKI | 1.38 | 0.240 | 0.80, 2.39 | 1.39 | 0.286 | 0.75, 2.57 |
| New RRT | 0.79 | 0.781 | 0.15, 4.05 | 1.72 | 0.600 | 0.22, 13.29 |
| Prolong ventilator | 0.72 | 0.394 | 0.33, 1.54 | 0.70 | 0.442 | 0.28, 1.73 |
| Tracheostomy | 1.64 | 0.609 | 0.24, 11.01 | 1.37 | 0.789 | 0.13, 14.01 |
| RLN injury | - | - | - | - | - | - |

**Abbreviations:** RD; Risk difference, RR; Risk ratio, Re-op, Re-operation; AKI, Acute kidney injury; RRT, Renal replacement therapy; RLN, Recurrent laryngeal nerve.
Statistically significant at p<0.05

**TABLE 4.** Prognostic risk factor of paraplegia in frozen elephant trunk technique by logistic regression.

| | Univariable | | | Multivariable* | | |
|---|---|---|---|---|---|---|
| | OR | p | 95%CI | OR | p | 95%CI |
| Age >60 years | 4.23 | 0.207 | 0.45, 39.81 | 7.78 | 0.403 | 0.06, 957.9 |
| Male | 2.83 | 0.363 | 0.30, 26.64 | 0.67 | 0.836 | 0.02, 27.91 |
| LVEF <50 | 1.94 | 0.575 | 0.19, 19.55 | 1.58 | 0.510 | 0.06, 38.19 |
| Dissection cause | 0.47 | 0.426 | 0.07, 3.01 | 0.97 | 0.977 | 0.09, 10.87 |
| Aneurysm cause | 2.54 | 0.325 | 0.39, 16.20 | 1.04 | 0.977 | 0.09, 11.66 |
| Fusiform type | 1.92 | 0.492 | 0.29, 12.47 | 0.77 | 0.831 | 0.08, 7.83 |
| Saccular type | 1.93 | 0.575 | 0.19, 19.56 | 1.37 | 0.789 | 0.13, 14.37 |
| Aortic Diameter >50 mm | 0.71 | 0.726 | 0.11, 4.61 | 0.25 | 0.265 | 0.02, 2.89 |
| Re-sternotomy | 1.50 | 0.729 | 0.15, 14.83 | 1.43 | 0.762 | 0.14, 15.02 |
| Emergency operation | 1.67 | 0.591 | 0.26, 10.73 | 3.58 | 0.636 | 0.02, 70.82 |
| Pre-op spinal drainage | 1.47 | 0.740 | 0.14, 14.58 | 0.33 | 0.513 | 0.01, 9.06 |
| Aortic clamp >3 hours | 0.82 | 0.870 | 0.08, 8.06 | 0.31 | 0.572 | 0.01, 17.67 |
| Circulatory arrested >1 hours | 0.62 | 0.684 | 0.06, 6.02 | 0.27 | 0.613 | 0.01, 41.38 |
| Stent graft length >200 mm | 1.06 | 0.948 | 0.15, 7.54 | 0.47 | 0.699 | 0.01, 20.9 |

**Abbreviations:** OR; Odd ratio, LVEF; left ventricular ejection fraction, pre-op; Pre-operative.
*Multivariable was calculated in an exploratory model based on the risk factor of paraplegia including age, sex, type of emergency, aortic disease etiology, pre-operative spinal drainage, operative time, aortic clamp time, and length of the stent.
Statistically significant at $p < 0.05$

shortens clamping time during the second opening of the thoracoabdominal aortic surgery.[2,3] The FET technique was developed from ET by using a stent graft to replace the tubing graft in descending aorta.[13] In acute type A aortic dissection, FET is recommended for treating the entry tear in the distal arch or the proximal part of the descending aorta.[4] In acute and chronic type B aortic dissection when the endovascular repair is in the presence of an inadequate proximal landing zone, FET is the preferred procedure.[3,4]

In this study, the results showed that operative-related mortality was comparable between the FET and cTAR. Similar to Hirano, et al.[9] studied FET and cTAR and found that there was no difference in operative mortality between the two techniques (FET 5.3%, cTAR 2.6%, p=0.500). A meta-analysis by Preventza et al.[14] focused on the mortality rate in FET procedures in which overall mortality was 8.8%. Kremer, et al.[15] found that FET operative mortality was 13.2%, which was close to this study's aortic-related mortality result.

The FET was developed to decrease the incidence of re-operation, but FET still had occurrences of aortic reintervention. Ius F, et al.[16] found that at 1-, 5- and 10-year freedom from distal aortic re-operation were 81 ± 4, 67 ± 5, and 43 ± 13%, respectively for the FET procedure. Nonetheless, in this study, the aortic re-intervention rate was significantly lower in the FET group compared to the cTAR group. The difference in the pathology of aortic disease is also the factor in the difference in re-intervention. The patients who had aortic dissection had a high incidence of aortic reintervention.[4,13] Ius F, et al.[16] also found that chronic aortic dissection was identified as an independent risk factor for distal aortic operation (odds ratio (OR) = 3.8; 95% CI 1.5-9.3; p = 0.004). In this study, the cTAR might had a higher re-intervention rate because it had a higher incidence of aortic dissection.

Additionally, there was no significant difference in the incidence of stroke, acute kidney injury, and

re-operation due to postoperative bleeding. The meta-analysis by Preventza and colleagues[14] reported a 7.6% stroke rate, similar to another meta-analysis, which found no difference between FET and ET in the stroke (6.5% vs. 9.7%).

Even though there was no statistically significant difference, the result showed the incidence of RLN injury was low in the FET group (FET 0%, cTAR 6.5%). The most frequent distal aortic anastomosis site in this study was Ishimaru's zone 3 in cTAR and Ishimaru's zone 1 in FET. The difference in anastomosis site location may be the reason why the incidence of RLN injury was higher in the cTAR group. Similar to the previous study results by Hirano et al showed that recurrent nerve injury was low in the FET group (9.2%) compared with the cTAR group (25.6%).[9]

With an average stent length of 179.4 millimeters for FET in this study, FET patients had a significantly increased risk of paraplegia by 21% when compared to those who underwent cTAR. A meta-analysis study by Preventza, et al[14] showed that the overall rate of spinal cord ischemia was 7.6% with 95% CI 2.9% to 12.3%. They found that when the spinal cord coverage beyond T8 or stent length was more than 150 millimeters, patients had a higher incidence of spinal cord ischemia when compared to those with a stent length of 100 millimeters (11.6% vs 2.5%). Furthermore, Hirano et al[9] also found that chronic dissection or spinal drainage had high OR for paraplegia.

Several limitations in this study warrant mentioning. First, this study was a retrospective cohort study and there was heterogeneity in patient characteristics such as aorta pathology differences. However, statistical methods were used to correct this confounding factor and unequal baselines were adjusted to be properly statistically compared. In addition, the most frequent sites of distal aortic anastomosis in the FET group were in Ishimaru's zone 3. However, over the last two years, as the FET operative strategy evolved, a more simplified distal aortic anastomosis was performed at zone 2 or more proximally. Therefore, the outcomes of the FET group may differ from the initiation of the study to the present time.

## CONCLUSION

The FET technique had comparable early outcomes in terms of mortality, renal function, postoperative bleeding, and recurrent laryngeal nerve injury. However, the incidence of postoperative paraplegia increased. The FET technique had favorable outcomes that reduced the aortic re-intervention rate without increasing aortic-related death. Therefore, treatment methods and strategies should be carefully selected according to the patient's risk factors.

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## REFERENCES

1. Cekmecelioglu D, Coselli JS. Aortic arch repair with frozen elephant trunk versus conventional elephant trunk. Ann Cardiothorac Surg. 2020;9(3):223-5.
2. Czerny M, Schmidli J, Adler S, van den Berg JC, Bertoglio L, Carrel T, et al. Current options and recommendations for the treatment of thoracic aortic pathologies involving the aortic arch: an expert consensus document of the European Association for Cardio-Thoracic surgery (EACTS) and the European Society for Vascular Surgery (ESVS). Eur J Cardiothorac Surg. 2019; 55(1):133-62.
3. Di Bartolomeo R, Murana G, Di Marco L, Pantaleo A, Alfonsi J, Leone A, et al. Frozen versus conventional elephant trunk technique: application in clinical practice. Eur J Cardiothorac Surg. 2017;51(Suppl 1):i20-i8.
4. Uchida N, Shibamura H, Katayama A, Shimada N, Sutoh M, Ishihara H. Operative strategy for acute type a aortic dissection: ascending aortic or hemiarch versus total arch replacement with frozen elephant trunk. Ann Thorac Surg. 2009;87(3):773-7.
5. Nienaber CA, Kische S, Rousseau H, Eggebrecht H, Rehders TC, Kundt G, et al. Endovascular repair of type B aortic dissection: long-term results of the randomized investigation of stent grafts in aortic dissection trial. Circ Cardiovasc Interv. 2013;6(4): 407-16.
6. Poon SS, Theologou T, Harrington D, Kuduvalli M, Oo A, Field M. Hemiarch versus total aortic arch replacement in acute type A dissection: a systematic review and meta-analysis. Ann Cardiothorac Surg. 2016;5(3):156-73.
7. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(41):2873-926.
8. Tian DH, Ha H, Joshi Y, Yan TD. Long-term outcomes of the frozen elephant trunk procedure: a systematic review. Ann Cardiothorac Surg. 2020;9(3):144-51.
9. Hirano K, Tokui T, Nakamura B, Inoue R, Inagaki M, Hirano R, et al. Impact of the Frozen Elephant Trunk Technique on Total Aortic Arch Replacement. Ann Vasc Surg. 2020;65:206-16.
10. Shrestha M, Martens A, Kaufeld T, Beckmann E, Bertele S, Krueger H, et al. Single-centre experience with the frozen elephant

trunk technique in 251 patients over 15 years. Eur J Cardiothorac Surg. 2017;52(5):858-66.
11. Griepp RB, Stinson EB, Hollingsworth JF, Buehler D. Prosthetic replacement of the aortic arch. J Thorac Cardiovasc Surg. 1975; 70(6):1051-63.
12. Al Kindi AH, Al Kimyani N, Alameddine T, Al Abri Q, Balan B, Al Sabti H. "Open" approach to aortic arch aneurysm repair. J Saudi Heart Assoc. 2014;26(3):152-61.
13. Rylski B, Beyersdorf F, Desai ND, Euringer W, Siepe M, Kari FA, et al. Distal aortic reintervention after surgery for acute DeBakey type I or II aortic dissection: open versus endovascular repair. Eur J Cardiothorac Surg. 2015;48(2):258-63.
14. Preventza O, Liao JL, Olive JK, Simpson K, Critsinelis AC, Price MD, et al. Neurologic complications after the frozen elephant trunk procedure: A meta-analysis of more than 3000 patients. J Thorac Cardiovasc Surg. 2020;160(1):20-33.e4.
15. Kremer J, Preisner F, Dib B, Tochtermann U, Ruhparwar A, Karck M, et al. Aortic arch replacement with frozen elephant trunk technique - a single-center study. J Cardiothorac Surg. 2019; 14(1):147.
16. Ius F, Fleissner F, Pichlmaier M, Karck M, Martens A, Haverich A, et al. Total aortic arch replacement with the frozen elephant trunk technique: 10-year follow-up single-centre experience. Eur J Cardiothorac Surg. 2013;44(5):949-57.

# Occupational Post-exposure Prophylaxis after Blood and Body Fluids Exposure among Healthcare Workers in Siriraj Hospital

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## ABSTRACT

**Objective:** The present study aimed to describe the characteristics of occupational exposure to bloodborne pathogens and occupational post-exposure prophylaxis (oPEP) in Siriraj Hospital.

**Materials and Methods:** A descriptive, retrospective cohort study was performed of healthcare workers (HCWs) who had experienced occupational injury in Siriraj Hospital in 2015. Data were extracted from the hospital database.

**Results:** In total, 389 injury episodes were described; of which 293 (75.3%) involved female staff, and 112 (28.8%) involved nurses. The highest number of accidents (112, 28.8%) occurred in the operation room. Needlestick injury (210, 54%) was the most common injury.

Overall, 94 (24.1%) HCWs received oPEP; 67 (71.2%) events carried a risk of HIV acquisition, and in 27 (28.7%) cases, the patients decided to take oPEP. Common oPEP regimens were TDF/XTC/LPV/r (33, 35.1%) and TDF/XTC/RPV (32, 34%). Nearly half of the HCWs who received an LPV/r-based oPEP regimen had gastrointestinal intolerance and switched to second-line regimens. Among those who received oPEP, 52 (77.6%) returned at 1 month and 26 (38.8%) returned at 3 months after exposure for a serology test. There was no seroconversion in this cohort.

**Conclusion:** Occupational exposure to bloodborne pathogens is a common and increasing risk of infection among HCWs. oPEP with effective antiretroviral drugs within 72 hours after exposure is the main strategy for HIV prevention. The selection of an oPEP regimen with less toxic pills should be considered for efficacy, safety, and adherence. Interventions such as a tracking system or message reminders should be implemented to improve the follow-up rate among HCWs.

**Keywords:** Healthcare worker; Occupational post-exposure prophylaxis; antiretroviral drugs; HIV prevention (Siriraj Med J 2022; 74: 787-791)

## INTRODUCTION

Healthcare workers (HCWs) are at risk of blood or body fluids exposure through sharp and needlestick injuries or mucocutaneous exposure during patient care or waste disposal. Many pathogens can be transmitted via blood or body fluids. The most important bloodborne pathogens in healthcare settings are human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Exposure to blood or body fluids poses a risk of infection of these pathogens and psychological concerns after injury among HCWs.[1,2] In Thailand, the annual incidence of occupational blood and body fluid exposure was estimated to be 10.0–51.5 events per 100 HCWs during the period 1991–1997.[3-5]

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The uptake of antiretroviral drugs for occupational post-exposure prophylaxis (oPEP) not later than 72 hours after exposure has been shown to decrease the risk of HIV seroconversion since the early 2000s.[6,7] Since early 2000s, Centers for Disease Control (CDC) and the World Health Organization(WHO) published oPEP guidelines for healthcare settings, and these guidelines have been updated regularly based on the availability of recommended antiretroviral regimens for oPEP and follow-up schedules.[8,9] oPEP courses with highly effective, less toxic, combination pills and once daily dosing regimens are currently recommended worldwide to reduce risk of HIV acquisition after exposure to blood or body fluids.

Siriraj Hospital is a 2,300-bed university hospital in Bangkok, Thailand, that has more than 13,000 clinical staff and students. Despite training and implementing strategies to prevent HCWs from being exposed to bloodborne pathogens, occupational exposure to bloodborne pathogens are frequently reported among all levels of clinical staff and workers. This study aimed to describe the characteristics of the occupational exposure to blood or body fluids and post-exposure management in Siriraj Hospital.

## MATERIALS AND METHODS

### *Data collection*

A retrospective study was conducted among HCWs who experienced occupational exposure to blood and body fluids in Siriraj Hospital between January 1 and December 31, 2015. We excluded accidents that occurred outside Siriraj Hospital. The informed consent process was waived due to this being a retrospective study.

Data were abstracted from medical records and the occupational health registry. De-identified data, including age, sex, type of HCW; hospital unit; work shift; injury details; serologic status of HIV, HBV, and HCV of the exposed persons and sources; antiretroviral regimens for oPEP; adverse effects; and follow-up visit were recorded. High risk exposure is defined as a sharp, needlestick, non-intact skin or mucosal exposure to blood or body fluid of an HIV seropositive or suspected HIV source. oPEP is eligible when an accident is defined as carrying a high risk of HIV acquisition, the injured person presents no later than 72 hours and has negative HIV serostatus at baseline.

### *Statistical analysis*

Descriptive statistics were presented as a number and percentage for categorical variables and as the mean with standard deviation for continuous variables. All the statistical analyses were performed using the SPSS Statistics program, version 18.0.

**IRB / IEC Certification:** The study was conducted under the Siriraj Institutional Review Board's (SIRB) approval (Si 363/2016).

## RESULTS

A total of 389 episodes were reported over a 1-year period. The incidence of occupational injury was 7.5 episodes per week. The majority of the exposed HCWs were female (293, 75.3%). Nurses (112, 28.8%) were the most frequently exposed, followed by residents and fellows (101, 26%). The highest incidence occurred in the operation room (112, 28.8%). Needlestick injury (210, 54%) and exposure to blood (328, 84.3%) were the most common type of injury and exposed substance, respectively. The characteristics of the occupational exposures are shown in Table 1.

### *HCW serologic status*

All the HCWs were seronegative for HIV at baseline. Nine (2.3%) HCWs were seropositive for HBsAg. A total of 342 (87.9%) HCWs were considered immune to HBV (anti-HBs ≥ 10 mIU/mL). One HCW had HCV infection.

### *Source serologic status*

The sources known to be positive for HIV, HBV, and HCV numbered 39 (10%), 27 (6.9%), and 12 (3.1%), respectively. Sources with unknown HIV, HBV, and HCV status were 40 (10.3%), 59 (15.2%), and 57 (14.7%), respectively.

### *Post-exposure management*

Of the 389 episodes reported during the study period, 94 (24.2%) HCWs initiated oPEP; 24 (25.5%) discontinued oPEP earlier because of confirmation of an HIV-negative source, 3 (3.2%) were lost to follow-up before the completion of oPEP.

Of the 67 HCWs who received a 28-day course; 18 (25.7%) switched to second-line oPEP due to drug toxicities or exposure to drug-resistant HIV (15 gastrointestinal adverse effects; 1 hepatitis; 1 drug allergy; 1 exposed to an HIV-resistant source). Table 2 shows the oPEP regimens prescribed in this cohort. Fifty-two (77.6%) HCWs attended follow-up at 1 month and 26 (38.8%) attended follow-up at 3 months after exposure. There was no seroconversion in this study.

## DISCUSSION

Exposure to blood or body fluids is a common injury among healthcare workers and increases the risk of HIV, HBV, and HCV acquisition. Appropriate wound care, prompt risk identification, and the administration

**TABLE 1.** Demographic characteristics of 389 episodes of occupational exposure to bloodborne pathogens.

| Characteristics | Number (%) |
|---|---|
| Female | 293 (75.3%) |
| Mean age in years; mean (SD) | 27.8 (7.14) |
| **Personnel type** | |
| Nurse | 112 (28.8) |
| Resident and Fellow | 101 (26) |
| Medical student | 91 (23.4) |
| Nurse assistant | 29 (7.5) |
| Worker | 20 (5.1) |
| Attending physician | 17 (4.4) |
| Laboratory officer | 16 (4.1) |
| Nurse student | 3 (0.8) |
| **Location of injury** | |
| Operation room | 112 (28.7) |
| Inpatient ward | 97 (24.9) |
| Non-emergency outpatient unit | 54 (13.8) |
| Labor room | 48 (12.3) |
| Emergency room/Trauma | 40 (10.3) |
| Critical care unit | 16 (4.1) |
| Laboratory | 9 (2.3) |
| Other workplaces (waste management, laundry, sterilization unit) | 14 (3.6) |
| **Work shift** | |
| Morning | 241 (62.0) |
| Afternoon | 90 (23.1) |
| Night | 58 (14.9) |
| **Mechanism of injury** | |
| Needlestick injury | 210 (54) |
| Mucous membrane exposure | 102 (26.2) |
| Sharp injury | 48 (12.3) |
| Non-intact skin exposure | 17 (4.4) |
| Intact skin exposure | 12 (3.1) |
| **Exposure substance** | |
| Blood | 328 (84.3) |
| Potential infectious body fluids | 33 (8.5) |
| Non-infectious body fluids | 28 (7.2) |

**TABLE 2.** Initial prescribed oPEP regimens and switching oPEP regimens.

| Antiretroviral regimens for oPEP | Number (%) |
|---|---|
| **First oPEP regimens** | |
| TDF+XTC+LPV/r | 33 (35.1) |
| TDF+XTC+RPV | 32 (34.0) |
| TDF/FTC | 12 (12.7) |
| TDF+XTC+RAL | 12 (12.7) |
| TDF+XTC+ATV/r | 1 (1.1) |
| TDF+AZT+RAL | 1 (1.1) |
| TDF+RAL+DRV/r | 1 (1.1) |
| AZT+RAL+DRV/r | 1 (1.1) |
| 3TC+LPV/r | 1 (1.1) |
| **Second oPEP regimens** | |
| TDF+XTC+RAL | 8 (44.4) |
| TDF+XTC+RPV | 4 (22.2) |
| TDF+XTC+ATV/r | 3 (16.6) |
| TDF+XTC+LPV/r | 1 (5.6) |
| TDF+AZT+RAL | 1 (5.6) |
| TDF+RAL+DRV/r | 1 (5.6) |

**Abbreviations:** TDF, tenofovir disoproxil fumarate; XTC, lamivudine or emtricitabine; LPV/r, lopinavir/ritonavir; RPV, rilpivirine; FTC, emtricitabine; RAL, raltegravir; ATV/r, atazanavir/ritonavir; AZT, zidovudine; DRV/r, darunavir/ritonavir; 3TC, lamivudine

of post-exposure prophylaxis with an effective oPEP regimen in a timely manner are important measures to mitigate the risk of acquiring an infection.

The present study demonstrated a similar incidence of occupational exposure to blood or body fluids compared with other reported studies in Thailand.[3-5,10] Nurses and in-training physicians are at an increased risk of exposure due to their more frequent involvement in direct patient care and performing medical procedures. Medical students were the third most common personnel type at risk of exposure, possibly due to them practicing medical procedures while still having less experience. Needlestick injuries were more common than mucocutaneous exposure, which was similar to reported in other studies.[3,4,10-13] Several studies reported needle stick injuries occurred commonly among medical students during perineorrhaphy and reported time pressure and lack of skills as perceived causes.[14,15]

Recommended antiretroviral drugs for oPEP have changed over time in order to improve the efficacy to drug-resistant HIV, toxicities, and adherence. In early 2000s, overall adverse effects were reported between 64-76%.[16-18] The common prescribed drugs at that time were AZT, ritonavir-boosted nelfinavir or indinavir or lopinavir, which are not used as first-line drugs for HIV treatment and prevention due to their toxicities and pill burden. The overall adverse effects led to oPEP discontinuation in approximately 34% of cases in a study in Thailand[19], confirming that oPEP regimen selection with less toxic pills should be considered to improve tolerability and adherence. Currently, integrase inhibitor-based, rilpivirine-based, and DRV/r-based in combination with with tenofovir disoproxil fumarate or tenofovir alafenamide (TXF)/lamivudine or emtricitabine (XTC) are recommended for oPEP.[20,21] These regimens are potent, less adverse effects, less drug-drug interactions, and convenient compared to previous regimens and hence adherence improves.

Our study reported a poor follow-up rate (38.8%) at 3 months after exposure among those who were eligible for 28-day oPEP. Compared to another study from Thailand, the follow-up rates were higher than in our study, 89% at 6 weeks and 77% at 3 months, respectively.[10] However, we did not explore the reasons for the loss to follow-up. We did not have a tracking system or send reminders via a text message or phone call to HCWs. Thus, strategies to improve adherence, such as a tracking system or reminders, should be implemented as part of an occupational injury care system.

We also found that some HCWs in this study did not have immunity to HBV. In our hospital, pre-placement evaluation of HBV vaccine status and a quantitative anti-HBs antibody test are required for clinical staff. Nevertheless, some HCWs are employed as general workers but they have to work with medical instruments during disposal or waste management, which pose a risk of blood or body fluid exposure. The local pre-placement evaluation policy for HBV vaccine and immune status to HBV should be customized with details of the job description, not only the position.

This study has several limitations to note. First, some data that might affect the incidence, such as work experience and personal protective equipment use, were not recorded. Second, the incidence was probably underreported because we did not collect data from the central occurrence report system. Those who were exposed to a known negative source may not have visited the occupational clinic for a proper risk evaluation.

In conclusion, occupational exposure to blood and

body fluids is common and poses a risk of acquiring bloodborne pathogens among HCWs. Antiretroviral regimens with highly effective, less toxicity, combination pills that are applied in a timely manner can mitigate the risk of HIV infection and improve adherence to oPEP. Despite training and policy implementation on safety procedures to prevent injury, occupational exposure to bloodborne pathogens occurs frequently. A regular training program for common medical procedures and safety practices should be implemented for all HCWs that may be exposed to blood or body fluids. In addition, interventions such as a tracking system or message reminders should be further studied and implemented to improve the follow-up rate among HCWs.

**Conflict of interest:** The authors declares no conflict of interest.

## REFERENCES


1. Zhang MX, Yu Y. A study of the psychological impact of sharps injuries on health care workers in China. Am J Infect Control. 2013;41(2):186-7.
2. Lee JM, Botteman MF, Xanthakos N, Nicklasson L. Needlestick injuries in the United States. Epidemiologic, economic, and quality of life issues. AAOHN J. 2005;53(3):117-33.
3. Danchaivijitr S, Kachintorn K, Sangkard K. Needlesticks and cuts with sharp objects in Siriraj Hospital 1992. J Med Assoc Thai. 1995;78 Suppl 2:S108-11.
4. Pungpapong S, Phanuphak P, Pungpapong K, Ruxrungtham K. The risk of occupational HIV exposure among Thai healthcare workers. Southeast Asian J Trop Med Public Health. 1999;30(3): 496-503.
5. Hiransuthikul N, Tanthitippong A, Jiamjarasrangsi W. Occupational exposures among nurses and housekeeping personnel in King Chulalongkorn Memorial Hospital. J Med Assoc Thai. 2006;89 Suppl 3:S140-9.
6. Wnuk AM. Occupational exposure to HIV infection in health care workers. Med Sci Monit. 2003;9(5):CR197-200.
7. Cardo DM, Culver DH, Ciesielski CA, Srivastava PU, Marcus R, Abiteboul D, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group. N Engl J Med. 1997;337(21):1485-90.
8. Center for Disease Control. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. MMWR Recomm Rep. 2001;50(RR-11):1-52.
9. Occupational and non-occupational post-exposure prophylaxis for HIV infection (HIV-PEP): Joint ILO/WHO Technical Meeting for the Development of Policy and Guidelines: summary report2005. Available from: https://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/--ilo_aids/documents/publication/wcms_116563.pdf.
10. Chaiwarith R, Ngamsrikam T, Fupinwong S, Sirisanthana T. Occupational exposure to blood and body fluids among healthcare workers in a teaching hospital: an experience from northern Thailand. Jpn J Infect Dis. 2013;66(2):121-5.
11. Kiertiburanakul S, Wannaying B, Tonsuttakul S, Kehachindawat P, Apivanich S, Somsakul S, et al. Use of HIV Postexposure Prophylaxis in healthcare workers after occupational exposure: a Thai university hospital setting. J Med Assoc Thai. 2006;89(7): 974-8.
12. Wilburn SQ, Eijkemans G. Preventing needlestick injuries among healthcare workers: a WHO-ICN collaboration. Int J Occup Environ Health. 2004;10(4):451-6.
13. Frijstein G, Hortensius J, Zaaijer HL. Needlestick injuries and infectious patients in a major academic medical centre from 2003 to 2010. Neth J Med. 2011;69(10):465-8.
14. Liyanage IK, Caldera T, Rwma R, Liyange CK, De Silva P, Karunathilake IM. Sharps injuries among medical students in the Faculty of Medicine, Colombo, Sri Lanka. Int J Occup Med Environ Health. 2012;25(3):275-80.
15. Panichyawat N LT. The incidence of needlestick injuries during perineorrhaphy and attitudes toward occurrence reports among medical students. Siriraj Medical Journal. 2016;68:209-17.
16. Tetteh RA, Nartey ET, Lartey M, Mantel-Teeuwisse AK, Leufkens HG, Nortey PA, et al. Adverse events and adherence to HIV post-exposure prophylaxis: a cohort study at the Korle-Bu Teaching Hospital in Accra, Ghana. BMC Public Health. 2015;15:573.
17. Lee LM, Henderson DK. Tolerability of postexposure antiretroviral prophylaxis for occupational exposures to HIV. Drug Saf. 2001; 24(8):587-97.
18. Wang SA, Panlilio AL, Doi PA, White AD, Stek M, Jr., Saah A. Experience of healthcare workers taking postexposure prophylaxis after occupational HIV exposures: findings of the HIV Postexposure Prophylaxis Registry. Infect Control Hosp Epidemiol. 2000; 21(12):780-5.
19. Hiransuthikul N, Hiransuthikul P, Kanasuk Y. Human immunodeficiency virus postexposure prophylaxis for occupational exposure in a medical school hospital in Thailand. J Hosp Infect. 2007;67(4):344-9.
20. Ruxrungtham K CK, Chetchotisakd P, Chariyalertsak S, Kiertburanakul S, Putacharoen O, et al. Thailand National Guidelines on HIV/AIDS Treatment and Prevention 2021/2022. Nonthaburi: Division of AIDS and STIs, Department of Disease Control; 2022.
21. Cresswell F, Asanati K, Bhagani S, Boffito M, Delpech V, Ellis J, et al. UK guideline for the use of HIV post-exposure prophylaxis 2021. HIV Med. 2022;23(5):494-545.

# Untargeted Metabolomics Analysis using LC-MS-QTOF for Metabolite Profile Comparison between Patients with Myofascial Pain of Upper Trapezius Muscle versus Controls

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## ABSTRACT

**Objective:** This study aims to identify different biomarkers of Myofascial pain syndrome (MPS) using untargeted metabolomics screening.

**Materials and Methods:** In a case-control study, serum samples from MPS patients (n = 19) and healthy controls (n = 10) were analyzed using reverse-phase liquid chromatography and mass spectrometry quadrupole time-of-flight (MS-QTOF). The resulted raw data was processed with Progenesis QI data analysis software. The HMBD database was used to identify the metabolites based on their fold change (>1.2), variable importance plot (>1) with $P < 0.05$. MetaboAnalyst 5.0 was used to generate metabolic network analysis for all identified metabolites.

**Results:** The MPS group reported significantly higher pain on visual analog scale when compared with control while most of the other routine blood chemical profiles were not different. Twenty-seven metabolites were analyzed and identified with untargeted metabolomics analysis which could distinguish MPS patients from healthy controls. Inosine and chenodeoxycholic acid were abundant in the MPS group, whereas the others were low. Metabolites were divided into three categories: lipids, nucleotides, and organic compounds. Possible MPS metabolites included lysoSM (sphingomyelin), lysoPC (lysophosphatidylcholine), lysoPE (lysophosphatidylethanolamine), triglyceride, and inosine.

**Conclusion:** These metabolite profiles, including glycerophospholipids mechanism and purine metabolism, indicate that the inflammatory process might be related to the mechanisms of MPS. A larger sample size, a different trigger point location, and modifications in therapy afterward should all be further explored.

**Keywords:** Myofascial pain; trigger point; metabolomics; untargeted metabolomics; mass spectrometry (Siriraj Med J 2022; 74: 792-803)

## INTRODUCTION

Myofascial pain syndrome (MPS) is a type of musculoskeletal discomfort that is a widespread health issue and a cause of employee sick leave.[1] The prevalence of MPS is approximately 85% of the population. A clinical characteristic of MPS is the appearance of myofascial trigger points (TrPs). Trigger point is a hyperirritable muscular region accompanied by a sensitively detectable nodule in a taut band. The diagnostic criteria for identifying TrPs

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are a taut band, a hypersensitive area, and referred pain.[2] Trigger point also can cause spontaneous pain, referred pain, fatigue, reduced range of motion, and autonomic dysfunction, such as sweating or piloerection.[3,4] Trigger point can form in a variety of locations throughout the body. The neck and shoulder are the most prevalent sites for TrPs. In a previous study, TrPs of the upper trapezius muscles were observed in more than 80% of chronic nonspecific neck pain patients.[5] Trigger point could be triggered by overuse, muscle trauma, or psychological stress. The most typical causes include poor ergonomics, improper postural alignment, and continuous repetition of daily activities.[6] However, the initiation of TrPs remains unclear.

The mechanism of MPS and the pathogenesis of TrPs are not completely understood. In the TrP region, hypercontracture of the sarcomere was discovered.[6,7] Ultrasound techniques can also be used to determine anatomical and physiological changes relating to TrPs. In the non-TrP region, the tissue echo strength is the same as the surrounding structures or tissues. The TrP region shows solid tissue and a reduction in blood flow. It revealed a localized stiffness region of TrPs.[8] According to the integrated theory, it originated with excessive acetylcholine release from the motor endplate.[9] Increased acetylcholine release results in metabolic stress and an energy crisis. A deficit of energy causes longer sarcomeres to shorten, reducing blood and oxygen supply.[6] In addition, local hypoxia produces physiological abnormalities and cell stress; myokines, inflammatory cytokines, and neurotransmitters, such as bradykinin, substance P, tumor necrosis factor α, interleukin 1β (IL-1β), interleukin 6, serotonin, and norepinephrine, are produced.[10-12] The release of biochemical substances produces pain-activating nociceptors and alters autonomic regulation. This change produces tissue sensitivity and contributes to the persistence of the TrPs and MPS.[6]

Metabolomics is an omics analytical technique that identifies thousands of low-molecular-weight compounds using high-throughput technology.[13] It can be used for detecting metabolites representing human phenotypes in normal and pathological states and also suggesting the pathophysiological processes. It is widely used to identify biomarkers in biological samples that are relevant to disease biomarkers, pharmaceutical development, nutrition, and physiological process. Biomarkers illustrate why disease risk factors and etiologies have changed.[14] The mapping of biomarkers in the metabolic pathway enables diseases to be addressed.[15] Previous studies have found systemic changes in the metabolite profiles of patients suffering from nonspecific neck-shoulder pain and chronic widespread pain. Several metabolite changes suggest the relation with lipid metabolism and energy consumption.[16] Because there is no solid evidence of MPS pathogenesis, untargeted metabolomics research was performed to discover different metabolites of MPS. The objectives of this study are to (1) investigate possible differences in metabolomics profiles between MPS patients and a control group, and (2) analyze the pathways associated with MPS patients. It could be used to explore alterations in a variety of biochemical pathways, as well as to understand further about pathophysiology and treatments.

## MATERIALS AND METHODS

### Subjects

Twenty-nine subjects aged between 18 and 65 years were recruited at Siriraj Hospital, Bangkok, Thailand (10 control subjects and 19 MPS patients). The MPS group was recruited based on the diagnosis with myofascial pain of the upper trapezius muscle.[4] The followings criteria were considered for the MPS to be eligible for the study:

- Severity of pain greater than 40 on a visual analog scale for at least 3 months
- Presence of at least 1 TrP in the upper trapezius muscle identified by palpation that included palpable taut bands with local hypersensitivity and referral pain

Patients with other musculoskeletal diseases, tumors, psychological problems, metabolic diseases, pregnancy or lactation, previous neck or shoulder pain therapies or medicine, history of alcohol abuse and smoking, and abnormal liver or renal function at the time of screening were all excluded from the study. Healthy control subjects were non-MPS with the same exclusion criteria as those of the MPS group.

The study was approved by the Siriraj Institutional Review Board at Faculty of Medicine Siriraj Hospital, Mahidol University (Si259/2017).

### Sample collection

Fasting blood samples were collected between 7 and 9 am to reduce variation in sample collection. Basal clinical laboratory profiles were assessed by central laboratory of the Siriraj Hospital. For metabolomics analysis, the blood was obtained in BD Vacutainer serum blood collection tubes (Becton Dickinson, Franklin Lakes, New Jersey) to initiate clotting. After centrifugation for 10 minutes at 4,500g at 4°C, the supernatant was collected, aliquoted, and kept at −80°C until analysis. The sample collection was performed in accordance with good clinical practice, which included ethical and safety considerations.

**Sample preparation for metobolomics analysis**

The MPS and healthy control samples were analyzed in random order. The protocol was modified from a previous study for metabolic profiling of serum using LCMS.[17] Serum samples were retrieved from the –80°C freezer and allowed to thaw on ice. After that, 50 µL of 1 ng/µL mixed internal standard solution (l-phenylalanine [13CC8H11N1O2], caffeine [13CC7H10N4O2], cholic acid [D4C24H36O5]) was added to a 200 µL serum sample. Serum samples were extracted by adding 600 µL of methanol. The samples were continuously mixed at 4°C for 15 minutes at 2000 revolutions per minute using a Multitube vortexer (BenchMixer; Benchmark Scientific Inc, Sayreville, New Jersey) and then frozen for 1 hour at –80°C. The samples were then centrifuged for 15 minutes at 4°C at 15,800g. Then, the supernatant was collected and dried in a speed vac (CentriVap Mobile System Console, Labconco, USA) for 300 mins at 30°C. After completely dry, samples were store at -80°C for analysis.

Quality control samples were utilized in the study to examine technical stability and repeatability. For quality control, 29 serum samples were pooled and extracted using the same methods as the individual samples.

**Liquid chromatography and mass spectrometry quadrupole time-of-flight analysis**

On the day of analysis, dried samples were reconstituted with 100 µL of water and shaken at 2000 revolutions per minute for 10 minutes at 4°C. The samples were centrifuged for 10 minutes at 4°C at 15,800g. The supernatant was transferred to a total recovery vial (Waters Corp, Milford, Massachusetts). Extracted serum samples were maintained the temperature at 4°C during analysis.

Extracted serum samples were analyzed using ultraperformance liquid chromatography system (Waters Corp, Wilmslow, United Kingdom) coupled with Synapt G2-Si QTOF mass spectrometer (Quadrupole Time-of-Flight; Waters Corp). The ultraperformance liquid chromatography system was performed using an Acquity HSS T3 column with a 100-mm length 2.1-mm internal diameter and 1.8 microns in particle size. The protocol for LCMS-QTOF analysis was modified from a previous study.[17] The temperatures in the column and sample manager were 40°C and 4°C, respectively. The gradient elution was mobile phases A1 and B1 at a flow rate of 0.4 mL/min. In the mobile phase, solvents A and B were 0.1% formic acid in water (vol/vol) and 0.1% formic acid in MeOH (vol/vol), respectively. The elution gradient was as follows: initial conditions at 100% A1; from 1 to 16 minutes, increased to 100% B1; from 16 to 20 minutes, maintained at 100% B1; from 20 to 22 minutes, increased to 100% A1; and from 22 to 24 minutes, maintained at 100% A1.

For mass spectrometer, the instrument was used in resolution mode with the MSe data acquisition function with electrospray ionization in positive and negative ion modes. The parent ion's trap collision energy was 6 electron volts (eV), whereas the fragmentation's ramp trap collision energy was 15 to 40 eV. The capillary voltage was set to 3 kV, whereas the sampling cone voltage was set to 40 V. The desolvation gas temperature was set at 500°C, with the source temperature set at 150°C. The desolvation gas flow rate was set at 1000 L/h, whereas the cone gas flow rate was set at 50 L/h.

**Biomarker identification and pathway analysis**

Progenesis QI data analysis software (Nonlinear Dynamics, Newcastle, United Kingdom) was used to import and process the raw data. A search of the Human Metabolomics Database, HMDB 5.0 (https://hmdb.ca) was used to identify compounds. MetaboAnalyst 5.0 (www.metaboanalyst.ca) was used to perform metabolic network analysis on all chemical identifications.

Progenesis QI data analysis software (Nonlinear Dynamics, Newcastle, UK) was used to import and process the raw data. All of the samples were aligned to ensure that retention duration, mass measurements, isotopic composition, and fragmentation were all correct. The experiment comprised a between-subject design with an unpaired T-test for the different groups (CON versus MPS). The following criteria were used to select compounds: p-value < 0.05, fold change between two groups >1.2. The significant metabolites were selected.

Multivariate Analysis (MVA) and Univariate Analysis were used to examine all chemical values in normalized compound abundances (UVA). The scale was Pareto for principal component analysis (PCA) and orthogonal partial least-square discriminant analysis (OPLS-DA). S-plots were used to filter metabolites biomarkers when p (1) and p (corr) (1) from the OPLS-DA model were > ±0.04. The variable importance plot (VIP) > 1 was chosen. After matched the significant metabolites with selection biomarkers from S-plot. The metabolites biomarkers were searched from the online Human Metabolomics Database (HMDB 5.0). The precursor tolerance and fragmentation tolerance were both set to 20 ppm, with a retention time of less than 0.1 minute. When the isotope similarity was greater than 70%, the identification was confirmed.

MetaboAnalyst 5.0 (www.metaboanalyst.ca) was used to perform metabolic network analysis on all chemical identifications. Significant pathways had a p-value less than 0.05 and impact more than 0.05.

### Statistical analysis

The metabolite profile was assessed using Multivariate Analysis and Univariate Analysis, as previously described. All demographic and other parameters were evaluated using SPSS software (PASW version 18; IBM Corp, Chicago, Illinois). To test the normalization of data distribution, the Shapiro-Wilk test was performed. An unpaired t test or Chi-square was used to compute the differences between groups. $P < 0.05$ was considered statistically significant.

## RESULTS

### Subject demographics and clinical profiles

The demographic parameters and blood chemical profiles of the subjects under study are shown in Table 1. Subject characteristics differed between MPS and healthy controls in age and gender, but not in body mass index. Myofascial pain syndrome and healthy controls had significantly different pain intensity and pain duration. Most of the blood profiles were not different between groups. Creatinine in the MPS group was significantly lower than that of the healthy control group ($P = 0.015$). Multiple linear regression was used to adjust for age and gender, and the results revealed that there is no association between biomarkers and these variables ($P = 0.573$ for age, $P = 0.393$ for sex).

**TABLE 1.** Demographic and Clinical Characteristics of the Study Population.

| Characteristics | Healthy controls (CON) | Myofascial pain syndrome (MPS) | *P*-value |
|---|---|---|---|
| Number of subjects | 10 | 19 | - |
| Male/female (%) | 30/70 | 0/100 | 0.033# |
| Age (years) | 26.90 (3.45) | 33.89 (8.80) | 0.005* |
| Body mass index (kg/m$^2$) | 22.04 (2.14) | 21.46 (3.22) | 0.612 |
| **Pain parameter** | | | |
| Visual analog score | 0 | 49.55 (11.40) | <0.001* |
| Pain duration (months) | 0 | 5.53 (2.51) | <0.001* |
| **Blood chemical profiles** | | | |
| Aspartate aminotransferase (U/L) | 17.20 (3.97) | 18.77 (8.04) | 0.567 |
| Alanine aminotransferase (U/L) | 16.96 (11.52) | 17.61 (12.10) | 0.890 |
| Alkaline phosphatase (U/L) | 58.22 (9.54) | 58.13 (18.33) | 0.988 |
| Albumin (g/dL) | 4.64 (0.17) | 4.58 (0.21) | 0.458 |
| Blood urea nitrogen (mg/dL) | 10.50 (2.16) | 9.60 (1.83) | 0.244 |
| Creatinine (mg/dL) | 0.81 (0.14) | 0.69 (0.10) | 0.015* |
| Glucose (mg/dL) | 89.82 (5.65) | 88.41 (6.28) | 0.558 |
| Triglyceride (mg/dL) | 64.41 (19.91) | 80.52 (50.80) | 0.347 |
| High-density lipoprotein-cholesterol (mg/dL) | 64.55 (16.82) | 66.01 (15.44) | 0.816 |
| Cholesterol (mg/dL) | 175.91 (19.93) | 175.68 (25.55) | 0.981 |
| Creatine kinase (U/L) | 104.20 (45.50) | 81.79 (43.40) | 0.204 |
| Mb isoenzyme of creatine kinase (ng/mL) | 1.10 (0.49) | 1.10 (0.41) | 0.985 |
| Lactate (mmol/L) | 1.16 (0.76) | 1.06 (0.59) | 0.689 |

Data are presented with mean (SD) unless otherwise noted.
*Significant $P < 0.05$ with unpaired *t* test.
#Significant $P < 0.05$ with $\chi^2$.

**Metabolomics differences between MPS and healthy control subjects**

A data matrix of 19,643 peak compounds was obtained after alignment and filtering processes. A clustering of samples was observed using MVA. PCA was employed to summarize data and present an overview of each sample, each plot on the PCA represents a sample. The OPLS-DA approach was utilized to compare two groups, In the OPLS-DA model, the x-axis represented a score scatter plot. The horizontal direction of the provided score scatter plot represents group variation. The principal component analysis score plot was unable to differentiate between MPS and healthy control groups (Figs 1A, B). The metabolomics data were analyzed using supervised MVA and visualized with OPLS-DA. The OPLS-DA revealed that MPS and healthy controls could be differentiated (Figs 1C, D). S-plots were generated from the OPLS-DA model to visualize the distance between differential metabolites (Figs 1E, F).

A total of 40 metabolites were investigated as possible biomarkers. Twenty-seven metabolites were analyzed and identified using HMDB to differentiate individuals with MPS from healthy controls (Table 2). In the MPS group, inosine and chenodeoxycholic acid were highly abundant, whereas the others were lower.

The hierarchical clustering and heat maps of the 27 metabolites were different in their peak intensity between healthy controls and MPS (Fig 2). The heat map displays the relative abundance of each identified compound in each sample. The association between samples represented by the color and horizontal dendrogram. It splits samples into two primary groups, with the left showing high intensity of metabolites or mean increase metabolites that were largely associated to the CON group, and the

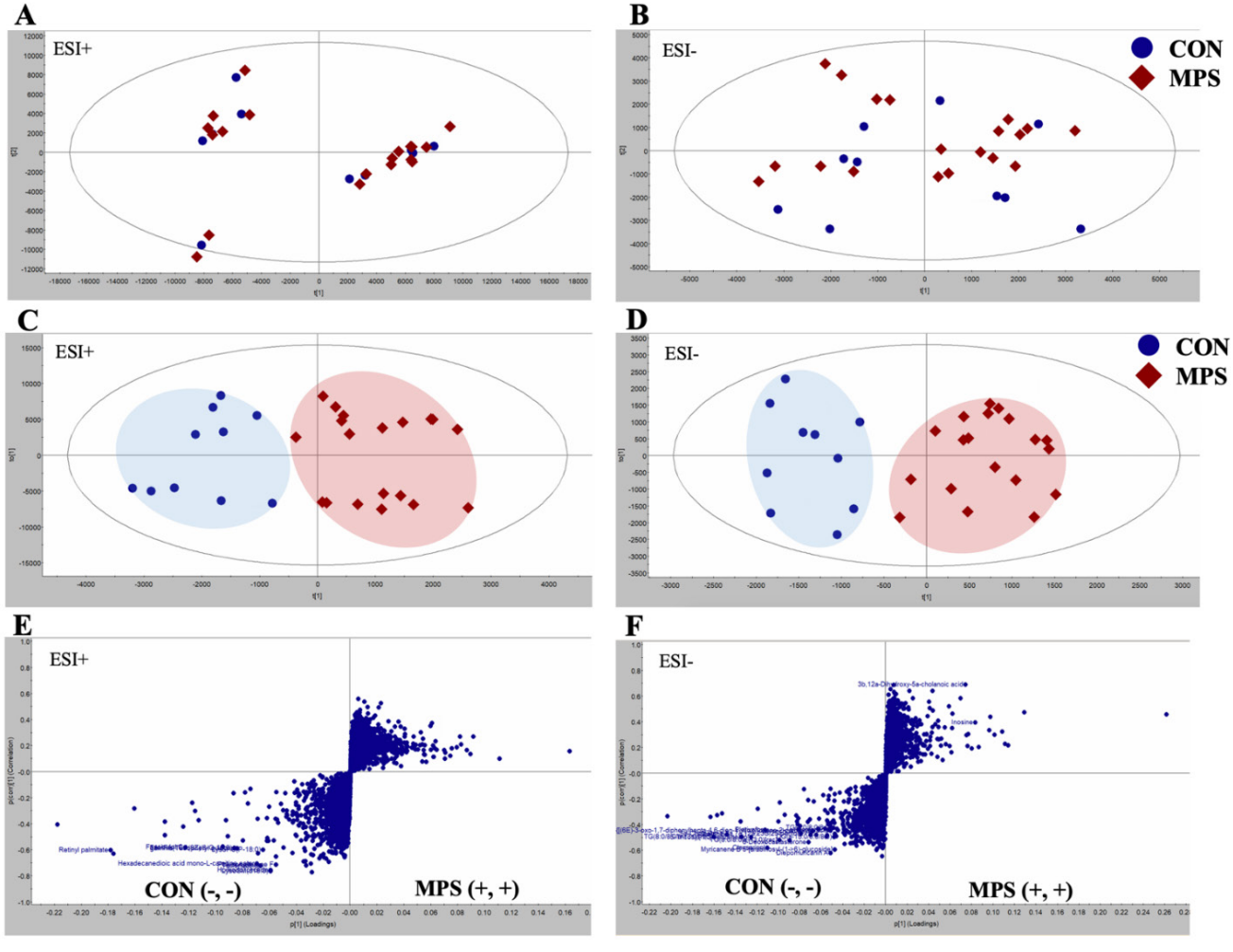


**Fig 1.** Multivariate analysis for the myofascial pain syndrome (MPS) patient group differentiates from the healthy control group based on all detected metabolites. A and B, Principal component analysis score plot of (A) positive and (B) negative electrospray ionization (ESI) modes. C and D, Orthogonal partial least-squares discriminant analysis score plot of (C) positive and (D) negative ESI modes. Healthy control group (CON, blue dots). Myofascial pain syndrome group (red diamonds). E and F, S-plot of (E) positive and (F) negative ESI modes. In positive and negative ESI, the dependent variables ($Y$) were $R^2 = 0.849$, $Q^2 = -0.058$ and $R^2 = 0.796$, $Q^2 = 0.381$, respectively. The model had a moderate prediction accuracy, and the negative value of $Q^2$ prevented overfitting. It was also stable and reliable.

**TABLE 2.** Untargeted liquid chromatography and mass spectrometry indicating significant differences in metabolites between MPS patients and healthy controls.

| Metabolite identification | m/z | *P*-value | Fold change | Trend in MPS | Metabolite class |
|---|---|---|---|---|---|
| Inosine | 267.0719 | 0.039 | 1.73 | Up | Purine nucleosides |
| Chenodeoxycholic acid | 391.2828 | 0.007 | 2.05 | Up | Steroids and steroid derivatives |
| Sunitinib | 397.2034 | 0.017 | 1.63 | Down | Organoheterocyclic compounds |
| Clausarinol | 413.1984 | 0.003 | 1.67 | Down | Coumarins and derivatives |
| Momordol | 421.3355 | 0.039 | 1.3 | Down | Fatty Acyls |
| gamma-Tocopheryl quinone | 433.3663 | 0.029 | 1.31 | Down | Prenol lipids |
| 3,4,5-trihydroxy-6-{[(6E)-3-oxo-1,7-diphenylhepta-4,6-dien-1-yl]oxy} oxane-2-carboxylic acid | 435.1444 | 0.036 | 1.34 | Down | Phenylpropanoids and polyketides |
| DG(8:0/15:0/0:0) | 441.3553 | 0.042 | 1.47 | Down | Glycerolipids |
| Trihydroxycoprostanoic acid | 447.344 | 0.046 | 1.2 | Down | Steroids and steroid derivatives |
| 6-Deoxocastasterone | 449.3617 | 0.022 | 1.37 | Down | Steroids and steroid derivatives |
| 5b-Cholestane-3a,7a,12a,23S,25-pentol | 451.3413 | 0.036 | 1.33 | Down | Steroids and steroid derivatives |
| Polyporusterone F | 463.3357 | 0.024 | 1.28 | Down | Steroids and steroid derivatives |
| 5-Tricosyl-1,3-benzenediol | 467.3707 | 0.014 | 1.29 | Down | Phenols |
| TG(8:0/8:0/8:0) | 469.352 | 0.039 | 1.2 | Down | Glycerolipids |
| Cholestane-3,7,12,24,25-pentol | 475.3364 | 0.018 | 1.31 | Down | Steroids and steroid derivatives |
| LysoSM(d18:0) | 489.3488 | 0.016 | 1.37 | Down | Sphingolipids |
| LysoSM(d18:0) | 489.3518 | 0.017 | 1.3 | Down | Sphingolipids |
| Fasciculol C | 491.3678 | 0.025 | 1.26 | Down | Prenol lipids |
| LysoPE(0:0/20:4(5Z,8Z,11Z,14Z)) | 500.2784 | 0.041 | 1.22 | Down | Glycerophospholipids |
| LysoPC(P-18:0) | 508.3731 | 0.037 | 1.28 | Down | Glycerophospholipids |
| TG(8:0/8:0/13:0) | 521.4131 | 0.01 | 1.34 | Down | Glycerolipids |
| Plerixafor | 537.4156 | 0.024 | 1.39 | Down | Benzene and substituted derivatives |
| TG(13:0/8:0/8:0) | 539.4305 | 0.022 | 1.43 | Down | Glycerolipids |
| FAHFA(16:1(9Z)/8-O-18:0) | 559.466 | 0.043 | 1.43 | Down | Fatty Acyls |
| TG(8:0/8:0/a-13:0)[rac] | 563.4279 | 0.034 | 1.4 | Down | Glycerolipids |
| Diepomuricanin A | 581.4449 | 0.002 | 1.25 | Down | Fatty Acyls |
| Myricanene B 5-[arabinosyl-(1->6) -glucoside] | 615.2468 | 0.002 | 1.39 | Down | Phenylpropanoids and polyketides |

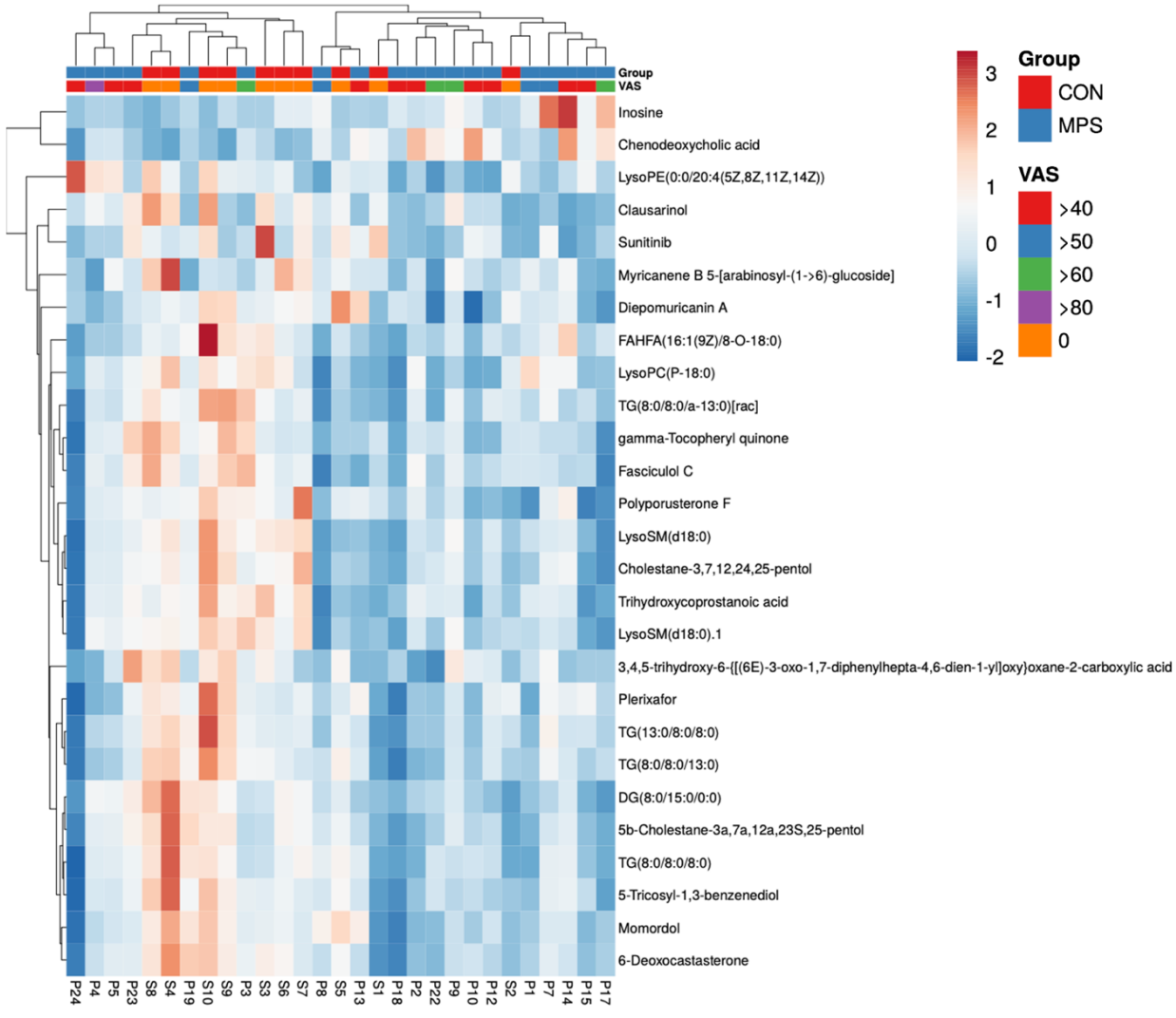


**Fig 2.** Heat maps of the significantly different metabolites between the healthy control (CON) (n = 10) and myofascial pain syndrome (n = 19) groups. *X* axis represents individual samples. *Y* axis represents 27 metabolites. Red represents high normalized intensity, and blue represents low normalized intensity of the metabolite. Color bars on *X* axis show visual analog scale (VAS) score.

right showing low intensity or decrease metabolites that were mostly related to the MPS group. The color bars representing each subject's VAS score were mapped to the X-axis. A horizontal dendrogram and a VAS scale were used to investigate the relationship between two groups. The VAS scale had a range of >40 to >80. In the MPS group, pain severity may be related to increased metabolite intensity. Vertical dendrograms indicated a relationship between compounds that our results could not be observed.

There were significant differences in the amount of possible biomarker metabolites that were linked to the MPS mechanism when comparing the MPS group with the control group as shown in Fig 3. Using MetaboAnalyst 5.0, the metabolites revealed MPS-related pathways, including glycerophospholipids mechanism, primary bile acid biosynthesis, and purine metabolism (Fig 4).

## DISCUSSION

Mechanism of MPS is not well understood. This study used the untargeted metabolomics analysis with liquid chromatography and mass spectrometry quadrupole time-of-flight to identify possible biomarkers of MPS of the upper trapezius muscle in a case-control study. Nineteen subjects with chronic MPS of upper trapezius muscle for at least 3 months were recruited. All subjects have an average pain intensity of 50 on the visual analog scale, whereas there was no pain in the control groups. All MPS subjects were female of the young-adult group (average age, 33 years), which was the common age group for MPS.[18] The control groups were mostly female (70%) with lower average age than the MPS group. The baseline clinical laboratory profiles were within reference range and mostly similar between the two groups except the creatinine, which was lower in the MPS group.

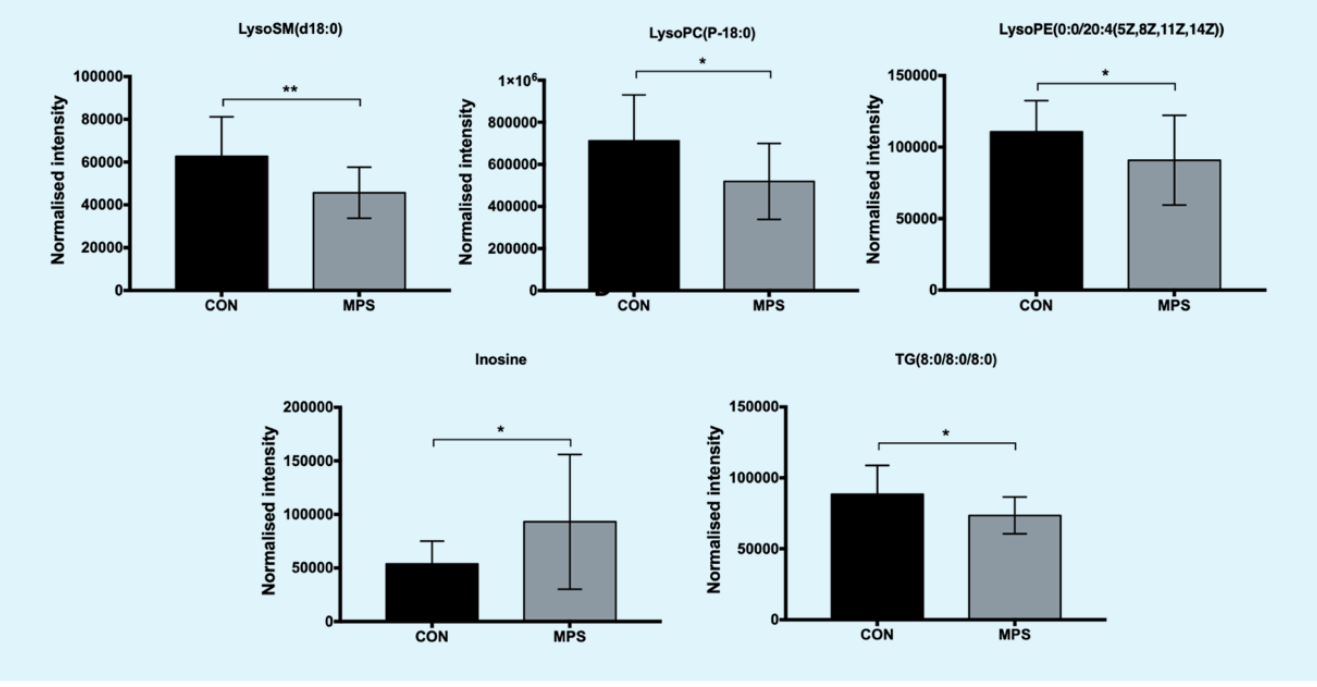


**Fig 3.** Significant differences in the amount of possible biomarker metabolites in the myofascial pain syndrome group (MPS) compared with the control group (CON) (*$P < 0.05$ and **$P < 0.01$).

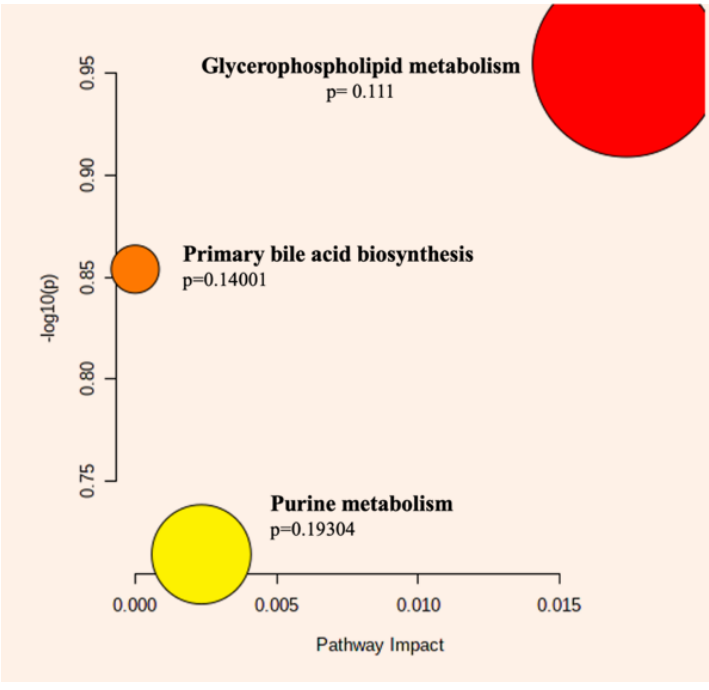


**Fig 4.** Pathways involving 27 metabolites that distinguish MPS patients from healthy controls were identified. Metabo Analyst 5.0 was used to create the plot. The *x* axis shows impact of the discovered metabolites on the indicated pathway. The *y* axis shows relatively abundant discovered metabolites are in the designated pathway. The significance of pathway enrichment is shown by the color of the circles. The size of the circle shows the pathway's impact.

Disease status is pathogenic and manifests characteristics that can be identified through biomarkers. As a result, metabolomics is a clinical research tool that may detect components in health or disease in order to understand the mechanism. It can map the metabolites associated with pathologies along the metabolic pathway. In this study, the possible metabolites involved mainly in glycerophospholipid metabolism and purine metabolism differed between healthy subjects and MPS patients. The metabolism of glycerophospholipids is linked to the structure of the cell membrane.[19,20] Metabolites linked to glycerophospholipid metabolism in MPS include lysoSM (sphingomyelin), lysoPC (lysophosphatidylcholine), lysoPE (lysophosphatidylethanolamine), and triglyceride (TG). Purine metabolism has an impact on all living organisms because it produces components for DNA and RNA.[21,22] Metabolite linked to purine metabolism in MPS is inosine.

The study discovered a decrease in lysoSM in MPS patients. LysoSM is involved in signal transduction of the axon nerve. It is a type of sphingolipid that helps to regulate immune cell function during inflammation.[23] Sphingomyelin is regulated by a protein called sphingomyelinase, which breaks down sphingomyelin into ceramide. Ceramide and sphingomyelinase play a role in the enhancement of proinflammatory cytokines, which cause inflammation.[24] Sphingolipids involved in sphingomyelin-ceramide metabolism were shown to be higher in chronic neuropathic pain patients.[25] Ceramide levels and sphingomyelin degradation both increased. The level of sphingomyelin may be affected by the upstream pathway. Total ceramides were also found to be lower in individuals with episodic migraine compared with controls, whereas sphingomyelin species were higher.[26] In patients with nociceptive and neuropathic pain, sphingomyelin and lipid metabolites were altered.[27,28] The decrease in lysoSM could be due to the conversion of sphingomyelin to ceramides, including this study. As a result, a rise in ceramide causes an increase in inflammation. It can lead to pain-related peripheral and central sensitization in MPS patients.

In MPS patients, we discovered a reduction in lysoPC and lysoPE. LysoPC is a lipid signaling molecule that interacts with lysophospholipid receptors.[29] LysoPC and lysoPE are involved in the inflammatory response.[30] A previous study found that, after medication therapy, lysoPC levels increased in arthritis knee patients. An elevation in LysoPC can exacerbate the inflammatory response.[31] LysoPC levels were shown to be higher in fibromyalgia patients in a previous metabolomic investigation. It was hypothesized that it possessed proinflammatory compounds and produced reactive oxygen species, which were linked to fibromyalgia pathogenesis.[32] LysoPC could be used as a fibromyalgia biomarker. It works by causing the release of proinflammatory cytokines including tumor necrosis factor α and IL-1b through the platelet-activating factor receptor. In fibromyalgia, LysoPC may play a role in allodynia and atypical pain.[33] The decreases in lysoPC and lysoPE were similar to those seen in migraine patients in a previous study. In migraine patients, lysoPC and lysoPE concentrations were lower. The decrease in lysoPC and lysoPE was thought to be linked to a reactive oxidant species imbalance. In migraine, oxidants can activate phospholipase $A_2$, which can affect the production of lysoPC and lysoPE. They have been suggested as migraine biomarkers.[34] Furthermore, the decrease in lysoPC could be due to the conversion of lysophosphatidic acid via autotaxin. Lysophosphatidic acid can cause descending pain inhibition.[35] The drop in lysoPE could be due to a drop in phosphatidylethanolamines, which would result in a drop in endocannabinoids. As a result, pain inhibition is reduced.[36] As a conclusion, the pathophysiology of pain in MPS patients may be explained by a decrease in lysoPC and lysoPE.

In MPS patients, we discovered a reduction in TG. Triglyceride is a kind of triacylglycerol that has a role in the inflammatory process.[37] Inflammatory macrophage function is regulated by TG synthesis, which results in the release of proinflammatory mediators such as IL-1, IL-6, and prostaglandin $E_2$. The suppression of the TG metabolite is a marker of anti-inflammation and a therapy target.[38] Triglyceride levels were shown to be higher in patients with peripheral and central sensitization in a previous study.[39] Phosphatidylcholine levels can impact TG storage.[40] Because lysoPC levels were found to be lower in MPS patients, lipid products and TG levels may also be lower. As a result, the level of lipid metabolites may be linked to MPS, and therefore more investigation is necessary.

In MPS patients, we discovered an increase in inosine. Inosine is a component of the purinergic system. Adenosine is transformed into inosine. Adenosine is phosphorylated again to form adenosine monophosphate. Adenosine monophosphate is transformed to adenosine triphosphate, which is the primary source of energy in cells.[41] Neuroprotective, cardioprotective, and cytoprotective properties of adenosine have been reported.[42] In tissue damage and muscle injury, adenosine has been shown to suppress the release of proinflammatory cytokines. Antinociception is a property of adenosine. It affected pain behavior and pain modulation by adenosine receptors, as shown in a previous study.[43] This study found a significant elevation in inosine, which was consistent with the previous report in fibromyalgia patients.[44] The rise in inosine is due to adenosine conversion. Increased inflammatory mediators and pain sensitivity are caused by a decrease in adenosine.[41,45] In chronic myofascial pain, an increase in inosine could indicate a decrease in cell proliferation. It induces proinflammatory cytokines to infiltrate the tissue. Furthermore, inhibiting adenosine deaminase may help to balance the adenosine-to-inosine ratio, which can serve to reduce pain.[41] However, this study found a wide range of SD that inosine might be characterized as a possible metabolite biomarker, and future targeted analysis should be investigated.

Lipids and purine metabolites were determined to contribute to MPS and could be used as biomarkers and diagnostic tools in this research. Myofascial pain syndrome is a type of localized pain disorder, but this research revealed metabolic biomarkers linked to the

inflammatory process and pain mechanism. This could imply that MPS causes inflammation not only in the muscle but also in the system as a whole. It has the potential to be used as a target therapy. To confirm the identification of metabolites with fragmentation and standard, all possible biomarkers should be investigated for targeted analysis in future research. The average pain score for MPS patients is half of the maximal pain score. One of the biomarkers that could be connected to pain sensitivity is inosine levels. However, we were unable to detect a correlation between metabolite levels and pain severity in our research.

This study used a reproducible workflow for untargeted LCMS analysis in serum samples. It covered polar and non-polar compounds observed from internal standard spikes. The linearity was observed at 3 different concentrations of pooled QCs. The robustness of 60 pooled QC samples was compared. Non-polar compounds were similar to previous studies of fibromyalgia patients[33,45] for the biomarkers that we can detect the difference between CON and MPS. However, we were unable to identify any amino acids that could be linked to glutamate receptor[46,47], such as tryptophan[48], arginine[49], L-leucine[50], and carbohydrate[16], as previously found in chronic musculoskeletal pain studies. Furthermore, the method of amino acid investigation and identification should be further investigated. Additionally, future studies in a broader demographic population could confirm whether amino acid compounds are MPS biomarkers.

In this investigation, there were no significant differences in the laboratory testing of blood chemical profiles between those with no MPS and MPS patients. Metabolomics research was more sensitive in identifying disease biomarkers. Although the relationship between metabolites and MPS pathophysiology could not be demonstrated directly in this study, the findings could imply the involvement of a systemic pain and inflammatory mechanism. Future study should investigate on targeted metabolomics analysis of compounds related to MPS pathogenesis. Our investigation was limited by a small sample size due to the study strict control of all factors that potentially interact with metabolites. Another limitation was that the study only included female MPS of varying ages with CON. The impact of sex and age on the metabolites should be investigated. As a consequence, a larger sample size should be explored to see the pattern of MPS metabolite alterations.

## CONCLUSION

This untargeted metabolomics profiling study revealed serum metabolites implicated in lipids and purine metabolites in MPS. LysoSM, lysoPC, lysoPE, TG, and inosine were all possible MPS metabolites. Mechanism of MPS is not well understood. However, the

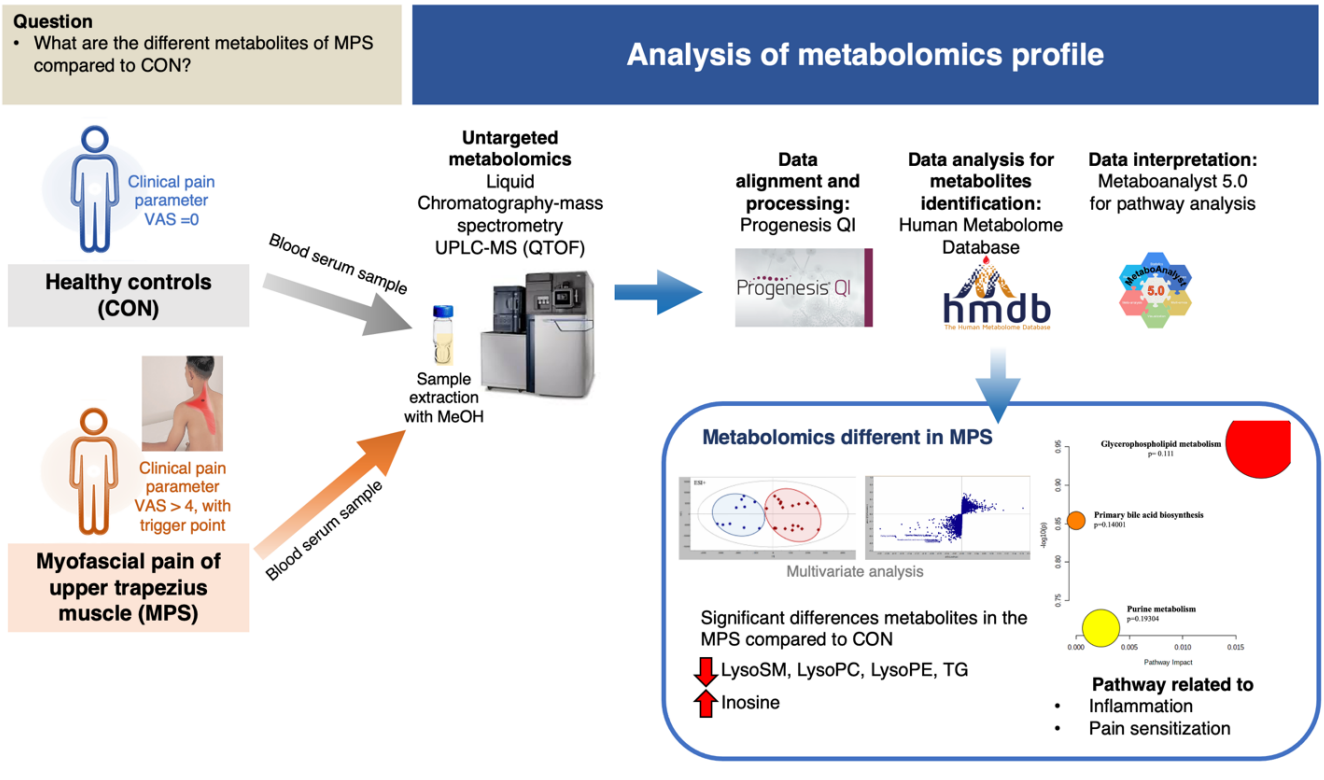


**Fig 5.** Summary of the study

key biomarkers are linked to the inflammatory process and the mechanism of pain. The findings of this exploratory study reveal that changes in metabolites in the MPS of the upper trapezius muscle differ from those in the control group. A larger sample size, a different TrP site, and changes in subsequent therapy should all be investigated further.

**Conflicts of interest:** The authors declare no conflict of interest.

## REFERENCES


1. Fejer R, Kyvik K, Hartvigsen J. The prevalence of neck pain in the world population: a systematic critical review of the literature. Eur Spine J. 2006;15:834-48.
2. Fernández-de-las-Peñas C, Dommerholt J. International Consensus on Diagnostic Criteria and Clinical Considerations of Myofascial Trigger Points: A Delphi Study. Pain Medicine. 2017;19:142-50.
3. Borg-Stein J, Simons D. Myofascial pain. Arch Phys Med Rehabil. 2002;83:S40- S7.
4. Huguenin L. Myofascial trigger points: the current evidence. Physical Therapy in Sport. 2004;5:2-12.
5. Cerezo-Tellez E, Torres-Lacomba M, Mayoral-Del Moral O, Sanchez-Sanchez B, Dommerholt J, Gutierrez-Ortega C. Prevalence of Myofascial Pain Syndrome in Chronic Non-Specific Neck Pain: A Population-Based Cross-Sectional Descriptive Study. Pain Med. 2016;17:2369-77.
6. Jafri M. Mechanisms of myofascial pain. Int Sch Res Notices. 2014.
7. Mense S. Morphology of myofascial trigger points: What does a trigger point look like? Springer. 86-100.
8. Adigozali H, Shadmehr A, Ebrahimi E, Rezasoltani A, Naderi F. Reliability of upper trapezius morphology, its mechanical properties and blood flow in female patients with myofascial pain syndrome using ultrasonography. J Bodyw Mov Ther. 2017;21(1): 35-40.
9. Hong C-Z, Simons D. Pathophysiologic and electrophysiologic mechanisms of myofascial trigger points. Arch Phys Med Rehabil. 1998;79:863-72.
10. Pedersen-Bjergaard U, Nielsen L, Jensen K, Edvinsson L, Jansen I, Olesen J. Calcitonin gene-related peptide, neurokinin A and substance P: effects on nociception and neurogenic inflammation in human skin and temporal muscle. Peptides. 1991;12:333-7.
11. Shah J, Gilliams E. Uncovering the biochemical milieu of myofascial trigger points using in vivo microdialysis: an application of muscle pain concepts to myofascial pain syndrome. J Bodyw Mov Ther. 2008;12:371-84.
12. Shah J, Phillips T, Danoff J, Gerber L. An in vivo microanalytical technique for measuring the local biochemical milieu of human skeletal muscle. J Appl Physiol (1985). 2005;99:1977-84.
13. Nielsen J, Oliver S. The next wave in metabolome analysis. Trends in biotechnology. 2005;23:544-6.
14. Klupczynska A, Derezinski P, Korot Z. Metabolomics in medical sciences - trends, challenges and perspectives. Acta Pol Pharm. 2015;72:629-41.
15. Holmes E, Wilson I, Nicholson J. Metabolic phenotyping in health and disease. Cell. 2008;134:714-7.
16. Hadrévi J, Björklund M, Kosek E, Hällgren S, Antti H, Fahlström M, et al. Systemic differences in serum metabolome: a cross sectional comparison of women with localised and widespread pain and controls. Scientific Reports. 2015;5:15925.
17. Dunn WB, Broadhurst D, Begley P, Zelena E, Francis-McIntyre S, Anderson N, et al. Procedures for large-scale metabolic profiling of serum and plasma using gas chromatography and liquid chromatography coupled to mass spectrometry. Nature Protocols. 2011;6:1060-83.
18. Vazquez-Delgado E, Cascos-Romero J, Gay-Escoda C. Myofascial pain syndrome associated with trigger points: a literature review. (I): Epidemiology, clinical treatment and etiopathogeny. Med Oral Patol Oral Cir Bucal. 2009;14:e494-8.
19. Farooqui AA, Horrocks LA, Farooqui T. Glycerophospholipids in brain: their metabolism, incorporation into membranes, functions, and involvement in neurological disorders. Chem Phys Lipids. 2000;106:1-29.
20. Han X. Lipidomics for studying metabolism. Nat Rev Endocrinol. 2016;12:668-79.
21. Berens RL, Krug EC, Marr JJ. 6 - Purine and pyrimidine metabolism. In: Marr JJ, Müller M, editors. Biochemistry and Molecular Biology of Parasites. San Diego: Academic Press; 1995.p.89-117.
22. Jinnah HA, Sabina Rl, Van Den Berghe G. Chapter 187 - Metabolic disorders of purine metabolism affecting the nervous system. In: Dulac O, Lassonde M, Sarnat HB, editors. Handbook of Clinical Neurology. 113: Elsevier; 2013.p.1827-36.
23. Maceyka M, Spiegel S. Sphingolipid metabolites in inflammatory disease. Nature. 2014;510:58-67.
24. Nixon GF. Sphingolipids in inflammation: pathological implications and potential therapeutic targets. Br J Pharmacol. 2009;158:982-93.
25. Patti GJ, Yanes O, Siuzdak G. Metabolomics: the apogee of the omics trilogy. Nat Rev Mol Cell Biol. 2012;13:263-9.
26. Peterlin BL, Mielke MM, Dickens AM, Chatterjee S, Dash P, Alexander G, et al. Interictal, circulating sphingolipids in women with episodic migraine: A case-control study. Neurology. 2015;85:1214-23.
27. Ale A, Argyriou AA, Bruna J. Sphingolipid metabolism products: potential new players in the pathogenesis of bortezomib-induced neuropathic pain. Ann Transl Med. 2018;6:S78.
28. Finco G, Locci E, Mura P, Massa R, Noto A, Musu M, et al. Can urine metabolomics be helpful in differentiating neuropathic and nociceptive pain? a proof-of-concept study. PLoS One. 2016; 11:e0150476.
29. Tokumura A, Nishioka Y, Yoshimoto O, Shinomiya J, Fukuzawa K. Substrate specificity of lysophospholipase D which produces bioactive lysophosphatidic acids in rat plasma. Biochim Biophys Acta. 1999;1437:235-45.
30. Dinkla S, van Eijk LT, Fuchs B, Schiller J, Joosten I, Brock R, et al. Inflammation-associated changes in lipid composition and the organization of the erythrocyte membrane. BBA Clin. 2016;5:186-92.
31. Zhai G, Pelletier JP, Liu M, Randell EW, Rahman P, Martel-Pelletier J. Serum lysophosphatidylcholines to phosphatidylcholines ratio is associated with symptomatic responders to symptomatic drugs in knee osteoarthritis patients. Arthritis Res Ther. 2019; 21:224.
32. Menzies V, Starkweather A, Yao Y, Thacker LR, 2nd, Garrett TJ, Swift-Scanlan T, et al. Metabolomic differentials in women

with and without fibromyalgia. Clin Transl Sci. 2020;13:67-77.
33. Caboni P, Liori B, Kumar A, Santoru ML, Asthana S, Pieroni E, et al. Metabolomics analysis and modeling suggest a lysophosphocholines-PAF receptor interaction in fibromyalgia. PLoS One. 2014;9:e107626.
34. Ren C, Liu J, Zhou J, Liang H, Wang Y, Sun Y, et al. Lipidomic analysis of serum samples from migraine patients. Lipids Health Dis. 2018;17:22.
35. Kuwajima K, Sumitani M, Kurano M, Kano K, Nishikawa M, Uranbileg B, et al. Lysophosphatidic acid is associated with neuropathic pain intensity in humans: An exploratory study. PLoS One. 2018;13:e0207310.
36. Rockel JS, Kapoor M. The metabolome and osteoarthritis: possible contributions to symptoms and pathology. Metabolites. 2018;8:92.
37. van der Kleij D, Yazdanbakhsh M. Control of inflammatory diseases by pathogens: lipids and the immune system. Eur J Immunol. 2003;33:2953-63.
38. Castoldi A, Monteiro LB, van Teijlingen Bakker N, Sanin DE, Rana N, Corrado M, et al. Triacylglycerol synthesis enhances macrophage inflammatory function. Nat Commun. 2020;11:4107.
39. Starkweather A, Julian T, Ramesh D, Heineman A, Sturgill J, Dorsey SG, et al. Circulating lipids and acute pain sensitization: an exploratory analysis. Nurs Res. 2017;66:454-61.
40. Lee J, Ridgway ND. Phosphatidylcholine synthesis regulates triglyceride storage and chylomicron secretion by Caco2 cells. J Lipid Res. 2018;59:1940-50.
41. Nascimento F, Jr Sr, Santos A. The Involvement of Purinergic System in Pain: Adenosine Receptors and Inosine as Pharmacological Tools in Future Treatments. 2012.
42. Modis K, Gero D, Stangl R, Rosero O, Szijarto A, Lotz G, et al. Adenosine and inosine exert cytoprotective effects in an in vitro model of liver ischemia-reperfusion injury. Int J Mol Med. 2013;31:437-46.
43. de Oliveira ED, Schallenberger C, Bohmer AE, Hansel G, Fagundes AC, Milman M, et al. Mechanisms involved in the antinociception induced by spinal administration of inosine or guanine in mice. Eur J Pharmacol. 2016;772:71-82.
44. Cinalli AR, Guarracino JF, Fernandez V, Roquel LI, Losavio AS. Inosine induces presynaptic inhibition of acetylcholine release by activation of A3 adenosine receptors at the mouse neuromuscular junction. Br J Pharmacol. 2013;169:1810-23.
45. Fais A, Cacace E, Corda M, Era B, Peri M, Utzeri S, et al. Purine metabolites in fibromyalgia syndrome. Clin Biochem. 2013;46:37-9.
46. Alexander GM, Reichenberger E, Peterlin BL, Perreault MJ, Grothusen JR, Schwartzman RJ. Plasma amino acids changes in complex regional pain syndrome. Pain Res Treat. 2013;2013:742407.
47. Clos-Garcia M, Andrés-Marin N, Fernández-Eulate G, Abecia L, Lavín JL, van Liempd S, et al. Gut microbiome and serum metabolome analyses identify molecular biomarkers and altered glutamate metabolism in fibromyalgia. EBioMedicine. 2019;46:499-511.
48. Hackshaw KV, Rodriguez-Saona L, Plans M, Bell LN, Buffington CA. A bloodspot-based diagnostic test for fibromyalgia syndrome and related disorders. Analyst. 2013;138:4453-62.
49. Zhang W, Sun G, Likhodii S, Liu M, Aref-Eshghi E, Harper PE, et al. Metabolomic analysis of human plasma reveals that arginine is depleted in knee osteoarthritis patients. Osteoarthritis Cartilage. 2016;24:827-34.
50. Hadrévi J, Ghafouri B, Sjörs A, Antti H, Larsson B, Crenshaw AG, et al. Comparative metabolomics of muscle interstitium fluid in human trapezius myalgia: an in vivo microdialysis study. Eur J Appl Physiol. 2013;113:2977-89.

# The Intention to Use Telemedicine by Surgical Patients in Response to COVID-19

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## ABSTRACT

**Objective:** This study explored patients' intention to use telemedicine instead of traveling to a hospital during the current global COVID-19 crisis. The framework focused on the relationships between variables derived from the technology acceptance model and the extended unified theory of acceptance and use of technology model.

**Materials and Methods:** Multistage sampling procedures were applied to recruit samples using nonprobability sampling methods. Adult patients who had undergone surgery at a university hospital participated; all were experienced in using online meeting applications and online payment services in their daily lives. Consent forms and online questionnaires were distributed via a Google Forms link.

**Results:** Between October and December 2021, 502 patients undergoing procedures participated in the study. Five variables—social influence, trust, price, perceived usefulness, and perceived ease of use—significantly impacted intention to use. Perceived ease of use significantly impacted perceived usefulness, with a value of 0.679***. In addition, perceived ease of use indirectly influenced intention to use (impact value, 0.103***). Performance expectancy did not significantly impact intention to use, with an impact value of -0.012.

**Conclusion:** The contributions of this study will enable developers, medical professionals, and marketers to improve telemedicine services to better satisfy patients undergoing surgery and increase their intention to use telemedicine. However, the performance expectancy aspect may not warrant patients' intention. Additionally, the research is recommended on other potential variables influencing telemedicine utilization, such as psychological expectations, performance expectations, and technical conditions.

**Keywords:** Telemedicine; Covid 19; surgery; intention to use (Siriraj Med J 2022; 74: 804-818)

## INTRODUCTION

The word "telemedicine" was coined in the late 1970s to denote a system of "healing at a distance."[1] It draws upon information communication technology to enhance the outcomes of patients by broadening their options for obtaining healthcare services and information on medical conditions. In terms of surgical application, telemedicine has been employed for consultations and patient monitoring both before and after operations. Bullard and coauthors[2] reported that computerized tomography scans transmitted via mobile telephones provided sufficient clarity to permit neurosurgeons to make decisions about their patients' surgical management. Moreover, mobile telephone technology obviated the need to physically move 30% to 50% of patients from referring hospitals to other facilities. Other research on the postoperative management revealed that telemedicine was safe, effective and significantly reduced the need to travel to the hospital.[3,4]

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Before the COVID-19 pandemic, surgical specialists rarely accepted the use of telemedicine. This was primarily because access to broadband or satellite services was unreliable,[5] even though telemedicine services across Thailand would offer substantial benefits to medical providers and patients. Nevertheless, following the COVID-19 pandemic, several Thai providers developed applications and telemedicine services for use at various clinics and hospitals, including Siriraj Hospital.[6-8] Siriraj Hospital launched a telemedicine application, named "Siriraj Connect," to service patients in April 2020. Patients could request telemedicine consultations via Siriraj Connect. The notification message allowed patients to confirm the appointments and prepare their mobile devices for the doctor's video call. Patients could use Siriraj Connect to pay for consultations and medications via online banking. Siriraj Connect also allowed patients to cancel or postpone their surgery follow-up sessions. Patients were encouraged to have online follow-ups to avoid the need to physically visit the hospital. Nevertheless, only 3,916 patients (2.7%) out of 145,515 patients who had hospital appointments were actual users of Siriraj Connect between March 2020 and January 2021.[9]

Several theoretical models have been proposed to examine factors associated with adopting new information technology. The Technology Acceptance Model (TAM) is particularly attractive because of its consistently good predictive records in healthcare settings.[10] According to the TAM, there are two beliefs are recognized as key to individual acceptance, which are perceived usefulness and perceived ease of use. Perceived usefulness refers to the extent to which someone considers that a system's usage will boost their work performance. As to perceived ease of use, it references the extent that a person considers that the usage will be without physical or mental effort.[11] Venkatesh and associates introduced the extended unified theory of acceptance and use of technology model (UTAUT2). This model demonstrates a rich understanding of information technology and an ability to help consumer technology organizations develop improved designs and enhanced market technologies.[12] The key constructs in UTAUT2 relate to psychology and sociology. The constructs include performance expectancy, effort expectancy, social influence, and facilitating conditions. Additional key constructs of UTAUT2 are hedonic motivation, habit, and price value.[12] All key constructs were proposed as direct antecedents of behavioral intention.

In addition to the barriers that need to be eliminated to promote the spread of telemedicine technology, patients' intentions to utilize the technology are facilitated or influenced by an array of factors. The current work focused on the relationships between the variables. Therefore, the objective of this study was to explore factors influencing patients' intention to use telemedicine instead of traveling to the hospital for activities such as health education, laboratory investigations, or follow-up during the global COVID-19 crisis.

## MATERIALS AND METHODS

### *Research framework, hypotheses, and contextualized scale items*

The conceptual framework used in this research (Fig 1A) was based on 2 core theories and 4 major research studies.[13] The relationships between 7 variables were investigated. There were 6 independent variables (social influence, performance expectancy, trust, price, perceived usefulness, and perceived ease of use) and 1 dependent variable (intention to use). The following hypotheses are proposed:

*H1.* There is a statistically significant relationship between social influence and intention to use Siriraj Telemedicine application.

*H2.* There is a statistically significant relationship between performance expectancy and intention to use Siriraj Telemedicine application.

*H3.* There is a statistically significant relationship between trust and intention to use Siriraj Telemedicine application.

*H4.* There is a statistically significant relationship between price and intention to use Siriraj Telemedicine application.

*H5.* There is a statistically significant relationship between perceived usefulness and intention to use Siriraj Telemedicine application.

*H6.* There is a statistically significant relationship between perceived ease of use and intention to use Siriraj Telemedicine application.

*H7.* There is a statistically significant relationship between perceived ease of use and perceived usefulness.

This study used a quantitative approach and drew upon a survey questionnaire as a data collection tool. An information sheet, informed consent form, and questionnaire were created and presented to participants through a Google Forms survey. The questionnaire contained 36 items exploring the 7 variables influencing telemedicine usage (Appendix 1). The items were grouped into 4 main sections. The first was a set of screening questions, while the second section measured the 6 independent variables (social influence, performance expectancy, trust, price, perceived usefulness, and perceived ease of use). The third part measured the sole dependent variable (intention to use),

## APPENDIX 1

### QUESTIONNAIRE ENGLISH VERSION

This questionnaire is developed for the determination of the research on "Factors influencing the intention to use of telemedicine among surgical patients in response to the COVID 19 pandemic at Siriraj Hospital". The study is conducted with regards to fulfilment the requirement of Philosophy Degree in Technology Education Management at Assumption University, Bangkok, Thailand. All the information collected of this study will be kept privately and will be used as the resolution of this study only. Thank you for your time and patience for response the answer.

**Part I: Screening Questions**

1. Have you ever undergone surgery or surgery follow up at Siriraj Hospital? (Select only 1)

❏ Yes

❏ No

2. Have you experienced using online meeting application such as Line VDO call, ZOOM, WebEx or Microsoft team? (Select only 1)

❏ Yes

❏ No

3. Have you experienced using online payment? (Select only 1)

❏ Yes

❏ No

**Part II: Measuring Variables**

Please answer the following question by mark "✓" in the space given below and do kindly answer truthfully and complete all questions.

1 = strongly disagree

2 = disagree

3 = neither agree nor disagree

4 = agree

5 = strongly agree

| No | Items | 1= strongly disagree | 2= disagree | 3= neither agree nor disagree | 4= agree | 5= strongly agree |
|---|---|---|---|---|---|---|
| **Social Influence** | | | | | | |
| 1 | Friend suggestion and recommendation will affect my decision to use Siriraj telemedicine. | | | | | |
| 2 | Family members/ relatives have influence on my decision to use Siriraj telemedicine. | | | | | |
| 3 | I will use Siriraj telemedicine if the surgeon recommends to use it. | | | | | |
| 4 | Mass media (e.g., TV, newspaper, articles radio) will influence me to use Siriraj telemedicine. | | | | | |
| 5 | I will use Siriraj telemedicine if the service is widely used by people in my community. | | | | | |
| **Performance Expectancy** | | | | | | |
| 6 | I can communicate with a doctor online. | | | | | |
| 7 | I can pay essential bills via Internet conveniently. | | | | | |
| 8 | I can manage my appointment online at anytime | | | | | |
| 9 | Siriraj telemedicine keeps a record of my health | | | | | |
| 10 | Siriraj telemedicine reduce obstacle to visit hospital in person. | | | | | |
| 11 | Siriraj telemedicine is easy to access | | | | | |
| **Trust** | | | | | | |
| 12 | I think that Siriraj telemedicine will keep the promises and commitments that it makes | | | | | |
| 13 | Siriraj telemedicine makes me feel trustworthy the same as I visit the doctor at the hospital in person. | | | | | |
| 14 | I would describe Siriraj telemedicine as honest | | | | | |
| 15 | I think that Siriraj telemedicine is responsible | | | | | |
| 16 | In general, I trust in Siriraj telemedicine | | | | | |
| **Price** | | | | | | |
| 17 | I am willing to use Siriraj telemedicine even though the follow-up fee may be increased | | | | | |
| 18 | I am willing to pay for Siriraj telemedicine service even I may need to pay more than I see the doctor in person at the hospital. | | | | | |

| No | Items | 1= strongly disagree | 2= disagree | 3= neither agree nor disagree | 4= agree | 5= strongly agree |
|---|---|---|---|---|---|---|
| **Price** | | | | | | |
| 19 | I am willing to pay for additional service fees for using Siriraj telemedicine. | | | | | |
| 20 | Siriraj telemedicine service fees may burden me. | | | | | |
| 21 | I am willing to use Siriraj telemedicine even though the total expenses are more expensive than visiting the doctor at the hospital. | | | | | |
| **Perceived usefulness** | | | | | | |
| 22 | I find that Siriraj telemedicine is useful for follow-up my surgery conditions. | | | | | |
| 23 | Siriraj telemedicine makes me manage my health conditions effectively. | | | | | |
| 24 | Using Siriraj telemedicine makes me monitor my health condition conveniently. | | | | | |
| 25 | Using Siriraj telemedicine save me time to travel to the hospital. | | | | | |
| 26 | Using Siriraj telemedicine enables me to manage my health-related matters quickly. | | | | | |
| **Perceived ease of use** | | | | | | |
| 27 | I believe that using Siriraj telemedicine system will not make me get confused. | | | | | |
| 28 | I believe that Siriraj telemedicine system is easy to understand. | | | | | |
| 29 | I believe that Siriraj telemedicine system is easy to use. | | | | | |
| 30 | I believe that Siriraj telemedicine is not cumbersome. | | | | | |
| **Intention to use** | | | | | | |
| 31 | I am likely to use Siriraj telemedicine for my follow-up after surgery in the near future. | | | | | |
| 32 | I will see the surgeon via Siriraj telemedicine if Ihave given the opportunity. | | | | | |
| 33 | I am willing to use Siriraj telemedicine in the near future | | | | | |
| 34 | I have an intention to use Siriraj telemedicine for follow-up with the surgeon. | | | | | |

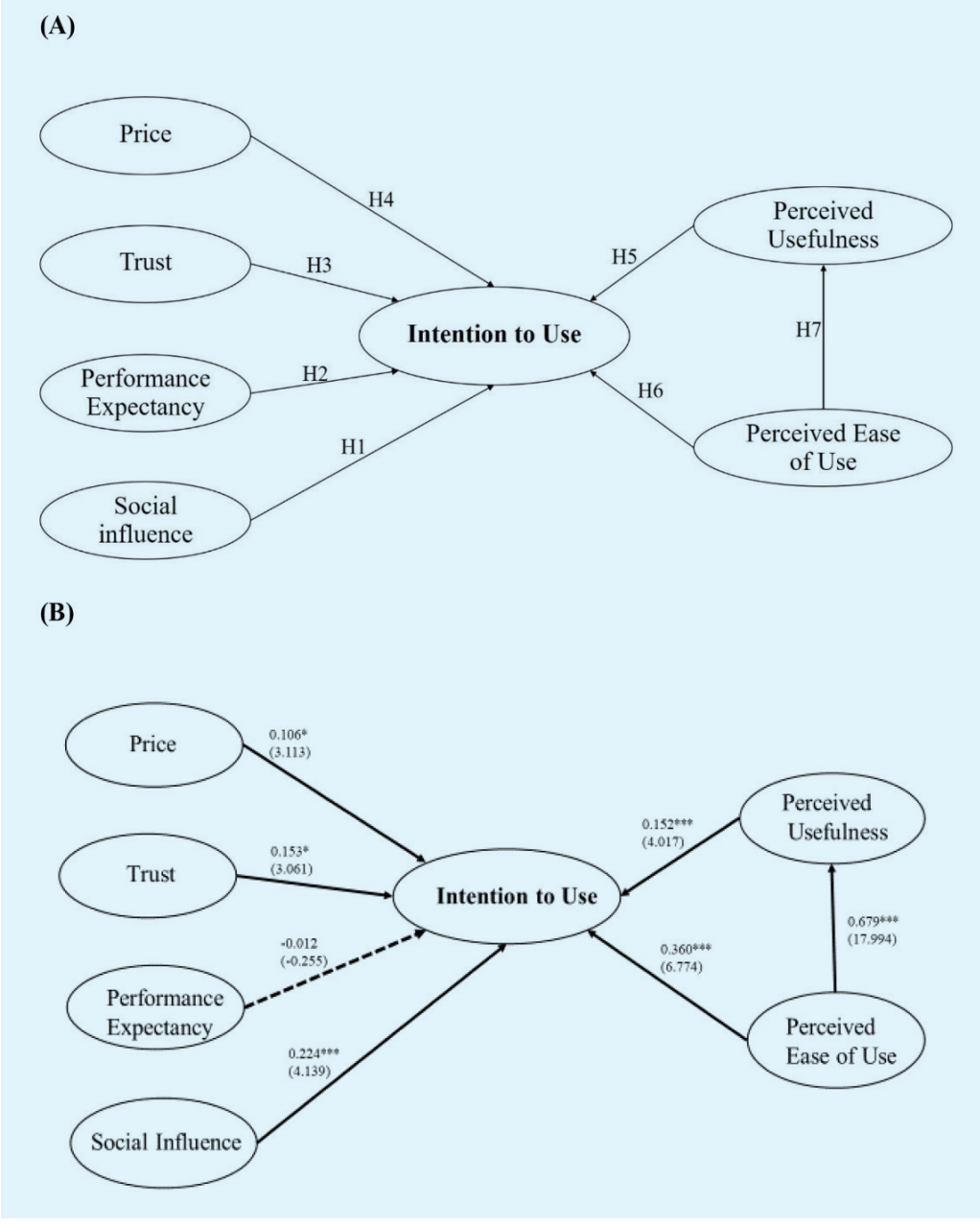


**Fig 1.** (A) Conceptual framework; (B) Results of structural model.

and the last section collected demographic information. The questionnaire employed a 5-point Likert scale, with choices ranging from "strongly disagree" (1) to "strongly agree" (5). Before data collection, 3 experts tested the questionnaire scores to ensure that the item-objective congruence was > 0.6. A pilot study was administered to assess reliability, with the questionnaire distributed through a Google Forms survey to patients who had undergone surgery at Siriraj Hospital. Cronbach's alpha reliability coefficient tested the internal consistency of the questionnaire. As all of the constructs in this study had an alpha coefficient above 0.8, they were reliable and adequate for use as a research instrument.

***Respondents and sampling procedure***

Before starting this research, the protocol was approved by the Ethics Review Committee for Research, Assumption University Institutional Review Board (AU IRB No. 1/2021). Written informed consent was obtained from anonymous respondents before they responded to the self-completion questionnaires. This study applied the nonprobability sampling technique to the quantitative sampling procedures with multistage sampling (judgment, quota, and convenience sampling). The questionnaire was distributed via Google Forms during October to December 2021. The inclusion criteria were adult patients (over 18 years) who had undergone surgery at Siriraj

Hospital and needed appointments for surgery follow-up. The patients had to be experienced in using online meeting applications and payment systems. Patients were excluded if they could not read or had difficulty using a smart phone, for example, vision problem or reading literacy problem.

### *Sample size calculation and statistical analysis*

Given the framework of 7 latent variables with 36 observed variables, an anticipated effect size of 0.2, and a probability level of 0.05, it was calculated that a minimum sample size of 425 would be required to determine effects. A goal of 500 responses was set and exceeded. Descriptive statistics were applied to describe respondents' demographic information in the form of frequencies and percentages. In addition, the mean and standard deviation are reported for the respondents' perceptions of the constructs.

A normality test was used to determine whether the data set was well modeled by a normal distribution and to calculate the probability that the random variables in the data set were normally distributed. Based on the work of Kim et al. (2013),[14] thresholds of skewness values between -0.500 and 0.500 denote that data are reasonably symmetrical. The values between -1.000 and -0.500, or between 0.500 and 1.000, indicate that the data are moderately skewed. However, values below -1.000 or exceeding 1.000 signify that the data are highly skewed. George and Mallery[15] assumed that the ideal value level for kurtosis ranges from -2.000 to +2.000.

Confirmatory factor analysis (CFA) and structural equation modeling (SEM) using the maximum likelihood method were performed. The internal consistency of the CFA factors was assessed with Cronbach's alpha coefficient. The statistical analyses were performed using IBM SPSS Statistics for Windows, version 28.0 (IBM Corp, Armonk, NY, USA). Analysis of Moment Structures (version 18.0) was used for the CFA and SEM analyses.

## RESULTS

### *Demographics, descriptive analysis of observed variables, and assessment of normality*

In this study, 502 patients responded to the questionnaire. The majority were women, representing 50.6% of the respondents, with men contributing 248 respondents (49.4%). As for the type of surgery, 41.8% of the respondents underwent minor surgery, 41.1% had intermediate surgery, and the remainder (17.2%) had major surgery. Half of the participants had a bachelor's degree or higher as their highest education level. Regarding the location of their permanent domicile, most respondents lived in Bangkok or the central region of Thailand (Table 1).

The 5-point Likert scale measured respondents' perceptions of the 7 observed variables (social influence, performance expectancy, trust, price, perceived usefulness, perceived ease of use, and intention to use). Descriptive statistics (mean and standard deviation) were calculated and used to interpret the levels of agreement of the respondents on the observed variables influencing their intention to use the Siriraj Connect application. The mean values of the observed variables ranged from 3.19 to 4.32, and the standard deviations ranged from 0.81 to 1.07. The descriptive statistics and assessments of normality are detailed in Appendix 2. The overall values of skewness and kurtosis of this paper were acceptable.

### *Confirmation factor analysis*

CFA was utilized to evaluate the convergent and discriminant validity of the constructs and determine the model fit. To test convergent validity, the following criteria should be met, as suggested by Hair et al.[16]:

- The construct reliability (Cronbach alpha value) should be greater than 0.7.
- The explained variance (AVE) within each construct should be larger than 0.5.
- The standardized factor loading of each observed variable to the latent construct should be at least 0.60.
- The composite reliability (CR) should be at least 0.70.

All 4 criteria were met (Table 2). All the observed variables had a factor loading exceeding the recommended minimum of 0.774. Cronbach's alpha values were well above the minimum of 0.896. The AVE values for all constructs exceeded the minimum of 0.633, and the CR values met the minimum of 0.905. These results demonstrate that all of the constructs in this study achieved an acceptable level of convergent validity.

Campbell and Fiske[17] introduced the concept of discriminant validity in their research on evaluating test validity. They emphasized the importance of employing identification and convergence verification techniques when evaluating new tests. Discriminant validity occurs when the number of trait-correlation evaluations is ≥ 2, with standard errors less than 1.00.[18] According to the data of discriminant validity (Table 3), the square roots of AVE demonstrated in the diagonal were 0.789, 0.873, 0.913, 0.887, 0.915, 0.939, and 0.947, and the maximum value of the coefficient for any two latent variables was 0.755. Based on these statistical data, discriminant validity for this study was achieved. Since convergent

## APPENDIX 2

Mean, standard deviation and assessment of normality

| Construct | Items | Mean | SD | Skewness | SE | Kurtosis | SE |
|---|---|---|---|---|---|---|---|
| Social Influence (SI) | SI1 | 3.753 | 1.002 | -0.594 | 0.109 | -0.078 | 0.218 |
| | SI2 | 3.902 | 0.941 | -0.736 | 0.109 | 0.212 | 0.218 |
| | SI3 | 4.235 | 0.880 | -1.195 | 0.109 | 1.440 | 0.218 |
| | SI4 | 3.717 | 0.981 | -0.494 | 0.109 | -0.185 | 0.218 |
| | SI5 | 3.939 | 0.972 | -0.812 | 0.109 | 0.314 | 0.218 |
| Performance Expectancy (PE) | PE1 | 4.221 | 0.812 | -1.008 | 0.109 | 1.026 | 0.218 |
| | PE2 | 4.193 | 0.861 | -0.977 | 0.109 | 0.606 | 0.218 |
| | PE3 | 4.234 | 0.865 | -1.040 | 0.109 | 0.624 | 0.218 |
| | PE4 | 4.102 | 0.886 | -0.760 | 0.109 | 0.094 | 0.218 |
| | PE5 | 4.321 | 0.822 | -1.288 | 0.109 | 1.836 | 0.218 |
| | PE6 | 4.086 | 0.937 | -0.865 | 0.109 | 0.165 | 0.218 |
| Trust (Trust) | Trust1 | 4.087 | 0.853 | -0.672 | 0.109 | -0.023 | 0.218 |
| | Trust2 | 3.941 | 0.941 | -0.598 | 0.109 | -0.282 | 0.218 |
| | Trust3 | 4.124 | 0.860 | -0.667 | 0.109 | -0.174 | 0.218 |
| | Trust4 | 4.121 | 0.860 | -0.751 | 0.109 | 0.153 | 0.218 |
| | Trust5 | 4.106 | 0.854 | -0.609 | 0.109 | -0.230 | 0.218 |
| Price (Price) | Price1 | 3.292 | 1.052 | -0.101 | 0.109 | -0.595 | 0.218 |
| | Price2 | 3.203 | 1.071 | -0.075 | 0.109 | -0.643 | 0.218 |
| | Price3 | 3.185 | 1.064 | -0.084 | 0.109 | -0.631 | 0.218 |
| | Price4 | 3.202 | 1.063 | -0.168 | 0.109 | -0.438 | 0.218 |
| | Price5 | 3.220 | 1.072 | -0.132 | 0.109 | -0.519 | 0.218 |
| Perceived Usefulness (PU) | PU1 | 4.102 | 0.864 | -0.722 | 0.109 | -0.083 | 0.218 |
| | PU2 | 3.991 | 0.871 | -0.493 | 0.109 | -0.384 | 0.218 |
| | PU3 | 4.124 | 0.870 | -0.706 | 0.109 | -0.295 | 0.218 |
| | PU4 | 4.287 | 0.860 | -1.170 | 0.109 | 1.113 | 0.218 |
| | PU5 | 4.152 | 0.870 | -0.791 | 0.109 | -0.070 | 0.218 |
| Perceived Ease Of Use (PEOU) | PEOU1 | 3.816 | 0.925 | -0.499 | 0.109 | -0.241 | 0.218 |
| | PEOU2 | 3.848 | 0.903 | -0.495 | 0.109 | -0.256 | 0.218 |
| | PEOU3 | 3.823 | 0.914 | -0.487 | 0.109 | -0.290 | 0.218 |
| | PEOU4 | 3.811 | 0.922 | -0.505 | 0.109 | -0.053 | 0.218 |
| Intention to use (ITU) | ITU1 | 3.932 | 0.944 | -0.549 | 0.109 | -0.242 | 0.218 |
| | ITU2 | 3.935 | 0.941 | -0.516 | 0.109 | -0.373 | 0.218 |
| | ITU3 | 3.975 | 0.950 | -0.583 | 0.109 | -0.368 | 0.218 |
| | ITU4 | 3.942 | 0.950 | -0.573 | 0.109 | -0.291 | 0.218 |

**Abbreviations:** SD; Standard Deviation, SE; Standard error

**TABLE 1.** Analysis of demographic characteristic (n = 502).

| Demographic Information | Frequency (%) |
|---|---|
| **Age group (year)** | |
| < 34 years (young) | 128 (25.5) |
| 35–49 years (early middle-aged adults) | 217 (43.2) |
| 50–64 years (late middle-aged adults) | 111 (22.1) |
| ≥ 65 years (older adults) | 46 (9.2) |
| **Sex** | |
| Male | 248 (49.4%) |
| Female | 254 (50.6%) |
| **Type of surgery** | |
| Minor surgery | 210 (41.8%) |
| Intermediate surgery | 206 (41.0%) |
| Major surgery | 86 (17.2%) |
| **Education levels** | |
| Primary school | 52 (10.4%) |
| High school/Higher secondary school | 57 (11.4%) |
| Bachelor's degree | 284 (56.5%) |
| Postgraduate (Master's/Doctorate) | 109 (21.7%) |
| **Address** | |
| Bangkok | 292 (58.2%) |
| **Other Regions** | |
| Central | 117 (23.3%) |
| Northern | 24 (4.7%) |
| North-eastern | 35 (7.0%) |
| Western | 6 (1.2%) |
| Eastern | 8 (1.6%) |
| Southern | 20 (4.0%) |

Data presented as n (%)

**TABLE 2.** Confirmatory factor analysis result, composite reliability, average variance extracted, source of questionnaires, and number of questionnaire items.

| Variable | Source of Questionnaire | No. of Questionnaire Items | Factor Loading > 0.5 | CR (pc) > 0.7 | AVE (pv) > 0.5 |
|---|---|---|---|---|---|
| Social Influence | Wei et al.[47] | 5 | 0.774-0.846 | 0.896 | 0.633 |
| Performance Expectancy | Yuen et al.[48] | 7 | 0.825-0.918 | 0.953 | 0.772 |
| Trust | Kalinić et al.[49] | 5 | 0.846-0.940 | 0.962 | 0.836 |
| Price | Anouze and Alamro[50] | 5 | 0.670-0.961 | 0.942 | 0.766 |
| Perceived usefulness | Leon[51] | 5 | 0.866-0.939 | 0.963 | 0.839 |
| Perceived ease of use | Ozturk[52] | 4 | 0.890-0.962 | 0.968 | 0.882 |
| Intention to use | Zhao et al.[53] | 5 | 0.916-0.965 | 0.972 | 0.897 |

**Abbreviations:** CR, composite reliability; AVE, average variance extracted

**TABLE 3.** Discriminant validity output.

| | SI | PE | Trust | Price | PU | PEOU | ITU |
|---|---|---|---|---|---|---|---|
| SI | **0.789** | | | | | | |
| PE | 0.648 | **0.873** | | | | | |
| Trust | 0.653 | 0.707 | **0.913** | | | | |
| Price | 0.448 | 0.372 | 0.508 | **0.887** | | | |
| PU | 0.645 | 0.678 | 0.670 | 0.424 | **0.915** | | |
| PEOU | 0.604 | 0.624 | 0.707 | 0.544 | 0.646 | **0.939** | |
| ITU | 0.655 | 0.616 | 0.710 | 0.545 | 0.669 | 0.755 | **0.947** |

The diagonally listed values are the AVE square roots of the variables.
**Abbreviations:** SI, social influence; PE, performance expectancy; PU, perceived usefulness; PEOU, perceived ease of use; ITU, intention to use

and discriminant validity were proven, construct validity was established.

Based on the suggestion by Hair et al.,[19] the following criteria were used to determine model fit: chi-squared goodness of fit statistic over degrees of freedom (CMIN/DF); goodness- of-fit index (GFI); adjusted goodness-of-fit index (AGFI); normed fit index (NFI); comparative fit index (CFI); Tucker–Lewis index (TLI); and root mean square error of approximation (RMSEA). A research model with a good fit meets the following criteria: CMIN/DF > 5; GFI > 0.85; AGFI, NFI, CFI, and TLI > 0.8; and REMSEA < 0.08. The research model exceeded every criterion and achieved an acceptable model fit (Table 3).

### *Structural equation model*

The objective of this section was to evaluate and verify the structural instrument. After the first data examination stage in SEM, the investigators confirmed the goodness of fit for the SEM. Two classifications of the goodness of fits were performed to modify the SEM matrix. They included CMIN/DF, GFI, AGFI, and RMSEA from the absolute fit indices; and CFI and TLI from the incremental fit indices.

Next, the investigators modified the matrix according to the modification indices. The covariance was used to determine the interrelated deviation correlate and hence to obtain better fitness for the SEM matrix. The goodness-of-fit results before and after adjustment are summarized in Table 4 and illustrated in Fig 1B. Alternative hypotheses were examined after modifying the structural equation matrices whose goodness of fit matched the relevant standards. Table 5 details the hypothetical test results of the alternatives.

### *Direct, indirect, and total effects*

This research has 6 independent variables (social influence, performance expectancy, trust, price, perceived usefulness, and perceived ease of use) and 1 dependent variable (intention to use). The statistical results were related to the direct, indirect, and overall impacts of the 7 variables. The corresponding path analysis data are depicted in Fig 2B. $R^2$ was 0.683; this indicated that a 68.3% variance of intention to use could be determined by social influence, performance expectancy, trust, price, perceived usefulness, and perceived ease of use. Five variables—social influence, trust, price, perceived usefulness, and perceived ease of use—significantly impacted intention to use. The impact points were equivalent to 0.224***, 0.153**, 0.106**, 0.152*** and 0.360***, respectively. Perceived ease of use significantly impacted perceived usefulness, with a value of 0.679***. In addition, perceived ease of use indirectly influenced intention to use (impact value, 0.103***). Performance expectancy had no significant impact on intention to use, with an impact value of -0.012.

## DISCUSSION

This study explored factors influencing patients' intention to use telemedicine for health activities, such as health education, laboratory investigations, and annual follow-ups, instead of traveling to the hospital. To construct a conceptual model, the study drew upon factors influencing patients' intention to use the Siriraj Connect mobile application and 2 research models (the technology acceptance model, and the extended unified theory of acceptance and use of technology model). The research target group consisted of 502 patients who had

**TABLE 4.** Goodness of fit for measurement model before and after adjustment.

| Index | Acceptable values | Sources | Statistical values before adjustment | Statistical values after adjustment |
|---|---|---|---|---|
| CMIN/DF | < 5.00 | Awang[54]; Al-Mamary and Shamsuddin[55] | 6.603 | 2.853 |
| GFI | ≥ 0.85 | Sica and Ghisi[56] | 0.660 | 0.857 |
| AGFI | ≥ 0.80 | Sica and Ghisi[56] | 0.612 | 0.829 |
| NFI | ≥ 0.80 | Wu and Wang[57] | 0.845 | 0.936 |
| CFI | ≥ 0.80 | Bentler[58] | 0.865 | 0.957 |
| TLI | ≥ 0.80 | Sharma *et. al.*[59] | 0.854 | 0.952 |
| RMSEA | < 0.80 | Pedroso *et. al.*[60] | 0.106 | 0.061 |
| **Model summary** | | | **Unacceptable model fit** | **Acceptable model fit** |

**Abbreviations:** CMIN/DF, ratio of the chi-squared value to degree of freedom; GFI, goodness-of-fit index; AGFI, adjusted goodness-of-fit index; RMSEA, root-mean-square error of approximation; CFI, comparative fit index; TLI, Tucker–Lewis Index.

**TABLE 5.** Hypotheses Results of Structural Model.

| Hypothesis | Standardized Path Coefficients (β) | t-Value | Hypothesis Result |
|---|---|---|---|
| H1: There is a significant relationship between social influence and intention to use. | 0.224 | 4.139*** | Supported |
| H2: There is a significant relationship between performance expectancy and intention to use. | -0.012 | -0.255 | Not Supported |
| H3: There is a significant relationship between trust and intention to use. | 0.153 | 3.061** | Supported |
| H4: There is a significant relationship between price and intention to use. | 0.106 | 3.113** | Supported |
| H5: There is a significant relationship between perceived usefulness and intention to use. | 0.152 | 4.017*** | Supported |
| H6: There is a significant relationship between perceived ease of use and intention to use. | 0.360 | 6.774*** | Supported |
| H7: There is a significant relationship between perceived ease of use and perceived usefulness. | 0.679 | 17.994*** | Supported |

*** = $P < 0.001$; ** = $P < 0.01$; * = $P < 0.05$.

undergone surgery and were being monitored through follow-up visits at Siriraj Hospital.

The results revealed that perceived ease of use, social influence, and perceived usefulness are the key factors that must be addressed when designing a new service platform. Perceived ease of use had the greatest influence on the patients' intention to use Siriraj Connect. The factors of trust and price had a lesser degree of influence on their intention to use the application. Perceived ease of use also had an indirect but significant impact on the perceived usefulness of the application. However, performance expectancy was not directly influential on intention to use.

From the consumer perspective, "social influence" refers to the extent to which consumers perceive that important others believe they should use a particular technology.[12] New technologies are considered products or services of high risk. For this reason, potential users tend to seek opinions about new technologies from others in their social surroundings, and the opinions of important others can influence them. Many researchers have confirmed the significant relationship between social influence and behavioral intentions.[20-22] In the context of the current investigation, the potential reference groups may not be just family members and friends. The groups may also include surgeons, nurses, people in the local community, and the mass media. The positive opinions of those members may encourage patients to contribute through the Siriraj Connect mobile application and increase their intention to use the application. Therefore, the hospital's public relations department and customer service staff should actively promote the concept that mobile applications are a new and helpful service interface. They should also indirectly enhance patients' intentions to use telemedicine by communicating its value to influential internal groups, such as surgeons, healthcare providers, and younger (technology-oriented) caregivers.

"Performance expectancy" refers to individuals' belief that using a particular technology or method will benefit them or improve their performance to at least some extent.[23] Performance expectancy has generally been demonstrated to be the primary predictor of intention to use a new form of information technology, irrespective of environmental factors.[12,24,25] Much research has supported the impact of performance expectancy on the behavioral intentions of consumers to adopt mobile banking services.[26-29] Performance expectancy was found to be significant for all the measurement points used in voluntary and mandatory settings, as participants were generally interested in knowing the benefits of technology for their performance.

In the context of telemedicine, performance expectancy can be viewed as the extent to which a new service route can assist patients in performing specific tasks related to healthcare services, such as conveniently communicating with doctors online, making electronic payments, and managing appointments. Therefore, it is reasonable to assume that performance expectancy would be critical in patients' decisions about service channels. Nevertheless, an insignificant relationship was found in the current investigation. This finding is similar to the work of Khatun et al. (2017).[30] They used the unified theory of acceptance and use of technology model to explain the end-user acceptance of MyOnlineClinic, an Australian telehealth service operating since 2015. However, the absence of a significant relationship does not mean that this variable should be excluded from further research: it may still prove to be a factor affecting intention to use.

Trust has been established as a critical antecedent to patient acceptance of telemedicine,[31] and it is related to the views of patients and healthy individuals on the practical value of storing health records electronically.[32] Numerous investigations have been conducted on the importance of trust in consumers' behaviors. It has been proposed that trust is an essential antecedent of their propensity to engage in activities of a collaborative nature.[33]

Consumers' intention to purchase products is affected by the "acceptable price level."[34] If product prices exceed what consumers deem acceptable, their intention to purchase the products declines. Many studies have indicated that the intention to use new technological applications and services is closely associated with what consumers consider a reasonable price, with lower prices more likely to entice them to take up the particular technology offered.[35,36]

Perceived usefulness is the term used to refer to the extent to which individuals consider the usage of a system to be likely to enhance their performance in a job. The perception of usefulness is vital in determining the degree of consumer adoption of innovations. This factor has been confirmed as key in earlier related studies. There is much evidence in support of the substantial effect that perceived usefulness has on consumers' adoption intentions.[37-40]

Perceived ease of use is the extent to which people consider that the actual usage of a new form of technology will be without effort.[41] If the technology fails to be easy to use and the user interface is complicated, they will have a negative attitude toward it. Conversely, technological applications that consumers perceive will be easier to operate than other applications have a higher probability

of being adopted.[42] The present investigation determined that perceived ease of use had the greatest influence on patients' intention to use the Siriraj Connect application.

Finally, previous studies reported that perceived ease of use affected attitudes and their intention to use mobile banking applications via perceived usefulness.[43-46] In the case of telemedicine, the easier it is to use a telemedicine service, the more valuable it is likely to be perceived by patients, and hence the greater the degree to which they will accept it. Patients are likely to perceive that they can easily use telemedicine if the service appears user-friendly and not complicated to use, they can recall how to use it, and the service is relatively free of hassles during use.

This study sought insight into factors influencing individuals' intention to use telemedicine during the COVID-19 pandemic. Given the results described above, it is suggested that factors related to patients' intention to use telemedicine should be considered when designing a system and developing the associated business model. Patients tend to use telemedicine when they perceive it is as easy to use and useful and if their surgeons have recommended it. Trust and price also influence patients' intentions. Future research should be broader focused and more complex to determine the influence of psychological expectations, performance expectations, and technical anxiety on telemedicine utilization.

Like any other research, this study has some limitations that must be acknowledged. First, it employed a cross-sectional design that investigated phenomena at 1 point in time. More specifically, the investigators explored patients' intention to use the Siriraj Connect telemedicine application among patients undergoing surgery when few hospital service options were available due to the COVID-19 pandemic. It would be expected that the results may differ in a normal situation when patients can visit the hospital and obtain the full benefits offered by face-to-face consultations with their doctors. Future researchers may investigate patients' behavior in the "next-normal," or postviral, to ensure that telemedicine remains a prominent part of the clinical enterprise. Doing so will provide a clearer picture of the factors influencing patients' intention to use Siriraj Connect. Second, this study was conducted at an academic medical center. Consequently, replicating the current research model at other hospital levels could produce different findings. Third, the research did not sufficiently sample the target groups by age, sex, educational level, or socioeconomic status. The scope of research was limited to patients who underwent surgery at Siriraj Hospital. Hence, future research could be extended to other patient groups because they may have different levels of digital health literacy. Last, this research did not add all exogenous variables when examining patients' intention to use the Siriraj Connect telemedicine application. Therefore, the current research model could be extended with information system and service quality factors.

## CONCLUSION

Patients' intention to use telemedicine services mainly depends on their perceived ease of use and usefulness, and social influences on patients. The contributions of this study will enable developers, medical professionals, and marketers to improve telemedicine services to better satisfy patients undergoing surgery and increase their intention to use telemedicine. As patients think the most important aspect of telemedicine services is their ease of use, online services should be designed to be user friendly, with all relevant information and resources readily accessible. Moreover, patients expect telemedicine services to be useful and available at a reasonable price. To encourage patients to try online services, information should be provided by hospital surgeons and public relations department staff. Further study should investigate other potentially relevant factors impacting telemedicine services' uptake and continued use. Among these are the attitude of surgeons and healthcare providers toward online services, the stability of telemedicine platforms, and legal considerations related to providing personal health details online.

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## REFERENCES

1. Strehle EM, Shabde N. One hundred years of telemedicine: does this new technology have a place in paediatrics? Arch Dis Child. 2006;91:956-9.
2. Bullard JE. Contemporary glacigenic inputs to the dust cycle. 2013;38:71-89.
3. Costa D, Soares J, Lindert J, Hatzidimitriadou E, Sundin Ö, Toth O, et al. Intimate partner violence: a study in men and women from six European countries. Int J Public Health. 2015; 60:467-78.
4. Urquhart AC, Antoniotti NM, Berg RL. Telemedicine--an efficient and cost-effective approach in parathyroid surgery. Laryngoscope. 2011;121:1422-5.
5. National Center for Immunization and Respiratory Diseases

(NCIRD). 2020. [cited 27 January 2021]. Available from: https://www.cdc.gov/ncird/index.html.
6. Chiiwii. chiiwiidoctor. 2021 [cited 27 January 2021]. Available from: https://www.chiiwiidoctor.com/.
7. Seedoctornow. Seedoctornow. 2017. [cited 27 January 2021]. Available from: https://www.seedoctornow.com/.
8. Ooca. Ooca It's Okay. 2021. [cited 27 January 2021]. Available from: https://www.ooca.co/.
9. Value Driven Care Unit. The number of actual used of siriraj telemedicine platform by patients with medical diseases Bangkok: Faculty of Medicine Siriraj Hospital, Value Driven Care Unit; 27 January 2021.
10. Razmak J, Bélanger C. Interdisciplinary Approach: A Lever to Business Innovation. Int J High Educ. 2016;5.
11. Bundot GY, Md Yunos J, Mohammed M. Technology Acceptance Model Of Intention To Use ICT By Academics In Nigerian Higher Education. Online Journal for TVET Practitioners. 2017;2:3-7.
12. Venkatesh V, Thong J, Xu X. Consumer Acceptance and Use of Information Technology: Extending the Unified Theory of Acceptance and Use of Technology. MIS Quarterly. 2012;36: 157-78.
13. Naranjo-Zolotov M, Oliveira T, Casteleyn S. Citizens' intention to use and recommend e-participation: Drawing upon UTAUT and citizen empowerment. Inf Technol People. 2018;32.
14. Kim HY. Statistical notes for clinical researchers: assessing normal distribution (2) using skewness and kurtosis. Restor Dent Endod. 2013;38:52-4.
15. George D, Mallery P. IBM SPSS Statistics 26 Step by Step: A Simple Guide and Reference 16th ed. New York: Routledge; 2019.
16. Hair J, Hult GTM, Ringle C, Sarstedt M. A Primer on Partial Least Squares Structural Equation Modeling (PLS-SEM) 2022.
17. Campbell DT, Fiske DW. Convergent and discriminant validation by the multitrait-multimethod matrix. Psychol Bull. 1959;56:81-105.
18. Schmitt N, Stults DM. Methodology Review: Analysis of Multitrait-Multimethod Matrices. Appl Psychol Meas. 1986;10: 1-22.
19. Hair.Jr. JF, Black. WC, Babin. BJ, Anderson. RE, L. Tatham. R. Multivariant Data Analysis. New Jersey: Pearson International Edition; 2006.
20. Alalwan AA, Dwivedi YK, Rana NP. Factors influencing adoption of mobile banking by Jordanian bank customers: Extending UTAUT2 with trust. Int J Inf Manage. 2017;37:99-110.
21. Blaise JH, Park JE, Bellas NJ, Gitchell TM, Phan V. Caffeine consumption disrupts hippocampal long-term potentiation in freely behaving rats. Physiol Rep. 2018;6(5):e13632.
22. Tan E, Lau J. Behavioural intention to adopt mobile banking among the millennial generation. Young Consum. 2016;17: 18-31.
23. Ogunsola K, Fontaine R, Jan M. Impact of surface acting and deep acting techniques on teachers' organizational commitment. PSU Research Review. 2020;4:61-79.
24. Luo X, Li H, Zhang J, Shim JP. Examining multi-dimensional trust and multi-faceted risk in initial acceptance of emerging technologies: An empirical study of mobile banking services. Decis Support Syst. 2010;49:222-34.
25. Venkatesh V, Morris MG, Davis GB, Davis FD. User acceptance of information technology: Toward a unified view. MIS Quarterly. 2003;27:425-78.
26. Afshan S, Sharif A. Acceptance of mobile banking framework in Pakistan. Telemed Inf. 2016;33:370-87.
27. Bhatiasevi V. An Extended UTAUT Model to Explain the Adoption of Mobile Banking. Inf Dev. 2016;32:799-814.
28. Oliveira T, Faria M, Thomas MA, Popovič A. Extending the understanding of mobile banking adoption: When UTAUT meets TTF and ITM. Int J Inf Manage. 2014;34:689-703.
29. Slade EL, Dwivedi YK, Piercy NC, Williams MD. Modeling consumers' adoption intentions of remote mobile payments in the United Kingdom: Extending UTAUT with innovativeness, risk, and trust. Psychol Mark. 2015;32:860-73.
30. Khatun F, Palas MJU, Ray P. Using the Unified Theory of Acceptance and Use of Technology model to analyze cloud-based mHealth service for primary care. Digit Med. 2017;3:69-75.
31. Park H, Chon Y, Lee J, Choi Ie J, Yoon KH. Service design attributes affecting diabetic patient preferences of telemedicine in South Korea. Telemed J E Health. 2011;17:442-51.
32. Cocosila M, Archer N. Perceptions of chronically ill and healthy consumers about electronic personal health records: a comparative empirical investigation. BMJ Open. 2014;4:e005304.
33. Lee MKO, Turban E. A Trust Model for Consumer Internet Shopping. Int J Electron Commer. 2001;6:75-91.
34. Dodds WB. In search of value: how price and store name information influence buyers' product perceptions. J Consum Mark. 1991;8:15-24.
35. Gupta S. Impact of Sales Promotions on when, what, and how Much to Buy. J Mark Res. 1988;25:342-55.
36. Rayport J, Sviokla J. Managing the marketspace. Harv Bus Rev. 1994;72:141-50.
37. Chen Y-H, Barnes S. Initial trust and online buyer behavior. Ind Manag Data Syst. 2007;107:21-36.
38. Eriksson K, Kerem K, Nilsson D. Customer acceptance of Internet banking in Estonia. Int J Bank Mark. 2005;23:200-16.
39. Guriting P, Ndubisi N. Borneo online banking: Evaluating customer perceptions and behavioural intention. Manag Res News. 2006;29:6-15.
40. Jaruwachirathanakul B, Fink D. Internet banking adoption strategies for a developing country: The case of Thailand. Internet Res. 2005;15:295-311.
41. Venkatesh V, Davis F. A Theoretical Extension of the Technology Acceptance Model: Four Longitudinal Field Studies. Manag Sci. 2000;46:186-204.
42. Davis F, Bagozzi R, Warshaw P. User Acceptance of Computer Technology: A Comparison of Two Theoretical Models. Manag Sci. 1989;35:982-1003.
43. Abbad M. E-banking in Jordan. Behav Inf Technol. 2013;32:681-94.
44. Çelik H. What determines Turkish customers' acceptance of Internet banking? Int J Bank Mark. 2008;26:353-70.
45. Kesharwani A, Tripathy T. Dimensionality of Perceived Risk and Its Impact on Internet Banking Adoption: An Empirical Investigation. Serv Mark Q. 2012;33:177-93.
46. Lee M-C. Factors influencing the adoption of internet banking: An integration of TAM and TPB with perceived risk and perceived benefit. Electron Commer Res Appl 2009;8:130-41.
47. Wei W, Kim G, Miao L, Behnke C, Almanza B. Consumer inferences of corporate social responsibility (CSR) claims on packaged foods. J Bus Res. 2018;83:186-201.

48. Yuen YY, Yeow PH, Lim N. Internet banking acceptance in the United States and Malaysia: a cross-cultural examination. Mark Intell Plan. 2015; 33:292-308.
49. Kalinić Z, Liébana-Cabanillas FJ, Muñoz-Leiva F, Marinković V. The moderating impact of gender on the acceptance of peer-to-peer mobile payment systems. Int J Bank Mark. 2020;38:138-58.
50. M. AAL, Alamro AS. Factors affecting intention to use e banking in Jordan. Int J Bank Mark 2019;38:86-112.
51. Leon S. Service mobile apps: a millennial generation perspective. Ind manage data syst. 2018;118:1-20.
52. Ozturk AB. Customer acceptance of cashless payment systems in the hospitality industry. Int J Contemp Hosp. 2016;28:801-17.
53. Zhao H, Sophia A, Lini Z, Nannapat J. Understanding the impact of financial incentives on near field communication (NFC) mobile payment adoption: an experimental analysis. Int J Bank Mark. 2019;37:1296-312.
54. Awang Z. Structural Equation Modeling Using Amos Graphic: UiTM Press; 2012.
55. Al-Mamary YH, Shamsuddin A. Testing of the Technology Acceptance Model in Context of Yemen. Mediterr J Soc Sci. 2015;6:268-73.
56. Sica C, Ghisi M. The Italian versions of the Beck Anxiety Inventory and the Beck Depression Inventory-II: Psychometric properties and discriminant power. 2007.p.27-50.
57. Wu J-H, Wang Y-M. Measuring KMS success: A respecification of the DeLone and McLean's model. Inf Manag. 2006;43:728-39.
58. Bentler PM. Comparative fit indexes in structural models. Psychol Bull. 1990;107:238-46.
59. Sharma GP, Verma RC, Pathare P. Mathematical modeling of infrared radiation thin layer drying of onion slices. J Food Eng. 2005;71:282-6.
60. Pedroso R, Zanetello L, Guimarães L, Pettenon M, Gonçalves V, Scherer J, et al. Confirmatory factor analysis (CFA) of the Crack Use Relapse Scale (CURS). Arch Clin Psychiatry. 2016;43:37-40.

# The Prevalence of Cleft Lip and Palate and Their Effect on Growth and Development: A Narrative Review

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## ABSTRACT

Cleft lip and/or cleft palate (CL±P) in addition to the cleft palate (CP) are a category of anomalies known as orofacial clefts (OC). These anomalies are accompanied by several aesthetic and functional problems. Information on the prevalence of OC showed different values between studies worldwide. In addition, the presence of cleft lip and/or cleft palate is determined by several changes during the embryonic stage. Besides, cleft repair may lead to a significant impact on the overall aesthetic and function and could negatively affect maxillary growth on certain occasions. Therefore, having the background and knowledge on this phenomenon is essential in designing the overall treatment and obtaining outcomes that are as close to normal as possible. This article reviews the maxillary development, occurrence of cleft lip and/or palate and their prevalence, facial growth in the presence of clefts, effect of cleft repair, an overview of alveolar cleft treatment, as well as the essential information related the prevention of cleft lip and palate.

**Keywords:** Alveolar bone grafting; cleft lip; cleft palate; maxilla; orofacial cleft (Siriraj Med J 2022; 74: 819-827)

## INTRODUCTION

Cleft lip and/or cleft palate (CL±P) in addition to the cleft palate (CP) are a category of anomalies known as orofacial clefts (OC).[1] These anomalies are stated as significant congenital deformities in the oral and maxillofacial region and have a notable morbidity throughout the individual's lifespan, as well as complex etiology.[2] Several patients with OC do not present with other manifestations (non-syndromic OC), however, a good portion (30% to 50%) have other abnormalities that can be involved or presented as a syndrome (syndromic OC).[3]

Factors related to the etiology for the greatest number of incidences include genetic and environmental effects, in addition to the phenotypic differences that take action in early development.[4] Around 70% of the cases are listed as (non-syndromic) with complexity in their etiology, including environmental and genetic factors, in relation to a multifactorial threshold pumped by hereditary.[5] Mendelian/heterogeneous anomalies and teratogenic causes are the following possible etiologies.[6]

Clefts are normally accompanied by several aesthetic and functional problems, including the discontinuity of the lip, abnormal muscle attachments, phonetic issues,

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infections, tooth eruption within the clefts, oronasal fistula, and the deviation of alveolar segments. This will lead to speech problems in the case of large defects.[7,8] Certainly, patients with any type of cleft require critical care from birth until the adult stage.[9] This necessitates an understanding of the etiology, manifestations, associated issues, and possible complications that accompany this malformation, in order to provide acceptable treatment that will help restore the optimal function and aesthetics for these patients.

This article reviews the maxillary development, occurrence of cleft lip and/or palate and their prevalence, facial growth in the presence of clefts, effect of cleft repair, as well as an overview of alveolar cleft treatment.

## Prevalence of cleft lip and/or palate

Information on the prevalence of OC showed different values between studies worldwide. The basic accepted estimation of OC prevalence is one in 700 infants. Moreover, the prevalence of cleft lip and palate is 9.9 per 10,000. Similar numbers were reported in the United States, with 10.2 per 10,000. In Japan, however, the prevalence of CL/P was twice that of the United States.[10] In a systematic review published in 2015, the prevalence of OFC birth was 1.57, 1.56, 1.55, 1.33, 0.99, and 0.57 in Asia, North America, Europe, Oceania, South America, and Africa, respectively. The highest prevalence rate was 2.62 per 1000 live-births among American Indians, followed by 1.73, 1.56, and 1.55 per 1,000 live-births among Japanese, Chinese, and whites, respectively.[9]

With regards to gender, males were found to have a higher chance of having CL/P and CL than females, while females were found to have CP at a higher rate than males. Females were more severely affected.[10,11] The most common cleft type was CLP, followed by CL and CP.[11]

According to European and American studies on non-syndromic cleft prevalence, unilateral cleft lip and palate (UCLP) is the most prevalent type, occupying 30-35% of the cases. Isolated CL and CP account for 20-25% of all cases, while bilateral cleft lip and palate (BCLP) is the most uncommon (about 10%), with submucosa and other clefts accounting for the rest.[12] As for the cleft palate, 30.2% had bilateral cleft and 69.8% had a unilateral cleft. The defect ratio on the right side was 41.1%, while on the left side it was 58.9%. CL is predominantly unilateral (around 90%), with approximately 2/3 (63.1%) of cases occurring on the left side.[13,14]

As can be noticed, CL and CLP tend to occur more frequently on the left side.[15] A possible reason for this higher incidence could be that development of the facial artery is slower on the left side compared to the right side. Moreover, the proximity of the blood vessels that supply the fetal head on the right side leaves the aortic arch closer to the heart, making this side possibly better perfused by blood than the left side.[11,13] This, however, has not been confirmed.

The incidence or birth prevalence of CLP in Thailand is known to vary by region. Oral clefts affect about 1.1-2.4 out of every 1000 live births. CLP was noted to occur more frequently than CL or CP alone, showing a percentage of 59.8, while CP had 21.9%, and CL had 18.3%.[15] Female patients showed relatively higher incidences of cleft lip or cleft palate alone, with CP 53.5% and CL 53.2%. On the other hand, male patients were more affected with cleft lip and palate (CL/P 58.3%).[16]

According to a study conducted in Thailand, more than half of CL/P patients were from the Northeastern region. In 2015, the average birth prevalence at Tawanchai Cleft Center was 1.51 per 1000 live births. Regarding cleft palate, Phisanulok had the highest CLP birth rate of 2.01 per 1000 live births, while Songkhla had the lowest rate of 1.06 CLP per 1000 live births. The CLP birth prevalence was 1.31, 2.01, 1.69, and 1.06 per 1000 live births in the Northeast, North, Center, and South, respectively,[17] as shown in Fig 1.

## Embryology of cleft lip and palate

Cleft lip and palate are a defect resulting from the insufficient integration of facial prominences through the embryonic phase.

### *Maxillary bone growth*

Changes in maxillary size have been well stated in the literature. The increase in the maxillary height occurs towards the frontal and zygomatic bones, as well as the lower aspect of the alveolar process. This takes place concurrently with the eruption of teeth in the maxilla. Growth in the length of the maxilla appears suturally directed to the palatine bones, accompanied by the maxillary tuberosities.[18]

Transverse palatine suture and tuberosity play an important role in elongating the maxilla in the anterior-posterior direction.[19] At the age of 13-15 years old, the hard palate had grown to its full length. The apposition appears to last for several years after this period. The posterior part of the palate was lower in the vertical direction than the anterior part of the palate.[20] Using the implant method, Bjork discovered that transverse growth is greater in the posterior than in the anterior. The median palatine suture grew at a rate comparable

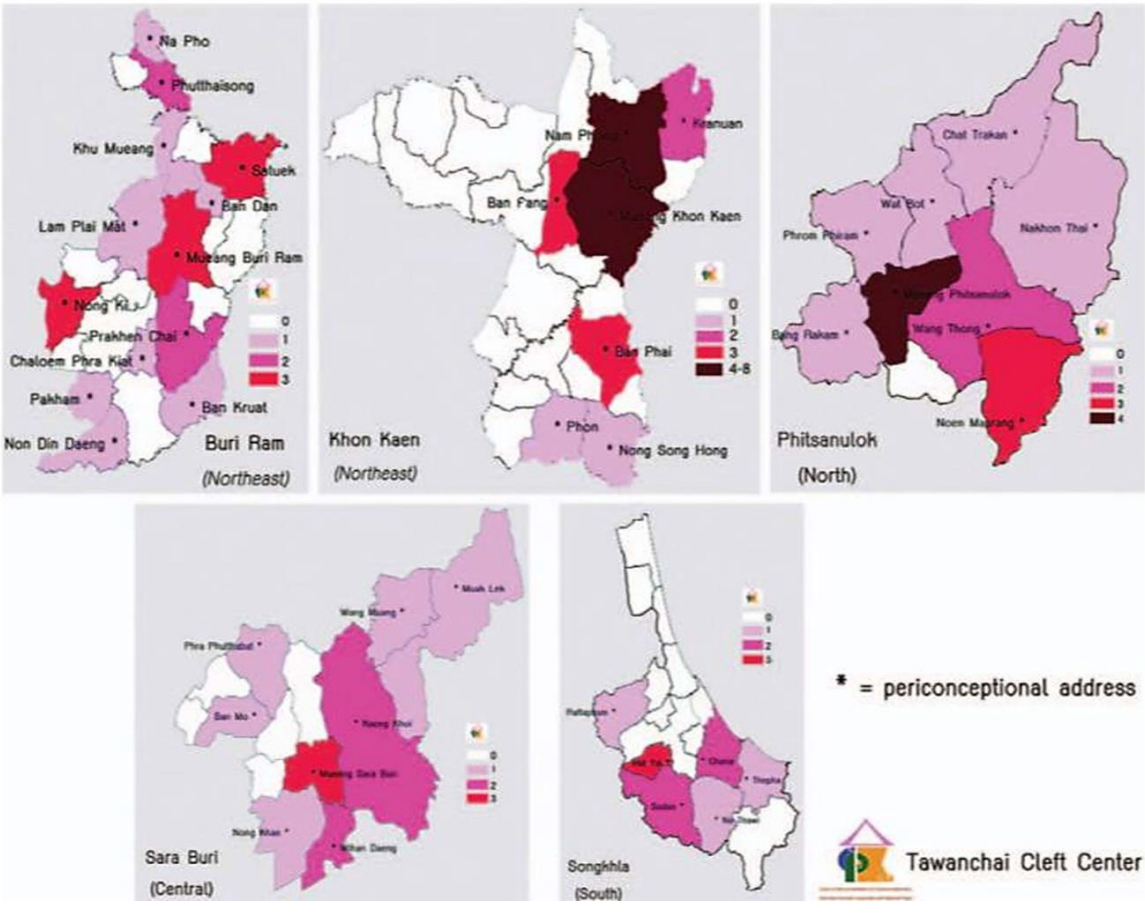


**Fig 1.** The number of newborns with CLP in 5 provinces by Tawanchai cleft center (Adapted from Chowcheun, 2015).

to that of the body height. The median suture grew two years faster than the rest of the body.[20,21] Sutural growth takes 18 years to complete, while body height growth takes 20 years. Sutural growth accounts for only about a quarter of the total width increase.[21]

The failure of the lateral palatine processes to meet and fuse results in a cleft palate. It takes place as a response to divergence from normal formation during frontonasal prominence development and fusion. This can be due to the lack of palatal shelf growth or the failure of these palatal shelves failure to rise above the tongue. Other factors such as the absence of any contact between the shelves, or any disturbance during or after fusion of the shelves will also result in cleft palate.[21] (Fig 2) The presence of cleft palate will cause a malformed maxillary process and distress the process of tooth eruption.[22] The most common cleft is situated in the area between the canine and the lateral incisor.[23]

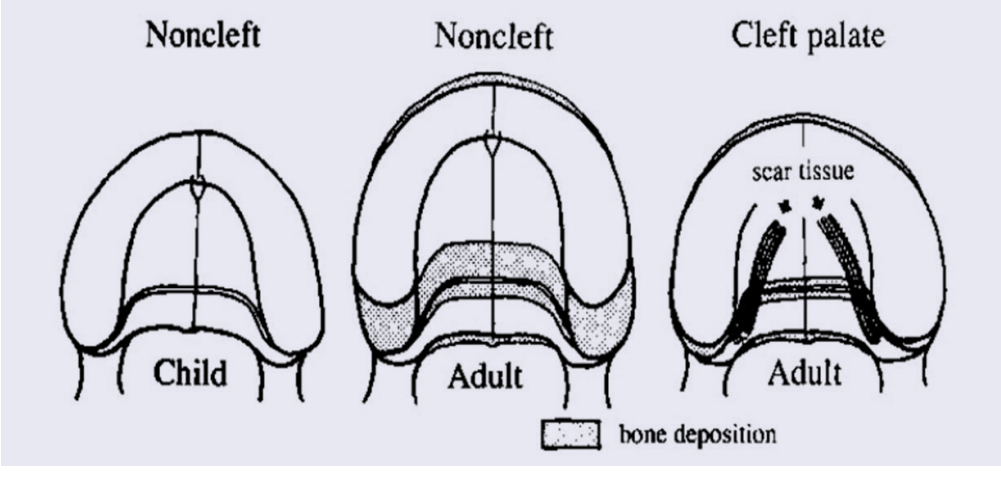


**Fig 2.** Growth of maxilla in non-cleft and cleft patients (adapted from Friede, 1998).

*Surrounding soft tissue growth*

The muscle systems that affect maxillary growth are composed of two different groups. The upper part of the orbicularis oris muscle and the nasolabial muscle ring represent the anterior facial muscle chain, while the posterior facial muscle chain consists of the deep facial and cervical muscle chains. The soft palate and tongue are supported by the upper part of the later ring, which provides momentum for the growth of the upper jaw, particularly the posterior and lateral aspects of the maxilla.[24,25] However, when clefts are present, the ossification takes place 2 weeks following the presence of muscle precursors. Consequently, bone formation occurs under the effect of asymmetrical muscular pull.[26] In addition, anatomical malformations that participate in the occurrence of cleft lip nasal defect involve a short columella, malpositioning of the lesser maxillary segment, as well as the displacement of the lower lateral cartilage.[27] (Fig 3)

**Effect of cleft lip/palate on growth and development**

*Growth in cleft lip and palate*

CL/P has an impact on craniofacial development due to a variety of factors, including inherent developmental deficiencies, functional distortions, and iatrogenic factors resulting from surgical treatment.[19] In patients with CL/P, the growth and form of the maxillary arch are affected in three planes: vertical, anteroposterior, and transverse. Skeletal class III in anteroposterior direction due to maxillary hypoplasia as a result of scar tissue. Occlusal canting, excessive freeway space, and altered mandibular posture were all found to be signs of vertical deficiency. In the transverse plane, a narrow maxilla with a lack of bony development, as well as scar tissue from previous palatal repair, can restrict maxilla growth.[28]

Patients with CL/P have trouble in the palatal suture system. The median palatine suture has an abnormal position lateral to the midline in complete unilateral clefts, and the segment on the cleft side has no sutural connection with the maxilla on the noncleft side in the untreated condition. The midpalatal suture is completely absent in the bilateral case, and the maxillary complex is divided into three parts.[21,28]

Considering the general growth of individuals with clefts, it has been documented that such patients have lower weight and are smaller in size, compared to children with no clefts. Becker et al[29] compared infants with isolated cleft palate, as well as cleft lip and palate, with the control group. Their results showed that these infants were lighter and shorter than the control subjects. Similarly, Jones[30] noticed that weight gain per week was lower in neonates with clefts, as opposed to normal individuals. In addition, Lee et al.[31] found that growth was disturbed during early infancy in patients with clefts. However, children reached their anticipated weight by the age of two. On the other hand, a study on a group of boys with clefts, that are aged between 6 to 20, indicated delayed skeletal maturity in these patients over the entire evaluation period, compared to the control group (subjects with no clefts).[32] All these data from previous studies suggest that clefts will have a potential impact on growth and development.

*Effect of cleft lip/palate on food intake*

As mentioned earlier, newborns with CL/P will have developmental delays. Aside from the genetic alterations that may lead to such incidences, food intake in cleft patients plays a role as a contributing factor. The main point is that a cleft lip, for instance, can result in issues in making a seal around the nipple when the infant is being breastfed, nevertheless, this may still be achieved in general.[33] In contrast, a cleft palate causes extreme difficulty for newborns, preventing them from generating the negative pressure that is essential for milk intake.[34] Moreover, having a cleft palate can also lead to problems in breathing while feeding. This will considerably prolong

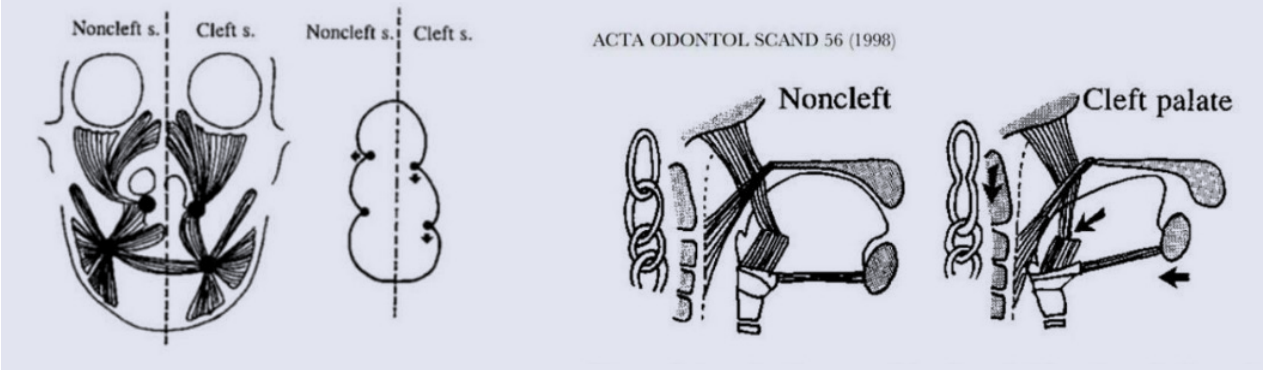


**Fig 3.** surrounding soft tissue affects growth (adapted from Friede, 1998).

the feeding time, keeping in mind that clefts of the hard palate also diminish the ability to utilize the tongue to compress the nipple and feed.

Based on all the mentioned problems with food intake that accompany children with CL/P, feeding is one of the main reasons why the surgical repair of clefts should be carried out and completed. Vries et al.[35] showed that the surgical repair of the palate led to a significant improvement in feeding, as reported by 79% of parents of children with cleft palate included in their study.

*Effect of cleft lip/palate on speech and expression*

Several investigations in the literature stated that patients with cleft lip and palate manifest problems with expressive language, as indicated by acquiring words and sounds at a slower rate, compared with individuals with no clefts.[36,37] Abnormalities in word production are seen in children with clefts due to the several factors; altered orofacial growth, anomalies in oronasal function and composition, affected neuromotor patterns during early development of infants, not to mention the disturbed psychosocial development for most of these individuals.[38] Children with cleft palate produce atypical consonants, have abnormal nasal resonance and airflow, and the laryngeal voice quality will also be impaired.[39] All these features will lead to what is termed "cleft palate speech". In addition, the major concern is that even with the early surgical intervention and the treatment of cleft palate, children still demonstrated delays in speech development and it was noted that they still had "cleft palate speech".[40] On the other hand, treating cleft lips resulted in better outcomes, as patients obtained age-suitable communication skills.[37]

Previous studies also showed that these early obstacles in language acquisition may continue throughout the childhood stage in some patients,[41] which reveals the importance of the early assessment of language acquisition and speech therapy for individuals with cleft lip and palate.

## Growth in un-operated cleft patients

The growth of the maxilla in unoperated CL/P is similar to that of those without a cleft.[42] The cephalometric analysis revealed that the craniofacial growth pattern was normal, resulting in normal facial morphology.

Normal facial projection was seen in unoperated CL, with only dental arch malalignment in the cleft region. On the non-cleft side, the dental arch was normal, but there was medial collapse on the cleft side and lateral rotation of the premaxillary segment on the non-cleft side.[42,43] The nasal septum and columella were found to be shifted to the non- cleft side of the facial midline, while the incisor teeth shifted to the cleft side. Unoperated CLP, on the other hand, had a smaller and more protrusive maxilla, and the arch form was more V-shaped,[44] while unoperated cleft lip and alveolus showed greater premaxilla projection, increased maxillary length, prominence of the anterior teeth (labial tipping), a wider ANB angle, which represents the relative position of the maxilla to the mandible (Fig 4), as well as increased maxillary projection.[42]

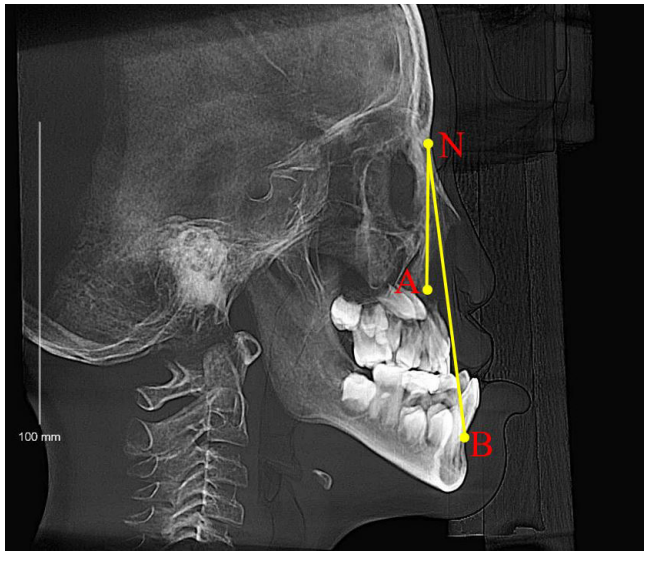


**Fig 4.** ANB angle of cleft lip and cleft palate patient.

## Growth in operated cleft patients

Patients with CL/P can be treated by a multidisciplinary team of experts. From center to center, the surgical and orthodontic treatment schedules differ slightly. It usually includes the following components: infant orthopedics, surgical lip closure, surgical soft/hard palate closure, alveolar cleft bone grafting, orthodontic treatment, secondary lip and nose corrections, and maxillofacial skeleton osteotomies.

Early surgical closure of the lip and palate allows patients to return to normal in terms of both appearance and function. Early surgical treatment disrupted skeletal and dentoalveolar development. Negative consequences appear gradually during facial development, peaking when the patient reaches adulthood. On a skeletal level, the maxilla is frequently underdeveloped in three planes.

A transverse maxillary arch collapse often occurs on the dental level, resulting in a unilateral or bilateral crossbite, crowding, and retroclination of the upper incisors. The longitudinal study found that the growth curve for maxillary width in operated clefts differed significantly from that of normal clefts. The average increase in maxilla width from 10-11 years to adulthood

was 0.3 mm, which is significantly less than the growth in width observed for other transverse dimensions.[45]

The transverse maxillary width growth curve did not resemble the growth curve for body height. In these patients, the curve's shape was inhibited. The outcome is largely determined by the cleft type and the implemented method of surgery. Surgical procedures that may lead to osseous closure of the cleft should be postponed until the sutural growth of the upper part of the face has ceased, to reduce the adverse effects that cause reduction of total maxillary width and decrease the frequency of crossbite in cleft lip and palate patients.[25]

Surgical repair of a cleft is still thought to be the most important secondary factor in the development of specific transverse malocclusion. Bony ankylosis is formed, and scar tissue acts as fibrous ankylosis.

**Effect from lip repair**

During the months following birth, cleft lip procedure is normally performed, and the lip is closed. The impact of lip closure on the final development of the facial and skeleton, as well as tooth position, is disputable. Lip closure is regarded to have a minor influence by some authors.[45] Others, on the other hand, believe it has a significant impact on the final development of the face.[46] The effect of lip closure is limited to the anterior portion of the maxilla.

**Effect from palatal surgery**

The importance of palatal surgery for optimal speech development cannot be overstated. The operation to close the hard and soft palates is widely regarded as the most important factor in the development of dentoalveolar and facial growth problems. Palatal surgery may have a minor short-term effect on palatal growth, but because the posterior region continues to grow until maturity, it has no effect on palatal growth. Palatal surgery may have a significant limiting effect on the three-dimensional growth of the maxilla. It affects the upper face by shortening the maxilla and lowering the posterior maxillary height. With signs of an altered maxillary position in relation to the cranial base, the maxilla was retrognathic.[45]

Some authors believe that hard palate surgery is the most important factor in maxillary segment collapse, while others believe that lip closure is the most important factor. Most authors agree that palatal surgery appears to have a significant sagittal, vertical, and transversal impeding influence on the maxilla's development.

**Alveolar cleft repair**

An alveolar cleft is a well-explained inborn deformity that occupies 0.18–2.50 per 1000 births.[47] When cleft lip is present, alveolar clefts accompany this incidence in 75% of the cases.[48] when the fusion of the nasal process and oropalatal shelves does not fully manifest, this will result in alveolar clefts.[49] This malformation essentially involves the alveolar bone in the site of the canines and lateral incisors, with a possibility to include the central incisors as well.[50]

The guidelines of the surgical repair for clefts rely on obtaining sufficient closure of the mucosa of the nasal floor, aiming to terminate any contact between the nasal and oral cavities, augmenting this anomaly with bone grafts and reaching a proper seal of the oral mucosa on the palatal and labial aspects to attain a complete coverage over the grafted bone.[51]

Knowledge of etiology and risk factors is critical to set how prevention and treatment are planned and applied in the best way, in addition, to measuring the effectiveness of this specific intervention.[5] Bone grafting is a procedure that augments a defect or malformation in shape and size using biological materials,[52] based on the concept of bone regeneration, which is one of the major research fields and aims for craniofacial and orthopedic clinicians.[53]

This method in general has been implemented to treat patients with alveolar clefts as one of the important steps of the intricate treatment plan for cleft lip and palate repair.[54] Augmentation of defects associated with alveolar clefts is an essential part in the construction of bony flow of the dental arch,[22] thus, reestablishing the continuity of jaw segments and avoiding alveolar arch collapse. Bone grafts may also provide a suitable site for the eruption of the canines and can establish proper support for the periodontal tissues of maxillary incisors.[7] In addition, the grafted site offers support for the lip and takes part of the base for nasal floor elevation.[55]

Primary bone grafting (PBG) to repair the alveolar cleft using the rib bone during infancy was the dominant surgical procedure that was performed until the 1970s.[56] However, negative outcomes after PBG were noticed upon accurate examination and during the long-term follow-up, including anterior crossbite and midface retrusion. Conversely, positive results after secondary bone grafting (SBG) have been found.[57] Secondary alveolar bone grafting (SBG) is basically done during the mixed dentition stage of the patient, since the procedure during this stage will cause a minimal effect on maxillary growth.[47]

Moreover, optimal thickness of the bone graft is also a crucial aspect, as the prosthetic restoration might be inserted into the grafted portion in the absence of the desired eruption.[57] Nevertheless, a study was conducted

to evaluate the factors that may affect success when conducting alveolar bone grafting.[58] It was stated that older patients still ended the final follow-up with success. These patients attained bone continuity and healing (Bergland scale I or II), as well as the stabilization of the maxillary arch, without any complications or failure due to graft rejection, and no fistula formation up to one-year post-surgery. In addition, it is important to emphasize that the main idea of treating the alveolar clefts during the mixed dentition stage is to allow for canine eruption in the defect area, which took place inconsistently in the previous reports.[59,60] Therefore, the age of the patient is not likely a drawback that sets the surgical procedure far from success, as acceptable outcomes after bone grafting can still be achieved.

The iliac crest bone graft (ICBG) has been the most applicable grafting material for the secondary alveolar bone grafting procedure, since it provides a large volume of bone, is fairly easy to harvest, and the procedure can be done concurrently with the alveolar cleft preparation.[61] It is considered the gold standard for alveolar cleft repair, keeping in mind that the autogenous bone holds the three features of ideal bone formation; osteoconduction, osteoinduction, and osteogenicity.[62,63] The survival of ICBG is 84%, as stated by Oberoi et al.[64] A retrospective study reviewed cleft cases of 468 patient.[65] Cleft repair was performed at an age between 7 and 11 years.

It was concluded that the autogenous bone graft is a good option because it provides instant revascularization, can be placed easily in the cleft site, gives the possibility for the eruption of canine teeth in a suitable environment, and can be the graft for placing dental implants. The spongious bone allows faster healing of the defect than the cortical bone. Nevertheless, other sources of bone grafts are showing promising results that are comparable to the autogenous bone, with the valuable benefit of eliminating the second surgery and the donor site morbidity.[52] Therefore, future studies on the use of these grafts are of high importance, to confirm the outcomes provided by these alternatives to autogenous bone.

### Prevention of cleft lip and palate

Prevention can be divided into 3 main categories. Primary prevention refers to blocking a disease process from starting. With respect to clefts, this could be achieved by eliminating any identified etiologic and risk factors. Secondary prevention entails the early diagnosis and treatment of this condition. In other words, prenatal diagnosis, as well as the earliest possible check-up at the hospital to obtain a thorough consultation, promptly manage this incidence and carry out the necessary treatment on time. When the possibility of primary prevention becomes inapplicable, and following secondary prevention, tertiary prevention is necessary. This focuses on psychosocial care and proper management of the condition, aiming to improve the patient's quality of life. Speech therapy to improve the patient's social life, in addition to later orthodontic treatment and orthognathic surgery to enhance function and aesthetics are essential steps in tertiary prevention. The most effective strategy to decrease the occurrence of cleft lip and palate is primary prevention.[66]

Environmental risk factors are also of importance in cleft lip and palate. These include maternal exposure to tobacco smoke, alcohol, poor nutrition, viral infection, medicinal drugs, and teratogens in early pregnancy. Moreover, advanced maternal and paternal age is known to result in gene mutation and chromosomal abnormalities. On the other hand, maternal use of multivitamin supplements in early pregnancy has been linked to decreased risk of orofacial clefts.[67] A previous meta-analysis concluded that the use of multivitamins resulted in a 25% reduction in birth prevalence of CL/Ps.[68]

Therefore, it becomes clear that best method for achieving an effective prevention of cleft lip and palate is likely to be the awareness of potential etiology and risk factors and proper counseling of physicians, which has been confirmed in previous reports.[67,69,70] Health care professionals must be fully informed about the various prevention strategies available, in order to deliver the necessary information and knowledge to parents, aiming to reduce the prevalence of cleft lip and palate in future generations.

## CONCLUSION

Cleft lip and/or palate is a condition that necessitates critical and concise treatment planning and execution, keeping in mind all the factors that are involved in this phenomenon and all the possible manifestations and complications. This will ensure that each case will be handled with care, aiming to reach a result that is the closest to normal when possible.

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## REFERENCES


1. Souza J, Raskin S. Clinical and epidemiological study of orofacial clefts. J Pediatr (Rio J) 2013;89:137-44.
2. Schutte BC, Murray JC. The many faces and factors of orofacial clefts. Hum Mol Genet 1999;8:1853-9.
3. Stoll C, Alembik Y, Dott B, Roth MP. Associated malformations in cases with oral clefts. Cleft Palate Craniofac J 2000;37:41-47.
4. Manyama M, Rolian C, Gilyoma J, Magori CC, Mjema K, Mazyala E, Kimwaga E, Hallgrimsson B. An assessment of orofacial clefts in Tanzania. BMC Oral Health 2011;11:5.
5. Gil-da-Silva-Lopes VL, Monlleó IL. Risk factors and the prevention of oral clefts. Brazilian Oral Research 2014;28:1-5.
6. FitzPatrick DR, Raine PA, Boorman JG. Facial clefts in the west of Scotland in the period 1980-1984: epidemiology and genetic diagnoses. J Med Genet 1994;31:126-9.
7. Shirzadeh A, Rahpeyma A, Khajehahmadi S. A Prospective Study of Chin Bone Graft Harvesting for Unilateral Maxillary Alveolar Cleft During Mixed Dentition. J Oral Maxillofac Surg 2018;76:180-8.
8. Ungkanont K, Tabthong A, Komoltri C, Leelaporn A, Vathanophas V, Tanphaichitr A, Wensanthia T. Long-term Outcome of the Management of Otitis Media with Effusion in Children with and Without Cleft Palate Using the House-brand Polyethylene Ventilation Tube Insertion. Siriraj Med J 2021;73:245-51.
9. Panamonta V, Pradubwong S, Panamonta M, Chowchuen B. Global Birth Prevalence of Orofacial Clefts: A Systematic Review. J Med Assoc Thai 2015;98 Suppl 7:S11-21.
10. Watkins SE, Meyer RE, Strauss RP, Aylsworth AS. Classification, epidemiology, and genetics of orofacial clefts. Clin Plast Surg 2014;41:149-63.
11. Nagase Y, Natsume N, Kato T, Hayakawa T. Epidemiological Analysis of Cleft Lip and/or Palate by Cleft Pattern. J Maxillofac Oral Surg 2010;9:389-95.
12. Hagberg C, Larson O, Milerad J. Incidence of cleft lip and palate and risks of additional malformations. Cleft Palate Craniofac J 1998;35:40-45.
13. Mossey PA, Modell B. Epidemiology of oral clefts 2012: an international perspective. Front Oral Biol 2012;16:1-18.
14. Prevalence at birth of cleft lip with or without cleft palate: data from the International Perinatal Database of Typical Oral Clefts (IPDTOC). Cleft Palate Craniofac J 2011;48:66-81.
15. Yılmaz HN, Özbilen E, Üstün T. The Prevalence of Cleft Lip and Palate Patients: A Single-Center Experience for 17 Years. Turk J Orthod 2019;32:139-44.
16. Ittiwut R, Siriwan P, Suphapeetiporn K, Shotelersuk V. Epidemiology of cleft lip with or without cleft palate in Thais. Asian Biomed 2016;10:335-38.
17. Chowchuen B, Thanaviratananich S, Chichareon V, Kamolnate A, Uewichitrapochana C, Godfrey K. A Multisite Study of Oral Clefts and Associated Abnormalities in Thailand: The Epidemiologic Data. Plast Reconstr Surg Glob Open 2015;3:e583.
18. Mogavero FJ, Buschang PH, Wolford LM. Orthognathic surgery effects on maxillary growth in patients with vertical maxillary excess. Am J Orthod Dentofacial Orthop 1997;111:288-96.
19. Ross RB. Treatment variables affecting facial growth in complete unilateral cleft lip and palate. Cleft Palate J 1987;24:5-77.
20. Björk A. The use of metallic implants in the study of facial growth in children: method and application. Am J Phys Anthropol 1968;29:243-54.
21. Björk A, Skieller V. Growth in width of the maxilla studied by the implant method. Scand J Plast Reconstr Surg 1974;8:26-33.
22. Kamal M, Ziyab AH, Bartella A, Mitchell D, Al-Asfour A, Holzle F, Kessler P, Lethaus B. Volumetric comparison of autogenous bone and tissue-engineered bone replacement materials in alveolar cleft repair: a systematic review and meta-analysis. Br J Oral Maxillofac Surg 2018;56:453-62.
23. Kang NH. Current Methods for the Treatment of Alveolar Cleft. Arch Plast Surg 2017;44:188-93.
24. Markus AF, Delaire J, Smith WP. Facial balance in cleft lip and palate. II. Cleft lip and palate and secondary deformities. Br J Oral Maxillofac Surg 1992;30:296-304.
25. Friede H. Growth sites and growth mechanisms at risk in cleft lip and palate. Acta Odontol Scand 1998;56:346-51.
26. Breitsprecher L, Fanghänel J, Metelmann HR, Mlynski G, Würfel F, Freise K, Knape U. The influence of the muscles of facial expression on the development of the midface and the nose in cleft lip and palate patients. A reflection of functional anatomy, facial esthetics and physiology of the nose. Ann Anat 1999;181:19-25.
27. Bagatain M, Khosh MM, Nishioka G, Larrabee WF. Isolated nasalis muscle reconstruction in secondary unilateral cleft lip nasal reconstruction. Laryngoscope 1999;109:320-3.
28. Björk A, Skieller V. Growth of the maxilla in three dimensions as revealed radiographically by the implant method. Br J Orthod 1977;4:53-64.
29. Becker M, Svensson H, Källén B. Birth weight, body length, and cranial circumference in newborns with cleft lip or palate. Cleft Palate Craniofac J 1998;35:255-61.
30. Jones WB. Weight gain and feeding in the neonate with cleft: a three-center study. Cleft Palate J 1988;25:379-84.
31. Lee J, Nunn J, Wright C. Height and weight achievement in cleft lip and palate. Arch Dis Child 1997;76:70-72.
32. Jensen BL, Dahl E, Kreiborg S. Longitudinal study of body height, radius length and skeletal maturity in Danish boys with cleft lip and palate. Scand J Dent Res 1983;91:473-81.
33. Bessell A, Hooper L, Shaw WC, Reilly S, Reid J, Glenny AM. Feeding interventions for growth and development in infants with cleft lip, cleft palate or cleft lip and palate. Cochrane Database Syst Rev 2011;2011:Cd003315.
34. Amstalden-Mendes LG, Magna LA, Gil-da-Silva-Lopes VL. Neonatal care of infants with cleft lip and/or palate: feeding orientation and evolution of weight gain in a nonspecialized Brazilian hospital. Cleft Palate Craniofac J 2007;44:329-34.
35. de Vries IA, Breugem CC, van der Heul AM, Eijkemans MJ, Kon M, Mink van der Molen AB. Prevalence of feeding disorders

in children with cleft palate only: a retrospective study. Clin Oral Investig 2014;18:1507-15.
36. Chapman KL, Hardin-Jones M, Schulte J, Halter KA. Vocal development of 9-month-old babies with cleft palate. J Speech Lang Hear Res 2001;44:1268-83.
37. Nagarajan R, Savitha VH, Subramaniyan B. Communication disorders in individuals with cleft lip and palate: An overview. Indian J Plast Surg 2009;42 Suppl: S137-43.
38. Henningsson G, Kuehn DP, Sell D, Sweeney T, Trost-Cardamone JE, Whitehill TL. Universal parameters for reporting speech outcomes in individuals with cleft palate. Cleft Palate Craniofac J 2008;45:1-17.
39. Sell D, Harding A, Grunwell P. GOS.SP.ASS.'98: an assessment for speech disorders associated with cleft palate and/or velopharyngeal dysfunction (revised). Int J Lang Commun Disord 1999;34:17-33.
40. Jones CE, Chapman KL, Hardin-Jones MA. Speech development of children with cleft palate before and after palatal surgery. Cleft Palate Craniofac J 2003;40:19-31.
41. Lohmander-Agerskov A, Söderpalm E, Friede H, Lilja J. A comparison of babbling and speech at pre-speech level, 3, and 5 years of age in children with cleft lip and palate treated with delayed hard palate closure. Folia Phoniatr Logop 1998;50:320-34.
42. Bishara SE, de Arrendondo RS, Vales HP, Jakobsen JR. Dentofacial relationships in persons with unoperated clefts: comparisons between three cleft types. Am J Orthod 1985;87:481-507.
43. Ye Z, Xu X, Ahmatjian A, Bing S. The Craniofacial Morphology in Adult Patients with Unoperated Isolated Cleft Palate. Bone Res 2013;1:195-200.
44. McCance AM, Roberts-Harry D, Sherriff M, Mars M, Houston WJ. A study model analysis of adult unoperated Sri Lankans with unilateral cleft lip and palate. Cleft Palate J 1990;27:146-54; discussion 174-145.
45. Dahl E. Transverse maxillary growth in combined cleft lip and palate. A longitudinal roentgencephalometric study by the implant method. Cleft Palate J 1979;16:34-41.
46. Capelozza Filho L, Normando AD, da Silva Filho OG. Isolated influences of lip and palate surgery on facial growth: comparison of operated and unoperated male adults with UCLP. Cleft Palate Craniofac J 1996;33:51-56.
47. Wu C, Pan W, Feng C, Su Z, Duan Z, Zheng Q, Hua C, Li C. Grafting materials for alveolar cleft reconstruction: a systematic review and best-evidence synthesis. Int J Oral Maxillofac Surg 2018;47:345-56.
48. Chen GC, Sun M, Yin NB, Li HD. A Novel Method to Calculate the Volume of Alveolar Cleft Defect Before Surgery. J Craniofac Surg 2018;29:342-6.
49. Khojasteh A, Kheiri L, Behnia H, Tehranchi A, Nazeman P, Nadjmi N, Soleimani M. Lateral Ramus Cortical Bone Plate in Alveolar Cleft Osteoplasty with Concomitant Use of Buccal Fat Pad Derived Cells and Autogenous Bone: Phase I Clinical Trial. BioMed Research International 2017;2017:12.
50. Kaura AS, Srinivasa DR, Kasten SJ. Optimal Timing of Alveolar Cleft Bone Grafting for Maxillary Clefts in the Cleft Palate Population. J Craniofac Surg 2018;29(6):1551-7.
51. Aly LA, Hammouda N. Secondary closure of alveolar cleft with resorbable collagen membrane and a combination of intraoral autogenous bone graft and deproteinized anorganic bovine bone. Ann Maxillofac Surg 2016;6:165-71.
52. Sun J, Zhang X, Li R, Chen Z, Huang Y, Chen Z. Biological Effects of Orthodontic Tooth Movement Into the Grafted Alveolar Cleft. J Oral Maxillofac Surg 2018;76:605-15.
53. Rachmiel A, Emodi O, Aizenbud D, Rachmiel D, Shilo D. Two-stage reconstruction of the severely deficient alveolar ridge: bone graft followed by alveolar distraction osteogenesis. Int J Oral Maxillofac Surg 2018;47:117-24.
54. Elhaddaoui R, Bahije L, Zaoui F, Rerhrhaye W. [Timing of alveolar bone graft and sequences of canine eruption in cases of cleft lip and palate: a systematic review]. Orthod Fr 2017;88:193-8.
55. Salyer KE, Taylor DP. Bone grafts in craniofacial surgery. Clin Plast Surg 1987;14:27-35.
56. Kyung H, Kang N. Management of Alveolar Cleft. Arch Craniofac Surg 2015;16:49-52.
57. Cohen M, Polley JW, Figueroa AA. Secondary (intermediate) alveolar bone grafting. Clin Plast Surg 1993;20:691-705.
58. Mahardawi B, Boonsiriseth K, Pairuchvej V, Wongsirichat N. Alveolar cleft bone grafting: factors affecting case prognosis. J Korean Assoc Oral Maxillofac Surg 2020;46:409-16.
59. Troxell JB, Fonseca RJ, Osbon DB. A retrospective study of alveolar cleft grafting. J Oral Maxillofac Surg 1982;40:721-5.
60. El Deeb M, Messer LB, Lehnert MW, Hebda TW, Waite DE. Canine eruption into grafted bone in maxillary alveolar cleft defects. Cleft Palate J 1982;19:9-16.
61. Bajaj AK, Wongworawat AA, Punjabi A. Management of alveolar clefts. J Craniofac Surg 2003;14:840-6.
62. Liang F, Leland H, Jedrzejewski B, Auslander A, Maniskas S, Swanson J, Urata M, Hammoudeh J, Magee W, 3rd. Alternatives to Autologous Bone Graft in Alveolar Cleft Reconstruction: The State of Alveolar Tissue Engineering. J Craniofac Surg 2018;29: 584-93.
63. Mahardawi B, Rochanavibhata S, Jiaranuchart S, Arunjaroensuk S, Mattheos N, Pimkhaokham A. Autogenous tooth bone graft material prepared chairside and its clinical applications: a systematic review. Int J Oral Maxillofac Surg 2022 May 23;S0901-5027(22)00193-X. doi: 10.1016/j.ijom.2022.04.018.
64. Oberoi S, Chigurupati R, Gill P, Hoffman WY, Vargervik K. Volumetric assessment of secondary alveolar bone grafting using cone beam computed tomography. Cleft Palate Craniofac J 2009;46:503-11.
65. Morselli PG, Giuliani R, Pinto V, Oranges CM, Negosanti L, Tavaniello B, Morellini A. Treatment of alveolar cleft performing a pyramidal pocket and an autologous bone grafting. J Craniofac Surg 2009;20:1566-70.
66. Oginni FO, Adenekan AT. Prevention of oro-facial clefts in developing world. Ann Maxillofac Surg 2012;2:163-9.
67. Ren A, Zhang L, Li Z, Hao L, Tian Y, Li Z. Awareness and use of folic acid, and blood folate concentrations among pregnant women in northern China--an area with a high prevalence of neural tube defects. Reprod Toxicol 2006;22:431-6.
68. Shah PS, Ohlsson A. Effects of prenatal multimicronutrient supplementation on pregnancy outcomes: a meta-analysis. Cmaj 2009;180:E99-108.
69. Nawapun K, Phupong V. Awareness of the benefits of folic acid and prevalence of the use of folic acid supplements to prevent neural tube defects among Thai women. Arch Gynecol Obstet 2007;276:53-57.
70. Shaw GM, Nelson V, Carmichael SL, Lammer EJ, Finnell RH, Rosenquist TH. Maternal periconceptional vitamins: interactions with selected factors and congenital anomalies? Epidemiology 2002;13:625-30.