E-ISSN 2228-8082
Volume 76, Number 11, November 2024

136 YEAR SIRIRAJ

SMJ

Siriraj Medical Journal

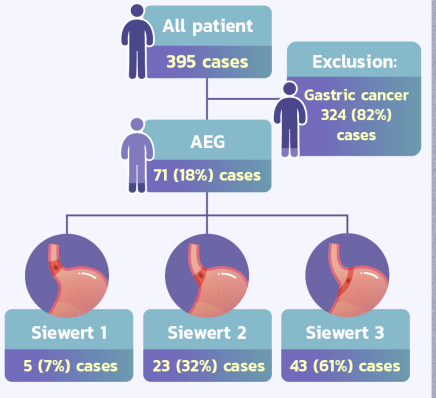
The world-leading biomedical science of Thailand

MONTHLY

ORIGINAL ARTICLE

Outcomes of Microscopic Residual Tumor after Curative-Intent Surgery in Adenocarcinoma of Esophagogastric Junction

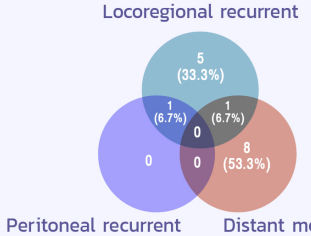
R1 resection is clearly associated with poorer survival outcomes.



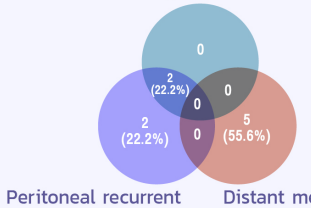
71 patients with adenocarcinoma

of the **esophagogastric junction** who underwent curative-intent surgery

Oncologic outcome of **microscopic residual tumor (R1)** after surgery

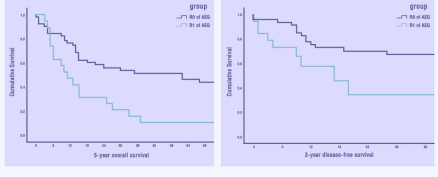


(a) RO group N=52



(b) R1 group N=19

- **R1 26.8%** (positive resection margins 11.3%, malignant cells from peritoneal washing fluid cytology 14.0%, and both 1.4%)
- **RO VS. R1 group:** Median OS 31.3 vs 11.9 month
  - **5-year** OS 26.2% vs 11.9%
  - **3-year** DFS 24.4% vs 9.8%



Distant metastasis is the most common site of recurrence in both **RO and R1 groups.**

SCAN FOR FULL TEXT

SMJ SIRIRAJ MEDICAL JOURNAL | Nampoolsuksan, et al. *Siriraj Med J* 2024;76(11):758-65.
©Siriraj Medical Journal. All rights reserved. Graphical abstract by Y Krimouy

Indexed by Scopus® DOAJ

https://he02.tci-thaijo.org/index.php/sirirajmedj/index
E-mail: sijournal92@gmail.com

SMJ
Siriraj Medical Journal
The world-leading biomedical science of Thailand
Volume 76 Number 11
November 2024

ORIGINAL ARTICLE

735 Comparison of Second-Trimester Uterine Artery Doppler Indices between Pregnant Women with and without Prior Cesarean Delivery and Effect on Perinatal Outcomes
Bundaree Chaiprasit, Suthasinee Mataneedol, Buppa Smanchat, Kornkarn Bhamarapravatana, Komsun Suwannarurk

746 Health Survey of Monks Residing in Urban Areas: The Bangkok Noi Model
Wasumadee Ko-amornsup, Arunotai Siriussawakul, Kanuch Aosangdeekul, Rinrada Preedachitkul, Varalak Srinonprasert, Pawit Somnuke, Weerasak Muangpaisan, Ponnapa Petchthai, Naris Kitnarong

758 Outcomes of Microscopic Residual Tumor after Curative-Intent Surgery in Adenocarcinoma of Esophagogastric Junction
Chawisa Nampoolsuksan, Khajohnsak Bhocksombud, Thammawat Parakonthun, Tharathorn Suwatthanarak, Thikhamporn Tawantanakorn, Nicha Srisuworanan, Voraboot Taweerutchana, Atthaphorn Trakarnsanga, Chainarong Phalanusitthepha, Jirawat Swangsri, Thawatchai Akaraviputh, Asada Methasate, Vitoon Chinswangwatanakul

766 Use of Child Restraint Systems in Thailand and Factors Associated with It: A Cross-Sectional Study
Pakawadi Vuttipittayamongkol, Roungtiva Muenpa, Prakasit Wannapaschaiyong

774 Correlation of American Urological Association Symptom Index Domains with Uroflowmetric Peak Flow in Thai Patients with Suspected Benign Prostatic Hyperplasia
Sidaporn Chayochaichana, Julin Opanurak, Apirak Santingamkun, Supoj Ratchanon

781 Improvement in the Youthfulness of Facial Skin after a Single Treatment with Platelet Rich Plasma
Nutthawut Akaranuchat, Natthapong Kongkunnavat

789 Optimization of the Use of the DOTATATE Kit Manufactured by the Thailand Institute of Nuclear Technology Using a SiO_2-based $^{68}Ge/^{68}Ga$ Generator
Phattarayut Jaiuea, Somlak Kongmuang, Kanyapat Lumyong, Thanete Doungta, Shuichi Shiratori

SIRIRAJ MEDICAL JOURNAL

https://he02.tci-thaijo.org/index.php/sirirajmedj/index

Executive Editor:
Professor Apichat Asavamongkolkul, Mahidol University, Thailand

Editorial Director:
Professor Aasis Unnanuntana, Mahidol University, Thailand

Associate Editors
Assistant Professor Adisorn Ratanayotha, Mahidol University, Thailand
Professor Pieter Dijkstra, University of Groningen, Netherlands
Professor Phunchai Charatcharoenwitthaya, Mahidol University, Thailand
Professor Varut Lohsiriwat, Mahidol University, Thailand



Editor-in-Chief:
Professor Thawatchai Akaraviputh,
Mahidol University, Thailand

International Editorial Board Members

Allen Finley, Delhousie University, Canada
Christopher Khor, Singapore General Hospital, Singapore
Ciro Isidoro, University of Novara, Italy
David S. Sheps, University of Florida, USA
David Wayne Ussery, University of Arkansas for Medical Sciences, USA
Dennis J. Janisse, Medical College of Wisconsin, USA
Dong-Wan Seo, University of Ulsan College of Medicine, Republic of Korea
Folker Meyer, Argonne National Laboratory, USA
Frans Laurens Moll, University Medical Center Ultrecht, Netherlands
George S. Baillie, University of Glasgow, United Kingdom
Gustavo Saposnik, Unity Health Toronto, St. Micheal Hospital, Canada
Harland Winter, Harvard Medical School, USA
Hidemi Goto, Nagoya University Graduate School of Medicine, Japan
Ichizo Nishino, National Institute of Neuroscience NCNP, Japan
Intawat Nookaew, University of Arkansas for Medical Sciences, USA
James P. Doland, Oregon Health & Science University, USA
John Hunter, Oregon Health & Science University, USA
Karl Thomas Moritz, Swedish University of Agricultural Sciences, Sweden
Kazuo Hara, Aichi Cancer Center Hospital, Japan
Keiichi Akita, Institute of Science Toko, Japan
Kyoichi Takaori, Kyoto University Hospital, Japan
Marcela Hermoso Ramello, University of Chile, Chile
Marianne Hokland, University of Aarhus, Denmark
Matthew S. Dunne, Institute of Food, Nutrition, and Health, Switzerland
Mazakayu Yamamoto, Tokyo Women's Medical University, Japan
Mitsuhiro Kida, Kitasato University & Hospital, Japan
Moses Rodriguez, Mayo Clinic, USA
Nam H. CHO, Ajou University School of Medicine and Hospital, Republic of Korea
Nima Rezaei, Tehran University of Medical Sciences, Iran
Noritaka Isogai, Kinki University, Japan
Philip A. Brunell, State University of New York At Buffalo, USA
Philip Board, Australian National University, Australia
Ramanuj Dasgupta, Genome Institution of Singapore
Richard J. Deckelbaum, Columbia University, USA
Robert W. Mann, University of Hawaii, USA
Robin CN Williamson, Royal Postgraduate Medical School, United Kingdom
Sara Schwanke Khilji, Oregon Health & Science University, USA
Seigo Kitano, Oita University, Japan
Seiji Okada, Kumamoto University
Shomei Ryozawa, Saitama Medical University, Japan
Shuji Shimizu, Kyushu University Hospital, Japan
Stanlay James Rogers, University of California, San Francisco, USA
Stephen Dalton, Chinese University of HK & Kyoto University
Tai-Soon Yong, Yonsei University, Republic of Korea
Tomohisa Uchida, Oita University, Japan
Victor Manuel Charoenrook de la Fuente, Centro de Oftalmologia Barraquer, Spain
Wikrom Karnsakul, Johns Hopkins Children's Center, USA
Yasushi Sano, Director of Gastrointestinal Center, Japan
Yik Ying Teo, National University of Singapore, Singapore
Yoshiki Hirooka, Nagoya University Hospital, Japan
Yozo Miyake, Aichi Medical University, Japan
Yuji Murata, Aizenbashi Hospital, Japan

Editorial Board Members

Vitoon Chinswangwatanakul, Mahidol University, Thailand
Jarupim Soongswang, Mahidol University, Thailand
Jaturat Kanpittaya, Khon Kaen University, Thailand
Nopphol Pausawasdi, Mahidol University, Thailand
Nopporn Sittisombut, Chiang Mai University, Thailand
Pa-thai Yenchitsomanus, Mahidol University, Thailand
Pornprom Muangman, Mahidol University, Thailand
Prasit Wattanapa, Mahidol University, Thailand
Prasert Auewarakul, Mahidol University, Thailand
Somboon Kunathikom, Mahidol University, Thailand
Supakorn Rojananin, Mahidol University, Thailand
Suttipong Wacharasindhu, Chulalongkorn University, Thailand
Vasant Sumethkul, Mahidol University, Thailand
Watchara Kasinrerk, Chiang Mai University, Thailand
Wiroon Laupattrakasem, Khon Kaen University, Thailand
Yuen Tanniradorn, Chulalongkorn University, Thailand

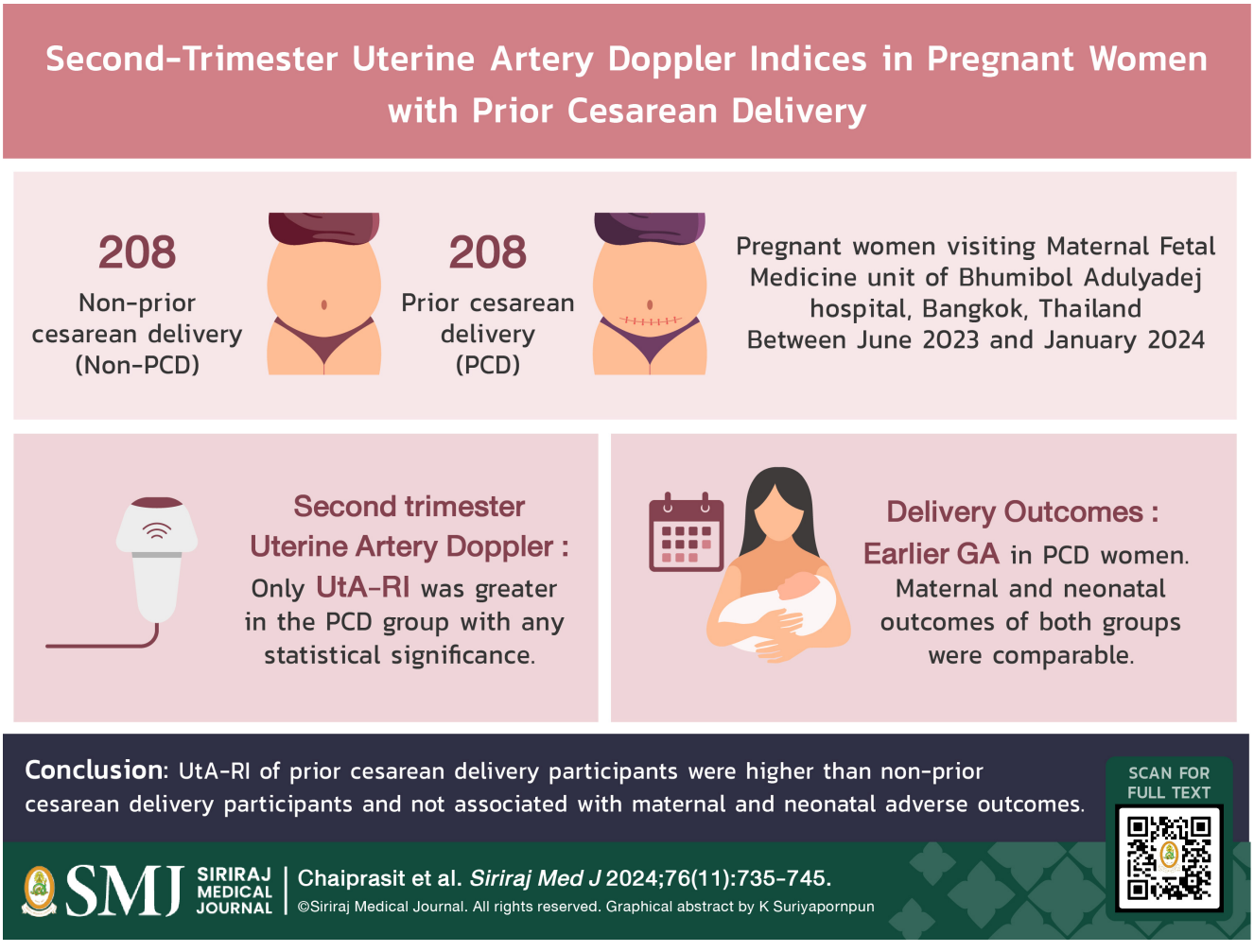
Editorial Assistant: Nuchpraweepawn Saleeon, Mahidol University, Thailand
Proofreader: Amornrat Sangkaew, Mahidol University, Thailand, Nuchpraweepawn Saleeon, Mahidol University, Thailand

Office: His Majesty the King's 80th Birthday Anniversary 5th December 2007 Building (SIMR), 2nd Fl., Room No.207
Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand
E-mail: sijournal92@gmail.com

Comparison of Second-Trimester Uterine Artery Doppler Indices between Pregnant Women with and without Prior Cesarean Delivery and Effect on Perinatal Outcomes

Bundaree Chaiprasit, M.D.[1], Suthasinee Mataneedol, M.D.[1,*], Buppa Smanchat, M.D.[1], Kornkarn Bhamarapravatana, Ph.D.[2], Komsun Suwannarurk, M.D.[3]

[1]Department of Obstetrics and Gynecology, Bhumibol Adulyadej Hospital, Royal Thai Air Force, Bangkok, Thailand, [2]Department of Preclinical Sciences, Faculty of Medicine, Thammasat University, Pathumthani, Thailand, [3]Department of Obstetrics and Gynecology, Faculty of Medicine, Thammasat University, Pathumthani, Thailand.



*Corresponding author: Suthasinee Mataneedol
E-mail: sutha_koi@hotmail.com
Received 12 May 2024 Revised 22 July 2024 Accepted 22 July 2024
ORCID ID:http://orcid.org/0009-0001-2356-6803
https://doi.org/10.33192/smj.v76i11.269247

All material is licensed under terms of the Creative Commons Attribution 4.0 International (CC-BY-NC-ND 4.0) license unless otherwise stated.

ABSTRACT

Objective: To evaluate the effects of prior cesarean delivery on second-trimester Uterine Artery (UtA) Doppler and its effect on perinatal outcomes.

Materials and Methods: This prospective cohort study was conducted at the Maternal Fetal Medicine unit of Bhumibol Adulyadej hospital, Bangkok, Thailand between June 2023 and January 2024. Healthy pregnant women aged between 18 and 45 years old were recruited and divided into prior (PCD) and non-prior cesarean delivery (non-PCD) groups. Both groups underwent UtA Doppler study from 18 to 24 weeks of gestation. UtA Doppler indices consisted of pulsatility index (UtA-PI), resistance index (UtA-RI) and systolic/diastolic ratio (S/D). Demographics, maternal and neonatal outcomes were collected.

Results: Total of 416 participants were recruited and divided equally. The mean age of participants was 30.5 years old. Diabetes mellitus in pregnancy and hypertensive disorder were reported as 18.9 (79/416) and 5.5 (23/416) percent, respectively. From univariate analysis, subjects in the PCD group had higher UtA-PI, UtA-RI and UtA S/D than the non-PCD group with statistical significance. After multiple logistic regressions, only UtA-RI was greater in the PCD group with any statistical significance. The mean gestational age at delivery was 38.41 weeks. Prevalence of small for gestational age deliveries, preeclampsia, and preterm birth were 4.4 (17/376), 3.1 (12/376) and 10 percent (38/376), respectively. Maternal and neonatal outcomes of both groups were comparable. Number of cesarean deliveries, parity, miscarriage, and anterior placentation were not associated with UtA Doppler indices.

Conclusion: UtA-RI of prior cesarean delivery participants were higher than non-prior cesarean delivery participants and not associated with maternal and neonatal adverse outcomes.

Keywords: Uterine artery Doppler indices; cesarean deliveries; second trimester (Siriraj Med J 2024; 76: 735-745)

INTRODUCTION

In recent years, the global rate of cesarean delivery has risen.[1-3] There are various maternal and fetal adverse consequences associated with increased cesarean delivery rates. Uteroplacental insufficiency is one of these consequences.[4-8] According to current evidence, uteroplacental insufficiency contributes to fetal growth restriction, Small for Gestational Age delivery (SGA), and preeclampsia.[9] Frequent monitoring and early screening for abnormal Uterine Doppler Indices in pregnant women with increased risk of uteroplacental insufficiency due to previous cesarean deliveries might improve the quality of their clinical care.[10-13]

Various tools have been studied to predict uteroplacental insufficiency. However, the most extensively researched one is Uterine Artery Doppler Indices.[14] Uterine Artery Doppler Indices consist of uterine artery pulsatility index (UtA-PI), uterine artery resistance index (UtA-RI), and uterine artery S/D ratio (S/D ratio). The values of UtA-PI higher than the 95th percentile is considered abnormal and indicates uteroplacental insufficiency.[15] High-risk pregnant women with abnormal uterine blood flow in their second trimester have a 45 percent preeclampsia (PE) detection rate.[16] The appearance of a diastolic notch in the uterine artery waveform in the second trimester was also used to monitor pregnant women who may have adverse outcomes.[17] Meta-analysis of fetal growth restriction (FGR) and PE pregnant women has shown that an increased UtA-PI in concert with presentation of notch had the most positive predictor ratio for PE (21 in a high-risk population and 7.5 in a low-risk population).[18] Previous studies reported a correlation between women with prior cesarean deliveries (PCD) and increased uterine artery Doppler indices especially the UtA-PI.[19,20] However, some studies showed contradicting results, making the previous claim inconclusive.[21-24]

The primary aim of this study was to investigate the difference in uterine artery Doppler indices between PCD and non-PCD pregnant groups. The secondary aim was to correlate index results with perinatal outcomes, including preeclampsia, abruptio placentae, oligohydramnios, preterm deliveries, fetal acidemia, low Apgar score, prolonged neonatal intensive care unit (NICU) stay, and respiratory complications.

MATERIAL AND METHODS

This prospective cohort study was conducted at Bhumibol Adulyadej Hospital (BAH), Bangkok, Thailand, between June 2023 and January 2024. The study was approved by the ethical committee of BAH in 2023 (IRB No. 31/66). Thai Clinical Trials Registry was approved with registration number TCTR20230529002. Participants were singleton pregnant women aged between 18 and 45 years old who were literate in Thai. Gestational age was

corrected by comparing the accuracy of the last menstrual period (LMP) with the results of the ultrasonographic study during the first trimester. Subjects were divided into study and control groups. The study and control groups were cases with prior (PCD) and no history of cesarean deliveries (non-PCD), respectively. Exclusion occurred with pregnant women where major fetal anomalies were detected from first trimester scanning and participants with abnormal genetic testing results. Characteristics of all eligible participants were collected. Information regarding pregnancy outcomes were also collected from labor and delivery records. The gathered data included gestational age at delivery, preterm delivery, gestational diabetes mellitus (GDM), gestational hypertension (GHT), preeclampsia, non-reassuring fetal heart rate status, oligohydramnios, stillbirth, placental abruption, fetal growth restriction (FGR) and small for gestational age delivery (SGA) (birth weight below the 10th percentile according to Borisut's work).[25] For neonatal outcomes, collected data consisted of birthweight, low Apgar score, NICU admission, length of NICU stay, and respiratory complications.

Informed consent was obtained from all the participants. Both groups underwent second trimester ultrasonographic study at a gestational age between 18 and 24 weeks. The ultrasonographic study consisted of anomaly scans and uterine artery Doppler studies. The machine used in this study was a Voluson E10 model (GE, Chicago, IL, USA). The operator was a certified OB-GYN attending the maternal-fetal medicine unit at BAH. The study flow is summarized and presented in Fig 1.

Before starting the ultrasonography, participants were placed in a supine position. The transducer was placed on the inguinal canal and then medially rotated on both sides. The uterine artery was identified at the bifurcation across the iliac vessels. After identification of the uterine artery, measurement was performed at the distal end approximately one centimeter from the bifurcation across the iliac vessels with angle insonation of at less than 30 degrees. Measurement of uterine artery Doppler indices was represented in Fig 2. These measurements were performed on each side of the uterine artery for three times. Mean values were used for further calculation. Doppler indices collected were: UtA-PI, UtA-RI, and UtA S/D ratio. Each parameter was considered abnormal when the values were higher than the 95th percentile for the corresponding gestational age. Bilateral uterine artery notching waveform (UtA-NW) at the beginning of diastole is considered abnormal and therefore be recorded. Notching was defined as a persistent decrease in blood flow velocity in early diastole.[26] Collected values were transferred to Viewpoint 6 data collection software (GE, Chicago, IL, USA).

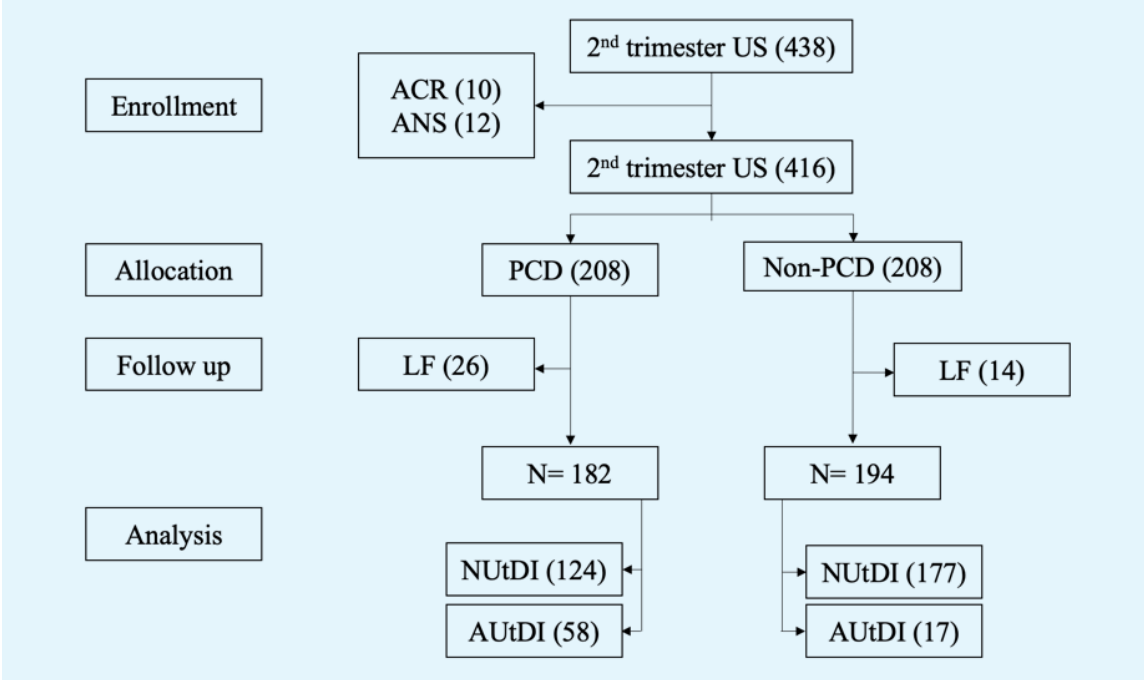


Fig 1. Flow chart of UtADI study in PCD and non-PCD.

Abbreviations: UtADI= uterine artery Doppler indices; PCD= prior cesarean delivery; non-PCD= non-prior cesarean delivery; ACR= abnormal chromosome; ANS= abnormal anatomical structure; US= ultrasound; LF= loss follow up; AUtDI= abnormal uterine artery Doppler indices; NUtDI= normal uterine artery Doppler indices

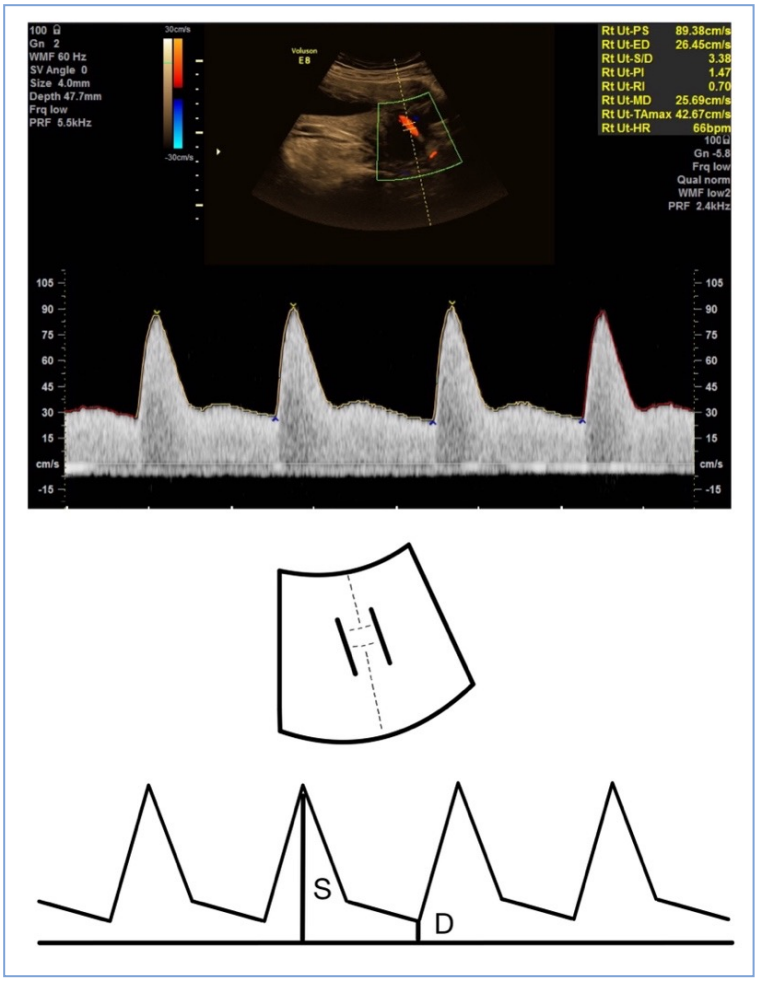


Fig 2. Ultrasonography image demonstrating the measurement of uterine artery Doppler indices.

This Doppler ultrasonography display the peak systolic and diastolic ratio (S= peak systolic velocity, D= end diastolic velocity), Mean= The time average mean velocity is obtained from calculation by computer-digitalized waveforms, S/D ratio= S/D, Resistance index= (S-D)/S, Pulsatility index= (S-D)/Mean

Statistical analyses were performed using SPSS statistical software (version 18.0.0: PASW, Chicago, IL, USA). Numerical data was presented with mean, standard deviation (SD) and median with interquartile range (IQR). Categorical data was presented in percentages. Correlation between control and study groups was analyzed using the Chi-square test, Fisher's exact test and independent sample t-test. To determine the effects of prior cesarean delivery on the Doppler measurement, Mann-Whitney U test were used. Our study then included all the concerning baseline characteristic including maternal age, BMI, gestational age at measurement, history of abortion and anterior placental location into linear regression analysis in order to adjust the confounding factors. The sample size was calculated using the N4 study calculation program.[27] Data used for sample size calculation was based on a previously published prospective cohort study from Iskalan, conducted between 18 and 24 weeks of gestation that reported the mean ± SD of UtA-PI in PCD and non-PCD groups of 1.18 ± 0.40 and 1.07 ± 0.35, respectively.[20] Testing of two independent means was generated with 80 percent power with alpha and beta errors of 0.05 and 0.2, respectively. The estimated odd ratios with 95% confidence intervals (95% CI) and p-values less than 0.05 were considered statistically significant. The calculated sample size was 184 cases per group. After including the loss to follow-up rate at 10 percent, the sample size required for each group was 203 cases. This resulted in a total of 406 participants.

RESULTS

Our prospective cohort study recruited 416 participants. Subjects were equally divided into PCD and non-PCD groups. The average age of subjects was 30.5 years old. Advanced maternal age (AMA) was 22.3 percent (93/416). Half of the participants (215/416) were classified as obese. One-fifth (79/416) of participants had Diabetes mellitus in pregnancy. Hypertensive disorder was 5 (23/416) percent. The mean age of participants, parity, and incidence of gestational diabetes mellitus (GDM) in the study group were all higher than the control group with statistical significance. Baseline maternal characteristics and uterine artery Doppler indices were presented in Table 1.

For uterine artery Doppler measurement showed that the median with interquartile range (IQR) of UtA-PI, UtA-RI, and S/D ratio were 0.94 (0.80-1.21), 0.57 (0.52-0.65) and 2.38 (2.07-2.90), respectively. From univariate

TABLE 1. Baseline demographic data and comparison of the uterine artery (UtA) Doppler indices between study (prior cesarean delivery: n=208) and control group (non-prior cesarean delivery: n=208), simple and multiple linear regression of uterine artery Doppler indices.

	Total*	Study*	Control*	*p*-value
Age (years)	30.5±5.7	31.4±5.5	29.7±5.2	0.002
AMA**	93 (22.36)	55 (26.44)	38 (18.27)	0.045
BMI (kg/m^2)	25.9±5.3	26.4±5.4	25.4±5.0	0.075
Obesity**	215 (51.68)	114 (54.81)	101 (48.56)	0.202
GA (weeks)	21.3±2.3	21.7±2.6	21.0±2.1	0.010
Parity	1 (0 - 1)	1 (1 - 1)	0 (0 - 1)	<0.001
Multiparity	299 (71.88)	208 (100)	91 (43.75)	<0.001
Abortion**	81 (19.47)	43 (20.67)	38 (18.27)	0.536
UD**				
CHT	16 (3.86)	10 (4.81)	6 (2.90)	0.312
GHT	7 (1.69)	3 (1.44)	4 (1.93)	0.724
DM	12 (2.89)	4 (1.92)	8 (3.86)	0.238
GDM	67 (16.14)	44 (21.15)	23 (11.11)	0.005
AP location**	205 (49.28)	109 (52.4)	96 (46.15)	0.202
UtA Doppler***				
PI	0.94 (0.80-1.21)	0.98 (0.84 - 1.23)	0.91 (0.75 - 1.19)	0.022
RI	0.57 (0.52 - 0.65)	0.58 (0.54 - 0.66)	0.56 (0.50 - 0.65)	0.010
S/D ratio	2.38 (2.07 - 2.90)	2.42 (2.16 - 2.94)	2.29 (2.01 - 2.87)	0.038
Notching	81 (19.47)	45 (21.63)	36 (17.31)	0.265
Abnormal PI	70 (16.83)	35 (16.83)	35 (16.83)	1.000
Abnormal RI	140 (33.65)	79 (37.98)	61 (29.33)	0.062
	Simple φ		Multiple φ	
	β (95% CI)	p-value	β (95% CI)	p-value
PI	0.04 (-0.04 -0.12)	0.347	0.05 (-0.03 - 0.13)	0.223
RI	0.02 (0.01 - 0.04)	0.017	0.03 (0.01 - 0.05)	0.006
S/D ratio	-0.03 (-0.25 - 0.19)	0.775	-0.02 (-0.24 - 0.21)	0.879

* mean ± standard deviation (SD), ** n (%), ***median with interquartile range (IQR), AMA: advance maternal age (≥ 35 years old), BMI: body mass index, Obesity: BMI ≥ 25 kg/m^2, GA: gestational age, AP location: placenta located at anterior wall of uterus, abortion: history of abortion, UD; underlying disease, PI: pulsatility index, RI: resistance index, S/D ratio: systolic/diastolic ratio, Notching: persistent bilateral notching, φ; adjusted for age, BMI, GA, abortion and AP location.

analysis, subjects in the PCD group had significantly greater UtA-PI, UtA-RI and UtA S/D than in the non-PCD group (0.98/0.91, 0.58/0.56 and 2.42/2.29) as shown in Table 1 and Fig 3. After adjusting related confounding factors with multiple logistic regression, it was determined that only mean UtA-RI values were higher in the PCD group. UtA-NW was found in 19.5 percent (81/416) of the participants. Both groups had comparable UtA-NW percentages, with 21.6% (45/208) in the study group and 17.3% (36/208) in the control group.

Based on the obstetric statistics from labor and delivery records, the study group showed statistically lower gestational age at delivery than the control group (38.1 vs 38.7 weeks). Approximately one-third (71/194) of subjects of non-PCD group underwent cesarean delivery. Other adverse outcomes collected in the study were comparable between groups as shown in Table 2. Prevalence of small for gestational age at delivery (SGA), preeclampsia and preterm birth was 4.4 (17/376), 3.1 (12/376) and 10 percent (38/376), respectively. Total adverse outcome in the current study was 20.7 (78/376) percent. Placental abruption, stillbirth, and 5 min Apgar score lower than 7 were not found in this study.

Focusing on abnormal uterine artery Doppler indices in all participants, there were effects on abnormal outcome as shown in Table 3. Abnormal UtA-PI showed significantly more cases of preterm birth, fetal growth restriction, oligohydramnios, non-reassuring fetal status, adverse maternal outcome, neonatal outcome and total adverse outcome. In the same trend as abnormal UtA-RI and UtA-NW. However, this correlation was shown only in all participants but were not shown in subanalysis for PCD group.

In our study, the analysis of the placental location and the number of previous cesarean deliveries were performed. Moreover, parity and history of abortion were also included in the analysis. However, our study showed no significant effect regarding uterine artery Doppler indices of the current pregnancy from all previously mentioned aspects.

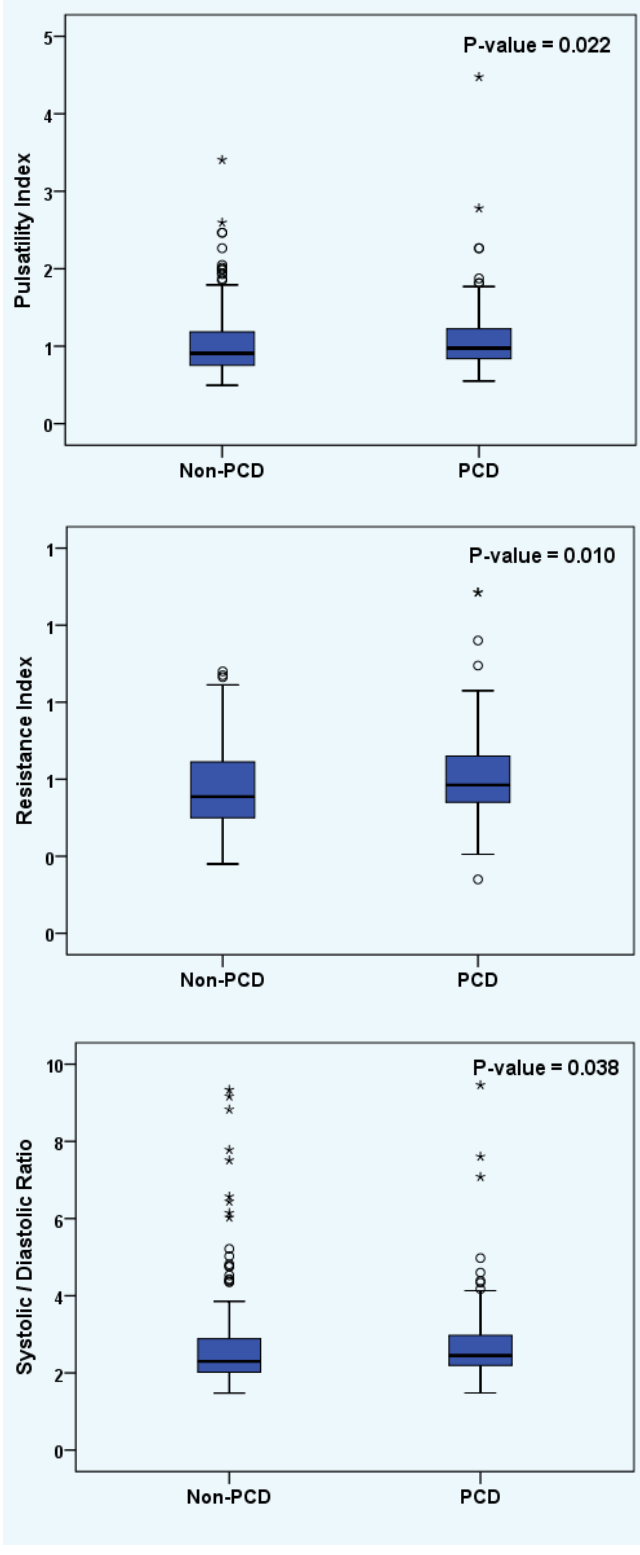


Fig 3. (A) A boxplot comparing the distribution of UtA-PI between non-PCD and PCD. (B) A boxplot comparing the distribution of UtA-RI between non-PCD and PCD. (C) A boxplot comparing the distribution of UtA-S/D between non-PCD and PCD.

Abbreviations: UtA-PI= uterine artery pulsitility index; UtA-RI= uterine artery resistance index; UtA-S/D= uterine artery systolic/diastolic ratio; non-PCD= non-prior cesarean delivery; PCD= prior cesarean delivery

DISCUSSION

The current study found that only the UtA-RI of the PCD group was significantly higher than the non-PCD group. This supported Torabi's report from Iran in 2018 that the mean UtA-PI and UtA-NW of the PCD group were significantly higher than the non-PCD group.[19] Another study of Iskalan from Turkiye showed UtA-PI in multiple of median (MoM), which is the ratio between PI values of the patients and the median PI values for gestational age, the study also reported values

TABLE 2. Neonatal outcome, gestational age at delivery (GAD) and complication from uteroplacental insufficiency between study (prior cesarean delivery) and control group. (non-prior cesarean delivery).

	Study (n= 182)*	Control (n= 194)*	*p*-value
Maternal			
GAD (weeks)**	38.10 ±1.06	38.72± 1.39	<0.001
Preterm birth	21 (11.54)	17 (8.76)	0.372
SGA	5 (2.75)	12 (6.19)	0.109
FGR	1 (0.55)	6 (3.09)	0.123
Oligohydramnios	1 (0.55)	4 (2.06)	0.372
Preecalmpsia	6 (3.30)	6 (3.09)	0.910
Nonreassuring	1 (0.55)	4 (2.06)	0.373
PPROM	6 (3.30)	3 (1.55)	0.325
Preterm labor	11 (6.04)	5 (2.58)	0.096
AMO	36 (19.78)	40 (20.62)	0.840
Neonatal			
Birthweight (kg) **	3.121±0.46	3.09±0.48	0.563
NICU admission	9 (4.95)	4 (2.06)	0.126
NICU stay (days) ***	16 (11-12)	6.5 (2.5-26.5)	0.355
NCO	16 (8.79)	17 (8.76)	0.992
TAO	41 (22.53)	40 (20.62)	0.653

*n (%), **mean ± standard deviation (SD), ***median with interquartile range (IQR), NCO; neonatal composite outcome namely small for gestational age (SGA), fetal growth restriction (FGR) and neonatal complication, AMO; adverse maternal outcome, TAO; total adverse outcomes.

in their PCD group significantly higher than the non-PCD group.[20] In contrast, Yapan's study from Thailand in 2021 reported no difference in UtA-PI, UtA-RI, UtA S/D ratio and UtA-NW between PCD and non-PCD groups.[21] Baron from Israel and Flo from Norway also reported PCD and non-PCD groups had comparable mean UtA-PI values.[22,23]

The primary outcome of this study can be explained by cesarean deliveries causing increased resistance in the uterine artery from uterine scar formation. During cesarean delivery, the lower segment of the uterus is incised and sutured. This supports the theory that cesarean delivery may have consequences on uterine artery hemodynamics by interfering with normal trophoblastic invasion and normal uterine blood flow.[10] Our study, in line with findings from Torabi and Iskalan, found that high values of UtA-PI, UtA-NW and UtA-RI, strongly indicated decreased uterine blood flow.[19,20] Torabi's study indicated anterior placentation as a factor causing increased UtA-PI[19] this association however could not be duplicated in the current study.

In contrast to this study, Yapan's, Baron's and Flo's studies reported that cesarean delivery was not associated with increased UtA Doppler indices.[21-23] The reason behind the contradicting result could be that UtA Doppler indices are multifactorial and are affected by multiple different baseline characters. Further study with strict confounder controls and larger sample sizes is needed for future investigation.

From the study by Iskalan, more than two repeated cesarean deliveries were associated with increase in UtA-PI, UtA-RI and UtA S/D ratio.[20] Considering the effects of multiple cesarean deliveries, most of the subjects in the current study and Yapan's study had only one cesarean delivery prior to their participation in both works.[21] Nearly half (34/73) of the participants in Iskalan's study had a history of multiple cesarean deliveries. In contrast, our study and Yapan's, participants had multiple cesarean deliveries for only 3.5 (5/140) and 3 (8/269) percent of participants, respectively. Therefore, the number of multiple cesarean deliveries in our study was too small to fully analyze for any association.

TABLE 3. Comparison of neonatal outcome, gestational age at delivery (GAD) and complication from uteroplacental insufficiency between normal and abnormal Doppler indices including abnormal pulsatility index (PI), abnormal resistance index (RI) and persistent bilateral notching.

	Normal PI (n= 306)*	Abnormal PI (n= 70)*	*p*-value	Normal RI (n= 236)*	Abnormal RI (n= 140)*	*p*-value	No notching (n=295)*	Notching (n=81)*	*p*-value
Maternal									
GAD (weeks)**	38.56±1.19	38.14±1.46	<0.001	38.57±1.21	38.14±1.34	0.002	38.54±1.22	37.94±1.39	<0.001
Preterm birth	23 (7.52)	15 (21.43)	<0.001	18 (7.63)	20 (14.29)	0.038	26 (8.81)	12 (14.81)	0.112
SGA	6 (1.96)	11 (15.71)	0.071	6 (2.54)	11 (7.86)	0.016	8 (2.71)	9 (11.11)	0.001
FGR	3 (0.98)	4 (5.71)	0.007	2 (0.85)	5 (3.57)	0.059	3 (1.02)	4 (4.94)	0.021
Oligohydramnios	2 (0.65)	3 (4.29)	0.017	2 (0.85)	3 (0.21)	0.289	3 (1.02)	2 (2.47)	0.312
Preecalmpsia	5 (0.16)	7 (10.00)	<0.001	3 (1.27)	9 (6.43)	0.006	5 (1.69)	7 (8.64)	0.002
Nonreassuring	2 (0.65)	3 (4.29)	0.017	2 (0.85)	3 (2.14)	0.289	5 (1.69)	0	-
PPROM	7 (2.29)	2 (1.43)	0.779	5 (2.12)	4 (2.86)	0.651	8 (2.71)	1 (1.23)	0.441
Preterm labor	12 (3.92)	5 (7.14)	0.242	8 (3.39)	9 (6.43)	0.170	14 (4.75)	3 (3.70)	0.689
AMO	47 (15.36)	29 (41.43)	<0.001	36 (15.30)	40 (28.57)	0.002	53 (17.97)	23 (28.40)	0.038
Neonatal									
Birthweight (kg) **	3.18±0.42	2.77±0.54	<0.001	3.18±0.44	2.95±0.50	<0.001	3.17±0.43	2.87±0.53	<0.001
NICU admission	9 (2.94)	4 (5.71)	0.252	9 (3.81)	4 (6.67)	0.624	9 (3.05)	4 (4.94)	0.410
NICU stay (days) **	15.2±11.8	19.8±17.9	0.643	15.2 ±11.8	19.7 ±17.8	0.643	15.4±11.5	19.3±18.4	0.758
NCO	19 (6.21)	14 (20.00)	<0.001	18 (7.63)	15 (10.71)	0.192	21 (7.12)	12 (14.81)	0.018
TAO	52 (16.99)	29 (41.43)	<0.001	41 (17.40)	40 (28.57)	0.011	57 (19.32)	24 (29.63)	0.046

*n (%), **mean ± standard deviation (SD), ***median with interquartile range (IQR), NCO; neonatal composite outcome namely small for gestational age (SGA), fetal growth restriction (FGR) and neonatal complication, AMO; adverse maternal outcome, TAO; total adverse outcomes.

Differences between UtA-RI and UtA-PI came from the calculation between systolic and diastolic flow. In the worst cases that diastolic flow is zero, values of RI and PI would be one and two, respectively. Mean UtA-RI and UtA-PI in the current study were 0.57 and 0.94, respectively. When classified into abnormal RI and PI according to the reference values, one-third (140/416) and one-sixth (70/416) of RI and PI were classified as abnormal values, respectively. In our opinion, UtA-RI could also be used as an indicator of decreased uterine blood flow in the same way as UtA-PI because the calculation were based from the same values as previously mentioned.

Torabi had presented an association of increased UtA-PI and adverse maternal outcomes including preterm birth, SGA delivery, preeclampsia, and placental abruption.[19] Yapan's study reported PCD and non-PCD groups had comparable Doppler indices and maternal/neonatal outcomes.[21] Our current study also reported no significant difference in maternal and neonatal outcomes between study and control group. When comparing Torabi to current study PIH, SGA and preterm birth were 5 (20/400) vs 3.2 (12/376), 11.5(35/400) vs 4.5(17/376) and 5 (20/400) vs 10.1 (38/376) percent, respectively.[19] From our current study, the contradicting outcome to the result of Torabi's study might be a consequence of low prevalence of PIH and SGA among participants in our current study.[19] In addition, multifactorial factors may be attributed to maternal and neonatal outcomes. Data from the previous studies were summarized and presented in Table 4.

TABLE 4. Comparison of the current study to previous studies.

	Present		Yapan		Isikalan		Torabi		Baron		Flo	
Years	2024		2021		2020		2018		2015		2014	
Country	Thailand		Thailand		Turkiye		Iran		Israel		Norway	
Case (n)	416		538		153		400		106		64	
Trimester	2		1, 2, 3		2		2		PP		2	
Age (yr)	30.5		31.23		29.3		32.95		30.5		33	
BMI (kg/m^2)	25.1		24.05		25.86		26.7					
UtA PI	NS		NS		P>NP		P>NP		NS		NS	
Type	Me		MoM		MoM		M		M		M	
UtA RI	P>NP		NS		NS							
S/D ratio	NS		NS		NS							
Notching	NS		NS		NS		P>NP				NS	
Increased PI	NS				P>NP		P>NP					
	P	NP	P	NP	P	NP	P	NP	P	NP	P	NP
Parity	1	1			2	2			3	3		
BW (kg)	3.1	3.1	3.1	3.1	3.0	3.1			3.4	3.3	3.5	4.0
Preterm birth	11.5	8.7	9.1	5.2			6	4				
SGA	2.8	6.2	9.8	8.1			12	10.5			6.3	9.4
PIH	3.3	3.1	3.4	3.4			7.5	2.5				
Oligo	0.5	1.9	0.0	1.5			4.5	4	0.0	0.0		
PA	NS	NS	NS	NS			1.5	0.5				
AMO	19.78	20.62										
NAO	8.79	8.76										
TAO	22.5	20.6					23.5	14				

Abbreviations: PA; placental abruption, AMO; adverse maternal outcome, NAO; neonatal adverse outcome, TAO; total adverse outcome, P; prior cesarean delivery group, NP; non-prior cesarean delivery group, Me; median, M; mean, MoM; multiple of median, NS; not significant.

For the strength of this study, information about neonatal outcome was studied in extensive aspects and collected as neonatal composite outcome. Moreover, our sample size calculation was powered and sufficient for the primary objective. In addition, analysis of the primary outcome with confounding factors were adjusted by multiple logistic regressions which made the results sound. Sub analysis was performed with all possible aspects to find a correlation with uterine artery Doppler. However, limitations include underpowered sub analysis due to small sample size. For example, our study also had too small number of multiple cesarean deliveries participants to determine the effects of number of cesarean deliveries on concerning outcomes. In addition, some participants failed to follow up which may affect the results for labor and delivery outcomes.

In conclusion, this study confirms that cesarean delivery is potentially a significant causative factor in decreased uterine blood flow. Only uterine artery resistance index (UtA-RI) had an association with cesarean delivery. However, this study could not represent an association between cesarean delivery and perinatal outcomes. For the UtA Doppler measurement, we recommend using all three parameters including UtA-PI, UtA-RI and UtA S/D ratio as each index all represent an alteration of uterine artery blood flow. It is important that cesarean delivery should be performed only when indicated as recommended by the WHO to minimize adverse outcomes.[1] We recommend measuring uterine artery Doppler indices in all participants with maternal risk factors of PE and/or FGR, whether with PCD or non-PCD. The optimal time or uterine artery Doppler assessment is in the second trimester.

What is already known in this topic?

Uteroplacental insufficiency is one of the consequences of cesarean delivery. Uteroplacental insufficiency contributes to fetal growth restriction, small for gestational age, and preeclampsia. Uterine artery Doppler indices (UtA-PI, UtA-RI, S/D ratio) indicate uteroplacental insufficiency. There were inconclusive effects of cesarean delivery and uterine artery Doppler indices.

What has this study contributed to this topic?

Cesarean delivery affected the subsequent pregnancy by alteration of uterine artery Doppler indices. UtA-RI of prior cesarean delivery participants were higher than non-prior cesarean delivery participants and not associated with maternal and neonatal adverse outcomes.

ACKNOWLEDGEMENTS

Special thanks to Dr. Apisapol Intharakanchit for the manuscript preparation.

DECLARATION

Grants and Funding Information

This study was supported by Bhumibol Adulyadej Hospital research fund in the year 2022.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Author Contributions

Conceptualization and methodology, B.C., S.M. and B.S.; Investigation, B.C., S.M.; Formal analysis, B.C., S.M. and B.S.; Visualization and writing – original draft, B.C., S.M., B.S., K.S. and K.B.; Writing – review and editing, B.C., S.M. and B.S.; Funding acquisition, B.C.; Supervision, B.C., S.M. and K.S. All authors have read and agreed to the final version of the manuscript.

REFERENCES

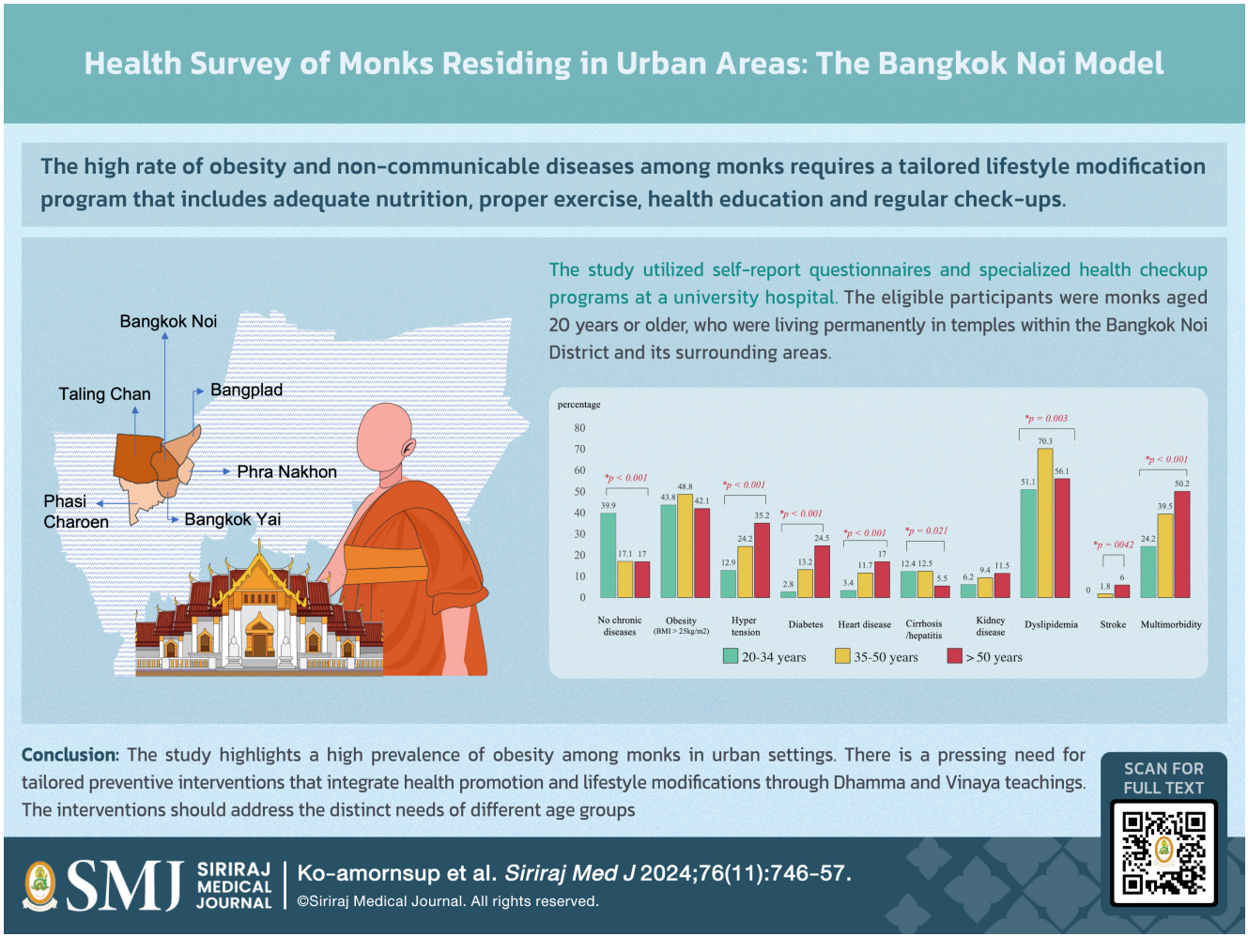
1. Angolile CM, Max BL, Mushemba J, Mashauri HL. Global increased cesarean section rates and public health implications: A call to action. Health Sci Rep. 2023;6(5):e1274.
2. Boerma T, Ronsmans C, Melesse DY, Barros AJD, Barros FC, Juan L, et al. Global epidemiology of use of and disparities in caesarean sections. Lancet. 2018;392(10155):1341-8.
3. Betran AP, Ye J, Moller AB, Zhang J, Gulmezoglu AM, Torloni MR. The Increasing Trend in Caesarean Section Rates: Global, Regional and National Estimates: 1990-2014. PLoS One. 2016;11(2):e0148343.
4. Murphy DJ, Stirrat GM, Heron J, Team AS. The relationship between Caesarean section and subfertility in a population-based sample of 14 541 pregnancies. Hum Reprod. 2002;17(7):1914-7.
5. Negishi H, Kishida T, Yamada H, Hirayama E, Mikuni M, Fujimoto S. Changes in uterine size after vaginal delivery and cesarean section determined by vaginal sonography in the puerperium. Arch Gynecol Obstet. 1999;263(1-2):13-6.
6. Kuwata T, Matsubara S, Kaneko Y, Izumi A, Nakata M, Suzuki M. Asymptomatic uterine artery pseudoaneurysm after cesarean section. J Obstet Gynaecol Res. 2010;36(2):405-10.
7. Morris H. Surgical pathology of the lower uterine segment caesarean section scar: is the scar a source of clinical symptoms? Int J Gynecol Pathol. 1995;14(1):16-20.
8. Getahun D, Oyelese Y, Salihu HM, Ananth CV. Previous cesarean delivery and risks of placenta previa and placental abruption. Obstet Gynecol. 2006;107(4):771-8.
9. Jung E, Romero R, Yeo L, Gomez-Lopez N, Chaemsaithong P, Jaovisidha A, et al. The etiology of preeclampsia. Am J Obstet Gynecol. 2022;226(2S):S844-S66.
10. Cho GJ, Kim LY, Min KJ, Sung YN, Hong SC, Oh MJ, et al. Prior cesarean section is associated with increased preeclampsia

risk in a subsequent pregnancy. BMC Pregnancy Childbirth. 2015;15:24.
11. Pahirah N, Laosooksathit W, Kongsomboon K, Kitporntheranunt M. Sonographic Lower Uterine Segment Thickness to Predict Cesarean Scar Defect in Pregnant Women. Siriraj Med J. 2021; 73(5):330-6.
12. Hosiriphon K, Chayachinda C, Keawpoonsub K, Taibowornpitak K, Tuangrattanasirikun D. A Survey of Daily Genital Care Practices among Reproductive-aged Female Personnel at Siriraj Hospital. Siriraj Med J. 2023;75(4):259-65.
13. Sunsaneevitayakul P, Sompagdee N, Dehghan MA, Talungchit P. Effect of Gestational Weight Gain on Overweight and Obese Pregnant Women. Siriraj Med J. 2022;74(6):364-70.
14. Tian Y, Yang X. A Review of Roles of Uterine Artery Doppler in Pregnancy Complications. Front Med (Lausanne). 2022;9:813343.
15. Mary E, Leslie M, Vickie A. Fetal Doppler Assessment (Noncardiac). In: Mary E, editors. Callen's Ultrasonography in Obstetrics and Gynecology. Philadelphia: Elsevier; 2017.p.1204-5.
16. Li N, Ghosh G, Gudmundsson S. Uterine artery Doppler in high-risk pregnancies at 23-24 gestational weeks is of value in predicting adverse outcome of pregnancy and selecting cases for more intense surveillance. Acta Obstet Gynecol Scand. 2014;93(12):1276-81.
17. Barati M, Shahbazian N, Ahmadi L, Masihi S. Diagnostic evaluation of uterine artery Doppler sonography for the prediction of adverse pregnancy outcomes. J Res Med Sci. 2014;19(6): 515-9.
18. Cnossen JS, Morris RK, ter Riet G, Mol BW, van der Post JA, Coomarasamy A, et al. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. CMAJ. 2008;178(6):701-11.
19. Torabi S, Sheikh M, Fattahi Masrour F, Shamshirsaz AA, Bateni ZH, Nassr AA, et al. Uterine artery Doppler ultrasound in second pregnancy with previous elective cesarean section. J Matern Fetal Neonatal Med. 2019;32(13):2221-7.
20. Isikalan MM, Yeniceri H, Toprak E, Guleroglu FY, Acar A. Effect of previous cesarean sections on second-trimester uterine artery Doppler. J Obstet Gynaecol Res. 2020;46(9):1766-71.
21. Yapan P, Tachawatcharapunya S, Surasereewong S, Thongkloung P, Pooliam J, Poon LC, et al. Uterine artery Doppler indices throughout gestation in women with and without previous Cesarean deliveries: a prospective longitudinal case-control study. Sci Rep. 2022;12(1):20913.
22. Baron J, Hershkovitz R, Baumfeld Y, Imterat M, Sciaky-Tamir Y, Mastrolia SA, et al. Postpartum uterine artery blood flow impedance following cesarean section or vaginal delivery. J Clin Ultrasound. 2016;44(5):278-83.
23. Flo K, Widnes C, Vartun A, Acharya G. Blood flow to the scarred gravid uterus at 22-24 weeks of gestation. BJOG. 2014;121(2): 210-5.
24. Nakai Y, Imanaka M, Nishio J, Maeda T, Ozaki A, Sun TT, et al. Uterine blood flow velocity waveforms during early postpartum course following caesarean section. Eur J Obstet Gynecol Reprod Biol. 1997;74(2):121-4.
25. Borisut P, Kovavisarach E. Standard intrauterine growth curve of Thai neonates delivered at Rajavithi hospital. J Med Assoc Thai. 2014;97(8):798-803.
26. Horsager R, Roberts S, Rogers V, Patricia Santiago-Muñoz P, Woreley K, Hoffman B. Williams Obstetrics, 24th Edition, Study Guide. New York (NY): McGrawHill Professional; 2014.
27. Ngamjarus C, Chongsuvivatwong V, McNeil E. n4Studies: Sample size Calculation for an Epidemiological Study on a Smart Device. Siriraj Med J. 2016;68:160-70.

Health Survey of Monks Residing in Urban Areas: The Bangkok Noi Model

Wasumadee Ko-amornsup, B.Sc.[1], Arunotai Siriussawakul, M.D., Ph.D.[2,*], Kanuch Aosangdeekul, B.H.E.[1], Rinrada Preedachitkul, M.Sc.[1], Varalak Srinonprasert, M.D.[1,3], Pawit Somnuke, M.D., Ph.D.[2], Weerasak Muangpaisan, M.D.[4], Ponnapa Petchthai, B.N.S.[1], Naris Kitnarong, M.D.[5]

[1]Siriraj Health Policy Unit, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand, [2]Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand, [3]Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand, [4]Department of Preventive and Social Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand, [5]Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.



*Corresponding author: Arunotai Siriussawakul
E-mail: arunotai.sir@mahidol.ac.th
Received 16 May 2024 Revised 13 August 2024 Accepted 21 August 2024
ORCID ID:http://orcid.org/0000-0003-0848-6546
https://doi.org/10.33192/smj.v76i11.269296

All material is licensed under terms of the Creative Commons Attribution 4.0 International (CC-BY-NC-ND 4.0) license unless otherwise stated.

ABSTRACT

Objective: This study aimed to assess the prevalence of obesity and identify associated health problems and behaviors among monks residing in Bangkok Noi and its adjacent districts.

Materials and Methods: Employing a cross-sectional design, this research incorporated self-report questionnaires and specialized health checkup programs at a university hospital. Eligible participants were monks aged 20 years or older, living permanently in temples within the Bangkok Noi District and its adjacent districts. Monks in short-term ordination were excluded. Data collection occurred between February 2022 and July 2023.

Results: Out of 560 monks who participated by completing both the questionnaires and health examinations, the average age was 46.49±16.97 years. Most participants resided in the Taling Chan (35.4%) and Bangkok Noi (31.8%) districts. Significant health issues included non-communicable diseases, with dyslipidemia affecting 57.8% and obesity 44.2% of the cohort. Monks over the age of 50 exhibited a remarkably higher rate of multimorbidity (50.2%) than their younger counterparts (24.2%, $p < 0.001$, 95% CI 20.71–27.97). Dietary habits revealed that younger monks were more prone to consuming fried, sweet and instant foods (74.5%, $p < 0.001$, 95% CI 70.67–78.07). Moreover, a significant proportion of younger monks demonstrated proficient e-health literacy (74.2%, $p < 0.001$, 95% CI 70.37–77.78).

Conclusion: The study highlights a high prevalence of obesity among monks in urban settings. There is a pressing need for tailored preventive interventions that integrate health promotion and lifestyle modifications through Dhamma and Vinaya teachings. The interventions should address the distinct needs of different age groups.

Keywords: Buddhist monks; Health survey; Noncommunicable diseases; Thailand; Urban (Siriraj Med J 2024; 76: 746-757)

INTRODUCTION

The Asia-Pacific region hosts the most substantial Buddhist populations globally, with Thailand being a prominent Buddhist-majority nation.[1] Buddhism profoundly impacts Thai society, where monks are crucial in preserving and propagating religious teachings.[2] However, urban Thai monks face significant health challenges, due to their increasing adoption of a layperson's lifestyle.[3]

Urbanization is a pivotal 21st-century trend impacting health worldwide. Urban environments, characterized by pollution, heat islands, and confined spaces, hinder active lifestyles and amplify the prevalence of non-communicable diseases (NCDs) while contributing to climate change.[4] In Thailand, NCDs are the predominant cause of mortality, accounting for 74% of all NCD-related deaths and over 400 000 fatalities annually—equivalent to more than 1000 deaths daily. Thai citizens face a 14% risk of premature death (before 70 years) from major NCDs such as cardiovascular diseases, diabetes, chronic respiratory diseases, and cancer, with men and women facing risks of 18% and 11%, respectively.[5,6]

Despite monks' critical roles in practicing and teaching Buddhist principles to alleviate suffering,[7] recent findings indicate a troubling escalation in NCD prevalence within this group. Notably, the prevalence of hypertension in monks is three times higher than in the broader Thai population, at 76% versus 24.7%.[8,9] Furthermore, approximately 62% of monks are classified as overweight, with a body mass index (BMI) of 25 kg/m^2 or higher.[10,11]

The health challenges faced by monks, particularly those related to NCDs, profoundly affect their quality of life. Consequently, there is a critical need for prevention measures and healthcare support systems tailored specifically for this population. In response, in 2017, several pivotal Thai institutions, including the Ministry of Public Health, the National Buddhism Office, the National Health Security Office, and the National Health Commission Office, jointly passed a resolution to enforce nationwide health regulations for monks. The primary goal is to empower monks to manage their health in accordance with Buddhist disciplinary principles.[12] This initiative encompasses efforts in five strategic areas: enhancing knowledge, improving access to information, fostering community health development, providing healthcare services, and conducting research to better support monk health and manage risk factors.

The Bangkok Noi Model, a community health system study conducted by the Faculty of Medicine Siriraj Hospital, collected extensive data on the physical, mental, and social health of Bangkok Noi residents.[13,14] However, monks were not included in that study. Our research specifically targeted the health and lifestyle of monks, aiming to provide comprehensive health data for

the urban setting of Bangkok Noi, thus encompassing all demographic groups within the community. Current data indicates there are 457 temples in Bangkok, with the Bangkok Noi district having the highest concentration at 32 temples, followed by the Taling Chan district with 30 temples.[15] This study aimed to assess the prevalence of obesity and identify associated health problems and behaviors among monks residing in Bangkok Noi and its adjacent districts.

MATERIALS AND METHODS

This cross-sectional investigation forms part of the "Sustainable Development of Health Promotion System for Monks by Interdisciplinary Teams and Public Participation: Bangkok Noi model," authorized under COA number 048/2564 (IRB2). The program's goal is to enhance health knowledge among monks through advanced healthcare services that facilitate remote communication system integration and the generation of tailored health plans based on collected monk health data.

Ethical approval for the study was obtained from the pertinent ethics committee, which confirmed adherence to established ethical standards and guidelines for human research. Monks residing in temples within the Bangkok Noi district and its adjacent areas were invited to engage in this study voluntarily. The inclusion criteria specified monks aged 20 years and above residing at temples in Bangkok Noi District and its vicinity. Conversely, the exclusion criteria encompassed monks undergoing short-term ordination, such as temporary ordination, ordination for a specific ritual, or ordination lasting less than 1 year (Supplementary Materials: Fig 1). Research assistants provided comprehensive explanations about the health checkup programs and the self-report questionnaires. These explanations covered the objectives, procedures, potential benefits, and possible risks involved. This discussion took place before the participants scheduled their appointments at the hospital.

Sample size estimation and statistical analysis

The total sample size of this study was 560 monks, drawn from a total population of 13 112 monks in Bangkok in 2021.[15] The primary objective of this study was to survey the behavior and health status of monks in Bangkok, with a specific focus on chronic diseases such as obesity, diabetes, and hypertension. The estimation of the sample size was based on previous research concerning non-communicable diseases and social determinants of health among Buddhist monks,[9] alongside data from a study of urban health among 283 monks in Samut Prakan Province, Thailand.[16] The latter study revealed that 25.4% of monks were obese. Using the estimated population proportion formula, with an assumed obesity prevalence of 25.4% among monks, an acceptable margin of error of 3.8% was set. This margin was calculated from a 15% margin of the population proportion (d = 15% * 0.254 = 0.038), alongside a confidence level of 95% and a two-sided type I error of 0.05. Thus, the required sample for monks in the Bangkok Noi District was approximately 505 individuals.

Statistical analyses were performed using IBM SPSS Statistics (version 29; IBM Corp, Armonk, NY, USA). Baseline demographic data were summarized by data type. Continuous variables are presented with means and standard deviations if normally distributed, or medians and ranges for non-normally distributed data. Categorical data are represented as frequencies and percentages.

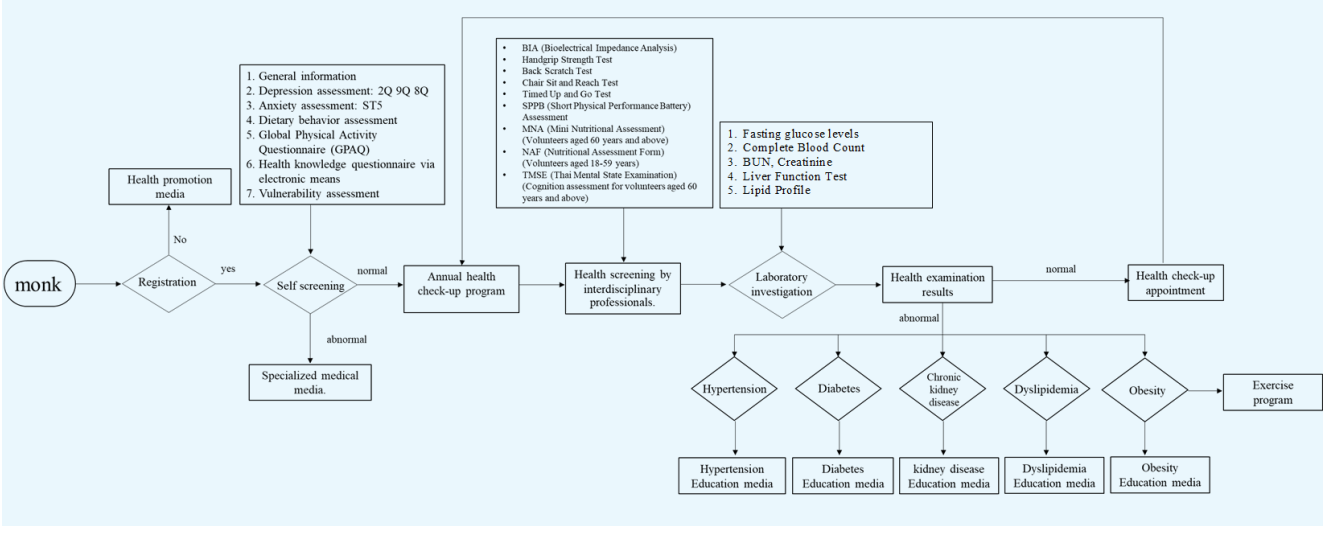


Fig 1. Overview of specialized health checkup program initiative.

Data collection

Data collection was conducted via health checkup stations and standardized questionnaires. Surveys were conducted in Bangkok Noi area from February 2022 to July 2023. Fig 1 provides an overview of the specialized health checkup program initiative. Monk volunteers completed self-screening questionnaires before undergoing a scheduled health checkup at the Siriraj Checkup Center. Nurses, nutritionists, health educators, and trained personnel collected data on the health checkup day. All gathered data were electronically logged and securely maintained in a dedicated database. Rigorous protocols were in place to guarantee the confidentiality and privacy of all monks participating in the study throughout the data collection phase.

Self-report questionnaire

The questionnaire employed in this study was a paper-based structured survey designed to captured comprehensive details about participants' health, lifestyle, and medical history (see Supplementary Materials Table 1 for references). To evaluate mental health, three primary tools were utilized: the 2Q and 9Q depression-rating scales for depressive symptoms assessment and the ST-5 stress test questionnaire for stress levels. Lifestyle and quality of life measurements included the frailty questionnaire, the EQ-5D-5L for health-related quality of life, a dietary behavior assessment, the Global Physical Activity Questionnaire, and an evaluation of e-health literacy.

Health screening and laboratory investigations

Health screenings were meticulously conducted by an interdisciplinary team comprising nurses, nutritionists, health educators, and trained personnel. Laboratory investigations were performed by personnel from the Siriraj Checkup Center, including nurses and physicians (details of laboratory investigations are provided in Supplementary Materials Tables 2 and 3). These included blood tests for fasting glucose levels and lipid profiles, along with other essential biochemical parameters. Imaging tests, such as chest X-rays and electrocardiograms, were performed based on each participant's age and health condition.

Physical fitness was assessed by health educators and trained personnel at the Siriraj Checkup Center using multiple tests to evaluate different physical capabilities. Body composition was analyzed using bioelectrical impedance analysis. Muscle strength was measured with a hand-grip test. Flexibility was assessed using the back scratch test and the chair sit-and-reach test. Balance and activities of daily living were evaluated through the timed up and go test and the Short Physical Performance Battery.

Multimorbidity

Multimorbidity is defined as the simultaneous occurrence of at least two chronic conditions within an individual.[17] The likelihood of multimorbidity escalates with age, potentially increasing susceptibility to diseases and diminishing resistance to acute health threats, such as infections.[18] In this study, health data were gathered from health checkups conducted at Siriraj Checkup Center. Multimorbidity was diagnosed by physicians and assessed by analyzing chronic disease data. The condition was identified when an individual was diagnosed with at least two chronic conditions, including hypertension, diabetes, heart disease, cirrhosis/hepatitis, kidney disease, dyslipidemia, and stroke.

RESULTS

Demographic information of the participants

In total, 560 monks across six districts participated, completing both the questionnaire and health checkups. The distribution was primarily in Taling Chan (197 monks, 35.4%) and Bangkok Noi (177 monks, 31.8%; Table 1). Participants were grouped into three age categories. Monks older than 50 years represented the largest contingent (253 monks, 45.18%), followed by the 20–34 year age group (178 monks, 31.79%) and the 35–50 year age group (129 monks, 23.04%). High educational levels (i.e., high school level or higher) were prevalent among the participants. Older age groups reported more physical issues, such as problems with vision, hearing, and dental health, than their younger counterparts.

According to the health checkup data (Table 2), only 24.3% of participants were free from any diseases. Among those aged over 50, multimorbidity was the most common condition, succeeded by dyslipidemia, hypertension, and diabetes. Conversely, among the middle-aged group, dyslipidemia surfaced as the predominant health issue with a significantly higher incidence than other age groups. Younger participants primarily faced health challenges related to dietary behavior and physical activity levels, exhibiting prevalent conditions such as obesity, dyslipidemia, and hepatitis.

The survey yielded vital insights into the health status of Buddhist monks (Table 2), highlighting a substantial prevalence of elevated BMI: 44.2% of all monks had a BMI exceeding 25 kg/m^2. The obesity rate was notably highest among monks aged between 35 and 50 years, at 48.8%. The age groups of 20–34 and over 50 years showed obesity rates of 43.8% and 42.1%, respectively.

TABLE 1. Demographic characteristics of participating monks (n=560).

Variable	Total (n=560)	20-34 years (n=178)	35-50 years (n=129)	> 50 years (n=253)	*p*
District					<0.001
Bangkok Noi	177 (31.6%)	48 (27.0%)	39 (30.2%)	90 (35.6%)	
Taling Chan	199 (35.5%)	55 (30.9%)	39 (30.2%)	105 (41.5%)	
Bangkok Yai	86 (15.4%)	42 (23.6%)	29 (22.5%)	15 (5.9%)	
Bangplad	76 (13.6%)	25 (14.0%)	15 (11.6%)	36 (14.2%)	
Phra Nakhon	17 (3.0%)	8 (4.5%)	4 (3.1%)	5 (2.0%)	
Phasi Charoen	5 (0.9%)	0 (0.0%)	3 (2.3%)	2 (0.8%)	
Education level					
Less than high school diploma	161 (29.0%)	37 (21.0%)	27 (21.1%)	97 (38.6%)	<0.001
High school diploma or higher	394 (71.0%)	139 (79.0%)[a]	101 (78.9%)[a]	154 (61.4%)[b]	
Not available	5 (0.9%)	2 (1.1%)	1 (0.8%)	2 (0.8%)	
Buddhist education					0.659
Uneducated	70 (12.5%)	22 (12.4%)	13 (10.1%)	35 (13.8%)	
Nak-Dham Tri and Tho	141 (25.2%)	40 (22.5%)	33 (25.6%)	68 (26.9%)	
Nak-Dham Aek and above	344 (61.4%)	114 (64.0%)	82 (63.6%)	148 (58.5%)	
Not available	5 (0.9%)	2 (1.1%)	1 (0.8%)	2 (0.8%)	
Treatment method					
Hospital or nearby healthcare facility	506 (90.4%)	159 (89.3%)[a]	109 (84.5%)[a]	238 (94.1%)[b]	0.009
Self-medication, traditional medicine	494 (88.2%)	154 (86.5%)	118 (91.5%)	222 (87.7%)	0.402
Smoking habits					
Smoker: currently smoking	80 (14.3%)	23 (12.9%)	19 (14.7%)	38 (15.0%)	0.837
Smoker: quit smoking	129 (23.0%)	26 (14.6%)[a]	31 (24.0%)	72 (28.5%)[b]	0.003
Vision problems	286 (51.5%)	64 (36.4%)[b]	69 (53.9%)[a]	153 (61.0%)[a]	<0.001
Hearing problems	82 (14.8%)	11 (6.3%)[b]	21 (16.4%)[a]	50 (19.9%)[a]	<0.001
Dental health problems	213 (38.4%)	44 (25.0%)[a]	43 (33.6%)	126 (50.2%)[b]	<0.001

[a, b] The letter difference is significant at the 0.05 level.

The prevalence of chronic diseases exhibited considerable variation among different age groups. In participants aged over 50, multimorbidity was notably prevalent, affecting 50.2% of this group, in stark contrast to 24.2% in the younger cohort ($p < 0.001$). Furthermore, 56.1% of the older participants suffered from dyslipidemia, followed by hypertension at 35.2% and diabetes at 17.0%. Interestingly, the prevalence of hepatitis was significantly lower in this older group (5.5%) compared to the other age groups ($p < 0.001$).

In the middle-age group (35–50 years), dyslipidemia emerged as the most prevalent condition, affecting 70.3% of participants. This rate was significantly higher than in the older and younger groups, which recorded dyslipidemia prevalences of 56.1% and 51.1%, respectively (p 0.003). The pattern of disease presence in this group aligned somewhat with the older cohort, with prevalences of hypertension, diabetes, and hepatitis at 24.2%, 13.2%, and 12.5%, respectively. For the younger group, the principal health concerns were tied to dietary behavior

and physical activity levels. This group exhibited obesity in 43.8% of individuals, dyslipidemia in 51.1%, and hepatitis in 12.4%.

Self-screening reports

Health behavior

The health behavior screening highlighted the dietary patterns and physical activity levels among monks. Overall, a common dietary behavior was the consumption of fruit and vegetables. Despite this, younger and middle-aged monks tended to consume significantly higher amounts of sweets, desserts, fried foods, and instant food than the older age group. However, there were no significant differences in food hygiene across the age groups.

Physical activity levels among the monks were assessed using the Global Physical Activity Questionnaire. This instrument helped differentiate physical activity by intensity across various age groups. For low and moderate-intensity activities, which include moderate labor and transportation movements, the median value across all age groups was 1680 MET-minutes. This indicates a moderate engagement in these types of activities among monks. Regarding vigorous-intensity physical activity, characterized by activities requiring maximal oxygen uptake,[19] such as carrying heavy loads, the median value for all age groups was documented at 1200 MET-minutes (ranging from 80 to 30 240 MET-minutes). This also reflects a moderate level of engagement in vigorous activities among monks. The assessment of basal metabolic rate, which measures the caloric expenditure for basal life-sustaining functions,[20] revealed age-related differences among participants. Older monks exhibited a significantly lower metabolic rate (1350.54±196.51) than the younger (1546.66±269.78) and middle-aged groups (1520.38±215.82), with $p < 0.001$.

The self-screening reports provided further insights into the health status across different age groups. The EQ5D5L quality of life questionnaire scores averaged at 0.919±0.119 for the older group, which was lower than the 0.947±0.982 score of the younger group (p 0.023; Table 3). However, no significant differences were observed in mental health as assessed by the Depression and Stress Test questionnaires; most participants reported no issues. The FRAIL questionnaire results also indicated that a majority of participants were categorized as fit.

Physical fitness

Muscle mass and handgrip strength were also found to be lower in the older age group relative to younger participants. Similarly, flexibility assessments, measured through the back scratch test and the chair sit-and-reach test, demonstrated reduced flexibility in the older monks. The timed up and go test, a measure of dynamic balance and functional mobility, showed that older monks, with

TABLE 2. Prevalence of chronic conditions and multimorbidity among monks (n=560).

Variable	Total (n=560)	20-34 years (n=178)	35-50 years (n=129)	> 50 years (n=253)	*p*
Diseases					
No chronic diseases	136 (24.3%)	71 (39.9%)[b]	22 (17.1%)[a]	43 (17.0%)[a]	<0.001
Obesity (BMI > 25 kg/m^2)	247 (44.2%)	78 (43.8%)	63 (48.8%)	106 (42.1%)	0.432
Hypertension	143 (25.6%)	23 (12.9%)[b]	31 (24.2%)[a]	89 (35.2%)[a]	<0.001
Diabetes	84 (15.0%)	5 (2.8%)[b]	17 (13.2%)[a]	62 (24.5%)[a]	<0.001
Heart disease	64 (11.4%)	6 (3.4%)[b]	15 (11.7%)[a]	43 (17.0%)[a]	<0.001
Cirrhosis/hepatitis	52 (9.3%)	22 (12.4%)[a]	16 (12.5%)[a]	14 (5.5%)[b]	0.021
Kidney disease	52 (9.3%)	11 (6.2%)	12 (9.4%)	29 (11.5%)	0.178
Dyslipidemia	323 (57.8%)	91 (51.1%)[a]	90 (70.3%)[b]	142 (56.1%)[a]	0.003
Stroke	9 (3.3%)	0 (0.0%)	1 (1.8%)[a]	8 (6.0%)	0.042
Multimorbidity	221 (39.5%)	43 (24.2%)[b]	51 (39.5%)[a]	127 (50.2%)[a]	<0.001

[a, b] The letter difference is significant at the 0.05 level.

TABLE 3. Monk self-report data compilation (n=560).

Variable	Total (n=560)	20-34 years (n=178)	35-50 years (n=129)	> 50 years (n=253)	*p*
Dietary behavior assessment (during the past week, how often did you consume)					
Fresh or cooked vegetables	540 (96.4%)	171 (96.1%)	126 (97.7%)	243 (96.0%)	0.707
Fruits	526 (93.9%)	167 (93.8%)	119 (92.2%)	240 (94.9%)	0.581
Sweets or desserts	482 (86.3%)	135 (76.3%)[a]	97 (75.2%)[a]	167 (66.0%)[b]	0.037
Fried foods	454 (81.5%)	158 (89.3%)[a]	109 (84.5%)[a]	187 (74.5%)[b]	<0.001
Instant food	393 (70.8%)	149 (84.2%)[a]	103 (79.8%)[a]	141 (56.6%)[b]	<0.001
Food hygiene					
Washing fruit and vegetables before cooking	492 (87.9%)	156 (87.7%)	112 (86.8%)	224 (88.5%)	0.891
Using clean food containers for storage	376 (67.1%)	125 (70.2%)	79 (61.2%)	172 (68.0%)	0.411
Eating freshly cooked foods	524 (93.6%)	174 (97.7%)	120 (93.1%)	230 (90.9%)	0.102
Global Physical Activity Questionnaire: GPAQ					
Work activity (low intensity; corresponding to 4 MET/min)	1680 (40, 100 800)	1920 (80, 15 240)	1560 (40, 20 480)	1680 (60,100 800)	0.406
Transport activity (moderate intensity; corresponding to 4 MET/min)	1680 (40, 16 800)	1680 (40, 8400)	1680 (160, 3360)	1680 (40, 16 800)	0.870
Recreation (vigorous intensity; corresponding to 8 MET/min)	1200 (80, 30 240)	1040 (120, 5040)	1160 (80, 6720)	1560 (80, 30 240)	0.145
Depression					0.444
No depression (scores 0–6)	509 (90.9%)	157 (88.2%)	122 (94.6%)	230 (90.9%)	
Mild depression (scores 7–12)	43 (26.7%)	16 (22.2%)	7 (21.9%)	20 (35.1%)	
Moderate depression (scores 13–18)	6 (3.7%)	4 (5.6%)	0 (0.0%)	2 (3.5%)	
Major depression (scores ≥ 19)	2 (1.2%)	1 (1.4%)	0 (0.0%)	1 (1.8%)	
Stress Test Questionnaire (ST5)					<0.001
No problem (scores < 4)	436 (77.9%)	119 (66.9%)	101 (78.3%)	216 (85.4%)	
Might have a problem (scores 5-6)	79 (14.1%)	32 (18.0%)	23 (17.8%)	24 (9.5%)	
Has a problem (scores 7-9)	24 (4.3%)	16 (9.0%)	3 (2.3%)	5 (2.0%)	
Severe problem (scores 10-15)	21 (3.8%)	11(6.2%)	2 (1.6%)	8 (3.2%)	
FRAILTY					0.368
0 (fit)	375 (67.0%)	123 (69.1%)	92 (71.3%)	160 (63.2%)	
1-2 (pre-frail)	169 (30.2%)	52 (29.2%)	34 (26.4%)	83 (32.8%)	
3-5 (frail)	16 (2.9%)	3 (1.7%)	3 (2.3%)	10 (4.0%)	
EQ5D5L	0.933±0.106	0.947±0.982[a]	0.939±0.087	0.919±0.119[b]	0.023
VAS	80.26±14.22	81.87±13.68	80.63±13.91	78.94±14.45	0.100

* The analyzed patients were the ones who answered "yes" to ≥ 1 question of 2Q questionnaire (n=161)

[a, b] The letter difference is significant at the 0.05 level.

an average completion time of 10.61±3.81 seconds, still maintain independence in mobility, including stair navigation and outdoor walking.[21] However, this group's performance was significantly slower compared to the middle-aged (8.05±2.50 seconds) and young (7.53±1.66 seconds) monks ($p < 0.001$; Table 4). Furthermore, the Short Physical Performance Battery, which objectively evaluates functional capacity,[22] produced an average score among all monks of 11.26±1.54, reflecting minimal physical limitations. However, the older age group scored lower (10.73±1.99) than both the younger (11.77±0.68) and middle-aged groups (11.56±0.97, $p < 0.001$), indicating a higher degree of functional impairment in this cohort.

Electronic health literacy

Table 5 outlines the levels of electronic health literacy among monks, showcasing significant age-related disparities. The results indicated that these skills were markedly higher among the younger (74.2%) and middle-aged groups (62.0%). In stark contrast, less than a third of the older participants (30.4%) demonstrated proficiency in electronic health literacy. Within these groups, distinct patterns emerged concerning specific electronic health literacy skills. The younger monks displayed the greatest proficiency in utilizing the related resources available on the internet, with 58.4% demonstrating competence. Meanwhile, the middle-aged group excelled in locating health information online that could be beneficial to their needs, recording a proficiency rate of 48.8%. However, both the younger and middle-aged groups showed lower confidence in using information from the internet to make informed health decisions, reflecting a potential area for educational enhancement.

DISCUSSION

In Thailand, a predominantly Buddhist nation, monks serve as key figures in disseminating Buddhist teachings and represent about 0.3% of the population.[9] Historical perspectives have proposed that health issues among monks are often linked to their adoption of urbanized lifestyles.[3] To address this, our study implemented a strategic approach to gather health data specifically from monks in urban locales, notably Bangkok. This included the establishment of health checkup stations at community temples and comprehensive medical evaluations at Siriraj Hospital.

The preliminary findings from this health survey indicated a demographic skew towards older individuals, with 45% of participants being over the age of 50. This segment of the population exhibited pronounced physical and mental health challenges, including hearing and vision impairments, dental issues, metabolic disorders, multimorbidity, frailty, and symptoms of depression. Due to the monastic discipline that governs Buddhist monks, engaging in vigorous physical activities or sports is generally discouraged. Instead, monks often engage in less strenuous activities such as alms gathering from the Buddhist laity and fulfilling moderate duties at temples.[3,23] Notably, the dietary habits of monks typically depend on food offerings collected during morning alms and lunchtime merit-making events at temples. This diet often mirrors urban eating habits, characterized by easily accessible convenience foods, which may be nutrient-deficient yet calorie-dense, particularly in fats and sugars. Such dietary patterns are contributory factors to the prevalent health issues observed among monks, including dyslipidemia, hypertension, diabetes mellitus, and obesity.[3,24-26] This correlation underscores the need for tailored health interventions that consider both the unique dietary and lifestyle aspects of monastic life and the broader urban health challenges.

By segmenting the monks into three age categories, it became evident that distinct health profiles emerge across different life stages. The youngest group, aged 20–34 years, had the lowest incidence of comorbidities. Nevertheless, stress surfaced as a prevailing issue among all age groups, highlighting the critical need for enhanced mental health support within this community. Among the younger monks, a common dietary pattern included the frequent consumption of desserts, fried foods, and processed items. However, occurrences of dyslipidemia and obesity were comparatively less prominent within this group. This observation could potentially be explained by a combination of higher metabolic rates typically seen in younger individuals and more active lifestyles, which gradually decline with age.[27]

The middle-aged group, 35–50 years, demonstrated the greatest susceptibility to obesity, a trend that decreases with advancing age. This result indicated that the metabolic rate declined with advancing age.[28] This could be related to age-associated reductions in appetite and metabolic shifts.[29] Given the limitations on physical activities imposed by monastic life, there have been suggestions for alternative approaches to maintain physical health among monks. These include engaging in less vigorous but beneficial exercises such as hand, arm, shoulder, and lower body stretching, as well as practices like yoga and qigong. These activities could be effectively integrated with routine temple duties and lifestyle adjustments to promote better health outcomes.[23]

The monks in the senior age group (> 50 years) exhibited the highest frequency of comorbidities, including frailty,

TABLE 4. Assessment of physical fitness parameters at Siriraj Checkup Center.

Variable	Total (n=560)	20-34 years (n=178)	35-50 years (n=129)	> 50 years (n=253)	*p*
Weight (kg)	69.16±15.64	71.55±19.33[a]	72.49±14.91[a]	65.75±1.06[b]	<0.001
Height (cm)	166.51±7.19	168.60±7.20[a]	167.43±7.27[a]	164.57±6.64[b]	<0.001
Body mass index (kg/m^2)	24.95±5.02	25.26±6.24	25.85±4.77[a]	24.27±4.00[b]	0.008
< 18.5 (underweight)	38 (6.8%)	18 (10.1%)	4 (3.1%)	16 (6.3%)	
18.5 - 22.99 (normal weight)	170 (30.4%)	57 (32.0%)	30 (23.3%)	83 (32.9%)	
23 - 24.99 (overweight)	104 (18.6%)	25 (14.0%)	32 (24.8%)	47 (18.7%)	
>24.99 (obese)	247 (44.2%)	78 (43.8%)	63 (48.8%)	106 (42.1%)	
Thai Mental State Examination (TMSE)					-
≤ 23 (dementia)	26 (18.1%)	-	-	26 (18.1%)	
> 23	118 (81.9%)	-	-	118 (81.9%)	
Mini Nutritional Assessment (MNA)					-
Normal nutritional status	100 (68.0%)	-	-	100 (68.5%)	
At risk of malnutrition	43 (29.3%)	-	-	43 (29.5%)	
Malnourished	4 (2.7%)	-	1 (100.0%)	3 (2.1%)	
Nutritional Assessment Form (NAF)					0.028
Low risk of malnutrition	398 (95.9%)	174 (97.8%)	126 (97.7%)	98 (90.7%)	
Moderate risk of malnutrition	16 (3.9%)	4 (2.2%)	3 (2.3%)	9 (8.3%)	
Severe malnutrition	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	
Physical fitness test					
Bioelectrical impedance analysis					
BMR (calories)	1452.37±244.44	1546.66±269.78[a]	1520.38±215.82[a]	1350.54±196.51[b]	<0.001
Body fat (%)	23.53±7.89	22.87±9.40	23.72±7.89	23.90±6.80	0.405
Muscle mass (kg)	49.11±7.60	50.93±8.08[a]	51.70±6.40[a]	46.50±6.98[b]	<0.001
Handgrip right (kg)	29.76±6.82	32.96±6.56[a]	31.52±5.85[a]	26.59±6.07[b]	<0.001
Handgrip left (kg)	28.40±6.90	31.34±6.33[a]	30.35±6.16[a]	25.32±6.38[b]	<0.001
Back scratch right (in)	-4 (-22, 6.5)	0 (-15, 6.5)[a]	0 (-17, 5)[a]	-7 (-22, 6)[b]	<0.001
Back scratch left (in)	-7 (-27, 15.5)	-3.5 (-19.5, 8)[a]	-6.9 (-21.5, 3.5)[a]	-9 (-27, 15.5)[b]	<0.001
Chair sit-and-reach test, right (in)	0 (-19.5, 10)	0 (-13.5, 8)[a]	0 (-14, 9)	0 (-19.5, 10)[b]	0.003
Chair sit-and-reach test, left (in)	0 (-19, 25)	0 (-14, 7)[a]	0 (-13, 25)	0 (-19, 9.4)[b]	0.002
Timed up and go (sec)	8.86±3.22	7.53±1.66[a]	8.05±2.50[a]	10.61±3.81[b]	<0.001
Short Physical Performance Battery	11.26±1.54	11.77±0.68[a]	11.56±0.97[a]	10.73±1.99[b]	<0.001
Severe limitations	5 (0.9%)	0 (0.0%)	0 (0.0%)	5 (2.0%)	
Moderate limitations	7 (1.3%)	0 (0.0%)	1 (0.8%)	6 (2.4%)	
Mild limitations	38 (6.8%)	3 (1.7%)	2 (1.6%)	33 (13.1%)	
Minimal limitations	507 (91.0%)	174 (98.3%)	126 (97.7%)	207 (82.5%)	

[a, b] The letter difference is significant at the 0.05 level.

TABLE 5. Electronic health literacy levels among monks.

Electronic health literacy	20-34 years (n=178)	35-50 years (n=129)	> 50 years (n=253)	*p*
1. What are the electronic health literacy resources that can be used on the internet?	104 (58.4%)[a]	59 (45.7%)[a]	54 (21.3%)[b]	<0.001
2. Where can you find health information that will benefit you on the internet?	95 (53.4%)[a]	62 (48.1%)[a]	58 (22.9%)[b]	<0.001
3. Do you know the way to find health information that will benefit you?	99 (55.6%)[a]	63 (48.8%)[a]	50 (19.8%)[b]	<0.001
4. Do you know how to use the internet to find information about health?	93 (52.2%)[a]	62 (48.1%)[a]	52 (20.6%)[b]	<0.001
5. Do you know how to utilize health information on the internet to take care of yourself?	86 (48.3%)[a]	57 (44.2%)[a]	49 (19.4%)[b]	<0.001
6. Do you have the necessary skill to assess the reliability of the source on the internet?	76 (42.9%)[a]	57 (44.2%)[a]	45 (17.8%)[b]	<0.001
7. Can you identify reliable health information sources on the internet?	73 (41.2%)[a]	47 (36.4%)[a]	40 (15.9%)[b]	<0.001
8. Do you feel confident in using information from the internet to make health decisions?	71 (39.9%)[a]	47 (36.7%)[a]	44 (17.4%)[b]	<0.001
A high score (4-5) of electronic health literacy in 5 or more questions	132(74.2%)[a]	80 (62.0%)[a]	77 (30.4%)[b]	<0.001

[a,b] The letter difference is significant at the 0.05 level.

diminished quality of life, malnutrition, reduced muscle mass and strength, and decreased physical performance. Compounded by significantly lower levels of electronic health literacy, these factors align with studies suggesting that advanced age often correlates with limitations in digital health literacy.[30-33] Furthermore, cognitive decline is a significant concern in this demographic, with an 18% incidence rate of dementia noted, potentially leading to impaired self-care abilities and increased reliance on external healthcare support.[34]

Given these multifaceted health challenges, lifestyle interventions are crucial for maintaining and enhancing health in senior monks. Dietary modifications and engagement in moderate physical exercises, such as resistance training through temple chores, yoga, and qigong, alongside stretching and morning alms rounds, are advocated. These measures are not only feasible within the constraints of monastic life but are also effective in battling obesity.[35] Importantly, past studies suggest that while heavy exercise might generate proinflammatory cytokines and disrupt serotonin biosynthesis by breaking down essential amino acids such as tryptophan, resulting in fatigue, low mood, and carbohydrate cravings,[36] moderate exercise can offer substantial health benefits without these adverse effects. Thus, tailored physical activities are recommended to optimize well-being and mitigate health risks for aging monks.

Our research represents one of the few studies examining the health status of urban Buddhist monks. However, the study did have limitations. The health survey was conducted by inviting monks primarily from six highly urbanized districts out of the 50 districts in Bangkok. Additionally, about 70% of the participants had achieved at least a high school education, which may correlate with better dietary and food hygiene practices. Consequently, the demographic characteristics of the participating monks might hinder the generalizability of our findings across a broader monk population. Future studies could consider a prospective case-cohort approach to allow a deeper exploration into the health dynamics within this group. Nevertheless, the study showcased several strengths. Although the sample may not fully

represent all monks in Bangkok or in other urban settings, the thorough data collection from central business districts effectively captured the influence of an urbanized lifestyle. Stratifying monks into three distinct age groups illuminated specific health issues and contributory factors relevant to each cohort, particularly highlighting gaps in electronic health literacy.

This investigation significantly enhances our understanding of the health challenges and disparities faced by monks, a group often constrained in terms of engaging in health-promoting activities, such as regular exercise and sustaining a healthy diet. By focusing on a predominantly male cohort, this study also draws attention to diseases that disproportionately impact men, such as stroke and cardiovascular diseases. The extensive data collected provide valuable insights into how urbanization and modern lifestyle factors influence monk health. These findings lay a crucial foundation for devising targeted interventions aimed at boosting health and well-being among monks and similar populations, ultimately fostering enhanced healthcare access and promoting healthier lifestyles within these communities.

ACKNOWLEDGMENTS

This research project received financial support from the Office of The National Broadcasting and Telecommunications Commission (A 63-1-(2)-006). The funder did not participate in any aspect of the study. We would like to express our gratitude to the following individuals and units: Prof. Dr. Prasit Watanapa, Mrs. Sunaree Pengrungrungwong, Mrs. Bongkot Prathumphan, Mrs. Arthittaya Saejang, Siriraj Checkup Center and Siriraj Health Policy for their assistance in the work. We are grateful to Mr. Monai Sauejui for administrative support.

DECLARATION

Grants and Funding Information

This project is not funded by any external sources.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Author Contributions

AS, VS and WM were responsible for the conceptualization. AS ,VS and WM handled the methodology. WS, KA and PP performed data collection. RP carried out the formal analysis. AS, VS and NK managed resources and provided access to crucial research components. AS and WK evaluated the data. WK, RP, PS and AS drafted the original manuscript. WK, RP, PS and AS reviewed and edited the manuscript. AS supervised the project, handled administration, and acquired funding.

REFERENCES

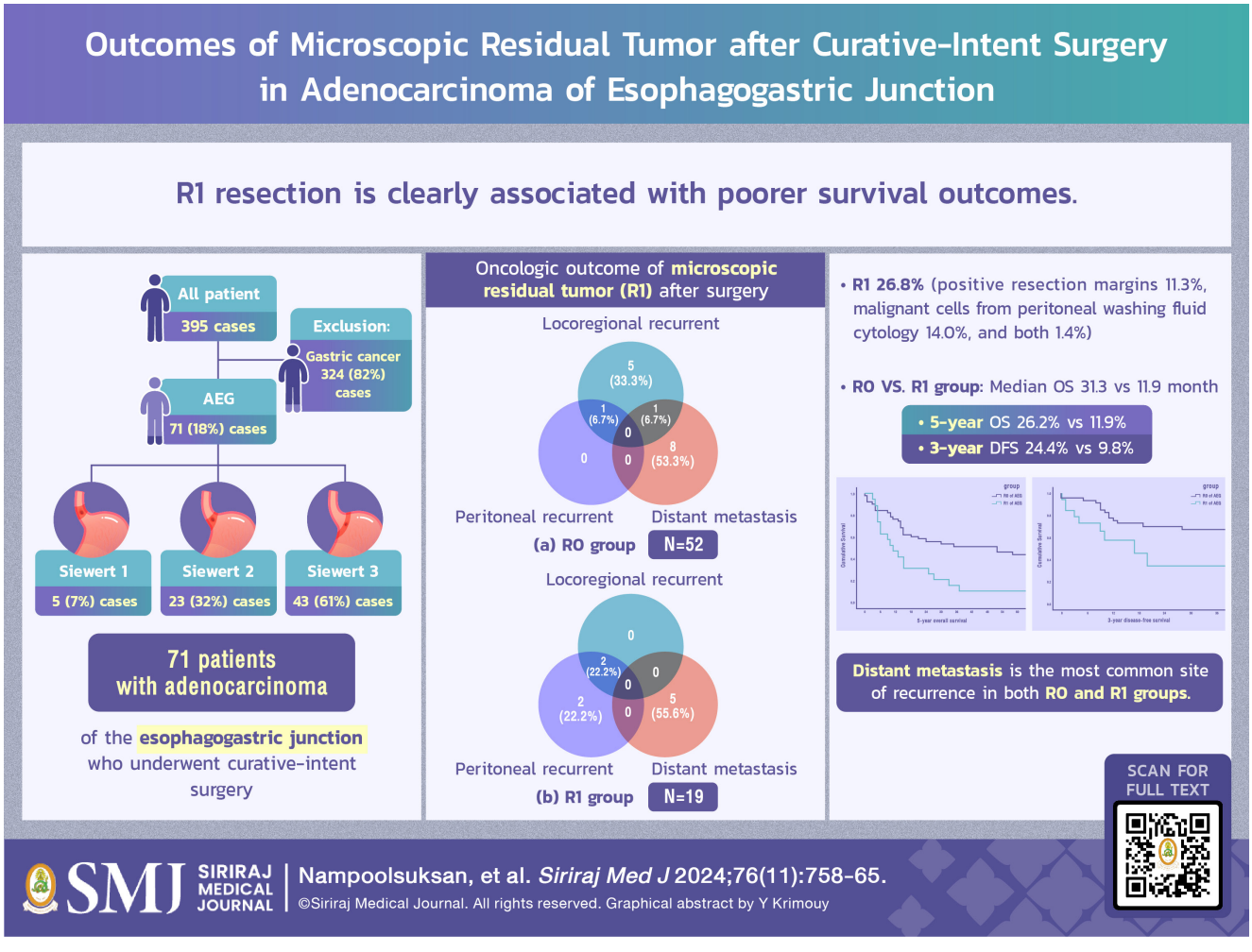
1. Hackett C, Grim B, Stonawski M, Skirbekk V, Potančoková M, Abel G. The Global Religious Landscape: A Report on the Size and Distribution of the World's Major Religious Groups as of 20102012.
2. Arunsutalangkarn P. role of thai buddhist monks and education in thai society. Journal of Buddhist Anthropology. 2023;8(2): 96-103.
3. Attaworakun S, Ngamdee N, Cherdsuntia V. Monk's health in urban area: The Problem that should be considered. Vajira Medical Journal: Journal of Urban Medicine. 2019;63(Supplement):S177-S84.
4. WHO. Urban health ; 2021[cite 2024 June 20] [Available from: https://www.who.int/health-topics/urban-health.
5. World Health Organization. Noncommunicable diseases country profiles 2018. Geneva; 2018. Licence: CC BY-NC-SA 3.0 IGO.
6. World Health Organization (WHO) SEA, Thailand. Prevention and Control of Noncommunicable Diseases in Thailand – The Case for Investment. 2021.
7. Phra Maha Wichian Wachiramotamonuen KA, Kanchanaphet, Phra Khru Sutthakit Somso. The role of monks in modern Thai society development. Journal Maha Chula tani Mahachulalongkorn-rajavidyalaya University. 2021;3(6):42–9.
8. Puckcharern; WALM-sNRWSH. Thai National Health Examination Survey, NHES V. Health Systems Research Institute (HSRI). 2016.
9. Jeamjitvibool T, Tankumpuan T, Lukkahatai N, Davidson PM. Noncommunicable diseases and social determinants of health in Buddhist monks: An integrative review. Res Nurs Health. 2022;45(2):249-60.
10. Angkatavanich J, Ariyapitipun, T., Wisesrith, W., Prasobtham, J., &Punpanich, D. . Situation of Nutritional Problem in Buddhist Monks from Project "Sonkthaiglairok". Bangkok: Thai Health Promotion Foundation (in Thai). 2016.
11. Srimantayamas V, Fongkaew W, Suksatit B, Aree P, Kosachunhanun N. Health Behaviors and Health-Related Quality of Life among Buddhist Monks with Metabolic Syndrome. Pacific Rim Int J Nurs Res. 2020;24(2):159-71.
12. Phrakru Phiphit Sutatorn, PC, WB, TP, PL, NY, et al. National Monks Health Statute. 3rd Floor, National Health Building, 88/39 Tiwanon Road 14, Village No. 4, Talat Khwan Subdistrict, Mueang District, Nonthaburi Province 11000: National Health Commission Office (NHCO); 2017.
13. University FoMSHM. Bangkok Noi Model 2020 [Available from: https://www2.si.mahidol.ac.th/en/sustainable/good-health-and-well-being/bangkok-noi-model/.
14. Gozzoli P, Rongrat T, Gozzoli R. Design Thinking and Urban Community Development: East Bangkok. Sustainability. 2022; 14:4117.
15. Group IT, Department OotS, Buddhism NOo. Basic Information on Buddhism for the Year 20212021.
16. Suchar C. The Relationship between Food Consumption Behavior, and Blood Sugar, Lipid Levels, AND Body Mass Index Among Monks in Samutprakarn Province. HCU Journal. 2018;21(42): 107-21.

17. Skou ST, Mair FS, Fortin M, Guthrie B, Nunes BP, Miranda JJ, et al. Multimorbidity. Nat Rev Dis Primers. 2022;8(1):48.
18. World Health Organization. Multimorbidity: Technical Series on Safer Primary Care. Geneva; 2016. Licence: CC BY-NC-SA 3.0 IGO.
19. CDC. Physical Activity ; 2022 [cite 2024 June 20]. Available from: https://www.cdc.gov/physicalactivity/basics/adults/index.htm.
20. Health Promotion Division FoMSHMU. Basal Metabolic Rate (BMR) 2021. Available from: https://www.si.mahidol.ac.th/th/healthdetail.asp?aid=1472.
21. Wellmon R. Chapter 32 - Gait Assessment and Training. In: Cameron MH, Monroe LG, editors. Physical Rehabilitation. Saint Louis: W.B. Saunders; 2007. p. 844-76.
22. de Fátima Ribeiro Silva C, Ohara DG, Matos AP, Pinto A, Pegorari MS. Short Physical Performance Battery as a Measure of Physical Performance and Mortality Predictor in Older Adults: A Comprehensive Literature Review. Int J Environ Res Public Health. 2021;18(20):10612.
23. Laochai W TD, Jiraprapapong N. Promoting Physical Activity among Buddhist Monks: The Role of Nurse. J Food Health Bioenv Sci. 2023;13(2):59-66.
24. Angthawanich J SA. Thai remote distant media of disease: integrated nutrituon to the Buddhist way 4 sectors. Bangkok: Chor Langa. 2015.
25. hospital P. Health examination program for novice monks 2017. Nonthaburi: Department of Medical Services, Ministry of Public Health2017
26. Bureau H. Screning of the health of monks in Bangkok in 2013: Bangkok: Health Bureau; 2014.
27. Palmer AK JM. Metabolic changes in aging humans: current evidence and therapeutic strategies. J Clin Invest. 2022;27(5):29-35.
28. Shimokata H, Kuzuya F. [Aging, basal metabolic rate, and nutrition]. Nihon Ronen Igakkai Zasshi. 1993;30(7):572-6.
29. Pilgrim AL RS, Sayer AA, Roberts HC. An overview of appetite decline in older people. Nurs Older People. 2015;27(5):29-35.
30. Wang X LW. Research progress on digital health literacy of older adults: A scoping review. Front Public Health. 2022;10:906089.
31. De Santis KK JT, Sina E, Wienert J, Zeeb H. Digitization and Health in Germany: Cross-sectional Nationwide Survey. JMIR Public Health Surveill 2021;7(11):e32951.
32. Papp-Zipernovszky O HM, Schulz PJ, Csabai M. Generation Gaps in Digital Health Literacy and Their Impact on Health Information Seeking Behavior and Health Empowerment in Hungary. Front Public Health. 2021;9:635943.
33. Lin CY GM, Griffiths MD, Bravell ME, Broström A, Pakpour AH. Mediated effects of insomnia, psychological distress and medication adherence in the association of eHealth literacy and cardiac events among Iranian older patients with heart failure: a longitudinal study. Eur J Cardiovasc Nurs. 2020;19(2):155-64.
34. Rees J TR, Burton A, Walters K, Cooper C. Supporting self-care of long-term conditions in people with dementia: A systematic review. Int J Nurs Stud. 2021;116:103432.
35. Clark JE. Diet, exercise or diet with exercise: comparing the effectiveness of treatment options for weight-loss and changes in fitness for adults (18-65 years old) who are overfat, or obese; systematic review and meta-analysis. J Diabetes Metab Disord. 2015;14:31.
36. Strasser B FD. Diet Versus Exercise in Weight Loss and Maintenance: Focus on Tryptophan. Int J Tryptophan Res. 2016;9:9-16.

Outcomes of Microscopic Residual Tumor after Curative-Intent Surgery in Adenocarcinoma of Esophagogastric Junction

Chawisa Nampoolsuksan, M.D.[1,2], Khajohnsak Bhocksombud, M.D.[1], Thammawat Parakonthun, M.D.[1,2,*], Tharathorn Suwatthanarak, M.D.[1], Thikhamporn Tawantanakorn, M.D.[1], Nicha Srisuworanan, M.D.[1], Voraboot Taweerutchana, M.D.[1], Atthaphorn Trakarnsanga, M.D.[1], Chainarong Phalanusitthepha, M.D.[1], Jirawat Swangsri, M.D.[1,2], Thawatchai Akaraviputh, M.D.[1], Asada Methasate, M.D.[1,2], Vitoon Chinswangwatanakul, M.D.[1]

[1]Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand, [2]Siriraj Upper GI Cancer Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.



*Corresponding author: Thammawat Parakonthun
E-mail: t.parakonthun@gmail.com
Received 28 May 2024 Revised 26 August 2024 Accepted 26 August 2024
ORCID ID:http://orcid.org/0000-0002-2990-0649
https://doi.org/10.33192/smj.v76i11.269480

All material is licensed under terms of the Creative Commons Attribution 4.0 International (CC-BY-NC-ND 4.0) license unless otherwise stated.

ABSTRACT

Objective: Radical surgery is the mainstay treatment for adenocarcinoma of the esophagogastric junction. The presence of microscopic residual tumor tissue after curative-intent surgery is associated with recurrence. This study compared the outcomes of patients with microscopic residual tumor (Residual$^+$ group) and those without microscopic residual tumor (Residual$^-$ group).

Material and Methods: We retrospectively reviewed the medical records of 71 patients with adenocarcinomas of the esophagogastric junction who underwent curative-intent surgery between January 2005 and August 2018. We evaluated the clinical and pathological characteristics and compared recurrences, rates and patterns, between groups. Five-year overall survival (OS) and 3-year disease-free survival (DFS) were analyzed by Kaplan-Meier analysis.

Results: Nineteen (26.8%) patients had microscopic residual tumors, consisting of 8 (11.3%) with positive resection margins, 10 (14.0%) with malignant cells from peritoneal washing fluid cytology, and 1 (1.4%) with both. The median OS in the Residual$^-$ group was significantly better than that in the Residual$^+$ group (31.3 vs 11.9 months, $P = 0.003$). The Residual$^-$ group had better 5-year OS (26.2% vs 11.9%, $P = 0.015$) and 3-year DFS (24.4% vs 9.8%, $P = 0.003$) than the Residual$^+$ group. During follow-up period, 48% of the patients in the Residual$^+$ group experienced recurrent disease, with a median follow-up time at 7.7 months. Distant metastasis was the most common site of recurrence.

Conclusion: Microscopic residual tumor after resection is associated with poorer survival outcomes and higher recurrence rates. Curative surgery should aim to achieve R0 resection in all patients with resectable adenocarcinomas of the esophagogastric junction.

Keywords: Adenocarcinoma of esophagogastric junction; microscopic residual tumor; positive margin; prognosis
(Siriraj Med J 2024; 76: 758-765)

INTRODUCTION

Patients with cancer originating at the transition zone between the stomach and esophagus are diagnosed with esophagogastric junction cancer regardless of the histopathologic type.[1-3] Most of these cancers are adeno carcinomas.[2,3] Currently, complete resection with adequate lymphadenectomy is the standard curative management for patients. Proximal submucosal extension may occur in adenocarcinomas, necessitating optimal esophageal resection.[4] The surgical treatment of adenocarcinomas of esophagogastric junction (AEG) is determined by the tumor location, classified according to Siewert classification and presence of lymph node metastasis. Surgery aims to achieve complete resection with microscopically negative for residual tumor (Residual$^-$, R0) and minimize postoperative morbidity.[5,6]

In case of Siewert type I tumors, a transthoracic approach is chosen to ensure sufficient proximal margins and adequate mediastinal lymph node harvesting. In case of Siewert type II tumors, transhiatal esophagogastrectomy or extended total gastrectomy is preferred if complete tumor-free esophageal resection is feasible. In case of Siewert type III tumors, total gastrectomy together with D2 lymphadenectomy is the recommended.[7,8]

Although R0 resection is attempted in all patients, recurrences occur in 40% to 80% of patients.[9-11] Advanced disease stage, lymph node involvement, and microscopic residual tumor are associated with predictive factors.[12,13] Distant metastasis is the most common recurrence and often cannot be resected, typically resulting in a shorter survival time. Therefore, perioperative systemic therapy has become the standard treatment for locally advanced disease to improve surgical outcomes and life expectancy.[14-17] Our study focused on oncologic outcomes after curative-intent surgery with microscopic residual tumor to demonstrate the adverse consequences of Residual$^+$ (R1) resection specifically on AEG. Determining associated factors of poor survival outcome would facilitate prognosis prediction and enhance further intensive surveillance.

MATERIALS AND METHODS

This study was approved by the Siriraj Institutional Review Board (CoA no. Si 552/2018) and was retrospectively registered with the Thai Clinical Trials Registry (TCTR20220721004). We reviewed the medical records and operative notes of patients aged over 18 years who were diagnosed with adenocarcinomas of the esophagogastric junction through tissue biopsy via esophagogastroduodenoscopy. These patients underwent curative-intent surgery between January 2005 and August 2018 at the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. Tumor location was classified according to Siewert based on endoscopic findings.[5,6] Chest and abdominal computed tomography were performed for disease staging in every patient. Exclusion were patients who underwent palliative surgery, who underwent R2

resection, or who received neoadjuvant chemotherapy. The following clinical and pathological characteristics were recorded age, gender, tumor size and location, operative approach, pathological staging according to the TNM classification, associated pathological findings, and lymph node involvement.

Patients were divided into 2 groups: the R0 and the R1 group. The R0 group was determined by the absence of microscopic residual tumor. The R1 group included cases with presence of microscopic residual tumor, confirmed by histopathological examination of either a positive surgical resection margin or malignant cells from peritoneal washing fluid. Positive intraoperative frozen section which had undergone reresection to achieve a negative margin were classified into the R0 group. Adjuvant treatment, including chemotherapy and radiotherapy, was offered in cases of locally advanced pathological stage or the presence of microscopic residual tumors. Routine postoperative surveillance was conducted to evaluate both locoregional and distant recurrence.

Statistical analyses

Statistical analyses were performed by using IBM SPSS Statistics, version 21 (IBM Corp, Armonk, NY, USA). The quantitative data are presented as the n (%) and mean ± SD for data with normal distribution or as the median (P25, P75) for data with nonnormal distribution. Comparisons of patient clinical and pathological characteristics between groups were analyzed using chi-square tests for categorical variables and independent t tests or Mann-Whitney U test for continuous variables. Survival analysis was conducted using the Kaplan–Meier method and log rank test. Cox regression analysis was used to identify associating factors of poor survival outcome. *P*-value less than 0.05 was considered to indicate statistical significance.

RESULTS

Patient clinicopathological characteristics

A total of 395 patients were diagnosed with gastric and esophagogastric junction adenocarcinoma. After excluding 324 patients of gastric origin, 71 patients who underwent curative-intent surgery with adequate systematic lymph node dissection were included in our study (Fig 1). Nineteen (26.7%) patients had microscopic residual tumors after surgery (R1 group). In this group, 8 (11.3%) patients had a positive resection margin, 10 (14.0%) patients had malignant cells in the peritoneal washing fluid, and 1 (1.4%) patient had both positive results. The remaining 52 (73.2%) patients had no microscopic residual tumors (R0 group). There were no statistical differences in age, gender, preoperative serum albumin level, tumor size, Siewert classification, operative approach, or the number of harvested nodes between groups. Significantly more advanced pathological stages, greater metastatic lymph node involvement, and lymphovascular and perineural invasion were observed in the R1 group. Similar postoperative complications, severity grades according to the Clavien–Dindo classification, and length of admission were observed in both groups (Table 1).

After surgery, 24 (47%) patients in the R0 group underwent adjuvant treatment according to their pathological stage. Specifically, 13 (25.5%) patients received chemotherapy, 2 (3.9%) patients underwent radiation therapy, and 9 (17.6%) patients were administered both. In the R1 group, a greater percentage, up to 89.4% (17 patients), were given adjuvant treatment. Of these, 10 (52.6%) patients received chemotherapy, and 5 (25.3%) patients underwent chemoradiation therapy. Two (10.5%) patients had only radiation therapy due to poor performance status. Additionally, two (10.6%) patients declined adjuvant treatment and requested best supportive care.

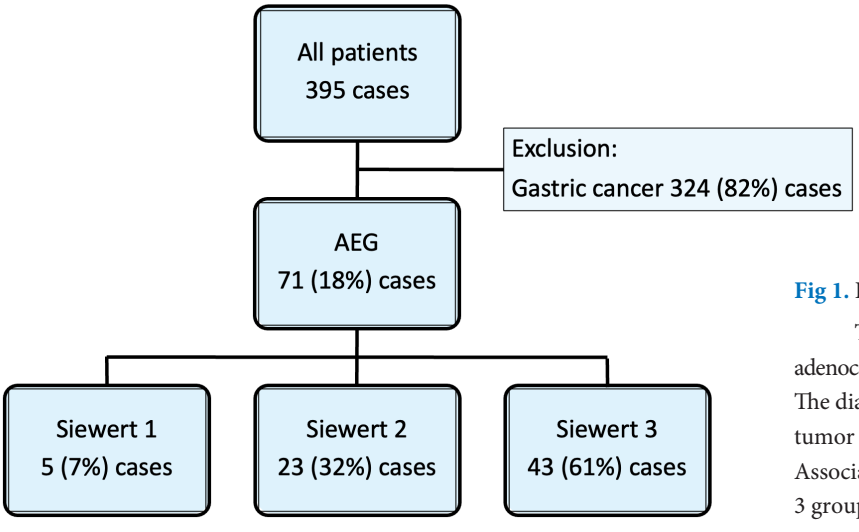


Fig 1. Flow diagram of patient cohort

This flow diagram demonstrates all cases of adenocarcinoma of gastric and esophagogastric junction. The diagnosis was made according to the location of tumor by definitions from Japanese Gastric Cancer Association.[1] Classification of AEG was divided into 3 groups by Siewert classification.[5,6]

TABLE 1. Characteristics of the study population.

Characteristics	R0 group (n=52)	R1 group (n=19)	*P*
Age (years)	64.3 ± 13.4	61.3 ± 12.1	0.406
Sex (male)	34 (64.5)	13 (68.4)	0.811
Tumor size (cm)	5.8 ± 3.3	6.3 ± 3.2	0.587
Siewert classification			0.208
Type I	2 (3.8)	3 (15.8)	
Type II	18 (34.6)	5 (26.3)	
Type III	32 (61.5)	11 (57.9)	
Operative approach			
Open	43 (82.7)	18 (94.7)	
Laparoscopic	8 (15.4)	1 (5.3)	
Robotic-assisted	1 (1.9)	0 (0.0)	0.422
No. of harvested lymph nodes	30 (0, 46)	34 (0, 52)	0.392
No. of positive lymph nodes	2 (0, 7)	7 (2, 12)	**0.022**
Tumor differentiation			0.404
Well to moderately	31 (59.6)	10 (52.6)	
Poorly	21 (40.4)	9 (47.4)	
Pathological T stage			0.363
T1	6 (11.7)	1 (5.3)	
T2	11 (21.6)	2 (10.5)	
T3	14 (27.5)	8 (42.1)	
T4	20 (39.2)	8 (42.1)	
Pathological N stage			**0.017**
N0	18 (34.6)	1 (5.3)	
N1	9 (17.3)	5 (26.3)	
N2	9 (17.3)	2 (10.5)	
N3	15 (28.8)	11(57.9)	
Pathological stage			0.062
I	12 (23.6)	0 (0.0)	
II	11 (21.5)	5 (26.3)	
III	27 (52.9)	13 (68.4)	
IV	1 (2.0)	1 (5.3)	
Lymphovascular invasion	24 (46.2)	15 (78.9)	**0.014**
Perineural invasion	31 (60.8)	17 (89.5)	**0.021**
Postoperative complication			0.911
Grade I-II	20 (38.5)	4 (21.1)	
Grade III-IV	30 (57.7)	15 (78.9)	
Grade V	2 (3.8)	0 (0.0)	
Length of hospital stay (days)	12 (10, 18)	15 (12, 24)	0.106

Abbreviations: R0 group=absence of microscopic residual tumors after surgery, R1 group=presence of microscopic residual tumors after surgery

Values are presented in n(%), mean ± SD for normally distributed data, and median (P25, P75) for non-normally distributed data. Comparisons between groups were analyzed using chi-square tests for categorical variables and independent t tests or Mann-Whitney U test for continuous variables.

Outcomes

Twenty-four (34%) patients experienced disease recurrence during follow-up, with 17 (70%) of these recurrences occurring within 12 months after surgery. Median follow-up time was 14 months for R0 group and 7.7 months for R1 group. The recurrence rates were 28% (15 patients) and 48% (9 patients), respectively. Most common site of recurrence was distant metastasis in both groups. In the R0 group, 8 (53.3%) patients had distant metastasis, 5 (33.3%) patients had locoregional recurrence, 1 (6.7%) patient had both locoregional and peritoneal recurrence, and 1 (6.7%) patient had locoregional recurrence with distant metastasis. In the R1 group, 5 (55.6%) patients had distant metastasis, 2 (22.2%) patients had peritoneal metastasis, and 2 (22.2%) patients had both locoregional and peritoneal metastasis (Fig 2).

The median overall survival (OS) in R0 group was significantly higher than in the R1 group (31.3 (12.3, 91.7) vs 11.9 (5.3, 16.7) months, P = 0.003). In R0 group, the 5-year OS rate was 26.2%, and the 3-year disease-free survival (DFS) rate was 24.4%. In contrast, in the R1 group, these percentages were only 11.9% (P = 0.015) and 9.8% (P = 0.003), respectively (Fig 3). Additionally, the median OS was greatest for patients who had Siewert type I tumors (68.5 months), followed by 15.6 months for type II tumors and 31.3 months for type III tumors (P = 0.09) in the R0 group. Conversely, in the R1 group, the median OS was greatest for type II tumors (28 months), followed by type I tumors (9.8 months) and type III tumors (6.8 months; P = 0.389). Presence of lymphovascular invasion was the independent factors for associating factors of poor survival outcome from multivariate analysis (Table 2).

After subgroup analysis according to the Siewert classification, the median OS of Siewert type III tumors was 53.5 months in R0 group, which was significantly superior to 6.8 months in R1 group (P = 0.003). Other two subtypes did not differ significantly between the two groups.

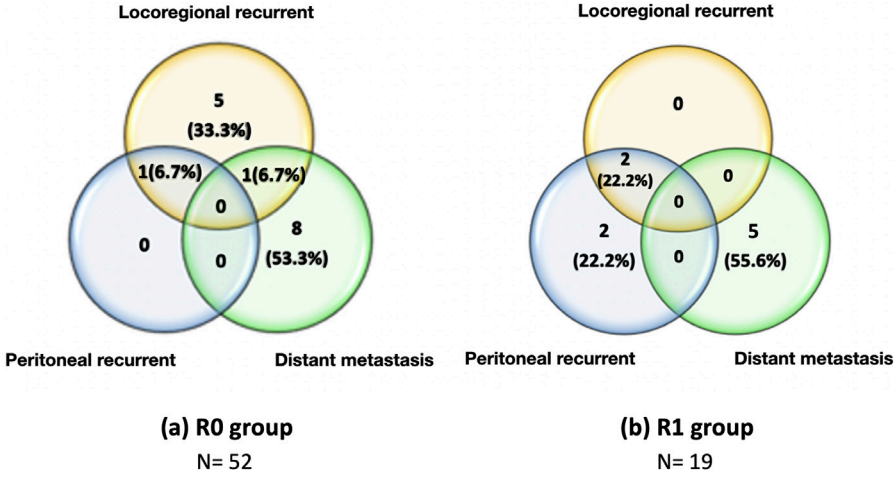


Fig 2. Patterns of disease recurrence.

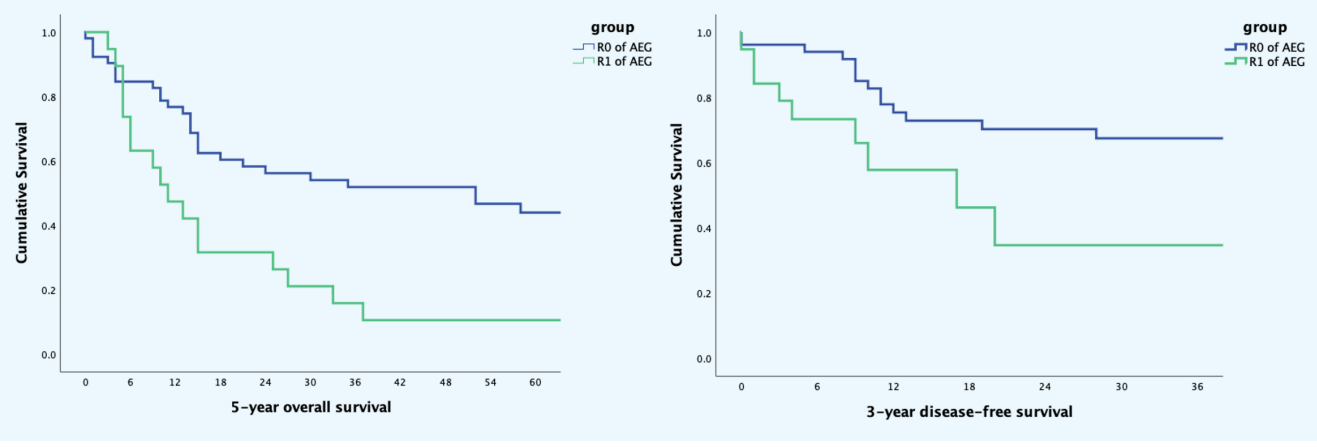


Fig 3. Kaplan–Meier survival analysis.

Abbreviations: R0 group=absence of microscopic residual tumors after surgery, R1 group=presence of microscopic residual tumors after surgery, AEG=adenocarcinoma of esophagogastric junction

TABLE 2. Associating factors for poor survival outcome.

	Crude HR (95%CI)	*P*	Adjusted HR (95%CI)	*P*
Differentiation		0.826		
Well to moderately	1			
Poorly	0.9 (0.3; 2.4)			
Pathological T		0.012		0.117
pT1-2	1			
pT3-4	11.5 (1.2; 106.9)		6.1 (0.6; 58.4)	
Pathological N		0.063		0.095
Negative	1			
Positive	2.7 (0.9; 8.1)		0.3 (0.1; 1.3)	
Pathological stage		0.019		0.210
I-II	1			
III	3.7 (1.2; 11.6)		2.0 (0.7; 6.1)	
LVI		0.018		**0.026**
No	1			
Yes	3.3 (1.2; 9.2)		4.4 (1.2; 16.4)	
PNI		0.939		
No	1			
Yes	1.0 (0.4; 2.9)			
Resection category		0.008		0.095
R0	1			
R1	6.7 (1.4; 32.2)		2.4 (0.9; 6.4)	

Abbreviations: LVI=lymphovascular invasion, PNI=perineural invasion

DISCUSSION

Surgical resection remains the best curative approach for esophagogastric junction adenocarcinoma. The general principle of this procedure is to achieve complete clearance of tumor cells with minimal morbidity. After diagnosis and clinical staging, multidisciplinary care is essential for patient management. Enhanced recovery after surgery protocols improves postoperative recovery and shorten hospital stays. Treatment planning, patient counseling, and education on disease prognosis should be anticipated. Nutritional assessment should be routinely performed in all patients, and nutritional support should be provided if malnutrition is present before the operative procedure. In the early stages, upfront surgery is recommended unless the patient is unfit for surgery. For more locally advanced disease, perioperative systemic therapy may be added following a risk-benefit assessment.[16-18]

Previous studies have demonstrated superior survival benefits and favorable postoperative outcomes after adequate surgery.[19] Various factors have been investigated to improve survival rates. Unfortunately, advanced disease and lymph node involvement at the time of diagnosis are unavoidable factors. A potentially avoidable negative factor is microscopic residual tumor, which can be reduced by perioperative therapy and adequate surgical techniques.

This is the first study in Thailand to report the survival prognosis and recurrence of microscopic residual tumors in patients who underwent curative-intent surgery for adenocarcinoma of the esophagogastric junction. Our study demonstrated worse survival outcomes and higher recurrence rates with microscopic residual tumors after curative-intent surgery than after complete curative surgery. Furthermore, achieving R0 resection did not increase postoperative morbidities or severe complications, nor did it lengthen the duration of hospitalization.

In our study, 26.7% of patients had residual disease, which was higher than in other studies. The incidence of microscopic residual tumors in prior studies ranged

from 16% to 21.5%. Prospectively maintained database from Italian study had reported 16 of 100 patients (16%) with positive resection margins, and another multicenter retrospective analysis also reported 145 of 674 patients (21.5%) with positive resection margins.[19,20]; however, we included both positive resection margins and the presence of cancer cells in peritoneal washing fluid cytology. After excluding patients with positive fluid cytology, the incidence of positive surgical resection margins was 12.7%, which is lower than that reported in the studies mentioned above.

During the surveillance period, the recurrence rate of the disease differed from that reported by other studies. Common sites of recurrence include distant metastasis, peritoneal metastasis, and locoregional recurrences.[9,11] Similarly, we found that distant metastasis was the most common site of recurrence in both groups. However, there was higher rate of peritoneal recurrence in R1 group compared to R0 group. Currently, there is no standard consensus or guideline for managing positive surgical resection margins. Adjuvant treatment with systemic chemotherapy or radiation therapy may be administered. Consistent with other studies, our median OS time, 5-year OS rate, and 3-year DFS rate in the R0 group were superior to those in the R1 group.

A limitation of this study that data were obtained from a single supertertiary center in Thailand, and details of treatment may differ from those of other centers. The concept of surgery and systematic lymphadenectomy has become more standardization. Additionally, variation in systemic treatment has changed over the years. Some of our patients were referred to our hospital for operation. After surgery, some had received adjuvant therapy at their primary hospital and continued the surveillance. This resulted in lack of postoperative documents for our analysis. For patients who completed their systemic course at our hospital, the majority of regimen is the doublet chemotherapy which is a combination of 5-FU/LV and oxaliplatin.

Second, there is selection bias inherent in the retrospective study design and the small sample size. Clinical characteristics in the R1 group included higher pathological stages, lymphovascular and perineural invasion, and more lymph node metastasis. These factors may explain the poorer prognosis, higher recurrence rates, and shorter survival times in the residual tumor group. Nonetheless, this study confirmed the adverse consequences of microscopic residual tumors after surgery. Adjuvant systemic or local therapy may improve these outcomes and should be routinely offered to patients in this setting. Future research should be conducted as a prospective multicenter study to combine entire patient's treatment journey in order to minimize the above-mentioned limitations.

CONCLUSION

Microscopic residual tumors clearly worsen oncologic outcomes in esophagogastric junction adenocarcinoma patients. Complete resection and negative peritoneal washing cytology are essential considerations in operable patients. Tumor with lymphovascular invasion is an indicative factor for poorer survival outcome.

ACKNOWLEDGMENTS

We are thankful to Dr Saowalak Hunnangkul, Miss Wathanaphirom Mangmee, and Miss Chorlada Keatrungarun for their assistance with the statistical methods and analysis.

DECLARATION

Grants and Funding Information

This project is not funded by any external sources.

Conflict of Interests

The authors declare that they have no conflicts of interest.

Author Contributions

TP was the corresponding author and was responsible for conceptualization, study methodology, data analyses, and final manuscript editing. CN designed the study, collected and analyzed the data, and wrote the original draft of the manuscript. KB, JS, and AM reviewed and edited the manuscript. All authors approved the final manuscript.

REFERENCES

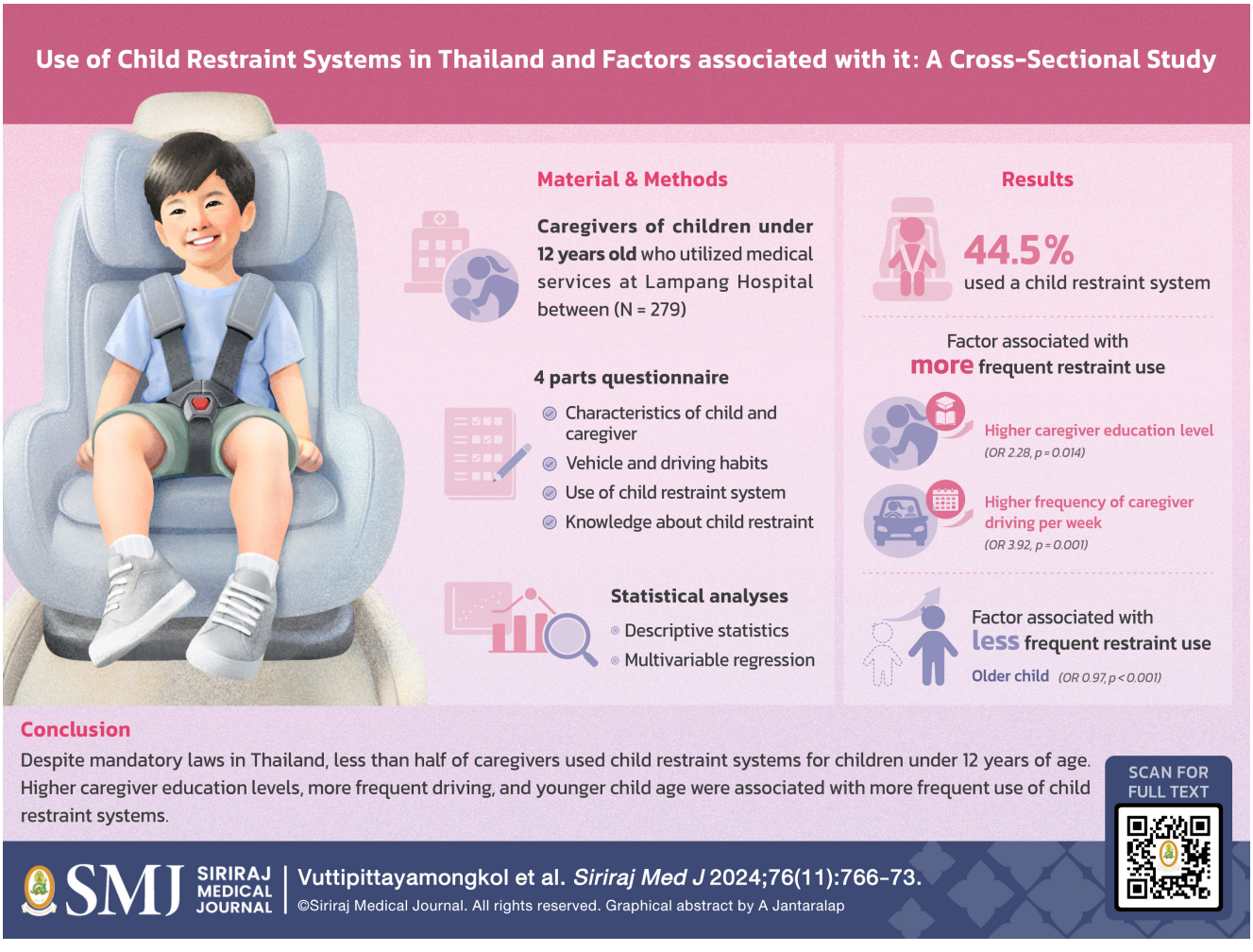
1. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer. 2011; 14:101-12.
2. Buas MF, Vaughan TL. Epidemiology and risk factors for gastro-esophageal junction tumors: understanding the rising incidence of this disease. Semin Radiat Oncol. 2013; 23:3-9.
3. Hasegawa S, Yoshikawa T. Adenocarcinoma of the esophagogastric junction: incidence, characteristics, and treatment strategies. Gastric Cancer. 2010;13:63-73.
4. Gao F, Chen J, Wang T, Wang G, Zhang Z, Shen L. Incidence of microscopically positive proximal margins in adenocarcinoma of the gastroesophageal junction. PLoS One. 2014;9(2):e88010.
5. Siewert J, Stein H. Carcinoma of the gastroesophageal junction-Classification, pathology, and extent of resection. Dis Esophagus. 1996;9:173-82.
6. Siewert J, Feith M. Adenocarcinoma of the esophagogastric junction, results of Surgical Therapy Based on Anatomical/

Topographic Classification in 1,002 Consecutive Patients. Ann Surg. 2000;232(3):353-61.
7. Van Laethem JL, Carneiro F, Ducreux M, Messman H, Lordick F, Ilson DH, et al. The multidisciplinary management of gastro-oesophageal junction tumours: European Society of Digestive Oncology (ESDO): Expert discussion and report from the 16th ESMO World Congress on Gastrointestinal Cancer, Barcelona. Dig Liver Dis. 2016;48(11):1283-9.
8. Hölscher AH, Law S. Esophagogastric junction adenocarcinomas: individualization of resection with special considerations for Siewert type II, and Nishi types EG, E=G and GE cancers. Gastric Cancer. 2002;23(1):3-9.
9. Hosokawa Y, Kinoshita T, Konishi M, Takahashi S, Gotohda N, Kato Y, et al. Recurrence patterns of esophagogastric junction adenocarcinoma according to Siewert's classification after radical resection. Anticancer Res. 2014;34(8):4391-7.
10. Wang G, Wu A, Cheng X, Ji J. Risk factors associated with early recurrence of adenocarcinoma of gastroesophageal junction after curative resection. Chin J Cancer Res. 2013;25(3):334-8.
11. Xu H, Zhang L, Miao J, Liu S, Liu H, Jia T, et al. Patterns of recurrence in adenocarcinoma of the esophagogastric junction: a retrospective study. World J Surg Oncol. 2020;18(1):144.
12. Parakonthun T, Parichardsombat N, Salomon H, Paredes R, Phalanusittheph C, Taweerutchana V, et al. Significance of Microscopic Residual Tumor in Adenocarcinoma of Stomach and Esophagogastric Junction after Gastrectomy with D2 Lymphadenectomy. Siriraj Med J. 2018;70(2):95-102.
13. Mariette C, Castel B. Surgical management of and long-term survival after adenocarcinoma of the cardia. Br J Surg. 2002; 89(9):1156-63.
14. Greally M, Agarwal R, Ilson DH. Optimal Management of Gastroesophageal Junction Cancer. Cancer 2019;125(12):1990-2001.
15. Oo AM, Ahmed S. Overview of gastroesophageal junction cancers. Mini-invasive Surg. 2019;3:13.
16. Kurokawa Y, Sasako M, Doki Y. Treatment Approaches to Esophagogastric Junction Tumors. Dig Surg. 2013;30(2):169-73.
17. Maruyama S, Imamura Y, Kanie Y, Sakamoto K, Fujiwara D, Okamura A, et al. Recent updates of therapeutic strategy of esophagogastric junction adenocarcinoma. J Cancer Metastasis Treat. 2021;7:53.
18. Leers JM, DeMeester SR, Chan N, Lipham JC, Hagen JA, DeMeester TR. Clinical characteristics, biologic behavior, and survival after esophagectomy are similar for adenocarcinoma of the gastroesophageal junction and the distal esophagus. J Thorac Cardiovasc Surg. 2009;138(3):594-602.
19. Carboni F, Lorusso R, Santoro R, Lepiane P, Mancini P, Sperduti I, et al. Adenocarcinoma of the esophagogastric junction : the role of abdominal-transhiatal resection . Ann Surg Oncol. 2009; 16(2):304-10.
20. Bissolati M, Desio M, Rosa F, Rausei S, Marrelli D, Baiocchi GL, et al. Risk factor analysis for involvement of resection margins in gastric and esophagogastric junction cancer: an Italian multicenter study. Gastric Cancer. 2017; 20(1):70-82.

Use of Child Restraint Systems in Thailand and Factors associated with it: A Cross-Sectional Study

Pakawadi Vuttipittayamongkol, M.D.[1], Roungtiva Muenpa, Ph.D.[2], Prakasit Wannapaschaiyong, M.D.[3,*]

[1]Department of Pediatrics, Lampang Hospital, Lampang 52000, Thailand, [2]Department of Pharmacy, Lampang Hospital, Lampang 52000, Thailand, [3]Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.



**Corresponding author: Prakasit Wannapaschaiyong*
E-mail: prakasit.wan@mahidol.ac.th
Received 15 June 2024 Revised 30 July 2024 Accepted 30 July 2024
ORCID ID:http://orcid.org/0000-0001-7099-0183
https://doi.org/10.33192/smj.v76i11.269751

All material is licensed under terms of the Creative Commons Attribution 4.0 International (CC-BY-NC-ND 4.0) license unless otherwise stated.

ABSTRACT

Objective: To determine the use of child restraint systems among caregivers of children in Thailand and to identify factors associated with it.

Materials and Methods: Caregivers of children under 12 years old who utilized medical services at Lampang Hospital between March 2023 and March 2024 were asked to participate in this cross-sectional study. Data on characteristics of child and caregiver, driving behavior, and knowledge about child restraint systems were collected via a questionnaire. Multivariable regression was applied to analyze associated factors.

Results: Of the 322 eligible caregivers, 279 (86.6%) participated, of which 127(44.5%) used a child restraint system. A higher caregiver education level (odds ratio [OR] 2.28, 95% CI 1.18; 4.39), and driving 3–7 days per week (OR 3.92, 95% CI 1.82; 8.40) were associated with more frequent restraint use. A higher age of the child (OR 0.97, 95% CI 0.96; 0.98) was associated with less frequent restraint use.

Conclusion: Fewer than half of the caregivers utilized child restraint systems. Higher caregiver education levels and more frequent driving were associated with more frequent use, while older child age was associated with less frequent use of child restraint systems. Targeted interventions are needed to improve the use of child restraint systems.

Keywords: Car seats; caregiver knowledge; child restraint systems; Thailand (Siriraj Med J 2024; 76: 766-773)

INTRODUCTION

Road traffic accidents are a leading cause of child mortality worldwide, with the World Health Organization reporting over 186,300 annual deaths in children under 18 years of age.[1] Those who survive these accidents frequently end up with lifelong disabilities.[1] The non-use of a child restraint system is a primary contributor to child road fatalities.[2]

Child restraint systems include all devices and components used to secure children safely in vehicles. Child restraint seats, also known as child safety seats or car seats, are designed to accommodate the small size of infants and young children and to provide protection in case of an accident. Safety belts are the standard restraints built into vehicles for older children and adults. They are not designed for younger children and do not provide protection in case of an accident.[3]

Prior research has identified various factors associated with the use of child restraint systems. Family-level factors associated with more frequent use include higher parental education[4,5], higher household income[4,6], prior accident experience[7], and caregiver awareness of the importance of using child restraints.[8-10] Environmental factors, such as rural roads and nighttime travel, have been associated with less frequent use of child restraint system.[11]

In Thailand, between 2017 and 2021, road accidents claimed the lives of 1,155 children aged 0-6 years. Of these fatalities, 221 occurred while the children were passengers in vehicles. The same survey revealed that 96.5% of children who died as passengers were not using a child restraint system.[12]

Thailand enacted a law in May 2022 mandating the use of child restraint seats for passengers under 6 years old. Children under 135 cm tall were also required to use a safety belt or child restraint seat, regardless of their seating position.[13] However, no surveys have examined the actual usage rates of child restraint systems or the associated factors since the law's enactment. This study aimed to assess the use of child restraint systems among caregivers of children aged under 12 years in Thailand and to identify factors associated with it. Understanding these factors may be important for promoting the use of child restraint systems and thereby improving child passenger safety.

MATERIALS AND METHODS

Study design and population

This observational cross-sectional study targeted caregivers of children under 12 years old who utilized medical services at Lampang Hospital between March 2023 and March 2024. A previous study[7] found an 82% use of child restraint systems among caregivers. To estimate the current use we applied the population proportion formula to determine the sample size. A 5% margin of error and a 95% confidence level resulted in a sample size of approximately 280 participants. The inclusion criteria were possession of a private vehicle, literacy in reading and writing in Thai, and driving with a child less than 12 years of age.

Data collection

The Lampang Hospital Ethics Committee for Human Research approved the study protocol (EC 27/66). Caregivers

who met inclusion criteria were invited to participate and complete a questionnaire. The research assistant was available solely to answer any questions the participants had regarding the survey items.

The questionnaire assessed 4 domains, including characteristics of child and caregiver, vehicle and driving habits, use of child restraint system, and knowledge about child restraint systems. The characteristics included age, sex, weight, height, and underlying medical conditions of the child, as well as age, sex, marital status, monthly household income, education level, and occupation of the caregiver. Vehicle and driving information included vehicle type, frequency and duration of driving or riding with the child, distance driven with the child per week, prior motor vehicle accident experience, and caregiver safety belt usage.

Use of child restraint systems included familiarity with child restraint systems, their usage of such systems, and their reasons for using or not using the systems. This questionnaire section included open-ended questions to gather qualitative data on caregivers' reasons for their choices. These questions were: "Why do you choose to use a child restraint system?" (for users), and "Why do you choose not to use a child restraint system?" (for non-users). Participants were encouraged to provide detailed responses. The research team conducted a thematic analysis of these responses. Two researchers independently coded the responses, identifying recurring themes. They then compared their findings and resolved any discrepancies through discussion to reach a consensus on the main themes representing reasons for the use and non-use of child restraint systems.

Knowledge about child restraint systems was assessed by means of 5 multiple-choice questions, each with 4 options, and respondents must select the single most correct answer for each question. The questions addressed the effectiveness of standard safety belts alone in protecting children under 4 years old during motor vehicle accidents, the best position for a child restraint seat, the age range for which child restraint seats are required by traffic law, the most suitable child restraint system for children under 2 years old, and the correct installation of a 5-point harness in a child restraint seat. Caregivers who answered 4 or 5 of the knowledge questions correctly were categorized as having a good level of knowledge. The others were categorized as having a poor level of knowledge. Five experts with at least 10 years of experience in child restraint system research assessed the content validity of the knowledge questions. Interobserver reliability of the experts expressed in Cohen's kappa was 0.99. A pilot test was conducted with 30 individuals similar to the target sample. Internal consistency was analyzed Cronbach's alpha was 0.70.

Statistical analysis

Descriptive statistics were used to analyze the prevalence of child restraint system use, characteristics of caregivers and their children, caregiver driving practices, child usage patterns, and caregiver knowledge about child restraints. Chi-square and Fisher's exact tests were used to examine the associations between independent variables and the decision to use a child restraint system. Independent t-tests and Mann–Whitney U tests were used to analyze continuous data between caregivers who used child restraint systems and those who did not. Variables associated ($P < 0.05$) with system use were entered into a multivariable logistic regression model to control for potential confounders. All analyses were performed using IBM SPSS Statistics, version 25 (IBM Corp, Armonk, NY, USA), with statistical significance set at $P < 0.05$.

RESULTS

Caregiver and child

A total of 350 caregivers were screened for eligibility, of which 322 met the inclusion criteria. Of these potential participants, 279 agreed to participate. In total, 127 (44.5%, 95% CI 38.8%, 50.3%) used child restraint systems. Caregivers who used child restraint systems were significantly younger than those who did not use child restraint systems. Child restraint systems were significantly more often used in younger children (Table 1).

Socioeconomic factors

Caregivers who used child restraint systems were more likely to have a bachelor's degree or higher, be government officers or company employees, and have a monthly income exceeding 814 US dollars (Table 1).

Child health characteristics

An underlying disease in a child was significantly associated with more frequent use of a child restraint system (Table 1).

Caregiver driving behavior

Driving a sedan and more frequent driving was associated with more frequent use of child restraint systems (Table 2).

TABLE 1. Characteristics of participants and their children.

Characteristics	Use child restraint systems (N=127)	Do not use child restraint systems (N=152)	*P*
Caregiver variables			
Age[a] (year)	34.9 (7.3)	38.1 (10.8)	0.004
Sex			1.000
Male	23 (18.1)	28 (18.4)	
Female	104 (81.9)	124 (81.5)	
Marital status			0.247
Married	115 (90.5)	127 (83.5)	
Separated	9 (7.1)	18 (11.8)	
Single	3 (2.4)	7 (4.6)	
Education level			<0.001
Below bachelor's degree	44 (34.6)	107 (70.4)	
Bachelor's degree and above	83 (65.4)	45 (29.6)	
Occupation			<0.001
None/Student	18 (14.2)	35 (23.0)	
Freelance/Self-employed	47 (37.0)	84 (55.3)	
Government/Private enterprise	62 (48.8)	33 (21.7)	
Monthly income			<0.001
<814 US dollars[+]	18 (14.2)	67 (44.1)	
≥814 US dollars[+]	109 (85.8)	85 (55.9)	
Child variables			
Age[b] (months)	31 (14, 47)	59 (22.5, 95)	<0.001
Sex			0.229
Male	61 (48.0)	85 (55.9)	
Female	66 (52.0)	67 (44.1)	
Weight for age			0.541
Low (<3rd percentile)	11 (8.7)	18 (11.8)	
Average (3rd – 97th percentile)	111 (87.4)	125 (82.2)	
High (>97th percentile)	5 (3.9)	9 (5.9)	
Height for age			0.052
Low (<3rd percentile)	11 (8.7)	19 (12.6)	
Average (3rd – 97th percentile)	111 (87.4)	116 (76.8)	
High (>97th percentile)	5 (3.9)	16 (10.6)	
Underlying disease			0.001
No	95 (74.8)	91 (59.9)	
Yes	32 (25.2)	61 (40.1)	

Data are presented as numbers (percentages)

[+]1 UD dollar = 36.87 bahts

[a] Data are presented as means (standard deviations). [b] Data are presented as medians (interquartile ranges).

TABLE 2. Driving behavior and knowledge about child restraint systems among participants.

Independent variables	Use child restraint systems (N=127)	Do not use child restraint systems (N=152)	*P*
Type of vehicle			<0.001
Sedan	104 (81.9)	74 (49.0)	
Pickup	22 (17.3)	74 (49.0)	
Van	1 (0.8)	3 (2.0)	
Frequency of caregiver driving			<0.001
≤2 days/week	24 (18.9)	72 (47.4)	
3-7 days/week	103 (81.2)	80 (52.7)	
Frequency of caregiver safety belt use			0.547
Never used	1 (0.8)	0 (0.0)	
Used on some occasions	11 (8.6)	24 (15.8)	
Used on almost every occasion	115 (90.5)	124 (81.6)	
History of motor vehicle accidents			0.673
No	12 (9.5)	12 (7.9)	
Yes	115 (90.6)	140 (92.1)	
Knowledge about child restraint systems			0.011
Poor	48 (37.8)	81 (53.3)	
Good	79 (62.2)	71 (46.7)	

Data are presented as numbers (percentages).

Knowledge about child restraint systems

A good level of knowledge about using child restraint systems was significantly associated with the use of child restraint systems (Table 2).

Reasons for use and nonuse

The qualitative data analysis revealed that caregivers used child restraint systems primarily to prioritize the child's safety (97.6%) and to comply with legal requirements (67.7%). Conversely, the participants who did not use child restraint systems stated that the children under their care refused to use them (57.9%), that they felt it was inconvenient for travel (57.9%), and that child restraint systems, especially car seats, were expensive (30.9%).

Factors influencing caregiver use of child restraint systems

After adjusting for potential confounders, a bachelor's degree or higher was associated with more frequent use of child restraint systems, while a higher age of the child was associated with less frequent use of a child restraint system (Table 3). Driving more frequently was also associated with more frequent use of child restraint systems (Table 3).

DISCUSSION

The prevalence of use of child restraint systems in this study was 44.5%, a marked improvement from the 20%, reported in Thailand in 2015.[14] This increase likely reflects heightened awareness due to the legal mandate introduced in 2022. Despite this progress, more than half of caregivers still did not use these systems, indicating the need for further interventions to promote compliance and enhance child passenger safety.

This study revealed that several socioeconomic and behavioral factors were significantly associated with the use of child restraint systems, which is consistent with findings from other countries.[4-6] Higher levels of caregiver education were associated with increased restraint usage, likely due to enhanced knowledge and awareness about child safety practices among more educated individuals.[4,5,15]

TABLE 3. Result of Multivariable logistic regression analysis of factors associated with caregivers' use of child restraint systems.

Variable	Coef.	Std. Err	95% CI	OR	*P*
Caregiver variables					
Age	-0.01	0.02	0.96, 1.03	0.99	0.656
Education level					
Below bachelor's degree	Reference				
Bachelor's degree and above	0.82	0.33	1.18, 4.39	2.28	0.014
Occupation					
None/Student	Reference				
Freelance/Self-employed	-0.34	0.37	0.35, 1.47	0.71	0.359
Government/Private enterprise	-0.26	0.49	0.29, 2.02	0.77	0.594
Monthly income					
<814 US dollars[+]	Reference				
≥814 US dollars[+]	0.52	0.43	0.73, 3.92	1.69	0.222
Child variables					
Age	-0.01	0.02	0.96, 0.98	0.97	<0.001
Underlying disease					
No	Reference				
Yes	-0.19	0.34	0.42, 3.42	0.82	0.774
Caregiver driving characteristics					
Type of vehicle					
Sedan	0.79	1.30	0.59, 89.29	7.28	0.120
Pickup	1.99	1.28	0.17, 27.79	2.20	0.544
Van	Reference				
Frequency of caregiver driving					
≤ 2 days/week	Reference				
3-7 days/week	1.36	0.39	1.82, 8.40	3.92	0.001
Knowledge about child restraint systems					
Poor	Reference				
Good	0.23	0.32	0.67, 2.37	1.26	0.473

[+]1US dollar = 36.87 bahts

Abbreviations: OR, odds ratio; CI, confidence interval

Percentage correctly predicted: 75.3%

In other studies a higher household income was positively associated with the utilization of child restraint systems, as the financial burden of purchasing and installing these systems can be a barrier for lower-income families.[6,7]

Child age is inversely associated with the use of a child restraint system, with older children being less likely to be properly restrained. This trend may result from perceptions that older children are at reduced risk or no longer require restraints. Furthermore, older children are more likely to resist using restraints, making it challenging for caregivers to ensure that the children always use the systems.[10,16,17]

Caregiver driving behavior significantly influenced restraint practices. Caregivers who drove more frequently had greater odds of using child restraint systems, likely due to increased risk exposure from spending more time on the road and a heightened perceived need for restraint use.[18]

Although good knowledge about child restraint systems was more common among caregivers who used them, it did not emerge as an independent predictor after adjusting for other factors. This finding suggests that while education is important, other factors may have a greater impact on use of child restraint systems.[10]

The strengths of this study include the comprehensive assessment of various potential influences and the robust sample size. However, several limitations should be noted. The single-center design may limit the generalizability of our findings to other regions or populations in Thailand. The reliance on self-reported data may introduce recall bias, where participants may not accurately remember or report their behaviors. Furthermore, the presence of research assistant during data collection may introduce observer bias. To reduce observer bias researcher assistants had been trained to use a neutral tone and avoid using gestures that could guide responses. They were instructed not to judge participants based on their answers and maintain the confidentiality of research participants. The social desirability of using child safety devices could have further influenced participants to report more favorably on their behaviors.

Additionally, of the 322 eligible caregivers who were approached, 43 (13.4%) declined to participate. This non-participation could lead to selection bias if those who declined differed systematically from those who participated. However the non-participation is small relative to the total sample.

Future research could address these limitations through several approaches. Multi-center studies across different regions of Thailand would improve generalizability. Observational studies of actual child restraint system use, rather than relying solely on self-reports, could provide more accurate prevalence estimates. Anonymous surveys might reduce social desirability bias. Additionally, collecting basic characteristics from those who decline participation could help assess potential selection bias.

Despite these limitations, our findings provide valuable insights into the current state of child restraint system use in Thailand and the factors associated with their use. These results can inform targeted interventions to improve use rates. For instance, educational campaigns could focus on the importance of continued use as children grow older. Policies to make child restraint systems more affordable or accessible could address financial barriers.

Although legislative efforts have been made, the use of child restraint systems in Thailand remains suboptimal, indicating the need for additional measures. In addition to continuing education and awareness campaigns, tailored interventions targeting specific risk groups could help bridge the gap and enhance child passenger safety nationwide.

CONCLUSION

Despite mandatory laws in Thailand, less than half of caregivers used child restraint systems for children under 12 years of age. Higher caregiver education levels, more frequent driving, and younger child age were associated with more frequent use of child restraint systems.

ACKNOWLEDGMENTS

The authors express their gratitude to the individuals who participated in this study.

DECLARATION

Grants and Funding Information

This project is not funded by any external sources.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Author Contributions

All authors approved the final article. The authors were involved with the study: P.V. ; Conceptualization; Methodology; Investigation and data collection; and Writing–original draft. R.M. ; Investigation and data collection. P.W. ; Conceptualization; Writing–review and editing.

REFERENCES

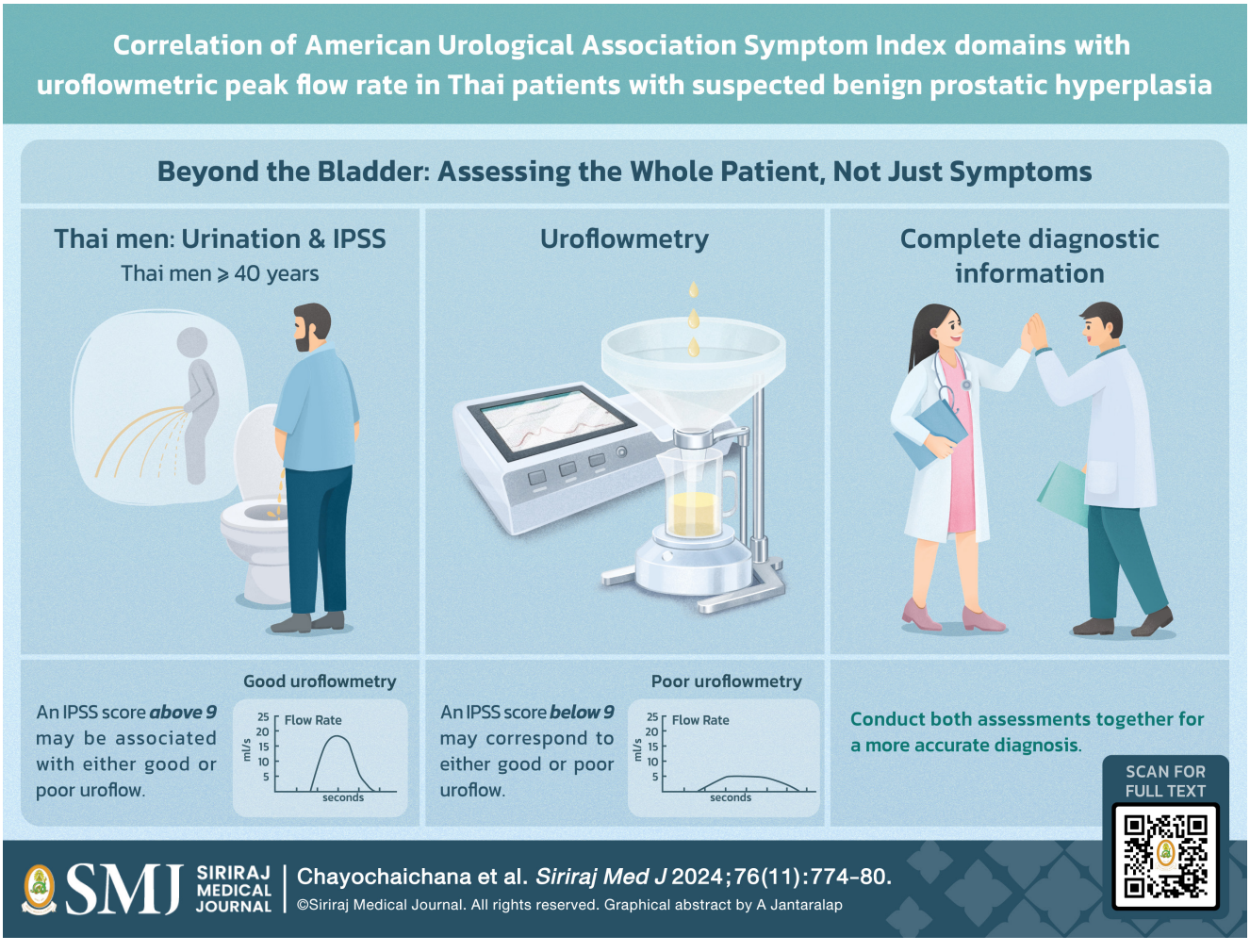
1. World Health Organization. Global status report on road safety 2023. Available from: https://assets.bbhub.io/dotorg/

sites/64/2023/12/WHO-Global-status-report-on-road-safety-2023.pdf
2. Chen SY, Garcia I, Ourshalimian S, Lowery C, Chaudhari PP, Spurrier RG. Childhood opportunity and appropriate use of child safety restraints in motor vehicle collisions. World J Pediatr Surg. 2024;7(2):e000703.
3. Durbin DR, Hoffman BD, Agran PF, Denny SA, Hirsh M, Johnston B, et al. Child passenger safety. Pediatrics. 2018;142(5):e2018246.
4. Rok Simon M, Korosec A, Bilban M. The influence of parental education and other socio-economic factors on child car seat use. Zdr Varst. 2017;56(1):55-64.
5. Li Y, Zhao T, Kang N, Wang W, Liu Q, Namgung M. Analysis of the factors influencing parents' support for child safety seat legislation in Nanjing. Traffic Inj Prev. 2022;23(4):187-92.
6. Armouti I. Factors affecting the use of Child Car Seats for nursery school travel. A study in Athens. In: Transportation Research Board 95th Annual Meeting 2016.
7. Termworasin P, Lumbiganon D, Prueksapraopong C. Car Seat Knowledge and Car Seat Use among Parents of Preschool Children in Bangkok, Thailand. Vajira Med J. 2021;65(2):95-106.
8. Kim SH, Park SW, Lee YK, Ko SY, Shin SM. Use of child safety seats during transportation of newborns. Korean J Pediatr. 2018;61(8):253-7.
9. AlSallum GA, Alwassel AA, Alshushan AM, Abaalkhail AK, Alhasoon MA, Aldamigh AS. Parent's knowledge, attitude, and practice about children car seats at Unaizah city, KSA. J Family Med Prim Care. 2019;8(3):805-11.
10. Jones AT, Hoffman BD, Gallardo AR, Gilbert TA, Carlson KF. Rear-facing car safety seat use for children 18 months of age: prevalence and determinants. J Pediatr. 2017;189:189-195.e9.
11. Dissanayake S, Amarasingha N. Restraint usage characteristics and other factors associated with safety of children involved in motor vehicle crashes. J Civil Eng Archit. 2016;10(1):81-95.
12. Bangkok Media and Broadcasting [Internet]. Recommendations for choosing a "Car Seat" for children to reduce "injury and death" from accidents; 2021 [cited 2024 Jun 7]. Available from: https://www.pptvhd36.com/automotive/news/172026
13. Kannika Pusara. Road Traffic Act (No. 13), B.E. 2565, and the Requirement for Children to Sit in Car Seats. Senate Journal [Internet]. November 2022 [cited 2024 Jun 7]. Available from: https://www.senate.go.th/assets/portals/93/fileups/253/files/Analysis/65/11_66_1.pdf
14. A Situation Study Report: Car Seat in Thailand. Report No: 296-2015-16. [Internet]. 2015 [cited 2024 June 6]. Available from: http://kb.hsri.or.th/dspace/handle/11228/4326?locale-attribute-th
15. Wannapaschaiyong P, Penphattarakul A, Rojmahamongkol P, Sutchritpongsa S. The Relationship Between Primary Caregivers' Psychosocial Factors and Self Esteem in Children and Adolescents with ADHD: An Exploratory Crossectional Study. Siriraj Med J. 2023;75(8):584-91.
16. Sauber-Schatz EK, Ederer DJ, Dellinger AM. Vital Signs: Motor Vehicle Injury Prevention - United States and 19 Comparison Nations. MMWR Morb Mortal Wkly Rep. 2016;65(26):672-7.
17. Lee G, Pope CN, Nwosu A, McKenzie LB, Zhu M. Child passenger fatality: Child restraint system usage and contributing factors among the youngest passengers from 2011 to 2015. J Safety Res. 2019;70:33-8.
18. Sayed I, Abdelgawad H, Said D. Studying driving behavior and risk perception: a road safety perspective in Egypt. J Eng Appl Sci. 2022;69(22).

Correlation of American Urological Association Symptom Index Domains with Uroflowmetric Peak Flow in Thai Patients with Suspected Benign Prostatic Hyperplasia

Sidaporn Chayochaichana, M.D., Julin Opanurak, M.D., Apirak Santingamkun, M.D., Supoj Ratchanon, M.D.*

Department of Surgery, King Chulalongkorn Memorial Hospital, Thai Redcross Society, Bangkok, Thailand.



*Corresponding author: Supoj Ratchanon
E-mail: supoj.r@chula.ac.th
Received 22 June 2024 Revised 31 July 2024 Accepted 1 August 2024
ORCID ID:http://orcid.org/0009-0001-4389-1400
https://doi.org/10.33192/smj.v76i11.269863

All material is licensed under terms of the Creative Commons Attribution 4.0 International (CC-BY-NC-ND 4.0) license unless otherwise stated.

ABSTRACT

Objective: This study aimed to investigate the correlations between the obstructive and irritative domain scores of the total AUA-SI and the uroflowmetric peak flow rate (Qmax) in Thai patients suspected of having benign prostatic hyperplasia (BPH).

Methods: A retrospective observational study was conducted on 510 patients who presented with lower urinary tract symptoms (LUTSs) and were suspected of having BPH at the Urology Outpatient Department of King Chulalongkorn Memorial Hospital, Thailand. A self-administered AUA-SI score was used to determine the severity of symptoms, and uroflowmetry was conducted to determine parameters, including flow rate variable.

Results: A significant correlation was observed between the AUA-SI score and uroflowmetric peak flow (Qmax). The AUA-SI and its obstructive domain had weak negative Pearson correlations with uroflowmetric peak flow ($r = -0.164$ and -0.185, respectively; $P < 0.01$). The irritative domain was inversely associated with Qmax ($r = 0.097$, $P = 0.028$). However, when patients in each subgroup with mild (AUA-SI = 0 - 7), moderate (AUA-SI = 8–19), and severe symptoms (AUA-SI = 20–35) were considered, the relationship was found to be not significant.

Conclusion: The study revealed a significant weak negative correlation between the AUA-SI score and Qmax, but no significant correlations were found between the obstructive and irritative domains and Qmax in the subgroup analysis.

Keywords: BPH; Benign Prostatic Hyperplasia; AUA-SI; Uroflowmetry (Siriraj Med J 2024; 76: 774-780)

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a prevalent condition that significantly impacts the quality of life of aging men.[1] It is the primary cause of lower urinary tract symptoms (LUTSs), which are often the main reason for seeking medical attention and may require surgical intervention. Half of men over 50 years of age exhibit evidence of BPH.[2] LUTSs can impose a substantial economic burden, and they are a significant concern for patients' overall health and wellbeing.[3,4] Taking a comprehensive medical history, including symptoms, previous procedures, sexual history, medication use, and overall fitness and health, is essential when evaluating patients with LUTSs.

The International Prostate Symptom Score (IPSS) or the American Urological Association (AUA) Symptom Index (AUA-SI) is a validated self-administered questionnaire that provides valuable information about the symptom burden experienced by patients. Although newer questionnaires have been developed, they have not gained worldwide popularity.[5-7]

The questionnaire consists of seven questions, each with five levels of severity. Questions 1, 3, 5, and 6 pertain to the obstructive domain, and questions 2, 4, and 7 are related to the irritative domain. IPSS has been translated and validated in Thai.[6] It includes the AUA-SI score and one question on the quality-of-life score.

Although IPSS, digital rectal examination (DRE), serum prostate-specific antigen (PSA), and uroflowmetry are important predictors of disease progression and acute urinary retention, the AUA 2020 guidelines recommend considering IPSS, DRE, and serum PSA in all patients. They also recommend performing uroflowmetry before intervening for LUTSs, particularly in patients with moderate-to-severe symptoms.

However, past studies by Setthawong et al. (2018) in Thailand found that the level of education, especially among the elderly, affects the implementation of IPSS. This finding serves as the rationale for the present study. Considering that the level of education impacts IPSS scores, the relationship between IPSS and uroflowmetry may not align with the guidelines. Previous studies in Thai population identified a weak correlation, but the results were not statistically significant because the primary outcomes of these studies were not specifically designed to address this particular question.[7]

In many countries, studies found that the relationship between AUA-SI and uroflowmetry (Qmax) varies. Some studies showed a strong correlation, whereas others demonstrated a weak correlation. As a result, the use of uroflowmetry should be adapted on the basis of each country's study outcomes. Furthermore, studies that have been used as references in guidelines showed a clear relationship between increasing AUA scores and decreasing maximum flow rate in the overall population. However, an independent relationship was observed in subgroup studies. This independence is evident when assessing patients with AUA score > 7 points (moderate

to severe symptoms) and Qmax between 5 and 15 mL/s only.[3] This outcome suggests that only a subset of symptom scores had a weak correlation with Qmax in their study. Whether the relationship between AUA score and peak flow rate in Thai patients aligns with that in previous research is unclear, thereby raising questions about the consistency of this relationship in Thai patients compared with previous studies. The present study aimed to determine the correlation between symptom severity index scores, subgroup the obstructive and irritative domains, and examine the uroflowmetric parameter (Qmax).

MATERIALS AND METHODS

Study design and participants

A historical cohort study that involved newly diagnosed adult male patients with LUTS secondary to BPH at King Chulalongkorn Memorial Hospital from 2017 to 2021 was conducted. Eligible participants for the study were men over 45 years old with untreated lower urinary tract symptoms (LUTS) who had not previously received treatment with alpha blockers, 5 alpha reductase inhibitors, or PDE5 inhibitors. Additionally, they were required to have a negative digital rectal examination and a PSA level below 4 ng/dL. All patients completed the AUA-SI questionnaire and underwent uroflowmetry testing. The exclusion criteria were as follows: patients with voided volume < 150 mL, patients with indwelling catheters, patients with evidence of neurogenic bladder/urethral stricture/urinary tract infection, and patients with neurological disorders. This study was conducted in accordance with the Good Clinical Practice guidelines and the Belmont Report. It was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University.

Procedures

Demographic and other relevant data were recorded. The severity of the patients' symptoms was assessed using a Thai self-administered AUA-SI questionnaire that included a quality-of-life score in Thai language. Uroflowmetry was conducted using Andromeda Helix, a commercialized urodynamics instrument (Taufkirchen, Germany). Parameters, including the Qmax, the voided volume, and the average flow rate (Qave), were recorded. Flowmetry was conducted in an outpatient clinic with adequate privacy. Patients were asked to void when they felt a normal desire for normal urination, without performing any invasive procedure. The uroflowmetry that can be used must have a urine volume of more than 150 mL. The obstructive voiding patterns were classified on the basis of Qmax < 10 mL/s.

Study outcomes

The primary objective was to determine the correlation among the AUA-SI score, the scores for the obstructive and irritative domains, and the Qmax in patients suspected of having BPH. The secondary objective was to determine the dependent and independent relationships between the subgroups for the severity of symptoms and Qmax.

Statistical analysis

The sample size estimation for the correlation was calculated using a bivariate Pearson correlation with the expected correlation (r) = 0.4. The initial sample size target was 474 patients, including a 10.0% dropout allowance. All the statistical analyses were performed using IBM SPSS Statistics for Windows (version 22; IBM Corp, Armonk, NY). Pearson correlation and linear regression were used to assess correlations and relationships between variables. The level of significance was set at $P < 0.05$.

RESULTS

A total of 605 patients with LUTSs with suspected BPH admitted to the Urology Outpatient Department completed the AUA-SI and underwent uroflowmetry. After the exclusion criteria were applied, data from 510 patients were ultimately analyzed.

The mean age of the patients was 64.4 years (range of 45–88 years). The distribution of symptom severity among the patients was as follows: 192 had mild symptoms (IPSS = 0–7), 241 experienced moderate symptoms (IPSS = 8–19), and 77 reported severe symptoms (IPSS = 20–35) according to the IPSS categorization. Most of the patients had moderate symptoms, as shown in Table 1.

The mean maximal flow rate was within the no obstruction range, but the majority of the patients fell into the obstruction category, as shown in Table 1. The study revealed an intriguing relationship between the total AUA-SI scores and Qmax ($P < 0.001$), thus addressing the primary endpoint, as illustrated in Fig 1A.

Additionally, the correlations among the obstructive domain scores, irritative domain scores, quality-of-life scores, and Qmax exhibited a significantly weak negative relationship, as shown in Table 2. Similar results were found with respect to Qave (average flow rate). The AUA-SI scores and the obstructive and irritative domains had weak, negative correlations with Qave.

However, when patients were categorized into mild, moderate, and severe symptom groups on the basis of their IPSS scores, the correlation between AUA-SI and Qmax within each symptom severity group was weak and non-significant, as demonstrated in Table 3 and Figs 1B–1D.

TABLE 1. AUA-SI score, categorized by severity and results of uroflowmetry parameters, categorized by maximal flow rate.

	Total (510)	Mild (n = 192)	Moderate (n = 241)	Severe (n=77)
Age	64.4 (45-88)	63.8 (48-84)	64.7 (45-88)	64.9 (46-80)
PSA (ng/mL)	1.32 (0.1-3.9)	1.29 (0.1-3.9)	1.31 (0.1–2.9)	1.43 (0.3-3.79)
AUA-SI score				
Obstructive	5.9 ± 4.7	1.7 ± 1.4	6.75 ± 2.8	13.8 ± 2.9
Irritative	5.1 ± 3.0	2.55 ± 1.3	5.8 ± 2.0	9.7 ± 2.2
Quality of life	2.4 ± 1.5	1.5 ± 1.0	2.7 ± 1.3	4.2 ± 1.2
Uroflow parameters				
Maximal flow rate (mL/sec)	17.4 (4.5–51.8)	19.3 (5.8-45)	16.2 (4.5-51.8)	16.1 (4.5-31.2)
Average flow rate (mL/sec)	9.3 (1.8-79)	10.7 (2.8-79)	8.7 (1.8-56)	7.8 (2.1-19.9)
Voided volume (mL)	335 (150-1222)	362.4 (154-1222)	321 (150-741)	310.3 (154-677)
Post-voided residual (mL)	57.6 (0-584)	53.9 (0-307)	60.1 (0-584)	57.6 (0-273)
Nonobstructive (Qmax > 15)	283 (55.5%)	128 (66.67%)	116 (48.13%)	39 (50.65%)
Equivocal (Qmax = 10–15)	153 (30%)	50 (26.04%)	79 (32.78%)	24 (31.17%)
Obstructive (Qmax < 10)	74 (14.5%)	14 (7.29%)	46 (19.09%)	14 (18.18%)

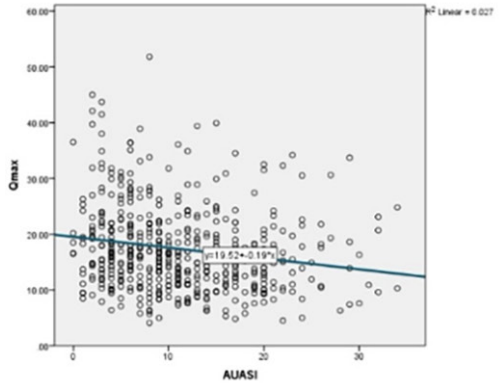
AUA-SI, AUA-Symptom Index

TABLE 2. Correlation coefficient among AUA-SI score + quality of life, and Qmax.

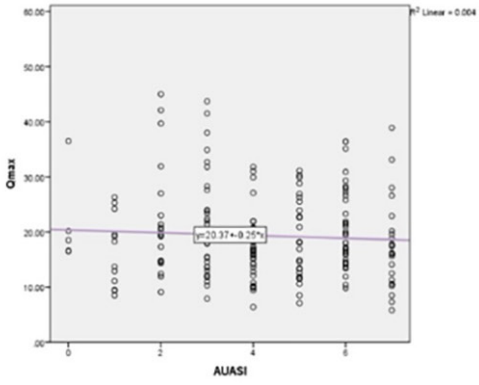
AUA-SI + Qulity-of-life	Correlation coefficient (R)	*P*
Total scores (Q1–7)	−0.164	< 0.001*
Obstructive domain scores (Q1, Q3, Q5, and Q6)	−0.164	< 0.001*
Irritative domain scores (Q2, Q4, and Q7)	−0.097	0.028*
Quality-of-life	−0.165	< 0.001*

AUA-SI, AUA-Symptom Index

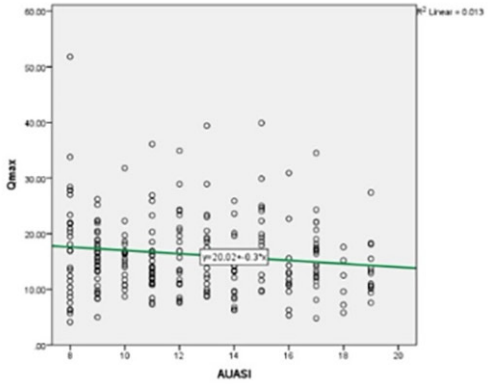
* Statistically significant.



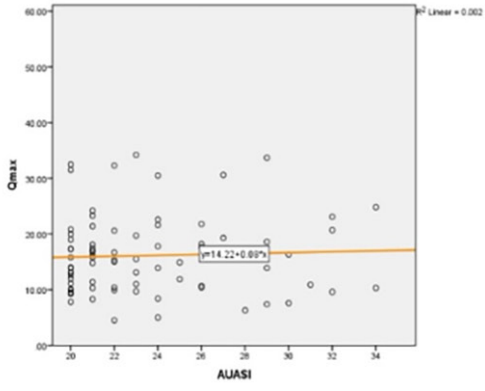
(A) r = -0.164, R^2, 0.027; *P* < 0.001*



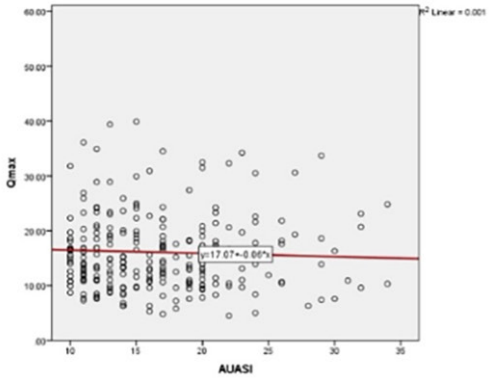
(B) r = -0.060; R2, 0.002; *P* = 0.411



(C) r = -0.113; R2, 0.013; *P* = 0.079



(D) r = 0.045, R2, 0.002; *P* = 0.699



(E) R, -0.038; R2, 0.001; *P* = 0.544

Fig 1. Simple linear regression of Qmax on AUA-SI; **(A)** total number of patients; **(B)** patients with mild symptoms (AUA-SI ≤ 7); **(C)** patients with moderate symptoms (AUA-SI = 8–19); **(D)** patients with severe symptoms (AUA-SI ≥ 20); **(E)** patients with AUA-SI ≥ 10
R, correlation coefficient; R2, coefficient of determination,* statistically significant)

TABLE 3. Correlation coefficient between AUA-SI subscore and Qmax.

AUA-SI	Correlation coefficient (R)	*P*
Mild symptoms (0–7)	−0.060	0.411
Moderate symptoms (8–19)	−0.113	0.079
Severe symptoms (20–35)	0.045	0.699
Treatment-needed group	-0,051	0.544

AUA-SI, AUA-Symptom Index

When looking at the treatment-needed group (moderate-to-severe symptoms), the symptom scores were unable to determine the relationship with Qmax. Linear regression models were employed to show the relationship among the total AUA-SI score, the scores of the treatment-needed group, and Qmax, as demonstrated in Table 3 and Fig 1E.

DISCUSSION

Studies showed that most patients with LUTSs sought treatment in the form of medicine or medical intervention, with a majority being over 40 years old and presenting with mild-to-severe symptoms. In the present study, the connection between LUTS caused by BPH, as quantified by the AUA-SI, and the objective noninvasive parameters of lower urinary tract dysfunction was assessed. The results indicated that the overall severity of symptoms had a weak correlation with uroflowmetry results only. This finding supported the hypothesis that symptom scores may be influenced by various factors such as educational level, language proficiency, and comprehension of the questionnaire. These observations demonstrated that for an individual patient, the lack of correlation between symptoms and flow rate results should not alter the diagnosis. Patients seeking initial treatment often presented with mild-to-moderate symptoms, with nearly 40% exhibiting mild conditions. Uroflowmetry stands out as a widely adopted diagnostic tool in the field of urology for evaluating LUTSs.[8] All uroflowmetry parameters, such as maximum flow rate, average flow rate, voided volume, and residual urine volume, in Thai patients did not differ from those in a previous study.[7]

In cases where medical treatment was unsuccessful, surgical intervention may have been necessary for patients suffering from LUTSs caused by BPH, especially in situations where symptoms were compromising kidney function or leading to recurrent complications like urinary retention or infections. The decision for surgery was often made in consultation between the patient and their healthcare provider, as demonstrated by the findings of the Medical Therapy of Prostatic Symptoms (MTOPS) study, a large-scale, long-term study that involved 3047 men with BPH and had a mean follow-up period of 4.5 years.[9,10] According to the PLESS study, a prostate volume > 40 mL and a serum PSA level > 1.5 ng/mL were predictors of acute urinary retention and/or surgery.[11] Uroflowmetry was used to predict acute urinary retention, with a Qmax of < 10 mL/s, indicating a higher risk. Evaluation of patients by using AUA-SI/IPSS showed that those with moderate or severe symptoms were more likely to experience disease progression and complications or require surgery. Ensuring a comprehensive assessment of disease progression, complications, and the necessity for surgery involved evaluating all four predictors: IPSS, PSA, prostate volume, and uroflowmetry (Qmax). Among them, uroflowmetry was particularly recommended for further assessment in patients with moderate-to-severe symptoms or those in need of surgical intervention. The subjective nature of IPSS highlighted the importance of considering the patient's understanding and educational level because they could vary greatly among individuals and regions.[7]

Several studies across various nations investigated the correlation between the IPSS and uroflowmetry parameters.[8,12-20]

The study on Thai patients revealed a weak correlation between AUA-SI and Qmax, particularly evident in those with mild-to-severe symptoms, suggesting a weak relationship between symptom score and Qmax ($P < 0.001$).

A significant negative correlation was found in the relationship between IPSS and Qmax in other countries, such as Thailand ($r = -0.16$), Brazil ($r < -0.3$)[13], India ($r = -0.26$)[14], the Netherlands ($r = -0.2$)[15], and China ($r = -0.26$).[16] Countries that demonstrated moderate-to-strong correlations included Nepal ($r = -0.729$)[18], Nigeria ($r = -0.492$)[19], and the United States ($r = -0.4$).[3] Contrary to common assumptions, Qmax could not be predicted on the basis of patient symptoms in the authors' center. Therefore, instead of subjectively evaluating patient complaints only, uroflowmetry should have been used to objectively measure all patients with LUTSs, even if there were mild symptoms. In countries that have their own guidelines and have not adopted those of other nations, it is recommended to perform uroflowmetry in the initial assessment of male LUTS, as seen in India. Therefore, for Thailand, which is currently developing its own guidelines, this information may be helpful in considering and determining these guidelines.[21] However, this study had the limitation of being a single-center, retrospective investigation.

CONCLUSION

The study revealed a significant negative correlation between the AUA-SI score and Qmax, but no significant correlations were found between the obstructive and irritative domains and Qmax in the subgroup analysis, indicating that uroflowmetry is a more objective method for evaluating LUTS in all patients.

DECLARATION

Grants and Funding Information

This project is not funded by any external sources.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Author Contributions

Conceptualization and methodology, S.C. and S.R. ; Historical cohort, S.C., J.O., A.S. and S.R. ; Formal analysis, S.C. and S.R. ; Investigation, S.C., J.O., A.S. and S.R. ; Resources, S.C., J.O., A.S. and S.R. ; Original draft, S.C. and S.R. ; Writing – review and editing, S.R. ; Funding acquisition, S.R. All authors have read and agreed to the final version of the manuscript.

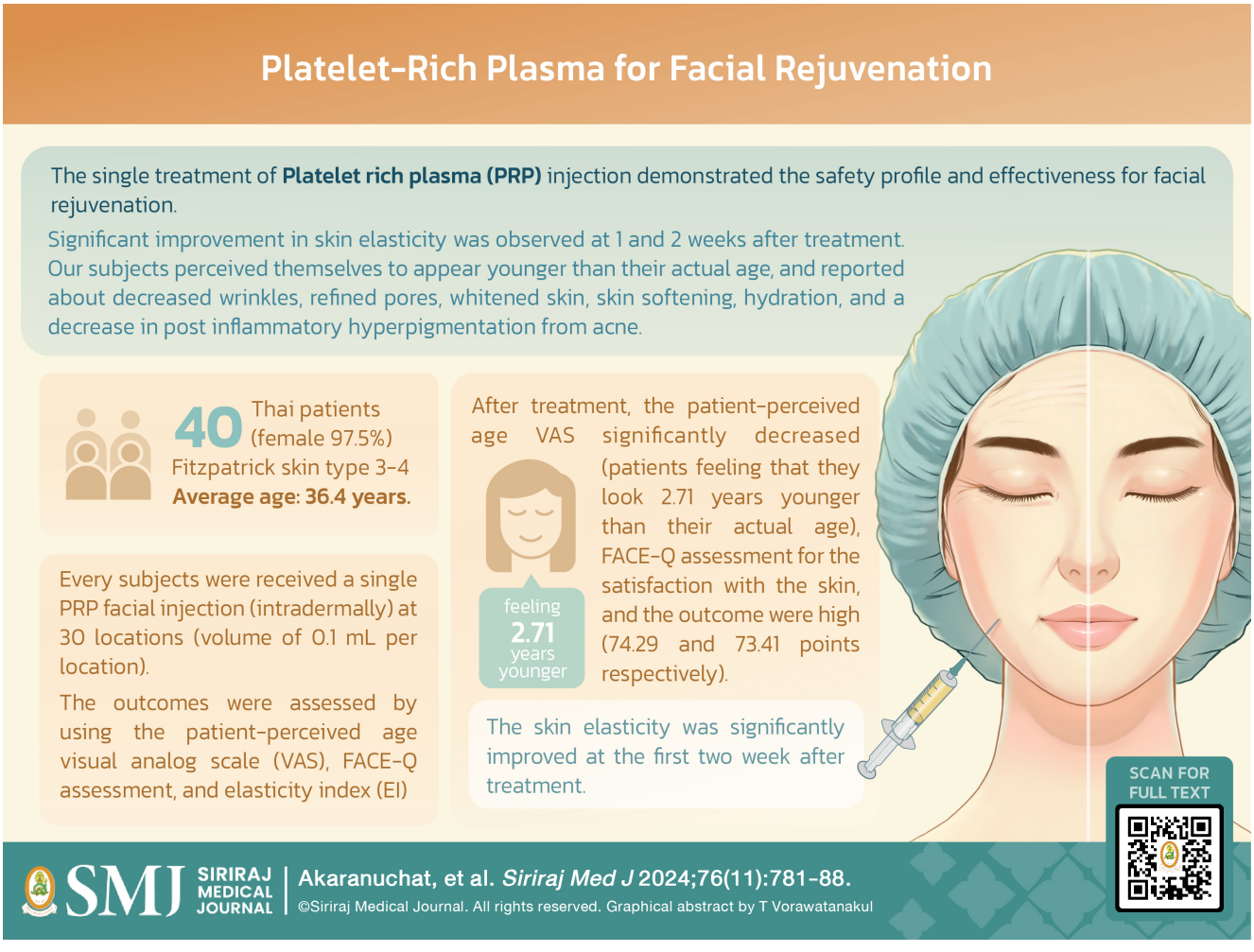
REFERENCES

1. Platz EA, Joshu CE, Mondul AM, Peskoe SB, Willett WC, Giovannucci E. Incidence and progression of lower urinary tract symptoms in a large prospective cohort of United States men. J Urol. 2012;188(2):496-501.
2. Chughtai B, Forde JC, Thomas DDM, Laor L, Hossack T, Woo HH, Te AE, Kaplan SA. Benign prostatic hyperplasia. Nat Rev Dis Primers. 2016;2:16031.
3. Roehrborn CG, McConnell JD. Etiology, pathophysiology, epidemiology and natural history of benign prostatic hyperplasia. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. Campbell's Urology. 8th ed. Philadelphia: Saunders; 2002.p.1297-336.
4. Speakman M, Kirby R, Doyle S, Ioannou C. Burden of male lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) - focus on the UK. BJU Int. 2015; 115(4):508-19.
5. Hongthong P, Santingamkun A. Correlation evaluation of a new visual prostate symptom score and the international prostate symptom score in Thai men with lower urinary tract symptoms. Insight Urol. 2013;34(2):29-35.
6. Nontakaew K, Kochakarn W, Kijvika K, Viseshsindh W, Silpakit C. Reliability of a Thai version of the International Prostate Symptom Score (IPSS) for the Thai population. J Med Assoc Thai. 2014;97(6):615-20.
7. Setthawong V, Mahawong P, Pattanachindakun N, Amnattrakul P, Dar FM, Thanavongvibul S. To investigate the correlation between the visual prostate symptom score, the international prostate symptom score, and uroflowmetry parameters in adult Thai males of different educational levels. Prostate Int. 2018; 6(3):115-8.
8. Ezz el Din K, Kiemeney LA, de Wildt MJ, Debruyne FM, de la Rosette JJ. Correlation between uroflowmetry, prostate volume, postvoid residue, and lower urinary tract symptoms as measured by the International Prostate Symptom Score. Urology. 1996;48(3):393-7.
9. Bautista OM, Kusek JW, Nyberg LM, McConnell JD, Bain RP, Miller G, Crawford ED, et al. Study design of the Medical Therapy of Prostatic Symptoms (MTOPS) trial. Control Clin Trials. 2003;24(2):224-43.
10. Wehrberger C, Madersbacher S, Jungwirth S, Fischer P, Tragl KH. Lower urinary tract symptoms and urinary incontinence in a geriatric cohort - a population-based analysis. BJU Int. 2012; 110(10):1516-21.
11. Roehrborn CG, Boyle P, Bergner D, Gray T, Gittelman M, Shown T, Melman A, et al. Serum prostate-specific antigen and prostate volume predict long-term changes in symptoms and flow rate: results of a four-year, randomized trial comparing finasteride versus placebo. PLESS Study Group. Urology. 1999;54(4):662-9.
12. Oranusi CK, Nwofor AE, Mbonu O. Correlation between International Prostate Symptom Score and uroflowmetry in patients with benign prostatic hyperplasia. Niger J Clin Pract. 2017;20(4):454-8.
13. Zambon JP, da Silva Batezini NS, Karam AJ, Oliveira Conceição RD, de Carvalho JAM, Almeida FG. Uroflowmetry in a large population of Brazilian men submitted to a health check up program and its correlation with IPSS and prostate size. Int Braz J Urol. 2013;39(6):841-6.
14. Chatterjee S, Kumar A, Pal DK. Study of correlation between visual prostate symptom score and international prostate symptom score in men with lower urinary tract symptoms with reference to uroflowmetry parameters in Indian population. Urologia. 2023;90(2):377-80.
15. Yee CH, Li JK, Lam HC, Chan ES, Hou SS, Ng CF. The prevalence of lower urinary tract symptoms in a Chinese population, and the correlation with uroflowmetry and disease perception. Int Urol Nephrol. 2014;46(4):703-10.
16. Bhomi KK, Subedi N, Panta PP. Correlation of visual prostate symptom score with international prostate symptom score and uroflowmetry parameters in Nepalese male patients with lower urinary tract symptoms. JNMA J Nepal Med Assoc. 2017;56(206): 217-20.
17. Keskin MZ, Karaca E, Uçar M, Ateş E, Yücel C, İlbey YÖ. Comparison of uroflowmetry tests performed with a sensation of normal desire to void versus urgency and correlation of test results with IPSS. Turk J Urol. 2020;46(5):378-82.
18. Abhulimen V, Raphael JE. Correlation between uroflowmetry and International Prostate Symptoms Score in the evaluation of Nigerian men with benign prostatic enlargement. Niger Med J. 2021;62(5):219-25.
19. Affusim EA, Amu OC, Eneje CL, Iwenofu C, Ugwumba F. Correlation between physician-administered International Prostate Symptoms Score and peak urine flow rate in assessment of benign prostatic enlargement patients. Niger J Clin Pract. 2023;26(11): 1642-6.
20. Huang Foen Chung JWNC, van Mastrigt R. Correlation of non-invasive urodynamics with International Prostate Symptom Score (IPSS) and prostate volume. Neurourol Urodyn. 2005; 24(1):25-30.
21. Sabnis RB, Mulawkar PM, Joshi RN. The Urological Society of India guidelines on management of benign prostatic hyperplasia/ benign prostatic obstruction (executive summary). Indian J Urol. 2021;37(3):210-3.

Improvement in the Youthfulness of Facial Skin after a Single Treatment with Platelet Rich Plasma

Nutthawut Akaranuchat, M.D.*, Natthapong Kongkunnavat, M.D.

Division of Plastic Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.



*Corresponding author: Nutthawut Akaranuchat
E-mail: nutthawut.aka@mahidol.ac.th
Received 5 July 2024 Revised 8 August 2024 Accepted 8 August 2024
ORCID ID:http://orcid.org/0000-0003-1798-8484
https://doi.org/10.33192/smj.v76i11.270077

All material is licensed under terms of the Creative Commons Attribution 4.0 International (CC-BY-NC-ND 4.0) license unless otherwise stated.

ABSTRACT

Objective: Platelet rich plasma (PRP) is an autologous substance widely used to stimulate dermal collagen synthesis. This study aimed to investigate the efficacy of a single PRP treatment for facial rejuvenation.

Materials and Methods: This study was conducted at the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand from August 2020 to March 2021. Enrolled patients underwent a single intradermal injection treatment of 0.1 mL PRP at 30 locations on the face. Outcomes were assessed at 1, 2, and 4 weeks post-intervention using the patient-perceived age visual analog scale (VAS), FACE-Q assessment, and elasticity index (EI) with a Cutometer.

Results: Forty Thai patients with an average age of 36.4 years, Fitzpatrick skin type 3-4 were enrolled. The mean Patient-perceived Age VAS significantly decreased one month after treatment (-2.71±2.42, $p<0.001$). FACE-Q satisfaction with facial skin was 74.29±14.49, and satisfaction with the outcome was 73.41±16.26 (scale 0-100). The PRP significantly affected skin EI, with the peak improvement observed at 1-2 weeks post-injection, predominantly at the cheek, crow's feet, and perioral area (all $p<0.05$). All patients had an overall improvement in satisfaction scores throughout the study.

Conclusion: A single treatment of PRP injection resulted in overall satisfaction in facial skin rejuvenation as measured by patient-perceived age VAS and FACE-Q assessment. The PRP showed positive outcomes in EI with peak performance at 1-2 weeks post-treatment.

Keywords: Youthfulness; platelet rich plasma; facial rejuvenation; aging face; improvement (Siriraj Med J 2024; 76: 781-788)

INTRODUCTION

Aging of the face is a multifactorial process influenced by both endogenous and exogenous factors. Endogenous factors are modified by individual genetic variation and epigenetics. Ultraviolet (UV) rays significantly contribute to dermal collagen degradation via enzymatic activation of matrix metalloproteinase (MMP).[1-5] Several studies have explored the prevention and treatment of skin aging using platelet rich plasma (PRP). Cho, *et al*. reported a significant reduction of UVB-induced wrinkles in nude mice following PRP injection, which increased collagen and dermal fibroblasts.[6]

Skin aging involves atrophy and laxity of the skin, a decrease in the number of fibroblasts, and a decrease in collagen production. Hence, treatments that stimulate fibroblasts play an important role in skin rejuvenation.[7] Autologous PRP is centrifuged plasma with a much higher concentration of platelets. The normal range of platelet concentration in plasma is 150,000-400,000/microliter, and this concentration is increased 4-7-fold in PRP.[3, 8-12]

PRP contains several growth factors, cytokines, and chemokines in the α-granules of platelets that can stimulate various types of cells, such as dermal fibroblasts, myofibroblasts, and epidermal cells. Growth factors, such as epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), and vascular endothelial growth factor (VEGF), can synchronously promote dermal collagen production.[13-19] (Table 1)

This study aimed to investigate the efficacy of a single PRP injection treatment for the rejuvenation of facial skin.

MATERIALS AND METHODS

This study was conducted at the Division of Plastic Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. Adult patients were enrolled from August 1, 2020, to March 31, 2021, to undergo PRP facial injection by a single physician (NA). Patients with a history of connective tissue disease, facial palsy, coagulopathy, conditions affecting wound healing, pregnancy, or active facial skin infection were excluded. Patient demographics, comorbidities, and history of facial skin surgery and treatment were collected and recorded. Additionally, details of the PRP, skin elasticity index, FACE-Q assessment scores, and adverse events were also documented. The Siriraj Institutional Review Board (SIRB) of the Faculty of Medicine Siriraj Hospital, Mahidol University approved this study (approval number 228/2564 [IRB3]), and all study patients provided written informed consent to participate.

TABLE 1. Growth factors found in α-granules of platelets[10-13]

Growth factors	Effects
Epidermal growth factor (EGF)	Fibroblast and keratinocyte proliferation, Re-epithelialization, Tissue tensile strength
Fibroblast growth factor (FGF)	Stem cell differentiation, Proliferation and activation of fibroblasts, Collagen production, Angiogenesis
Platelet-derived growth factor (PDGF)	Proliferation and chemotaxis in fibroblasts and monocytes-macrophages, Angiogenesis
Transforming growth factor-beta (TGF-β)	Proliferation and differentiation of fibroblasts, Collagen formation, Angiogenesis, Extracellular matrix deposition and remodeling, Re-epithelialization
Vascular endothelial growth factor (VEGF)	Angiogenesis
The key growth factors, found in the α-granules of platelets, can stimulate fibroblast activity and support new collagen production in the skin through various mechanisms.	

Preparation of PRP

Twenty milliliters (mL) of venous blood was collected from each patient and stored in 3.2% sodium citrate 3.0 mL sandwich tubes (VACUETTE®; Grenier Bio-one, Monroe, NC, USA). Two rounds of centrifugation were performed sequentially. The first round aimed to separate the blood cells from plasma by centrifugation at 1,500 revolutions per minute (rpm) for 10 minutes. The supernatant was then transferred to new citrate tubes. In the second round, the new plasma tubes were centrifuged at 3,000 rpm for 10 minutes to separate the platelets from the plasma. After the second round of centrifugation, the upper 70% of the supernatant was removed, leaving the platelet pellets. The platelet pellets were then mixed with the remaining 30% of the supernatant located at the bottom of the tube to create PRP for facial injection (Fig 1).

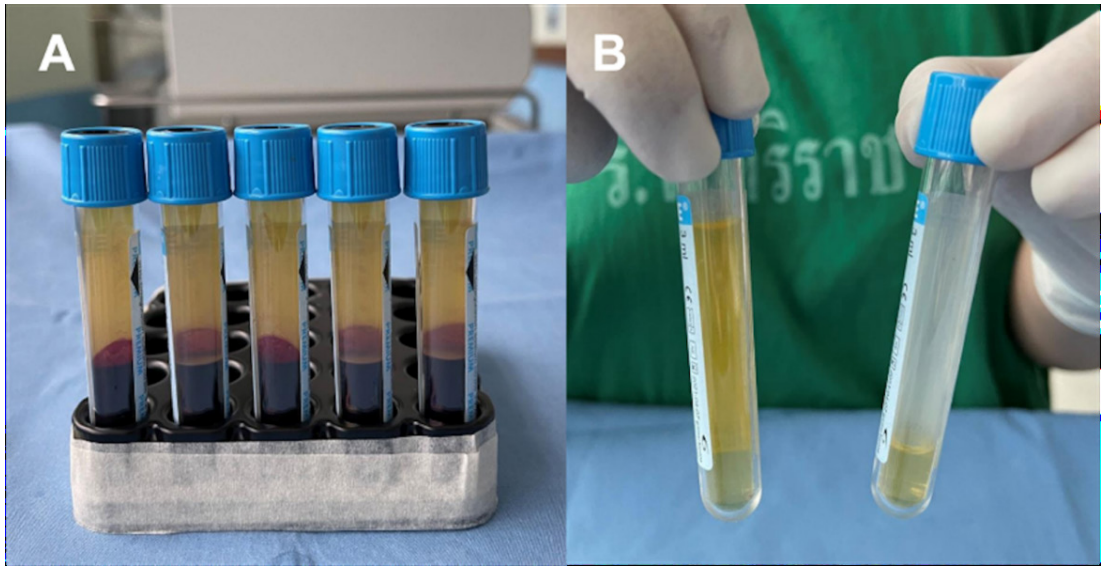


Fig 1. (A) Centrifuged venous blood after the first round of centrifugation at 1,500 rpm for 10 minutes. The supernatant from the first centrifugation was transferred to new citrate tubes. (B) The second centrifugation was performed at 3,000 rpm for 10 minutes. After completion of the second round of centrifugation, the upper 75% of the supernatant was removed and platelet pellets were produced. The platelet pellets were then mixed with the remaining 25% of the supernatant located at the bottom of the tube to create PRP for facial injection.

PRP facial injection

After the facial skin was cleaned, topical anesthesia (EMLA®; AstraZeneca LP, Wilmington, DE, USA) was applied for 60 minutes before the start of PRP injections. A volume of 0.1 mL of PRP was injected intradermally at 30 locations on the face, for a total PRP dose of 3.0 mL per patient (Fig 2). After treatment, the patient was observed in the recovery room for 15 minutes and discharged home if no adverse reactions were observed.

Outcome measurements

The elasticity index (EI) of the skin was measured using the Cutometer Dual MPA580® (Courage & Khazaka GmbH, Cologne, Germany) before and at 1, 2, and 4 weeks after PRP treatment. Ten surrogate reference points were assigned bilaterally at the forehead, lower eyelid, crow's feet, cheek, and perioral region.

The forehead region was measured at 1 cm above the brow ridge in the mid-pupillary line. The lower eyelid region was measured at 1 cm below the lower eyelid rim in the mid-pupillary line. The crow's feet region was measured at 1 cm lateral to the lateral canthus. The cheek area was measured at 5 cm below the lower eyelid rim in the mid-pupillary line. Finally, the perioral region was measured at 1 cm above Cupid's bow and the mid-philtrum line, and at 1 cm below the lower lip border and mid-philtrum line (Fig 3).

For the follow-up evaluation protocol, subjects cleansed their face and acclimatized for 15 minutes at room temperature, ranging from 21°C to 25°C, and a humidity level of 31% to 50%. R2 and R7 parameters were used as the main parameters to assess skin elasticity and aging. The R2 parameter represents the gross elasticity of the skin, and the R7 parameter represents biological elasticity, which is the ratio of immediate retraction to total distension.[20]

Study patients completed the FACE-Q assessment questionnaire, a validated patient-reported outcome measurement, one month after PRP treatment. The subscales used in this study included FACE-Q satisfaction with skin, FACE-Q satisfaction with outcome, and patient-perceived age visual analog scale (VAS). The first two subscales are scored from 0-100, with higher scores reflecting higher satisfaction. The age VAS was reported in years, with a more negative value indicating that the respondent feels they look younger than their actual age.[21-23]

Statistical analysis

Demographic data, elasticity index, and FACE-Q results were presented using descriptive statistics, including number and percentage, mean ± standard deviation, and range. Differences in the elasticity index at each time point and the decrease in patient-perceived age VAS were calculated using a paired *t*-test from SPSS Statistics for Windows, version 26.0 (SPSS, Inc., Chicago, IL, USA). A *p*-value lower than 0.05 was considered statistically significant.

RESULTS

Forty Thai patients aged from 22 to 53 years (mean: 36.4 years) were enrolled. The patients had Fitzpatrick skin type 3-4. Most patients were female (97.5%, 39 of 40). Patients were available for cutometer evaluation in 67.5% (27 of 40) of cases. Significant improvement in skin elasticity (as measured by elasticity index [EI])

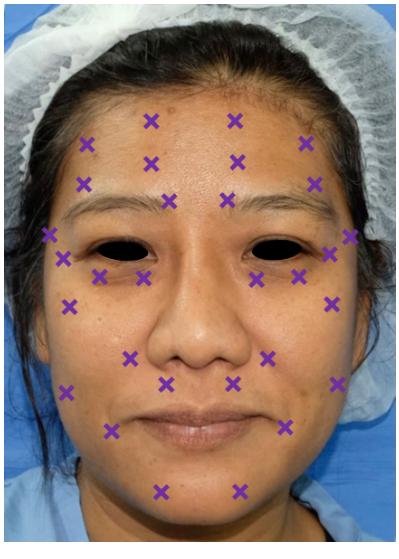


Fig 2. The 0.1 mL of PRP was injected into the intradermal plane at 30 points on the face (purple crosses).



Fig 3. Reference points for elasticity index measurement by cutometer. Ten surrogate reference points (blue dots) were assigned bilaterally at the forehead, lower eyelids, crow's feet, cheeks, and perioral regions.

was observed at 1 and 2 weeks after PRP treatment in the crow's feet, perioral, and cheek area (all $p<0.05$). The effects of PRP had an impact on the gross and biological elasticity of the cheek area. However, the effect on the crow's feet only affected biological elasticity at 1-week post-treatment and can be seen through gross elasticity for the perioral area at 2 weeks post-treatment. These significant improvements were not sustained at 4 weeks after PRP treatment. The EI values in other areas of the face did not show significant differences between baseline and after treatment (Table 2).

Regarding patient satisfaction, the FACE-Q assessment for satisfaction with the skin was 74.29±14.49 points, and satisfaction with the outcome was 73.41±16.26 points, both measured one month after receiving a single PRP treatment. Subjects reported significant improvement in the patient-perceived age visual analog scale one month after treatment compared to baseline (-2.71±2.42 years *vs.* -0.05±2.87 years, respectively; $p<0.01$). This translates to patients feeling that they look 2.71 years younger than their actual age (Table 3).

At one week after PRP treatment, 26.5% of patients reported a decrease in wrinkles, and 23.5% noted refined pores and whitened skin. At two weeks after PRP treatment, all patients reported perceiving the rejuvenating effects of PRP. The number of patients experiencing skin whitening, decreased wrinkles, hydrated skin, and softening of the skin had further increased at four weeks after treatment compared to two weeks after treatment (Table 4). The number of patients who reported skin whitening continuously increased to 40% by 4 weeks after treatment (Fig 4). Additionally, some patients reported a reduction in post-inflammatory hyperpigmentation (PIH) from acne.

DISCUSSION

PRP rejuvenates the skin by stimulating DNA synthesis, delaying cell apoptosis, and promoting the expression of genes associated with tissue regeneration. Kakudo, *et al.* proposed that PDGF and TGF-β contribute to the proliferation of adipose-derived stem cells and dermal fibroblasts.[24] Several studies reported the efficacy of PRP for skin rejuvenation with satisfactory outcomes and other clinical applications Since autologous PRP is harvested from the patient receiving the injections, it carries a low risk for allergic reactions and blood-related infection transmission.[25]

Significant improvement in skin elasticity was observed at 1 and 2 weeks after PRP treatment compared to baseline measurements (cheek, crow's feet, and perioral area [$p<0.05$]). However, these effects appear transient as the significant improvement was not sustained at 4 weeks after treatment. Further studies should explore the potentially cumulative effect of two or more sessions of PRP injections to determine if they have long-lasting effects and significantly improved outcomes.

Maisel-Campbell, *et al.* conducted a systematic review of the effects of PRP on skin aging. The review demonstrated that PRP can temporarily improve facial skin appearance, texture, lines, and pigmentation.[26] However, the review included 24 studies and was limited by variations in PRP preparation, follow-up evaluations, and the lengthy evaluation period of over 4 weeks. Our study conducted follow-up evaluations at 1, 2, and 4 weeks intervals after a single PRP treatment, using FACE-Q, VAS, and EI for a more precise evaluation at each visit. This approach allowed the research to observe the dynamic effects of PRP progression, which had not been thoroughly discussed in previous studies.

Despite the lack of significant differences in many elasticity indices, most participants reported being satisfied with the results. FACE-Q scores for satisfaction with skin and satisfaction with outcome were both high one month after a single PRP treatment. Subjects perceived themselves to appear 2.7 years younger than their actual age. These subjective outcomes indicate the rejuvenating effects of PRP. Moreover, our patients reported decreased wrinkles, refined pores, and whitened skin in just one week after PRP treatment. The number of patients experiencing satisfactory results increased by the four-week mark. Improvements were also reported in skin softening, hydration, and a decrease in PIH from acne.

Limitations

Many participants reported improvement in periorbital darkness, suggesting that further objective measurement of this parameter should be considered. The drawback of the study was that the number of participants eligible for cutometer measurement was lower than anticipated due to limitations and restrictions caused by the COVID-19 pandemic.[27] If more study patients had undergone elasticity index evaluation, it is possible that the analysis would have yielded more statistically significant results.

CONCLUSION

A single treatment of platelet rich plasma (PRP) injection demonstrated the safety profile and effectiveness for rejuvenating facial skin. This is evidenced by a marked reduction in the Patient-Perceived Age Visual Analog Scale (VAS), enhancements in various facial skin parameters, and significant improvements in the elasticity index outcomes.

TABLE 2. *P*-values from paired samples *t*-test of the elasticity index from Cutometer for each area of the face at different time points compared to baseline.

Area	Evaluation parameter	Time point	Mean	SD	P-value
Forehead	R2 (Ua/Uf)	Pre-treatment	0.4644	0.2914	
		1 week	0.5867	0.2384	0.526
		2 weeks	0.5938	0.1808	0.308
		4 weeks	0.7128	0.0865	0.920
	R7 (Ua/Uf)	Pre-treatment	0.2240	0.1649	
		1 week	0.2171	0.1481	0.315
		2 weeks	0.3054	0.1725	0.392
		4 weeks	0.1369	0.0853	0.072
Lower eyelid	R2 (Ua/Uf)	Pre-treatment	0.4688	0.2636	
		1 week	0.5484	0.1927	0.835
		2 weeks	0.5084	0.1820	0.788
		4 weeks	0.6875	0.1694	0.833
	R7 (Ua/Uf)	Pre-treatment	0.2169	0.1124	
		1 week	0.2054	0.1715	0.753
		2 weeks	0.2981	0.2019	0.232
		4 weeks	0.2086	0.1780	0.653
Crow's feet	R2 (Ua/Uf)	Pre-treatment	0.4334	0.2375	
		1 week	0.5447	0.2007	0.277
		2 weeks	0.4939	0.2095	0.718
		4 weeks	0.7040	0.0929	0.113
	R7 (Ua/Uf)	Pre-treatment	0.1996	0.1220	
		1 week	0.2803	0.1161	**0.035***
		2 weeks	0.2811	0.1438	0.104
		4 weeks	0.2664	0.1971	0.674
Cheek	R2 (Ua/Uf)	Pre-treatment	0.4522	0.2145	
		1 week	0.5851	0.2030	**0.018***
		2 weeks	0.5746	0.2051	0.087
		4 weeks	0.7273	0.1158	0.227
	R7 (Ua/Uf)	Pre-treatment	0.2503	0.1352	
		1 week	0.2546	0.1389	0.861
		2 weeks	0.3586	0.2035	**0.017***
		4 weeks	0.2406	0.2195	0.787
Perioral	R2 (Ua/Uf)	Pre-treatment	0.4367	0.2392	
		1 week	0.5160	0.2085	0.623
		2 weeks	0.5176	0.2023	**0.034***
		4 weeks	0.6018	0.2098	0.780
	R7 (Ua/Uf)	Pre-treatment	0.2302	0.1902	
		1 week	0.2244	0.1380	0.995
		2 weeks	0.2968	0.2242	0.171
		4 weeks	0.1278	0.0805	0.429

The paired T-test was done by comparing each parameter at each time point to the baseline values before treatment. *A p-value less than 0.05 was considered statistically significant.

TABLE 3. Mean FACE-Q assessment scoring.

FACE-Q scale	Mean ± S.D.	
FACE-Q satisfaction with skin	74.29±14.49	
FACE-Q satisfaction with outcome	73.41±16.26	
Patient-Perceived Age VAS		**p-value**
Before treatment	-0.05±2.87	
One month after treatment	-2.71±2.42	**<0.001***

The FACE-Q satisfaction with skin and satisfaction with outcome scores range from 0-100. The Patient-Perceived Age VAS statistically significantly decreased after 1 month after a single PRP treatment ($p<0.001$).
Abbreviation: VAS, visual analog scale.

TABLE 4. Subjective patient-reported perceptions after PRP treatment.

Effects	1st week	2nd week	4th week
Decreased wrinkles	26.5%	25.8%	33.3%
Refined pores	23.5%	29.0%	26.7%
Whitening of skin	23.5%	29.0%	40.0%
Softening of skin	20.6%	19.4%	20.0%
Hydrated skin	20.6%	19.4%	20.0%
Decreased PIH after acne	17.6%	22.6%	20.0%
No change	8.8%	0.0%	0.0%

Abbreviation: PIH, Post-inflammatory hyperpigmentation.

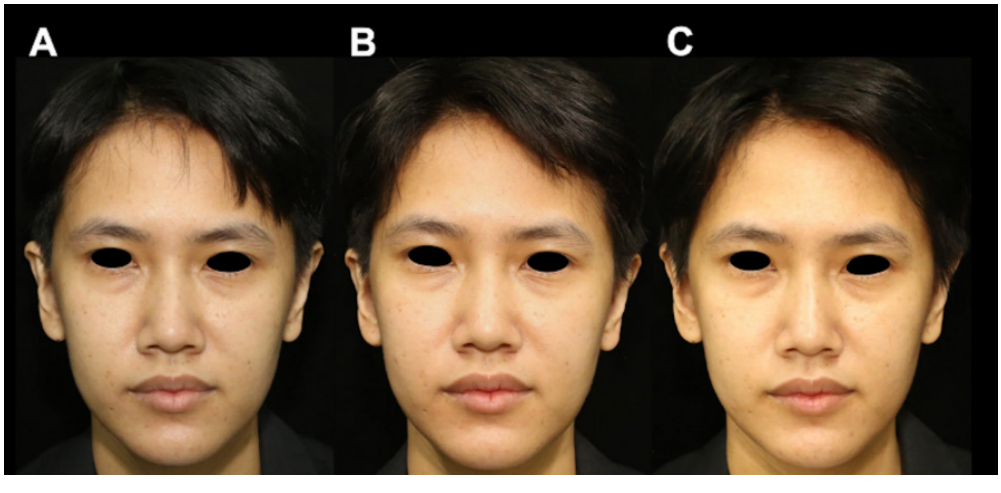


Fig 4. The patient initially presented with post-inflammatory hyperpigmentation (PIH) from acne, fine wrinkles, and periorbital darkness. The results of PRP injection were compared between (A) pre-treatment, (B) two weeks post-treatment, and (C) four weeks post-treatment.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the patients that agreed to participate in this study, and Miss Nachasa Khongchu for her assistance with statistical analysis.

DECLARATION

Grants and Funding Information

This was an unfunded study.

Conflict of Interest

Both authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report.

Author Contributions

Both authors, N.A. and N.K. are involved in 1) substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work; 2) drafting the work or revising it critically for important intellectual content; 3) final approval of the version to be published; 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

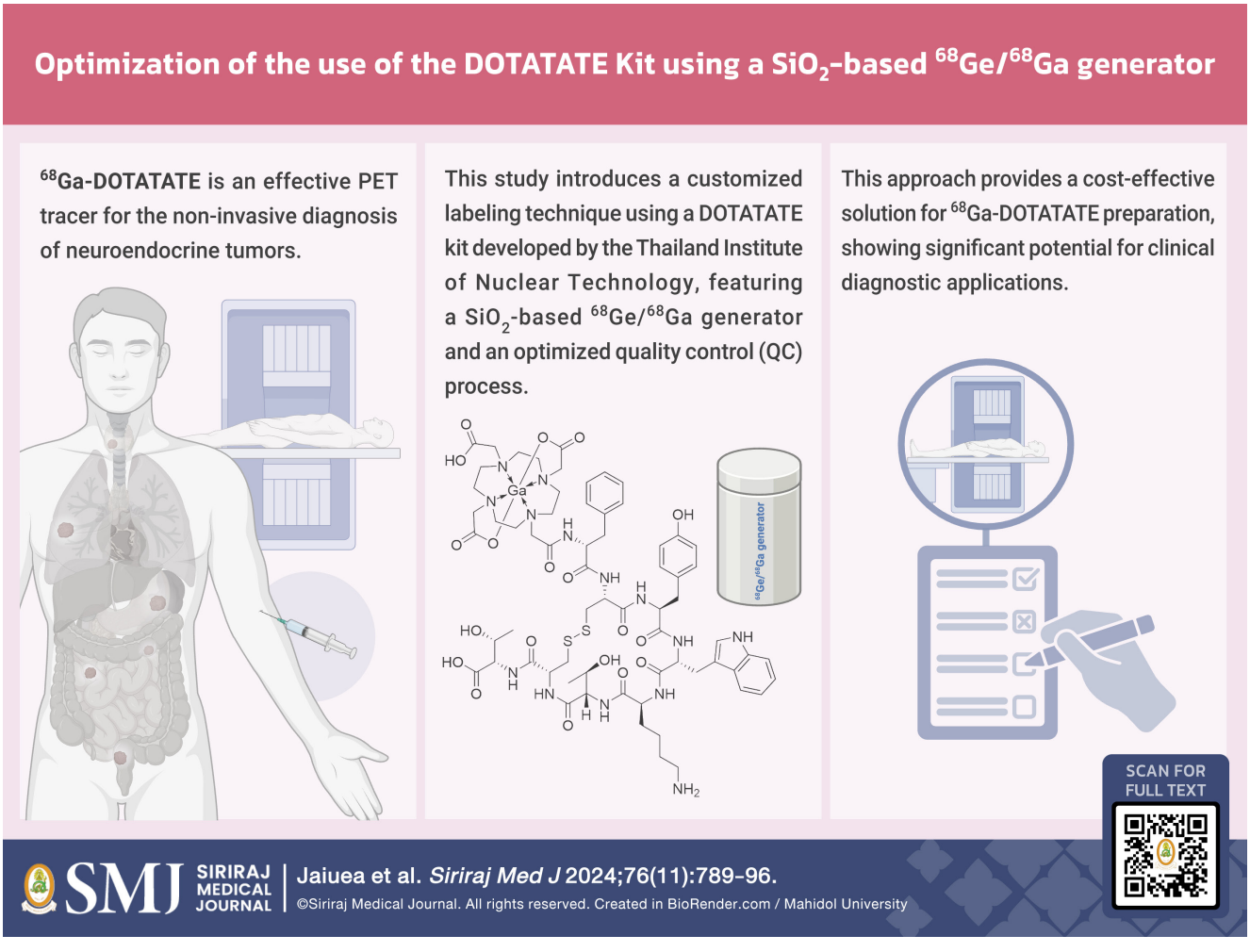
REFERENCES

1. Alexiades-Armenakas MR, Dover JS, Arndt KA. The spectrum of laser skin resurfacing: nonablative, fractional, and ablative laser resurfacing. J Am Acad Dermatol. 2008;58(5):719-37; quiz 738-40.
2. Borrione P, Fagnani F, Di Gianfrancesco A, Mancini A, Pigozzi F, Pitsiladis Y. The Role of Platelet-Rich Plasma in Muscle Healing. Curr Sports Med Rep. 2017;16(6):459-63.
3. Cervelli V, Nicoli F, Spallone D, Verardi S, Sorge R, Nicoli M, et al. Treatment of traumatic scars using fat grafts mixed with platelet-rich plasma, and resurfacing of skin with the 1540 nm nonablative laser. Clin Exp Dermatol. 2012;37(1):55-61.
4. Ince B, Yildirim MEC, Dadaci M, Avunduk MC, Savaci N. Comparison of the Efficacy of Homologous and Autologous Platelet-Rich Plasma (PRP) for Treating Androgenic Alopecia. Aesthetic Plast Surg. 2018;42(1):297-303.
5. Martinez-Zapata MJ, Martí-Carvajal AJ, Solà I, Exposito JA, Bolibar I, Rodriguez L, et al. Autologous platelet-rich plasma for treating chronic wounds. Cochrane Database Syst Rev. 2016; 2016(5):CD006899.
6. Cho JM, Lee YH, Baek RM, Lee SW. Effect of platelet-rich plasma on ultraviolet b-induced skin wrinkles in nude mice. J Plast Reconstr Aesthet Surg. 2011;64(2):e31-9.
7. Yuksel EP, Sahin G, Aydin F, Senturk N, Turanli AY. Evaluation of effects of platelet-rich plasma on human facial skin. J Cosmet Laser Ther. 2014;16(5):206-8.
8. Alves R, Grimalt R. A Review of Platelet-Rich Plasma: History, Biology, Mechanism of Action, and Classification. Skin Appendage Disord. 2018;4(1):18-24.
9. Eppley BL, Pietrzak WS, Blanton M. Platelet-rich plasma: a review of biology and applications in plastic surgery. Plast Reconstr Surg. 2006;118(6):147e-59e.
10. Leo MS, Kumar AS, Kirit R, Konathan R, Sivamani RK. Systematic review of the use of platelet-rich plasma in aesthetic dermatology. J Cosmet Dermatol. 2015;14(4):315-23.
11. Marx RE. Platelet-rich plasma (PRP): what is PRP and what is not PRP? Implant Dent. 2001;10:225-8.
12. Shin MK, Lee JH, Lee SJ, Kim NI. Platelet-rich plasma combined with fractional laser therapy for skin rejuvenation. Dermatol Surg. 2012;38(4):623-30.
13. Bielecki T, Dohan Ehrenfest DM, Everts PA, Wiczkowski A. The role of leukocytes from L-PRP/L-PRF in wound healing and immune defense: new perspectives. Curr Pharm Biotechnol. 2012;13(7):1153-62.
14. Borrione P, Gianfrancesco AD, Pereira MT, Pigozzi F. Platelet-rich plasma in muscle healing. Am J Phys Med Rehabil. 2010;89(10): 854-61.
15. Marx RE. Platelet-rich plasma: evidence to support its use. J Oral Maxillofac Surg. 2004;62(4):489-96.
16. Pavlovic V, Ciric M, Jovanovic V, Stojanovic P. Platelet Rich Plasma: a short overview of certain bioactive components. Open Med (Wars). 2016;11(1):242-7.
17. Sclafani AP, Romo T, 3rd, Ukrainsky G, McCormick SA, Litner J, Kevy SV, et al. Modulation of wound response and soft tissue ingrowth in synthetic and allogeneic implants with platelet concentrate. Arch Facial Plast Surg. 2005;7(3):163-9.
18. Wang HL, Avila G. Platelet rich plasma: myth or reality? Eur J Dent. 2007;1(4):192-4.
19. Yu W, Wang J, Yin J. Platelet-rich plasma: a promising product for treatment of peripheral nerve regeneration after nerve injury. Int J Neurosci. 2011;121(4):176-80.
20. Ahn S, Kim S, Lee H, Moon S, Chang I. Correlation between a Cutometer and quantitative evaluation using Moire topography in age-related skin elasticity. Skin Res Technol. 2007;13(3):280-4.
21. Denadai R, Chou PY, Su YY, Lin HH, Ho CT, Lo LJ. The Impacts of Orthognathic Surgery on the Facial Appearance and Age Perception of Patients Presenting Skeletal Class III Deformity: An Outcome Study Using the FACE-Q Report and Surgical Professional-Based Panel Assessment. Plast Reconstr Surg. 2020;145(4):1035-46.
22. Kappos EA, Temp M, Schaefer DJ, Haug M, Kalbermatten DF, Toth BA. Validating Facial Aesthetic Surgery Results with the FACE-Q. Plast Reconstr Surg. 2017;139(4):839-45.
23. Sinno S, Schwitzer J, Anzai L, Thorne CH. Face-Lift Satisfaction Using the FACE-Q. Plast Reconstr Surg. 2015;136(2):239-42.
24. Kakudo N, Minakata T, Mitsui T, Kushida S, Notodihardjo FZ, Kusumoto K. Proliferation-promoting effect of platelet-rich plasma on human adipose-derived stem cells and human dermal fibroblasts. Plast Reconstr Surg. 2008;122(5):1352-60.
25. Marques LF, Stessuk T, Camargo IC, Junior NS, Santos L, Ribeiro-Paes JT. Platelet-rich plasma (PRP): methodological aspects and clinical applications. Platelets. 2015;26(2):101-13.
26. Maisel-Campbell AL, Ismail A, Reynolds KA, Poon E, Serrano L, Grushchak S, et al. A systematic review of the safety and effectiveness of platelet-rich plasma (PRP) for skin aging. Arch Dermatol Res. 2020;312(5):301-15.
27. Wamaphutta K, Thasen C, Sereeaphinan C, Chaweekulrat P, Boonchai W. Impact of the COVID-19 pandemic on tertiarycare university dermatology outpatient clinic and dermatology procedures. Siriraj Med J. 2022;74(12):836-43.

Optimization of the Use of the DOTATATE Kit Manufactured by the Thailand Institute of Nuclear Technology Using a SiO_2-based $^{68}Ge/^{68}Ga$ Generator

Phattarayut Jaiuea, B.Sc.[1], Somlak Kongmuang, Ph.D.[2], Kanyapat Lumyong, M.Sc.[3], Thanete Doungta M.Sc.[3], Shuichi Shiratori, Ph.D.[1,*]

[1]*Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand,* [2]*Department of Industrial Pharmacy, Faculty of Pharmacy, Silpakorn University, Thailand,* [3]*Thailand Institute of Nuclear Technology, Bangkok, Thailand.*



*Corresponding author: Shuichi Shiratori
E-mail: shuichi.shi@mahidol.ac.th
Received 9 July 2024 Revised 29 August 2024 Accepted 7 September 2024
ORCID ID:http://orcid.org/0000-0003-4560-0803
https://doi.org/10.33192/smj.v76i11.270157

All material is licensed under terms of the Creative Commons Attribution 4.0 International (CC-BY-NC-ND 4.0) license unless otherwise stated.

ABSTRACT

Objective: The presence of somatostatin receptors on neuroendocrine tumours enables ^{68}Ga-DOTATATE to precisely detect lesion localization and staging. Thailand Institute of Nuclear Technology (TINT) recently developed a DOTATATE kit for labelling with Ga-68, which is compatible with a TiO_2-based ^{68}Ge/^{68}Ga generator eluted with 0.1 M HCl, but presents a discrepancy with other types of ^{68}Ge/^{68}Ga generators. This research aimed to optimize a radiolabelling method using TINT's kit with a SiO_2-based ^{68}Ge/^{68}Ga generator eluting Ga-68 in 0.05 M HCl. Additionally, a quality control protocol was developed to ensure the formulation's efficacy and reliability in compliance with the 10th edition of the European Pharmacopoeia.

Material and Methods: The SiO_2-based ^{68}Ge/^{68}Ga generator was eluted with 2–4 ml of 0.05 M HCl, added into a lyophilized kit, heated in a dried-block heater at 100 °C for 15 min, cooled down at room temperature, and finally purified using Sep-Pak C18 cartridge. The radiochemical purity was determined by radio thin-layer chromatography and the radioactivity was measured by a gamma well counter. Reproducibility and stability tests were conducted three times.

Results: Employing 4 ml of eluted material, comprising the second and fifth millilitres of $^{68}GaCl_3$, provided a radiochemical purity (RCP) exceeding 95% after purification. Also, ^{68}Ga-DOTATATE remained stable in refrigerator for at least 4 half-lives.

Conclusion: TINT's DOTATATE kit can be successfully labelled with a SiO_2-based ^{68}Ge/^{68}Ga generator, providing ^{68}Ga-DOTATATE with an RCP > 95% for at least 4 half-lives when stored in refrigerator after production. This radiolabelling procedure is suitable for routine clinical application.

Keywords: ^{68}Ga-DOTATATE ; TINT kit ; neuroendocrine tumor, Ga-68 elution ; radiochemical purity (Siriraj Med J 2024; 76: 789-796)

INTRODUCTION

Neuroendocrine tumors (NETs) encompass a diverse group of malignancies arising from neuroendocrine cells, which can be found in various organs throughout the body. As non-functioning tumours, NETs may not cause noticeable symptoms until they grow large enough and metastasize to the liver.[1,2] The global incidence rate of NETs is on the rise, and is currently estimated to affect approximately 4 per 100,000 adults.[3]

Somatostatin receptors (SSTRs), found on the surface of neuroendocrine cells, play critical roles in regulating physiological processes and maintaining homeostasis within the endocrine and nervous systems. SSTRs belong to a family of G protein-coupled receptors with various subtypes, including SSTR1, SSTR2, SSTR3, SSTR4, and SSTR5. Among these SSTRs, SSTR2 stands out as a crucial theranostic target.[4] The SSTR2 RNA yields two splice variants: SSTR2a and SSTR2b, differing in length. The activation of SSTRs occurs through somatostatin (SST), a neuropeptide, which exists in two isoforms known as somatostatin-14 (SST-14) and somatostatin-28 (SST-28), both displaying high affinity for SSTRs.[5,6] The SST-system plays a pivotal role in regulating numerous physiological processes. It operates through multiple pathways activated upon SST binding to SSTRs, leading to either the inhibition of hormone secretion and cell proliferation or the induction of apoptosis.[7,8]

The overexpression of somatostatin receptors (SSTRs) on NET cells surfaces has significant clinical implications as a target for the specific binding of somatostatin analogues, such as octreotide[9], octreotate[10], lanreotide[11], and vapreotide[12], leading to the inhibition of hormone secretion and tumour growth. In addition, these somatostatin analogues can be further conjugated to DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid[13], which can be chelated to trivalent radionuclides in theranostic approaches.[14-16]

On 1 June 2016, the DOTATATE kit (Netspot®, previously Somakit-TATE) was approved by the US Food and Drug Administration (FDA)[17] for preparation of ^{68}Ga-DOTATATE (Fig 1), which is used to detect somatostatin receptor positive NETs in adult and paediatric patients. Various Ga-68 labelling kits are commercially available, predominantly sourced from Europe, notably Germany.[18-23] Recently, the Thailand Institute of Nuclear Technology (TINT) introduced a DOTATATE kit tailored for Ga-68 labelling, showcasing the domestic capability of Thai researchers in cold kit production. This kit formulation aligns with a TiO_2-based ^{68}Ge/^{68}Ga generator eluted with 5 ml of 0.1 M HCl.

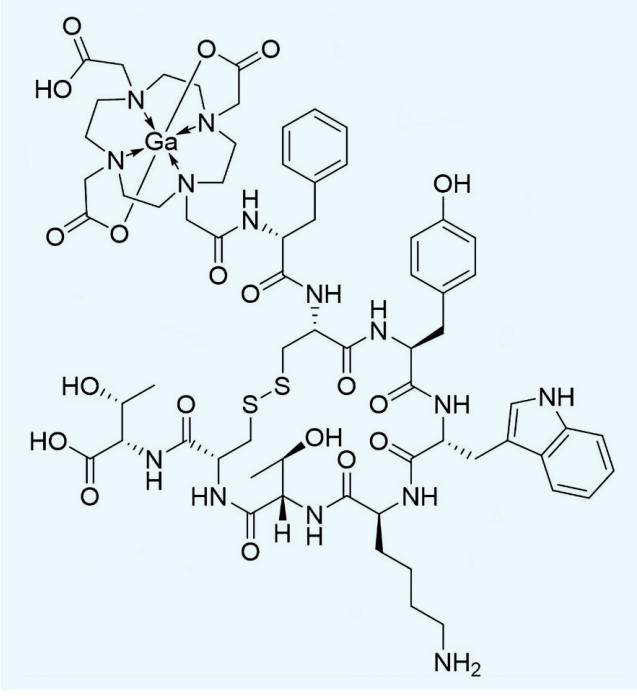


Fig 1. The chemical structure of ^{68}Ga-DOTATATE

However, contemporary commercially available ^{68}Ge/^{68}Ga generators employ solid-phase SiO_2 matrices to yield $^{68}GaCl_3$ through elution with highly diluted HCl, effectively leaving the parent Ge-68 radionuclide on the matrix. This method offers an improved quality of $^{68}GaCl_3$ and superior labelling protocols. This research aims to optimize the radiolabelling process using TINT's DOTATATE kit with a SiO_2-based ^{68}Ge/^{68}Ga generator eluted Ga-68 in 4 ml of 0.05 M HCl. Additionally, a practical quality control protocol was developed to ensure the formulation's efficacy and reliability in compliance with the 10th edition of the European Pharmacopoeia.

MATERIALS AND METHODS

The ^{68}Ge/^{68}Ga generator was purchased from Isotope Technologies München AG (ITM), Medical Isotopes GmbH, Germany. Lyophilized DOTATATE kits were obtained from the Thailand Institute of Nuclear Technology (TINT). All the solvents and reagents were purchased from commercial suppliers and used without further purification. 0.05 M HCl (GMP) was obtained from the pharmacy department at Siriraj Hospital. The Sep-Pak C18 cartridge was purchased from Waters Co., Ltd., USA. The Ga-68 activity was measured with a dose calibrator (CRC25R, Capintec, USA) and measured by gamma-ray spectrometry using a multichannel analyser (MCA), which was integrated with a gamma spectrometer system (Ortec DSPEC jr 2.0) coupled with a high-purity germanium probe (HPGe probe, Ortec Gem20P4-70) for use in the experiments.

Evaluation of Ga-68 elution

The SiO_2-based ^{68}Ge/^{68}Ga generator (ITM, Munich, Germany) was manually eluted with 5.0 ml of 0.05 M HCl with collecting 1.0 ml fractions to determine the Ga-68 activity. The radioactivity of the Ga-68 elution in each fraction was immediately determined in a dose calibrator.

Optimization of the labelling method for the preparation of 68Ga-DOTATATE

General labelling procedure: the ^{68}Ge/^{68}Ga generator was eluted with 2–4 ml of 0.05 M HCl for labelling. It was ensured that an elution had been conducted at least 24 hours in advance. The fraction of $^{68}GaCl_3$ solution was collected and added into a lyophilized cold kit of DOTATATE, then heated in a dried-block heater at 100 °C for 15 min and cooled down at room temperature for 5 min.

In experiment 1, the fraction of $^{68}GaCl_3$ solution comprising the 2nd to 3rd millilitre (2 ml) of the overall volume was collected. No further purification was performed.

In experiment 2, the fraction of $^{68}GaCl_3$ solution comprising the 1st to 4th millilitre (4 ml) of the overall volume was collected. No further purification was performed.

In experiment 3, the fraction of $^{68}GaCl_3$ solution comprising the 2nd to 4th millilitre (3 ml) of the overall volume was collected. No further purification was performed.

In experiment 4, the fraction of $^{68}GaCl_3$ solution comprising the 2nd to 5th millilitre (4 ml) of the overall volume was collected. No further purification was performed.

In experiment 5, the fraction of $^{68}GaCl_3$ solution comprising the 2nd to 5th millilitre (4 ml) of the overall volume was collected. The labelled product was purified using pre-treatment with the Sep-Pak C18 cartridge eluting ethanol (EtOH) 2.0 ml and later washed with 2 ml of normal saline solution. The Sep-Pak C18 cartridge was then eluted with EtOH:H_2O (1:1) 2 ml. The RCP was determined by radio thin-layer chromatography (RTLC) using 1 M NH_4OAc:MeOH (1:1) and the radioactivity was measured by a gamma well counter. The pH of ^{68}Ga-DOTATATE was also measured using a pH meter.

Radiochemical purity analyses

Radiochemical purity (RCP) analyses were conducted using radio thin-layer chromatography (RTLC) with silica paper strips as the stationary phase. The mobile phase consisted of 1 M NH_4OAc:MeOH (1:1), and the radioactivity was measured using a gamma well counter.

Reproducibility and stability test

To assess the reproducibility and consistency of

the labelling method in experiment 5, the experiment was replicated 4 times. At regular time points, a 2 µl sample was taken for RTLC analysis. The stability of ^{68}Ga-DOTATATE was evaluated by incubating at 4 °C in a refrigerator for 4 half-lives and monitored by RTLC every half-life, which was approximately 68 min.

RESULTS AND DISCUSSION

Ga-68 elution profile

The ITM ^{68}Ge/^{68}Ga generator, utilizing modified dodecyl-3,4,5 trihydroxybenzoate hydrophobically bound to an octadecyl silica resin (C-18) as an adsorbent, was developed in GMP-grade tailored for effectively eluting $^{68}GaCl_3$ solution without metal impurities in highly diluted HCl (0.05 M). The Ga-68 eluate does not require further pre-concentration and pre-purification, making it ready for radiolabelling. The elution profiles of each eluate are shown in Fig 2. The majority of the Ga-68 activity was found in fractions 2 to 4. Fraction 1 contained a trace amount of Ga-68 activity, while fraction 5 provided approximately 5% of the overall Ga-68 activity. During the period studied, the elution profile of Ga-68 remained unchanged. This Ga-68 elution pattern aligns with the findings from our prior study.[24] Moreover, the pH of each fraction fell within the range of 1.7–1.9, which is suitable for labelling with DOTA.[25,26]

Optimization of the labelling method for the preparation of ^{68}Ga-DOTATATE

The TINT kits contained 20 µg DOTATATE, 34 mg NaOAc, and 1 mg ascorbic acid. These components were dissolved in sterile water, and the solution was adjusted pH to 6.5 with NaOH. After filtering through a 0.22 µm membrane, each 1 ml of the filtered solution was dispensed into a 10-ml vial. All the vials were then frozen at -40 °C for 3 h and subsequently lyophilized at -20 °C overnight in a vacuum freeze-dryer. There was no further optimization of the DOTATATE content, as that had already been done in the formulation. Instead, this systematic approach aimed to develop an optimum labelling method.

Based on the formulation, the manufacturer suggested using a 5 ml solution of 0.1 M HCl eluting into a TiO_2-based ^{68}Ge/^{68}Ga generator at an approximate flow rate of 1–2 ml/min. The second and third millilitres (2 ml) of the eluted $^{68}GaCl_3$ solution were collected and added to a lyophilized DOTATATE cold kit. For these optimization experiments, we used the same amount of $^{68}GaCl_3$ solution, specifically the second and third millilitres (2 ml) as a reference collected from the ITM ^{68}Ge/^{68}Ga generator, added to the TINT's lyophilized DOTATATE kit. The labelling was conducted in a dry-block heater at 100 °C for 15 min and then cooled to room temperature for 5 min. The manufacturer did not advise any purification step.

The radiochemical purity (RCP) in the first experiment was 13.72%. The low RCP might be due to the high concentration of Ga-68 eluate from the SiO_2-based ^{68}Ge/^{68}Ga generator, which could cause significant impurities. By increasing the amount of $^{68}GaCl_3$ solution to 3 ml, specifically collected from the second to fourth millilitres, the impurity levels were found to be significantly reduced, resulting in an increased RCP of 58.27%. This improvement can be attributed to the larger amount of $^{68}GaCl_3$ collected.

Based on the results of experiment 2, the volume

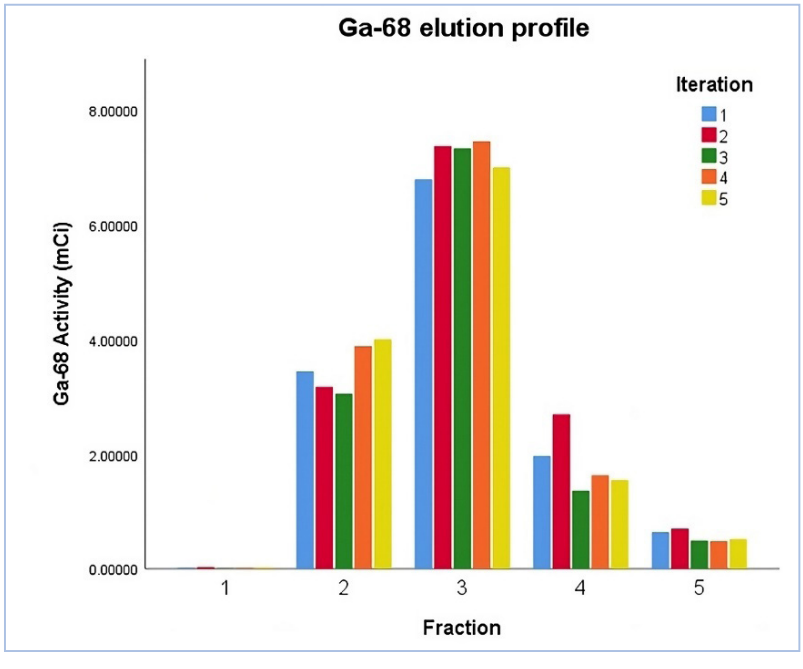


Fig 2. The Ga-68 elution profile

of Ga-68 eluate was increased to 4 ml in subsequent experiments. In experiment 3, the eluate was collected from the first to the fourth millilitre, resulting in an RCP of 13.06%, whereas in experiment 4, the eluate was collected from the second to the fifth millilitre, resulting in an RCP of 29.75%. Due to the greater amount of Ga-68 in the fifth fraction compared to the first fraction, there was more Ga-68 available to chelate with DOTATATE in experiment 4. However, both experiments still showed higher levels of unbound Ga-68 compared to in experiment 2.

According to the standard labelling procedure recommended by ITM, the suitable amount of Ga-68 is 4 ml. In experiment 5, to achieve a higher RCP, the second to fifth millilitres (4 ml) of $^{68}GaCl_3$ were used. Additionally, a purification step using a Sep-Pak C18 cartridge was incorporated into the method. Consequently, the RCP in experiment 5 was measured at 95.08% (Table 1), a result that was corroborated by the RTLC scanner (Fig 3).

Reproducibility and stability

Based on the optimized outcomes (Table 1), the labelling process in experiment 5 was replicated three times to ensure reproducibility. The RCP was observed to fall within the range of 98.36%–99.22% (Table 2). The obtained RCPs through the RTLC indicated the presence of minute colloidal traces. The use of the post-labelling Sep-Pak C18 purification suggested that Ge-68 breakthrough was not detected in any of the ^{68}Ga-DOTATATE preparations. These findings collectively

TABLE 1. Optimization of labelling method

Experiment	1	2	3	4	5
Ga-68 fraction	2 - 3	2 - 4	1 - 4	2 - 5	2 - 5
Ga-68 volume (mL)	2	3	4	4	4
Ga-68 activity (mCi)	12.06	13.67	12.74	11.15	12.81
pH before labelling	1.35	1.37	1.34	1.29	1.21
Purification	No	No	No	No	Yes
RCP (%)	13.72	58.27	13.06	29.25	95.08

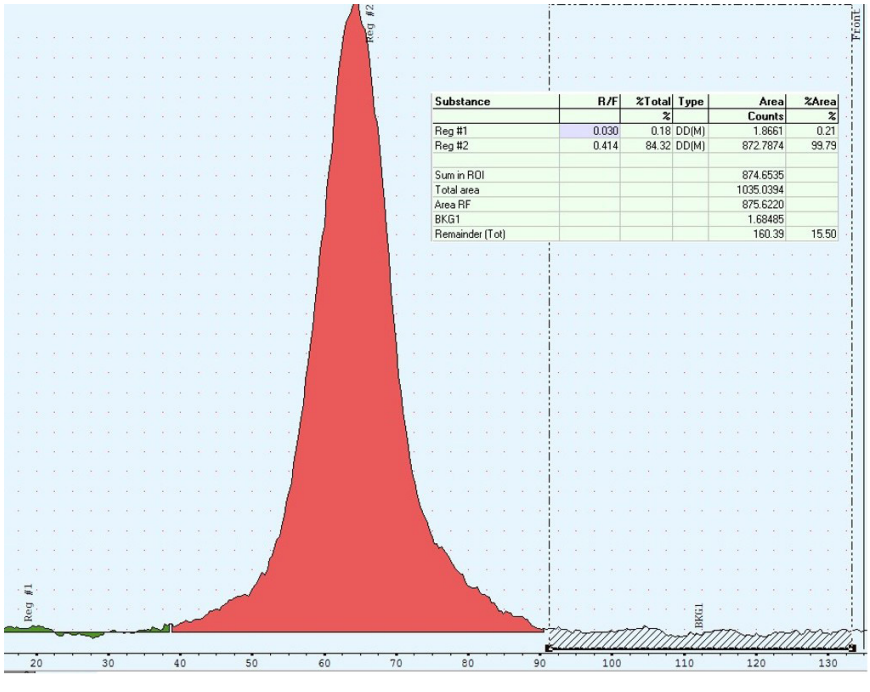


Fig 3. RTLC chromatogram of ^{68}Ga-DOTATATE

TABLE 2. Reproducibility and stability.

Iteration	5.1	5.2	5.3	Mean± SD.
Ga-68 activity (mCi)	13.50	13.18	13.55	13.41+0.20
^{68}Ga-DOTATATE activity (mCi)	9.65	9.57	9.63	9.62+0.04
RCP of final product (%)	98.36	98.94	99.22	98.84+0.44
RCP after 1st half-life (%)	98.46	99.10	98.87	98.81+0.32
RCP after 2nd half-life (%)	98.44	99.12	99.22	98.93+0.42
RCP after 3rd half-life (%)	98.42	98.84	99.09	98.78+0.34
RCP after 4th half-life (%)	98.37	99.15	98.62	98.71+0.40

imply that the quality of ^{68}Ga-DOTATATE prepared under these conditions aligned with the standards outlined for ^{68}Ga-DOTATOC in the 10th edition of the European Pharmacopoeia.[27]

Additionally, conducting a basic RTLC analysis can identify impurities before the preparation is diluted for injection, offering a significant advantage in terms of the procedure's duration and consequently the overall radiochemical yield. Here, when the final product of ^{68}Ga-DOTATATE was stored in a refrigerator at 4–8 °C, the RCP remained stable, with less than 5% label loss for at least 4 half-lives.

This study reveals successful radiolabelling of ^{68}Ga-DOTATATE using TINT's kit and $^{68}GaCl_3$ eluted from a SiO_2-based ^{68}Ge/^{68}Ga generator, with a focus on ensuring compliance with the 10th edition of the European Pharmacopoeia. The targeted binding of ^{68}Ga-DOTATATE to somatostatin receptors (SSTRs) enables highly sensitive and specific imaging, which is essential for the precise localization of both primary and metastatic NETs. This precision plays a critical role in accurate staging, guiding treatment decisions, and monitoring the response to therapy. Additionally, the identification of SSTRs expression on NETs through ^{68}Ga-DOTATATE PET/CT scans not only aids in visualization but also has therapeutic implications. Patients with SSTR-positive tumors may be candidates for peptide receptor radionuclide therapy (PRRT) using agents like ^{177}Lu-DOTATATE or ^{225}Ac-DOTATATE. This form of therapy delivers targeted radiation directly to tumor cells, minimizing damage to normal tissues and potentially leading to improved patient outcomes. The use of ^{68}Ga-DOTATATE in this way represents a significant advancement in both diagnostic imaging and targeted radionuclide therapy, offering a comprehensive approach to managing neuroendocrine tumors.

CONCLUSION

The optimized radiolabelling method of ^{68}Ga-DOTATATE using the TINT kit with the SiO_2-based ^{68}Ge/^{68}Ga generator was successful. In clinical practice, an injection dose of approximately 5 mCi of ^{68}Ga-DOTATATE is recommended for the diagnosis of NET. In this study, the activity of ^{68}Ga-DOTATATE in the final product was 9.14 ± 0.96 mCi, which is sufficient to administer to one patient per production batch. ^{68}Ga-DOTATATE was stable with a radiochemical purity of more than 95% for at least 4 half-lives in the refrigerator after production, in accordance with the 10th edition of the European Pharmacopoeia.

Thus, the DOTATATE cold kit manufactured by TINT can be effectively and reliably labelled with a SiO_2-based ^{68}Ge/^{68}Ga generator-eluted Ga-68 in 4 ml of 0.05 M HCl, suitable for routine clinical application. It is expected that widespread utilization of the TINT kit with this radiolabelling method will have a beneficial impact on ^{68}Ga-DOTATATE preparation at a reasonable expense. The utility of ^{68}Ga-DOTATATE in clinical practice significantly enhances the precision of lesion localization and improves diagnostic accuracy. By providing detailed and specific imaging of NETs, it plays a critical role in informing personalized treatment planning. This imaging technique also serves as a foundation for targeted therapies such as PRRT and offers insights that can directly influence patient outcomes. The ability

to precisely identify and target tumor cells with ^{68}Ga-DOTATATE not only supports more effective treatment strategies but also contributes to improved prognoses for patients with SSTR-positive NETs.

ACKNOWLEDGEMENTS

This research project was supported by the Faculty of Medicine Siriraj Hospital, Mahidol University, Grant Number (IO) R016632023. The authors gratefully acknowledge Ms. Phattaranan Phawaphutanon for the project execution; and Ms. Dollaporn Polyeam, Mr. Karnchana Sae-jang, and Mr. Yuti Jirawattanapalin for support with the statistical analyses.

DECLARETION

Grants and Funding Information

This project is not funded by any external sources.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Author Contributions

Conceptualization and methodology, P.J., S.K., K.L., T.D. and S.S.; Formulation and Kit manufacture, K.L., T.D.; Formal analysis, S.K. and S.S.; Visualization and writing – original darft, P.J.; Writing – review and editing, S.K. and S.S.; Funding acquisition, S.S.; Supervision, S.S. All authors have read and agreed to the final version of the manuscript.

REFERENCES

1. Ichikawa Y, Kobayashi N, Takano S, Kato I, Endo K, Inoue T. Neuroendocrine tumor theranostics. Cancer Sci. 2022;113(6):1930-8.
2. Klomp M, Dalm S, De Jong M, Feelders R, Hofland J, Hofland L. Epigenetic regulation of somatostatin and somatostatin receptors in neuroendocrine tumors and other types of cancer. Rev Endocr Metab Disord. 2021;22(3):495-510.
3. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017;3(10):1335-42.
4. Papotti M, Bongiovanni M, Volante M, Allia E, Landolfi S, Helboe L, et al. Expression of somatostatin receptor types 1–5 in 81 cases of gastrointestinal and pancreatic endocrine tumors: a correlative immunohistochemical and reverse-transcriptase polymerase chain reaction analysis. Virchows Arch. 2002;440(5):461-75.
5. Olias G, Viollet C, Kusserow H, Epelbaum J, Meyerhof W. Regulation and function of somatostatin receptors. J Neurochem. 2004;89(5):1057-91.
6. Barnett P. Somatostatin and somatostatin receptor physiology. Endocrine. 2003;20(3):255-64.
7. Gatto F, Barbieri F, Arvigo M, Thellung S, Amarù J, Albertelli M, et al. Biological and biochemical basis of the differential efficacy of first and second generation somatostatin receptor ligands in neuroendocrine neoplasms. Int J Mol Sci. 2019;20(16):3940.
8. Barbieri F, Bajetto A, Pattarozzi A, Gatti M, Würth R, Thellung S, et al. Peptide receptor targeting in cancer: the somatostatin paradigm. Int J Pept. 2013;2013:926295.
9. Battershill PE, Clissold SP. Octreotide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in conditions associated with excessive peptide secretion. Drugs. 1989;38(5):658-702.
10. Sanli Y, Garg I, Kandathil A, Kendi T, Zanetti MJB, Kuyumcu S, et al. Neuroendocrine tumor diagnosis and management: ^{68}Ga-DOTATATE PET/CT. AJR Am J Roentgenol. 2018;211(2):267-77.
11. Capdevila J, Sevilla I, Alonso V, Antón Aparicio L, Jiménez Fonseca P, Grande E, et al. Evaluation of the efficacy and safety of lanreotide in combination with targeted therapies in patients with neuroendocrine tumours in clinical practice: a retrospective cross-sectional analysis. BMC Cancer. 2015;15:495.
12. Calès P. Vapreotide acetate for the treatment of esophageal variceal bleeding. Expert Rev Gastroenterol Hepatol. 2008;2(2):185-92.
13. Kubicek V, Havlickova J, Kotek J, Tircso G, Hermann P, Toth E, et al. Gallium (III) complexes of DOTA and DOTA–monoamide: kinetic and thermodynamic studies. Inorg Chem. 2010;49(23):10960-9.
14. Stueven AK, Kayser A, Wetz C, Amthauer H, Wree A, Tacke F, et al. Somatostatin analogues in the treatment of neuroendocrine tumors: past, present and future. Int J Mol Sci. 2019;20(12):3049.
15. Bergsma H, van Vliet EI, Teunissen JJ, Kam BL, de Herder WW, Peeters RP, et al. Peptide receptor radionuclide therapy (PRRT) for GEP-NETs. Best Pract Res Clin Gastroenterol. 2012;26(6):867-81.
16. Van Essen M, Krenning EP, De Jong M, Valkema R, Kwekkeboom DJ. Peptide receptor radionuclide therapy with radiolabelled somatostatin analogues in patients with somatostatin receptor positive tumours. Acta Oncologica. 2007;46(6):723-34.
17. U.S. Food and Drug Administration. FDA approves new diagnostic imaging agent to detect rare neuroendocrine tumors 2016. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-diagnostic-imaging-agent-detect-rare-neuroendocrine-tumors.
18. Mukherjee A, Pandey U, Chakravarty R, Sarma HD, Dash A. Development of single vial kits for preparation of ^{68}Ga-labelled peptides for PET imaging of neuroendocrine tumours. Mol Imaging Biol. 2014;16(4):550-7.
19. Mukherjee A, Pandey U, Chakravarty R, Sarma HD, Dash A. Single vial kit formulation for preparation of PET radiopharmaceutical: ^{68}Ga-DOTA-TOC. Journal of Radioanalytical and Nuclear Chemistry. 2014;302:1253-8.
20. Das T, Bhadwal M, Sarma H, Banerjee S. Formulation and radiochemical evaluation of a freeze-dried mixed peptide kit for the preparation of ^{68}Ga-labeled peptides for PET imaging of somatostatin receptor positive neuroendocrine cancers. Journal of Radioanalytical and Nuclear Chemistry. 2014;302:1259-64.
21. Asti M, Iori M, Capponi PC, Rubagotti S, Fraternali A, Versari A.

Development of a simple kit-based method for preparation of pharmaceutical-grade ^{68}Ga-DOTATOC. Nucl Med Commun. 2015;36(5):502-10.

22. Mukherjee A, Korde A, Sarma HD, Samuel G. Single vial formulation for theranostic radiopharmaceutical preparation. Journal of Radioanalytical and Nuclear Chemistry. 2014;302: 889-94.
23. Prince D, Rossouw D, Davids C, Rubow S. Development and evaluation of user-friendly single vial DOTA-peptide kit formulations, specifically designed for radiolabelling with ^{68}Ga from a tin dioxide ^{68}Ge/^{68}Ga generator. Mol Imaging Biol. 2017;19(6):817-24.
24. Sriprapa T, Doungta T, Sakulsamart N, Taweewatthanasopon N, Madputeh L, Ragchana P, et al. Evaluation of the Efficacy and Safety of the ITM ^{68}Ge/^{68}Ga Generator After its Recommended Shelf-life. Siriraj Med J. 2023;75(10):752-8.
25. Breeman WA, de Jong M, de Blois E, Bernard BF, Konijnenberg M, Krenning EP. Radiolabelling DOTA-peptides with ^{68}Ga. Eur J Nucl Med Mol Imaging. 2005;32(4):478-85.
26. Velikyan I, Beyer GJ, Långström B. Microwave-supported preparation of ^{68}Ga bioconjugates with high specific radioactivity. Bioconjug Chem. 2004;15(3):554-60.
27. European Pharmacopeia. Gallium (^{68}Ga) Edotreotide injection monograph. In: European Pharmacopeia (EP). 10th editor. European Pharmacopeia; 2019.p.1208-10.