136 YEAR SIRIRAJ

E-ISSN 2228-8082

Volume 76, Number 12, December 2024

SMJ

Siriraj Medical Journal

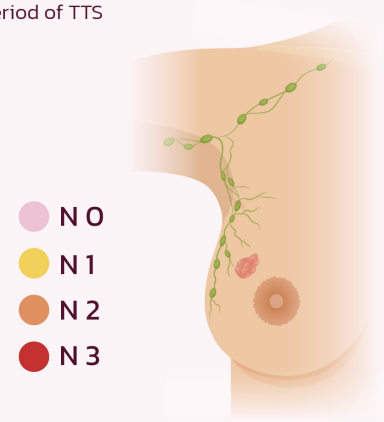
The world-leading biomedical science of Thailand

MONTHLY

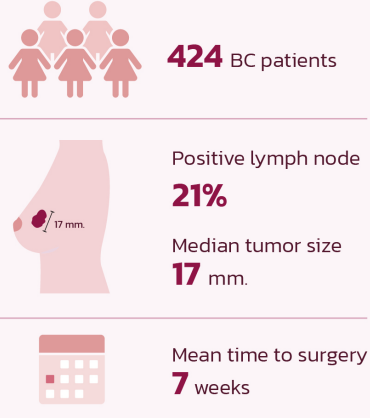
ORIGINAL ARTICLE

Post-biopsy to surgery interval (TTS) increase axillary nodal metastasis, especially in early breast cancer patients

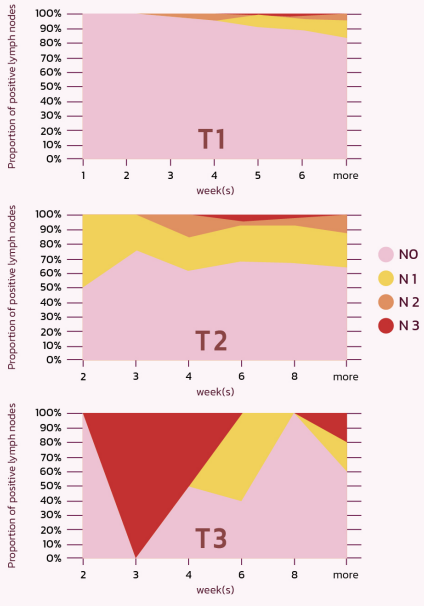
Theoretically, proportion of N Stage should be the same in each T Stage in every time period of TTS



Cross-sectional retrospective study



Result: Proportion of N Stage by T Stage



Conclusions: Longer time to surgery is associated with more advanced N stages, particularly in early breast cancer and small size tumors (T1).

SCAN FOR FULL TEXT

SMJ SIRIRAJ MEDICAL JOURNAL | Prasitviset, et al. *Siriraj Med J* 2024;76(12):831-39.

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 12
December 2024

ORIGINAL ARTICLE

SIRIRAJ MEDICAL JOURNAL

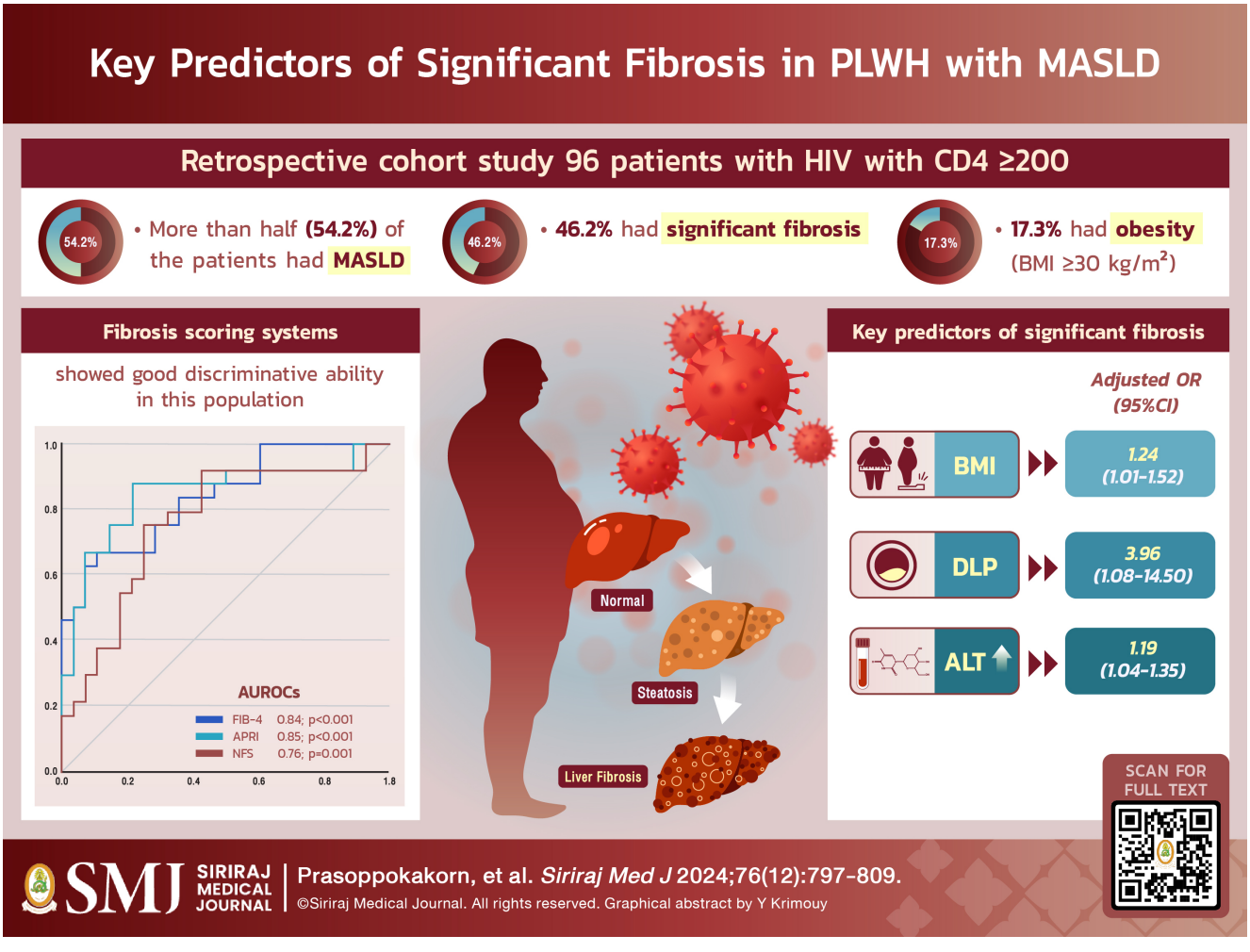
https://he02.tci-thaijo.org/index.php/sirirajmedj/index

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

Predictors of Significant Fibrosis Among People Living with HIV with Metabolic Dysfunction-Associated Steatotic Liver Disease

Thaninee Prasoppokakorn, M.D.[1,2], Varisa Limpijankit[2], Siravich Seesodsai, M.D.[2], Palakorn Panarat, M.D.[2], Teerarat Shanthachol, M.D.[2], Kanokwan Sonsiri[1], Prooksa Ananchuensook, M.D.[1], Kessarin Thanapirom, Ph.D.[1], Chusana Suankratay, M.D., Ph.D.[3], Sombat Treeprasertsuk, M.D., Ph.D.[1,*]

[1]Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand, [2]Department of Medicine, Queen Savang Vadhana Memorial Hospital, Chonburi, Thailand, [3]Division of Infectious disease, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand.



*Corresponding author: Sombat Treeprasertsuk
E-mail: battan5410@gmail.com
Received 23 August 2024 Revised 29 September 2024 Accepted 30 September 2024
ORCID ID:http://orcid.org/0000-0001-6459-8329
https://doi.org/10.33192/smj.v76i12.270742

ABSTRACT

Objective: Metabolic dysfunction-associated steatotic liver disease (MASLD) is highly prevalent among people living with HIV (PLWH) due to comorbidities and factors related to HIV infection. This study aimed to identify clinical predictors of significant fibrosis among PLWH with MASLD.

Materials and Methods: A retrospective cohort study was conducted with PLWH having CD4 counts ≥200, enrolled between April and October 2023 at two tertiary hospitals. The primary outcome was identifying the clinical predictors of significant fibrosis (F≥2) defined by TE≥8 kPa. Secondary outcomes included MASLD prevalence and characteristics.

Results: Among 96 PLWH, 52 (54.2%) had MASLD. The mean age was 49.7±8.0 years, 63.5% were male, and the mean BMI was 25.8±4.1 kg/m^2. Obesity, diabetes, and dyslipidemia were present in 17.3%, 19.2%, and 46.2% of participants, respectively. The mean CAP and TE were 285±36 dB/m and 8.7±7.8 kPa, respectively. Significant fibrosis was present in 24 patients (46.2%). Fibrosis scoring systems (FIB-4, APRI, NFS) demonstrated good accuracy (AUROCs: 0.84, 0.85, 0.76, respectively). Multivariate analysis identified predictors of significant fibrosis: higher BMI (aOR 1.24, p=0.042), dyslipidemia (aOR 3.96, p=0.038), and higher AST (aOR 1.19, p=0.011). The AGA pathway using two steps (FIB-4 and TE) improved reclassification of significant fibrosis risk, reducing the number of individuals at indeterminate risk, 12 out of 52 in the first step to 7 out of 52 in the second step.

Conclusion: MASLD is highly prevalent in PLWH, with about half experiencing significant fibrosis. Predictors of significant fibrosis include dyslipidemia, higher BMI, and elevated AST levels. Fibrosis scoring systems accurately predict significant fibrosis.

Keywords: Metabolic Dysfunction-Associated Steatotic Liver Disease; steatotic liver disease; metabolic syndrome; HIV infection; People Living with HIV (Siriraj Med J 2024; 76: 797-809)

INTRODUCTION

People living with HIV (PLWH) in Thailand nowadays experience extended lifespans comparable to those of the general population due to advances in antiretroviral therapy (ART).[1,2] However, the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) in PLWH is rising globally, with estimates ranging between 30-50%.[3-5] This association is attributed to factors such as an aging population, a high prevalence of metabolic risk factors, comorbidities, and HIV-related infection.[6-9] Additionally, ART has been associated with negative metabolic side effects, such as weight gain and hepatic steatosis, further elevating the risk of MASLD.[10-12]

MASLD in PLWH is concerning due to its association with advanced fibrosis, cirrhosis, hepatocellular carcinoma, and reduced survival.[13-15] Early detection of MASLD can inform clinical management, allowing for lifestyle modification or therapeutic intervention to mitigate potential complications. While the reference standard for assessing prognosis and disease monitoring involves the histologic examination of liver biopsy specimens, this invasive procedure may not be the preferred approach in patients with HIV and MASLD. In such case, the utilization of non-invasive scoring systems is valuable for facilitating risk stratification and longitudinal assessment of disease progression.[16-18]

Several non-invasive scoring systems, including the fibrosis-4 (FIB-4) score, aspartate aminotransferase to platelet ratio index (APRI), and non-alcoholic fatty liver disease (NAFLD) fibrosis score (NFS), are commonly used for detecting liver fibrosis in this population.[19] These scoring systems are generally safer and more acceptable for patients, making them well-suited for serial monitoring of disease progression or response to treatment.

The identification of advanced liver fibrosis serves as a crucial prognostic marker for unfavorable outcomes in individuals with MASLD. Currently, imaging-based biomarkers play a significant role, offering rapid and outpatient-compatible procedures. Among the ultrasound-based techniques, vibration-controlled transient elastography (VCTE), commercially available as FibroScan® (Echosens, Paris, France), was the first to be introduced and is currently the most extensively validated.[20-21] This non-invasive imaging technique provides a dual advantage for screening, offering simultaneously information on both liver stiffness measurement (LSM) and the degree of hepatic steatosis, estimated through the controlled attenuation parameter (CAP).

It is important to note that the diagnostic performance of these tests can vary based on the specific population studies, the prevalence of liver fibrosis in that population,

and the reference standard used for comparison.[22-24] The diverse influences of ethnicity, race, socioeconomic status, and varying lifestyles contribute to the impact of liver fibrosis in people living with HIV. However, there is limited data about the importance of liver fibrosis and fatty liver in PLWH, particularly among Asian population.[25-26] Therefore, this study aims to identify clinical predictors of significant fibrosis in PLWH with MASLD in Thailand.

MATERIALS AND METHODS

Study design and participants

We conducted a retrospective cohort study, enrolling patients from two tertiary hospitals between April and October 2023. The inclusion criteria were patients aged ≥18 years who visited outpatient liver and infectious disease clinics with HIV infection, had been treated with standard antiretroviral therapy for ≥6 months, and had an HIV RNA count ≤200 copies/mL. Our study included patients with hepatitis B and C coinfections, as well as those who consumed alcohol. There were no exclusion criteria. Baseline patient characteristics such as age, gender, body weight, body mass index (BMI), waist and hip circumference, and underlying comorbidities including type 2 diabetes mellitus, dyslipidemia, and hypertension were recorded. Personal history information on smoking and alcohol consumption was also retrieved. Laboratory tests included liver function tests, metabolic profiles (fasting blood sugar, HbA1C, lipid profile), CD4 counts, and HBV and HCV status. The laboratory tests were conducted within six months of the hepatic steatosis and fibrosis assessment.

Steatosis and fibrosis assessment: All PLWH underwent a FibroScan® study conducted by dedicated operators after fasting for less than 3 hours. Two parameters derived from this vibration-controlled transient elastography (VCTE) were the controlled attenuation parameter (CAP) and liver stiffness measurement (LSM), which reflected steatosis (in decibels per meter or dB/m) and fibrosis (in kilopascals or kPa), respectively. The cut-off values to define steatosis were: no signs of steatosis (S0) < 238 dB/m, beginning steatosis (S1): 238-259 dB/m, advanced steatosis (S2): 260-291 dB/m, and severe steatosis (S3) > 292 dB/m. A TE cut-off value of at least 6.5 kPa indicated liver fibrosis (F1), and 8.0 kPa indicated significant fibrosis (F2). For more advanced stages, a TE value of ≥9.5 kPa was used to define advanced fibrosis (F3), while a TE value of ≥12.5 kPa indicated cirrhosis (F4).[28]

Fibrosis scoring systems were also calculated. The fibrosis-4 score (FIB-4 score) was determined using the formula [Age (years)×AST (U/L)/[platelet (10^9/L)×ALT$^{1/2}$ (U/L)],[29] the AST to platelet ratio index (APRI) was computed as [AST (IU/L)/AST upper limit of normal (IU/L)/platelets (10^9/L) x 100],[30] and the NAFLD fibrosis score (NFS) was derived from the formula [-1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio - 0.013 × platelet count (x10^9/L) - 0.66 × albumin (g/dL).[31]

Individual consent for retrospective analysis was exempted. The study protocol was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB No.903/63), and adhered to the principles outlined in the Helsinki Declaration of 1983.

Definition of MASLD and dyslipidemia

According to a recently published international consensus statement,[32] a diagnosis of MASLD required the presence of hepatic steatosis, as defined by a CAP of ≥ 238 dB/m. Apart from the identification of hepatic steatosis detected by imaging or biopsy, at least one of the following five criteria had to be evident: 1) overweight/obesity (BMI > 23 kg/m^2) or waist circumference > 90 cm in men, > 80 cm in women, 2) fasting serum glucose levels > 100 mg/dL or 2-hour post-load glucose level > 140 mg/dL or HbA1c > 5.7%, or specific drug treatment, 3) blood pressure > 130/85 mmHg or specific drug treatment, 4) plasma TG levels > 150 mg/dL or specific drug treatment, 5) plasma HDL-C levels below 40 mg/dL for men and 50 mg/dL for women or specific drug treatment. Dyslipidemia was defined as elevated levels of serum TC, LDL-C, TG, or a reduced serum HDL-C concentration.

Outcomes

The primary outcome was identifying clinical predictors of significant fibrosis (F ≥2), defined as TE ≥ 8 kPa in PLWH with MASLD. Secondary outcomes included: 1) the prevalence and clinical characteristics of MASLD, defined as CAP ≥ 238 dB/m in those meeting cardiometabolic criteria; 2) the performance of non-invasive fibrosis scoring systems among these patients; and 3) the clinical applicability of the two-step non-invasive testing recommended by the American Gastroenterological Association (AGA) pathway, using the FIB-4 score and VCTE.

Statistical analysis

Continuous variables were reported as mean ± standard deviation and analyzed using unpaired t-tests for normally distributed data. Skewed variables were expressed as median with interquartile range and assessed

for differences using the Mann-Whitney U test. Categorical variables were expressed as numbers (percentages) and compared using Fisher's exact test or Chi-square test as appropriate. Factors associated with significant fibrosis were determined using a logistic regression model. Age, sex, and other factors with a p-value of < 0.05 in the univariate model were included in the multivariate model. Statistical analyses were performed using SPSS version 22.0.0 (SPSS Inc., Chicago, Illinois, USA). A p-value of < 0.05 was considered statistically significant.

Ethical Statement

The study protocol received approval from the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB number 903/63).

RESULTS

Baseline patient characteristics

A total of 96 participants with HIV infections were enrolled at two tertiary hospitals. Of these, 52 (54.2%) were diagnosed with MASLD. Table 1 demonstrates the baseline characteristics between the MASLD and non-MASLD groups. Patients with MASLD had significantly higher body weight (70.9 ± 11.9 kg vs. 61.1 ± 8.8 kg, p < 0.001), BMI (25.8 ± 4.1 kg/m² vs. 21.6 ± 3.0 kg/m², p < 0.001), waist circumference (WC) (35.8 ± 3.5 inches vs. 31.4 ± 3.2 inches, p < 0.001), and hip circumference (HC) (39.4 ± 3.6 inches vs. 35.7 ± 3.2 inches, p < 0.001) compared to those without MASLD. Additionally, 100% of the MASLD group had a BMI ≥30, while none of the non-MASLD group did (p < 0.001). Comorbidities such as impaired fasting glucose (IFG), diabetes (DM), dyslipidemia (DLP), and hypertension (HT) showed a trend towards higher incidence in the MASLD group compared to the non-MASLD group, although these differences did not reach statistical significance (IFG: 44.2% vs. 27.3%, p = 0.083; DM: 19.2% vs. 6.8%, p = 0.068; DLP: 46.2% vs. 36.4%, p = 0.331; HT: 34.6% vs. 20.5%, p = 0.121).

Regarding laboratory values, fasting blood sugar (FBS) was significantly higher in the MASLD group compared to the non-MASLD group (103.8 ± 25.5 mg/dL vs. 96.5 ± 9.4 mg/dL, p = 0.029). Triglyceride (TG) levels were also significantly higher in the MASLD group (158.7 ± 82.9 mg/dL vs. 121.3 ± 72.6 mg/dL, p = 0.010), and LDL cholesterol was significantly elevated in the MASLD group as well (118.8 ± 36.7 mg/dL vs. 107.0 ± 28.9 mg/dL, p = 0.041). However, there were no significant differences in AST, ALT, or HDL cholesterol between the two groups. Liver stiffness, as measured by transient elastography (TE), was significantly higher in the MASLD group (8.7 ± 7.8 kPa vs. 7.5 ± 8.6 kPa, p = 0.014). Additionally, the CAP score, indicating hepatic steatosis, was also significantly higher in the MASLD group (285 ± 36 dB/m vs. 195 ± 28 dB/m, p < 0.001).

Among the MASLD patients, the mean age was 49.7 ± 8.0 years, and 33 (63.5%) were male. The mean BMI was 25.8 ± 4.1 kg/m². Obesity, defined by WHO criteria for the Asia-Pacific region (BMI ≥ 30.0 kg/m²), was present in 9 (17.3%) patients. Dyslipidemia was the most common comorbidity, affecting 24 (46.2%) patients, followed by diabetes in 10 (19.2%) patients and hypertension in 18 (34.6%) patients. Regarding hepatitis virus coinfection, 5 (9.6%) patients had HBV and 7 (13.5%) had HCV. Additionally, two-thirds of the patients (67.3%) had a history of alcohol consumption. Baseline characteristics of the total cohort are shown in Table 2.

Regarding steatosis, the mean CAP was 285 ± 36 dB/m, and the median CAP was 276 (255, 303) dB/m. Among the patients, 16 (30.8%) had steatosis grade 1, 17 (32.7%) had grade 2, and 19 (36.5%) had grade 3. For liver fibrosis, the mean TE was 8.7 ± 7.8 kPa, and the median TE was 6.1 (5.2, 8.8) kPa. Significant fibrosis (F ≥2) was found in 24 patients (46.2%), advanced fibrosis (F ≥3) in 8 patients (15.4%), and cirrhosis (F ≥4) in 4 patients (7.7%).

Comparison of Patient Characteristics Between Fibrosis Grades 0-1 and ≥2

Patients with significant fibrosis (≥ F2) compared to those with fibrosis stage 0-1 had significantly higher BMI (27.1 ± 4.6 vs 24.7 ± 3.3 kg/m², p = 0.016), higher waist circumference (37.1 ± 3.4 vs 34.6 ± 3.3 inches, p = 0.004), and higher hip circumference (40.7 ± 3.7 vs 38.3 ± 3.2 inches, p = 0.008). These patients also had a higher prevalence of dyslipidemia (62.5% vs 32.1%, p = 0.029) and HCV co-infection (29.2% vs 0%, p = 0.002). Additionally, they exhibited higher AST levels (53.5 vs 28.2 U/L, p < 0.001), ALT levels (72.1 vs 37.9 U/L, p = 0.002), and globulin levels (3.5 ± 0.6 vs 3.3 ± 0.3 g/dL, p = 0.035). Furthermore, they had a lower platelet count (221 ± 88 vs 290 ± 84, p = 0.003) and lower HDL-cholesterol (41.4 ± 11.4 vs 48.3 ± 8.6 mg/dL, p = 0.008) (Table 2). However, no association was found between CAP grades and the degrees of liver fibrosis (p = 0.893).

Performance of Non-Invasive Tests in Predicting Significant Fibrosis

Patients with significant fibrosis had significantly higher levels of all non-invasive fibrosis tests, including the FIB-4 score (2.54 ± 3.89 vs 0.86 ± 0.32, p < 0.001), APRI

TABLE 1. Baseline characteristics of the entire cohort compared between MASLD and non- MASLD (n=96).

Variables	Total (n=96)	MASLD (n=52)	Non-MASLD (n=44)	p-value
Age (yr), mean ±SD	48.9±9.9	49.7±8.0	48.1±11.8	0.213
Sex Male, n(%)	68 (70.8%)	33(63.5%)	35 (79.5%)	0.081
BW (kg)	66.4±11.6	70.9±11.9	61.1±8.8	<0.001
BMI (kg/m^2)	23.9±4.2	25.8±4.1	21.6±3.0	<0.001
BMI ≥30, n(%)	9 (9.4%)	9 (100%)	0 (0%)	<0.001
WC (inch)	33.8±4.0	35.8±3.5	31.4±3.2	<0.001
HC (inch)	37.7±3.8	39.4±3.6	35.7±3.0	<0.001
IFG, n(%)	35 (36.5%)	23 (44.2%)	12 (27.3%)	0.083
T2DM, n(%)	13 (13.5%)	10 (19.2%)	3 (6.8%)	0.068
DLP, n(%)	40 (41.7%)	24 (46.2%)	16 (36.4%)	0.331
HT, n(%)	27 (28.1%)	18 (34.6%)	9 (20.5%)	0.121
HBV, n(%)	6 (6.3%)	5 (9.6%)	1 (2.3%)	0.120
HCV, n(%)	18 (18.8%)	7 (13.5%)	11 (25%)	0.149
Alcohol, n(%)	69 (71.9%)	35 (67.3%)	34 (77.3%)	0.521
Smoking, n(%)	37 (38.5%)	22 (42.3%)	15 (34.1%)	0.585
AST (U/L)	38.9±23.5	39.9±25.4	37.8±21.3	0.329
ALT (U/L)	49.6±42.5	53.7±43.2	44.8±41.7	0.155
ALP (U/L)	87.7±30.3	89.1±26.0	86.1±34.9	0.634
Albumin (g/dL)	4.3±0.4	4.3±0.3	4.2±0.4	0.638
Globulin (g/dL)	3.4±0.5	3.4±0.5	3.4±0.5	0.788
Hb (g/dL)	14.9±13.1	13.3±1.9	16.8±19.3	0.246
WBC (cell/µL)	6829±1957	7087±2264	6525±1487	0.149
Platelet (x10^9/µL)	251±85	258±92	243±77	0.387
Creatinine (mg/dL)	1.0±0.3	1.0±0.2	1.0±0.3	0.867
FBS (mg/dL)	100.5±20.1	103.8±25.5	96.5±9.4	0.029
TC (mg/dL)	183.0±37.8	188.9±40.9	176.0±32.9	0.045
TG (mg/dL)	141.5±80.2	158.7±82.9	121.3±72.6	0.010
HDL-chol (mg/dL)	45.7±10.4	45.1±10.5	46.3±10.3	0.581
LDL-chol (mg/dL)	113.4±33.7	118.8±36.7	107.0±28.9	0.041
CD4 (cell count)	640±269	679±269	595±264	0.125
ARV used, n(%)	96 (100%)	52 (100%)	44 (100%)	NA
CAP (dB/m)				
Mean ±SD	244±55	285±36	195±28	<0.001
Median (IQR)	246 (200,285)			
TE (kPa)				
Mean ±SD	8.1±8.2	8.7±7.8	7.5±8.6	0.014
Median (IQR)	5.8 (4.5,8.7)			

TABLE 2. Baseline characteristics compared between Fibrosis stage 0-1 and Fibrosis stage ≥2 of MASLD in PWLH (n=52).

Variables	Total (n=52)	Fibrosis stage F0-1 (n=28)	Fibrosis stage ≥2 (n=24)	p-value
Age (yr), mean ±SD	49.7±8.0	48.3±9.1	51.3±6.4	0.085
Male, n (%)	33 (63.5%)	17 (60.7%)	16 (66.7%)	0.775
BW (kg)	70.9±11.9	68.4±9.7	73.7±13.8	0.058
BMI (kg/m^2)	25.8±4.1	24.7±3.3	27.1±4.6	0.016
BMI ≥30, n (%)	9 (17.3%)	3 (10.7%)	6 (25.0%)	0.175
WC (inch)	35.8±3.5	34.6±3.3	37.1±3.4	0.004
HC (inch)	39.4±3.6	38.3±3.2	40.7±3.7	0.008
IFG, n (%)	23 (44.2%)	12 (42.9%)	11 (45.8%)	0.829
T2DM, n (%)	10 (19.2%)	7 (25.0%)	3 (12.5%)	0.254
DLP, n (%)	24 (46.2%)	9 (32.1%)	15 (62.5%)	0.029
HT, n (%)	18 (34.6%)	8 (28.6%)	10 (41.7%)	0.322
HBV, n (%)	5 (9.6%)	4 (14.3%)	1 (4.2%)	0.217
HCV, n (%)	7 (13.5%)	0 (0.0%)	7 (29.2%)	0.002
Alcohol, n (%)	35 (67.3%)	19 (67.9%)	16 (66.7%)	0.838
Smoking, n (%)	22 (42.3%)	15 (53.6%)	7 (29.2%)	0.184
Laboratory tests				
AST (U/L)	39.9±25.4	28.2±11.4	53.5±6.2	<0.001
ALT (U/L)	53.7±43.2	37.9±27.8	72.1±50.7	0.002
ALP (U/L)	89.1±26.0	88.6±25.1	89.7±27.6	0.445
Albumin (g/dL)	4.3±0.3	4.3±0.2	4.3±0.4	0.387
Globulin (g/dL)	3.4±0.4	3.3±0.3	3.5±0.6	0.035
Hb (g/dL)	13.3±1.9	13.6±2.1	13.1±1.6	0.152
WBC (cell/µL)	7087±2264	7496±2243	6608±2239	0.080
Platelet (x10^9/µL)	258±92	290±84	221±88	0.003
Creatinine (mg/dL)	1.02±0.24	1.0±0.2	1.1±0.3	0.056
FBS (mg/dL)	103.8±25.5	102.7±21.6	105.1±29.8	0.376
TC (mg/dL)	188.9±40.9	193.9±43.1	183.0±38.3	0.171
TG (mg/dL)	158.7±82.9	151.7±87.4	166.9±78.3	0.257
HDL-chol (mg/dL)	45.1±10.5	48.3±8.6	41.4±11.4	0.008
LDL-chol (mg/dL)	118.8±36.7	123.2±38.3	113.6±34.9	0.177

TABLE 2. Baseline characteristics compared between Fibrosis stage 0-1 and Fibrosis stage ≥2 of MASLD in PWLH (n=52). (Continue)

Variables	Total (n=52)	Fibrosis stage F0-1 (n=28)	Fibrosis stage ≥2 (n=24)	p-value
HIV parameters				
CD4 (cell count)	679±269	697±265	658±279	0.304
ARV used, n (%)	52 (100%)	28 (100%)	24 (100%)	NA
FibroScan® study				
CAP grade, n (%)				
1	16 (30.8%)	8 (28.6%)	8 (33.3%)	0.893
2	17 (32.7%)	9 (32.1%)	8 (33.3%)	
3	19 (36.5%)	11 (39.3%)	8 (33.3%)	
CAP (dB/m)				
Mean ±SD	285±36	291.9±41.5	276.5±25.5	0.054
Median (IQR)	276 (255,303)			
TE (kPa)				
Mean ±SD	8.7±7.8	5.1±0.8	12.8±10.1	<0.001
Median (IQR)	6.1 (5.2,8.8)			
Non-invasive fibrosis testing				
FIB-4 score				
Mean ±SD	1.64±2.75	0.86±0.32	2.54±3.89	<0.001
Median (IQR)	1.06 (0.71,1.58)			
APRI score				
Mean ±SD	0.54±0.68	0.27±0.15	0.87±0.89	<0.001
Median (IQR)	0.32 (0.20,0.63)			
NFS score				
Mean ±SD	-2.17±1.63	-2.78±1.24	-1.46±1.76	0.001
Median (IQR)	-2.30 (-3.30,-1.41)			

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; ARV, antiretroviral; BMI, body mass index; BW, body weight; CAP, controlled attenuation parameter; CD-4, cluster of differentiation 4; FBS, fasting blood sugar; DLP, dyslipidemia; FIB-4 score, fibrosis index based on 4 factors; IFG, impaired fasting glucose; IQR, interquartile range; Hb, hemoglobin; NFS, HBV, hepatitis B virus; HC, hip circumference; HCV, hepatitis C virus; HDL, high-density lipoprotein; HT, hypertension; LDL, low-density lipoprotein; NAFLD fibrosis score; SD, standard deviation; T2 DM, type 2 diabetes mellitus; TC, total cholesterol; TE, transient elastography; TG, triglyceride; WBC, white blood cell; WC, waist circumference.

score (0.87 ± 0.89 vs 0.27 ± 0.15, p < 0.001), and NFS score (-1.46 ± 1.76 vs -2.78 ± 1.24, p = 0.001), compared to those with fibrosis stage 0-1. Using transient elastography as the reference diagnostic test, we assessed the efficacy of different non-invasive tests. The areas under the receiver operating characteristic curves (AUROCs) for FIB-4, APRI, and NFS were 0.84, 0.85, and 0.76, respectively (Fig 1). Both FIB-4 and APRI demonstrated comparable and superior performance to NFS in predicting liver fibrosis among adults at risk, particularly in PLWH and those susceptible to MASLD.

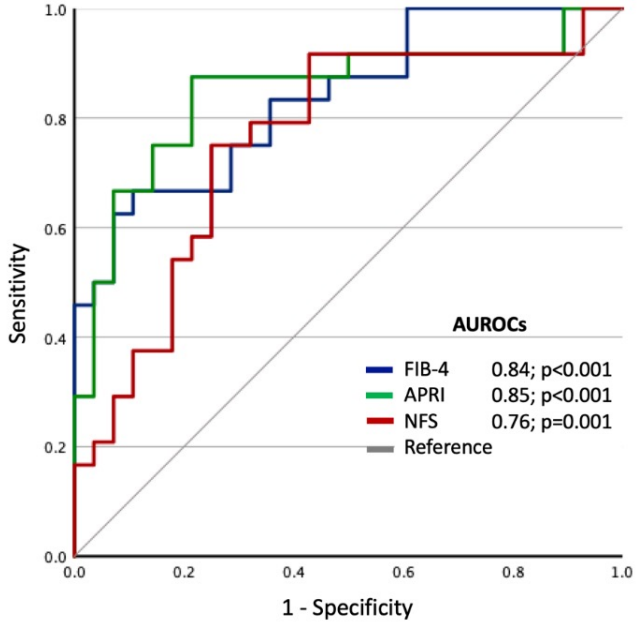


Fig 1. The AUROCs of the FIB-4 score, APRI score, and NFS score for predicting significant fibrosis (F≥2) in MASLD Patients with PLWH

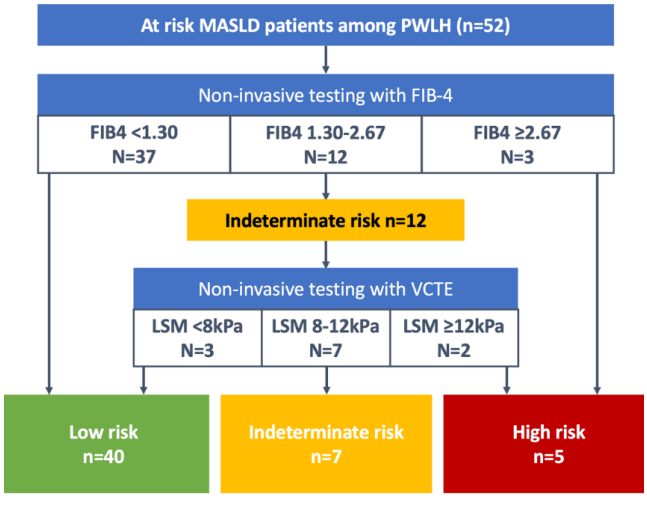


Fig 2. Implementation of a two-step approach involving non-invasive testing with FIB-4 and VCTE, as recommended by the American Gastroenterological Association (AGA) for MASLD in PLWH (n = 52).

Factors associated with significant fibrosis among MASLD with PLWH

Univariate analysis revealed several factors significantly associated with significant liver fibrosis: BMI (OR 1.17, p = 0.039), waist circumference (OR 1.28, p = 0.016), hip circumference (OR 1.24, p = 0.026), presence of dyslipidemia (OR 3.52, p = 0.031), AST levels (OR 1.08, p = 0.001), ALT levels (OR 1.03, p = 0.011), platelet count (OR 0.98, p = 0.017), and HDL-cholesterol level (OR 0.92, p = 0.024). After adjusting for age and sex in the multivariate analysis, higher BMI (aOR 1.24, p = 0.042), presence of dyslipidemia (aOR 3.96, p = 0.038), and elevated AST levels (aOR 1.19, p = 0.011) were independently associated with significant fibrosis (Table 3).

Two-Step Non-invasive Testing with FIB-4 Score and VCTE

To further enhance the accuracy of prediction, we analyzed the implementation of a two-step pathway using the FIB-4 score followed by TE, as recommended by the American Gastroenterological Association (AGA)[33], among PLWH with MASLD (n = 52). This approach improved risk reclassification for significant liver fibrosis, reducing the number of individuals at indeterminate risk from 12 out of 52 after the first step (FIB-4) to 7 out of 12 after the second step (VCTE), as illustrated in Fig 2. Consequently, among PLWH at risk for MASLD, patients were categorized into a low-risk group (40 patients, 76.9%), an indeterminate-risk group (7 patients, 13.5%), and a high-risk group (5 patients, 9.6%). This resulted in a reduced number of individuals in the indeterminate risk group, thereby minimizing the need for unnecessary liver biopsies.

DISCUSSION

In this analysis, the prevalence of MASLD among PLWH is notably high at 54.2%, comparable to rates observed in in Western countries.[3,4,8,9] Additionally, approximately half of these patients are experiencing significant fibrosis. With the improvement of healthcare in Thailand and the availability of ART, the burden of MASLD and significant fibrosis in this population is anticipated to become increasingly significant in the future. Therefore, targeted efforts to screen and diagnose MASLD in population are imperative.

Our study found that the MASLD group had significantly higher anthropometric measures (body weight, BMI, waist circumference, and hip circumference) and higher levels of triglycerides and LDL cholesterol, along with higher liver stiffness and hepatic steatosis,

TABLE 3. Univariate and multivariate logistic regression analysis of factors associated with significant fibrosis (F≥2) in MASLD among PLWH.

Variable	Univariate		Multivariate	
	OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
Age (years)	1.05 (0.98-1.13)	0.172		
Male gender	1.29 (0.42-4.04)	0.657		
BMI (kg/m^2)	1.17 (1.01-1.36)	0.039	1.24 (1.01-1.52)	0.042
BMI ≥30	2.78 (0.61-12.61)	0.186		
WC (inch)	1.28 (1.05-1.57)	0.016		
HC (inch)	1.24 (1.03-1.50)	0.026		
Presence of DM	1.13 (0.38-3.38)	0.829		
Presence of DLP	3.52 (1.12-11.06)	0.031	3.96 (1.08-14.50)	0.038
Presence of HT	1.79 (0.56-5.66)	0.325		
AST (U/L)	1.08 (1.03-1.14)	0.001	1.19 (1.04-1.35)	0.011
ALT (U/L)	1.03 (1.01-1.04)	0.011		
Globulin (g/dL)	3.83 (0.78-18.73)	0.098		
Platelet (x109/μL)	0.98 (0.98-0.99)	0.017		
Triglyceride (mg/dL)	1.00 (0.99-1.01)	0.509		
HDL-chol (mg/dL)	0.92 (0.87-0.99)	0.024		
LDL-chol (mg/dL)	0.99 (0.97-1.00)	0.350		
CAP (dB/m)	0.99 (0.97-1.01)	0.987		

compared to the non-MASLD group. Although trends in metabolic comorbidities such as IFG, DM, DLP, and HT were higher in the MASLD group, they did not reach statistical significance. These findings highlight the metabolic profile associated with MASLD and emphasize the importance of managing these metabolic risk factors to prevent disease progression.

As acknowledged, the reported prevalence is influenced by the chosen cut-off of CAP, and notably, the optimal cut-off in PLWH is not yet to be determined. While studies in this population suggest using a CAP of 248 dB/m as a cut-off for hepatic steatosis,[34,35] current practice guidelines for non-invasive tests recommend a cut-off of 275 dB/m, irrespective of HIV status.[34,36] However, our study employed an even lower cut-off of 238 dB/m, likely resulting in an overestimation of MASLD prevalence. Given the limited data for the Asian population, we opted for a lower cut-off CAP for use as a screening test to facilitate early detection, modification of risk factors, and adjustment of ART regimen to prevent liver complications.

In our study, we observed a lack of correlation between CAP and liver fibrosis. Several reasons contribute to this absence of direct correlation: 1) distinct pathological processes, as steatosis and fibrosis are separate yet often parallel occurrences; 2) variable progression rate, with liver diseases advancing at different rates in different individuals; 3) multiple factors influencing fibrosis, including inflammation, oxidative stress, and immune response, which may not be adequately captured by a marker primarily designed for fat content assessment; and 4) the heterogeneity of liver disease (e.g., non-alcoholic fatty liver disease, viral hepatitis, alcoholic liver disease, HIV infection), each potentially having

unique relationships between steatosis and fibrosis. While CAP may not predict liver fibrosis, it can serve as a valuable screening test, signaling the need for risk factor modification to prevent MASLD.

Characterizing PLWH based on MASLD, and liver fibrosis risk factors is crucial for identifying those at particular risk of developing advanced liver disease. In our study, significant MASLD and fibrosis were associated with high BMI, dyslipidemia, and a high level of AST, but not with HIV-related factors. These findings suggest that metabolic risk factors play a more substantial role in fibrosis development in PLWH, and targeted interventions such as weight management, diet modification, and exercise are crucial in preventing disease progression.

Overweight and obesity, as measured by BMI, is the main risk predictors for PLWH to develop fibrosis.[37] In contrast to the past, where HIV patients were often cachectic due to opportunistic infections and ineffective ART, today, with effective ART and increased treatment accessibility, people living with HIV can lead longer and healthier lives. The causes of weight gain are similar to metabolic syndrome population, and certain ART regimens, such as tenofovir-alafenamid and integrase strand transfer inhibitors, can contribute to weight gain.[10,38,39] Switching to tenofovir disoproxil fumarate has been independently associated with a lower risk of clinically significant weight gain, potentially slowing the development and progression of steatosis.[10] Therefore, it is crucial for HIV patients to focus on diet control, limit alcohol consumption, and engage in exercise to manage body weight. While metabolic factors such as BMI, dyslipidemia, and AST levels were found to be significant predictors of fibrosis in our study, we cannot overlook the potential influence of HIV-specific factors, such as viral load, CD4+ T-cell count, and the duration of HIV infection. These factors, which were not significant in our analysis, may still play a crucial role in liver disease progression among PLWH, and future studies should explore their impact further.

Dyslipidemia is a common concern in PLWH, attributed to specific antiretroviral medications, chronic inflammation, and immune activation associated with HIV infection.[40] Certain antiretroviral medications, especially protease inhibitors and some nucleoside reverse transcriptase inhibitors have been associated with increased level of TG and cholesterol.[41] Effective management of dyslipidemia in HIV population is important to reduce cardiovascular risk but presents multiple challenges due to interactions between ART agents and lipid-lowering medications. Optimal medical therapy, including lipid-lowering therapy and changing ART regimens, is vital for managing dyslipidemia and mitigating liver and cardiovascular risks.

While elevated AST levels were associated with hepatic steatosis and fibrosis in our study, it is important to recognize the limitations of using AST as a marker, as it lacks specificity for fibrosis. AST can be influenced by various factors, including ART-related mitochondrial injury, which could lead to overestimation of fibrosis severity.

Additionally, HIV and HBV or HCV coinfection or alcoholic consumption are additional predictors that warrant attention. HIV and viral hepatic coinfection promote hepatic injuries during MASLD through several mechanisms triggered by their persistent replication, enhanced inflammatory response and metabolic interference.[42] Although not proven as predictors of significant liver fibrosis in our study due to the small sample size, HIV patients are strongly encouraged to manage viral hepatitis coinfections and limit alcohol consumption to reduce liver damage. We included patients with hepatitis B and C in this study because these are common comorbidities in PLWH, reflecting real-world clinical practice. Excluding them could have compromised the statistical power of the study. Similarly, we examined the impact of alcohol consumption, which showed no significant association with fibrosis development in our cohort. However, this may be due to the limited sample size, and the influence of alcohol should still be carefully considered when managing MASLD in PLWH.

Early detection and prompt treatment are crucial to slowing progressions and preventing liver fibrosis and hepatic complications. Out study confirms the benefit of non-invasive fibrosis markers, particularly the FIB-4 score and APRI, which exhibited the highest AUROCs. These markers can serve as screening tests to alert HIV patients to the risk of liver fibrosis and prompt treatment. Combining different non-invasive assessments, such as FIB-4 or APRI score and VCTE, according to the AGA pathway of a two-step approach,[33] improves reclassification in the indeterminate group and reduces the need for unnecessary liver biopsy. It is essential to acknowledge that while liver biopsy remains the gold standard for assessing both steatosis and fibrosis, non-invasive methods are increasingly utilized due to their lower risk and greater patient acceptance. Although the AGA pathway is intended for advanced fibrosis, we adapted it for significant fibrosis due to the limited number of advanced fibrosis cases in our cohort. This adaptation allowed us to better capture the full spectrum of fibrosis in this population, but it will be acknowledged as a limitation. In addition to early detection, specific

clinical recommendations are essential. HIV patients should be counseled on lifestyle interventions such as diet modification, exercise, and alcohol reduction. Moreover, certain ART regimens associated with weight gain and dyslipidemia, such as integrase strand transfer inhibitors and tenofovir-alafenamide, should be re-evaluated. Switching to alternative regimens, such as tenofovir disoproxil fumarate, could mitigate some of the metabolic complications associated with MASLD progression.

This study has some limitations to acknowledge. First, the absence of liver biopsy data for correlation with TE findings is noteworthy. However, TE has demonstrated reasonable accuracy in estimating liver fibrosis and steatosis.[27,28] Second, the cross-sectional nature of this study, lacking a longitudinal design, prevent the provision of data on cumulative exposure to specific ART regimens, which could potentially influence the development of hepatic steatosis and fibrosis over time. Third, variations in the defined cut-offs for significant fibrosis and hepatic steatosis have a determining impact on overall results and observed associations. Our utilization of cut-offs at 238 dB/m, in contrast to the recommended 275 dB/m by the European Association for the Study of the Liver (EASL) guideline[36] for non-invasive tests, may have included patients with lesser degree of steatosis. Consequently, our results might not be directly comparable with other studies. Lastly, this study may not have comprehensively accounted for all confounding variables, such as herbs, medicines, and antioxidant supplements, as well as boarder factors like socioeconomic and concomitant treatment. Despite these limitations, our study underscores the importance of early detection and targeted interventions for MASLD in PLWH, especially in the context of rising metabolic comorbidities. Future studies should consider a prospective design, more stringent exclusion criteria, and a larger sample size to further validate these findings.

CONCLUSION

The prevalence of MASLD and significant fibrosis is notably high among PLWH. The predictors of significant fibrosis include higher BMI, dyslipidemia, and elevated AST levels. Additionally, fibrosis scoring systems exhibit good accuracy for fibrosis prediction. The integration of two-step approach involving a fibrosis scoring system and liver stiffness measurement has further improved the accuracy of prediction. To ascertain the effectiveness of this approach, future prospective longitudinal studies are warranted to identify early interventions and novel therapies within this population.

ACKNOWLEDGEMENTS

We would like to thank the healthcare professionals and the data acquisition team at Queen Savang Vadhana Memorial Hospital in Chonburi and King Chulalongkorn Memorial Hospital in Bangkok, Thailand, for their assistance in facilitating the survey and managing the demographic and laboratory data.

DECLARATION

Grants and Funding Information

This study was supported by the Fatty Liver Research Fund, Faculty of Medicine Foundation, Chulalongkorn University.

Conflict of Interest

All authors declare no conflicts of interest.

Author Contributions

T.P., S.T. - Conceptual design of the work; T.P., V.L., S.S., P.P., T.S., K.S., P.A., K.T., C.S., S.T. - Data collection and data acquisition; T.P. - Data analysis and interpretation; V.L., T.P. - Drafting the manuscript; S.T. - Critical revision of the manuscript; All authors - Final approval of the version to be published.

Use of Artificial Intelligence

No artificial intelligence tools or technologies were used in the writing, analysis, or development of this research.

Abbreviations

AGA: American Gastroenterological Association
ALT: Alanine aminotransferase
aOR: adjusted odd ratio
APRI: Aspartate aminotransferase to platelet ratio index
ART: Antiretroviral therapy
AST: Aspartate aminotransferase
AUROC: Areas under the receiver operating characteristic curves
BMI: Body mass index
CAP: Controlled attenuation parameter
F: Fibrosis
FIB-4: Fibrosis-4 score
HBV: Hepatitis B virus
HCV: Hepatitis C virus
HIV: Human immunodeficiency virus
LSM: Liver stiffness measurement
MASLD: Metabolic dysfunction-associated steatotic liver disease
NFS: Non-alcoholic fatty liver disease (NAFLD) fibrosis score

OR: odd ratio
PLWH: People living with HIV
S: Steatosis
VCTE: Vibration-controlled transient elastography

REFERENCES

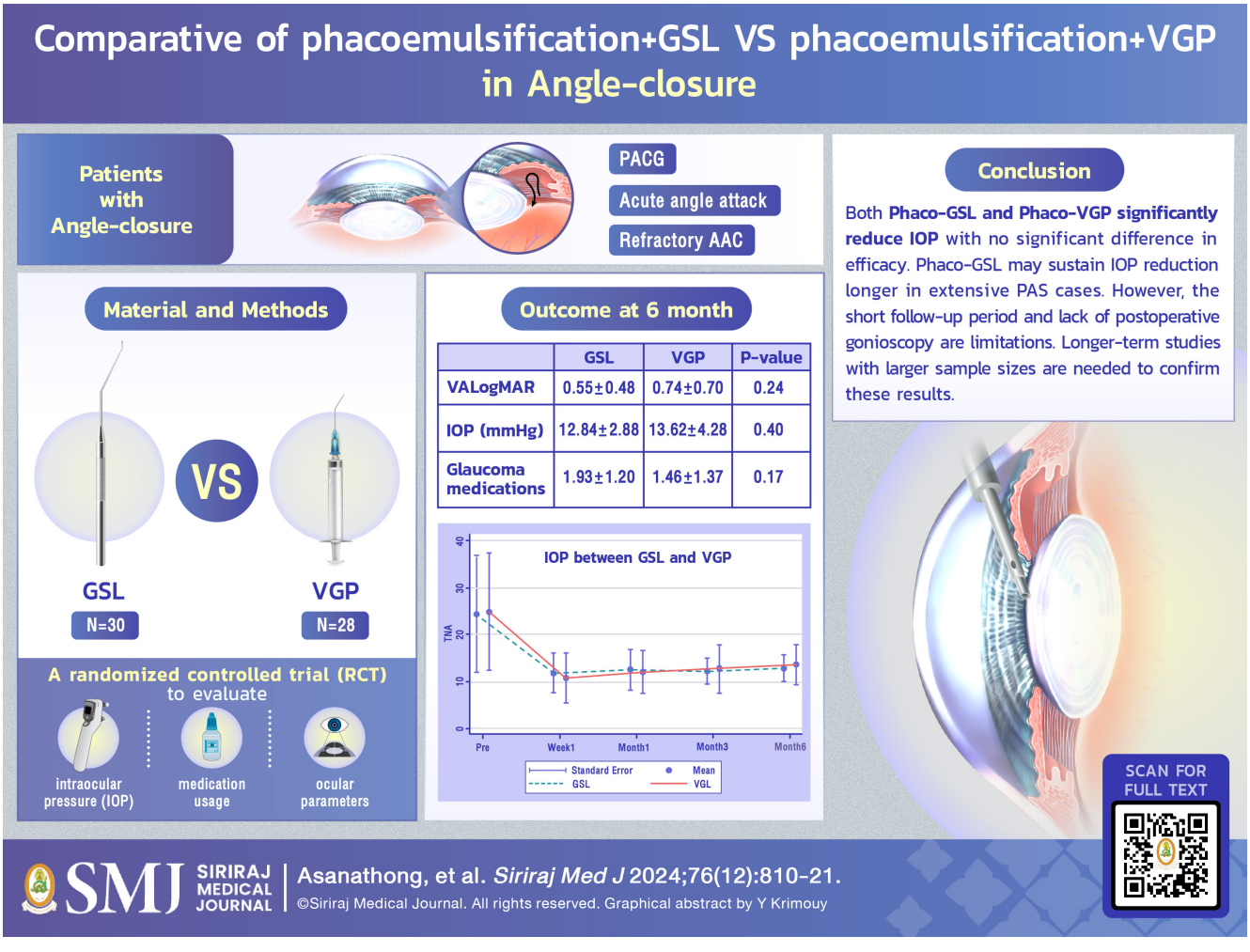
1. Teeraananchai S, Kerr S, Amin J, Ruxrungtham K, Law M. Life expectancy of HIV-positive people after starting combination antiretroviral therapy: a meta-analysis. HIV Med. 2017;18(4):256-66.
2. Teeraananchai S, Chaivooth S, Kerr SJ, Bhakeecheep S, Avihingsanon A, Teeraratkul A, et al. Life expectancy after initiation of combination antiretroviral therapy in Thailand. Antivir Ther. 2017;22(5):393-402.
3. Kalligeros M, Vassilopoulos A, Shehadeh F, Vassilopoulos S, Lazaridou I, Mylonakis E, et al. Prevalence and characteristics of nonalcoholic fatty liver disease and fibrosis in people living with HIV monoinfection: A systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2023;21(7):1708-22.
4. Macías J, González J, Tural C, Ortega-González E, Pulido F, Rubio R, et al. Prevalence and factors associated with liver steatosis as measured by transient elastography with controlled attenuation parameter in HIV-infected patients. AIDS. 2014;28(9):1279-87.
5. Michel M, Labenz C, Armandi A, Kaps L, Kremer WM, Galle PR, et al. Metabolic dysfunction-associated fatty liver disease in people living with HIV. Sci Rep. 2023;13(1):9158.
6. Paula AA, Falcão MC, Pacheco AG. Metabolic syndrome in HIV-infected individuals: underlying mechanisms and epidemiological aspects. AIDS Res Ther. 2013;10(1):32.
7. Seth A, Sherman KE. Fatty liver disease in persons with HIV infection. Top Antivir Med. 2019;27(2):75-82.
8. Maurice JB, Patel A, Scott AJ, Patel K, Thursz M, Lemoine M. Prevalence and risk factors of nonalcoholic fatty liver disease in HIV-monoinfection. AIDS. 2017;31(11):1621-32.
9. Michel M, Labenz C, Wahl A, Anders M, Armandi A, Huber Y, et al. Prevalence and risk factors of nonalcoholic steatohepatitis with significant fibrosis in people with HIV. AIDS. 2022;36(12):1665-74.
10. Bischoff J, Gu W, Schwarze-Zander C, Boesecke C, Wasmuth J-C, van Bremen K, et al. Stratifying the risk of NAFLD in patients with HIV under combination antiretroviral therapy (cART). EclinicalMedicine. 2021;40:101116.
11. Surial B, Mugglin C, Calmy A, Cavassini M, Günthard HF, Stöckle M, et al. Weight and metabolic changes after switching from tenofovir disoproxil fumarate to tenofovir alafenamide in people living with HIV. Ann Intern Med. 2021;174(6):758-67.
12. Riebensahm C, Berzigotti A, Surial B, Günthard HF, Tarr PE, Furrer H, et al. Factors associated with liver steatosis in people with human immunodeficiency virus on contemporary antiretroviral therapy. Open Forum Infect Dis. 2022;9(11):ofac538.
13. Simon TG, Roelstraete B, Sharma R, Khalili H, Hagström H, Ludvigsson JF. Cancer risk in patients with biopsy-confirmed nonalcoholic fatty liver disease: A population-based cohort study. Hepatology. 2021;74(5):2410-23.
14. Kim G-A, Jeong S, Jang H, Lee DH, Joo SK, Kim W. Metabolic dysfunction-associated steatotic liver disease and metabolic dysfunction-associated steatotic liver disease with increase alcohol intake increase the risk of developing hepatocellular carcinoma and incident or decompensated cirrhosis: a Korean nationwide study. Liver Cancer. 2023:1-12.
15. Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: Natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Med. 2011;43(8):617-49.
16. Boursier J, Hagström H, Ekstedt M, Moreau C, Bonacci M, Cure S, et al. Non-invasive tests accurately stratify patients with NAFLD based on their risk of liver-related events. J Hepatol. 2022;76(5):1013-20.
17. Younes R, Caviglia GP, Govaere O, Rosso C, Armandi A, Sanavia T, et al. Long-term outcomes and predictive ability of non-invasive scoring systems in patients with non-alcoholic fatty liver disease. J Hepatol. 2021;75(4):786-94.
18. Henry L, Eberly KE, Shah D, Kumar A, Younossi ZM. Noninvasive tests used in risk stratification of patients with nonalcoholic fatty liver disease. Clin Liver Dis. 2023;27(2):373-95.
19. Wattacheril JJ, Abdelmalek MF, Lim JK, Sanyal AJ. AGA Clinical practice update on the role of noninvasive biomarkers in the evaluation and management of nonalcoholic fatty liver disease: Expert review. Gastroenterology. 2023;165(4):1080-8.
20. Wong VW-S, Adams LA, de Lédinghen V, Wong GL-H, Sookoian S. Noninvasive biomarkers in NAFLD and NASH — current progress and future promise. Nat Rev Gastroenterol Hepatol. 2018;15(8):461-78.
21. Loomba R. Role of imaging-based biomarkers in NAFLD: Recent advances in clinical application and future research directions. J Hepatol. 2018;68(2):296-304.
22. Manzano-Nunez R, Rivera-Esteban J, Navarro J, Bañares J, Sena E, Schattenberg JM, et al. Uncovering the NAFLD burden in people living with HIV from high- and middle-income nations: a meta-analysis with a data gap from Subsaharan Africa. J Int AIDS Soc. 2023;26(3):e26072.
23. Wong VW-S, Ekstedt M, Wong GL-H, Hagström H. Changing epidemiology, global trends and implications for outcomes of NAFLD. J Hepatol. 2023;79(3):842-52.
24. Wang D, Xu Y, Zhu Z, Li Y, Li X, Li Y, et al. Changes in the global, regional, and national burdens of NAFLD from 1990 to 2019: A systematic analysis of the global burden of disease study 2019. Front Nutr. 2022;9:1047129.
25. Lui G, Wong VW -S, Wong GL -H, Chu WC -W, Wong C -K, Yung IMH, et al. Liver fibrosis and fatty liver in Asian HIV-infected patients. Aliment Pharmacol Ther. 2016;44(4):411-21.
26. Nishijima T, Gatanaga H, Shimbo T, Komatsu H, Nozaki Y, Nagata N, et al. Traditional but not HIV-related factors are associated with nonalcoholic fatty liver disease in Asian patients with HIV-1 infection. PLoS One. 2014;9(1):e87596.
27. Sasso M, Beaugrand M, de Ledinghen V, Douvin C, Marcellin P, Poupon R, et al. Controlled attenuation parameter (CAP): A novel VCTETM guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: Preliminary study and validation in a cohort of patients with chronic liver disease from various causes. Ultrasound Med Biol. 2010;36(11):1825-35.
28. Villani R, Lupo P, Sangineto M, Romano AD, Serviddio G. Liver ultrasound elastography in non-alcoholic fatty liver disease: A state-of-the-art summary. Diagnostics (Basel). 2023;13(7):1236.
29. Li Y, Chen Y, Zhao Y. The diagnostic value of the FIB-4 index for staging hepatitis B-related fibrosis: A meta-analysis. PLoS One. 2014;9(8):e105728.

30. De Matteis C, Cariello M, Graziano G, Battaglia S, Suppressa P, Piazzolla G, et al. AST to Platelet Ratio Index (APRI) is an easy-to-use predictor score for cardiovascular risk in metabolic subjects. Sci Rep. 2021;11(1):14834.
31. Treeprasertsuk S. NAFLD fibrosis score: A prognostic predictor for mortality and liver complications among NAFLD patients. World J Gastroenterol. 2013;19(8):1219-29.
32. Rinella ME, Lazarus J V, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Hepatology. 2023;78(6): 1966-86.
33. Kanwal F, Shubrook JH, Adams LA, Pfotenhauer K, Wai-Sun Wong V, Wright E, et al. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. Gastroenterology. 2021;161(5):1657-69.
34. Liu D, Shen Y, Zhang R, Xun J, Wang J, Liu L, et al. Prevalence and risk factors of metabolic associated fatty liver disease among people living with HIV in China. J Gastroenterol Hepatol. 2021;36(6):1670-8.
35. Jongraksak T, Sobhonslidsuk A, Jatchavala J, Warodomwichit D, Kaewduang P, Sungkanuparph S. Prevalence and predicting factors of metabolic-associated fatty liver disease diagnosed by transient elastography with controlled attenuation parameters in HIV-positive people. Int J STD AIDS. 2021;32(3):266-75.
36. Berzigotti A, Tsochatzis E, Boursier J, Castera L, Cazzagon N, Friedrich-Rust M, et al. EASL Clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis – 2021 update. J Hepatol. 2021;75(3):659-89.
37. Chandiwana NC, Siedner MJ, Marconi VC, Hill A, Ali MK, Batterham RL, et al. Weight gain after HIV therapy initiation: Pathophysiology and implications. J Clin Endocrinol Metab. 2024;109(2):e478-e87.
38. Sax PE, Erlandson KM, Lake JE, Mccomsey GA, Orkin C, Esser S, et al. Weight gain following initiation of antiretroviral therapy: Risk factors in randomized comparative clinical trials. Clin Infect Dis. 2020;71(6):1379-89.
39. Bares SH, Wu X, Tassiopoulos K, Lake JE, Koletar SL, Kalayjian R, et al. Weight gain after antiretroviral therapy initiation and subsequent risk of metabolic and cardiovascular disease. Clin Infect Dis. 2023;78(2):395-401.
40. Sugden M, Holness M. Management of dyslipidemia in HIV-infected patients. Clini Lipidol. 2011;6(4):447-62.
41. Calza L. Dyslipidaemia associated with antiretroviral therapy in HIV-infected patients. J Antimicrob Chemother. 2004;53(1): 10-14.
42. Iacob SA, Iacob DG. Non-alcoholic fatty liver disease in HIV/HBV patients – a metabolic imbalance aggravated by antiretroviral therapy and perpetuated by the hepatokine/adipokine axis breakdown. Front Endocrinol. 2022;13:814209.

Comparative Evaluation of Phacoemulsification with Goniosynechialysis and Phacoemulsification with Viscogonioplasty in Angle-Closure: A Randomized Clinical Trial

Dechathon Asanathong, M.D.

Department of Ophthalmology, Sisaket Hospital, Sisaket, Thailand.



*Corresponding author: Dechathon Asanathong
E-mail: dr.deacha@gmail.com
Received 1 September 2024 Revised 27 October 2024 Accepted 27 October 2024
ORCID ID:http://orcid.org/0009-0005-4091-3896
https://doi.org/10.33192/smj.v76i12.270908

ABSTRACT

Objective: To compare the effects of phacoemulsification with goniosynechialysis (GSL) versus viscogonioplasty (VGP) on intraocular pressure (IOP) reduction and medication use in angle-closure patients.

Materials and Methods: This randomized controlled trial at Sisaket Hospital, Thailand, from November 2021 to May 2024, enrolled patients with angle-closure and cataracts. Group 1 underwent phacoemulsification with GSL, and Group 2 with VGP. Visual acuity, IOP, and medication use were assessed before surgery, then at 1 week, 1 month, 3 months, and 6 months post-surgery.

Results: 58 eyes were included: 30 in Group 1 and 28 in Group 2. The average age was 67.16±9.65 years in Group 1 and 67.78±7.38 years in Group 2 (P=0.79). Baseline IOP was 24.31±12.34 mmHg in Group 1 and 24.92±12.50 mmHg in Group 2 (P=0.85). After 6 months, IOP decreased to 12.84±2.88 mmHg in Group 1 and 13.62±4.28 mmHg in Group 2 (P=0.40). Glaucoma medications decreased from 3.47±0.94 to 1.93±1.20 in Group 1 and from 3.54±0.58 to 1.46±1.37 in Group 2 (P=0.17). Hazard ratio: 4.29 (P=0.066, 95% CI: 0.91–20.18).

Conclusion: Both Phaco-GSL and Phaco-VGP significantly reduce IOP, with no significant difference in efficacy. Phaco-GSL may sustain IOP reduction longer in extensive PAS cases. However, the short follow-up period and lack of postoperative gonioscopy are limitations. Longer-term studies with larger sample sizes are needed to confirm these results.

Keywords: Phacoemulsification; goniosynechialysis; viscogonioplasty; angle-closure; primary angle-closure glaucoma
(Siriraj Med J 2024; 76: 810-821)

INTRODUCTION

Angle-closure is a disorder characterized by the presence of iridotrabecular contact (ITC), which can be either appositional or synechia.[1] This contact leads to the blockage of the aqueous drainage system of the anterior chamber, increasing intraocular pressure (IOP). ITC plays a significant role in the progression of various ocular diseases. Primary angle-closure glaucoma (PACG) is a condition where ITC causes a progressive increase in IOP, extensive peripheral anterior synechiae (PAS), and optic nerve damage. Acute angle closure (AAC) is a condition marked by the sudden onset of increased IOP, causing severe eye pain in patients. Several mechanisms are responsible for angle closure, including pupillary block, plateau iris, and lens-related factors.[2-5] These mechanisms contribute to ITC and lead to blockage of the aqueous drainage system. Secondary angle-closure glaucoma may involve other mechanisms, which are not included in this study.[6] The prevalence of angle closure increases with age.[7,8] The increasing thickness of the lens with age[9] may cause the presence of ITC and the extensive formation of synechiae. Cataract extraction can deepen the anterior chamber and open the iridotrabecular angle,[10-12] reducing IOP after phacoemulsification.[13-15] However, in some cases, the iridotrabecular angle does not widen, and the IOP does not decrease after cataract surgery, possibly due to the persistence of PAS. By breaking PAS and separating the iris from the trabecular meshwork, the anterior chamber drainage system may function more effectively, resulting in a decrease in IOP.[16-28]

Goniosynechialysis (GSL) is a glaucoma procedure that breaks PAS and ITC under direct visualization with a gonio lens. This procedure involves separating the iris from the angle using a spatula[21] to restore trabecular function and decrease IOP.[2,16-22] GSL is usually combined with cataract surgery, referred to as Phaco-GSL. Viscogonioplasty (VGP) is a similar procedure to GSL, but instead of using a spatula, VGP employs heavy viscoelastic[23-26] to separate the iris from the angle. Similar effects on decreasing IOP have been observed with VGP.[23-26] Many studies have compared the effects of Phaco-GSL with phacoemulsification alone and Phaco-VGP with phacoemulsification alone. However, few studies directly compare Phaco-GSL with Phaco-VGP.

Phaco-GSL and Phaco-VGP are widely utilized globally, particularly in Southeast Asia and China, where the prevalence of PACG is significantly higher in the Asian population[8] compared to other regions. This higher prevalence is due to anatomical predispositions,[27] such as shallower anterior chambers, thicker lens size, and narrower angles commonly seen in Asian eyes. In these regions, PACG represents a substantial public health concern, accounting for a significant portion of glaucoma-related blindness. As a result, surgical approaches like Phaco-GSL and Phaco-VGP are increasingly favored

as effective treatment options to address both cataracts and angle closure in a single procedure.

This randomized clinical trial compares the effects of combined phacoemulsification and GSL versus combined phacoemulsification and VGP on IOP, anterior segment parameters, and complications in angle closure.

MATERIALS AND METHODS

This prospective randomized clinical trial was conducted at Sisaket Hospital in Sisaket, Thailand. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Sisaket Hospital Research Ethical Committee REC No 094/2564, COA No.031. The trial was registered with the Thai Clinical Trials Registry (TCTR20240805005). Patients visiting the Ophthalmology Department, Glaucoma clinic, Sisaket Hospital, Thailand, from November 2021 to May 2024 were enrolled in the study.

The inclusion criteria were as follows: 1) patients with angle closure defined by the presence of ITC of at least 180 degrees, which can be either appositional or synechial; 2) patients with visually significant cataract with visual acuity (VA) worse than 20/50. The exclusion criteria were: 1) presence or history of any cause of secondary glaucoma, including traumatic glaucoma, uveitic glaucoma, neovascular glaucoma, phacomorphic glaucoma, and pseudo-exfoliation glaucoma; 2) history of previous intraocular surgery.

Examinations included VA assessment using the Snellen chart, IOP measurement with the ICare ic200 (Icare Finland Oy, Helsinki, Finland), slit lamp and fundus examination, and gonioscopy. A single glaucoma specialist performed all examinations and evaluations. Baseline clinical characteristics and demographic data were collected, including the history of anti-glaucoma medication use before the operation. Anterior segment optical coherence tomography (AS-OCT) (Cirrus 5000; anterior segment premier module; Carl Zeiss Meditec) collected the anterior segment parameters. Examination was done pre-operation and 1 week, 1 month, 3 months, and 6 months after surgery.

Gonioscopy was performed using a four-mirror gonio lens (Model G-4, Volk Optical). A narrow beam of the slit lamp was used to examine all quadrants in the primary position. Indentation of the gonio lens against the cornea was conducted to investigate the iridotrabecular angle. The angle was graded based on the presence of an ITC of at least 180 degrees.

AS-OCT was performed under dim lighting by a single technician. Scans were centered on the pupil and obtained along the horizontal axis using the anterior segment premier module protocol. The image of the best quality was selected for analysis. A single glaucoma specialist performed measurements. Anterior segment parameters were obtained, including central corneal thickness (CCT) and anterior chamber depth (ACD), defined as the distance from the endothelium to the anterior surface of the crystalline lens or the pupillary plane in pseudophakic eyes. Lens vault (LV) was defined as the perpendicular distance between the anterior lens surface and the horizontal line connecting the two scleral spurs. Angle parameters measured included the angle opening distance (AOD), trabecular-iris space area (TISA) at 500 μm and 750 μm from the scleral spur, and scleral spur angle (SSA) in the nasal and temporal quadrants. The means of the nasal and temporal AOD, TISA, and SSA were used. If the image of the angle parameters in the nasal or temporal quadrant was unclear, the data were excluded from the analysis. AS-OCT was done pre-operative and three months after the operation.

Randomization of subjects and sample size

The sample size was calculated using the method for randomized controlled trials involving continuous data as outlined by Bernard R. The calculation was based on the following parameters: the mean in the treatment group was 9 (from Moghimi et al.[23]) with a standard deviation (SD) of 4, while the mean in the control group was 12 (from Tekhasaenee et al.[2]) with an SD of 4. With an alpha level of 0.05, a beta level of 0.2, and a ratio of 1, the required sample size was determined to be 28 patients in each group. Accounting for an anticipated 20% dropout rate, the final sample size was adjusted to 34 patients in each group. Patients were randomized into two groups using block randomization to receive either phacoemulsification with GSL (Phaco-GSL) or phacoemulsification with VGP (Phaco-VGP).

Surgical technique

A single glaucoma specialist surgeon performed all surgeries. Both procedures were conducted under local anesthesia with a retrobulbar block. The periocular skin was prepared with a povidone-iodine solution, and a 10% povidone-iodine solution was used to irrigate the conjunctival sac. The area was draped using a Steri-Drape, and an eye speculum was applied. Phacoemulsification was performed with two side-port incisions and a 27 mm temporal clear corneal incision. The Phaco-chop technique was used, and an intraocular lens was implanted in the bag. Cohesive viscoelastic (Visiol, TRB CHEMEDICA, Geneva, Switzerland) was utilized during the procedure. A phacoemulsification machine (Centurion; Alcon

Laboratories Inc., Fort Worth, TX) was used in all cases. Postoperatively, topical antibiotics and steroids were prescribed to all patients, with the steroids tapered off over four weeks.

In the Phaco-GSL group, after inserting the intraocular lens (IOL), viscoelastic was filled in the anterior chamber and the angle area. A 27G cannula of viscoelastic was inserted through the main port. Under direct gonioscopic visualization using the Mori upright surgical gonio lens (Ocular Instruments, Inc., Bellevue, WA, USA), the PAS was gently released through the main port, accessing approximately 270 degrees of the angle.

In the Phaco-VGP group, viscoelastic was filled in the anterior chamber like the Phaco-GSL group after IOL implantation. Under direct gonioscopic visualization, a 27G viscoelastic cannula was inserted through the main port to the angle. Viscoelastic was then injected to fill the angle until the separation of the PAS was observed, covering approximately 270 degrees in the superior, nasal, and inferior quadrants, similar to the Phaco-GSL group. No surgical instruments were used to break the PAS physically.

Statistical analysis

Statistical analysis was performed using STATA software (StataCorp LP, College Station, TX, USA). Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as frequency and percentage. Paired t-tests were used to compare IOP, ocular parameters, and the average number of types of glaucoma medications before and after surgery. Kaplan-Meier survival curves were used to compare the success rates between Phaco-GSL and Phaco-VGP over the follow-up period, with a target IOP of 21 mmHg. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 68 eyes were recruited for the study. After excluding patients lost to follow-up, we evaluated 58 eyes. However, there was missing data for certain ocular parameters, including LV, AOD500, AOD750, TISA500, TISA750, and SSA, due to poor image clarity. This affected 3 cases in the Phaco-GSL group and 4 cases in the Phaco-VGP group. There were 30 in Group 1 (Phaco-GSL group) and 28 in Group 2 (Phaco-VGP group). The mean age of patients was 67.16±9.65 years in Group 1 and 67.78±7.38 years in Group 2 (P = 0.79). The mean baseline IOP was 24.31±12.34 mmHg in Group 1 and 24.92±12.50 in Group 2 (P = 0.85). The mean of cup-disc ratio was 0.71±0.22 in Group 1 and 0.77±0.21 in Group 2 (P=0.28). The average number of glaucoma medications was 3.47±0.94 in Group 1 and 3.54±0.58 in Group 2 (P = 0.74). The details of demographic data and ocular parameters are summarized in Table 1.

When considering the division of patients based on diagnosis, they can be divided into three groups as follows: 1) PACG, 2) Post-acute angle closure attack group (Post AAC), and 3) Refractory angle closure attack group (Refractory AAC).

In the PACG group, there were 20 eyes in Group 1 and 17 in Group 2. The mean age of patients was 54.25±15.78 years in Group 1 and 68.88±6.34 years in Group 2 (P = 0.63). The mean baseline IOP was 19.77±7.46 mmHg in Group 1 and 22.39±9.80 mmHg in Group 2 (P = 0.36). The mean cup-disc ratio was 0.73±0.20 in Group 1 and 0.82±0.16 in Group 2 (P = 0.13). The average number of glaucoma medications was 3.20±1.01 in Group 1 and 3.35±0.61 in Group 2 (P = 0.59).

In the Post AAC group, there were 4 eyes in Group 1 and 6 in Group 2. The mean age of patients was 70.00±7.30 years in Group 1 and 69.17±5.91 years in Group 2 (P = 0.06). The mean baseline IOP was 17.25±6.65 mmHg in Group 1 and 18.20±8.44 mmHg in Group 2 (P = 0.86). The mean cup-disc ratio was 0.58±0.32 in Group 1 and 0.72±0.33 in Group 2 (P = 0.51). The average number of glaucoma medications was 4.00±0 in Group 1 and 3.67±0.52 in Group 2 (P = 0.24).

In the Refractory AAC group, there were 6 eyes in Group 1 and 5 in Group 2. The mean age of patients was 66.33±4.76 years in Group 1 and 62.40±10.88 years in Group 2 (P = 0.44). The mean baseline IOP was 44.17±7.03 mmHg in Group 1 and 41.60±11.76 mmHg in Group 2 (P = 0.66). The mean cup-disc ratio was 0.73±0.20 in Group 1 and 0.66±0.23 in Group 2 (P = 0.58). The average number of glaucoma medications was 4.00±0 in Group 1 and 4.00±0 in Group 2 (P = 1.00).

There is a significant decrease in IOP after surgery, with an 11.47±2.34 mmHg reduction in the Phaco-GSL group at 6 months compared to preoperative (P<0.001) and an 11.29±2.50 mmHg reduction in the Phaco-VGP group at 6 months compared to preoperative (P<0.001). In both groups, a significant decrease in IOP from baseline was observed, but no significant difference between the two groups was found. The reduction in IOP at 6 months was 12.84±2.88 mmHg in group 1 and 13.62±4.28 mmHg in group 2 (P=0.40). When considering the diagnosis, there was a more significant decrease in IOP in Refractory AAC compared to other PACG and Post AAC in both the Phaco-GSL and Phaco-VGP groups. However, when comparing the two groups, they were equally effective: in PACG, Group 1 had a reduction

TABLE 1. Demographic data and Ocular parameters.

	GSL	VGP	P-value
Number of eyes	30	28	
Age	67.16±9.65	67.78±7.38	0.79
Sex			0.55
Male	8	10	
Female	22	18	
Cup-Disc ratio	0.71±0.22	0.77±0.21	0.28
VA LogMAR	0.98±0.50	1.39±0.57	0.005
IOP (mmHg)	24.31±12.34	24.92±12.50	0.85
Types of glaucoma medications	3.47±0.94	3.54±0.58	0.74
Diagnosis			0.67
PACG	20	17	
Post AAC	4	6	
Refractory AAC	6	5	
CCT (μm)	523.53±39.65	520.15±42.89	0.76
ACD (mm)	1.96±0.36	1.88±0.43	0.45
LV (μm)	775.57±280.06	801.19±211.66	0.70
AOD500 (mm)	0.155±0.9	0.165±0.11	0.73
AOD750 (mm)	0.249±0.11	0.265±0.17	0.69
TISA500 (mm^2)	0.060±0.40	0.070±0.74	0.56
TISA750 (mm^2)	0.141±0.17	0.111±0.74	0.43
SSA (degree)	16.85±8.80	17.13±11.04	0.92
PACG			
Number of eyes	20	17	
Age	70.00±7.30	68.88±6.34	0.63
Cup-Disc ratio	0.73±0.20	0.82±0.16	0.13
VA LogMAR	0.90±0.33	1.40±0.52	0.001
IOP (mmHg)	19.77±7.46	22.39±9.80	0.36
Types of glaucoma medications	3.20±1.01	3.35±0.61	0.59
CCT (μm)	518.15±38.20	511.31±29.04	0.56
ACD (mm)	2.09±0.37	2.03±0.48	0.65
LV (μm)	747.35±271.00	771.69±246.51	0.78
AOD500 (mm)	0.188±0.09	0.198±0.11	0.78
AOD750 (mm)	0.274±0.10	0.316±0.17	0.39
TISA500 (mm^2)	0.074±0.04	0.089±0.04	0.54
TISA750 (mm^2)	0.177±0.21	0.133±0.07	0.46
SSA (degree)	20.19±8.28	20.29±10.81	0.98

TABLE 1. Demographic data and Ocular parameters. (Continue)

	GSL	VGP	P-value
Post AAC			
Number of eyes	4	6	
Age	54.25±15.78	69.17±5.91	0.06
Cup-Disc ratio	0.58±0.32	0.72±0.33	0.51
VA LogMAR	0.70±0.22	12.27±0.64	0.13
IOP (mmHg)	17.25±6.65	18.20±8.44	0.86
Types of glaucoma medications	4.00±0	3.67±0.52	0.24
CCT (μm)	504.25±19.96	536.4±82.70	0.48
ACD (mm)	1.72±0.08	1.67±0.28	0.74
LV (μm)	1005.75±294.65	892.8±116.02	0.45
AOD500 (mm)	0.110±0.06	0.108±0.10	0.96
AOD750 (mm)	0.230±0.12	0.206±0.13	0.78
TISA500 (mm^2)	0.039±0.02	0.041±0.38	0.91
TISA750 (mm^2)	0.085±0.04	0.081±0.07	0.91
SSA (degree)	12.63±6.57	11.6±10.41	0.87
Refractory AAC			
Number of eyes	6	5	
Age	66.33±4.76	62.40±10.88	0.44
Cup-Disc ratio	0.73±0.20	0.66±0.23	0.58
VA LogMAR	1.46±0.80	1.49±0.79	0.95
IOP (mmHg)0	44.17±7.03	41.60±11.76	0.66
Types of glaucoma medications	4.00±0.63	4.00±0.00	1.00
CCT (μm)	554.33±42.20	532.20±25.90	0.34
ACD (mm)	1.70±0.12	1.64±0.09	0.41
LV (μm)	716.17±271.68	804.00±157.10	0.54
AOD500 (mm)	0.072±0.38	0.130±0.12	0.31
AOD750 (mm)	0.173±0.95	0.178±0.17	0.95
TISA500 (mm^2)	0.026±0.11	0.045±0.04	0.36
TISA750 (mm^2)	0.057±0.02	0.077±0.08	0.60
SSA (degree)	8.2±4.10	13.8±11.18	0.32

of 12.83±3.30 mmHg, and Group 2 had a decrease of 14.54±4.93 mmHg (P=0.22); in Post AAC, Group 1 had a decline of 11.65±1.70 mmHg and Group 2 had a reduction of 12.41±3.14 mmHg (P=0.67); and in Refractory AAC, Group 1 had a decrease of 13.67±1.75 mmHg and Group 2 had a decline of 12.00±2.23 mmHg (P=0.20), as shown in Table 2 and Fig 1.

At 6 months postoperatively, we found that 100% (30/30) of eyes in Group 1 had an IOP of less than 21 mmHg, with a 47.18% reduction in IOP, and 100% (28/28) of eyes in Group 2 had an IOP of less than 21 mmHg, with a 45.35% reduction in IOP, both with the use of glaucoma medications.

At the 6 months of follow-up, there was a significant decrease in the number of glaucoma medications, with a reduction of 1.54±0.28 in Group 1 (P<0.001) and 2.08±0.28 in Group 2 (P<0.001). In both groups, a significant decrease in glaucoma medication was observed, but no significant difference was found between the two groups. When comparing the two groups based on diagnosis, they were equally effective in decreasing the types of glaucoma medication: in PACG, Group 1 had a reduction of 1.95±1.28 and Group 2 had a decrease of 1.76±1.39 (P=0.68); in Post AAC, Group 1 had a reduction of 1.50±1.00 and Group 2 had a decline of 1.00±1.26 (P=0.53); and in Refractory AAC, Group 1 had a decrease of 2.17±1.17 and Group 2 had a reduction of 1.00±1.41 (P=0.17).

Significant widening of ocular parameters (ACD, LV, AOD500, AOD750, TISA500, TISA750, SSA) was

TABLE 2. Ocular parameters after surgery.

Overall (Angle closure)	GSL	VGP	P-value
VA LogMAR	0.55±0.48	0.74±0.70	0.24
IOP (mmHg)	12.84±2.88	13.62±4.28	0.40
Types of glaucoma medications	1.93±1.20	1.46±1.37	0.17
ACD (mm)	3.27±0.30	3.21±0.27	0.41
LV (μm)	-477.73±157.05	-474.80±188.87	0.95
AOD500 (mm)	0.307±0.09	0.280±0.10	0.32
AOD750 (mm)	0.483±0.13	0.470±0.17	0.76
TISA500 (mm^2)	0.109±0.04	0.126±0.16	0.59
TISA750 (mm^2)	0.208±0.05	0.190±0.07	0.34
SSA (degree)	30.81±7.13	28.30±9.02	0.27
PACG			
VA LogMAR	0.41±0.23	0.63±0.66	0.16
IOP (mmHg)	12.83±3.30	14.54±4.93	0.22
Types of glaucoma medications	1.95±1.28	1.76±1.39	0.68
ACD (mm)	3.27±0.28	3.19±0.29	0.45
LV (μm)	-432.80±127.76	-420.07±172.32	0.80
AOD500 (mm)	0.319±0.09	0.320±0.09	0.98
AOD750 (mm)	0.455±0.12	0.520±0.13	0.16
TISA500 (mm^2)	0.115±0.04	0.164±0.20	0.31
TISA750 (mm^2)	0.206±0.05	0.217±0.07	0.64
SSA (degree)	31.91±6.80	31.86±7.37	0.98

TABLE 2. Ocular parameters after surgery. (Continue)

Overall (Angle closure)	GSL	VGP	P-value
Post AAC			
VA LogMAR	0.56±0.40	1.08±0.99	0.35
IOP (mmHg)	11.65±1.70	12.41±3.14	0.67
Types of glaucoma medications	1.50±1.00	1.00±1.26	0.53
ACD (mm)	3.44±0.25	3.26±0.23	0.29
LV (μm)	-547.50±246.90	-521.20±183.60	0.86
AOD500 (mm)	0.233±0.05	0.213±0.08	0.66
AOD750 (mm)	0.520±0.13	0.352±0.16	0.12
TISA500 (mm^2)	0.080±0.02	0.070±0.02	0.52
TISA750 (mm^2)	0.205±0.05	0.144±0.05	0.12
SSA (degree)	24.88±4.62	22.70±7.73	0.64
Refractory AAC			
VA LogMAR	1.03±0.86	0.68±0.31	0.41
IOP (mmHg)0	13.67±1.75	12.00±2.23	0.20
Types of glaucoma medications	2.17±1.17	1.00±1.41	0.17
ACD (mm)	3.19±0.42	3.20±0.28	0.93
LV (μm)	-581.00±140.35	-592.60±212.40	0.91
AOD500 (mm)	0.322±0.11	0.234±0.12	0.27
AOD750 (mm)	0.552±0.13	0.449±0.25	0.43
TISA500 (mm^2)	0.11±0.04	0.08±0.04	0.20
TISA750 (mm^2)	0.214±0.06	0.165±0.08	0.30
SSA (degree)	31.6±8.76	23.9±11.13	0.26

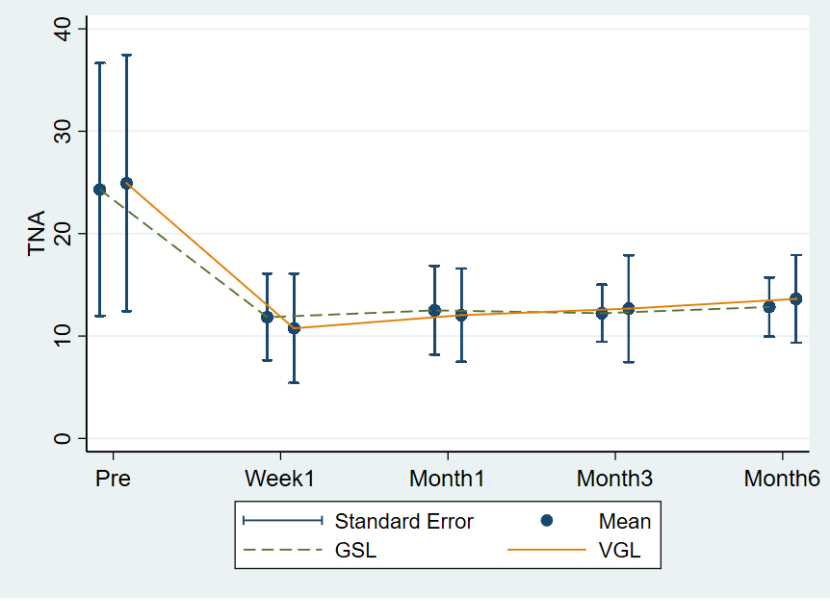


Fig 1. Shows the IOP between the Phaco-GSL and the Phaco-VGP groups.

observed in both groups at the 3 months compared to pre-operation. However, the difference between the two groups was not significant.

Surgical safety was assessed, and all patients were evaluated for complications. Three cases of hyphema were found: two in the Phaco-GSL group and one in the Phaco-VGP group. One case of Toxic anterior segment syndrome (TASS) was found in the Phaco-GSL group. No other complications were found in either group.

Fig 2 presents Kaplan-Meier survival curves for a success rate defined as an IOP of 21 mmHg or less after surgery. The hazard ratio was 4.29, with a P-value of 0.066 and a 95% confidence interval (CI) of 0.91 to 20.18.

DISCUSSION

GSL and VGP are commonly used procedures to separate ITC. The role of GSL in angle closure, such as PACG and AAC, has been well described in many studies,[2,16-21] while the role of VGP has been described in fewer studies.[21-24] However, there are limited comparative studies between phacoemulsification with GSL and phacoemulsification with VGP.

In our study, the mean age was not significantly different between the two groups, similar to the findings of Wanichwecharungruang et al.,[18] Eslami et al.,[25] and Moghimi et al.[26] However, the mean age in our study was higher compared to that reported by Teekhasaenee et al.[2] (59.6±10.6 years) and Angmo et al.[22] (57.50±9.17 years). The VA showed significant differences between the groups preoperatively, likely due to differences in cataract severity. However, after phacoemulsification and intraocular lens implantation, VA improved, and there was no significant difference between the groups (P=0.24). The mean baseline IOP was not significantly different between the two groups (P=0.85) and significantly improved in both groups postoperatively. Our results in the Phaco-GSL group are consistent with other studies, as indicated in Table 3. Additionally, our findings in the Phaco-VGP group show similar postoperative IOP at 6 months. Our baseline use of glaucoma medications was similar to that reported by Angmo et al.,[22] but higher than in other studies.[2,18,20,24-26] Similarly, our postoperative use of glaucoma medications was comparable to that of Angmo et al.[21] and remained higher than in other studies.[2,18,20,24-26]

When comparing the success rate, which targeted IOP at last follow up less than 21 mmHg. In Group 1, our results compare favorably to Teekhasaenee et al.,[2] who reported 90.4% (47/52) success without medications. Our results are comparable to Husain et al.,[20] who achieved a target pressure of 21 mmHg with a 92.1% success rate, and to Angmo et al.,[22] who reported a 91.18% success rate with a 20% reduction in IOP from baseline. In Group 2, our results are comparable to those of Moghimi et al.,[26] who reported a 38% reduction in IOP after surgery.

Our results for glaucoma medication usage in Group 1 are higher than those reported by Teekhasaenee et al.,[2] Wanichwecharungruang et al.,[18] and Husain et al.[20] but similar to those reported by Angmo et al.[22] In Group 2, our findings are higher than those reported by Eslami et al.[25] and Moghimi et al.[26] This may be due to the higher preoperative medication usage in our study compared to other studies.

After 3 months, we observed a significant widening in anterior chamber parameters on AS-OCT, including ACD, LV, AOD500, AOD750, TISA500, TISA750, and SSA, in both groups. However, there were no significant

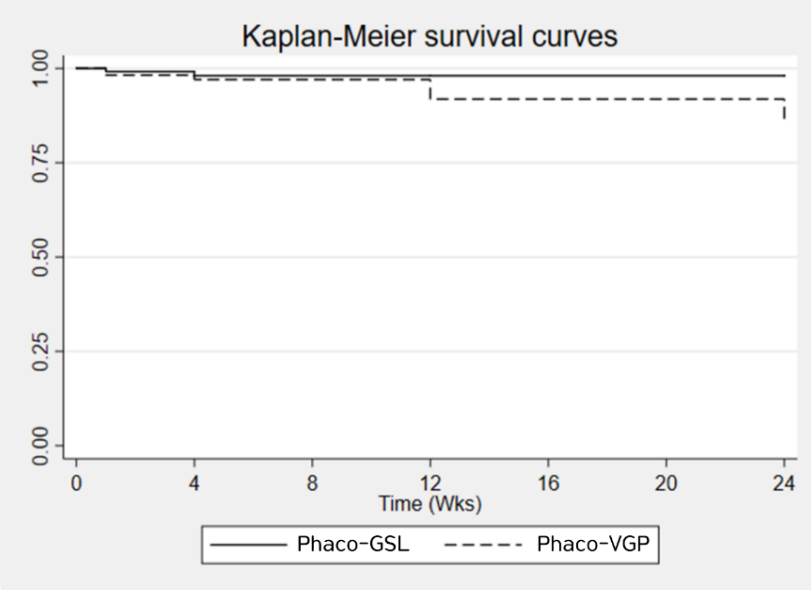


Fig 2. Shows the IOP between the Phaco-GSL and the Phaco-VGP groups in Kaplan-meier survival curves

TABLE 3. Our results compared to other studies.

	Intervention	Participation	Follow-up (Month)	Preoperative IOP (mmHg)	Postoperative IOP (mmHg)	Preoperative Medications	Post operative Medications
Our study	GSL	30	6	24.31±12.34	12.84±2.88	3.47±0.94	1.93±1.20
	VGP	28	6	24.92±12.50	13.62±4.28	3.54±0.58	1.46±1.37
Teekhasaenee[2]	GSL	52	6	29.7±7.9	13.2±2.9	2.4±0.9	0.1±0.3
Wanichwecharungruang[17]	GSL	76	6	24.5	13	3	0
Husain[19]	GSL	33	12	22.9	15.9	1.9	0.6
Angmo[21]	GSL	34	6	30.72±3.88	13.21±1.97	4.03±0.41	2.05±0.46
Varma[23]	VGP	25	12	30.12±7.03	13.7±2.89	-	-
Eslami[24]	VGP	33	1.5	24.5±6.8	16.9±4.9	1.3±1.2	0.1±0.4
Moghimi[25]	VGP	45	12	23.3±7.3	14.5±2.5	1.7±1.1	0.4±0.8

differences between the two groups. In Group 1, similar findings were reported by Angmo et al.[22] In Group 2, comparable results were reported by Eslami et al.[25] and Moghimi et al.[26]

Our findings from the Kaplan-Meier survival curves, where the success rate was defined as achieving a target IOP of 21 mmHg or less after surgery, were not statistically significant. However, when observing the trends in the graphs for the Phaco-GSL and Phaco-VGP groups, there appears to be a tendency towards a higher success rate in the Phaco-GSL group. This may be due to the higher rate of PAS re-adhesion in the Phaco-VGP group. Additionally, the severity of PAS may play an important role in the outcomes of the study. In this study, we did not differentiate the severity of synechiae between the two groups for analysis. Furthermore, since this surgical technique was performed by a single surgeon, it may also have influenced the outcomes. Further studies with longer follow-up periods, larger sample sizes, and stratified analyses of synechiae severity are necessary to validate these findings.

We observed three cases of hyphema: two in the Phaco-GSL group and one in the Phaco-VGP group. Additionally, there was one case of Toxic Anterior Segment Syndrome (TASS) in the Phaco-GSL group, which was effectively managed with steroids and resolved within a week. Our complication profile aligns with that reported by Teekhasaenee et al.[2], who noted plasmoid or fibrinoid aqueous as the most common complication, with hyphema being relatively limited.

The case of TASS in our study occurred in a patient who presented with a refractory acute angle-closure attack and severe inflammation prior to surgery. On the first postoperative day, plasmoid aqueous filled approximately half of the anterior chamber, and routine postoperative medications, including 1% prednisolone acetate every two hours, were initiated. However, two days after discharge, the patient returned with hypopyon and was readmitted. The treatment regimen was adjusted to include oral steroids (15 mg, four times daily) alongside topical steroids every two hours. With close monitoring, the symptoms improved. Based on our experience, we suggest that in cases of severe preoperative inflammation, the use of oral steroids may play a crucial role in reducing inflammation and minimizing postoperative complications.

Both Phaco-GSL and Phaco-VGP have demonstrated similar efficacy in widening the angle and lysing synechiae at the trabecular meshwork. In cases of extensive peripheral anterior synechiae (PAS), Phaco-GSL has shown greater efficacy in reducing intraocular pressure (IOP), as reported by Tian et al.[26] However, Phaco-VGP has not yet been extensively studied in this context, indicating the need for further research. In our view, for patients with extensive PAS where synechiae observed during gonioscopy do not

respond to VGP, Phaco-GSL may offer a more effective option for the mechanical removal of synechiae compared to the pressure exerted by viscoelastics.

Study limitations

Our study's limitations include the short follow-up period and the lack of postoperative gonioscopy documentation. For further evaluation, long-term follow-up with a larger population may be required.

CONCLUSION

According to our results, both phacoemulsification with GSL and phacoemulsification with VGP effectively reduce IOP and decrease the use of glaucoma medications. Additionally, both procedures similarly widen the ocular angle with comparable effects. In cases of extensive PAS, Phaco-GSL may sustain IOP reduction longer than Phaco-VGP. However, further studies are needed to confirm this observation.

ACKNOWLEDGMENTS

The author extends their deepest gratitude to the patients and their families, whose participation was essential to this research. Sincere appreciation is also extended to the medical and support staff at Sisaket Hospital for their invaluable assistance with data collection and patient care.

DECLARATION

Grants and Funding Information

This project is not funded by any external sources.

Conflicts of Interest

The author declares no conflict of interest and declares that the research was conducted in the absence of any commercial or financial relationships that could beconstructed as a potential conflict of interest.

Author Contributions

D.A. was solely responsible for the conceptualization, methodology, data collection, analysis, manuscript drafting, and final approval of the study.

REFERENCES

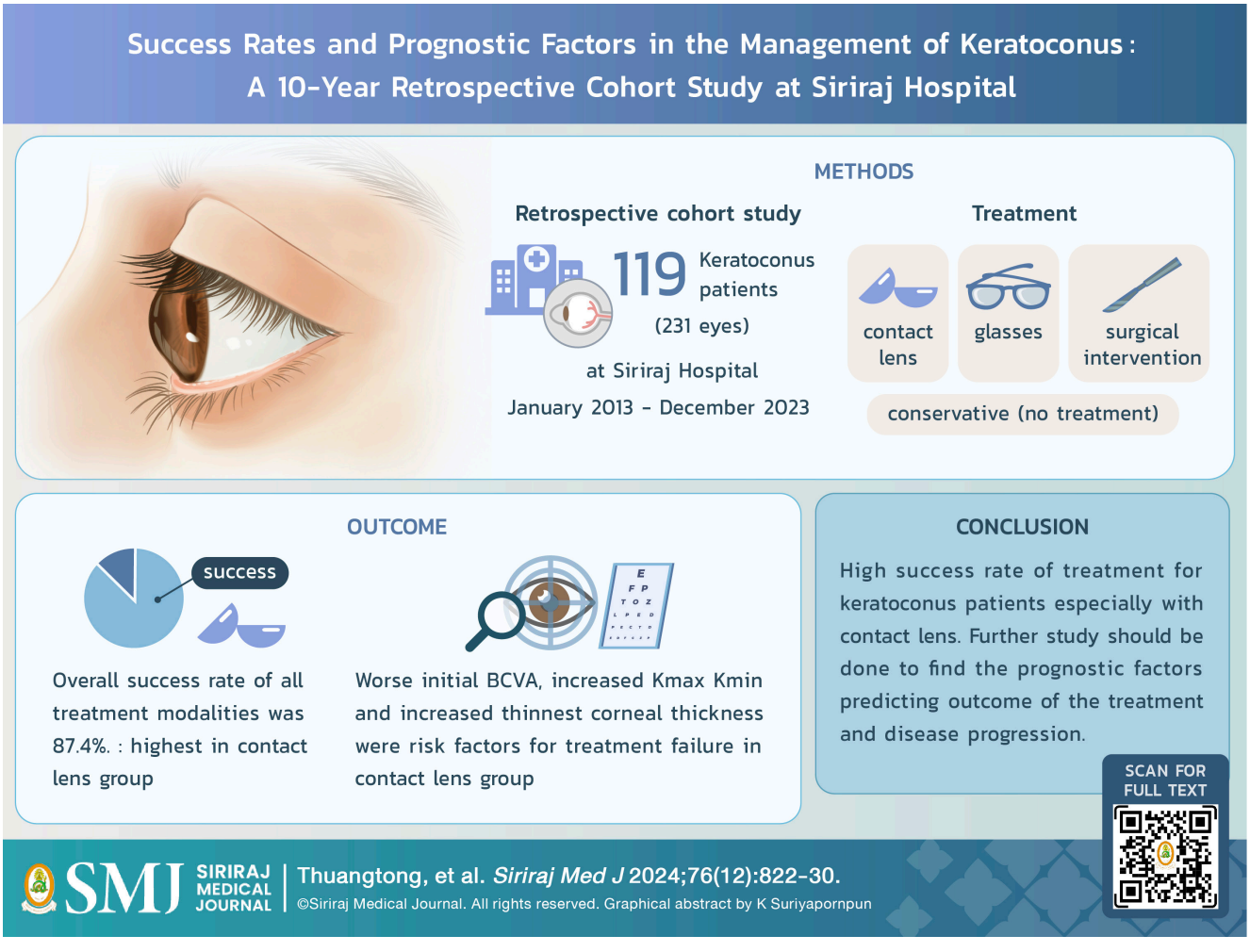
1. European Glaucoma Society Terminology and Guidelines for Glaucoma, 4th Edition - Chapter 3: Treatment principles and options Supported by the EGS Foundation. Br J Ophthalmol. 2017;101(6):130-95.
2. Teekhasaenee C. Combined phacoemulsification and goniosynechialysis for uncontrolled chronic angle-closure glaucoma after acute angle-closure glaucoma. Ophthalmology. 1999;106(4):669-74.
3. Anderson DR, Jai Chi Jin, Wright MM. The Physiologic Characteristics of Relative Pupillary Block. Am J Ophthalmol. 1991;111(3):344-50.
4. Husain R, Gazzard G, Aung T, Chen Y, Padmanabhan V, Oen FTS, et al. Initial management of acute primary angle closure: a randomized trial comparing phacoemulsification with laser peripheral iridotomy. Ophthalmology [Internet]. 2012 Nov 1 [cited 2021 Aug 8];119(11):2274–81. Available from: https://pubmed.ncbi.nlm.nih.gov/22885123/
5. Lam DSC, Leung DYL, Tham CCY, Li FCH, Kwong YYY, Chiu TYH, et al. Randomized Trial of Early Phacoemulsification versus Peripheral Iridotomy to Prevent Intraocular Pressure Rise after Acute Primary Angle Closure. Ophthalmology. 2008; 115(7):1134-40.
6. Petchyim S. Secondary Acute Angle-Closure Attack: Diagnosis and Management. Siriraj Med J [Internet]. 2018 Mar. 9 [cited 2024 Oct. 26];70(1):91-4. Available from: https://he02.tci-thaijo.org/index.php/sirirajmedj/article/view/114934
7. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global Prevalence of Glaucoma and Projections of Glaucoma Burden through 2040. Ophthalmology [Internet]. 2014 Nov;121(11):2081–90. Available from: https://www.aaojournal.org/article/S0161-6420(14)00433-3/fulltext
8. Zhang N, Wang J, Chen B, Li Y, Jiang B. Prevalence of Primary Angle Closure Glaucoma in the Last 20 Years: A Meta-Analysis and Systematic Review. Front Med (Lausanne). 2021;7:624179.
9. Knighton EA, Zoltoski RK, Roberts DK, Wilensky JT, Kuszak JR. Rate of Increase in Lens Thickness Decreases With Age. Investigative Ophthalmology & Visual Science [Internet]. 2011 Apr 22 [cited 2024 Sep 2];52(14):1540–0. Available from: https://iovs.arvojournals.org/article.aspx?articleid=2352248
10. Shin HC, Subrayan V, Tajunisah I. Changes in anterior chamber depth and intraocular pressure after phacoemulsification in eyes with occludable angles. J Cataract Refract Surg. 2010;36(8):1289-95.
11. Tai MC, Chien KH, Lu DW, Chen JT. Angle changes before and after cataract surgery assessed by Fourier-domain anterior segment optical coherence tomography. J Cataract Refract Surg. 2010;36(10):1758-62.
12. Huang G, Gonzalez E, Lee R, Chen YC, He M, Lin SC. Association of biometric factors with anterior chamber angle widening and intraocular pressure reduction after uneventful phacoemulsification for cataract. J Cataract Refract Surg. 2012;38(1):108-16.
13. H Viet Tran, Liebmann JM, Ritch R. Iridociliary apposition in plateau iris syndrome persists after cataract extraction. Am J Ophthalmol. 2003;135(1):40-3.
14. Yang CH, Hung PT. Intraocular lens position and anterior chamber angle changes after cataract extraction in eyes with primary angle-closure glaucoma. J Cataract Refract Surg. 1997;23(7): 1109-13.
15. Tham CCY, Leung DYL, Kwong YYY, Li FCH, Lai JSM, Lam DSC. Effects of phacoemulsification versus combined phaco-trabeculectomy on drainage angle status in primary angle closure glaucoma (PACG). Journal of Glaucoma [Internet]. 2010 [cited 2019 Nov 13];19(2):119–23. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19373107
16. Yu JG, Zhao F, Xiang Y. Phacoemulsification with Goniosynechialysis versus Phacoemulsification Alone in Angle-Closure Glaucoma: A Meta-Analysis of Randomized Controlled Trials. J Ophthalmol. 2021;2021:8831479.

17. Wang N, Jia S-B. Phacoemulsification with or without goniosynechialysis for angle-closure glaucoma: a global Meta-analysis based on randomized controlled trials. Int J Ophthalmol. 2019;12(5):826-33.
18. Wanichwecharungruang B, Phumratprapin C, Kongsomboon K, Seresirikachorn K. Real-world Surgical Outcomes of Primary Angle-closure Glaucoma. Clin Ophthalmol. 2021;15:2823-33.
19. Tian T, Li M, Pan Y, Cai Y, Fang Y. The effect of phacoemulsification plus goniosynechialysis in acute and chronic angle closure patients with extensive goniosynechiae. BMC Ophthalmol. 2019;19(1):65.
20. Husain R, Do T, Lai J, Kitnarong N, Nongpiur ME, Perera SA, et al. Efficacy of Phacoemulsification Alone vs Phacoemulsification With Goniosynechialysis in Patients With Primary Angle-Closure Disease. JAMA Ophthalmol. 2019;137(10):1107-13.
21. Campbell DG, Vela A. Modern Goniosynechialysis for the Treatment of Synechial Angle-closure Glaucoma. Ophthalmology. 1984;91(9):1052-60.
22. Angmo D, Shakrawal J, Gupta B, Yadav S, Pandey RM, Dada T. Comparative Evaluation of Phacoemulsification Alone versus Phacoemulsification with Goniosynechialysis in Primary Angle-Closure Glaucoma. Ophthalmol Glaucoma. 2019;2(5):346-56.
23. Varma D, Baylis O, Wride N, Phelan PS, Fraser SG. Viscogonioplasty: an effective procedure for lowering intraocular pressure in primary angle closure glaucoma. Eye [Internet]. 2006 Jan 13 [cited 2019 Nov 13];21(4):472-5. Available from: https://www.nature.com/articles/6702224
24. Fraser S, Adams, Varma, Phelan P, Bunce C, Fraser S. Viscogonioplasty in narrow angle glaucoma: a randomized controlled trial. Clin Ophthalmol. 2010;4:1475-9.
25. Eslami Y, Latifi G, Moghimi S, Ghaffari R, Fakhraie G, Zarei R, et al. Effect of adjunctive viscogonioplasty on drainage angle status in cataract surgery: a randomized clinical trial. Clin Exp Ophthalmol [Internet]. 2012 Oct 29 [cited 2019 Nov 13];41(4):368-78. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1442-9071.2012.02871.x
26. Moghimi S, Latifi G, ZandVakil N, Mohammadi M, Khatibi N, Soltani-Moghadam R, et al. Phacoemulsification Versus Combined Phacoemulsification and Viscogonioplasty in Primary Angle-Closure Glaucoma: A Randomized Clinical Trial. J Glaucoma [Internet]. 2015 [cited 2019 Nov 13];24(8):575-82. Available from: http://journals.lww.com/glaucomajournal/Abstract/2015/10000/Phacoemulsification_Versus_Combined.3.aspx
27. Tian T, Li M, Pan Y, Cai Y, Fang Y. The effect of phacoemulsification plus goniosynechialysis in acute and chronic angle closure patients with extensive goniosynechiae. BMC Ophthalmol. 2019;19(1):65.
28. Kitnarong N, Dagvadorj D. Effect of Multifocal Intraocular Lens on Contrast Sensitivity in Primary Angle-Closure Patients. Siriraj Med J [Internet]. 2023 Jul. 1 [cited 2024 Oct. 26];75(7):501-7. Available from: https://he02.tci-thaijo.org/index.php/sirirajmedj/article/view/263254

Success Rates and Prognostic Factors in the Management of Keratoconus: A 10-Year Retrospective Cohort Study at Siriraj Hospital

Atiporn Thuangtong, M.D.*, Theerajate Phongsuphan, M.D.

Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.



*Corresponding author: Atiporn Thuangtong
E-mail: atipornpam@yahoo.com
Received 25 June 2024 Revised 28 October 2024 Accepted 30 October 2024
ORCID ID:http://orcid.org/0000-0002-3613-4049
https://doi.org/10.33192/smj.v76i12.269895

ABSTRACT

Objective: To evaluate the success rates of different treatment modalities, identify prognostic factors associated with treatment outcomes and factors influencing disease progression in keratoconus patients.

Materials and Methods: A retrospective cohort study of keratoconus patients at Siriraj Hospital during January 2013 to December 2023 was done. Patient characteristics, symptoms and signs related to keratoconus, outcomes of corneal topography, treatment modalities, and best-corrected visual acuity (BCVA) before and after treatment were recorded. Treatment outcome was defined as a "success" when the BCVA post-treatment was equal to or better than 6/12. Progression of keratoconus was based on the Belin ABCD progression criteria.

Results: Total 119 patients (231 eyes) were analyzed. The mean age at diagnosis was 28.0 ± 9.5 years. Two hundred and sixteen eyes (93.5%) were clinical keratoconus. The overall success rate of all treatment modalities was 87.4%. Contact lenses were the most frequent treatment modality (147 eyes, 72.4%) with the highest success rate (90.5%). A worse initial BCVA, high keratometric reading and thinner cornea were risk factors for treatment failure in this group. Of 133 eyes disease progression could be evaluated (median follow-up time; 33 months) and 58 eyes (43.6%) met criteria for disease progression (median survival time; 8.8 years). No significant factors were found to be associated with disease progression.

Conclusion: Success rate in keratoconus treatment at Siriraj Hospital was 87.4%. Contact lenses were most frequently applied 72.4%. Factors associated with treatment failure were found in this group but for disease progression remained unclear due to limitations of the study.

Keywords: Keratoconus; success rate; progression; contact lens (Siriraj Med J 2024; 76: 822-830)

INTRODUCTION

Keratoconus is an eye disease characterized by protrusion and thinning of the cornea leading to astigmatism and blurred vision. While the condition commonly affects both eyes, it is often asymmetrical. Keratoconus has an incidence of approximately 2 per 100,000 individuals per year with a prevalence of 54.5 per 100,000 individuals. It can be found across all ethnicities and genders, typically manifesting during adolescence and progressing until the ages of 30–40 years old.[1,2]

In the initial stages, the treatment options[3] may include glasses or soft contact lenses to correct vision. As the condition progresses, these treatments may no longer effectively correct vision, necessitating the use of rigid contact lenses. In cases where rigid contact lenses are not suitable surgical interventions, like corneal transplantation, may be considered. Currently other treatments, such as intrastromal corneal ring segments (ICRS) implantation and collagen cross-linking (CXL), are utilized to reduce corneal curvature and increase corneal strength, respectively.[4-6] However, the contact lens remains the most popular treatment due to its convenience and non-invasiveness.[7]

Reported success rates of contact lens treatment for keratoconus range from 86.9% to 100%.[8-10] However disease progression following the treatment has been reported,[11] highlighting the increasing importance of collagen cross-linking to prevent disease progression.[1,12,13] While several studies have identified factors contributing to disease progression, investigations have not yet been conducted in a Thai population.

The aim of this study research was to analyze the success rate of keratoconus treatment at Siriraj Hospital, representing a Thai population, and to analyze prognostic factors for treatment outcome.

MATERIALS AND METHODS

Study population

The medical records of all patients aged 18 years old and older diagnosed with keratoconus and forme fruste keratoconus (ICD-10 code H18.6) between January 2013 and December 2023 at Siriraj Hospital, Mahidol University, Bangkok, Thailand were reviewed. Keratoconus was diagnosed according to the Rabinowitz criteria,[14] including central corneal power > 47.2 diopter (D), inferior–superior dioptric asymmetry over 1.2 D, sim K astigmatism > 1.5 D, and skew radial axis > 21 degrees. Forme fruste or subclinical keratoconus was diagnosed in an eye with an early stage of keratoconus with undetectable clinical findings and clinical keratoconus in the fellow eye.[15]

Patients with inconclusive diagnoses or other types of corneal ectasia were excluded. Also with patients that lost to follow-up before the treatment modalities were allocated were excluded from the treatment outcome

analysis. Furthermore, patients with less than two corneal topographic results from the Pentacam® system were excluded from the progression analysis. Approval for this study was obtained from the Siriraj Institutional Review Board [COA no. Si 628/2023 and SIRB protocol number 568/2566(IRB1)] in accordance with the principles outlined in the Declaration of Helsinki.

Data collection

Patient characteristics were recorded including age of diagnosis, sex, race, previous ocular trauma, history of atopic diseases, family history of keratoconus or other connective tissue diseases, eye rubbing, symptoms and signs related to keratoconus, such as scissoring reflex, Rizzutti's sign, Munson's sign, Fleischer's ring, and Vogt's striae, and corneal scarring. Outcomes of corneal topography including minimum keratometry (Kmin), maximum keratometry (Kmax), mean keratometry (Kmean), and thinnest corneal thickness at the time of diagnosis and at least one year follow-up were recorded. The treatment modalities, and best-corrected visual acuity (BCVA) before and after treatment were recorded.

Outcome measures

Treatment was classified into four groups: contact lenses, glasses, surgical intervention, and conservative (no treatment). The outcome was defined as a success when the BCVA post-treatment score was equal to or better than 6/12. All other outcomes were defined as failures. Additionally, in the contact lens treatment group, failure was also defined in patients who could not tolerate the contact lens even if the BCVA score equal to or better than 6/12. Progression of keratoconus was recorded if there were two or more of the followings: steepening of the anterior corneal surface, steepening of the posterior corneal surface and thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point. This criteria was ≥80% confidence interval (CI) (broken red line) on the Belin ABCD Progression Display as analyzed by the Pentacam® system, according to the Global Consensus on Keratoconus and Ectatic Disease published in 2015.[16]

Statistical analyses

Descriptive statistics were employed to summarize the patient and disease characteristics. Categorical data, including the success rate, were presented as numbers and percentages, while continuous data were presented as the mean ± standard deviation (SD). Due to bilateral diseases in individual patients, a generalized estimating equation (GEE) with exchangeable correlation structure was applied with binary logistic regression to determine the factors associated with the treatment outcome. The factors were analyzed between the treatment and no-treatment groups, as well as for each treatment modality separately. The median time to disease progression was analyzed using the Kaplan–Meier method. Censoring occurred when the patient was loss to follow-up or when data were missing. In addition, a mixed model for time to progression was employed to investigate the factors associated with disease progression. The statistical analysis was conducted using IBM SPSS Statistics version 29 (IBM Corp., Armonk, N.Y., USA) and Stata version 16.0.

RESULTS

A total of 319 patients with the ICD-10 code H18.6 were retrospectively reviewed. After applying eligibility criteria, data of 119 patients (231 eyes) were included in the analyses. In total 133 eyes were included for the progression analysis (Fig 1).

All the patients were Thai except for one Arabian patient. Eighty-six patients (72.3%) were male. Bilateral keratoconus was found in 112 patients (94.1%). The mean age at diagnosis was 28.0 ± 9.5 years (Table 1).

Data concerning family history of keratoconus or other corneal diseases, other comorbidities, history of atopic diseases, and even a history of eye rubbing could not be recorded consistently due to incomplete reporting in the medical records. For the available data, allergic rhinitis and allergic conjunctivitis were the most frequently associated findings.

The most common presenting symptom was blurred vision (91.1%). Therefore, signs related to keratoconus included corneal scarring, Vogt's striae, Munson's sign, Fleischer's ring, Rizzutti's and scissoring reflex were hard to described in number due to a lot of missing data.

Twenty-eight eyes were excluded due to the patients being lost to follow-up before the treatment modalities were allocated. Contact lenses were the most common treatment prescribed to the patients (147 eyes, 72.4%) followed by glasses (37 eyes, 16.7%), surgical intervention (6 eyes, 3%), and no treatment (13 eyes, 6.4%) due to the early stage of the disease or patient preference. Treatment choices were based on disease severity (corneal topography) and clinical experience.

Patients who received any treatment had a poorer initial BCVA score, higher keratometry values and lower thinnest corneal thickness compared to the no treatment group whereas the age at diagnosis did not differ significantly between the treatment groups (Table 2).

Among all the treatment modalities, surgery was preferred in patients with a poorer initial BCVA, higher keratometry values and thinner corneal thickness (Table 2). Surgery included ICRS for high astigmatism (3 eyes), deep anterior lamellar keratoplasty (DALK) for a dense central corneal scar (1 eye), and intracameral 14% C_3F_8 injection and compression sutures for corneal hydrops (2 eyes).

Contact lens treatment had the highest success rate of 90.5% followed by glasses and surgical treatment, with success rates of 81.4% and 50%, respectively (Table 2). For contact lens and glasses treatment group, the success of the treatment was determined immediate after the treatment but for the surgical group, the success of the treatment was determined at the average time of 1-3 months postoperative. Rigid gas permeable contact lenses were predominantly prescribed in the contact lens group (98.5%). The reasons for treatment failure in the contact lens group were unacceptable visual acuity (VA) (poorer than 6/12) (8 eyes, 57.1%), inability to obtain an

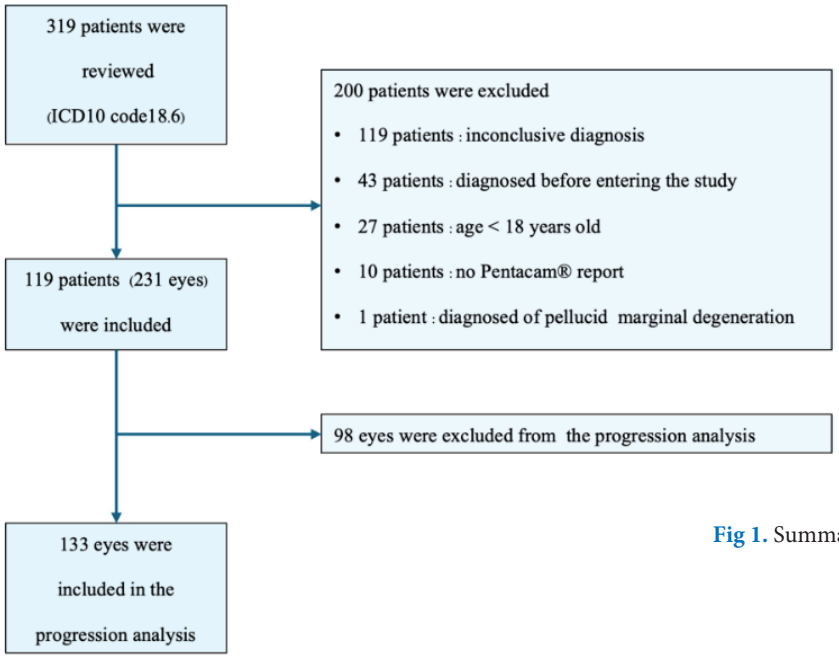


Fig 1. Summary of the study population.

TABLE 1. Characteristics of the eyes diagnosed with keratoconus in this study.

Characteristics	n = 231
Forme fruste keratoconus	15 (6.5%)
Keratoconus	216 (93.5%)
Advanced keratoconus	6 (2.8%)
Corneal hydrop	5 (2.2%)
Posterior keratoconus	4 (1.7%)
Initial BCVA (logMAR) †	0.46 ± 0.49
Kmin (D) †	48.5 ± 7.9
Kmax (D) †	53.3 ± 8.8
Kmean (D) †	50.7 ± 8.1
Thinnest corneal thickness (μm) †	460.5 ± 57.8

†Continuous variables are displayed by the mean ± SD.

Abbreviation: SD, Standard deviation; BCVA, Best-corrected visual acuity; Kmin, minimum keratometry; Kmax, maximum keratometry; Kmean, mean keratometry; D, Diopters; μm, micrometer.

TABLE 2. Success rate and baseline characteristics of the eyes in each treatment modality.

Factors	No treatment n = 13	Treatment n = 190	p-value*	Treatment modality: n (%) Treatment Contact lens n = 147	Glasses n = 37	Surgery n = 6	p-value**
Outcome							
Success	12 (92.3)	166 (87.4)	-	133 (90.5)	30 (81.4)	3 (50.0)	-
Failure	1 (7.7)	24 (12.6)	-	14 (9.5)	7 (18.9)	3 (50.0)	-
Male	12 (92.3)	134 (70.5)	-	113 (76.9)	18 (48.6)	3 (50.0)	0.002[a]
Allergy	8 (61.5)	72 (37.9)	-	60 (40.8)	15 (40.5)	0 (0.0)	0.153[a]
Corneal scarring	1 (7.7)	20 (10.5)	-	17 (11.6)	2 (5.4)	1 (16.7)	0.328[a]
Age at diagnosis (years)	26.3 ± 8.3	27.9 + 9.2	0.383	26.8 ± 8.0	32.2 ± 12.7	29.2 ± 5.6	0.043[b]
Initial BCVA (logMAR)†	0.10 ± 0.15	0.41 ± 0.4	< 0.01	0.43 ± 0.40	0.27 ± 0.30	0.97 ± 0.87	0.003[b]
Kmin (D)†	43.8 ± 1.4	48.0 ± 7.3	< 0.01	48.1 ± 6.3	45.2 ± 3.4	64.1 ± 20.1	0.002[b]
Kmax (D)†	46.9 ± 2.9	53.0 ± 8.3	< 0.01	53.1 ± 6.9	49.0 ± 4.1	73.1 ± 22.6	<0.001[b]
Kmean (D)†	45.3 ± 1.9	50.3 ± 7.6	< 0.01	50.4 ± 6.3	47.1 ± 3.6	68.2 ± 21.2	<0.001[b]
Thinnest corneal thickness (μm)†	508.9 ± 44.5	462.4 ± 51.2	< 0.01	456.0 ± 49.7	486.7 ± 75.8	468.67 ± 75.8	<0.001[b]

†Continuous variables are displayed by the mean ± SD.

*p=value between treatment and no-treatment group was calculated using Mann-Whitney U test

**p-value among baseline characteristics of each treatment modality was calculated using Fisher's exact test[a] and Kruskal-Wallis test[b]

Abbreviation: SD, Standard deviation; BCVA, Best-corrected visual acuity; Kmin, minimum keratometry; Kmax, maximum keratometry; Kmean, mean keratometry; D, Diopters; μm, micrometer

optimal position (4 eyes, 28.6%), and severe irritation (2 eyes, 14.3%). From the multivariable analysis, worse initial BCVA (OR 36.2, 95% CI: 5.7; 229.5), increased Kmax (OR 8.1, 95% CI: 1.7; 37.9), increased Kmin (OR 11.4, 95% CI: 2.6; 50.7) and increased thinnest corneal thickness (OR 1.0, 95% CI: 1.0; 1.1) were risk factors for treatment failure (Table 3).

For the glasses group, the multivariable analysis (Table 4) indicated that only an increased Kmean (OR 5.8, 95% CI: 1.3; 25.5) was the risk factor for treatment failure.

Fifty-eight eyes (43.6%) met the criteria for disease progression according to the Belin ABCD progression criteria with a mean follow-up time of 43.5 ± 33.8 months (range 1–121 months, median 33 months, IQR 55 months). Following progression, 30 eyes underwent CXL, 8 eyes underwent surgical interventions (including ICRS insertion and corneal transplantation), 12 eyes continued with their previous treatment based on patient preference, and 8 eyes continued with their previous treatment due to differing progression criteria. (The ABCD Berlin progression criteria have been implemented at Siriraj Hospital since 2020.)

In the a mixed-effect statistical analysis for binary model, no factors were significantly associated with disease progression (Table 5).

The time to progression survival curves of 133 keratoconus eyes were plotted in Fig 2. Based on Kaplan–Meier analysis, the median survival time was 105 months (8.8 years). The percentage of patients without disease progression at one year was 82.7%.

TABLE 3. Factors associated with the outcome in keratoconus patients in the contact lens treatment group.

Factors	Outcome: n (%)		Univariable analysis			Multivariable analysis		
	Success n=133	Failure n=14	OR	95% CI	p-value[b]	OR	95% CI	p-value[a]
Male	106 (79.7)	7 (50.0)	0.2	0.1;0.9	**0.033**	0.2	0.0;0.9	**0.039**
Allergy	54 (40.6)	6 (42.9)	1.1	0.3;3.9	0.919	-	-	-
Corneal scarring	13 (9.8)	4 (28.6)	3.9	1.2;13.2	**0.024**	0.9	1.0;9.2	0.961
Age at diagnosis (years)†	25.9 ± 6.0	35.1 ± 8.0	1.1	0.3;3.9	**<0.001**	0.9	0.9;1.0	0.100
Initial BCVA (logMAR)†	0.37 ± 0.30	1.00 ± 0.70	17.2	4.1;73.0	**<0.001**	**36.2**	5.7;229.5	**<0.001**
Kmin (D)†	47.9 ± 6.3	50.0 ± 6.1	1.0	0.9;1.0	**0.091**	**11.4**	2.6;50.7	**0.001**
Kmax (D)†	52.8 ± 6.7	56.7 ± 7.8	0.9	0.9;1.0	**0.042**	**8.1**	1.7;37.9	**0.008**
Kmean (D)†	50.2 ± 6.2	52.7 ± 6.3	0.9	0.9;1.0	**0.059**	0.009	0.0;0.2	**0.002**
Thinnest corneal thickness (µm)†	459.7 ± 49.4	420.7 ± 40.0	1.0	1.003;1.03	**0.009**	**1.0**	1.0;1.1	**0.042**

TABLE 4. Factors associated with the outcome in keratoconus patients in the glasses treatment group.

Factors	Outcome: n (%)		Univariable analysis			Multivariable analysis		
	Success n=30	Failure n=7	OR	95% CI	p-value[b]	OR	95% CI	p-value[a]
Male	14 (46.7)	4 (57.1)	0.7	0.1;4.6	0.738	-	-	-
Allergy	12 (40.0)	3 (42.9)	0.9	0.1;6.1	0.944	-	-	-
Corneal scarring	1 (3.3)	1 (14.3)	0.2	0.0;3.9	0.290	-	-	-
Age at diagnosis (years)†	31.6 ± 12.8	34.7 ± 12.8	1.0	1.0;1.1	0.546	-	-	-
Initial BCVA (logMAR)†	0.19 ± 0.19	0.63 ± 0.44	146.5	9.3;2,308.1	**<0.001**	73.9	0.3;19.3	0.130
Kmin (D)†	44.4 ± 2.2	49.0 ± 4.9	1.6	1.2;2.1	**0.002**	0.5	0.2;1.1	0.090
Kmax (D)†	47.9 ± 2.7	53.5 ± 5.9	1.6	1.0;2.4	**0.038**	0.5	0.2;1.8	0.327
Kmean (D)†	46.1 ± 2.3	51.3 ± 5.1	1.8	1.3;2.5	**0.001**	**5.8**	1.3;25.5	**0.021**
Thinnest corneal thickness (µm)†	495.2 ± 38.3	486.6 ± 46.5	1.0	0.96;1.00	**0.027**	1.0	1.0;1.1	0.589

†Continuous variables are displayed by the mean ± SD.

a. Statistically significant at p-value < 0.05; b. Factors with univariable p-value < 0.15 were entered into the multivariable analysis.

Abbreviation: RR, Relative risk; SD, Standard deviation; BCVA, Best-corrected visual acuity; Kmin, minimum keratometry; Kmax, maximum keratometry; Kmean, mean keratometry; D, Diopters; µm, micrometer

TABLE 5. Factors associated with progression based on the ABCD Belin progression criteria in keratoconus patients

Factors	Progression, n (%)		Univariable analysis		
	Yes n=58	No n=75	HR	95% CI	p-value[a]
Male	45 (77.6)	52 (69.3)	1.9	0.6;6.8	0.302
Age at diagnosis (years)†	26.7 ± 8.0	28.2 ± 9.0	1.0	0.9;1.0	0.305
Allergy	27 (46.6)	29 (38.7)	2.0	0.7;5.9	0.203
Initial BCVA (logMAR)†	0.39 ± 0.34	0.46 ± 0.52	0.7	0.3;1.7	0.424
Corneal scarring	6 (10.3)	11 (14.7)	0.7	0.2;2.0	0.474
Kmin (D)†	47.6 ± 4.5	48.6 ± 7.9	1.0	0.9;1.0	0.195
Kmax (D)†	52.7 ± 5.9	53.3 ± 8.0	1.0	0.9;1.0	0.698
Kmean (D)†	50.0 ± 5.0	50.7 ± 7.6	1.0	0.9;1.0	0.427
Thinnest corneal thickness (μm)†	458.3 ± 39.0	458.7 ± 58.1	1.0	0.99;1.01	0.993
ARC (mm)†	6.51 ± 0.72	6.48 ± 0.88	1.2	0.8;2.0	0.389
PRC (mm)†	4.98 ± 0.76	5.00 ± 1.00	1.2	0.8;1.9	0.378
Treatment modalities					
Contact lens	49 (87.5)	50 (66.7)	2.4	0.3;16.8	0.377
Glasses	2 (3.6)	13 (17.3)	0.2	0.0;4.0	0.310
Surgery	3 (5.4)	6 (8.0)	0.4	0.0;7.0	0.506
No treatment	2 (3.6)	6 (8.0)	Ref	-	-

†Continuous variables are displayed by the mean ± SD.

a. Statistically significant at p-value < 0.15; Ref = Reference of relative risk calculation for more than two categorical variables.

Abbreviation: HR, Hazard ratio; SD, Standard deviation; BCVA, Best-corrected visual acuity; Kmin, minimum keratometry; Kmax, maximum keratometry; Kmean, mean keratometry; D, Diopters; μm, micrometer; ARC, Anterior radius of curvature; PRC, Posterior radius of curvature; mm, millimeter.

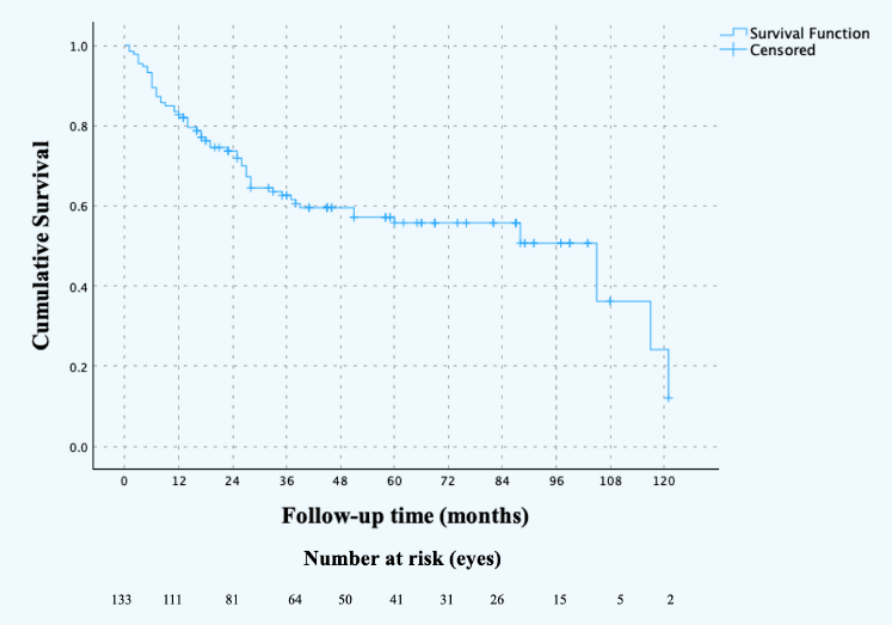


Fig 2. Kaplan–Meier plots of keratoconus disease progression in this study.

DISCUSSION

In our study, contact lenses were prescribed for 147 eyes (72.4%), followed by glasses for 37 eyes (16.7%), correlating with the results of the CLEK study, which reported a 74% utilization of contact lenses (including RGP lenses at 65%) and 16.1% for glasses. Our surgical intervention rate at initial presentation (6 eyes, 3%) was slightly lower compared to a previous study in Thailand (21.5% for corneal transplantation, 19.7% for ICRS, and 27.2% for CXL).[17]

The overall success rate of all treatment modalities was 87.4%. The success rate was observed to be higher in the contact lenses and glasses groups (90.5% and 81.4%, respectively) compared to the surgery group (50%) due to the poorer baseline characteristics, including visual acuity and keratoconus staging, in the surgery group. The success rate of contact lenses was consistent with previous studies, which have reported rates ranging from 86.9% to 100%.[8-10]

In the multivariate analysis to identify the risk factor for treatment failure, there was a difference in the risk factors in contact lens and glasses groups (worse initial BCVA, increased Kmax, Kmin and lower thinnest corneal thickness in contact lens group and only an increased Kmean in glasses group). The difference in both groups may be from the confounding by indication. Disease severity and clinical experience determined the treatment. Milder cases were treated with glasses

Binary logistic regression could not be performed to identify the risk factors in the surgical treatment group due to the limited number of patients in the present study.

According to the Global Consensus on Keratoconus and Ectatic Diseases (2015), there are no universal or definite criteria for keratoconus progression.[16] Our study opted to utilize the ABCD Berlin progression criteria due to their ability to detect disease progression early[11] and their accessibility through the "Pentacam®" application, which is widely available in Thailand.

Out of 133 eyes examined, 58 (43.6%) met the criteria for disease progression in our study. Ozalp et al.[11] demonstrated a higher percentage compared to ours (57%) using the same criteria (single baseline criteria). This discrepancy may be attributed to lower dropout rate, and the use of multiple-visit corneal topographic evaluations, which increased sensitivity in detecting progression. The mean follow-up time in their study was 53.6 months (range, 12.0-124.3 months). In comparison to other studies with different criteria, the proportion of progressors in other studies was significantly lower. For instance, between 18.6 % and 25.6% exhibited progression over the follow-up period based on criteria where topographic parameters were increased by > 1.00 D/year.[18] Additionally, 25 of 94 eyes (26.5%) showed progression of the central K ≥1.50 D, with a mean time to progression of 12 years, according to Choi et al.'s study.[19]

Although various factors have been shown to be associated with disease progression, such as a younger age, greater disease severity at baseline, and poorer best-corrected visual acuity,[1,12,18] our study did not identify any significant risk factors that could predict progression.

The limitations in our study were retrospective study, far different numbers of patients in each group, small sample size in certain treatment groups (e.g. surgical intervention) hindered the ability to perform robust statistical analyses, such as logistic regression to identify risk factors for treatment failure, incompletely collected data, which limits the study's ability to fully assess risk factors for treatment outcomes and disease progression and the variation of follow-up period that could affect the accuracy of the analysis regarding disease progression and treatment success over time. Further study should be done to find the prognostic factors predicting disease progression.

CONCLUSION

The overall success rate for all treatment modalities in keratoconus patients in Siriraj Hospital was 87.4%. Contact lenses were most frequently applied treatment (72.4%) with the highest success rates (90.5%). Treatment failure in contact lens group was associated with worse initial BCVA, increased Kmax, increased Kmin, and lower thinnest corneal thickness. No significant factors were found to be associated with disease progression.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the support from the Faculty of Medicine Siriraj Hospital, Mahidol University: Assist. Prof. Dr. Chulaluk Komontri (Research Department) for helping with the statistical analysis and interpretation; and the ChatGPT language model, developed by OpenAI based on the GPT-4.0 architecture for grammar correction.

DECLARATION

Grants and Funding Information

This was an unfunded study.

Conflict of Interest

All authors declare no personal or professional conflicts of interest relating to any aspect of this study.

Author Contributions

Conceptualization and methodology, A.T. and T.P.; Investigation, A.T. and T.P.; Formal analysis, A.T. and T.P.; Visualization and writing – original draft, A.T. and T.P.; Writing – review and editing, A.T. and T.P.; Funding acquisition, none; Supervision, A.T. All authors have read and agreed to the final version of the manuscript.

Use of artificial intelligence

ChatGPT language model, developed by OpenAI based on the GPT-4.0 architecture was used for grammar correction.

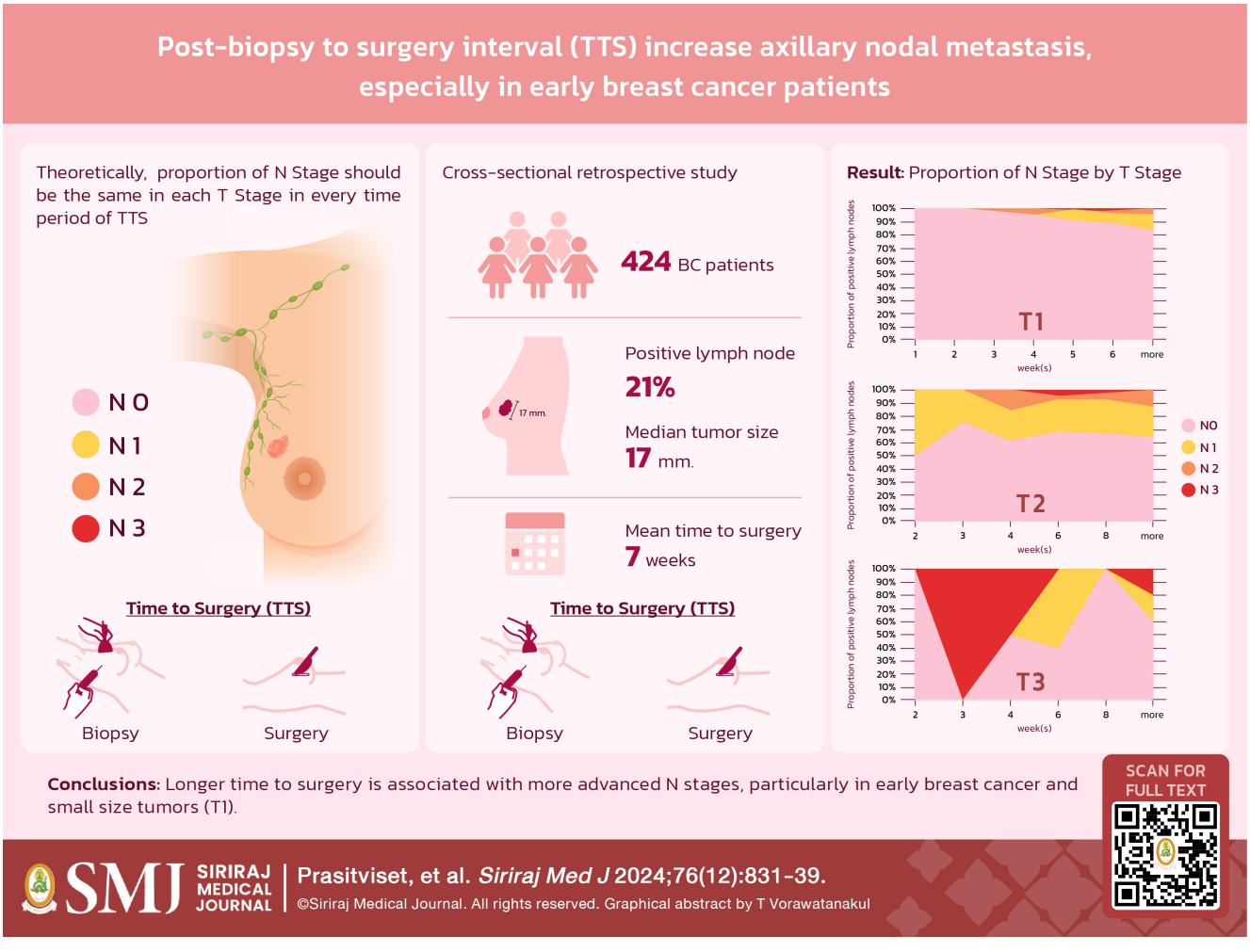
REFERENCES

1. Ferdi A, Nguyen V, Kandel H, Tan JC, Arnalich-Montiel F, Abbondanza M, et al. Predictors of progression in untreated keratoconus: a Save Sight Keratoconus Registry study. Br J Ophthalmol. 2022;106(9):1206-11.
2. Thuangtong A, Samsen P, Boonyakiatwatana S. Clinical Characteristics of Patients in Contact Lens Clinic, Siriraj Hospital. Siriraj Med J. 2012;64(1):7-10.
3. Arnold A, Dunn R, Taylor H, Keeffe J, Fox S, Goujon N, et al. National indigenous eye health survey: Minum Barreng (Tracking Eyes). National indigenous eye health survey: Minum Barreng (Tracking Eyes). 2009.
4. Wollensak G. Crosslinking treatment of progressive keratoconus: new hope. Curr Opin Ophthalmol. 2006;17(4):356-60.
5. Shabayek MH, Alió JL. Intrastromal corneal ring segment implantation by femtosecond laser for keratoconus correction. Ophthalmology. 2007;114(9):1643-52.
6. Chotikavanich S, Kosrirukvongs P, Duangpatra J, Prabhasawat P, Booranapong W, Chirapapaisan C, et al. A two-year outcome of intrastromal corneal ring segment implantation in keratoconus: Initial report in Thai patients. Siriraj Med J. 2019;71(4):302-9.
7. Rico-Del-Viejo L, Garcia-Montero M, Hernández-Verdejo JL, García-Lázaro S, Gómez-Sanz FJ, Lorente-Velázquez A. Nonsurgical Procedures for Keratoconus Management. J Ophthalmol. 2017;2017:9707650.
8. Abdalla YF, Elsahn AF, Hammersmith KM, Cohen EJ. SynergEyes lenses for keratoconus. Cornea. 2010;29(1):5-8.
9. Itoi M, Itoi M. Management of keratoconus with corneal rigid gas-permeable contact lenses. Eye Contact Lens. 2022;48(3):110-4.
10. Mandathara PS, Stapleton FJ, Willcox MD. Outcome of keratoconus management: review of the past 20 years' contemporary treatment modalities. Eye Contact Lens. 2017;43(3):141-54.
11. Ozalp O, Atalay E. Belin ABCD Progression Display identifies keratoconus progression earlier than conventional metrics. Am J Ophthalmol. 2022;236:45-52.
12. Tuft SJ, Moodaley LC, Gregory WM, Davison CR, Buckley RJ. Prognostic factors for the progression of keratoconus. Ophthalmology. 1994;101(3):439-47.
13. Wagner H, Barr J, Zadnik K, Group CLEoKS. Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study: methods and findings to date. Contact Lens Anterior Eye. 2007;30(4):223-32.
14. Rabinowitz YS. Videokeratographic indices to aid in screening for keratoconus. J Refract Surg. 1995;11(5):371-9.
15. Amsler M. The" forme fruste" of keratoconus. Wiener Klin Wochenschr. 1961;73:842-3.
16. Gomes JA, Tan D, Rapuano CJ, Belin MW, Ambrósio Jr R, Guell JL, et al. Global consensus on keratoconus and ectatic diseases. Cornea. 2015;34(4):359-69.
17. Piyacomn Y, Kasetsuwan N, Puangsricharern V, Reinprayoon U, Satitpitakul V, Chantaren P. Keratoconus in Thai population–a cross-sectional hospital-based study. Asian Biomedicine. 2022;16(6):316-21.
18. Gokul A, Patel DV, Watters GA, McGhee CN. The natural history of corneal topographic progression of keratoconus after age 30 years in non-contact lens wearers. Br J Ophthalmol. 2017;101(6):839-44.
19. Choi JA, Kim M-S. Progression of keratoconus by longitudinal assessment with corneal topography. Invest Ophthalmol Vis Sci. 2012;53(2):927-35.

Post-biopsy to Surgery Interval Tends to Increase Axillary Nodal Metastasis, Especially in Early Breast Cancer Patients

Phatcharawan Prasitviset, M.D., Pongthep Pisarnturakit, M.D., Adune Ratanawichitrasin, M.D.*

Division of Head Neck and Breast, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.



*Corresponding author: Adune Ratanawichitrasin
E-mail: adune.rat@gmail.com
Received 6 September 2024 Revised 23 September 2024 Accepted 7 October 2024
ORCID ID:http://orcid.org/0009-0009-0615-9155
https://doi.org/10.33192/smj.v76i12.270986

ABSTRACT

Objective: Delays between diagnosis and breast cancer surgery may raise concerns about tumor progression. Tumors of the same size should exhibit same proportions of N staging. We aimed to evaluate the impact of time to surgery (TTS) on the proportion of metastatic axillary lymph nodes (N-Staging), controlled by tumor size.

Materials and Methods: A cross-sectional study of primary breast cancer patients treated between October 2021 - December 2022 at the Division of Head Neck and Breast Surgery, Siriraj Hospital, Thailand examined the association between lymph node staging and TTS, stratified by primary tumor size. Patients with neoadjuvant therapy, DCIS, or underwent excisional biopsy were excluded.

Results: Of 424 patients, mean age 60.95 years, had an average tumor size 17±13.38 mm, and 20.8% LNs metastasis. The mean TTS was 7 ± 3.11 weeks. The proportion of + LNs patients stratified by tumor size was 10.6% for T1, 34.56% for T2, and 43.75% for T3 lesions. There was no significant difference between TTS and the proportion of N-staging for all T2 and T3 tumors. In contrast, a significant finding was observed among T1 tumors. Axillary nodal metastasis became more advanced as TTS increased (p-value = 0.022); and increased N2 and N3 nodal staging was noted in patients with delayed surgery. No significant additional differences were found concerning breast cancer subtype, pathological grading, or lympho-vascular/perineural invasion.

Conclusion: Increasing TTS was significantly associated with more advanced N staging. This finding highlights the need for timely intervention in early breast cancer, particularly in T1 tumors.

Keywords: Breast cancer; time to surgery; lymph node staging (Siriraj Med J 2024; 76: 831-839)

INTRODUCTION

Breast cancer is the most common cancer and is the second leading cause of cancer-related deaths in women.[1] The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) stages based on tumor size (T), lymph node metastasis (N), and distant metastasis (M). Tumor size and lymph node metastasis are the most powerful factors to evaluate breast cancer prognosis.[2,3] Axillary lymph node status is also an important predictor of prognosis in primary breast cancer.[4,5] There are several other factors that can predict the occurrence of lymph node metastasis, including, tumor size, histological grading, lateral and retro-areolar tumor location, presence of lympho-vascular invasion, HER-2 expression, grade 3 tumor, elevated Ki-67 and triple-negative.[6,7]

Tumor size and nodal metastasis has been evaluated with evidence that increasing tumor size is associated with a greater number of metastatic lymph nodes.[8] Most studies demonstrated a correlation between primary tumor size and the likelihood of either metastasis to lymph nodes or distant sites with a consistent linear relationship between tumor size (range of 1.0 and 5.0 cm) and metastasis. This relationship is thought to extend in both directions, allowing for the prediction of the likelihood proportions of nodal or distant metastases in cases of very small or very large tumors.[9-11]

The delay between diagnosis and surgery (time to surgery: TTS) can cause concerns in breast cancer patients due to potential tumor progression. Several studies reported association between delays in surgical treatment are significantly associated with lower survival rates in breast cancer, particularly when delay time was extended beyond 1 - 3 months.[12,13] The overall mortality hazard ratio (HR) was 1.10 (p<0.001) for each 60-day increase in delay TTS, with significant effects observed in stages I (HR 1.16, p<0.001) and II (1.09, p<0.001), after adjusting for demographic, tumor and treatment factors. Time to surgery was statistically significant concerning OS in stage I (HR 1.13, p<0.001, 95% CI 1.08–1.18) and stage II (HR 1.06, p=0.010, 95% CI 1.01–1.11), but not in stage III (HR 1.06, p=0.17, 95% CI 0.97–1.16). A longer time to surgery is associated with lower OS and DFS especially in early breast cancer. Reduce time required for preoperative evaluation and considerations can offer benefits to improve survival.[13] Previous studies demonstrate the impact of TTS on breast cancer-specific survival but do not fully explain why more advanced disease may develop due to prolonged treatment delays either from tumor growth or significantly progress in nodal metastasis staging.

Our objective was to assess the impact of the time interval between biopsy for diagnosis and subsequent surgery on the incidence of metastatic lymph nodes, while controlling for tumor size. We hypothesized that, within tumors of identical dimensions, a shorter interval between diagnosis and surgical intervention would be associated with a lower incidence of nodal metastasis.

Furthermore, we sought to examine how tumor subtype influences the likelihood of nodal metastasis.

MATERIALS AND METHODS

This cross-sectional retrospective study was conducted with primary breast cancer patients without metastasis, treated between October 2021 and December 2022, at the Division of Head Neck and Breast Surgery, Siriraj Hospital, Thailand. Patients with neoadjuvant systemic therapy, excisional biopsy-proven cancers, male breast cancer, and carcinoma in situ with or without micro-invasion were excluded from the study

Age, tumor size, lymph node status, pathologic subtypes, histologic grading, lympho-vascular/perineural invasion, and tumor biology of patients were collected. Details of the biopsy and surgery dates (time to surgery) were also recorded.

Tumor size and degree of lymph node status were classified according to AJCC criteria (T1a = tumor size > 0.1 cm. but <= 0.5 cm, T1b = > 0.5 but <= 1.0 cm., T1c = > 1.0 but <= 2 cm., T2 = >2.0 but <= 5.0 cm, T3 = >5 cm. in greatest dimension, N0 = negative LNs, N1 = 1-3 positive LNs, N2 or 4-9 positive LNs, N3 or >= 10 positive LNs). The time from biopsy to surgery (TTS) was categorized into 7 interval period: weekly intervals during the first month, bi-weekly in the second month, and as beyond eight weeks.

The proportion of N staging: (N0, N1, N2, N3) in each TTS interval, controlled by T staging, was calculated as a prognostic indicator.

We also analyzed the influence of nodal metastasis, controlled by different tumor subtypes.

Statistical analysis

Statistical analyses were conducted using PASW statistics version 18 (Mahidol Licensed Software). Baseline characteristics and clinical data were divided by T staging, N staging, pathologic type and subtype, grading, lympho-vascular/perineural invasion. These were presented as numbers and percentages. Continuous variables, such as age, tumor size, and time to surgery after a core needle biopsy, were presented as mean ± SD or median (minimum, maximum) accordingly. Time to surgery was classified into intervals: weekly in the first month, bi-weekly in the second month, and beyond eight weeks to assess the effects of delayed treatment. The association between time to surgery and proportion of nodal status (N staging), stratified by T stage, was assessed using the Chi-square test and the Cochran–Mantel–Haenszel test was used for each tumor size sub-group. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Among the 839 breast cancer patients treated during the study period, data were collected from 424 patients who met the eligibility criteria. Patient and tumor characteristics are presented in Table 1. The average age of the patients was 60.95 years (interquartile range, 25 to 97). The median tumor size was 17 ± 13.38 mm. Axillary lymph node metastasis was present in 21% of the patients (88 patients). The proportion of node-positive patients, stratified by tumor size, was 10.6% in T1 lesions, 34.56% for T2 lesions, and 43.75% in T3 lesions. The mean time to surgery after diagnosis was 7 ± 3.11 weeks, with only 12 patients (2.83%) undergoing surgery more than 12 weeks after diagnosis. Most patients had invasive ductal carcinoma (83%), with histologic grades 1, 2, and 3 accounting for 14.8%, 62%, and 23.2% respectively. Breast cancer subtypes included Luminal A (ER-positive and/or PR-positive with Ki 67 <=20%) at 28.6%, Luminal B (ER-positive and/or PR-positive with Ki 67 >20%) at 53.9%, HER-2 over-expression at 6.3%, and Triple negative at 11.3%. Lympho-vascular or perineural invasion was positive in only 18.7% of cases.

Almost half of the T3 tumors had lymph node involvement at the time of surgery, with N+ (nodal metastasis) present at the earliest time to surgery. Although more aggressive or advanced stages of N status (N2 and N3) were observed in the T3 group with increasing time to surgery, no significant difference was found between the time to surgery and the proportion of axillary nodal metastasis (p-value = 0.563) (Table 2 and Fig 1).

In patients with T2 tumors, lymph node involvement of at least N1 was observed in every patient group regardless of the time to surgery following diagnostic biopsy. However, a trend toward more aggressive nodal involvement was noted with increasing time to surgery: N2 involvement was seen after 3 weeks, and N3 after 4 weeks post-diagnosis. Despite these observations, there was no significant difference between the time to surgery and the proportion of axillary nodal metastasis (p-value = 0.562) as shown in Table 2. There was a trend toward conversion from N1 to N2 disease if delayed surgery was delayed beyond 4 weeks, with the proportion of N2 lymph node involvement increasing from 5% to 13.5% if the delay extended from 4 weeks to more than 8 weeks (Fig 1).

A significant finding was observed among patients with T1 tumors, where lymph node involvement was first detected in the 4th week after diagnosis, indicating more than 3 weeks of waiting time for surgery. Additionally, a higher proportion of node-positive patients was correlated with increased time to surgery. This difference was statistically

TABLE 1. Baseline characteristics of 424 breast cancer patients and tumor histologic reports.

Characteristic	Number (%)	Median ± SD
Age (years)		60.95 ± 12.31 (25-97)
Tumor size (mm.)		17 ± 13.38 (1-85)
T Staging		
T1 (<=2 cm.)	246 (58.02%)	
T2 (2.1-5 cm.)	162 (38.21%)	
T3 (>5 cm.)	16 (3.77%)	
Number of positive lymph nodes		0.68 (0-19)
N Staging		
N0 (negative node)	336 (79.2%)	
N1 (positive 1-3 nodes)	64 (15.1%)	
N2 (positive 4-9 nodes)	18 (4.2%)	
N3 (positive >=10 nodes)	6 (1.4%)	
Pathologic type		
Invasive ductal carcinoma	352 (83%)	
Invasive lobular carcinoma	32 (7.6%)	
Invasive mammary carcinoma	12 (2.8%)	
Favorable subtype *	28 (6.6%)	
Histologic grading		
1	62 (14.8%)	
2	259 (62%)	
3	97 (23.2%)	
Subtype		
Luminal A	119 (28.6%)	
Luminal B, HER2 negative	192 (46.2%)	
Luminal B, HER2 positive	32 (7.7%)	
HER2 over-expression	26 (6.3%)	
Triple negative	47 (11.3%)	
Lympho-vascular invasion/ Perineural invasion		
Negative	335 (81.3%)	
Positive	77 (18.7%)	
Time to surgery after core needle biopsy (weeks)		7 ± 3.11 (1-34)
Time to surgery after core needle biopsy by weeks		
1	1 (0.2%)	
2	17 (4%)	
3	24 (5.7%)	
4	39 (9.2%)	
6	103 (25.5%)	
8	109 (25.7%)	
More than 8 weeks	131 (54.1%)	

*favorable subtype: tubular, mucinous, cribriform, encapsulated or solid papillary carcinoma, adenoid cystic and other salivary carcinomas, secretory carcinoma, rare low-grade forms of metaplastic carcinoma

TABLE 2. Associations between time to surgery and nodal status by tumor size.

Tumor size N=424	Time to surgery within … week(s)	N0	N1	N2	N3	p-Value
T1	W1 (N=1)	1 (100%)	0	0	0	0.022 *
N=246	W2 (N=12)	12 (100%)	0	0	0	
(58.02%)	W3 (N=11)	11 (100%)	0	0	0	
	W4 (N=24)	23 (95.83%)	0	1 (4.17%)	0	
	W6 (N=59)	54 (91.53%)	5 (8.47%)	0	0	
	W8 (N=65)	58 (89.23%)	5 (7.69%)	1 (1.54%)	1 (1.54%)	
	More than 8 (N=74)	62 (83.78%)	9 (12.16%)	3 (4.05%)	0	
	Total	221(89.84%)	19 (7.72%)	5 (2.03%)	1 (0.41%)	
T2	W1 (N=0)	-	-	-	-	0.562
N=162	W2 (N=4)	2 (50%)	2 (50%)	0	0	
(38.21%)	W3 (N=12)	9 (75%)	3 (25%)	0	0	
	W4 (N=13)	8 (61.54%)	3 (23.08%)	2 (15.38%)	0	
	W6 (N=37)	26 (66.67%)	10 (25.64%)	2 (5.13%)	1 (2.56%)	
	W8 (N=42)	28 (66.67%)	11 (26.19%)	2 (4.76%)	1 (2.38%)	
	More than 8 (N=52)	33 (63.46%)	12 (23.08%)	7 (13.46%)	0	
	Total	106 (65.43%)	41 (25.31%)	12 (7.41%)	3 (1.85%)	
T3	W1 (N=0)	-	-	-	-	0.563
N=16	W2 (N=2)	1 (50%)	0	0	1 (50%)	
(3.77%)	W3 (N=1)	0	0	0	1 (100%)	
	W4 (N=1)	1 (100%)	0	0	0	
	W6 (N=5)	2 (40%)	3 (60%)	0	0	
	W8 (N=2)	2 (100%)	0	0	0	
	More than 8 (N=5)	3 (60%)	1 (20%)	0	1 (20%)	
	Total	9 (56.25%)	4 (25%)	0	3 (18.75%)	

* Statistically significant P <0.05

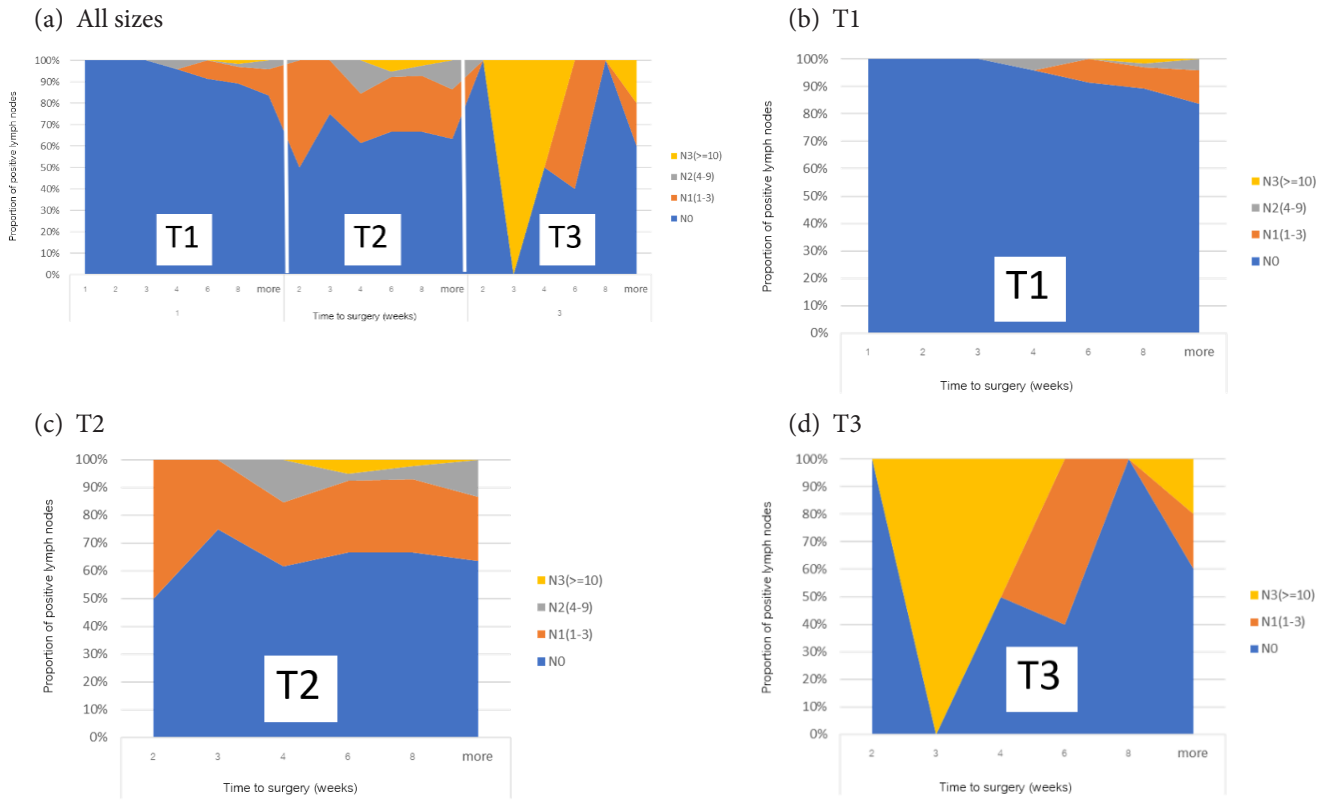
significant, with a p-value of 0.022, highlighting the relationship between the time to surgery and axillary nodal metastasis (N staging) in this group (Table 2).

Subgroup analysis of T1 tumors revealed distinct patterns regarding tumor size and the onset of lymph node involvement. Specifically, in patients with tumor sizes ranging from 1-2 cm (T1c), lymph node involvement was observed after the 3rd week post-diagnosis. In contrast, patients with tumors equal to or less than 1 cm exhibited no lymph node involvement until the 6th week (Table 3 and Fig 2 a, b, and c).

The findings regarding T1 tumors are particularly notable. Within less than three weeks after diagnosis, 89.84% of these cases (221 out of 246 patients) showed no lymph node metastasis, indicating that most patients with T1 tumors do not exhibit lymph node involvement early on.

There were no significant differences in lymph node metastasis based on breast cancer subtype, pathological grading, or lympho-vascular/perineural invasion (p-value = 0.147).

Among different breast cancer subtypes, Luminal A, Luminal B HER2 negative, Luminal B HER2 positive, HER-2 over-expression, and Triple negative, there was no significant difference correlation between the time to surgery and the proportion of axillary nodal metastasis. The p-values for these subtypes were 0.862, 0.253, 0.550, 0.357 and 0.941, respectively (Table 4).

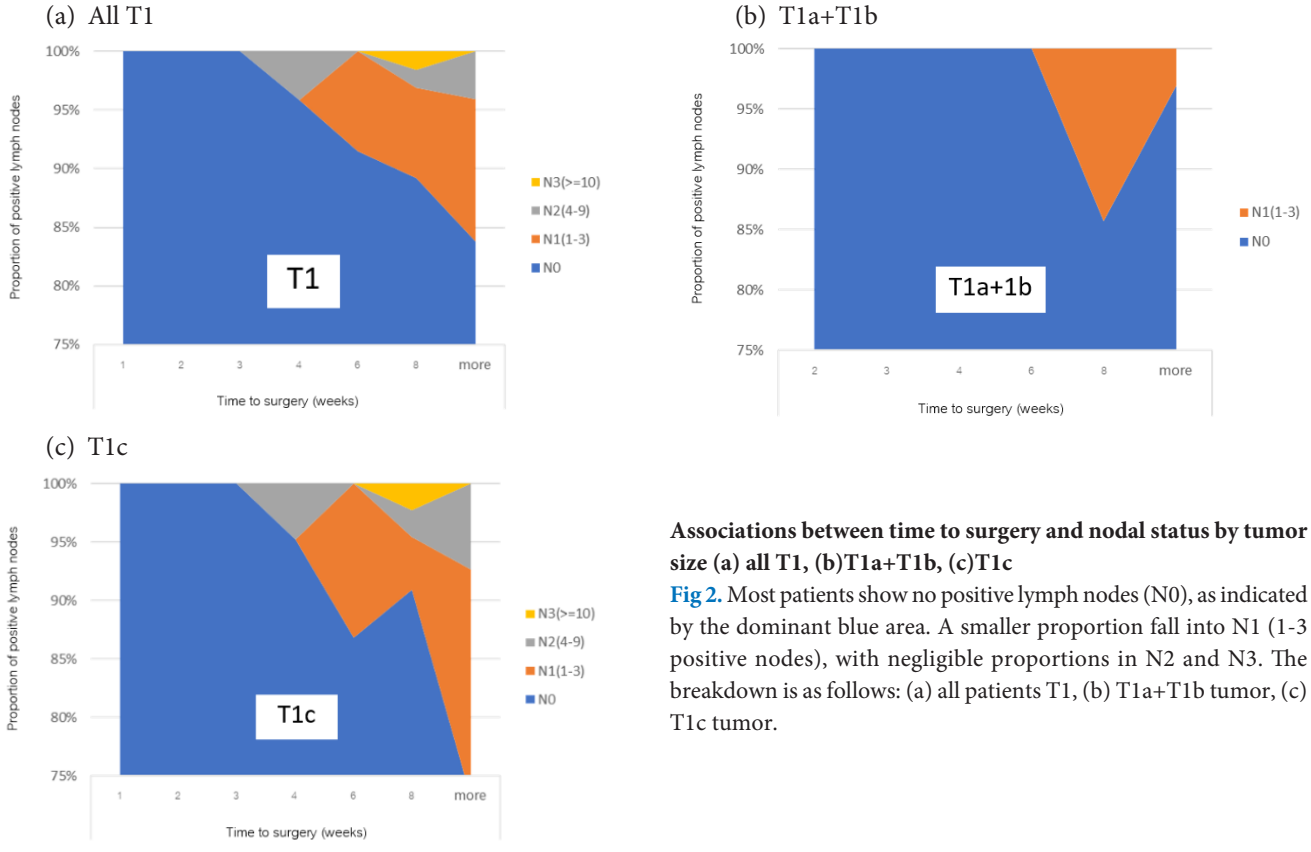


Associations between time to surgery and nodal status by tumor size (a) all sizes, (b) T1, (c) T2, (d) T3

Fig 1. Proportion of positive lymph nodes over time until surgery, categorized by the number of positive lymph nodes (N0, N1, N2, N3). The graph shows that as the time to surgery increases, the likelihood of having a greater number of positive lymph nodes also rises. Initially, most patients have no positive lymph nodes (N0), but with delays in surgery, es, there's a shift towards higher categories (N1, N2, N3). This trend suggests that earlier surgical intervention might help reduce the extent of lymph node involvement in (a) all patients, (b) those with T1 tumor, (c) those with T2 tumor, (d) and those with T3 tumor.

TABLE 3. Associations between time to surgery and nodal status by tumor size T1 only, T1a+T1b, T1c.

Tumor size (T1 only) N=246	Time to surgery within … week(s)	N0	N1	N2	N3
T1a+T1b	W1 (N=0)	-	-	-	-
N=85	W2 (N=2)	2 (100%)	0	0	0
(34.55%)	W3 (N=5)	5 (100%)	0	0	0
	W4 (N=3)	3 (100%)	0	0	0
	W6 (N=21)	21 (100%)	0	0	0
	W8 (N=21)	18 (85.71%)	3 (14.29%)	0	0
	More (N=33)	32 (96.97%)	1 (3.03%)	0	0
	Total	81 (95.29%)	4 (4.71%)	0	0
T1c	W1 (N=1)	1 (100%)	0	0	0
N=161	W2 (N=10)	10 (100%)	0	0	0
(65.45%)	W3 (N=6)	6 (100%)	0	0	0
	W4 (N=21)	20 (95.24%)	0	1 (4.76%)	0
	W6 (N=38)	33 (86.84%)	5 (13.16%)	0	0
	W8 (N=44)	40 (90.91%)	2 (4.55%)	1 (2.27%)	1 (2.27%)
	More (N=41)	30 (73.17%)	8 (19.51%)	3 (7.32%)	0
	Total	140 (86.96%)	15 (9.32%)	5 (3.11%)	1 (0.62%)



Associations between time to surgery and nodal status by tumor size (a) all T1, (b)T1a+T1b, (c)T1c

Fig 2. Most patients show no positive lymph nodes (N0), as indicated by the dominant blue area. A smaller proportion fall into N1 (1-3 positive nodes), with negligible proportions in N2 and N3. The breakdown is as follows: (a) all patients T1, (b) T1a+T1b tumor, (c) T1c tumor.

DISCUSSION

In this study, 79% of the patient population had early-stage breast cancer, with 58% presenting with T1 lesions and no LN metastasis. The proportion of LN metastasis was 10.16% for T1 lesions, 34.56% for T2 lesions, and 43.75% for T3 lesions. The LN involvement rates for T1 lesions are consistent with other studies, which report 10-27% nodal metastasis. However, our findings for T2 and T3 lesions differ from other studies, which report 44-62% and 68-78% LN metastasis, respectively.[14]

We hypothesized that tumors of the same T stage would have a consistent proportion of LN metastasis regardless of other factors. Our study aimed to evaluate the impact of the interval between biopsy for diagnosis and subsequent surgery (time to surgery, TTS) on the number of metastatic lymph nodes (N staging), stratified by tumor size. We anticipated that shorter intervals between biopsy and surgery would be associated with less aggressive nodal metastasis. Our findings indicate that, for T2 and T3 tumors, there was no statistically significant difference in nodal metastasis related to the time to surgery. However, there was a trend toward increased axillary lymph node metastasis with delayed surgery. Specifically, T2 lesions showed more advanced N2 and N3 after 3 weeks, while T3 lesions showed more advanced N3 metastasis after 2 weeks, with p-values of 0.562 and 0.563, respectively.

Our study revealed that varying times to surgery significantly affect the proportion of axillary nodal metastasis in small tumor (T1), with a p-value of 0.022. Patients with T1 lesions are more likely to have positive lymph nodes after a waiting period of 3 weeks, with this trend being more pronounced in T1c lesions, as reported in Table 3. This finding is novel and has not been reported in other studies. The results underscore the impact of time to surgery on lymph node involvement, particularly for T1 tumors. Smaller tumors tend to show lymph node metastasis later compared to larger tumors, indicating that small tumors are less likely to have lymph node metastasis early on compared to bigger tumors. This observation helps explain why delays in surgery can adversely affect overall survival, as prolonged waiting times lead to more advanced disease due to increased N staging over time. We recommend the threshold or safety period for waiting list before surgery in T1 patients as not more than 3 weeks.

We acknowledge that histologic subtype, pathological grading, and lympho-vascular/perineural invasion did not show significant differences in the aggressiveness of nodal metastasis. This aligns with some research suggesting that the effect of these factors on metastatic potential and survival is independent of the intrinsic breast cancer subtype.[15]

TABLE 4. Associations between time to surgery and nodal status by breast cancer subtype.

Subtypes of breast cancer	Time to surgery within … week(s)	N0	N1	N2	N3	p-value
Luminal A	W1 (N=1)	1 (100%)	0	0	0	0.862
N=119	W2 (N=4)	4 (100%)	0	0	0	
(28.06%)	W3 (N=8)	8 (100%)	0	0	0	
	W4 (N=15)	12 (80%)	2 (13.30%)	1 (6.70%)	0	
	W6 (N=28)	25 (89.30%)	2 (7.10%)	0	1 (3.60%)	
	W8 (N=26)	24 (92.30%)	2 (7.70%)	0	0	
	More than 8 (N=37)	32 (86.50%)	4 (10.80%)	1 (2.70%)	0	
	Total	106 (89.10%)	10 (8.40%)	2 (1.70%)	1(0.80%)	
Luminal B,	W1 (N=0)	-	-	-	-	0.253
HER2 negative	W2 (N=10)	8 (80%)	2 (20%)	0	0	
N=192	W3 (N=12)	8 (66.70%)	3 (25%)	0	1 (8.30%)	
(45.28%)	W4 (N=10)	8 (80%)	0	2 (20%)	0	
	W6 (N=43)	31 (72.10%)	10 (23.30%)	2 (4.70%)	0	
	W8 (N=60)	44 (73.30%)	13 (21.70%)	3 (5%)	0	
	More than 8 (N=57)	33 (63.20%)	14 (24.60%)	6 (10.50%)	1 (1.80%)	
	Total	135 (70.30%)	42 (21.90%)	13 (6.80%)	2 (1%)	
Luminal B,	W1 (N=0)	-	-	-	-	0.550
HER2 positive	W2 (N=2)	-	-	-	-	
N=32	W3 (N=1)	-	-	-	-	
(7.55%)	W4 (N=4)	3 (75%)	1 (25%)	0	0	
	W6 (N=14)	11 (78.6%)	3 (21.4%)	0	0	
	W8 (N=4)	4 (100%)	0	0	0	
	More than 8 (N=10)	7 (70%)	2 (20%)	1 (10%)	0	
	Total	25 (78.10%)	6 (18.8%)	1 (3.10%)	0	
HER2	W1 (N=0)	-	-	-	-	0.357
Overexpression	W2 (N=2)	2 (100%)	0	0	0	
N=26	W3 (N=1)	1 (100%)	0	0	0	
(6.13%)	W4 (N=1)	1 (100%)	0	0	0	
	W6 (N=6)	4 (66.70%)	2 (33.30%)	0	0	
	W8 (N=4)	2 (50%)	0	0	2 (50%)	
	More than 8 (N=8)	5 (62.50%)	1 (12.50%)	2 (25%)	0	
	Total	18 (69.20%)	3 (11.50%)	2 (7.70%)	3 (11.50%)	
Triple negative	W1 (N=0)	-	-	-	-	0.941
N=47	W2 (N=1)	1 (100%)	0	0	0	
(11.08%)	W3 (N=3)	3 (100%)	0	0	0	
	W4 (N=4)	4 (100%)	0	0	0	
	W6 (N=10)	9 (90%)	1 (10%)	0	0	
	W8 (N=12)	11 (91.70%)	1 (8.30)	0	0	
	More than 8 (N=5)	16 (94.10%)	1 (5.90%)	0	0	
	Total	44 (93.60%)	3 (6.40%)	0	0	

Consistent with other studies, the SMDB cohort of 94,544 patients showed that each increase in delay interval was associated with lower overall survival (hazard ratio [HR] 1.09, $p<0.001$), particularly in stage I (HR 1.13, $p<0.001$) and stage II (HR 1.06, $p=0.010$) patients. Breast cancer-specific mortality also increased with each 60-day delay (sub-hazard ratio 1.26, $p= 0.03$). The NCDB study, which included 115,790 patients >=18 years old, diagnosed between 2003 and 2005, found a similar trend of overall mortality for each additional interval, significant in stages I (HR 1.16, $p<0.001$) and II (1.09, $p<0.001$), adjusting for demographic, tumor and treatment factors. The overall mortality increase regardless of stages and causes was 9% (HR 1.09, $p<0.001$) for each preoperative interval. Time to surgery (TTS) was statistically significant in relation to OS in stage I (HR 1.13, $p<0.001$) and stage II (HR 1.06, $p=0.010$, 95% CI 1.01–1.11). Longer TTS is associated with lower overall and disease-specific survival, and reducing the delay is linked to benefits comparable to some standard therapies.[13] Our study provides a more precise evaluation of TTS effects on increasing N-stage, which could inform guidelines for recommending expedited treatment for breast cancer especially in early breast cancer.

CONCLUSION

In summary, our results suggest that longer time to surgery is associated with nodal negative/positive status especially in early breast cancer and small size tumors (T1). Performing surgery sooner may improve prognosis, highlighting the importance of timely intervention.

ACKNOWLEDGEMENT

Grants and Funding Information

No grants or funding applied

Conflict of Interest

At the time of submission for IRB approval, the title of research was “The association between post-biopsy interval and axillary nodal metastasis with the same tumor size in breast cancer” and the title has been changed to “Post-biopsy to surgery interval tends to increase axillary nodal metastasis, especially in early breast cancer patients” at the time of submission.

Author Contributions

Conceptualization and methodology, Ph.P., P.P. and A.R.; Investigation, Ph.P. and A.R.; Formal analysis, Ph.P. and A.R.; Visualization and writing – original darft, Ph.P.; Writing – review and editing, Ph.P., P.P. and A.R.; Supervision, A.R.. All authors have read and agreed to the final version of the manuscript.

Use of artificial intelligence

No artificial intelligence used

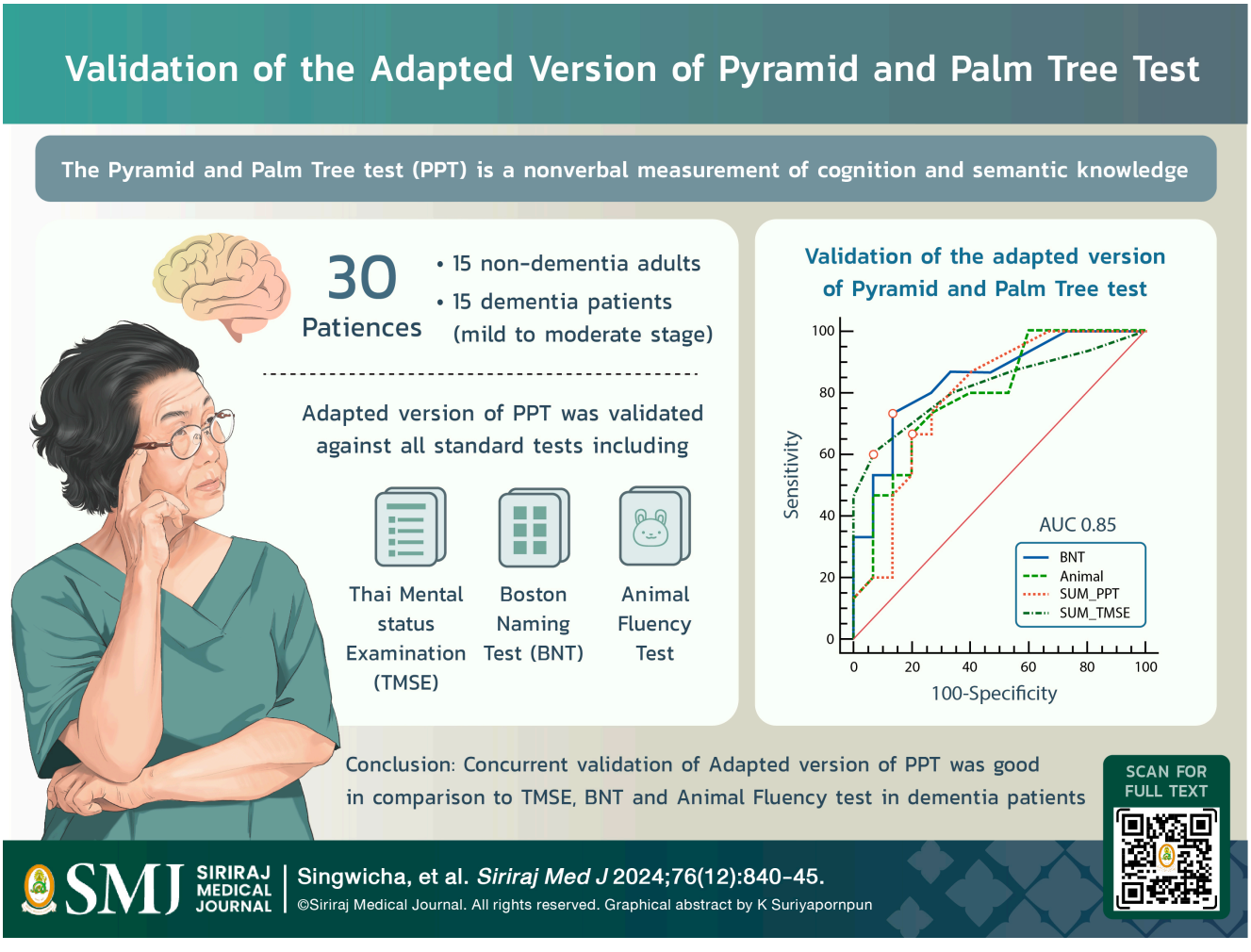
REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7-30.
2. Rosenberg J, Chia YL, Plevritis S. The effect of age, race, tumor size, tumor grade, and disease stage on invasive ductal breast cancer survival in the U.S. SEER database. Breast Cancer Res Treat. 2005;89(1):47-54.
3. Fitzgibbons PL, Page DL, Weaver D, Thor AD, Allred DC, Clark GM, et al. Prognostic factors in breast cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med. 2000;124(7):966-78.
4. Axelsson CK, Mouridsen HT, Zedeler K. Axillary dissection of level I and II lymph nodes is important in breast cancer classification. The Danish Breast Cancer Cooperative Group (DBCG). Eur J Cancer. 1992;28a(8-9):1415-8.
5. Beenken SW, Urist MM, Zhang Y, Desmond R, Krontiras H, Medina H, et al. Axillary lymph node status, but not tumor size, predicts locoregional recurrence and overall survival after mastectomy for breast cancer. Ann Surg. 2003;237(5):732-8; discussion 8-9.
6. Stevens A, Lowe JS, Scott I, Stevens A. Core pathology. 3rd ed. St. Louis, Mo: Elsevier; 2009.
7. Dahan M, Hequet D, Bonneau C, Paoletti X, Rouzier R. Has tumor doubling time in breast cancer changed over the past 80 years? A systematic review. Cancer Med. 2021;10(15):5203-17.
8. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer. 1989;63(1):181-7.
9. Sivaramakrishna R, Gordon R. Detection of breast cancer at a smaller size can reduce the likelihood of metastatic spread: a quantitative analysis. Acad Radiol. 1997;4(1):8-12.
10. Laura S, Coombs NJ, Ung O, Boyages J. Tumour size as a predictor of axillary node metastases in patients with breast cancer. ANZ J Surg. 2006;76(11):1002-6.
11. Yu KD, Jiang YZ, Shao ZM. Difference between observed and expected number of involved lymph nodes reflects the metastatic potential of breast cancer independent to intrinsic subtype. Oncotarget. 2015;6(18):16686-97.
12. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. Lancet. 1999;353(9159):1119-26.
13. Bleicher RJ, Ruth K, Sigurdson ER, Beck JR, Ross E, Wong YN, et al. Time to Surgery and Breast Cancer Survival in the United States. JAMA Oncol. 2016;2(3):330-9.
14. Sopik V, Narod SA. The relationship between tumour size, nodal status and distant metastases: on the origins of breast cancer. Breast Cancer Res Treat. 2018;170(3):647-56.
15. Wo JY, Chen K, Neville BA, Lin NU, Punglia RS. Effect of very small tumor size on cancer-specific mortality in node-positive breast cancer. J Clin Oncol. 2011;29(19):2619-27.

Validation of the Adapted Picture Version of the Pyramids and Palm Trees Test for Thais with Dementia

Duangkamol Singwicha, M.D.[1], Chatchawan Rattanabannakit, M.D.[2], Saowalak Hunnangkul[2], Atthapon Raksthaput[2], Sunisa Chaichanettee[2], Natthamon Wongkom[2], Pathitta Dujada[2], Vorapun Senanarong, M.D.[2,*]

[1]Division of Neurology, Department of Medicine, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand, [2]Division of Neurology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.



Corresponding author: Vorapun Senanarong
E-mail: Vorapun.sen@mahidol.ac.th
Received 16 July 2024 Revised 10 September 2024 Accepted 13 September 2024
ORCID ID:http://orcid.org/0000-0002-2774-4187
https://doi.org/10.33192/smj.v76i12.270244

ABSTRACT

Objective: We aimed to validate Pyramids and Palm Trees test (PPT) in dementia cohort and explore reliability measurement of this test.

Materials and Methods: The study was designed as a cross-sectional study. A total of 30 subjects were recruited from the Memory Clinic at Siriraj Hospital, Thailand: 15 non-dementia adults and 15 dementia patients (mild to moderate stage). In content validation, the picture version of the PPT was given to experts to evaluate the content of the test. According to consensus, some pictures with cultural issues were adapted to be more culturally appropriate. For concurrent validation, the PPT was compared against standard tests (Thai Mental Status Examination (TMSE), Boston Naming Test (BNT), Animal Fluency Test) using Spearman correlation and Receiver Operating Characteristic (ROC) analysis. The internal reliability of the PPT was assessed using Intraclass Correlation Coefficient (ICC) and Cronbach's Alpha.

Results: Among the 52 pictures in the PPT, 25 pictures were changed. The median score of the PPT was 49 for non-dementia group and 43 for dementia group. The PPT was significantly correlated with the Animal Fluency Test, the BNT, and the TMSE. ROC analysis revealed an Area Under the Curve (AUC) of 0.8. ICC was 0.86 (95% CI, 0.78 to 0.92), and internal consistency was 0.87, indicating good to satisfactory reliability.

Conclusions: The PPT demonstrated good concurrent validity compared to the TMSE, BNT, and Animal Fluency Test in dementia patients. Based on this study, it is recommended as a test for semantic memory in Thai individuals with dementia.

Keywords: Dementia; semantic memory; neuropsychiatric testing; pyramids and palm trees test (Siriraj Med J 2024; 76: 840-845)

INTRODUCTION

Similar to many other countries, the aging society in Thailand has become an important issue. The diseases that come from cognitive degeneration, such as Alzheimer's dementia, and Parkinson's, will be increasingly encountered. Such neurodegenerative diseases involve physical symptoms and a decrease in patient cognition. In the course of the diseases, they will impact the cognitive memory domain. Some patients will find themselves having problems in their language abilities, such as effortful speech, word-finding difficulty, or low speech production. These effects will decrease their quality of life.[1] Abnormalities in language are found in Alzheimer's disease, frontotemporal dementia, corticobasal degeneration, and vascular pathology. These conditions can lead to primary progressive aphasia (PPA).[2,3] The 3 variants of PPA are semantic variant PPA (svPPA), logopenic variant PPA (lvPPA), and nonfluent variant PPA (nfvPPA). Determining the cause of pathology, physical examination followed by neuropsychological testing is essential.

Semantic knowledge encompasses the general knowledge and features that form the concepts people acquire from their experiences.[4] These experiences culminate in memories related to people, places, and the meaning of words. This semantic memory is a component of declarative memory and can be retrieved from the anterior temporal lobe.[5,6] The most common neuropsychological tests to measure semantic memory are naming tests, verbal fluency tests for category and letter fluency, and the Pyramids and Palm Trees (PPT) test.

The PPT test is a nonverbal measurement of cognition and semantic knowledge. The test is available in both word and picture modalities to assess verbal and nonverbal semantic memory, respectively. It was designed by Howard and Patterson in 1992 and standardized in England.[7] Since then, it has been used across Europe. Nevertheless, applying the picture version of the test in other countries may have limitations due to cultural and education issues related to the pictures. Several studies have used the PPT test to investigate semantic memory in their population to establish normative data. The Spanish population's formal education level correlated with the PPT test results.[8] Similarly, an investigation of a Chinese population showed that schooling affected test performance.[9]

In Asian countries, including Thailand, the PPT test has not been used due to cultural issues related to the test pictures. This study aimed (1) to validate a Thai adaptation of the picture version of the PPT test with 2 standard tests—the Boston Naming Test (BNT) and the Verbal Fluency (VF) test—in a dementia cohort and (2) to explore its reliability in the Thai population.

MATERIALS AND METHODS

A cross-sectional study design was used. A total of 30 eligible participants were recruited from the Memory Clinic of Siriraj Hospital, Thailand. Participants were separated into 2 groups. There were 15 healthy subjects (the "non-dementia group") and 15 subjects with mild to moderate stages of Alzheimer's disease according to DSM-5 criteria and NIA-AA criteria of Alzheimer's disease dementia[13,14] which requires objective cognitive decline that is severe enough to interfere with activities daily living and decline of neuropsychiatric testing more than 2 standard deviation (the "dementia group"). Different inclusion criteria were applied to each group. In the case of the non-dementia group, the participants were (1) aged between 50 and 80, (2) did not have underlying diseases related to memory or language problems, and (3) could communicate in Thai. In the dementia group, the criteria were (1) aged between 50 and 80; (2) a mild to moderate stage of Alzheimer's disease (defined as a Thai Mental State Examination [TMSE] score of 10–23); and (3) capable of communicating in Thai. In both groups, the participants' levels of education were divided into under 12 years and over 12 years of formal education.

The picture version of the PPT test consists of 55 sets of pictures. The first 3 sets are examples used to instruct participants on the test, while the remaining 52 sets are the test stimuli. Each set comprises 3 pictures that are presented on a display board. One, the "stimulus," is positioned in the upper half of the board; the other 2 pictures (1 "target" and 1 "distractor") are in the lower half. Participants are requested to select the lower-level picture that they consider to be more relevant to the stimulus. The maximum test score is 52, and the median score for normal cognition is 49.

An expert panel evaluated the content of the picture version of the PPT test used in English-speaking cultures to develop content for a Thai adaptation. Six experts (2 neurologists and 4 psychiatrists) agreed that 25 of the 55 picture sets needed to be replaced by ones more appropriate to Thailand (Supplementary Table A). For instance, it was decided to replace a picture of an Eskimo and igloo with one of a farmer and hut. Similarly, a picture of a shepherd's cane and sheep was substituted with a picture of a herding stick and buffalo. Additionally, minor changes were made to some pictures, such as using a Thai bus ticket instead of a London bus ticket. Some picture images were also sharpened (eg, one of a star and the moon and another of a pillow with a wrinkle). A pilot study was performed on 6 adults of various ages and education levels. The final, Thai-oriented version was then used in this study.

The proposed Thai adaptation of the PPT test was validated with 2 tests that correlate with semantic knowledge: the VF test (both category and letter fluency) and the BNT. To establish a baseline, the TMSE was first administered to all participants. Those scoring less than 24 on the TMSE were assigned to the dementia group. At the same visit as the TMSE, the dementia group was assessed using the Thai adaptation of the PPT test, the VF test, and the BNT. All tests were administered to the participants by 2 certificated psychiatrist assessors by using papers of pictures. The administration of the 3 tests took 45 to 50 minutes.

Statistical analysis

Statistical analyses were conducted with PASW Statistics for Windows, version 18.0 (SPSS Inc, Chicago, IL, USA). Continuous data (age) are summarized using descriptive statistics (the mean ± standard deviation). Categorical variables (sex, education, and underlying diseases) are summarized using numbers (percentages).

Pearson's correlation coefficients were used to determine the validity of the Thai adaptation of the PPT test in both healthy and dementia patients, with statistical significance indicated by probability (P) values < 0.05 ($P < 0.050$). Spearman's rank correlation coefficient was used to perform concurrent validation[12] of the PPT test against the other instruments (TMSE, BNT, and VF). We also used Cronbach's alpha and intraclass correlation coefficients by using 95% confidence intervals to indicate the internal consistency of the proposed PPT test. A receiver operating characteristic (ROC) curve analysis was performed, with the area under the curve (AUC) indicating the reliability of the PPT test compared with the 3 standard tests. An AUC of 0.7 to 0.8 signified (fair reliability, while 0.8 to 0.9 indicated good reliability and 0.9 to 1.0 denoted excellent reliability.

RESULTS

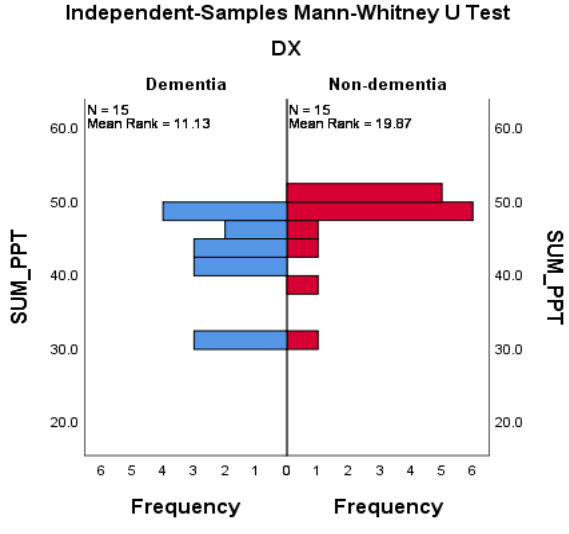
The 30 participants in the non-dementia and dementia groups had no significant differences in their baseline demographic characteristics (age, sex, education level, and underlying diseases; Table 1). However, the 2 groups had significant differences in their mean scores for all instruments (proposed PPT, TMSE, BNT, and VF; Table 2). The mean scores ± SD of the non-dementia and dementia groups were 46.93 ± 5.38 and 42.43 ± 6.27, respectively ($P = 0.044$). A Mann–Whitney U test determined that the median PPT test score was 49 for the non-dementia group and 43 for the dementia subjects ($P = 0.006$; Fig 1).

TABLE 1. Demographic characteristic.

	Non-dementia (N=15)	Dementia (N=15)	P-value
Sex			0.456
Male, n (%)	7(46.7)	5(33.3)	
Female, n (%)	8(53.3)	10(66.7)	
Age (mean ± SD)	65.47±8.58	72.0±10.92	0.790
Education (year), n (%)			0.713
≤ 12	9(60)	8(53.3)	
> 12	6(40)	7(46.7)	
Underlying disease, n (%)			
Hypertension	2(13.3)	5(33.3)	0.195
Dyslipidemia	7(46.7)	10(66.7)	0.269
Diabetes Mellitus	5(33.3)	9(60)	0.143
Atrial Fibrillation	2(13.3)	5(33.3)	0.195
Chronic Kidney Disease	0	1(6.7)	0.309
Others	0	1(6.7)	0.309

TABLE 2. Comparison between non-dementia and dementia group in all tests.

	Non-dementia (N=15) (Mean ± SD)	Dementia (N=15) (Mean ± SD)	P-value
Pyramid and palm	46.93±5.38	42.43±6.27	0.044
TMSE	28.27±1.28	24.33±4.25	0.002
Boston Naming Test	27.13±2.94	21.13±5.47	0.001
Verbal Fluency	20.60±5.73	14.00±5.33	0.003



Diagnosis	Sum PPT		p-value[a]
	Median	(IQR)	
Dementia	43	(42.0-47.5)	0.006
Non-dementia	49	(46.5-50.0)	

[a]Mann-Whitney U test

Fig 1. Median score of PPT test.

The 2 participant groups were combined to evaluate the correlation of the PPT test with the 3 standard tests for all patient types. Spearman's rank correlation coefficient was used to compare the PPT test with the other instruments. The PPT test was most correlated with the VF test (r = 0.652; $P < 0.001$), followed by the BNT (r = 0.641; $P < 0.001$), and last, the TMSE (r = 0.482; $P = 0.007$). Although the PPT test score also correlated with education level (r = 0.491, $P = 0.006$; Table 3), there was no correlation with age or sex.

Regarding the reliability of the test, an ROC analysis was performed to determine the AUC and make comparisons with the TMSE, BNT, and VF. The results showed that the proposed PPT test had an AUC of 0.85, the highest of the AUC values of the 4 instruments (Fig 2).

For the test's internal consistency, the intraclass correlation coefficient ($ICC_{3,k}$) was 0.86 (95% CI, 0.78-0.92), and Cronbach's alpha coefficient was 0.87.

DISCUSSION

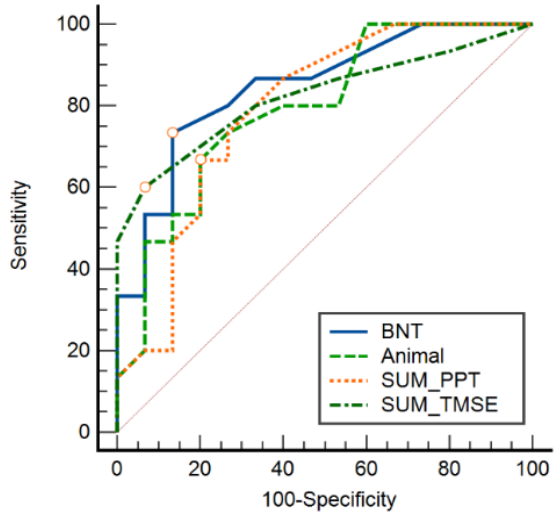
Several previous studies have been undertaken in various countries to determine the validity and reliability of the PPT test. Due to some cultural issues, normative data of a healthy population must be obtained before the test can be used with patients with dementia.

In Thailand, many tests are routinely used to evaluate multiple domains of cognition. In the case of the language domain, several tests are employed. The TMSE is a baseline test used to evaluate multiple domains for screening purposes, and it is administered to all patients

TABLE 3. Correlation of PPT with other tests.

Variables	Correlation coefficient	PPT	TMSE	BNT	Animal Fluency	Education
PPT	Spearman's Rho[a]	1				
	p-value	NA				
TMSE	Spearman's Rho[a]	0.482**	1			
	p-value	0.007	NA			
BNT	Spearman's Rho[a]	0.641**	0.583**	1		
	p-value	<0.001	0.001	NA		
Verbal Fluency	Spearman's Rho[a]	0.652**	0.650**	0.594**	1	
	p-value	<0.001	<0.001	0.001	NA	
Education	Spearman's Rho[a]	0.491**	0.455*	0.529**	0.585**	1
	p-value	0.006	0.012	0.003	0.001	NA

* Correlation is significant at the 0.05 level (2-tailed)., ** Correlation is significant at the 0.01 level (2-tailed).
[a] Spearman's rank correlation coefficient



Test	AUC
Boston Naming Test	0.071
Verbal Fluency	0.082
PPT	0.085
TMSE	0.080

Fig 2. Comparison of AUC of tests.

requiring neuropsychiatric assessment. Two tests that are more focused on language use are the BNT and the VF test (category and letter fluency). With the VF test, patients are given 1 minute to produce as many words as possible that either name animals (category fluency) or start with a given letter (letter fluency). The VF test can therefore be used to assess both language and executive functioning.

This study found that the proposed Thai adaptation of the picture version of the PPT test had a good correlation with other language tests and was highly correlated with the VF test ($r = 0.652$; $P < 0.001$). The adaptation also had a high ROC value, and the median scores for the Thai nondementia and dementia subjects were significantly different ($P = 0.006$). Additionally, the median PPT test score for the Thai patients without dementia was 49, which corresponds with the median score for the picture version used in English-speaking cultures. Furthermore, both the intraclass correlation and the internal consistency results were good to satisfactory (exceeding 0.8). Taken together, these results indicate that the proposed Thai adaptation is suitable for discriminating between dementia and non-dementia.

On the other hand, our investigation found an educational dependency in that participants' level of education (less than 12 years) was significantly associated with performance on the test. This finding is consistent with Guo and associates[9], whose investigation revealed that education level correlated with PPT test results in a Chinese population. Regarding age and sex, our research found no significant differences. Although these findings are consistent with Mehri[8], they conflict with the results of a study by Callahan and colleagues[10] on a Quebec-French population.

A limitation of this study is the size of the sample population. The small number of participants means that the findings may not be generalizable to the whole Thai population. It is recommended that further research should recruit a much larger sample.

CONCLUSION

The concurrent validation of the Thai adaptation of the picture version of the PPT test was good compared with the VF test, TMSE, and BNT in patients with dementia. Based on our investigation results, the Thai version of the PPT test can be employed as a test of semantic memory in Thais with dementia.

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 - none

VS and CR were responsible for the conceptualization. DS ,VS and CR handled the methodology. AR, SC, PD and NW performed data collection. SH carried out the formal analysis. VS and CR reviewed and edited the manuscript. VS supervised the project.

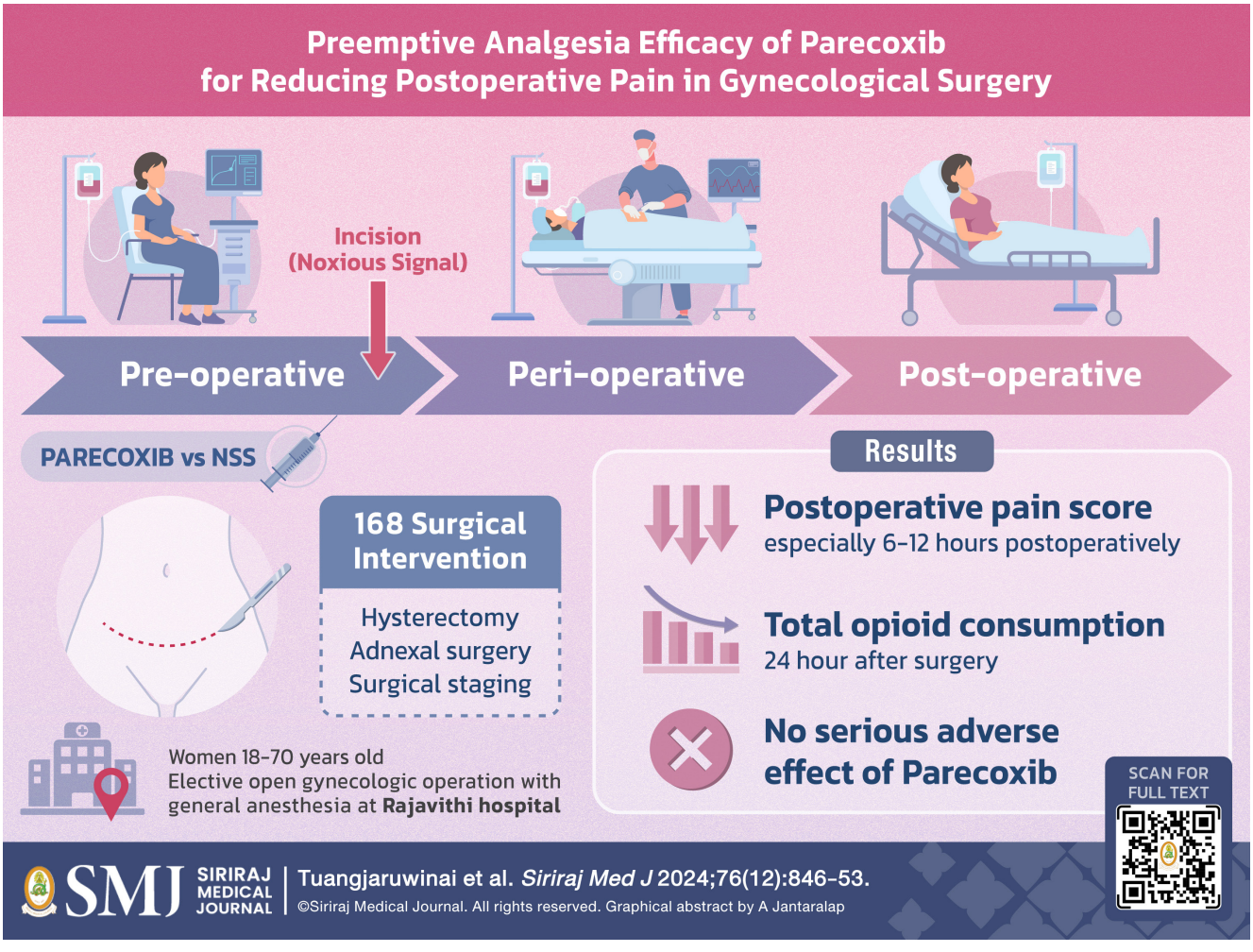
REFERENCES

1. Funnell E. Semantic memory. In: Hillis AE, Editor. The handbook of adult language disorders: integrating cognitive neuropsychology, neurology, and rehabilitation. New York, NY: Psychology Press; 2002.p.185–205.
2. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011; 76(11):1006–14.
3. Botha H, Josephs KA. Primary Progressive Aphasias and Apraxia of Speech. Continuum (Minneap Minn). 2019;25(1):101–27.
4. Kintz S, Wright HH. Semantic Knowledge Use in Discourse: Influence of Age. Discourse Process. 2017;54(8):670–81.
5. Dresang HC, Dickey MW, Warren TC. Semantic memory for objects, actions, and events: A novel test of event-related conceptual semantic knowledge. Cogn Neuropsychol. 2019;36 (7–8):313–35.
6. Willits JA, Amato MS, MacDonald MC. Language knowledge and event knowledge in language use. Cogn Psychol. 2015;78:1–27.
7. Howard D, Patterson K. The Pyramids and Palm Trees Test. A test of semantic access from words and pictures. Thames Valley Company, Bury St. Edmunds, 1992.
8. Mehri A, Mousavi SZ, Kamali M, Maroufizadeh S. Normative data for the Pyramids and Palm Trees Test in literate Persian adults. Iran J Neurol. 2018;17(1):18–23.
9. Guo Q, He C, Wen X, Song L, Han Z, Bi Y. Adapting the pyramids and palm trees test and the kissing and dancing test and developing other semantic tests for the Chinese population. Appl Psycholinguist 2014;35(6):1001–19.
10. Callahan BL, Macoir J, Hudon C, Bier N, Chouinard N, Cossette-Harvey M, et al. Normative Data for the Pyramids and Palm Trees Test in the Quebec-French Population. Arch Clin Neuropsychol. 2010;25(3):212–7.
11. Klein LA, Buchanan JA. Psychometric properties of the Pyramids and Palm Trees Test. J Clin Exp Neuropsychol. 2009;31(7):803–8.
12. Weber M, Van Ancum J, Bergquist R, Taraldsen K, Gordt K, Midolaizak AS, et al. Concurrent validity and reliability of the Community Balance and Mobility scale in young-older adults. BMC Geriatr. 2018;18:156.
13. Dubois B, Villain N, Frisoni GB, Rabinovici GD, Sabbagh M, Cappa S, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. Lancet Neurol. 2021;20(6): 484–96.
14. Apostolova LG. Alzheimer Disease. Continuum (Minneap Minn). 2016;22(2 Dementia):419–34.

Preemptive Analgesic Efficacy of Parecoxib for Reducing Postoperative Pain in Patients Undergoing Gynecological Surgery

Pasu Tuangjaruwinai, M.D.[1], Siriporn Thitisagulwong, M.D., M.SC. (HSE)[1,2,*]

[1]Department of Obstetrics and Gynecology, Rajavithi Hospital, Bangkok, Thailand, [2]College of Medicine, Rangsit University, Bangkok, Thailand.



*Corresponding author: Siriporn Thitisagulwong
E-mail: heroinsiporn@yahoo.com
Received 12 September 2024 Revised 9 October 2024 Accepted 9 October 2024
ORCID ID:http://orcid.org/0009-0000-0571-7164
https://doi.org/10.33192/smj.v76i12.271058

ABSTRACT

Objective: This study aimed to evaluate the effectiveness of preemptive parecoxib in reducing postoperative pain following gynecological surgery.

Materials and Methods: A double-blind, randomized study involved 168 patients undergoing laparotomy gynecological procedures, including total hysterectomy, adnexal surgery, and surgical staging, between November 2023 and July 2024. Patients were randomly assigned to receive either intravenous parecoxib (n = 82) or normal saline (n = 86) 15 minutes before surgery. Postoperative pain was measured using a visual analog scale at 2, 6, 12, and 24 hours. Morphine consumption within the first 24 hours post-surgery was recorded, along with any adverse events related to parecoxib and the length of hospital stay.

Results: Mean pain scores at 2, 6, 12, and 24 hours postoperatively were lower in the treatment group compared to the control group (5.3 vs. 5.7, $p = 0.261$; 3.7 vs. 5.0, $p < 0.001$; 3.3 vs. 5.1, $p < 0.001$; 3.5 vs. 4.0, $p = 0.164$, respectively). The mean 24-hour postoperative morphine consumption was significantly lower in the treatment group (4 ± 8 mg vs. 8 ± 5 mg, $p < 0.001$). No significant adverse events occurred between the groups. The total length of hospital stay was similar between the two groups (3.4 ± 1.8 vs. 3.5 ± 1.4 days, $p = 0.698$).

Conclusion: Preemptive parecoxib significantly reduced pain at 6 and 12 hours post-surgery and reduced morphine use within 24 hours, with no significant effect on hospital stay duration in gynecological surgery.

Keywords: Preemptive analgesia; parecoxib; gynecological surgery; postoperative pain (Siriraj Med J 2024; 76: 846-853)

INTRODUCTION

Postoperative pain is a common occurrence after any type of surgical procedure, with the most severe pain typically occurring within the first 24 hours. Poorly managed postoperative pain can lead to undesirable side effects, such as a prolonged recovery time, reduced quality of life, and increased use of opioids.[1] Excessive opioid use can cause adverse effects, including nausea, vomiting, and respiratory depression.[2] Therefore, effective postoperative pain management is important. Currently, a multimodal analgesic regimen is often utilized to relieve pain and minimize opioid-related side effects.[3] In addition to systemic treatments such as oral paracetamol and NSAIDs, regional and local analgesia are also studied and applied to reduce postoperative pain. For example, local dexamethasone infiltration[4] and transversus abdominis plane (TAP) blocks[5] are used. Recently, the concept of preemptive analgesia has been introduced to reduce postoperative pain. Administering analgesics before noxious stimuli are triggered can block pain receptors in the peripheral and central nervous systems. This results in reduced transmission of pain signals, leading to more effective short-term and long-term pain control.[6]

Various drugs and methods are used for preemptive analgesia, including local anesthesia, epidural blocks, intravenous N-methyl-d-aspartate (NMDA) antagonists, and especially nonsteroidal anti-inflammatory drugs (NSAIDs).[7] Considering that patients must fast before surgery, selective cyclooxygenase 2 (COX2) inhibitors are preferred over non-selective COX inhibitors due to their lower risk of side effects such as nausea, stomach pain, and gastric ulcers.[8] One of the most commonly used and cost-effective drugs in Thailand is parecoxib. This COX2 selective inhibitor has an onset time of approximately 7–14 minutes, reaches its peak analgesic effect at 2 hours, and has a duration of action of 6–24 hours[9], making it suitable for use as a preemptive analgesic. Although postoperative pain management follows the principles of multimodal analgesia, there is no standardized protocol for preemptive analgesia. Hence, we conducted research to evaluate the efficacy of parecoxib as preemptive analgesia to reduce postoperative pain in patients undergoing gynecological surgery.

MATERIALS AND METHODS

A prospective, double-blind, randomized controlled study was carried out at Rajavithi Hospital after receiving authorization from the Rajavithi Hospital ethics committee. The study involved patients undergoing total abdominal hysterectomy either with or without salpingo-oophorectomy, adnexal surgery (ovarian cystectomy and unilateral or bilateral salpingo-oophorectomy), and complete surgical staging under general anesthesia between November 2023 and July 2024.

The inclusion criteria were the female sex, age 18–70 years, capable of communicating in the Thai language, and an American Society of Anesthesiologists (ASA) physical status of I or II. The exclusion criteria were allergy to

NSAIDs, sulfa drugs, or opioids; underlying conditions that contraindicated NSAID use (e.g., coronary artery disease, cerebrovascular disease, a history of gastrointestinal bleeding, peptic ulcer, peripheral arterial disease, impaired renal or liver function with a glomerular filtration rate < 30 mL/min, or Child–Pugh class B or higher); blood pressure ≥ 160/110 mmHg on the day of admission; and antiplatelet medicine use within 7 days prior to surgery. In addition, patients who experienced intraoperative bowel or bladder injury were excluded.

The subjects were allocated to two groups using stratified block randomization. The parecoxib group was administered 40 mg (2 mL) of intravenous parecoxib 15 minutes prior to the operation, whereas the control group received 2 mL of intravenous normal saline. Both patients and assessors were blinded to the group allocation, with the groups labeled as A (the parecoxib group) or B (the control group). All patients were introduced to the visual analog scale (VAS), a pain evaluation instrument that ranges from 0 (no pain) to 10 (the most severe pain), the day before surgery.

All patients received standard general anesthesia and were then transported to the post-anesthesia care unit after surgery. Perioperative and immediate postoperative (0–2 hours) analgesic administration was recorded by the anesthesia nurse. Once transferred to the gynecology ward, pain assessments were conducted by the ward nurses (who had been trained by the researchers) at 2, 6, 12, and 24 hours after surgery, based on the surgical documentation time. Pain was assessed using the VAS, and any potential medication side effects were recorded at these specified times.

During the first 24 hours after surgery, morphine was administered for pain management, with dosages based on the patient's pain scores at the specified times. Standing orders were provided for the first 24 hours postoperatively. For a pain score > 7, morphine was injected intravenously at a dose of 0.075 mg/kg; for a pain score between 5 and 7, the dosage was 0.05 mg/kg. Morphine was not administered for a pain score < 5. After the first 24 hours after surgery, the patients were administered standard pain relievers as prescribed individually by the attending doctor, including oral analgesics such as paracetamol and NSAIDs, as well as intravenous morphine.

The primary outcome was the VAS pain scores assessed during the first 24 hours following surgery. The secondary outcomes were postoperative opioid consumption within 24 hours, the adverse effects of parecoxib, and the hospital length of stay after surgery.

Statistical analysis

Before commencing the study, the sample size was estimated based on primary outcome data from a prior trial, which reported a postoperative pain score of 2.85 ± 1.24 in the parecoxib group and 3.41 ± 1.27 in the placebo group at 24 hours after surgery. Given a power of 80% and a significance level of 0.05, 79 patients would be required for each group. To accommodate a possible 10% dropout or exclusion rate, a total of 176 individuals (88 patients per group) were enrolled.

SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Results are presented as means and standard deviations (SD) for normally distributed variables and as medians and interquartile ranges (IQR) for non-normally distributed variables. Categorical variables were compared using the chi-square test and unpaired t-test was used for normally distributed data while the Mann-Whitney U test was used for non-normally distributed data. A p-value of < 0.05 was considered statistically significant.

RESULTS

We recruited a total of 176 patients, but we excluded 8 for the following reasons: 3 patients underwent myomectomy, 2 patients experienced bowel/bladder injury, 1 patient had a laparoscopic operation, and 2 patients underwent tumor biopsy, which was not within the operation criteria. Therefore, we included 168 patients in the study, with 82 in the parecoxib group and 86 in the control group. Age, body mass index (BMI), ASA class, previous abdominal surgery history and surgical indication did not differ significantly between the groups (Table 1). Similarly, the operation, type of skin incision, presence of intra-abdominal adhesion, operative time, blood loss, and intraoperative and immediate postoperative analgesia did not differ significantly between the groups (Table 2).

We compared the preoperative baseline and postoperative VAS pain scores between the parecoxib and control groups on the day prior to surgery, and at 2, 6, 12, and 24 hours following surgery. The parecoxib group consistently experienced a lower average VAS pain score compared with the control group, with a significant difference at 6 and 12 hours after surgery. The baseline VAS pain score did not differ between the groups (Table 3).

The parecoxib group received a significantly lower amount of morphine within the initial 24-hour period after surgery compared with the control group (4 ± 8 and 8 ± 5 mg, respectively, $p < 0.05$). The total hospital length of stay after surgery did not differ significantly

TABLE 1. Baseline patient characteristics.

Characteristic	Parecoxib group (n = 82)	Control group (n = 86)	*p*
Age (years), mean ± standard deviation	47.9 ± 12.9	47.7 ± 14.5	0.918[a]
Body mass index (kg/m^2), mean ± standard deviation	26.1 ± 6.0	25.9 ± 5.8	0.874[a]
American Society of Anesthesiologists class, n (%)			
I	27 (32.9)	26 (30.2)	0.707[b]
II	55 (67.1)	60 (69.8)	
Underlying condition, n (%)	34 (41.5)	30 (30.9)	0.337[b]
Hypertension	21 (25.6)	42 (48.8)	
Diabetics mellitus	4 (4.9)	6 (7.0)	
Thyrotoxicosis	3 (3.7)	4 (4.7)	
Chronic kidney disease	0 (0.0)	1 (1.2)	
Human immunodeficiency virus	3 (3.7)	1 (1.2)	
Systemic lupus erythematosus	1 (1.2)	2 (2.3)	
Others*	6 (7.3)	6 (7.0)	
Drug allergy, n (%)	2 (2.4)	6 (7.0)	0.167[b]
Penicillin	2 (2.4)	4 (4.8)	
Ciprofloxacin	0 (0.0)	1 (1.2)	
Warfarin	0 (0.0)	1 (1.2)	
Previous abdominal surgery, n (%)	28 (34.1)	31 (36.0)	0.796[b]
Appendectomy	5 (6.1)	3 (3.5)	
Cesarean section	16 (19.5)	16 (18.6)	
Tubal abortion	6 (7.3)	12 (14.0)	
Nephrectomy	1 (1.2)	0 (0.0)	
Diagnosis, n (%)			0.996[b]
Leiomyoma	23 (28)	23 (26.7)	
Adenomyosis	8 (9.8)	8 (9.3)	
Leiomyoma with adenomyosis	17 (20.7)	19 (22.1)	
Ovarian tumor	5 (6.1)	4 (4.7)	
Cervical cancer	22 (26.8)	26 (30.2)	
Endometrial cancer	5 (6.1)	5 (5.8)	
Ovarian cancer	2 (2.4)	1 (1.2)	

[a] Unpaired *t*-test.

[b] Chi-square test.

* Including anemia, epilepsy, deep vein thrombosis, and pulmonary embolism.

TABLE 2. Surgical data.

Surgical factor	Parecoxib group (n = 82)	Control group (n = 86)	*p*
Operation, n (%)			0.996[b]
Total abdominal hysterectomy ± SO	42 (51.2)	44 (51.2)	
Adnexal surgery (cystectomy/USO/BSO)	12 (14.6)	13 (51.2)	
Surgical staging	28 (34.1)	29 (33.7)	
Surgical incision, n (%)			0.670[b]
Vertical	45 (54.9)	50 (58.1)	
Transverse	37 (45.1)	36 (41.9)	
Intraabdominal adhesion, n (%)			0.976[b]
Yes	37 (45.1)	39 (45.3)	
No	25 (54.9)	29 (54.7)	
Operative time (minutes), mean ± standard deviation	134.7 ± 38.9	141.1 ± 45.9	0.413[a]
Estimated blood loss (mL), median (IQR)	250 (100-450)	200 (100-300)	0.417[c]
Intraoperative analgesia, median (IQR)			
Morphine (mg)	9 (7-10)	8 (6-10)	0.367[c]
Fentanyl (mEq)	50 (0-100)	63 (0-100)	0.747[c]
Paracetamol (mEq)	0 (0-1,000)	0 (0-1,000)	0.845[c]
Marcaine (mL)	0 (0-0)	0 (0-0)	0.597[c]
Nefopam (mg)	0 (0-0)	0 (0-0)	0.306[c]
Immediate postoperative analgesia, median (IQR)			
Morphine (mg)	0 (0-3)	0 (0-3)	0.627[c]
Fentanyl (mEq)	0 (0-0)	0 (0-0)	0.106[c]
Pethidine (mg)	0 (0-0)	0 (0-0)	0.329[c]
Nefopam (mg)	0 (0-0)	0 (0-0)	0.306[c]

[a] Unpaired *t*-test.
[b] Chi-square test.
[c] Mann–Whitney U test.

TABLE 3. Comparison of the visual analog scale pain scores.

	Parecoxib group (n = 82)	Control group (n = 86)	Mean difference	95% confidence interval	*p*
Baseline pain score, mean ± standard deviation	0.1 ± 0.3	0.1 ± 0.3	0.04	(-0.13, 0.05)	0.314
Postoperative pain score, mean ± standard deviation					
2 hours	5.3 ± 2.9	5.7 ± 2.5	-0.46	(-1.28, 0.35)	0.261
6 hours	3.7 ± 2.2	5.0 ± 2.1	-1.38	(-2.03, 0.72)	<0.001*
12 hours	3.3 ± 1.8	5.1 ± 2.3	-1.75	(-2.37, -1.13)	<0.001*
24 hours	3.5 ± 2.2	4.0 ± 2.4	-0.49	(-1.18, 0.20)	0.164

* Significant difference ($p < 0.05$).

between the parecoxib and control groups (3.2 ± 1.8 and 3.5 ± 1.4 days, respectively, p = 0.698). Finally, no significant adverse events occurred between the two groups (Table 4).

DISCUSSION

In this randomized controlled experiment, we assessed the efficacy of preemptive analgesia using parecoxib to reduce postoperative pain and opioid usage in patients following gynecological surgery. We found that preemptive administration of parecoxib significantly reduced the VAS pain score at 6 and 12 hours after surgery compared with placebo, supporting the hypothesis that preemptive analgesia improves pain management outcomes. The finding that the VAS pain score at 2 hours after surgery did not differ between the two groups may be explained by immediate postoperative analgesic drugs given at 0–2 hours after surgery would still have an effect lasting up to 2 hours after surgery.

The reduction in overall morphine usage within the first 24 hours after surgery in the parecoxib group further supports the effectiveness of preemptive parecoxib administration. By reducing opioid usage, parecoxib may help minimize the risk of adverse effects associated with opioids, such as nausea, vomiting, and respiratory depression[2], thereby improving patient recovery and satisfaction.

Several trials have examined the effectiveness of parecoxib in reducing postoperative pain in the context of gynecological surgery. Unlike previous studies that focused on specific types of surgeries, we included patients undergoing a diverse range of laparotomy gynecological procedures, such as hysterectomy, adnexal surgery, and surgical staging for malignant gynecological diseases. This comprehensive inclusion enabled us to obtain a better understanding of parecoxib's efficacy in various surgical procedures.

Amornrat et al.[10] compared the preemptive administration of parecoxib to a placebo in patients who underwent abdominal hysterectomy and conservative surgery. The patients in the parecoxib group had significantly lower pain levels at 6 and 12 hours after surgery, along with a decrease in total opioid intake within the first 24 hours. These findings align with our outcomes. Similarly, Bunyavejchevin et al.[11] carried out a double-blinded randomized controlled trial on patients undergoing diagnostic laparoscopy. They showed that parecoxib significantly lowered both shoulder and incisional pain compared with placebo. The authors also reported reduced use of rescue analgesia without significant differences in postoperative side effects.[11] Nong et al.[12] also reported benefits of using parecoxib in setting of gynecological cancer surgery. Patients treated with parecoxib had significantly lower morphine use and pain scores, along with higher

TABLE 4. Total opioid consumption, the hospital length of stay, and adverse effects.

	Parecoxib group (n = 82)	Control group (n = 86)	*p*
Total morphine consumption (mg), median (IQR)	4 (0-8)	8 (5-10)	<0.001[c]
Postoperative morphine consumption (mg), median (IQR)			
2 hours	1 (0-4)	3 (0-4)	0.340[c]
6 hours	0 (0-3)	3 (0-3)	<0.001*[c]
12 hours	0 (0-0)	3 (0-4)	<0.001*[c]
24 hours	0 (0-3)	0 (0-3)	0.718[c]
Total hospital length of stay after surgery (day), mean ± standard deviation	3.4 ±1.8	3.5 ± 1.4	0.698[a]
Adverse effects, n (%)			0.331[b]
Nausea	0 (0.0)	3 (3.5)	
Vomit	2 (2.4)	1 (1.2)	
Epigastric pain	0 (0.0)	0 (0.0)	

[a] Unpaired *t*-test.
[b] Chi-square test.
[c] Mann–Whitney U test
* Significant difference ($p < 0.05$).

satisfaction compared with those in the control group. In contrast, Ratchanon et al.[13] observed that while parecoxib reduced postoperative meperidine use in patients who underwent laparoscopic gynecological surgery, the decrease in the pain scores was not statistically significant. This might be due to the specific surgical methods and how pain is generated differently in laparoscopic compared to open surgeries. Overall, while most studies support the use of parecoxib in reducing postoperative pain as well as opioid consumption, its efficacy may vary depending on the specific surgical procedure.

In our study, we closely observed the side effects of preemptive parecoxib after gynecological surgery. We found that only a few patients experienced mild side effects similar to those in patients who received placebo. The low incidence of side effects in our study suggests that parecoxib is a safe option for preemptive analgesia in patients undergoing gynecological surgery. However, clinicians should remain aware of potential complications, particularly in patients with a cardiovascular disease, kidney impairment, or gastrointestinal symptoms.

While parecoxib contributed to reducing the amount of opioids taken and postoperative pain, there was not a significant difference in the hospital length of stay between the parecoxib and control groups. A possible reason for this finding is that the gynecology department at Rajavithi Hospital typically discharges patients after about 3 days of recovery. Generally, patients are well enough to leave the hospital by that time unless they experience complications that require a longer stay. Our data show that both the treatment and control groups had a hospital stay of 3.2 ± 1.8 days and 3.5 ± 1.4 days, respectively, which matches this usual care pattern.

However, this study comes with some limitations. First, the sample size, although sufficient for detecting differences in pain scores, may not be large enough to generalize the findings across all types of gynecological surgery. Second, the potential applicability of our data to different clinical situations may be limited due to our focus on a single center. Finally, the absence of a standardized protocol for the postoperative care of patients in this study might have influenced the hospital length of stay after surgery.

In conclusion, we demonstrated that preemptive parecoxib administration effectively lowered postoperative pain and opioid consumption in patients who underwent gynecological surgery. While the hospital length of stay did not differ between the parecoxib and control groups, the pain relief provided by parecoxib and its safety profile indicate that this drug is a viable choice for postoperative pain control, even in a diverse patient population undergoing various types of gynecological surgery.

ACKNOWLEDGEMENTS

The authors would like to express their sincere gratitude to Assist. Prof. Dr. Marut Yanaranop for his assistance with the statistical analysis and interpretation. We also extend our appreciation to the obstetrics and gynecology staff, the nurses in the gynecology ward department, as well as the personnel of the anesthesiology department for their help with and support of this study.

DECLARATION

Grants and Funding Information

Thank you Rajavithi hospital for funding this research.

Conflicts of Interest

The authors declare that they have no conflicts of interest related to this study.

Author Contributions

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

Use of artificial intelligence

ChatGPT version 4o were used to correct the manuscript grammar.

REFERENCES

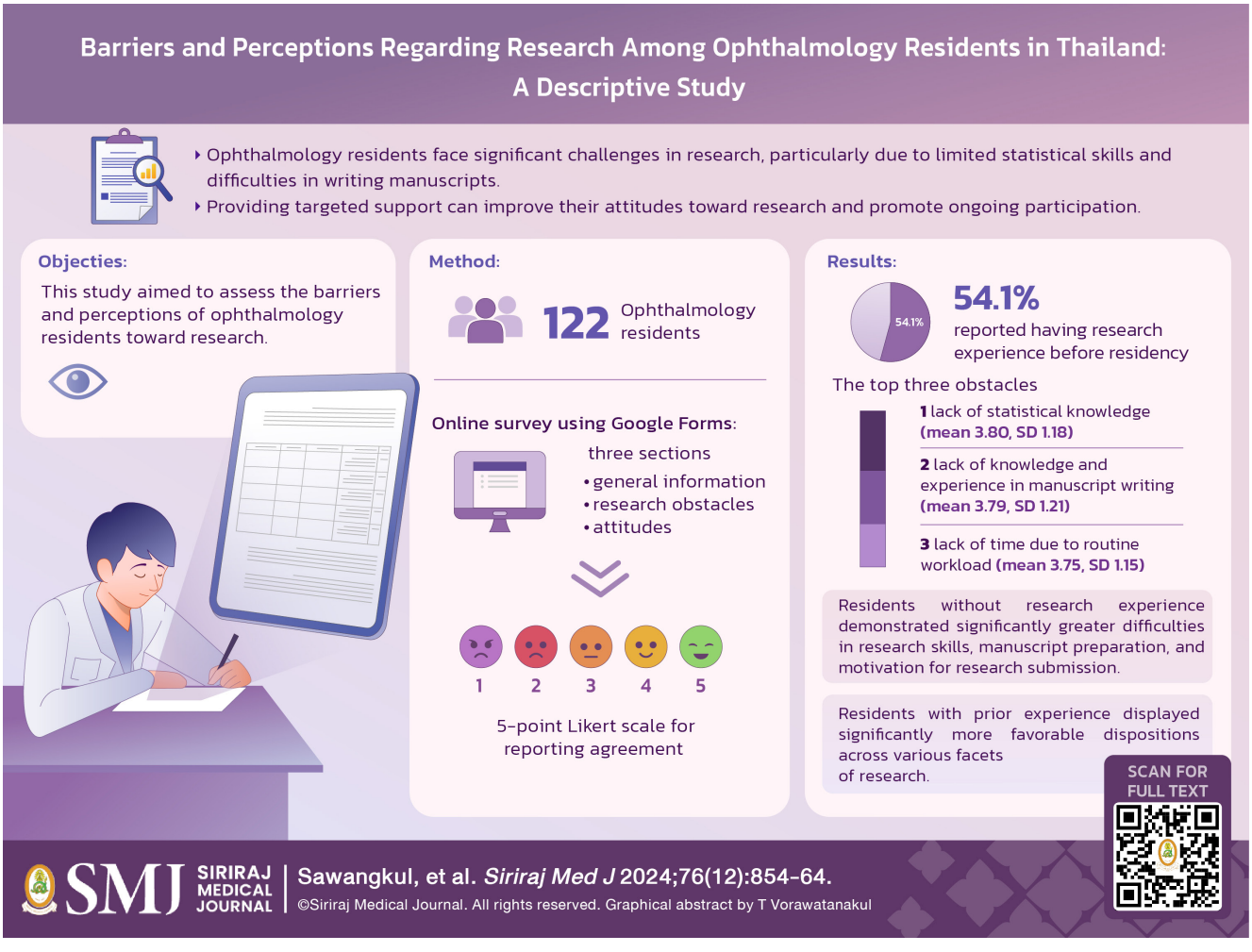
1. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. J Pain Res. 2017;10:2287-98.
2. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Opioid complications and side effects. Pain Physician. 2008;11(2 Suppl):S105-S20.
3. Schwenk ES, Mariano ER. Designing the ideal perioperative pain management plan starts with multimodal analgesia. Korean J Anesthesiol. 2018;71(5):345-52.
4. Smitasiri R, Chanthasenanont A, Chitkoolsamphan Y, Pongrojpaw D, Benchahong S, Suwannarurk K. Dexamethasone and Lidocaine Effects in 24 hours Post Cesarean Pain Reduction under Spinal Anesthesia: A Randomized Controlled Trial. Siriraj Med J. [Internet]. 2024 Sep. 1 [cited 2024 Oct 9];76(9):567-72. Available from: https://he02.tci-thaijo.org/index.php/sirirajmedj/article/view/268510
5. Boonyapalanant C, Woranisarakul V, Jitpraphai S, Chotikawanich E, Taweemonkongsap T, KC HB, et al. The Efficacy of Inside-Out Transversus Abdominis Plane Block vs Local Infiltration before Wound Closure in Pain Management after Kidney Transplantation: A Double-blind, Randomized Trial. Siriraj Med J. [Internet]. 2022 Apr. 1 [cited 2024 Oct. 9];74(4):233-8. Available from:

https://he02.tci-thaijo.org/index.php/sirirajmedj/article/view/256916
6. Ohnesorge H, Gunther V, Grunewald M, Maass N, Alkatout I. Postoperative pain management in obstetrics and gynecology. J Turk Ger Gynecol Assoc. 2020;21(4):287-97.
7. Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. Anesth Analg. 2005;100(3):757-73.
8. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA. 2000; 284(10):1247-55.
9. Pfizer. Dynastat (parecoxib sodium) - product information. Available from: https://labeling.pfizer.com/ShowLabeling.aspx?id=12244 [Accessed 12 August 2023].
10. Arponrat P, Pongrojpaw D, Tanprasertkul C, Suwannarurk K, Bhamarapravatana K. Postoperative pain relief in major gynaecological surgery by perioperative parecoxib administration: Thammasat University Hospital Study. J Med Assoc Thai. 2015;98(7):636-42.
11. Bunyavejchevin S, Prayoonwech C, Sriprajittichai P. Preemptive analgesic efficacy of parecoxib vs placebo in infertile women undergoing diagnostic laparoscopy: randomized controlled trial. J Minim Invasive Gynecol. 2012;19(5):585-8.
12. Nong L, Sun Y, Tian Y, Li H, Li H. Effects of parecoxib on morphine analgesia after gynecology tumor operation: a randomized trial of parecoxib used in postsurgical pain management. J Surg Res. 2013;183(2):821-6.
13. Ratchanon S, Phaloprakarn C, Traipak K. Pain control in laparoscopic gynecologic surgery with/without preoperative (preemptive) parecoxib sodium injection: a randomized study. J Med Assoc Thai. 2011;94(10):1164-8.

Barriers and Perceptions Regarding Research Among Ophthalmology Residents in Thailand: A Descriptive Study

Yanee Mukdar, B.Sc.[2], Wasawat Sermsripong, M.D.[1], Wilawan Sanphan, B.Ed.[2], Supattra Sawangkul, B.BA.[1,*] Pitipol Choopong, M.D., M.Sc.[1]

[1]*Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand,* [2]*Research Department, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.*



*Corresponding author: Supattra Sawangkul
E-mail: supattra.saw@mahidol.edu
Received 23 July 2024 Revised 10 September 2024 Accepted 21 September 2024
ORCID ID:http://orcid.org/0000-0002-7196-3926
https://doi.org/10.33192/smj.v76i12.270324

ABSTRACT

Objective: This study aimed to assess the barriers and perceptions of ophthalmology residents toward research and to discern the differences between residents with and without prior research experience before commencing ophthalmology training.

Materials and Methods: An online survey using Google Forms was conducted to collect data. The survey comprised three sections: general information, research obstacles, and attitudes. Participants utilized a 5-point Likert scale for reporting agreement.

Results: The survey was completed by 122 ophthalmology residents, representing a 51.3% response rate. Among them, 54.1% reported having research experience before residency. The top three obstacles identified were "lack of statistical knowledge" (mean 3.80, standard deviation 1.18), "lack of knowledge and experience in manuscript writing" (mean 3.79, SD 1.21), and "lack of time due to routine workload" (mean 3.75, SD 1.15). Residents without research experience demonstrated significantly greater difficulties in research skills, manuscript preparation, and motivation for research submission. While overall research attitudes were positive (mean 3.20, SD 1.18), residents with prior experience displayed significantly more favorable dispositions across various facets of research. These were preferences, perceived educational and career advantages, potential for income generation, and enhancement of communication skills. Conversely, the non-experienced residents primarily viewed research as a graduation requirement.

Conclusion: Ophthalmology residents encountered considerable challenges in conducting research, primarily stemming from limited statistical knowledge and inadequate competency in manuscript writing. Implementing targeted support measures to address these barriers can foster positive research attitudes and encourage sustained research engagement among residents.

Keywords: Attitudes; Obstacles; Ophthalmology; Research; Residency training (Siriraj Med J 2024; 76: 854-864)

INTRODUCTION

The ophthalmology residency training program, overseen by the Royal College of Ophthalmologists of Thailand and the Medical Council of Thailand, aims to provide resident trainees with comprehensive qualifications and knowledge.[1] This is accomplished through the development of six core competencies: patient care, medical knowledge and procedural skills, interpersonal and communication skills, practice-based learning and improvement, professionalism, and systems-based practice. An essential element of this higher education is residents' engagement in research, which not only generates new knowledge but also nurtures creativity, hones analytical skills, and facilitates the integration of information. Furthermore, research provides an opportunity to integrate medicine with other scientific domains while maintaining professional ethics.

The ability to independently conduct research is a critical competency expected to be attained by ophthalmology residents during their tenure in the program. Residents must participate as primary investigators or co-investigators in at least one research project. While the requirement to undertake research is obligatory, motivations for engaging in research extend beyond mere compliance. These incentives include a genuine interest in discovery and learning[2], a passion for scholarly inquiry, an aspiration for skill enhancement and professional growth, a desire to improve patient care[3], the pursuit of higher education, and the opportunity to establish professional connections. Like their counterparts across specialties and nations, ophthalmology residents in Thailand frequently encounter challenges while conducting research. The extant literature pinpoints several key hindrances: time constraints due to heavy clinical workloads[3,4]; inadequate skills and knowledge in areas such as statistics[5] and research methodology; and limited prior research experience.[6] Additional obstacles include insufficient research support; limited access to research equipment, facilities, and expert consultancy; difficulties obtaining and interpreting biostatistical data; and the complexities of securing approvals from human research ethics committees.[5-7]

Conversely, a study in Thailand focusing on radiology residents showed that the support and guidance provided by advisors fostered a highly positive attitude toward research during training.[8] These findings suggest that the obstacles and attitudes toward research can differ across specialties and regions. Therefore, this study aimed to investigate the barriers to and attitudes toward research within the context of ophthalmology residency in Thailand.

There are many ophthalmology resident training centers in Thailand provided training in research skills, such as research methodology, biostatistics, and manuscript writing. They also organized activities to promote research, like Research contests and Research quality fairs, which allowed researchers to share knowledge and experiences. In addition, some centers offered research funding, including grants for presenting work abroad.

Additionally, this study aimed to delineate the disparities in these factors between residents with and without research experience before commencing their residency. The insights garnered from this study will inform enhancements to the research framework of ophthalmology residency programs in Thailand, ensuring their adaptability to future challenges.

MATERIALS AND METHODS

The study protocol received approval from the Ethics Committee of the Siriraj Institutional Review Board (approval number Si-492/2022). This descriptive study was executed during the 2022 academic year. All 238 ophthalmology residents registered with the Royal College of Ophthalmologists of Thailand were included. Informed consent was obtained by requiring all respondents to answer the acceptance checkbox, before being included in the study.

Data collection instrument

The study utilized an online questionnaire developed using Google Forms. The development of the instrument was informed by an extensive review of the pertinent literature and the incorporation of feedback from residents about their research experiences. Four research advisors carefully reviewed and revised the questionnaire. To ensure efficacy, a pilot test was also conducted. The questionnaire comprised three parts:

- Part 1: Demographic information and research background (10 items). This section collected data on sex, age, current training status, institution, research training, research experience, number of ongoing research projects, average weekly research time, types of research projects, and research designs.
- Part 2: Obstacles to conducting research (23 items). This section explored challenges in six domains: scheduling meetings with a preceptor, proposal development, data collection, data analysis, manuscript writing, and article submission processes.
- Part 3: Attitudes toward research (20 items). This section assessed participants' attitudes toward research.

Measurement levels

The study utilized 5-point Likert scales in Part 2 (obstacles to conducting research) and Part 3 (attitudes toward research).[9,10] Participants rated their responses using the following options: 1 = "strongly disagree," 2 = "disagree," 3 = "neutral," 4 = "agree," and 5 = "strongly agree." These response choices facilitated the assignment of quantitative scores to the opinions expressed by respondents. The mean scores were interpreted as follows: 1.00–1.50 = strong disagreement, 1.51–2.50 = disagreement, 2.51–3.50 = neutral, 3.51–4.50 = agreement, and 4.51–5.00 = strong agreement.[10]

Data collection

The data were collected via an online questionnaire that was made available to the research coordinators of 11 ophthalmology training centers across Thailand. The institutions involved were Chiang Mai University, Chulalongkorn University, Khon Kaen University, Mahidol University (Ramathibodi and Siriraj Hospitals), Mettapracharak (Wat Rai Khing) Hospital, Navamindradhiraj University, Phramongkutklao College of Medicine, Prince of Songkla University, Rajavithi Hospital, and Thammasat University.

The research coordinators distributed the questionnaire to ophthalmology residents within their respective institutions by sharing a Google Form link. The data collection period ranged from October 2022 to February 2023. Participants had one month to complete the questionnaire. A reminder email was sent to participants who had not completed the questionnaire by each institution's coordinator one week before the due date. After this interval concluded, the responses were collected and analyzed.

Data analysis

Descriptive statistics were employed to summarize the data. Categorical variables are expressed as frequencies and percentages, while continuous variables are reported as means and standard deviations (SDs). The Mann–Whitney U test was used to assess differences in obstacles and attitudes toward research between residents with and without research experience before commencing the ophthalmology residency training program. A *P* value less than 0.05 indicated statistical significance. All the statistical analyses were conducted using PASW Statistics, version 18 (SPSS Inc, Chicago, IL, USA).

Definitions

- **Conducting Research:** From the preparation of the research proposal to the conclusion of the study, the activities that may occur include revising

the research proposal, IRB submission, collecting data, analyzing data, and summarizing the research results, etc.

- **Research Experience:** Research projects or research work carried out prior to entering the ophthalmology residency program, such as research activities during internships, thesis work, etc.
- **Participation in Research:** Participation in research may include roles such as Principal Investigator or Co-Investigator, or it may involve contributing to the research in other ways, such as collecting and analyzing data, even if one is not named in the proposal.
- **Manuscript Writing:** This was the final step in the research process, which took place after the research was completed. Writing a manuscript and presenting research results and abstracts were mandatory for ophthalmology residents to successfully complete the training program.
- **Submitting Research Papers:** This was one step in conducting research. In this study, it meant submitting research papers for academic contests. This step was not mandatory for ophthalmology residents to complete their training program.

RESULTS

Participant demographics and research backgrounds

Of the 238 eligible residents, 122 responded to the survey, yielding a response rate of 51.3%. The majority were female (71.3%), and most residents (82.8%) were between the ages of 24 and 29. Additionally, 33.6%, 27.9%, and 36.1% of the respondents were the first-, second-, and third-year residents, respectively (Table 1).

There were a total of 11 ophthalmology residency training institutions. The top three institutions in terms of response rates were the Faculty of Medicine Siriraj Hospital, Mahidol University (26.2%); the Faculty of Medicine, Chiang Mai University (21.3%); and the Faculty of Medicine Vajira Hospital, Navamindradhiraj University (9.8%). These three institutions had response rates that represented one hundred percent of the total number of residents at their respective institutions (Table 1).

Over half of the respondents (54.1%) had received research training before their residency, and 46.7% had conducted research. During their residency, a notable proportion (62.3%) were involved in one research project. Most respondents (83.6%) allocated between 0 and 7 hours per week to research activities (Table 1).

Participants with prior research experience had engaged in various types of studies before entering the residency. The most common types were retrospective chart reviews (37.5%), prospective cohort studies (19.6%), and questionnaire-based research (11.4%). The predominant research designs were descriptive (30.3%), cross-sectional (21.9%), and prospective cohort (15.2%) (Table 2).

Obstacles to research engagement

The research barriers were classified into six domains. Manuscript writing emerged as the most challenging aspect (mean ± SD: 3.68 ± 1.13). This was followed by data analysis (3.12 ± 0.95), the submission of research papers for academic conferences (2.81 ± 0.88), and proposal development (2.76 ± 0.78). These four areas were considered to present moderate levels of difficulty. Data collection (2.44 ± 1.02) and scheduling meetings with a preceptor (1.95 ± 0.84) were perceived as relatively less challenging (Fig 1).

In descending order of impact, the three primary obstacles were "lack of statistical knowledge" (3.80 ± 1.18), "lack of knowledge and experience in manuscript writing" (3.79 ± 1.21), and "lack of time due to routine workload" (3.75 ± 1.15; Table 3).

Significant disparities were found in the perceptions of the residents with and without prior research experience. The residents lacking experience reported greater difficulties with the following:

- Developing proposals, due to limited research knowledge and experience ($P = 0.002$).
- Writing manuscripts, hindered by a lack of experience ($P < 0.001$) and difficulties in composing manuscripts accurately in English ($P = 0.004$)
- Finding the motivation to submit research papers for academic contests ($P = 0.007$).

Conversely, both groups shared similar views regarding preceptor appointments, data collection, and statistical analysis (Table 3).

Attitudes toward research

The residents' attitudes toward research were predominantly positive. Their mean scores indicated a strong recognition of the importance of conducting research for their academic progress (mean ± SD: 4.30 ± 0.81). They also reported that mentorship from their preceptors facilitated their research (4.12 ± 0.91). Additionally, they highlighted the need for training in research methodologies (3.86 ± 0.93) (Table 4).

Notable differences emerged between residents with and without prior research experience. These included their enthusiasm for conducting research ($P = 0.01$), undertaking research primarily for graduation purposes ($P = 0.03$), valuing research for educational and career advancement ($P = 0.03$), aspirations to publish in academic

TABLE 1. Demographic information and research experience of participants (n=122).

	n (%)
Sex	
Female	87 (71.3)
Male	35 (28.7)
Age (years)	
24-29	101 (82.8)
30-35	21 (17.2)
Year of in-training	
First	41 (33.6)
Second	34 (27.9)
Third	44 (36.1)
Fourth	3 (2.4)
Institute	
Faculty of Medicine Siriraj Hospital, Mahidol University (Total Residents, n=32)	32 (26.2)
Faculty of Medicine, Chiang Mai University (n=26)	26 (21.3)
Faculty of Medicine Vajira Hospital, Navamindradhiraj University (n=12)	12 (9.8)
Mettapracharak (Wat Rai Khing) Hospital (n=19)	11 (9.0)
Rajavithi Hospital (n=21)	9 (7.4)
Faculty of Medicine, Khon Kaen University (n=24)	7 (5.7)
Faculty of Medicine, Thammasat University (n=20)	7 (5.7)
Faculty of Medicine Ramathibodi Hospital, Mahidol University (n=20)	6 (4.9)
Faculty of Medicine, Prince of Songkla University (n=20)	6 (4.9)
Faculty of Medicine, Chulalongkorn University (n=30)	4 (3.3)
Phramongkutklao College of Medicine (n=14)	2 (1.6)
Research experiences	
Did you receive any research training prior to attending ophthalmology residency training?	
Yes	66 (54.1)
No	56 (45.9)
Did you have any research-conducting experience before attending ophthalmology residency training?	
Yes	57 (46.7)
No	65 (53.3)
Total number of current research projects (in progress)	
0	10 (8.2)
1	76 (62.3)
2	25 (20.5)
3	11 (9.0)
The average research time (hour/week) during training	
0-7	102 (83.6)
8-15	20 (16.4)

TABLE 2. The types and designs of research conducted by residents prior to their ophthalmology training (n=122).

	n (%)
Research types	
Retrospective (chart) review	69 (37.5)
Prospective (cohort) study	36 (19.6)
Questionnaire-based research	21 (11.4)
Case series/ Case reports	16 (8.7)
Drug trial	9 (4.9)
Medical device trial	7 (3.8)
In vitro/ laboratory-based study	4 (2.2)
Research using repository of biological products (cells, blood, tissues, fluids, etc.)	4 (2.2)
Epidemiology research	3 (1.6)
Bioequivalence	1 (0.5)
Vaccine trial	-
Others	8 (4.3)
Not applicable	6 (3.3)
Research designs	
Descriptive study	54 (30.3)
Cross-sectional study	39 (21.9)
Prospective cohort study	27 (15.2)
Randomized-controlled trial	22 (12.4)
Pilot study	10 (5.6)
Pre-experimental study (manipulation only, without control and randomization)	8 (4.5)
Quasi-experimental study (manipulation and control only, without randomization)	3 (1.7)
Others	9 (5.0)
Not applicable	6 (3.4)

Note: In this section, respondents were able to select multiple answers.

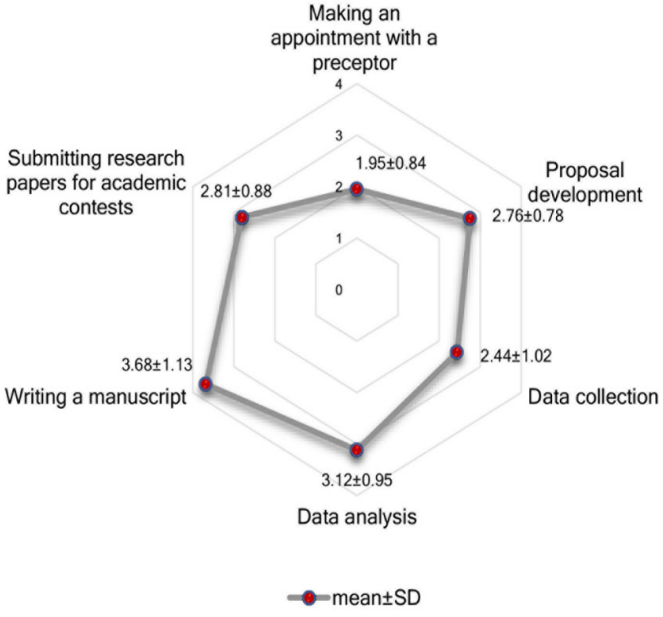


Fig 1. The mean and standard deviation values of the six domains related to research obstacles (n=122). SD: standard deviation.

TABLE 3. Obstacles in conducting research.

	Mean±SD Total (n=122)	With research experience (n=57)	Without research experience (n=65)	*P* *
1. Making an appointment with a preceptor				
1.1) Difficulty in making an appointment	2.26±1.18	2.44±1.19	2.11±1.15	0.11
1.2) Lack of mentorship support	1.84±1.01	1.72±1.01	1.94±0.99	0.14
1.3) Lack of interaction and communication skills	1.76±0.92	1.75±0.95	1.77±0.89	0.85
2. Proposal development				
2.1) Research topic misaligned with personal interest	2.33±1.09	2.32±1.21	2.34±1.08	0.92
2.2) Insufficient research experience and knowledge	3.65±1.23	3.25±1.35	4.00±1.00	0.002
2.3) Lack of funding support	2.34±1.18	2.44±1.25	2.26±1.12	0.56
2.4) Difficulty in obtaining approval from Institution Review Board (IRB)	2.20±1.05	2.19±1.19	2.20±0.92	0.59
2.5) Retrieving information or access to the institution's online database has difficulty	2.27±1.22	2.16±1.24	2.37±1.21	0.27
2.6) Lack of personnel to help conduct research	2.80±1.22	2.75±1.26	2.83±1.19	0.68
2.7) Lack of time due to routine workload	3.75±1.15	3.79±1.22	3.72±1.08	0.51
3. Data collection				
3.1) The process of requesting the use of a patient's medical records and statistics is complex	2.41±1.17	2.37±1.22	2.45±1.13	0.65
3.2) Difficulties in tracking volunteers to participate in research	2.56±1.29	2.49±1.27	2.62±1.33	0.64
3.3) Lack of research equipment and tools	2.35±1.22	2.44±1.23	2.28±1.22	0.46
4. Data analysis				
4.1) Lack of statistical knowledge	3.80±1.18	3.61±1.25	3.97±1.10	0.11
4.2) Extended wait times for consultations with a statistician	2.68±1.18	2.81±1.22	2.57±1.15	0.23
4.3) Difficulty in expressing research concepts to statisticians	2.87±1.15	2.95±1.19	2.80±1.12	0.44
5. Writing a manuscript				
5.1) Lack of knowledge and experience in manuscript writing	3.79±1.21	3.33±1.30	4.18±0.97	<0.001
5.2) Difficulty in writing accurate English manuscripts	3.57±1.27	3.19±1.38	3.91±1.06	0.004
6. Submitting research papers for academic contests				
6.1) Lack of motivation to submit research papers	3.37±1.14	3.09±1.06	3.62±1.16	0.007
6.2) Lack of confidence in one's own research	3.10±1.15	2.93±1.15	3.25±1.13	0.12
6.3) Lack of support from the department/faculty	2.28±1.12	2.23±1.07	2.32±1.17	0.69
6.4) Lack of support from The Royal College of Ophthalmologists of Thailand	2.39±1.13	2.39±1.08	2.40±1.17	0.89
6.5) Difficulties in the submission process	2.89±1.06	2.77±1.07	3.00±1.05	0.18

Notes: With research experience: This group had experience in research before attending ophthalmology residency training. Without research experience: This group had no experience in research before attending ophthalmology residency training. *Mann-Whitney U test ($P < 0.05$ is significant). SD: Standard deviation.

TABLE 4. Attitudes toward research.

	Mean±SD			
	Total (n=122)	With research experience (n=57)	Without research experience (n=65)	*P* *
Conducting research is challenging	3.73±1.05	3.74±0.97	3.72±1.13	0.79
I like to do research	2.38±1.06	2.67±1.14	2.12±0.93	0.01
I conduct research for graduation	4.30±0.81	4.12±0.87	4.45±0.73	0.03
Conducting research provides benefits to volunteers, professionals, and society	3.78±0.85	3.77±0.93	3.78±0.78	0.97
Research encourages self-learning	3.50±0.97	3.58±0.94	3.43±1.00	0.45
The mentorship from preceptors facilitated my research	4.12±0.91	4.18±0.87	4.08±0.96	0.65
I have enough time to conduct research	2.41±0.95	2.46±1.00	2.37±0.91	0.79
Research is helpful for me in pursuing higher education or advancing my career.	3.43±0.97	3.65±0.94	3.25±0.97	0.03
I have a good knowledge of research	2.46±0.90	2.60±0.86	2.34±0.92	0.15
Conducting research makes me create new ideas	3.06±1.02	3.14±0.99	2.98±1.04	0.44
Research skills training is a necessity	3.86±0.93	3.82±0.91	3.89±0.95	0.58
I do research for publication	3.12±1.03	3.32±0.99	2.95±1.04	0.03
Conducting research gives me more earnings	1.82±0.91	2.11±1.03	1.57±0.71	0.002
Research funding helps to conduct research more successfully and valuable	3.48±1.04	3.56±1.09	3.40±0.99	0.24
Conducting research improves interaction and communication skills	3.30±0.94	3.49±0.91	3.12±0.94	0.04
Conducting research makes me think systemically	3.51±0.92	3.61±0.90	3.42±0.93	0.29
A culture that promotes research	3.07±1.09	3.16±1.19	2.98±1.01	0.32
Lack of motivation in conducting research	3.41±1.07	3.23±1.07	3.57±1.05	0.09
Conducting research disturbs my personal time	3.58±0.91	3.60±0.99	3.57±0.83	0.74
I want to change my preceptor	1.84±1.08	1.82±1.09	1.85±1.08	0.94

Notes: With research experience: This group had experience in research before attending ophthalmology residency training. Without research experience: This group had no experience in research before attending ophthalmology residency training. *Mann-Whitney U test ($P < 0.05$ is significant). SD: Standard deviation.

journals ($P = 0.03$), perceiving research as a means to increase earnings ($P = 0.002$), and viewing it as an avenue to improve interaction and communication skills ($P = 0.04$). Conversely, in areas such as the perception of research as challenging, the recognition of the importance of research training, and the inclination to change research advisors, the attitudes of both groups were comparable (Table 4).

DISCUSSION

This study identified challenges faced by ophthalmology residents that hindered their research efforts, such as high clinical workloads, insufficient statistical knowledge, and difficulties in manuscript writing. Most residents considered research essential for graduation and believed that supervisor guidance would improve their research during residency. Training in research knowledge was

also viewed as important. These challenges particularly impacted residents without prior research experience, including a lack of exposure to research methodology, difficulties in writing English manuscripts, and reduced submission motivation. Despite these issues, both groups maintained positive attitudes toward research.

Several common barriers were identified for participants with and without prior research. These were a limited understanding of statistical concepts, difficulties in selecting appropriate statistical methods for medical research, time constraints due to routine clinical responsibilities, and a lack of experience in conducting research. These impediments are consistent with previous international studies[11-17], which consistently point to the lack of research training and time as major barriers to conducting research.

The residents' heavy clinical responsibilities, which include patient care, treatment, and educational activities, likely contribute to their limited availability for research. A Canadian study[3] suggested that allocating protected time for research and integrating research-related activities into the curriculum, such as designated research days, may address these temporal barriers effectively.

In India, Shaik et al.[16] found that ophthalmology residents lacked guidance in participating in research activities, which led to their failure to engage in such activities. Additionally, there was a problem with insufficient research funding, which contrasts with the results of this study. Most ophthalmology residents in Thailand did not perceive a lack of research funding, possibly because they received guidance and support from department or institutional staff.

In the study by Al Saeed et al.[17], it was found that ophthalmology residents faced problems with the ethics approval process. There were too many requirements, which resulted in long approval times. In contrast, the results of this study showed that most ophthalmology residents in Thailand encountered few issues with the ethics approval process. We believe that the speed of ethics approval may depend on the details and complexity of each project, as well as differences in the approval processes of ethics committees in each country.

The ophthalmology residents in our study reported having significant difficulties writing manuscripts, primarily due to limited knowledge and experience in this skill set. This challenge was compounded by limited proficiency in English, which is not their native language. These findings align with the challenges reported by anesthesiology residents in Thailand[6]. Implementing specialized English language lessons focused on manuscript writing and providing resources for grammatical corrections could be instrumental in addressing the language obstacles.

In contrast to the frequent worldwide reports of difficulty scheduling appointments with preceptors[7,12,13,17], our findings indicated that this issue was relatively minimal in Thailand. This finding suggests that the ophthalmology residents received adequate support from their preceptors in their research endeavors. This observation may be attributed to the demonstrably caring nature of Thai preceptors, who tend to closely mentor their residents and take great pride in their students' academic achievements. Furthermore, Ballard et al. emphasized the value of mentorship in residency research, highlighting the need for advisors who can guide, assist with challenges, and inspire residents during their training.[18] The supportive environment fostered by Thai preceptors may contribute to the relatively low difficulty of scheduling appointments and seeking guidance.

Our study underscores the significance of research experience in facilitating the research endeavors of residents during ophthalmology training. Additionally, prior research experience enriches medical education by fostering evidence generation, nurturing intellectual autonomy, and applying knowledge to scientific inquiry and clinical practice.[19,20] Our comparison between the residents with and without research experience before their training revealed notable differences in their perceived research obstacles. Residents without prior experience reported greater challenges, such as limited research knowledge, difficulties with manuscript composition, and decreased motivation for paper submission. These disparities suggest that the non-experienced group may have received inadequate training in research methodologies and manuscript writing during their medical school and internship years.

Therefore, the Medical Council of Thailand and educational authorities should promote the integration of research education within medical student and intern curricula to bolster research competencies at the undergraduate level. Additionally, facilitating research during residency training can be effectively achieved by organizing targeted educational initiatives. These may include master's degree research courses, journal clubs, research cafés, lab meetings, and manuscript writing, methodology, and biostatistics workshops.

Our findings on overall attitudes toward research revealed that ophthalmology residents in Thailand generally held slightly positive opinions. Most residents recognized the importance of conducting research for graduation and acknowledged the role of mentorship from their preceptors in facilitating the research process. The residents' recognition of the necessity for research skill

training aligns with findings in the literature.[4,6,7] Moreover, the participants acknowledged the beneficial effects of research on developing systematic thought processes, notwithstanding the challenges they encountered.

Comparisons between the two resident groups revealed differences in attitudes toward research. Residents without research experience demonstrated less enthusiasm for engaging in research, viewing it merely as a requirement for graduation. Their heavy workloads could influence this lack of interest, leading them to engage in research activities solely to fulfill academic obligations. To address this, concerted efforts are necessary by the Royal College of Ophthalmologists of Thailand and training institutions to cultivate a more positive research culture among residents. This can be achieved by emphasizing the diverse benefits of research beyond mere academic compliance.

In contrast, residents with prior research experience demonstrated a more positive and nuanced understanding of research. They expressed stronger agreement regarding the potential of research to enhance their future education and career prospects. This is consistent with the findings of Jayasundera et al.[21], which indicated that ophthalmologists in New Zealand viewed research as useful for their education, clinical practice, and career. Additionally, they valued publishing research findings in academic journals and recognized the positive impact of research on communication and interpersonal skills. These findings suggest that prior research experience fosters a deeper understanding and appreciation of the broader benefits and value of conducting research.

This study has a few limitations. A notable constraint is the participation rate of ophthalmology residents. It was approximately 50%, potentially introducing selection bias. This low rate might have been due to a lack of interest in participating, concerns about the time required to complete the questionnaire, or concerns about disclosing personal information. Additionally, the participants were recruited primarily from three major institutions, limiting the generalizability of our findings. Consequently, our data may not accurately reflect the full spectrum of obstacles and attitudes toward research prevalent across all ophthalmology residency programs in Thailand.

CONCLUSION

This investigation found that ophthalmology residents without prior research experience face more challenges than those with experience, particularly in attitudes toward research, manuscript writing, and motivation. Experienced residents generally had more favorable views and were more inclined toward research activities. We suggest that providing support and fostering a research-oriented environment might help overcome these challenges and improve attitudes toward research. Future studies will assess the effectiveness of these solutions.

ACKNOWLEDGEMENTS

We extend our gratitude to Julaporn Pooliam, M.Sc.; Simaporn Setthawong, M.D.; and Theerajate Phongsuphan, M.D., for their invaluable assistance with the statistical analyses.

DECLARATION

Grants and Funding Information

This work was supported by the Siriraj Research Development Fund (Managed by Routine to Research: R2R), Faculty of Medicine Siriraj Hospital, Mahidol University under Grant number R016635009.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Author Contributions

Conceptualization and methodology, S.S., Y.M., and P.C.; data collection, W.SA., Y.M., and S.S.; formal analysis, Y.M., W.SE.; writing—original draft, Y.M. and S.S.; writing—review and editing, P.C. and W.SE. All authors read and agreed to the published version of the manuscript.

REFERENCES

1. The Royal College of Ophthalmologists of Thailand. Curriculum prospectus of the diploma of the Thai Board of Ophthalmology (revised curriculum B.E. 2560) [Internet]. 2017. Available from: http://www.rcopt.org/index.php?r=arart010/detail&id=1998.
2. Habineza H, Nsanzabaganwa C, Nyirimanzi N, Umuhoza C, Cartledge K, Conard C, et al. Perceived attitudes of the importance and barriers to research amongst Rwandan interns and pediatric residents - a cross-sectional study. BMC Med Educ. 2019;19(1):4.
3. Al-Taha M, Al Youha S, Al-halabi B, Stone J, Retrouvey H, Samargandi O, et al. Barriers and Attitudes to Research Among Residents in Plastic and Reconstructive Surgery: A National Multicenter Cross-Sectional Study. J Surg Educ. 2017;74(6):1094-104.
4. Ting DSJ, Vrahimi M, Varma D, Steel DHW. Research attitudes and perceived barriers to conducting research among ophthalmology trainees. Eye (Lond). 2018;32(3):653-5.
5. Jaroonvanichkul V, Deerojanawong J. Residents' Obstacles and Attitudes Toward Research during Residency Training. J Med Assoc Thai. 2016;99(2):239-44.
6. Komonhirun R. Obstacles and Needs of Anesthesia Residents towards Research Supporting System in the Faculty of Medicine Ramathibodi Hospital, Mahidol University. Thai J Anesthesiol. 2021;47(4):287-92.
7. Mitwalli HA, Al Ghamdi KM, Moussa NA. Perceptions, attitudes, and practices towards research among resident physicians in training in Saudi Arabia. East Mediterr Health J. 2014;20(2):

99-104.
8. Kumsang Y, Atsawasena W, Jaovisidha S, Khowkham P, Tohsumlee S, Keatjidaro O, et al. The Factors Affecting Residents and fellows' Research Conduct in Department of Diagnostic and Therapeutic Radiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University. Rama Med J. 2012;35(1):48-53.
9. Likert R. A technique for the measurement of attitudes. Arch Psychol. 1932;22(140):55.
10. Pimentel JL. A note on the usage of Likert Scaling for research data analysis. USM R&D. 2010;18:109-12.
11. Sabzwari S, Kauser S, Khuwaja AK. Experiences, attitudes and barriers towards research amongst junior faculty of Pakistani medical universities. BMC Med Educ. 2009;9:68.
12. Gill S, Levin A, Djurdjev O, Yoshida EM. Obstacles to residents' conducting research and predictors of publication. Acad Med. 2001;76(5):477.
13. Levine RB, Hebert RS, Wright SM. Resident research and scholarly activity in internal medicine residency training programs. J Gen Intern Med. 2005;20(2):155-9.
14. Memarpour M, Fard AP, Ghasemi R. Evaluation of attitude to, knowledge of and barriers toward research among medical science students. Asia Pac Fam Med. 2015;14(1):1.
15. Silcox LC, Ashbury TL, VanDenKerkhof EG, Milne B. Residents' and program directors' attitudes toward research during anesthesiology training: a Canadian perspective. Anesth Analg. 2006;102(3):859-64.
16. Babu M, Shaik S, HU B. Researching the research: Ophthalmology residents' perspective. Journal of Medical Education Development. 2023;15(48):30-7.
17. Al Saeed AA, AlEnezi SH, Aljindan M, Alwadani F, Al Owaifeer AM. Experience, Attitude, and Perceived Barriers Toward Research Among Ophthalmology Residents in Saudi Arabia: A National Cross-Sectional Study. Clin Ophthalmol. 2022;16:265-72.
18. Ballard TN, Sando IC, Kasten SJ, Cederna PS. Successfully Integrating Research into Plastic Surgery Training Programs. J Craniofac Surg. 2015;26(8):2279-82.
19. Fisher WR. Medical student research: a program of self-education. J Med Educ. 1981;56(11):904-8.
20. Park SJ, McGhee CN, Sherwin T. Medical students' attitudes towards research and a career in research: an Auckland, New Zealand study. N Z Med J. 2010;123(1323):34-42.
21. Jayasundera T, Fisk M, McGhee CN. Attitudes to research and research training among ophthalmologists and ophthalmology trainees in New Zealand. Clin Experiment Ophthalmol. 2003;31(4):294-9.

A Case Series and Systematic Review: Results of Surgical Management of Glaucoma Drainage Device Tube Exposure

Nutnicha Neti, M.D., Theerajate Phongsuphan, M.D., Ngamkae Ruangvaravate, M.D., Pinnita Prabhasawat, M.D., Darin Sakiyalak, M.D., Naris Kitnarong, M.D., Anuwat Jiravarnsirikul, M.D., Sakaorat Petchyim, M.D.*

Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

*Corresponding author: Sakaorat Petchyim
E-mail: sakaoratpoy012@gmail.com
Received 27 July 2024 Revised 26 September 2024 Accepted 26 September 2024
ORCID ID:http://orcid.org/0000-0002-7550-8605
https://doi.org/10.33192/smj.v76i12.270377

ABSTRACT

Objective: To present a case series of patients who underwent surgical repair for glaucoma drainage device (GDD) tube exposure and conduct a systematic review to analyze results of various surgical techniques.

Materials and Methods: This study provides the details of GDD tube exposure repair at our hospital. Additionally, a systematic review was conducted using electronic databases including EMBASE, MEDLINE, and CENTRAL. Data extraction and analysis included demographic information, surgical techniques, results, and duration of follow-up.

Results: We reported nine cases of GDD tube exposure repair, with additional 109 cases from 24 previous studies. One of our challenging cases encountered multiple tube revision failures by the patch graft technique; the exposure issue was sustainably resolved by a hinge scleral flap with buccal mucosal graft technique. Of the 118 cases, various surgical techniques were used, including patch grafts, hinge scleral flaps, primary conjunctival closure and rerouting. Among the cases, 61.6% were classified as difficult cases. The overall first, fifth and thirteenth-year survival rate was 90.7%, 86.2% and 86.2%, respectively. Rerouting and scleral flap/tunnel techniques demonstrated the highest survival rate. No statistically significant differences in survival outcomes were observed among patch graft, scleral flap/tunnel and rerouting method (P = 0.129). The mean survival duration was 33.54 months. The duration of follow-up was 35.01 months.

Conclusion: Surgical management of GDD tube exposure yields favorable outcomes. A hinge scleral flap with buccal mucosal grafts can be a good option to treat challenging cases. The findings can shape an algorithm to manage GDD tube exposure.

Keywords: Glaucoma drainage device; glaucoma tube; glaucoma shunt; expose; treatment (Siriraj Med J 2024; 76: 865-875)

INTRODUCTION

Glaucoma is a prevalent chronic ocular disorder that affects a significant proportion of the global population. Among the various treatment modalities available for this condition, the implantation of a glaucoma drainage device (GDD) is a widely accepted and effective option. However, GDD-related complications such as tube exposure can occur, necessitating prompt and appropriate surgical management as the tube exposure can be the risk of ocular infection. The non-intact ocular barrier such as one caused by minor trauma can be associated with penetrating glaucoma surgery.[1] GDD tube exposure is a rare and sight-threatening complication of GDD implantation. The management of GDD tube exposure poses a significant challenge for ophthalmologists, as there is no consensus on the optimal surgical technique to repair the exposed tube. Several surgical strategies have been proposed, including primary conjunctival closure, repositioning the tube[2-4], covering the tube with a patch graft[5-21], scleral flap[22,23], scleral tunnel[24], and/or buccal mucosal graft.[19] However, there is no consensus on the optimal surgical technique.

To better understand the results of surgical treatment of GDD tube exposure, we present a case series of patients who underwent surgical repair of the exposed tube. In addition, we conduct a systematic review of the existing literature on the management of GDD tube exposure to provide a detailed analysis of the different surgical techniques and their respective results.

MATERIALS AND METHODS

This research was conducted in compliance with the principles of the Declaration of Helsinki. It received ethical approval from the Committee for the Protection of Human Participants in Research at the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. The research project has been registered in the Thai Clinical Trials Registry (TCTR20221004006).

We reported nine exposed GDD tubes repaired at the Department of Ophthalmology of the Faculty of Medicine of Siriraj Hospital, Mahidol University, Bangkok, Thailand. In this study, all cases of GDD tube exposure that required repair between October 2015 and March 2023 were included.

Also, we conduct a systematic review of GDD tube exposure repair. A comprehensive search of electronic databases was done, including EMBASE, MEDLINE, and CENTRAL, to identify all relevant studies. A search strategy was developed based on relevant keywords such as 'glaucoma drainage implant', 'glaucoma tube', 'glaucoma shunt', 'expose', 'erosion', and 'treatment' (Supplementary 1). The search was limited to studies published from January 1997 to April 2022. No restrictions on language and no filters were applied. All reports

of patients who had undergone GDD tube exposure repair were included. Studies were excluded if (1) they had insufficient data, (2) patients had GDD exposure concurrently with endophthalmitis, (3) they included patients with MIGS or other parts of GDD exposure, and (4) they were not a primary study.

The studies identified through the search underwent a two-step screening process. Two reviewers independently screened the titles and abstracts of all studies, and any discrepancies were resolved through discussion or by consulting a third reviewer. The interreviewer agreement to include an article for full-text review was strong (Cohen's kappa coefficient = 0.80). Full-text articles from potentially relevant studies were further screened using the same process. The reasons for excluding studies at each stage will be documented and reported according to the PRISMA 2020 Statement.[25]

The data extraction process included information on demographic data (sex, age, cause of glaucoma, type of GDD, time from GDD insertion to GDD tube exposure, previous ocular surgeries, previous tube exposure revision), the technique of tube exposure repair, survival time after repair and follow-up time. In one primary study, there was a lack of detailed information on the duration of survival for each individual case. The average survival duration was used to represent all the cases. Among the cases with sufficient available data, this study classified the cases as difficult cases if the patient met at least one of three criteria: (1) trauma-related glaucoma, (2) patients who had undergone at least one previous revision of tube exposure, or (3) patients who had undergone at least four previous ocular surgeries.

The quality of the included studies was independently evaluated by two reviewers using the tool proposed by Murad and colleagues[26], which was appropriate for the study design and assessed the risk of bias in the study, reported as high, moderate, or low. Any discrepancies will be resolved through discussion or by consulting a third reviewer.

All data analyzes were performed with SPSS Statistics version 18 (SPSS, Inc.). The data extracted from a systematic review and our reported cases were analyzed together. Continuous data were reported as mean in normally distributed data or median (IQR) in nonnormally distributed data. Categorical data were reported as numbers and percentages based on available data. Wilcoxon's signed rank test was used to compare postoperative and preoperative data. Kaplan-Meier analysis with a log-rank test showed survival function after tube exposure repair. Cox proportional hazards regression was used to assess the strength of association between surgical techniques with the respective 95% confidence interval (CI). $P<0.05$ indicated statistical significance.

Surgical technique

Tube coverage: Hinge scleral flap

As shown in Supplementary 2. After dissecting conjunctiva and Tenon's capsule (A), the scleral incision was made parallel to the tube approximately 1-2 mm from the tube with a depth of half the scleral thickness. From the incision, a half-thickness scleral tunnel was created using a crescent knife (B). The length of the flap was intended to cover 75-80 % of the entire length of the tube on the sclera. When the desired length of the flap was achieved, the Westcott tenotomy scissors were used to cut at each end of the tunnel to create a flap (C, D). Cover the tube with the flap and suture each corner of the flap with 10-0 nylon suture and then buried the knot (E, F).

Conjunctival substitute: Buccal mucosal graft

Prior to harvesting the graft, the patient should rinse their mouth with mouthwash three times. The buccal mucosa was painted with povidone-iodine. After measuring the size, the area was marked accordingly. The buccal mucosa was outlined with a sharp dissection using a 15-scalpel blade, and the graft was subsequently dissected with Westcott scissors. The buccal mucosal graft was placed to cover the GDD tube.

The important point is to reduce the wound tension by undermining the surrounding tissue until there is no tension between the graft and the surrounding tissue when the wounds are attached. The size of the graft should be larger than the defect because wound contraction can be powerful enough to cause wound dehiscence later. The bed of the graft is another thing to address, tenon tissue should be pulled and sewed to provide a nourishing bed for the oral mucosal graft. The favorable sign is tiny vessels that grow beyond the edge of the graft, thus the graft will start to get pinkish in color not pale.

RESULTS

Nine consecutive GDD tube exposures were repaired over a period of seven years. The baseline demographics and clinical characteristics of the patients are presented in Table 1. Of the nine patients, five were men (56%). The median age (IQR) was 51 (38, 76) years. Five different diagnoses of glaucoma were identified, uveitis being the most common. The Baerveldt implant was the most commonly used GDD implant and five GDDs were located superotemporal (56%). The median interval (IQR) between GDD insertion and tube exposure was 25.9 (5.9, 84.1) months. The patient had multiple previous

TABLE 1. Demographic and clinical characteristics of this current study.

Patient number	Age/Sex/ Eye	Glaucoma diagnosis	GDD model	Exposure quadrant	Time to exposure (month)	No. prior ocular surgery	Difficult case	IOP		BCVA		No. glaucoma medication	
								Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
2	36/F/R	Post PKP	Baerveldt	Superotemporal	58.5	6	Yes	Not tense	Not tense	0.56	0.5	2	2
3	74/M/L	Uveitis	Baerveldt	Superonasal	18.8	3	No	8	Not tense	0.3	0.34	0	0
4	40/F/L	Uveitis	Baerveldt	Superonasal	1	4	Yes	4	4	2.3	2.3	0	0
7	52/F/R	Uveitis	Baerveldt	Superotemporal	109.7	5	Yes	8	10	1.6	2	0	0
8	77/M/L	POAG	Ahmed	Superotemporal	10.4	2	No	14	10	0.6	0.8	3	2
9	85/F/R	Uveitis	Malteno	Inferotemporal	223.7	6	Yes	4	2	2	2	0	0
1	8/M/R	Congenital	Baerveldt	Superonasal	27.3	5	Yes	13	19	2	2	3	1
5	48/M/L	Blast injury	Baerveldt	Superotemporal	1.3	5	Yes	0	4	2.6	0.62	0	0
6	51/M/R	Blast injury	Baerveldt	Superotemporal	25.9	6	Yes	9	8	2	2.3	0	0
Median (IQR)	51 (38, 75.5)				25.9 (5.9, 84.1)	5 (4, 6)		8 (4, 12)	8 (4, 10)	2 (0.58, 2.15)	2 (0.56, 2.15)	0 (0, 2.50)	0 (0, 1.5)
P-value[#]								0.689		0.689		0.5	

[#]Wilcoxon signed rank test

Abbreviations: GDD = glaucoma drainage device; PKP = penetrating keratoplasty; POAG = primary open-angle glaucoma

ocular surgeries with a median (IQR) of 5 (4, 6) times. Various repair techniques were utilized to repair the nine consecutive GDD tube exposures. These included five patch grafts, one patch graft with buccal mucosal graft, two hinge scleral flaps, and one primary closure with a viable former patch graft. Seven out of nine cases (77.8%) were categorized as difficult cases. No statistically significant differences were observed in the pre and post repair values of IOP, BCVA, or the number of glaucoma medications used. The median follow-up time (IQR) after the first repair was 16.4 (5.5, 41.5) months. Surgical outcomes are presented in Table 2. Six cases were successfully repaired until the latest follow-up visit. No intraoperative complications were found. However, three cases required additional surgeries due to reexposure of the GDD tube. Further details regarding these failure cases are described below.

In case No. 1, an 8-year-old boy underwent a Baerveldt shunt implantation two years prior due to congenital glaucoma. The surgical procedure involved the use of a scleral flap and a corneoscleral patch graft to cover the tube. However, the patient experienced two instances of tube exposure, the first of which was repaired using a corneoscleral patch graft with a primary conjunctival closure technique. Nine days later, a second tube exposure occurred, which was repaired using a corneoscleral patch graft with a buccal mucosal graft. The tube remained covered for six months, but the patient later presented with a third exposure along with eye discharge and discharge inside the lumen of the tube. No vitritis was detected. The shunt was subsequently removed along with a subconjunctival antibiotic injection and there were no subsequent occurrences of endophthalmitis.

Case No. 5, a 48-year-old man with a firecracker injury to his left eye. A Baerveldt shunt implantation was performed using a patch graft covering the tube. Poor conjunctival integrity was noted intraoperatively with a few button holes. The buccal mucosal graft was used to cover the holes. A month later, the wound was dehisced with tube exposure and bleb leakage. The former patch graft was still in place, so primary conjunctival closure was performed. Nevertheless, the conjunctiva dehisced multiple times, necessitating two buccal mucosal grafts and one resuture. Later, a reexposure occurred with early signs of endophthalmitis. The shunt was removed and intravitreal antibiotics were injected. Endophthalmitis resolved. The patient received endoscopic cyclophotocoagulation to lower the IOP.

Case No. 6, a 51-year-old male, a victim of a gas explosion. He had multiple concurrent eye injuries including a ruptured globe, retinal detachment, rejection of the graft after penetrating keratoplasty surgery, and occlusion of the central retinal vein. The patient underwent multiple surgeries, received multiple intravitreal injections, and was on prolonged steroid therapy. Two years after the Baerveldt shunt implantation, the first tube exposure occurred. A corneal button graft with conjunctival autograft was used to cover the tube. Subsequently, several tiny tube reexposures (about 0.1 millimeters) with concurrent corneal graft rejection and persistent corneal epithelial defects were detected. The patient received 11 patches of the amniotic membrane covering both the persistent corneal epithelial defect and tube exposure. After stabilizing the corneal disease, tube exposure repair was performed using a corneal patch graft with primary conjunctival closure. Two weeks later, the reexposure occurred. The split-thickness hinge scleral flap with a buccal mucosal graft was used to cover the tube. The tube remains covered until the last follow-up visit, which was 3.3 years after the last repair.

Until April 2022, a total of 109 cases of GDD tube exposure were identified, originating from 24 primary research studies (Supplementary 3), apart from 9 cases from the current study.[2-24,27] The comprehensive results of the search are presented in PRISMA flow diagram (Supplementary 4). Demographic information for the 118 cases is presented in Table 3, although some data were not available. The average age of the participants was 61 years, with a nearly equal gender distribution of 51% male and 49% female. The common causes of glaucoma were primary open-angle glaucoma (POAG; 22.9%), uveitis (13.6%), and trauma (11%). There were some undetermined secondary causes in which further details were unavailable from the primary study. Other secondary causes (mentioned in Table 3) included post-encircling, corneal ulcers, multiple surgery, and steroid-induced glaucoma. The most commonly implanted type of GDD was the Ahmed model (59.3%). The patients had undergone a mean of 3.78 previous ocular surgeries and most of them (86%) had not received any previous repair for tube exposure. Tube erosion occurred after GDD implantation in a mean of 3 years. Among patients with sufficient data available (n = 86), 53 individuals (61.6%) met the criteria for difficult cases.

Of all 118 cases, the reexposure of GDD tubes occurred in 12 cases (10.2%). The average duration of follow-up after repair was 35.01 months. The mean survival duration after repair was 33.54 months. A cumulative survival rate was shown in the Kaplan-Meier curve (Fig 1). The first-year survival rate was 90.7%. Although the survival rates for the second to fourth year remained at 89.1%. Then it dropped to 86.2% in the fifth to thirteenth year.

TABLE 2. Details of operation techniques and repair outcomes.

Patient number	First repair method	First repair outcome	First repair survival duration (month)	No. total repair	For failure case			Follow-up time after the first repair (month)
					Final major repair method	Final outcome	Cause of GDD removal	
2	Patch graft	Success	54.7	1				54.7
3	Patch graft + buccal mucosal graft	Success	24.4	1				24.4
4	Hinge scleral flap + buccal mucosal graft	Success	28.3	1				28.3
7	Hinge scleral flap + patch graft + rerouting	Success	9	1				9
8	Patch graft	Success	3.1	1				3.1
9	Patch graft	Success	2.6	1				2.6
1	Patch graft	Failure	0.3	2	Patch + buccal mucosal graft	Removed	Sign of early infection	16.4
5	Primary closure	Failure	0.7	3 Major 1 Minor*	Buccal mucosal graft	Removed	Endophthalmitis	7.8
6	Patch graft	Failure	3.5	3 Major 11 Minor*	Hinge scleral flap + buccal mucosal graft	Success		59.3
Median (IQR)			3.5 (1.7, 26.4)					16.4 (5.5, 41.5)

*Minor procedure including resuture and amniotic membrane patching

TABLE 3. Baseline characteristics of all cases.

Characteristics	Value
Mean age (year)	61.15
Sex (M: F)	51:49
Glaucoma diagnosis; n (%)	
POAG	27 (22.9)
Uveitis	16 (13.6)
NVG	9 (7.6)
Trauma	13 (11)
Congenital	6 (5.1)
Post PKP	6 (5.1)
Post PPV	4 (3.4)
PACG	4 (3.4)
JOAG	3 (2.5)
PXG	2 (1.7)
ICE	2 (1.7)
Mix mechanism	7 (5.9)
Other secondary causes	5 (4.2)
Undetermined secondary cause	14 (11.9)
GDD type; n (%)	
Ahmed	70 (59.3)
Baerveldt	46 (39)
Molteno	2 (1.7)
Mean number of previous ocular surgery	3.78
Number of previous tube expose repair; n (%)	
0	98 (86)
1	11 (9.6)
2	4 (3.5)
3	1 (0.9)
Mean time from GDD insertion to tube erosion (month)	35.84
Difficult case; n (%)	53 (61.6)

Abbreviations: GDD = glaucoma drainage device; ICE = iridocorneal endothelial syndrome; JOAG = juvenile open angle glaucoma; NVG = neovascular glaucoma; PACG = primary angle-closure glaucoma; PKP = penetrating keratoplasty; POAG = primary open-angle glaucoma; PPV = pars plana vitrectomy; PXG = pseudoexfoliative glaucoma

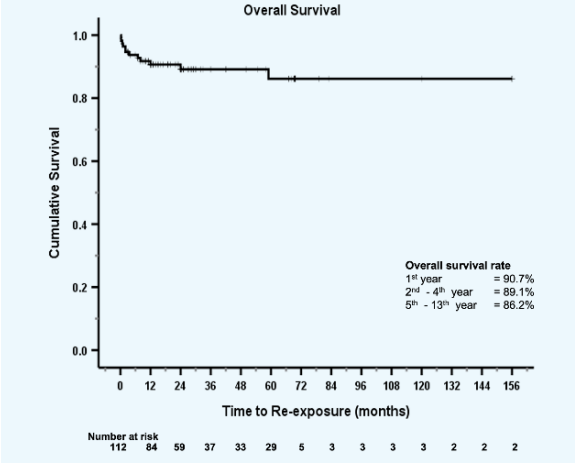


Fig 1. Kaplan-Meier survival analysis of the overall GDD tube-exposure repair.

Various surgical methods were performed for the repair of GDD tube exposure (Table 4). In 84 eyes, the repair involved the use of a novel patch graft placed on the exposed tube. This approach was applied in 24 cases with additional buccal mucosal grafts layered on top, while in 60 cases other conjunctival substitutes were used instead. Patch grafts consisted of 45 corneas, 20 pericardia, 7 scleras, 5 corneoscleras, 4 tenon capsules, 2 Ologen® collagen matrix and 1 perichondrium. In 15 eyes, the tubes were rerouted to a new location, either into the vitreous cavity or positioned above a new area of the sclera. Among these cases, 12 received supplementary patch grafts on top, while 3 did not. In 18 eyes, hinge scleral flaps or scleral tunnels were created to provide cover for the tubes. Among these, 14 cases used supplementary patch grafts, while 4 did not. Only one case was repaired by primary conjunctival closure without any additional patch graft or flap, noting that the former patch graft that had been placed during initial implantation of GDD still covered the tube.

Based on various surgical repair methods, the rate of reexposure, the follow-up time and the number of difficult cases are shown in Table 4. Repair techniques involving rerouting and scleral flap or scleral tunnel methods did not demonstrate instances of reexposure during the average follow-up periods of 26.7 and 14.2 months, respectively. Within these respective groups, 6 cases (54.5%) and 7 cases (38.9%) were classified as difficult cases. In a single difficult case that underwent primary conjunctival closure repair, reexposure was observed on the 21st day following the repair. Among the 24 cases using the patch graft method with buccal mucosal graft, 3 instances of reexposure (12.5%) occurred 1, 2, and 59 months after the repair, with an average follow-up duration of 67.4 months. The complexity of the cases within this particular group could not be determined due to inadequate data. Out of 60 cases in which patch grafts were employed with other conjunctival substitutes, eight cases (13.3%) exhibited reexposure. The reexposure occurred at 0.3, 0.3, 2, 3.5, 7, 8, 12, and 24 months after repair. This group exhibited the highest proportion of difficult cases, comprising 39 cases (71%).

The subgroup analysis of a survival probability is shown in Fig 2. Among the different methods used for tube exposure repair (Fig 2A), rerouting and scleral flap/tunnel techniques demonstrated the highest survival rate, followed by the patch graft with the buccal mucosal graft method, which demonstrated a higher survival rate compared to the patch graft with other conjunctival substitutes method. However, the primary conjunctival closure method was not shown in the graph. It exhibited the lowest survival rate. The first-year survival rates for these methods were 100%, 91.7%, 86.6%, and 0%, respectively. No statistically significant differences were observed among all the methods shown in Fig. 2A (P=0.129). Furthermore, the patch graft with other

TABLE 4. Methods of GDD tube exposure repair and outcomes.

Methods of GDD tube exposure repair	n	Reexposure n (%)	1st year survival	Mean follow-up time (month)	Difficult case n (%)
Total	118	12 (10.2)	90.7%	35.01	53 (61.6)
Patch graft	84	11 (13.1)	88.4%	41.3	39 (70.9)
With buccal mucosal graft	24	3 (12.5)	91.70%	67.4	Unidentified
With other conjunctival substitutes	60	8 (13.3)	86.60%	31.8	39 (70.9)
Rerouting	15	0	100%	26.7	6 (54.5)
With patch graft	12			26.8	3 (37.5)
Without patch graft	3			26.7	3 (100)
Scleral flap/tunnel	18	0	100%	14.2	7 (38.9)
With patch graft	14			13.8	6 (42.9)
Without patch graft	4			15.6	1 (25)
Conjunctival closure only (no patch graft/flap)	1	1 (100)	0%	7.8	1 (100)
Missing data (n)	0	0	6	9	32

Abbreviation: GDD = glaucoma drainage device

conjunctival substitutes group exhibited a higher risk of reexposure compared to the patch graft with buccal mucosal graft group, as indicated by a hazard ratio of 1.52 (95% CI 0.39-6.00). However, this difference did not reach statistical significance (P = 0.547). In terms of case complexity (Fig 2B), it was observed that difficult cases exhibited a lower survival rate and a higher risk of reexposure compared to nondifficult cases, with a first-year survival rate of 86.2% and 96.4%, respectively. The hazard ratio was 4.76 (95% CI 0.59-38.11) without statistical significance (P = 0.142).

DISCUSSION

Since there are various methods to manage tube exposure, choosing the right one for each patient can be challenging. To our knowledge, this study is the complete review of the literature according to the methods of managing tube exposure to this day. In this study, we found that rerouting and hinge scleral flap are the most successful method. The split-thickness hinge scleral flap technique has been proposed by Lee et al.[23] Furthermore, from our case report there was one patient who suffered a blast injury with multiple failures from the patch graft technique. Finally, the exposure was successfully ended with a hinged scleral flap together with a buccal mucosal graft.

Lack of guideline and high-quality RCTs due to the rarity of the disease and various surgical options, we attempt to complete the review with the idea that there is not only one best solution for all patients. However, there should be more sophisticated techniques for more challenging cases. Therefore, we classified the cases into difficult cases which are the cases that are more challenging from a surgical point of view to resolve the exposure of the tube. Recurrent tube exposure, widespread conjunctival damage caused by trauma, and multiple previous surgeries are criteria in this study where the patient can be classified as difficult cases if they meet at least one of these criteria.

Basically, when encountering a tube eroded, the causes needed to be identified. First, if the problem is with mechanical tube rubbing against the conjunctiva, then the tube should be secured firmly to the sclera. Second, if the problem is about patch graft dissolution, then proper tube coverage is mandatory. Third, if conjunctival health is a problem, one should search for appropriate conjunctival substitutes. Finally, other modifiable factors such as medications and some systemic conditions that were believed to have a negative impact on wound healing should be addressed. For example, changing the eye drop of steroids to other immune suppressors can help accelerate wound healing.[28,29]

Among a number of causes underlying the exposure of the GDD tube, patch graft melting has been widely discussed. Smith et al. had studied 64 eyes after GDD implantation with various types of patch graft, including donor sclera, dura mater, and pericardium. The result was similar in terms of percentage of graft melting during 2 years of follow-up.[30] The pathophysiology of graft dissolution is not fully understood, but it could be related to an immune-mediated process.[30] The hinge scleral flap is presumed to have some benefit over the other patch grafts due to its biocompatibility and demonstrates its own vascular supply. Therefore, it could be more resistant to melt. It has been confirmed by a comprehensive review comparing tube covering materials done by Silva et al.

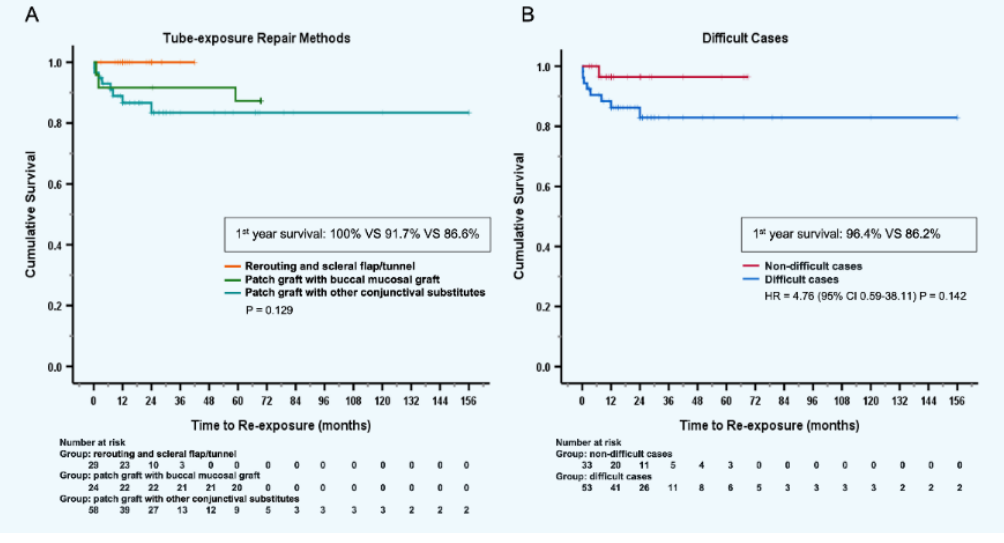


Fig 2. Kaplan-Meier survival analysis of GDD tube-exposure repair in different subgroups. (A) Survival rates corresponding to the use of different repair methods. (B) Survival rates for cases classified as difficult and nondifficult.

that scleral flap provides a low rate of tube exposure.[31] This might explain why hinge scleral flap have a higher success rate than patch grafts and could successfully close the defect of a patient in our series who had failed from multiple patch graft repair.

However, the patch graft group has a longer follow-up time with a more difficult case percentage compared to the rerouting and hinge scleral flap technique. Therefore, the interpretation must be done with care. Rerouting is another interesting technique that can be used with refractory cases. Theoretically, it eliminates all the problems of unhealthy conjunctiva and the localized wound healing problem by moving the tube to a more healthy area. Using this technique sometimes requires special instruments such as tube extender[3], vitrectomy tools, pars plana tube[4], etc. Compared to rerouting, hinge scleral flap requires simple technique and tools. However, the patient with thin sclera is not a good candidate for this method.

Not only tube coverage, but conjunctival replacement is another point to be concerned with. Especially in the case with scar, thin, and friable conjunctiva, severe ocular surface problem, and re-exposed tube where the defect tends to get bigger when the previous repair attempt had failed. The surgical options must be tailored. Both fresh and preserved human amniotic membranes have been widely used. These membranes consist of a dense basement membrane that facilitates epithelial healing, while also modulating inflammation and reducing scar formation.[32] However, when considering coverage for the exposed GDD tube, the oral mucosa is superior to the amniotic membrane because it is thicker and more stable.[33] Not only its durability but also the presentation of epithelial stem cells in the oral mucosa.[33] Compared to nasal mucosa, although oral mucosa has no goblet cells, it is easier to access the tissue, so the glaucoma specialist can do it herself. Furthermore, the grafts are not different in terms of durability.[33]

There are several limitations in this study. The first is the limited number of cases due to the rarity of this condition. Second, we have a variety of methods being used to manage the condition. Comparing between all the methods was difficult and made the number in each group smaller; then we grouped them into 3 groups to get some idea of how each group of methods performs. Third, most of the literature was case series and was reported retrospectively, so it lacks some information with different demographic data of patients. However, we present characteristics of the reports and evaluate the risk of bias to each paper. Most of the reports show a low risk of bias.

In conclusion, this study is the first complete systematic review to date regarding tube exposure repair with mostly low risk of bias literature was gathered and analyzed. Together with our case series, they can shape the algorithm managing tube exposure. The hinged scleral flap with oral mucosal graft can be a good choice to deal with more challenging cases. It could also be a guide for repairing tube erosion in a stepwise manner. No single method suits all, but this more sophisticated technique could be reserved for more difficult cases.

ACKNOWLEDGMENTS

We thank our contributors from the Faculty of Medicine Siriraj Hospital, Mahidol University: Yanee Mukdar (Research Department) and Bongkoch Prakittikul (Siriraj Medical Library) for full-text downloading; Anupong Veeraburinon (Research Department) for helping with manuscript editing; Assist. Prof. Dr. Chulaluk Komoltri (Research Department) for aiding with statistical analysis and interpretation.

DECLARATION

Grant and Funding Information

This project is not funded by any external sources.

Conflicts of Interest

The authors declare that there is no conflict of interest.

Author Contributions

S.P., N.N. and T.P. designed the study, collected data, recruit articles and extract data from articles. N.N. and S.P. interpreted the results. N.N. wrote the manuscript with support from S.P., N.R, P.P., D.S., N.K. and A.J. All authors provided critical feedback and helped shape the research.

Use of artificial intelligence

Artificial Intelligence tool was not used in this manuscript.

REFERENCES

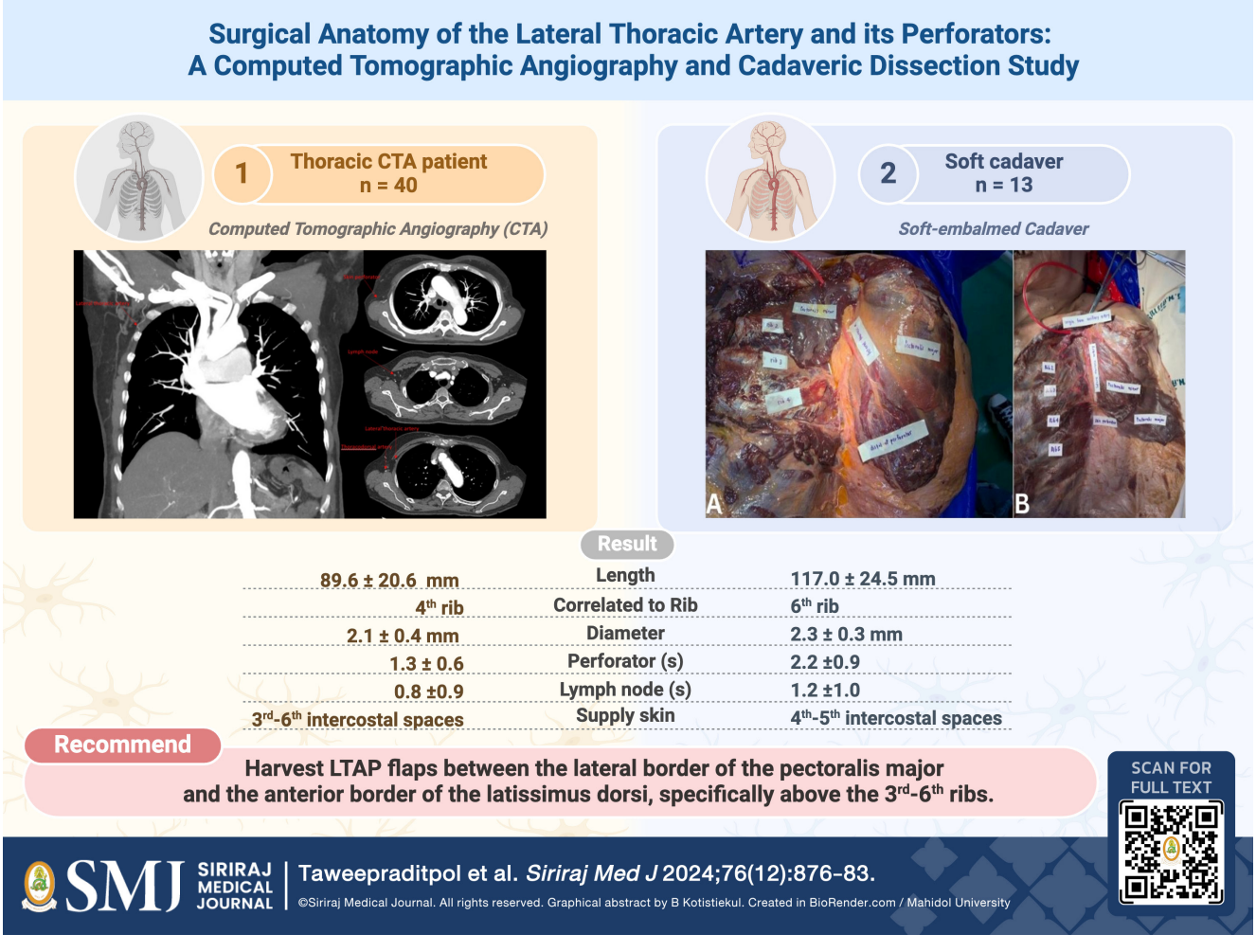
1. Petchyim S, Subhadhirasakul A, Sakiyalak D, Vessadapan P, Ruangvaravate N. Clinical Characteristics and Outcome of Bleb-Related Infection in Glaucoma Patients. Siriraj Med J. 2022;74:555-61.
2. Rosentreter A, Lappas A, Widder RA, Alnawaiseh M, Dietlein TS. Conjunctival repair after glaucoma drainage device exposure using collagen-glycosaminoglycane matrices. BMC Ophthalmol. 2018;18(1):60.
3. Merrill KD, Suhr AW, Lim MC. Long-term success in the correction of exposed 5glaucoma drainage tubes with a tube extender. Am J Ophthalmol. 2007;144:136-7.
4. Joos KM, Laviña AM, Tawansy KA, Agarwal A. Posterior

repositioning of glaucoma implants for anterior segment complications. Ophthalmology. 2001;108:279-84.
5. Prasher P, Lehmann JD, Aggarwal NK. Ahmed tube exposure secondary to prokera implantation. Eye Contact Lens. 2008; 34(4):244-5.
6. Chun YS, Kim KW, Kim JC. Autologous tragal perichondrium patch graft for ahmed glaucoma valve tube exposure. J Glaucoma. 2013;22:e27-30.
7. Rosentreter A, Schild AM, Dinslage S, Dietlein TS. Biodegradable implant for tissue repair after glaucoma drainage device surgery. J Glaucoma. 2012;21:76-78.
8. Song YJ, Kim S, Yoon GJ. Case series: Use of stromal lenticule as patch graft. Am J Ophthalmol Case Rep. 2018;12:79-82.
9. Singh M, Chew PT, Tan D. Corneal patch graft repair of exposed glaucoma drainage implants. Cornea. 2008;27:1171-3.
10. Choudhari NS, Neog A, Latka S, Srinivasan B. Fibrin sealant-assisted revision of the exposed Ahmed tube. Middle East Afr J Ophthalmol. 2015;22:115-6.
11. Grover DS, Merritt J, Godfrey DG, Fellman RL. Forniceal conjunctival pedicle flap for the treatment of complex glaucoma drainage device tube erosion. JAMA Ophthalmol. 2013;131(5): 662-6.
12. Godfrey DG, Merritt JH, Fellman RL, Starita RJ. Interpolated conjunctival pedicle flaps for the treatment of exposed glaucoma drainage devices. Arch Ophthalmol. 2003;121:1772-5.
13. Guajardo JM, Lim KS. Long-term Safety and Efficacy of Conjunctival Pedicle Graft Revision Combined With Repeated Pericardium Allograft for Exposed Glaucoma Drainage Devices. J Glaucoma. 2018;27:910-3.
14. Mohan S, Khattri M, Sah K, Pandey J, Sachan SK. Management of Tube Exposure Following Ahmed Glaucoma Valve Implantation by Allograft Corneoscleral Rim Patch. J Glaucoma. 2019;28:e67-e68.
15. Berezina TL, Fechtner RD, Cohen A, Kim EE, Chu DS. New Technique of Exposed Glaucoma Drainage Tube Repair: Report of a Case. J Curr Glaucoma Pract. 2015;9:62-64.
16. Ainsworth G, Rotchford A, Dua HS, King AJ. A novel use of amniotic membrane in the management of tube exposure following glaucoma tube shunt surgery. Br J Ophthalmol. 2006; 90:417-9.
17. Jabbour S, Lesk MR, Harissi-Dagher M. Patch graft using collagen matrix (Ologen) for glaucoma drainage device exposure in a patient with Boston Keratoprosthesis type 1. Am J Ophthalmol Case Rep. 2018;12:32-35.
18. Mansoori T. Recurrent scleral patch graft shrinkage and Ahmed valve tube exposure. Nepal J Ophthalmol. 2019;11:232-6.
19. Einan-Lifshitz A, Belkin A, Mathew D, Sorkin N, Chan CC, Buys YM, et al. Repair of Exposed Ahmed Glaucoma Valve Tubes: Long-term Outcomes. J Glaucoma. 2018;27:532-6.
20. Alvarez-Ascencio D, Lazcano-Gomez G, Flores-Reyes E, Dueñas-Angeles K, Jímenez-Roman J, Kahook MY. Tenon Cyst Patch Graft for Ahmed Glaucoma Valve Tube Exposure: Case Series Report. J Glaucoma. 2021;30:e367-e71.
21. Lama PJ, Fechtner RD. Tube erosion following insertion of a glaucoma drainage device with a pericardial patch graft. Arch Ophthalmol. 1999;117:1243-44.
22. Liu X, Law SK. Autologous Partial-thickness Scleral Flap and Donor Corneal Graft in Management of Tube Erosion of Glaucoma Drainage Device. J Glaucoma. 2019;28:347-51.
23. Lee ES, Kang SY, Kim NR, Hong S, Ma KT, Seong GJ, et al. Split-thickness hinged scleral flap in the management of exposed tubing of a glaucoma drainage device. J Glaucoma. 2011;20:319-21.
24. Nardi M, Maglionico MN, Posarelli C, Figus M. Managing Ahmed Glaucoma Valve tube exposure: Surgical technique. Eur J Ophthalmol. 2021;31:778-81.
25. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
26. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med. 2018;23:60-63.
27. Liu WW, Werner A, Chen TC. Repair of Tube Erosion by Modifying the Tube Extender. J Glaucoma. 2020;29:604-6.
28. Ehrlich HP, Hunt TK. Effects of cortisone and vitamin A on wound healing. Ann Surg. 1968;167:324-8.
29. Liang H, Baudouin C, Daull P, Garrigue JS, Brignole-Baudouin F. Ocular safety of cationic emulsion of cyclosporine in an in vitro corneal wound-healing model and an acute in vivo rabbit model. Mol Vis. 2012;18:2195-204.
30. Smith MF, Doyle JW, Ticrney JW, Jr. A comparison of glaucoma drainage implant tube coverage. J Glaucoma. 2002;11:143-7.
31. Silva N, Bollemeijer J, Ferreira A, Menéres M-J, Lemij H. Donor scleral graft vs pericardial graft vs scleral flap in tube drainage covering: advantages and disadvantages. Expert Review of Ophthalmology. January 2022; 1-10. Available from: Taylor & Francis Online. Accessed August 29, 2023.
32. Prabhasawat P. Amniotic membrane: a treatment for prevention of blindness from various ocular diseases. Siriraj Med J. 2007; 59(3):139-41.
33. Mai C, Bertelmann E. Oral mucosal grafts: old technique in new light. Ophthalmic Res. 2013;50(2):91-98.

Surgical Anatomy of the Lateral Thoracic Artery and Its Perforators: A Computed Tomographic Angiography and Cadaveric Dissection Study

Sitthichoke Taweepraditpol, M.D.[1,*], Prapasara Prapassorn, M.D.[1], Min Yongsuvimol, M.D.[1], Boonyaporn Kotistienkul, M.D.[1], Parkpoom Piyaman, M.D.[2], Jitladda Wasinrat, M.D.[3], Apirag Chuangsuwanich, M.D.[1]

[1]Division of Plastic Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [2]Department of Anatomy, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [3]Division of Diagnostic Radiology, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.



*Corresponding author: Sitthichoke Taweepraditpol
E-mail: ntdclub13@gmail.com
Received 13 August 2024 Revised 10 October 2024 Accepted 10 October 2024
ORCID ID:http://orcid.org/0009-0008-1706-8032
https://doi.org/10.33192/smj.v76i12.270603

ABSTRACT

Objective: This study explores the anatomical variations and characteristics of the lateral thoracic artery (LTA) and its perforators through thoracic computed tomographic angiographies (CTA) and cadaveric dissection, aiming to enhance surgical planning and patient outcomes.

Materials and Methods: Data were recorded for both thoracic CTA patients (n = 40) and soft cadavers (n = 13) for subsequent retrospective analyses of biological sex, age, body mass index (BMI), LTA characteristics (length, diameter, origin, number of perforators, number of lymph nodes), and locations (rib level and distance from the pectoralis major, latissimus dorsi, and acromioclavicular joint).

Results: Average LTA parameters for thoracic CTAs were 89.6 millimeters in length from origin and 2.1 millimeters in diameter, while cadavers were 117.0 millimeters in length and 2.3 millimeters in diameter. At least 1-2 cutaneous perforators and 1 proximal lymph node were found across both thoracic CTAs and cadavers. No significant differences were observed between the left and right sides for both groups. On average, 73.8% and 66.4% of LTAs from thoracic CTAs and cadavers, respectively, originated from the axillary artery.

Conclusion: This knowledge is crucial for surgical planning, both to minimize damage to the LTA and ensure the inclusion of its perforators and proximal lymph nodes in the lateral thoracic region. The researchers recommend lateral thoracic artery perforator flap harvest between the lateral border of the pectoralis major and the anterior border of the latissimus dorsi, specifically above the 3rd-6th ribs, which is correlated to the length of LTA at 89.6-117 millimeters from origins.

Keywords: Lateral thoracic artery; LTA Perforators; cadaveric dissection; CTA (Siriraj Med J 2024; 76: 876-883)

INTRODUCTION

Perforator flaps are now preferred over traditional reconstructive microsurgery methods due to their minimally invasive nature. These flaps consist of pedicle and soft tissue, harvested without sacrificing muscle or major vessels, thereby preserving surrounding tissue vasculature[1] and reducing functional loss and site-specific morbidities.[2] Developed in the late 1980s, the technique began with the inferior epigastric artery skin flap, which used only skin and subcutaneous adipose tissue, excluding the rectus abdominus muscle.[3,4]

The lateral thoracic artery perforator (LTAP) flap is based on the lateral thoracic pedicle and supplied by the lateral thoracic artery (LTA),[1,5-7] which typically arises from the axillary artery and sometimes from the subscapular and thoracodorsal arteries.[8-10] The LTA runs parallel to the lateral border of the pectoralis major and the anterior border of the latissimus dorsi on the serratus anterior fascia.[11] It supplies the serratus anterior, pectoralis major, pectoralis minor, subscapularis, as well as perforators of the direct cutaneous branch that lie perpendicular and supply the skin of the lateral thoracic region.[7,9,12,13] LTAP flaps are commonly used in conservative breast surgery (CBS) reconstruction for secondary defects or breast cancer.[11,14] Some studies have noted that vascularized lymph node transfer (VLNT) through LTAP or thoracodorsal artery perforator (TAP) flaps can achieve lymph flow restoration for patients with lymphedema.[15,16]

LTAP flaps offer several advantages over lateral intercostal artery perforator (LICAP) flaps. They conserve most of the lateral breast fold and can have scars concealed from LTAP flap harvest concealed by a bra strap.[11] The LTAP flap's pedicle partial or complete mobilization allows for greater reach and transposition for distant defect reconstruction compared to the LICAP flap.[11] Additionally, LTAP flaps result in minimal donor site morbidity and functional loss, preserved vasculature, and muscle tissue, leading to rapid recovery.[3,11,12] They are easy to harvest with the patient in a supine or lateral position and are effective in VLNT for lymphatic channels and lymph node (LN) present in the lateral thoracic region for lymphedema.[15-17] These findings support the use of LTAP flaps for reconstructive and plastic surgery through its numerous applications in wound closure.[5] However, research on LTAP flaps is limited due to few studies exploring its anatomical variations, characteristics, dimensions, and landmarks.[7] Characterizing the anatomical location and physiology of vasculature in the lateral thoracic region would help minimize the risk of damaging LTA and LTAP tissue during flap harvest.

This study aims to address a gap in literature by examining surgical anatomical characteristics, dimensions, and landmarks of the LTA and its perforators using thoracic computed tomographic angiographies (CTAs) and cadaveric dissection.

MATERIALS AND METHODS

This study was approved by the Siriraj Institutional Review Board, protocol number COA no. Si 420/2022.

Clinical studies

Clinical assessments of the LTA were conducted using 40 thoracic CTAs (80 sides) from Siriraj Hospital's Picture Archiving and Communication System (PACS), collected between January and December 2021, by the Siriraj Radiology Department (SIRAD). Healthy patients over 18 years of age, with no history of congenital or acquired thoracic anomalies, surgeries, or radiology of the breast and thorax were included in this retrospective assessment.

Cadaveric studies

Angiography assessments of the LTA were performed on 13 soft-embalmed cadavers (26 sides) dissected between July and December 2022 by Plastic surgeons from Division of Plastic Surgery, Department of Surgery, Siriraj Hospital and certified anatomist from the Department of Anatomy, Siriraj Training and Education Center for Clinical Skills (SiTEC), Siriraj Hospital. The epidermis, dermis, and subcutaneous layers were well-preserved.[18] Radio-dense silicone oil (3:1) was injected directly into the axillary artery through the costoclavicular space. The surgical approach involved trap-door thoracotomies with a transverse incision superior to the clavicle, descending to the midline sternum to the 10th interspace, and then laterally to the anterior-axillary line.[19] Individual tissue layers were carefully excised to expose the LTA and its perforators, minimizing damage to the vasculature.

Statistical analyses

All data was tested with test of normality. Descriptive statistics were used to describe baseline characteristics (age, weight, height, BMI). Data are presented as means with standard deviation or frequencies with percentages as appropriate. For normal distribution data, we used the paired sample T-test to compare between left and right side of cadaver-cadaver, CTA-CTA, and used independent sample T-test to compare between left and right side of cadaver-CTA (length, diameter, and distance from the lateral border of the pectoralis major, anterior border of the latissimus dorsi, and acromioclavicular joint). For non-parametric test the study used Wilcoxon test to compare between left and right side of cadaver-cadaver, CTA-CTA, and used Mann-Whitney U test to compare between left and right side of cadaver-CTA to describe LTA characteristics (number of perforators, number of LNs). A P-value <0.05 was set as the threshold for statistical significance. SPSS program version 18 was used for all statistical analyses. Pearson's correlation assessed the correlation between LTA and its perforators across both groups.

RESULTS

Demographic data

The thoracic CTA patients were 52.5% male (n = 21), with a mean (SD) age of 67 (11.9) years and a BMI of 24.5 (3.5) kg/m^2. Among the cadavers, 46.2% were male (n = 6), with an average age of 72 (8.0) years and a BMI of 23.0 (2.5) kg/m^2. No significant demographic differences were observed between groups (Table 1).

Clinical studies

No significant differences in LTA parameters were found between left and right thoracic CTAs (Table 2). Average LTA parameters were: length from origin, 89.6 ± 20.6 millimeters, diameter, 2.1 ± 0.4 millimeters, distance from the acromioclavicular joint, 136.6 ± 22.7 millimeters, distance from the lateral border of the pectoralis major, 5.3 ± 0.7 millimeters, and distance from the anterior border of the latissimus dorsi, 36.0 ± 13.2 millimeters. Approximately 1 perforator (1.3 ± 0.6) and 1 LN (0.8 ± 0.9) were found across both left and right lateral thoracic regions. Right perforators typically supplied skin between the 7.5-11 centimeters (4th-5th intercostal spaces), while left perforators typically supplied skin between the 6.0-12.0 centimeters (3rd-6th intercostal spaces) (Fig 1).

Cadaveric studies

No significant differences in left and right LTA parameters were observed in cadavers (Table 2). Average LTA parameters were: length from origin, 117.0 ± 24.5 millimeters, diameter, 2.3 ± 0.3 millimeters, distance from the acromioclavicular joint, 168.3 ± 17.4 millimeters, distance from the pectoralis major, 3.8 ± 0.7 millimeters, and distance from the latissimus dorsi, 37.9 ± 6.5 millimeters. Approximately 2 perforators (2.2 ± 0.9) and 1 LN (1.2 ± 1.0) were found across both left and right lateral thoracic regions. Right (Fig 2A) and left (Fig 3A-B) perforators, 0.3-0.5 millimeters in diameter, and 2.0 millimeters in length were typically observed supplying the skin between the 4th-5th intercostal spaces. Lateral thoracic LNs were also observed proximal to these vascular structures (Fig 2B).

Pearson's correlation

LTA length from origin ($p < 0.01$), distance from the acromioclavicular joint ($p < 0.008$), and number of cutaneous perforators ($p < 0.005$) were significantly greater in cadavers than in thoracic CTAs (Table 3).

TABLE 1. Patient demographic data.

Variable		Thoracic CTA	Cadavers	*p*-value
Age (yrs, mean ± SD)		67.1 ± 11.9	72.7 ± 8.0	0.120
Sex n (%)	Male female	21.0 (52.5) 19.0 (47.5)	6.0 (46.2) 7.0 (53.8)	0.671
Weight (kg, mean ± SD)		63.9 ± 11.0	60.8 ± 12.2	0.397
Height (cm, mean ± SD)		160.2 ± 10.6	161.8 ± 10.0	0.648
BMI (kg/m^2, mean ± SD)		24.5 ± 3.5	23.0 ± 2.5	0.160

Abbreviations: SD, Standard Deviation; BMI, Body Mass Index.

TABLE 2. Patient demographic data.

Variable	Side	Mean ± SD	*p*-value
From thoracic CTA (n = 40)			
Length from origin (mm.)	Right Left	91.6 ± 20.8 87.5 ± 20.4	0.374
Diameter (mm.)	Right Left	2.1 ± 0.4 2.0 ± 0.4	0.095
Distance from acromioclavicular joint (mm.)	Right Left	139.8 ± 23.4 133.5 ± 22.0	0.210
Distance from lateral border of pectoralis major (mm.)	Right Left	6.1 ± 0.8 4.5 ± 0.5	0.339
Distance from anterior border of latissimus dorsi (mm.)	Right Left	36.5 ± 13.4 35.5 ± 13.0	0.746
Number of perforators	Right Left	1.4 ± 0.7 1.2 ± 0.4	0.119
Number of lymph nodes	Right Left	0.8 ± 0.8 0.8 ± 1.0	0.807
From cadaveric dissection (n = 13)			
Length from origin (mm.)	Right Left	125.7 ± 26.0 108.2 ± 23.0	0.132
Diameter(mm.)	Right Left	2.3 ± 0.4 2.2 ± 0.2	0.424
Distance from acromioclavicular joint (mm.)	Right Left	170.6 ± 17.7 165.9 ± 17.1	0.553
Distance from lateral border of pectoralis major (mm.)	Right Left	3.4 ± 0.7 4.1 ± 0.7	0.848
Distance from anterior border of latissimus dorsi (mm.)	Right Left	38.6 ± 6.6 37.1 ± 6.3	0.579
Number of perforators	Right Left	2.0 ± 0.8 2.4 ± 1.0	0.281
Number of lymph node	Right Left	1.5 ± 1.2 0.9 ± 0.8	0.244

All specified lengths, diameters, and distances are in millimeters (mm).
Abbreviations: SD, Standard Deviation; CTA, Computed Tomography Angiography.

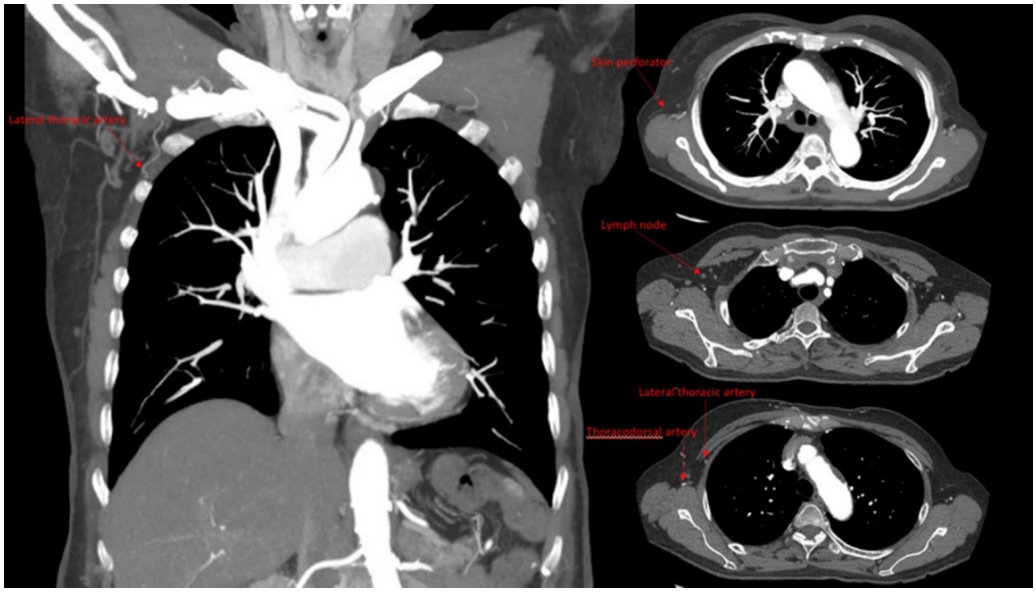


Fig 1. Thoracic computed tomography angiography (CTA) of the right lateral thoracic artery (LTA).

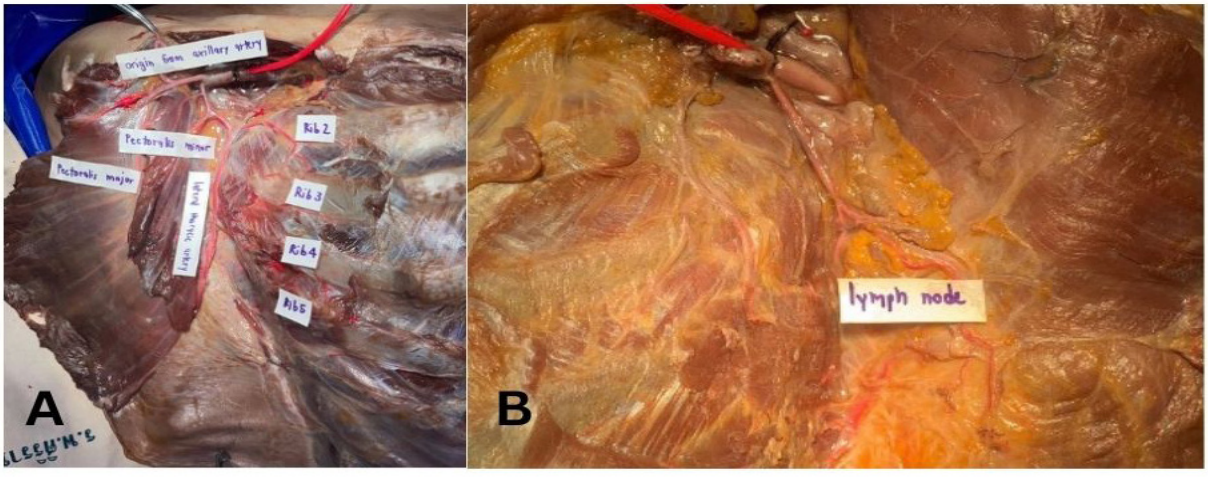


Fig 2. Cadaveric dissection of the (A) right lateral thoracic artery (LTA) and (B) lateral thoracic lymph node.

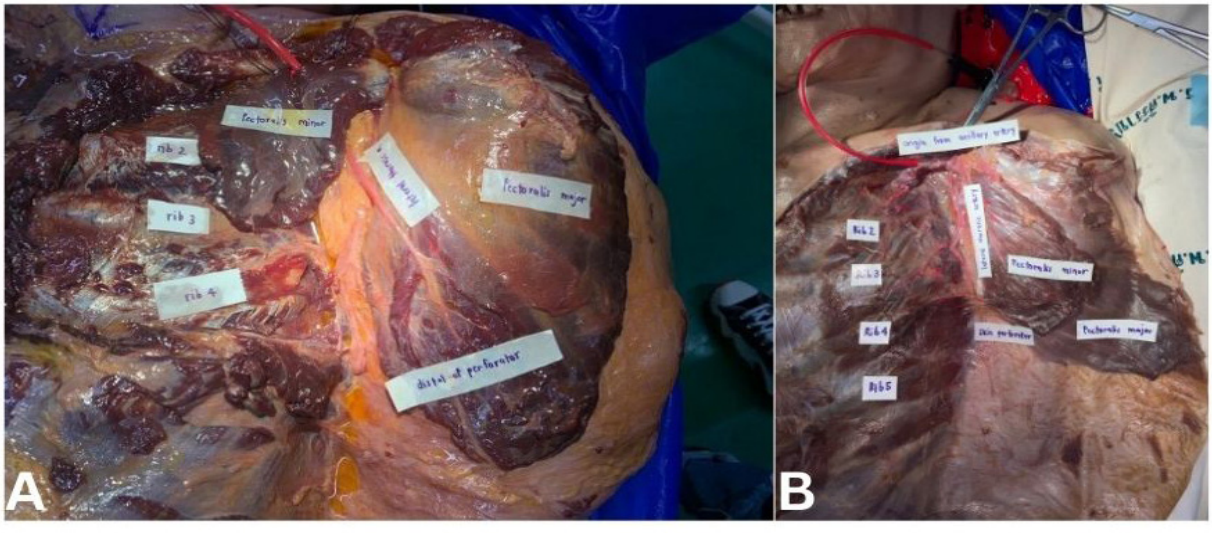


Fig 3. Cadaveric dissection of the (A) left lateral thoracic artery (LTA) and (B) lateral thoracic perforators of the skin between the 3rd to 5th ribs.

TABLE 3. Correlation between lateral thoracic artery and perforators of thoracic CTA and soft cadavers.

Variable	Thoracic CTA		Cadavers		*p*-value
	Right side	Left side	Right sode	Left side	
LTA type by origin					
Axillary	31 (77.5)	28 (70.0)	8 (72.7)	6 (60.0)	0.391
Thoracodorsal	0 (0)	1 (2.5)	1 (9.1)	2 (20.0)	
Subscapular	9 (22.5)	11 (27.5)	2 (18.2)	2 (20.0)	
Length from origin (mm.) (Mean ± SD)	91.6 ± 20.8	87.5 ± 20.4	125.7 ± 26.0	108.2 ± 23.0	**0.010**
Diameter (mm.) (Mean ± SD)	2.1 ± 0.4	2.0 ± 0.4	2.3 ± 0.4	2.2 ± 0.2	0.200
Distance from lateral border of pectoralis major (mm.) (Mean ± SD)	6.1 ± 0.8	4.5 ± 0.5	3.4 ± 0.7	4.1 ± 0.7	0.176
Distance from anterior border of latissimus dorsi (mm.) (Mean ± SD)	36.5 ± 13.4	35.5 ± 13.0	38.6 ± 6.6	37.1 ± 6.3	0.738
Distance from acromioclavicular joint (mm.) (Mean ± SD)	139.8 ± 23.4	133.5 ± 22.0	170.6 ± 17.7	165.9 ± 17.1	**0.008**
Number of perforators (Mean ± SD)	1.4 ± 0.7	1.2 ± 0.4	2.0 ± 0.8	2.4 ± 1.0	**0.005**
Number of lymph nodes (Mean ±SD)	0.8 ± 0.8	0.8 ± 1.0	1.5 ± 1.2	0.9 ± 0.8	0.754

All specified lengths, diameters, and distances are in millimeters (mm). Data is expressed as mean ± standard deviation or n (%).
Abbreviations: CTA, Computed Tomography Angiography; LTA, Lateral Thoracic Artery.

LTAs originated most frequently from the axillary artery (73.8% in thoracic CTAs and 66.4% in cadavers), followed by the thoracodorsal arteries (25.0% in thoracic CTAs and 19.1% in cadavers), and least frequently from the subscapular artery (1.3% in thoracic CTAs and 14.6% in cadavers). LTAs that originated from axillary arteries were more common in right LTAs, while those originating from the subscapular and thoracodorsal arteries were more common on the left side. There were no significant differences in LTA type by anatomical location, arterial diameter, distance from the pectoralis major and latissimus dorsi, or the number of proximal LNs across groups.

DISCUSSION

The authors assessed the anatomical characteristics, dimensions, and landmarks of the LTA and its perforators through thoracic CTAs and cadaveric dissection. They found that cadavers had a significantly greater LTA length from origin, distance from the acromioclavicular joint, and number of cutaneous perforators. LTAs most frequently originated from the axillary artery, followed by the subscapular and thoracodorsal arteries, respectively. To the authors' knowledge, no prior publications have reported on the diameter and lengths of cutaneous perforators of the LTA within the 4th intercostal space.

The lateral thoracic region flap, located between the pectoralis major and latissimus dorsi muscles, is highly vascularized with multiple cutaneous perforators that supply the skin. Its hairlessness and favorable length-to-width ratio make it highly versatile and convenient for mobilizing to adjacent wounds or defects for closure or reconstruction. This versatility supports the shift from conventional musculocutaneous or myocutaneous flaps to perforator flaps as plastic surgeons' knowledge regarding microsurgical methods and vascularization improves.[20] Perforators enable the harvesting of various thin flaps from the same region while preserving the source vessels, transforming traditional donor sites into universal donor sites. Flaps that can be harvested from the lateral thoracic region include the thoracodorsal artery perforator (TDAP) flap, LICAP flap, and LTAP flap.[21,22]

The researchers found that, on average, 73.8% of LTAs from thoracic CTAs and 66.4% from cadavers originated from the axillary artery. A smaller percentage variably originated from the subscapular artery or thoracodorsal artery, as noted previously. The LTA diameters averaged 2.1 and 2.3 millimeters, with lengths of 89.6 and 117.0 millimeters for thoracic CTAs and cadavers, respectively. This study confirmed that the LTA runs parallel to the lateral border of the pectoralis major and anterior border of the latissimus dorsi, supplying the pectoral muscles and serratus anterior through muscular branches, and providing blood to the skin between the 3rd-6th intercostal spaces of the lateral thoracic region through direct cutaneous perforators.

One study used magnetic resonance imaging (MRI) to confirm the LTA's anatomical location and enumerate its direct cutaneous perforators in the lateral thoracic region. It found that 94.3% of LTAP flaps were supplied by an average of 2 perforators located roughly 172.2 millimeters from the axillary artery.[13] Similar findings were noted in the study's cadaveric dissections, with 1-2 perforators observed between the 3rd-6th intercostal spaces. These cutaneous perforators were especially prevalent (up to 100%) between the 4th-5th intercostal spaces.

The researchers also confirmed that LTAP flaps contain at least one LN that can be transferred for treating lymphedema. Seventy percent of these LNs were found 10 millimeters proximal to the LTA, particularly within the 3rd-6th intercostal spaces, similar to the cutaneous perforators. One limitation of the LTAP flap is the small size of its venae comitantes, which often provides inadequate venous drainage. As a result, the lateral thoracic vein should typically be included when harvesting the flap. However, dissection of the pedicle can be challenging because it is often embedded in a thick layer of fat, and the lateral thoracic vein can follow a different course from the artery. Additionally, the lateral thoracic pedicle is generally shorter and smaller than the thoracodorsal vessels.

Limitations

This study had some limitations. The first was its exclusion of perforasome dimensions. LTA perforators narrower than 0.6 millimeters could not be accurately identified from thoracic CTA imaging, which may have influenced the recorded lengths and number of perforators for thoracic CTAs. Differences in positions during imaging and cadaveric dissection could potentially result in discrepancies of the data, especially in LTA length. Additionally, the narrow diameter prevented cannulation and ink injection for photographic contrast in cadavers. The second limitation was that LN counts were performed by eye. More accurate enumerations would require stereomicroscopic investigation.

Recommendations and future directions

LTAP dimensions for surgical removal are routinely oriented vertically and are elliptical in shape (10 × 5 centimeters).[16] It is recommended that the pointed ellipse be positioned between the anterior and posterior axillary lines, 20 millimeters away from the axillary neurovascular bundle.[16,23] An incision is typically made at the anterior axillary line, and the flap is harvested through dissection in the suprafascial plane between the lateral border of pectoralis minor and the second intercostal brachial nerve.[23] Based on our findings, the researchers recommend harvesting LTAP flaps between the lateral border of the pectoralis major and the anterior border of the latissimus dorsi, specifically above the 3rd-6th ribs. This approach avoids damaging the LTA while including perforators and proximal LNs of the lateral thoracic region. Incisions between the 4th-5th intercostal spaces should be executed cautiously to prevent damaging any structures within the lateral thoracic region. The researchers are also looking forward to using this flap as a vascularized lymphatic flap for treating lymphedema.[24]

CONCLUSION

LTAP flaps are an alternative, conservative approach to plastic reconstruction and microsurgery. This study determined the anatomical characteristics, dimensions, and landmarks of the LTA and its perforators through thoracic CTAs and cadaveric dissection. The authors confirmed the anatomical location, characteristics, and dimensions of the LTA and provided insights into the nature of its direct cutaneous perforators. Equipping surgeons and medical practitioners with this knowledge is crucial for surgical planning, minimizing damage to the LTA, and including perforators and proximal LNs of the lateral thoracic region. The researchers recommend harvesting LTAP flaps between the lateral border of the pectoralis major and the anterior border of the latissimus dorsi, specifically above the 3rd-6th ribs.

ACKNOWLEDGEMENT

None

DECLARATION

Grants and Funding Information

This research is funded by the Siriraj Research Development Fund, grant number R016631025.

Conflicts of Interest

All authors declare no personal or professional conflicts of interest related to any aspect of this study.

Author Contributions

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

Use of Artificial Intelligence

This study did not utilize any artificial intelligence.

REFERENCES

1. Yamamoto T, Yamamoto N, Kageyama T, Sakai H, Fuse Y, Tsuihiji K, et al. Definition of perforator flap: what does a" perforator" perforate? Glob Health Med. 2019;1(2):114-6.
2. Geddes CR, Morris SF, Neligan PC. Perforator flaps: evolution, classification, and applications. Ann Plast Surg. 2003;50(1):90-9.
3. Koshima I, Soeda S. Inferior epigastric artery skin flaps without rectus abdominis muscle. Br J Plast Surg. 1989;42(6):645-8.
4. Kroll SS, Rosenfield L, Kroll SJ. Perforator-based flaps for low posterior midline defects. Plast Reconstr Surg. 1988;81(4):561-6.
5. Kim JT, Ng S-W, Naidu S, Do Kim J, Kim YH. Lateral thoracic perforator flap: additional perforator flap option from the lateral thoracic region. J Plast Reconstr Aesthet Surg. 2011;64(12):1596-602.
6. Kim DY, Kim HY, Han YS, Park JH. Chest wall reconstruction with a lateral thoracic artery perforator propeller flap for a radiation ulcer on the anterior chest. J Plast Reconstr Aesthet Surg. 2013;66(1):134-6.
7. Mangialardi ML, Baldelli I, Salgarello M, Raposio E. Breast reconstruction using the lateral thoracic, thoracodorsal, and intercostal arteries perforator flaps. Plast Reconstr Surg Glob Open. 2021;9(1):e3334.
8. Bhattacharya S, Bhagia S, Bhatnagar S, Aabdi S, Chandra R. The anatomical basis of the lateral thoracic flap. European Journal of Plastic Surgery. 1990;13:238-40.
9. Taylor GI, Daniel RK. The anatomy of several free flap donor sites. Plast Reconstr Surg. 1975;56(3):243-53.
10. Rowsell AR, Davies DM, Eizenberg N, Taylor GI. The anatomy of the subscapular-thoracodorsal arterial system: study of 100 cadaver dissections. Br J Plast Surg. 1984;37(4):574-6.
11. McCulley SJ, Schaverien MV, Tan VK, Macmillan RD. Lateral thoracic artery perforator (LTAP) flap in partial breast reconstruction. J Plast Reconstr Aesthet Surg. 2015;68(5):686-91.
12. Harii K, Torii S, Sekicuchi J. The free lateral thoracic flap. Plast Reconstr Surg. 1978;62(2):212-22.
13. Kagaya Y, Arikawa M, Sekiyama T, Mitsuwa H, Takanashi R, Taga M, et al. The concept of "whole perforator system" in the lateral thoracic region for latissimus dorsi muscle-preserving large flaps: An anatomical study and case series. PLoS One. 2021;16(9):e0256962.
14. Munhoz AM, Montag E, Arruda E, Brasil JA, Aldrighi JM, Gemperli R, et al. Immediate conservative breast surgery reconstruction with perforator flaps: new challenges in the era of partial mastectomy reconstruction? Breast. 2011;20(3):233-40.
15. Yamamoto T, Yoshimatsu H, Yamamoto N. Complete lymph flow reconstruction: a free vascularized lymph node true perforator flap transfer with efferent lymphaticolymphatic anastomosis. J Plast Reconstr Aesthet Surg. 2016;69(9):1227-33.
16. Tinhofer IE, Meng S, Steinbacher J, Roka-Palkovits J, Gyori E, Reissig LF, et al. The surgical anatomy of the vascularized lateral thoracic artery lymph node flap—A cadaver study. J Surg Oncol. 2017;116(8):1062-8.
17. Loukas M, Du Plessis M, Owens DG, Kinsella Jr CR, Litchfield CR, Nacar A, et al. The lateral thoracic artery revisited. Surg Radiol Anat. 2014;36:543-9.
18. Ratanayotha A, Oo EM. Chronicle of Anatomical Education in Thailand: Experiences at Siriraj Medical School. Siriraj Med J. 2022;74(7):463-71.
19. Christison-Lagay ER, Darcy DG, Stanelle EJ, Dasilva S, Avila E, La Quaglia MP. "Trap-door" and "clamshell" surgical approaches for the management of pediatric tumors of the cervicothoracic junction and mediastinum. J Pediatr Surg. Jan 2014;49(1):172-6; discussion 176-7.
20. Kim JT, Kim SW. Perforator flap versus conventional flap. J Korean Med Sci. 2015;30(5):514-22.
21. Mangialardi ML, Baldelli I, Salgarello M, Raposio E. Breast reconstruction using the lateral thoracic, thoracodorsal, and intercostal arteries perforator flaps. Plast Reconstr Surg Glob Open. 2021;9(1):e3334.
22. McCulley SJ, Schaverien MV, Tan VKM, Macmillan RD. Lateral thoracic artery perforator (LTAP) flap in partial breast reconstruction. J Plast Reconstr Aesthet Surg. 2015;68(5):686-91.
23. Schaverien MV, Badash I, Patel KM, Selber JC, Cheng M-H. Vascularized lymph node transfer for lymphedema. Thieme Medical Publishers; 2018.p.028-035.
24. Turbpaiboon C, Puprasert C, Lohasammakul S, Dacharux W, Numwong T, Pandeya A, et al. Deep peroneal nerve: From an anatomical basis to clinical implementation. Siriraj Med J. 2022;74(7):448-62.