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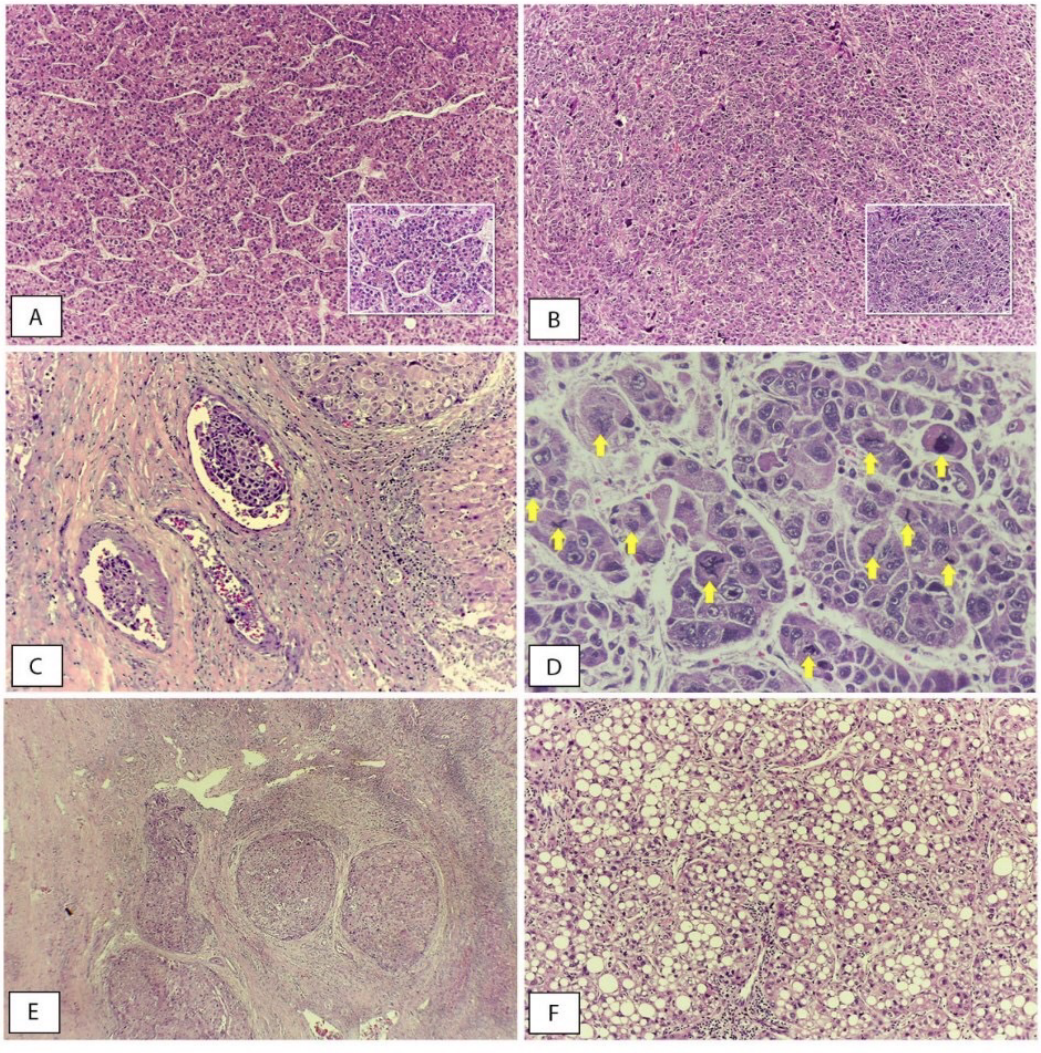

By Ignasia Andhini Retnowulan, et al.

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LETTER TO THE EDITOR

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Incidence of Infection-related Complications and Optimal Saline Irrigation Volume for Preoperative Bowel Preparation to Reduce Postoperative Infections in Hirschsprung's Disease

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ABSTRACT

Objective: The purpose of this study was to find incidence of infection-related complications and the optimal volume and duration (days) of rectal NSS irrigation that would result in the low post-operative complications following transanal endorectal pull-through (TERPT) in patients with Hirschprung's disease.

Materials and Methods: We conducted a retrospective chart reviews of 131 patients diagnosed with Hirschsprung's disease who underwent TERPT at Siriraj Hospital between January 2006 and December 2020.

Results: Infection-related complications were observed in 23(17.6%) patients, comprising 22(16.8%) cases of anastomotic strictures, 3(2.3%) cases of anastomotic leakages, and 2(1.5%) cases of intraabdominal collections. The median (Q1, Q3) volume of NSS irrigation (ml/kg/day) for those without complications (38.1 (33.9,50)) and those with complications (39.5 (35,45)) was statistically identical (p = 0.945). Similary, the median duration of for both groups was the same (p = 0.854). The mean (SD) volume of irrigated NSS in those with leakage (55.6 (32.7)) and those without leakage (44.3 (17.9)) showed no statistically significant difference (p = 0.291). Patients with post-operative stricture received the same amount of irrigated NSS (40.7 (11.9)) as those without stricture (45.4 (19.2)) (p = 0.138). Similarly, those with hyponatremia received the same amount of irrigated NSS as those without hyponatrema (p = 0.475).

Conclusion: The volume of rectally irrigated NSS did not correlate with infection-related complications such as anastomotic leakage, stricture and intraabdominal collection. However, this study observed a low complication rate, thus, future research should cover a larger population.

Keywords: Hirschsprung; endorectal pullthrough; complications; irrigation; bowel preparation (Siriraj Med J 2023; 75: 763-769)

INTRODUCTION

Hirschsprung's disease (HD) is caused by the absence of ganglion cells in the myenteric and submucosal plexus of the colon, inhibiting the propagation of peristaltic waves. It has an estimated incidence of roughly 1 in 5,000 live births.[1] The most effective surgical treatment involves resection of the aganglionic bowel segment and the identification of normally ganglionated proximal bowel for a level coloanal anastomosis. In 1988[2-4], L De la Torre and J A Ortega transformed the Soave-Boley endorectal pull-through procedure into a purely transanal approach known as the "transanal endorectal pull-through" (TERPT). If the transanal approach cannot be performed flawlessly, a combined method of abdominal

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and transanal approaches, dubbed "abdominal assisted transanal endorectal pull-through" (abdo + TERPT), is used.

The reduction of fecal loading is crucial to minimizing complications related to infection such as wound infection, intraabdominal collection, coloanal anastomosis leakage, wound dehiscence, anastomosis retraction and anastomosis stricture. This can be achieved through adequate bowel preparation.

Various bowel preparation regimens, which include rectal normal saline solution (NSS) irrigation before a definitive pull-through operation, have been followed. The Royal Children's Hospital, Melbourne[5] as well as the Children's Hospital, Pittsburgh[6] recommend NSS irrigation of 20 ml/Kg. However, no studies have compared the efficacy of these regimens. The Division of Pediatric Surgery, Faculty of Medicine Siriraj Hospital uses a preoperative bowel preparation regimen with rectal NSS irrigation of 20-50 ml/Kg/session, administered twice a day. The effectiveness of this quantity of NSS is neither proven nor known to be sufficient to do rectal NSS irrigation. Additionally, pre-operative reduction of stool production by altering the diet was implemented. At Siriraj Hospital, a low residual diet was introduced three days prior to the operation. A liquid diet was prescribed on the day prior to the operation, and only a clear liquid diet was allowed on the day of the operation. The required duration for this dietary change regimen remains uncertain, and excessive rectal NSS irrigation might result in hyponatremia.

Neither the optimal volume nor duration of NSS irrigation have been established with scientific evidence. Thus, this study was conducted to determine the most suitable volume and duration of rectal NSS irrigation to minimize infection-related complications following pull-through operations.

MATERIALS AND METHODS

After obtaining approval from the Siriraj Institutional Review Board (COA. no Si 757/2020), a retrospective study was carried out in children diagnosed with Hirschsprung's disease who underwent either a transanal endorectal pull-through or abdominal assisted transanal endorectal pull-through at Siriraj Hospital between January 2006 to December 2020. Children diagnosed with kidney disease causing hyponatremia, those who were immunocompromised, those who had previously underwent colostomy, and those with incomplete medical information were excluded from the study.

Infection-related complications were defined as complications occuring within three months postoperatively including wound infection, intraabdominal collection, coloanal anastomosis leakage, wound dehiscence, anastomosis retraction and anastomosis stricture.

Patients' demographic data, transitional zone level, preoperative bowel preparation (volume (cc/kg/day) and duration (days)), types of operation, and complications following either transanal endorectal pull-through or abdominal assisted transanal endorectal pull-through were collected. Complications, such as surgical site infection, anastomotic leakage, abscess at anastomosis, intraabdominal collection, wound dehiscence, anastomotic stricture, post-operative hyponatremia, were also recorded. The collected data were analyzed using SPSS software version 18 (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc). Continuous data were expressed as either median (Q1, Q3) or mean (standard deviation) depending on the distribution of the data and categorical data was expressed as numbers and percentages. A Chi-square test was used to compare proportional data and the Mann-Whitney U test was used to compare continuous data. Multiple binary logistic regression analysis was used to adjust confounding factors. A p-value of <0.05 was considered statistically significant.

RESULTS

This study included 131 patients diagnosed with Hirschsprung's disease, of whom 85 (64.9%) were male and 46 (35.1%) were female. Ninty-nine patients underwent TERPT, while 32 patients recieved the abdominal assisted TERPT. Postoperative infection-related complications were observed in 23 (17.6%) patients, including 22 (16.8%) anastomotic stricture, 3 (2.3%) cases of anastomotic leakages, and 2 (1.5%) instances of intraabdominal collection.

Patients' characteristics, with surgical complications (n = 23) and without surgical complications (n = 108), are shown in Table 1.

Among the two groups, there were no significant differences in terms of gender, age, weight, and transitional zone level (p = 0.998, 0.224, 0.629 and 0.732 respectively). The need for abdominal-assisted TERPT was found to be identical among patients with and without complications (p = 0.838)

Table 2 demonstrates the comparison between patients with and without surgical complications, considering factors such as pre-operative volume of NSS irrigation, duration of NSS irrigation, re-operation requirement, and length of hospital stay.

In relation to overall complications, the median (Q1, Q3) volume of rectal NSS irrigation (ml/kg/day) for patients

TABLE 1. Patients' characteristics: A comparison of those without surgical complications and those with surgical complications.

	No surgical complication (n=108)	Surgical complication (n=23)	Total (n=131)	P-value
Gender				0.998[a]
Male (%)	68 (63.0%)	17 (73.9%)	85 (64.9%)	
Female (%)	40 (37.0%)	6 (26.1%)	46 (35.1%)	
Age (Median (Q1,Q3)) (days)	30 (21,202.5)	30 (19,60)	30 (21,180)	0.224[b]
Weight (Median (Q1,Q3)) (kg)	4.1 (3.3,6.6)	4.0 (3.1,4.8)	5.9 (3.3,6.0)	0.629[b]
Transitional zone				0.732[a]
Rectum (%)	29 (26.9%)	7 (30.5%)	36 (27.5%)	
Rectosigmoid colon (%)	61 (56.5%)	11 (47.8%)	72 (55.0%)	
Long segment (%)	18 (16.6%)	5 (21.7%)	23 (17.6%)	
Operation				0.838[a]
TERPT (%)	82 (75.9%)	17 (73.9%)	99 (75.6%)	
Abdominal assisted TERPT (%)	26 (24.1%)	6 (26.1%)	32 (24.4%)	

TERPT: Transanal endorectal pull-through
[a]Chi-square test, [b]Mann-Whitney Test
Q1: The lower quartile, first quartile
Q3: The upper quartile, third quartile

TABLE 2. Comparison of pre-op volume of NSS irrigation, duration of NSS irrigation, re-operation frequency, and length of hospital stay between those without surgical complications and those with surgical complications.

	No surgical complication (n=108)	Surgical complication (n=23)	Total (n=131)	P-value
NSS irrigation volume (median (Q1,Q3)) (ml/kg/day)	38.1 (33.9, 50)	39.5 (35, 45)	38.4 (34.1, 48.7)	0.945[b]
Duration of NSS irrigation (median (Q1,Q3)) (days)	7.0 (5,10)	7.0 (4, 10)	7.0 (4, 10)	0.854[b]
Re-operation				<0.001[a]
Yes (%)	108 (100%)	2 (8.7%)	110 (84.0%)	
No (%)	0	21 (91.3%)	21 (16.0%)	
Length of hospital stay (median (Q1,Q3)) (days)	15.0 (10.2, 20)	18.0 (10, 25)	16 (10, 21)	0.204[b]

[a]Chi-square test, [b]Mann-Whitney Test
Q1: The lower quartile, first quartile
Q3: The upper quartile, third quartile

without post-operative complications (38.1 (33.9,50)) was comparable to that of patients with complications (39.5 (35,45)), showing no significant difference (p = 0.945). Likewise, the median (Q1, Q3) duration of rectal NSS irrigation was identical in both groups (7.0 (5, 10) days vs. 7.0 (4, 10) days) (p = 0.854). The incidence of each infection-related complication and a comparison of total saline irrigation volume (ml/kg/day) between those with each complication and those without each complication are described in Table 3.

Anastomotic leakage did not show a correlation with volume of rectal NSS irrigation. The mean (SD) volume of rectal NSS irrigation (ml/kg/day) for patients with leakage leakage (55.6 (32.7)) and those without leakage (44.3 (17.9)) displayed no significant difference (p = 0.291). However, the incidence of leakage in this series was only 2.3%.

Anastomotic stricture, the most common complication in this study (22 (16.8%)) did not show a difference in rectal NSS irrigation volumes. Patients with anastomotic stricture were irrigated with NSS at a mean volume of 40.7 (11.9) ml/kg/day, which was not significantly different from the mean volume of 45.4 (19.2) ml/kg/day for patients without anastomotic stricture (p = 0.138).

In our study, patients with hyponatremia received the same amount of rectal NSS irrigation as those without hyponatremia (p-value = 0.475).

In our study, the patient with Hirschsprung's disease without complications who received the minimal volume of rectal NSS irrigation received 16.19 ml/kg/day and irrigation duration for this patient was 5 days.

DISCUSSION

Prior to conducting a transanal endorectal pull-through/ abdominal assisted transanal endorectal pull-through, preoperative bowel preparation is required to minimize the amount of stool retained in the bowel.

There were three methods of bowel preparation before such operations:

1. Laxatives. These drugs induce strong contractions of the colon and rectum, and thereby facilitate stool evacuation. Two commonly used laxatives include Senna (anthraquinone group) and Bisacodyl (a derivative of the diphenylmethane group). The use of these drugs is contraindicated in cases where obstruction of the colon and rectum is present.

2. Drugs with osmotic effects: These include polyethylene glycol (PEG) and its variations such as

TABLE 3. Incidence of infection-related complications and comparison of total saline irrigation volume (ml/kg/day) between those with each complication and those without each complication.

	Number of patients (total n=131)	NSS irrigation volume (mean (SD)) (ml/kg/day)	P-value[a]
Anastomotic leakage			0.291
Yes	3 (2.3%)	55.6 (32.7)	
No	128 (97.7%)	44.3 (17.9)	
Anastomotic stricture			0.138
Yes	22 (16.8%)	40.7 (11.9)	
No	109 (83.2%)	45.4 (19.2)	
Intra-abdominal collection			0.089
Yes	2 (1.5%)	66.4 (38.1)	
No	129 (98.5%)	44.2 (17.9)	
Re-operation			0.740
Yes	21 (16.0%)	43.4 (16.7)	
No	110 (84.0%)	44.8 (18.6)	
Hyponatremia			0.475
Yes	2 (1.5%)	36.5 (14.2)	
No	129 (98.5%)	46.3 (19.2)	

[a]Independent-samples T test
SD: Stardard Deviation

PEG preparation with electrolytes (PEG-ELS) or PEG-3350 without electrolytes. These substances should not be used if an obstruction is suspected.

Regiments utilizing laxatives and drugs with osmotic effects are frequently used for bowel preparation prior to colonoscopy in pediatric patients.[7] However, they are not suitable for preoperative bowel preparation in patients with Hirschsprung's disease.

3. Rectal NSS irrigation. This preoperative bowel preparation method, performed with a catheter, is a safe and suitable approach for preparing for surgery in cases of Hirschsprung's disease. Other hypotonic solutions, including distilled water, tap water, or other types of water, are believed to potentially include hyponatremia due to water intoxication. This condition occurs when the colon and rectum absorb water.

Proper bowel prepartion prior to surgery is crucial. If the colon is not sufficiently cleaned, either due to inadequate volume of colonic irrigation or insufficient frequency of irrigation, this can lead to fecal stagnation, and heightened risk of post-surgical infection.

Clinical guidelines for rectal NSS irrigation vary. The Royal Children's Hospital, Melbourne recommends pre-operative bowel preparation with NSS rectal irrigation up to a maximum of 20 ml/Kg per session, not exceeding a total volume of 250 ml.[5] The Children's Hospital, Pittsburgh recommends a maximum NSS irrigation of 20 ml/Kg per session, but does not specify a total maximum volume of NSS.[6] The Great Ormond Steeet Hospital, London, United Kingdom, recommends that rectal irrigation should continue with NSS until the stool appears watery and free of fecal retention.[8] In patient with enterocolitis, treatment includes broad spectrum antibiotics and rectal irrigation. Immediate rectal washout with saline (10-20 ml/Kg) using a large bore soft tube should be initiated immediately and repeated from 2-4 times per day until appropriate decompression is achieved, as determined by clinical examination.[9,10]

The optimal duration of preoperative bowel preparation with daily NSS irrigation remains a topic of discussion. Songkhlanakarin University hospital in Thailand reported that rectal irrigation for three days prior to surgery failed to adequately cleanse the bowels.[11] However has also been reported that rectal NSS irrigation can be used effectively on the day before surgery, alone, with the first irrigation in the evening before the operation and a second irrigation on the morning of the operation. However, this method requires a large volume of NSS (500-2000 ml (mean 1000 ml)) per colonic irrigation session.[12]

At the Division of Pediatric Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, preoperative bowel preparation with normal NSS irrigation has been standard practice for over 40 years. For children under one month of age, the protocol involves NSS irrigation of no more more than 20 ml/Kg per session, twice a day, not exceeding 40 ml/Kg per day. For children older than one month, the quantity of NSS used in colonic irrigation does not exceed 50 ml/Kg per session, with colonic irrigation performed twice daily. Thus, the total daily volume of NSS irrigation does not surpass 100 ml/Kg/day. Nevertheless, questions remain regarding the ideal quantity of NSS irrigation and the optimal number of days required for bowel preparation before surgery. These were key questions of this study.

The demographic data in this study (age, weight, transitional zone, type of operation) showed no significant differences between patients who developed complications and those who did not. This allowed for a focused examination of potential effects of NSS irrigation, without these factors acting as confounding factors.

The findings from our study indicate no statistically significant correlation between volume of rectal NSS irrigation and overall postoperative complications. Patients who did not develop postoperative complications received a mean (Q1, Q3) volume of NSS similar to that of those who developed complications (38.1 (33.9, 50) ml/kg/day vs. 39.5 (35, 45) ml/kg/day) (p-value = 0.945). Moreover, the mean duration of irrigation between these two groups showed no significant difference (p = 0.854). The minimum NSS volume of rectal NSS irrigation in a patient who did not experience any complications in this study was just 16.19 ml/kg/day and the duration of irrigation for this patient was five days.

The incidence of anastomotic leakage showed no correlation with volume of rectal NSS irrigation. The mean (SD) volume of rectal NSS irrigation in patients with leakage was not statistically different from those without leakage (55.6 (32.7) ml/kg/day, vs. (44.3 (17.9) ml/kg/day) (p-value = 0.291). A possible reason for the lack of correlation between the amount of rectal NSS and anastomotic leakage could be the low incidence of leakage in our series. In our patient's cohort, anastomotic leakage occurred in only 2.3% of cases whereas other studies reported incidences of 5% to 10%.[13-15] A low incidence of leakage requires a larger sample sample size to statistically identify any differences in the volume of NSS irrigation.

Anastomic stricture following the pull-through procedure was the most common complication in our series, (n = 22 (16.8%)). Known risk factors for anastomotic stricture include anastomotic ischemia, cuff ischemia,

anastomotic leak, and small circular anastomosis.[16,17] Concealable leaks can subsequently lead to stricture of the colonanal anastomosis. In this study, the mean (SD) volume of NSS irrigation for patients who developed postoperative stricture (40.7 (11.9)) was not significantly different from those without stricture (45.4 (19.2)) (ml/Kg/day) (P = 0.138). Given that the risk of anastomotic leakage in our study was only 2.3%, the higher incidence of anastomotic stricture could be the result of an overly tight coloanal anastomoses, which may result in minor degree of anastomotic ischemia and stricture. However, our findings suggest that stricture of coloanal anastomosis was not associated with volume of rectal NSS irrigation.

In our study, we found that the volume and duration of NSS irrigation were similar for patients with infection-related surgical complications, such as anastomotic leakage, anastomotic stricture, intraabdominal collection and others, and those without complications. These results were corresponsed with our previous preliminary study.[18] The absence of correlation between the volume of rectally irrigated NSS and severe infecton-related complications might be due to low incidences of those complications in our series.

Theoretically, increasing NSS volume could elevate the risk of hyponatremia. However, in our study, those with hyponatremia received the same volume of rectal NSS irrigation as those without hyponatremia (p-value = 0.475).

Our study did have some limitations.

First, the study was designed retrospectively, which means there may be missing information. We were only able to include 131 patients who had complete medical records.

Second, the number of patients with infection-related complications was relatively small. This made it challenging to compare the group with post-operative complications and the group without complications, particularly in relation to different volumes and duration of rectal NSS irrigation. Due to the relatively low complication rate, further research is needed on a larger population.

Third, the generalizability of our findings is limited. The study was conducted in a single university hospital, and as such, the method and technique of rectal NSS irrigation may differ from those used in other institutions. Morover, the operative technique of transanal endorectal pull-through or abdominal assisted transanal endorectal pull-through may differ as well. Therefore, the incidence rates of post-operative complications we observed might not be applicable elsewhere.

CONCLUSION

Our study found that the volume of rectally irrigated NSS was not correlated with post-operative infection such as anastomotic leakage, anastomotic stricture and intraabdominal collection. The minimum volume of rectal NSS irrigation for patient with Hirschsprung's disease without complications in this study was 16.19 ml/kg/day over a duration of 5 days.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Cancer Detection Rate of MRI Ultrasound Fusion Prostate Biopsy in 1,039 Patients and Number Needed to Biopsy in Targeted Lesion

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ABSTRACT

Objective: To determine the cancer detection rate (CDR) of magnetic resonance imaging ultrasound fusion prostate biopsy (MRI/US fusion prostate biopsy) in Thailand. The secondary aim was to estimate the number needed to biopsy (NNB) for each prostate lesion in a targeted biopsy, classified by Prostate Imaging-Reporting and Data System (PI-RADS).

Materials and Methods: The data of 1,039 consecutive patients who underwent a MRI/US fusion prostate biopsy at Siriraj Hospital between September 2017 and February 2021 was included and retrospectively reviewed. Those included had previous negative biopsies and were biopsy naïve. The data was analyzed to find the detection rate and NNB.

Results: The overall detection rate of MRI/US fusion prostate biopsy was 58.71%, whereas that of systematic biopsy was 45.72%. Clinically significant prostate cancer (csPCa) (Gleason score ≥ 3+4) detection rate of MRI/US fusion prostate biopsy was 51.01%. When categorized by PI-RADS category 3, 4, and 5 were 12.16%, 44.98%, 85.71% respectively. NNB in targeted biopsy of PI-RADS 3, 4, and 5 were 8, 7, and 3 times sequentially. Positive predictive factors for prostate cancer (PCa) detection were age, prostate-specific antigen density (PSAD) and PI-RADS, whereas prostate volume was a negative predictive factor.

Conclusion: This study supports the role of MRI/US fusion prostate biopsy in PCa detection and should not avoid systematic biopsies. The higher the PI-RADS was, the greater the csPCa detection rate. NNB is helpful in guiding the least amount of biopsied cores for each lesion.

Keywords: Cancer detection rate, Magnetic resonance imaging ultrasound fusion prostate biopsy, Number needed to biopsy, PI-RADS score, Gleason score (Siriraj Med J 2023; 75: 770-777)

INTRODUCTION

Prostate cancer (PCa) is the third most common malignancy diagnosed[1], and is the eighth cause of cancer death in the world.[2] Thai guidelines for PCa screening recommend a prostate specific antigen (PSA) and digital rectal examination (DRE) screening in men aged 50-75, with at least 10 years of estimated life expectancy, and at the age of 45 and older in men with a family history of PCa. A prostate biopsy is indicated when any of the two investigation above are flagged as abnormal. Currently, prostate biopsies are widely performed following the transrectal ultrasound guided biopsy technique (TRUS biopsy) and 12-cores systematic biopsy strategy. Afterwards, obtained tissues are stained and examined by pathologists. Although it is a frequently used method, the cancer detection rate (CDR) of this method is about 44.4%.[3]

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The hypothesis of this study is that magnetic resonance imaging ultrasound fusion prostate biopsy (MRI/US fusion prostate biopsy) may be the key to improving the prostate detection rate. Currently, multiparametric magnetic resonance imaging (mpMRI) is the most interesting method utilized for identifying the presence of any suspicious lesions within the prostate. Suspicious lesions were classified into five categories, according to the Prostate Imaging-Reporting and Data System (PI-RADS), and ranged from 1 (no suspicious lesions visible) to 5 (aggressive lesion appearance which is resemble cancer).

As modern imaging technologies allow region of interest (ROI) for cancer become identifiable, numerous biopsy methods are proposed such as cognitive-target biopsy and in-bore MRI guided biopsy. Later, the MRI/US fusion prostate biopsy method was created to overcome inaccuracy problems as it provided real-time lesion tracking and required less effort and hassle.[4] Since 2017, MRI/US fusion prostate biopsies have become the preferred method of urologists at Siriraj Hospital.

Many studies[5-7] classified PCa into two categories; clinically insignificant prostate cancer (ciPCa) and clinically significant prostate cancer (csPCa). ciPCa is usually an organ-confined disease while csPCa often manifests as a non-organ-confined disease.[8] This study intended to report the CDR of MRI/US fusion prostate biopsies for overall and csPCa at our institute. It also proposed the estimated numbers required for a biopsy for each visible lesion targeted, as classified by the PI-RADS.

MATERIALS AND METHODS

Patients who underwent a MRI/US fusion prostate biopsy between September 2017 and February 2021 were included. All cases had at least one PI-RADS 3 lesion in the multiparametric magnetic resonance imaging (mpMRI) and underwent a MRI/US fusion prostate biopsy, targeted and systematic. Patients under active surveillance protocol, previous diagnosis of PCa, or those who had a radical prostatectomy or incomplete data were excluded. A total of 1,039 patients were eligible for this study. Patients' demographic data, urological history, DRE, PSA, MRI reports, operative notes, pathological reports, and post-operative complications were collected and analyzed.

Imaging

The mpMRI of the prostate in this study was performed with a 1.5 or 3 Tesla, without endorectal coil. The imaging protocol consisted of T2-weighted imaging, diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) value. Radiologists reported lesions within the prostate according to the PI-RADS.

Intervention

Most patients in this study were admitted one day prior to the operation. Only a few operations were performed as a one-day surgery. The trans-perineal biopsy approach was the preferred option of most surgeons, and thus, general anesthesia was almost always used to ensure adequate pain control. After a patient was under anesthesia, he was placed in the standard lithotomy position. Catheter placement wasn't mandatory and the decision was left to the surgeon. A MRI/US fusion prostate biopsy device, known as KOELIS Trinity® system (Koelis, France), was brought in to map current ultrasonographic images with MRI. After each lesion was identified, a targeted biopsy was performed, lesion by lesion, according to the guidance by systematic biopsy in a free-hand manner. Following the operation, patients were observed in the recovery room for two hours before transfer to the ward or discharge. In most cases, patients were discharged within one day after the operation unless they experienced complications.

Systematic biopsy was random biopsy that obtained tissue from both sides of prostate including the prostatic base, mid gland and apex.[7] Targeted biopsy was biopsy at the positive lesions on MRI (PI-RADS 3, 4, 5) with the use of MRI/US fusion prostate biopsy device to obtain tissue from regions of interest. Combination was MRI/US fusion prostate biopsy including both systematic and targeted biopsy.

Histology

Histopathological tissues were interpreted and reported by assigned pathologists within Siriraj Hospital using the International Society of Urological Pathology (ISUP) consensus definition of Gleason score (GS) and Grade groups (GG). A csPCa was defined as GS ≥ 3+4 or GG ≥ 2, and ciPCa was GS 3+3 or GG 1.[7,9,10]

Number needed to biopsy

The number needed to biopsy (NNB) was calculated by dividing the total number of biopsies of a particular prostate lesion by the number of positive prostate cancer biopsies. We modified the NNB from the NNB ratio to diagnose Melanoma (*Marchetti et al*).[11] We excluded patients with a benign pathology report and patients with multiple lesions within the prostate in this analysis. A single PI-RADS lesions represented specific patients and lesions and could be properly interpreted. The cumulative line plot of NNB was used to demonstrate cancer detection

yield for each additional biopsy core in each PI-RADS category.

Statistical analysis

The statistical analysis of this study was performed using Python (Python Software Foundation, Wilmington, DE, USA). Univariate and multivariate analyses were performed using linear regression and multiple linear regressions via the package statsmodels version 0.12.0. A p-value less than 0.05 was considered statistically significant difference.

RESULTS

Demographic data from 1,039 patients in this study revealed a median age of 69 (64.5-75), median PSA of 8.79 ng/mL (6.29-13.7), median prostate volume of 44.06 mL (29.9-63.6), median PSAD of 0.21 ng/mL^2 (0.14-0.34), and median maximal lesion diameter of 13 mm (9-19) (Table 1). Among the biopsied patients, there were 264 instances of previous negative biopsies and 775 biopsy-naïve cases. Most patients in both groups were PI-RADS 4 patients. The presence of PI-RADS 3 patients in each group was less common. A total of 659 patients (63.43%) had one visible lesion in the mpMRI. Another 301 patients (28.97%) had two ROI. There was also one person who had a total of six lesions within the prostate, representing the highest number of lesions in a single patient in this study (Table 2). This study revealed overall and csPCa detection rates of MRI/US fusion prostate biopsy of 58.71% and 51.01%, respectively. Fig 1 presents the proportion of different cell types found in suspicious lesions, categorized by the MRI findings. The patients with PI-RADS 5, which exhibited the most aggressive features in mpMRI, had highest detection rate for significant cancer at 85.71%. The CDR for csPCa in PI-RADS 4 and 3 were 44.98%, and 12.16% respectively. In PI-RADS 5, the most frequent highest GS was 4+5, or 27.47%, followed by 4+3 and 3+4 or 19.78% each, respectively. On the other hand, PI-RADS 3 and 4 mainly consisted of ciPCa or benign outcomes (GS 6 or lower) at 87.84% and 55.02%, respectively. The most frequent csPCa in PI-RADS 3 and 4 was a GS of 3+4 (4.05%, 23.62%) sequentially (Table 2). In this study, common complications in the first 14 days after biopsy were acute urinary retention (AUR) at 4.33%, and gross hematuria (GH) at 2.98%, however, sepsis was zero.

Regarding the Venn diagram in Fig 2, PCa was mostly found in both targeted core tissues and systematic core tissues, or in 409 patients (39.37%). Another 135 patients (12.99%) with a positive result in targeted biopsy tissue represented the edge of the MRI/US fusion technique over the systematic biopsy strategy. In contrast, 66 patients (6.35%) had infiltrative tumors, which were invisible on mpMRI and were only found by a systematic biopsy. About half of this group, or 34 patients, were diagnosed with csPCa. The rest, or 429 patients (41.29%), tested negative for PCa.

Univariate and multivariate analyses in Table 3 identified significant predictors, which were similar in outcomes. Age, PSAD, prostate volume, and PI-RADS

TABLE 1. Characteristics of 1,039 patients who underwent MRI/US fusion prostate biopsy.

Characteristics	Total (N=1,039)	PIRADS 5 (n=273, 26.28%)	PIRADS 4 (n=618, 59.48%)	PIRADS 3 (n=148, 14.24%)
Age (years)[a]	69 (64.50 - 75.00)	71 (67.00-77.00)	69 (64.25 - 74.00)	67 (62.00 - 72.00)
PSA (ng/mL)[a]	8.79 (6.29 - 13.70)	12 (7.74 - 20.16)	7.8 (5.85 - 11.36)	9.45 (6.49 - 14.26)
MRI-Prostate volume (g)[a]	44.06 (29.90 - 63.60)	37.75 (26.95 - 55.68)	44.95 (30.80 - 63.70)	55.6 (36.67 - 70.62)
PSAD (ng/mL^2)[a]	0.21 (0.14 - 0.34)	0.34 (0.20 - 0.59)	0.18 (0.12 - 0.27)	0.19 (0.12 - 0.28)
Maximum total size (mm)[a]	13 (9.00 - 19 .00)	20 (17.00 - 26.00)	11 (8.00 - 14.00)	11 (8.00 - 15.00)
Biopsy Naïve[b]	775 (74.59)	213 (78.02)	457 (73.95)	105 (70.95)
Previous negative biopsy[b]	264 (25.41)	60 (21.98)	161 (26.05)	43 (29.05)

[a] Data are presented as median (interquartile range)
[b] Data are presented as n (%)

TABLE 2. MRI lesion and MRI/US fusion prostate biopsy outcomes of 1,039 patients.

	Total (N=1,039)	PI-RADS 5 (n=273)	PI-RADS 4 (n=618)	PI-RADS 3 (n=148)
MRI (lesion)				
1	659 (63.43)	167 (61.17)	389 (62.94)	103 (69.59)
2	301 (28.97)	80 (29.30)	180 (29.13)	41 (27.70)
3	58 (5.58)	20 (7.33)	34 (5.50)	4 (2.70)
4	17 (1.64)	3 (1.10)	14 (2.27)	0
5	3 (0.29)	2 (0.73)	1 (0.16)	0
6	1 (0.10)	1 (0.37)	0	0
Single lesion	659 (63.43)	167 (61.17)	389 (62.94)	103 (69.59)
Multiple lesion	380 (36.57)	106 (38.83)	229 (37.06)	45 (30.41)
MRI/US fusion prostate biopsy				
Gleason score				
<3+3	429 (41.29)	32 (11.72)	281 (45.47)	116 (78.38)
3+3	80 (7.70)	7 (2.56)	59 (9.55)	14 (9.46)
3+4	206 (19.83)	54 (19.78)	146 (23.62)	6 (4.05)
4+3	118 (11.36)	54 (19.78)	58 (9.39)	6 (4.05)
4+4	55 (5.29)	30 (10.99)	23 (3.72)	2 (1.35)
3+5	13 (1.25)	6 (2.20)	7 (1.13)	0
5+3	3 (0.29)	0	3 (0.49)	0
4+5	115 (11.07)	75 (27.47)	36 (5.83)	4 (2.70)
5+4	15 (1.44)	11 (4.03)	4 (0.65)	0
5+5	5 (0.48)	4 (1.47)	1 (0.16)	0

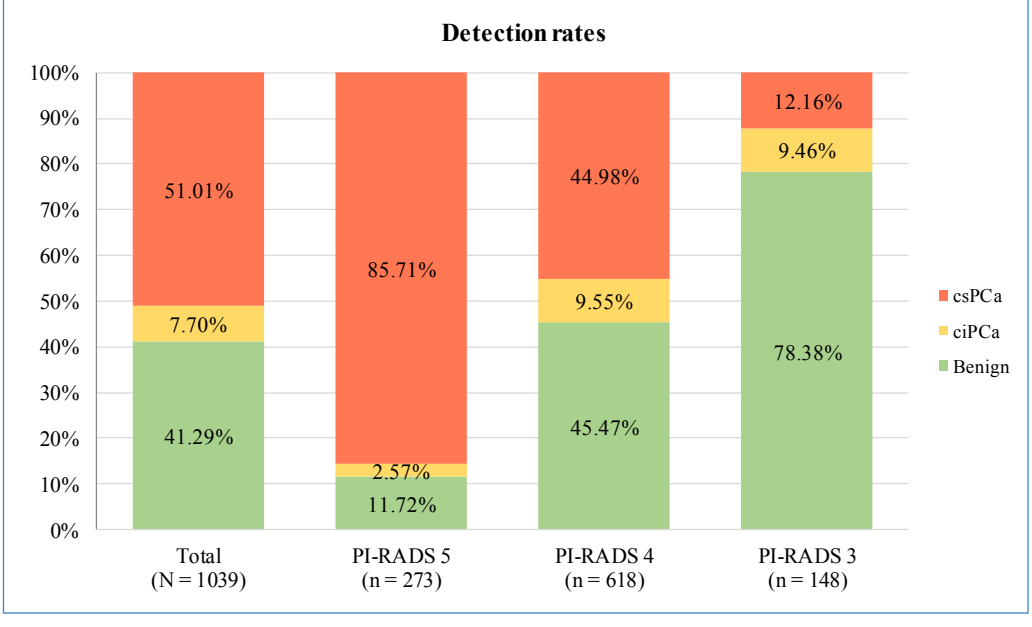

Fig 1. Cancer detection rate of MRI/US fusion prostate biopsy of 1,039 patients.

Clinical insignificant prostate cancer (ciPCa): GS 3+3 or GG 1,
Clinically significant prostate cancer (csPCa): GS ≥ 3+4 or GG ≥ 2

TABLE 3. Univariate and multivariate analysis in csPCa and overall cancer.

		csPCa outcome				Any cancer outcome			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)	<60	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
	61 to 80	1.81 (1.15, 2.86)	0.011	2.45 (1.40,4.26)	0.002	1.54 (0.99,2.39)	0.055	1.94 (1.14,3.32)	0.014
	>80	5.04 (2.51, 10.18)	<0.001	4.24 (1.80,9.97)	0.001	4.07 (1.97,8.41)	<0.001	3.3 (1.40,7.77)	0.006
PSA (ng/mL)	<4	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
	4 to 10	1.73 (0.86, 3.46)	0.123	1.14 (0.50,2.61)	0.749	1.93 (0.98,3.82)	0.056	1.34 (0.61,2.97)	0.464
	>10	2.40 (1.19, 4.85)	0.014	0.95 (0.36,2.51)	0.925	2.54 (1.28,5.05)	0.008	1.11 (0.44,2.83)	0.821
PSAD (ng/mL^2)	<0.15	1 (ref)		1 (ref)					
	0.15 to 0.30	2.17 (1.60, 2.94)	<0.001	1.86 (1.22,2.83)	0.004	2.35 (1.75,3.19)	<0.001	2.01 (1.35,3.00)	0.001
	>0.30	7.00 (4.95, 9.87)	<0.001	3.89 (2.18,7.17)	<0.001	6.78 (4.76,9.68)	<0.001	3.68 (2.01,6.69)	<0.001
Prostate Volume (g)	<30	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
	30 to 50	0.51 (0.36, 0.71)	<0.001	0.63 (0.41,0.97)	0.036	0.49 (0.34,0.71)	<0.001	0.61 (0.39,0.95)	0.03
	>50	0.21 (0.15, 0.30)	<0.001	0.39 (0.23,0.66)	<0.001	0.21 (0.14,0.29)	<0.001	0.37 (0.22,0.64)	<0.001
Average targeted core biopsy per lesion	≤6	1 (ref)		1 (ref)		1(ref)		1 (ref)	
	7 to 10	1.48 (1.12, 1.93)	0.006	1.06 (0.76,1.49)	0.73	1.4 (1.06,1.84)	0.018	1.06 (0.76,1.48)	0.72
	>10	2.02 (1.45, 2.83)	<0.001	1.19 (0.78,1.82)	0.421	1.94 (1.36,2.75)	<0.001	1.23 (0.80,1.88)	0.34
PI-RADS	MPI-RADS 3	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
	SPI-RADS 3	0.86 (0.30, 2.46)	0.773	0.85 (0.28,2.53)	0.764	0.95 (0.41,2.23)	0.907	0.93 (0.38,2.27)	0.876
	MPI-RADS 4	4.61 (1.88, 11.36)	0.001	4.68 (1.77,12.30)	0.002	4.06 (1.92,8.58)	<0.001	4.37 (1.90,9.97)	<0.001
	SPI-RADS 4	5.83 (2.41, 14.15)	<0.001	5.59 (2.20,14.15)	<0.001	4.33 (2.08,9.03)	<0.001	4.07 (1.86,8.84)	<0.001
	MPI-RADS 5	34.03 (12.43, 92.76)	<0.001	22.34 (7.39,67.36)	<0.001	25.04 (10.07,62.18)	<0.001	17.00 (6.17,46.99)	<0.001
	SPI-RADS 5	42.55 (16.12, 112.17)	<0.001	32.26 (11.59,90.02)	<0.001	27.08 (11.59,63.43)	<0.001	19.71 (8.00,48.91)	<0.001
Surgeon	Staff	1 (ref)				1 (ref)			
	2^{nd}-year residents	0.91 (0.51, 1.60)	0.732			0.8 (0.45,1.42)	0.454		
	3^{rd}-year residents	0.77 (0.52, 1.13)	0.174			0.81 (0.55,1.19)	0.283		
	4^{th}-year residents	1.08 (0.80, 1.46)	0.605			0.89 (0.66,1.21)	0.461		

Abbreviations: MPI-RADS: multiple lesion PI-RADS, SPI-RADS: single lesion PI-RADS

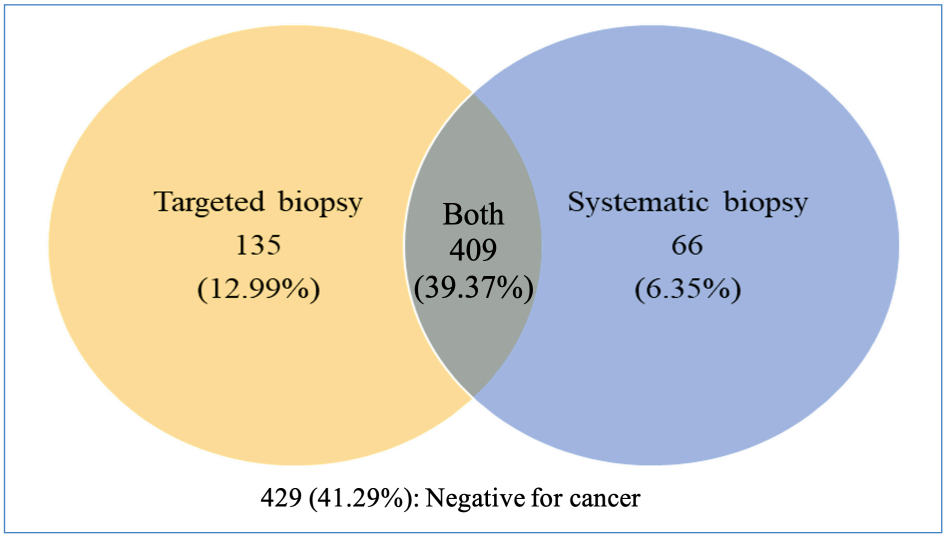

Fig 2. Venn diagram of MRI/US fusion prostate biopsy of 1,039 patients.

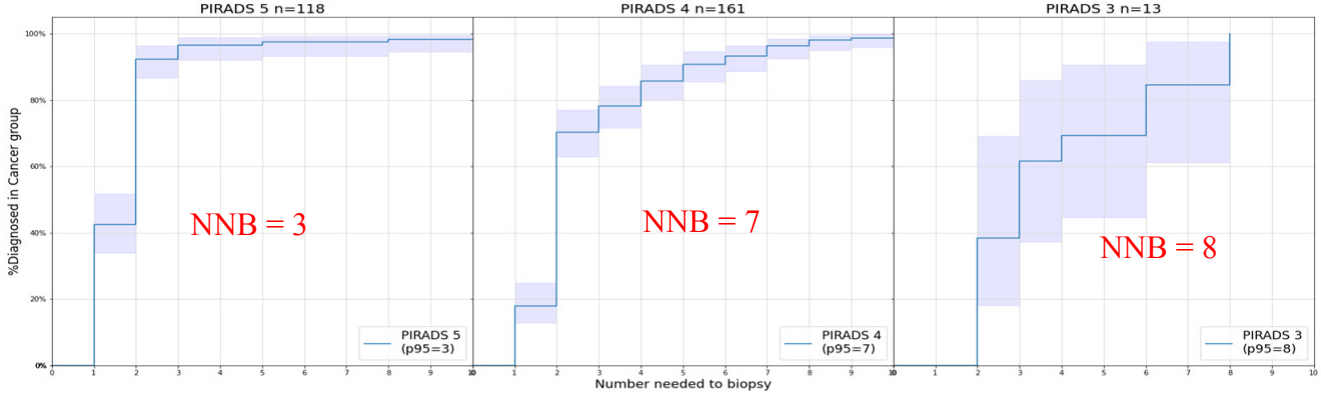

Fig 3. Number needed to biopsy (NNB) in each PI-RADS at the 95th Percentile

category were significant independent predictors regarding multivariate analyses, whereas prostate volume was the only negative predictor. PSA and average targeted core biopsy per lesion remained significant in univariate analyses, but multivariate analyses suggested otherwise due to their dependency on other factors. Surgeon experience proved to be insignificant regarding CDR when performed by second, third, and fourth postgraduate year residents and also board-certified urologists.

Of a total of 1,039 patients, 292 were eligible for the calculation of NNB, as they had a single lesion in MRI results and were diagnosed with PCa after a biopsy. According to Fig 3, the cumulative plot illustrates an increasing yield of cancer detection in each additional core in targeted biopsies regarding calculated NNBs. For PI-RADS 4 and 5 lesions, 7 and 3 were recommended as the minimum cores, as the curves reached the plateau approximately at 95% yield of cancer detection. In contrast, the number of eligible patients in PI-RADS 3 group was relatively too low to assure 95% yield at the minimum of 8 cores.

DISCUSSION

According to NCCN Guidelines Version 1.2023, mpMRI is recommended in patients with a high PSA and/or very suspicious DRE results, if accessible. Since it is utilized with MRI/US fusion biopsy devices, mpMRI improves the CDR of csPCa significantly, and reduces CDR of lower-risk cancers.[7,12-14] On the contrary, Thai guidelines still recommend 12-cores systematic TRUS biopsy as the gold standard in detection of PCa because of limited access to MRIs, scarcity of specialized radiologists, and a lack of other resources. However, this leads to a higher rate of false negatives and lower csPCa detection. When considering obvious beneficial evidence, Thai tertiary medical centers are starting to shift their focus towards targeted biopsies.

This study revealed an overall CDR of MRI/US fusion prostate biopsy was 12.99% higher compared to systematic biopsies, which had a detection rate of 45.72%. Our overall CDR was not different from other studies (47%-62.9%)[4-7,12,15-17], but in our study, csPCa was higher than in studies of *Kasivisvanathan et al.*[7],

Ahdoot et al.[12], *Benelli et al.*[5], and *Hansen et al.*[6] Thus, this potentially illustrates how the MRI/US fusion prostate biopsy system at our institute is not inferior to other studies. Our identified predictors are similar to another study[5] where PI-RADS is a strong predictor on the list in both overall PCa and csPCa, which advocates the use of an MRI before prostate biopsy, if possible. Moreover, this study confirmed that the higher PI-RADS, the greater the detection rate. After we studied the results of the univariate and multivariate analysis, we found that positive predictive factors for PCa detection were age, PSAD, and PI-RADS, whereas prostate volume was a negative predictive factor. Likewise the conclusion of *Walton et al.*[17], CDR decreased with increasing prostate volume. *Al-Khalil et al.*[18] suggested a larger prostate volume would lead to a lower positive CDR. It supposed that benign prostatic hyperplasia (BPH) caused transition zone (TZ) hyperplasia and led to atrophy and apoptosis of cell in peripheral zone (PZ), and this is the zone where most PCa develops. This decreases the likelihood of PCa in the remaining glands.

This study still recommends both systematic and targeted biopsies in MRI/US fusion prostate biopsy procedures because 34 (3.37%) out of 1,039 patients with csPCa would be missed, if targeted biopsy alone was done. Similar to the MRI-FIRST trial[14], which studied naïve biopsy, their results showed that 5.2% of csPCa would be missed if systematic biopsies were skipped. As we experienced several cases that involved an unnecessary biopsy, which is a waste of both time and resources of our pathologists, we use the NNB method to estimate how many core tissues were needed to gain enough yield to detect cancer. Moreover, we hoped this method would further decrease the workload of pathologists. Several previous studies[5,14] of biopsied targeted lesions revealed at least 3 cores per lesion, but they did not provide certain evidences for their recommendation. With our reporting system, which didn't specify or detail histopathological information for each and every biopsied lesion for research purpose, the calculated NNB for multiple ROI would become too susceptible to bias to draw any trustworthy conclusion. Our study selected patients with single ROI and calculated NNB of targeted lesion in PI-RADS 3, 4, and 5. Since, these NNB was derived from patients with single ROI, interference on multiple ROI was limited. We hope this study inspire clinicians to develop a method to study NNB of multiple ROIs in the future.

This study had a few limitations. First, this study was a retrospective study at a single institution. Second, a version difference (v2.0 and v2.1) of PI-RADS existed in our cohort, so there may be some inconsistency in distinguishing PI-RADS category 2 and 3, but PI-RADS 4 and 5 lesions are not affected. Third, the NNB we calculated was only usable for a single lesion.

CONCLUSION

This study supports the role of MRI/US fusion prostate biopsy in PCa detection. The combination of both targeted biopsy and systematic biopsy enhances CDR of PCa in comparison with systematic biopsy alone. The higher the PI-RADS on mpMRI was, the greater the csPCa detection rate. PI-RADS 3 mainly consisted of benign outcomes and ciPCa. Positive predictive factors for PCa detection were age, PSAD and PI-RADS, whereas prostate volume was a negative predictive factor. NNB is helpful in guiding the least amount of biopsied cores in single targeted lesion on MRI.

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Conflicts of interest

The authors declare they have no conflict of interest.

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Factors Associated with Age at Diagnosis of Autism Spectrum Disorder in Pediatric Patients at Sawanpracharak Hospital, Thailand

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ABSTRACT

Objective: This study aimed to determine the average age at diagnosis and the characteristics associated with the age of children at the diagnosis of autism spectrum disorder (ASD) at Sawanpracharak Hospital.

Materials and Methods: A retrospective cross-sectional study was conducted from May 2023 to July 2023. Data were collected from the medical patient files of all children diagnosed with ASD between 2020 to 2022. Descriptive analysis was used to examine the characteristics of the children and their caregivers, and the children's age at diagnosis. Factors associated with the age at diagnosis were assessed by chi-square test analysis.

Results: In total, 100 patient records with complete information were collected. The average age at the diagnosis of ASD was 4.57± 1.61 years old, with 60% of the patients diagnosed after four years of age. Social communication deficit symptoms, including non-response to name and lack of pointing out objects of interest, were significantly associated with an early ASD diagnosis (p-value = 0.023 and 0.002, respectively). Being a firstborn child and the presence of delayed development were found to delay the diagnosis of ASD meaning it occurred at a later age (p-value = 0.002 and 0.019, respectively). However, sex, the caregiver's education, and socioeconomic status were not related to the age at diagnosis.

Conclusion: Most children with ASD who received treatment at Sawanpracharak Hospital were diagnosed late. Being a firstborn child, poor response to name being called, lack of pointing out objects of interest, and delayed development were related to the age of the children at ASD diagnosis. Differences in diagnostic age based on sociodemographic and clinical characteristics indicate the need for coordinated measures for the early detection of ASD.

Keywords: Autism Spectrum Disorder; age of diagnosis; associated factors; delayed development; social communication deficit (Siriraj Med J 2023; 75: 778-783)

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that affects children's development, learning ability, and daily life activities. In addition, families caring for children with ASD face increased stress from the difficulty of caring for these children and the burden of the treatment costs, which can affect family relationships. The diagnostic criteria for ASD are based on the Diagnostic Standards and Statistical Manual for Psychological Disorders, fifth edition (DSM-5), consisting of two core symptoms: social communication deficits and restrictive, repetitive behavior or interest.[1] Currently, the reported prevalence rate of ASD is as high as 1 in 36 children[2], and the prevalence rate in boys is 2–3 times that of girls.[3] The cause of ASD is a combination of two factors: genetic and environmental factors.[4,5] The environmental

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factors that correlate with this disease include maternal exposure to certain drugs or chemicals, intrauterine infections, perinatal or postnatal complications, and advanced parental age.[5]

At present, there are many treatment modalities for children with ASD. However, the existing modalities are not a cure for this disease, but rather, current treatment methods are aimed at minimizing disabilities and minimizing children's dependence on others in society.[6] A study by Rogers and Vismara (2008) found that children with autism who received early treatment before age 3 had a better prognosis than those who received treatment after age 3.[7] The results of their study may be explained by the fact that children's brains develop rapidly and are highly adaptable before the age of 3. Early detection is crucial for early intervention in children with ASD. Therefore, the American Academy of Pediatrics (AAP) has issued recommendations for ASD screening in all children aged between 18 and 24 months old who attend health check-ups at a well-child clinic.[6]

In Thailand, there is no explicit recommendation for ASD screening. Previous studies have found that the average age at ASD diagnosis is between 3.9 and 5.7 years old[8], considered a delayed diagnosis. The factors related to a delayed diagnosis include living in rural areas, impoverished families, and lower parental education.[9,10] In contrast, severely impaired language development and abnormal noticeable repetitive movement contribute to the early diagnosis of ASD.[11] However, in Thailand, no study has yet analyzed the average age at ASD diagnosis and the factors related to the age at ASD diagnosis. Thus, this study aimed to narrow this knowledge gap and use the obtained information to develop future ASD screening guidelines for Nakhon Sawan, Thailand.

MATERIALS AND METHODS

Study design and population

This was a hospital-based, descriptive retrospective cross-sectional study that was conducted from May 2023 to July 2023. All children who were diagnosed with ASD at Sawanpracharak Hospital between 2020 and 2022, according to DSM-5 criteria, were included in this study. In 2020, a developmental and behavioral pediatrician started work at Sawanpracharak Hospital and set up a complete patient record system; this was thus defined as the starting period for the data collection. A total of 100 ASD patient files with complete patient records were collected. The data collected included sex, birth order, age at diagnosis, comorbidity, family history of ASD, number of primary physicians whom the patients consulted before diagnosis, residence, symptoms that caregivers notice before consulting physicians, and the primary caregiver's characteristics. Although Rogers and Vismara's study suggested that diagnosis after three years of age is late,[7] in our study, almost all the children were diagnosed with ASD after 3 years of age, so we decided to use the age of 4-years old to distinguish early diagnosis from late diagnosis.

The Institutional Review Board (IRB) of Sawanpracharak Hospital (COA. 38/2565) approved the study protocol.

Data analysis

The coding in the case record forms was verified and entered into the computer system using Microsoft Excel. SPSS Statistics Program Version 26 (IBM Corp., Armonk, NY) was used for data processing and statistical analysis. The frequency, percentage of categorical data, and mean ± standard deviation were used for the descriptive analysis. In order to investigate the factors related to the age at diagnosis, the chi-squared test or Fisher's exact test was used.

RESULTS

In this study, a total of 100 complete patient records of pediatric patients diagnosed with ASD at Sawanpracharak Hospital between 2020 and 2022 were collected and analyzed. The average age of the children at ASD diagnosis was 4.57 ± 1.61 years old. Most of the patients (88%) were boys and 61% were firstborn children. The most common comorbid conditions of these children were global developmental delay (60%) and ADHD (51%). At the same time, 9% had a positive family history of ASD. In addition, the majority of these children (84%) were diagnosed after consulting 1–2 primary physicians. Most of these children (73%) live outside the urban areas of Nakhon Sawan Province. When considering only the symptoms that caregivers observed before seeking medical consultation, the most common were hyperactivity (60%), lack of pointing out an object of interest (46%), and delayed development (39%) (Table 1).

Table 2 shows that almost all the primary caregivers (93%) were female, and almost half (44%) were between 30 and 39 years old. Most caregivers (81%) had an education level below a bachelor's degree. In addition, most of these children's families (82%) earned less than USD 886 a month.

Among all the children, 40 were diagnosed with ASD before the age of four, and were classified as an early diagnosis. In contrast, the other 60, who were diagnosed after age four, were classified as a late diagnosis. The frequency distribution of the age at diagnosis based on

TABLE 1. Demographic characteristics of children with ASD who received treatment and comparison of the patients' demographic characteristics between the "early age at diagnosis group" and "later age at diagnosis group.

Demographic characteristics	Descriptive results			
	Total number (100)	Early age at diagnosis <4 years old (n=40)	Later age at diagnosis ≥4 years old (n=60)	*P*-value
Sex				0.258
Boy	88 (88)	37 (92.5)	51 (85)	
Girl	12 (12)	3 (7.5)	9 (15)	
Birth order				0.002*
First born	61 (61)	15 (37.5)	41 (68.3)	
Not first born	39 (39)	25 (62.5)	19 (31.7)	
Comorbidity				
GDD	60 (60)	26 (65)	34 (56.7)	0.405
ADHD	51 (51)	19 (47.5)	32 (53.3)	0.568
Epilepsy	2 (2)	0 (0)	2 (3.3)	0.358
Positive family history of ASD	9 (9)	4 (10)	5 (8.3)	0.775
Number of primary physicians consulted before diagnosis				0.244[a]
1–2	84 (84)	32 (80)	52 (86.7)	
3–4	14 (14)	8 (20)	6 (10)	
≥5	2 (2)	0 (0)	2 (3.3)	
Residence				0.713
Urban	27 (27)	10 (25)	17 (28.3)	
Rural	73 (73)	30 (75)	43 (71.7)	
Symptoms that caregivers observed before seeking medical consultation				
Poor eye contact	82 (82)	31 (77.5)	51 (85)	0.339
Poor peer relationship	63 (63)	23 (57.5)	40 (66.7)	0.352
Hyperactive	60 (60)	27 (67.5)	33 (55)	0.211
Lack of pointing out objects of interest	46 (46)	26 (65)	20 (33.3)	0.002*
Delay development	39 (39)	10 (25)	29 (48.3)	0.019*
No response to name	32 (32)	18 (45)	14 (23.3)	0.023*
Delay speech	29 (29)	8 (20)	21 (35)	0.105
Aggressive	16 (16)	5 (12.5)	11 (18.3)	0.436
Loss of language skills	15 (15)	5 (12.5)	10 (16.7)	0.568
Food selectivity	8 (8)	4 (10)	4 (6.7)	0.403[a]
Sleep problem	7 (7)	3 (7.5)	4 (6.7)	0.585[a]

Abbreviations: ASD = autism spectrum disorder, GDD = global developmental delay, ADHD = attention deficit/hyperactivity disorder. Data presented as number (percentage)

The comparison of differences was analyzed by chi-square test. [a]The associations were assessed using Fisher's exact test. *Statistically significant at p-value < 0.05.

TABLE 2. Demographic characteristics of primary caregivers' children with ASD and comparison of the primary caregivers' demographic characteristics between the "early age at diagnosis group" and "later age at diagnosis group.

Demographic characteristics	Descriptive results			
	Total number (100)	Early age at diagnosis <4 years old (n=40)	Later age at diagnosis ≥4 years old (n=60)	*P*-value
Gender				0.699[a]
Male	7 (7)	2 (5)	5 (8.3)	
Female	93 (93)	38 (95)	55 (91.7)	
Age				0.906
20–29 years	15 (15)	7 (17.5)	8 (13.3)	
30–39 years	44 (44)	16 (40)	28 (46.7)	
40–49 years	24 (24)	10 (25)	14 (23.3)	
≥ 50 years	17 (17)	7 (17.5)	10 (16.7)	
Education level				0.061
Below bachelor's degree	81 (81)	36 (90)	45 (75)	
Bachelor's degree and above	19 (19)	4 (10)	15 (25)	
Family monthly income (US dollars)				0.671
<886[+]	82 (82)	32 (80)	50 (83.3)	
≥886[+]	18 (18)	8 (20)	10 (16.7)	

Data presented as number (percentage).
The comparison of differences was analyzed by chi-square test. [a]The associations were assessed using Fisher's exact test. *Statistically significant at p-value < 0.05.
[+]1 US dollar = 33.90 bahts

various variables is illustrated in Table 1&2 using chi-square or Fisher's exact test analysis. The symptoms observed by caregivers before the children received a medical consultation had a statistically significant association with the age at diagnosis. There was a substantial correlation between the earlier-diagnosed and the later-diagnosed age groups in having several symptoms, such as no response to name (p-value = 0.023) and lack of pointing out objects of interest (p-value = 0.002), with the earlier-diagnosed age group having a broader distribution (Table 1). On the other hand, delayed development was more common in the later-diagnosed age group (p-value = 0.019). In addition, being a firstborn child was associated with a late diagnosis of ASD (p-value = 0.002) (Table 1).

DISCUSSION

Our result reveals that the mean age at diagnosis of ASD in pediatric patients consulted at Sawanpracharak Hospital was 4.57± 1.61 years old. ASD typically shows its first signs at around 12 months of age. However, diagnosis is only possible from the age of 18 months.[12] According to previous studies, the range for the average age of diagnosis is 2.7 to 7.2 years old.[12,13] Looking at the overall situation, the age at diagnosis in our population is no different from previous studies. However, recent studies have shown a trend toward early diagnosis before 3 years of age.[14,15] Therefore, this result is important information to remind our hospital to actively adjust its policies to facilitate the early detection of this condition.

Considering the factors that may be associated with the age at diagnosis, our study found that firstborn children were more likely to be diagnosed with ASD later than non-firstborn children. Our findings are inconsistent with previous studies that did not find an association between birth order and age at diagnosis.[16,17] This disparity may be explained by the nature of our population, whose caregivers have a low education level and are unaware of the child's expected age-appropriate development.[18] However, once these caregivers had experience of raising children, they began to notice the

development difference between the first child and the non-first child. Therefore, non-firstborn children would have autism-specific symptoms noticed earlier.

In our study, the main symptoms observed by caregivers before seeking medical consultation were related to an early diagnosis of ASD, including unresponsiveness to name and lack of pointing out objects of interest. These results are consistent with Loubersak's study (2023), which found that delayed social communication skills are associated with a younger ASD diagnosis.[12] Social communication skills, including nonverbal communication, are often the symptoms that concern parents and that they notice first. Children with these symptoms are often not interested in interacting with their parents properly or using age-appropriate communication. Furthermore, early communication skills, including pointing out objects of interest and responding to names, can be found before a child is 12 months old, and observed even before children have linguistic ability. Thus, children with these symptoms are often diagnosed early.

In contrast, previous studies have shown that children with developmental delays are diagnosed with ASD earlier than those without delayed development.[12,16] That our findings are inconsistent with those studies may be explained by the fact that developmental retardation can mask the specific symptoms of autism.[19] Moreover, before 2020, pediatric patients who came for consultation at Sawanpracharak Hospital were examined by general pediatricians who may not have been skilled in diagnosing ASD. Thus, this reason may have led to a delay in diagnosing this group of children.

In addition, our study did not find differences in sex, caregiver's education, socioeconomic status, and distance to access treatment between the early- and late-diagnosed ASD groups. This finding is similar to Loubersak's study (2023).[12] These data indicate that the educational level or economic status of the caregiver is not a factor related to gaining the knowledge to observe the symptoms and characteristics of ASD. Therefore, educating caregivers to observe ASD symptoms is crucial for early diagnosis. In addition, nowadays, transportation is more convenient, so even children in remote areas far from the hospital should not have problems accessing treatment.

Our study is the first research study in Thailand to explore the factors associated with the age at diagnosis of ASD. A key benefit of finding the related factors is that they can inform the development of an intervention that can minimize the problem of the delayed diagnosis of ASD in Nakhon Sawan Province. Moreover, the average age at diagnosis data in this study may also support developing a proactive ASD screening policy for Thailand. The American Academy of Pediatrics (AAP) has issued recommendations since 2020 for standardized ASD screening in all children aged 18 to 24 months old who come to be vaccinated in well-child visits.[6] However, in Thailand, this important recommendation has not yet been implemented.

There are some limitations of this study to be noted, including this study involved a retrospective design, which means it omitted some data that may have affected the recruitment population in our study. The generalizability of our study results is also limited since our population was collected from a single-center site and involved relatively small numbers of patients. A multicenter prospective study design with a larger popopulation should be considered in a future study.

CONCLUSION

At Sawanpracharak Hospital, more than half of the children with ASD had a delayed diagnosis. Children with delayed social communication skills, including non-response to name and lack of pointing out objects of interest, were more likely to be diagnosed early. In contrast, firstborn children and children with delayed development tended to be diagnosed later.

Conflict of interest

All authors declare no conflict of interest.

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Self-evaluation of Sexual History Taking Skills Among Medical Students in Southern Thailand

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ABSTRACT

Objective: Sexual health is an important issue in a holistic approach in general clinical practice. Inappropriate sexual history taking could lead to improper clinical management. This study aimed to examine perceptions of practice, attitudes toward sexual history taking and their associated factors among final year medical students in southern Thailand.

Materials and Methods: This cross-sectional survey was conducted between September and October 2022, using a self-reported questionnaire via Google forms. The self-reported questionnaire consisted of questions related to the practice and attitude toward sexual history taking (α = 0.90 and 0.71, respectively), as well as perceptions of the undergraduate medical training on taking a sexual history (α = 0.91). Descriptive data analysis and multiple logistic regression was conducted by using Program R.

Results: Of 91 participants, most were male and Buddhist (54.9% and 87.9%). In general, most medical students rated their proficiency in sexual history taking skills as fair-to-good across all aspects. The majority showed a positive attitude toward sexual history taking (68.1%) and reported that contraception was the main reason that they usually have such discussions with female patients (36.3%), while the prevention of sexual transmitted diseases (STDs) was the most common issue during annual examinations, and when with patients with suspected STDs (27.5% and 49.5%). Male medical students and those who perceived good-to-very good knowledge and well-to very well-trained skills of sexual history taking were significantly associated with more regular sexual history taking. [adjusted OR (95%CI) = 4.51(1.19-17.11) and 5.3 (1.51-18.65), respectively] Moreover, students with a good attitude toward sexual history taking were significantly associated with a perceived good-to-very-good training in both history taking and communication skills.

Conclusion: Most medical students exhibited a positive attitude toward sexual history taking, and they stated that birth control and STDs symptoms were typically the primary subjects they discussed with patients in general. There was a significant association between being male, a perception of good knowledge and well-trained skills, and a more consistent practice of sexual history taking. Additionally, medical students who displayed a good attitude towards taking sexual history significantly showed a perception that they had received sufficient training in both the areas of history taking and communication skills.

Keywords: Clinical practice; medical history taking; sexual health; undergraduate medical education (Siriraj Med J 2023; 75: 784-793)

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INTRODUCTION

Sexual problems and their consequences, such as, sexually transmitted diseases (STDs), teenage pregnancy, and sexual dysfunction are important global issues. Thus, sexual history taking by health care providers can be very beneficial for both early detection and proper management, not only for mentioned sexual health issues but also holistic care, such as family relationships, which can be helpful in many aspects of medical treatment.[1-3] Although sexual history taking was known of being needed and expected by most patients, a study in the US found that only 58.0% of general practitioners (GPs) had asked their patients about their sexual activities.[4] Whereas 12.0-34.0% of them regularly took a complete sexual history, 76.0% of American GPs would take sexual history when their patient chiefly complained of sexual related issues.[5]

These incomplete clinical practices may lead to misdiagnosis of sexual-related diseases, especially STDs, teenage pregnancy, and erectile dysfunction, which are global public health concerns nowadays. The common reasons why most physicians have not taken a sexual history, were their lack of confidence and inexperience. A study discovered that the reason may be insufficient training and practice during their time at medical school.[6,7] 56.0% of American GPs reported that they were inadequately trained for sexual history taking according to their undergraduate medical curriculum. Another study in regard to Malaysian medical students found that about half of them felt uncomfortable discussing sexual issues with their patients.[6]

However, no current studies on sexual history taking in undergraduate medical education were conducted in Thailand, and there is a small amount of reported research in regard to low-and middle-income countries. Most relevant studies were from other countries where medical curriculum, cultures and contexts were different from Thailand, and especially southern Thailand.[6,7] Some parts of this region have been dubbed by the media as South border provinces (SBP) because of their complicated political and religious conditions which leads to ongoing violence and insurgency since 2004.[8] Hence, background and perspectives found from many previous studies on medical doctors, who studied or worked within these areas may be different from other regions of country.[9] For these reasons, this study aimed to examine clinical practices and attitudes toward sexual history taking among medical students in southern Thailand, as well as their associated factors. The researchers explored the Thai undergraduate medical curriculum in sexual health, especially Thai medical students' practice and attitude toward sexual history taking, which are the primary processes of sexual health care in clinical practice. Moreover, medical students' perceptions on undergraduate training could feed-back to the institute for developing medical education, which focuses on real-life educational content.

MATERIALS AND METHODS

Design and participants

This study used a cross-sectional design and was approved by the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC 65-296-9-1). The participants were final-year medical students at the Prince of Songkla University (PSU).

Study sample and sampling

$$n = \frac{Np(1-p)z^2_{1-\frac{\propto}{2}}}{d^2(N-1)+p(1-p)z^2_{1-\frac{\propto}{2}}}$$

The sample size was calculated based on the primary objective using the finite population proportion as: Due to the limited information reported on attitudes, practice, and perception on training toward sexual history taking among medical students; the researchers used prevalence = 0.5 for maximized sample size and alpha (α) = 0.05 for the margin of error (d).

The calculated sample size was 91 medical students. We invited all the 118 medical students who studied at PSU medical school. 92 students enrolled to the survey, but one of them withdraw her/himself before the survey was completed.

Data collection

The survey was circulated among the final year medical students, via google form, during September and October 2022. The form of the questionnaire was designed for participants to be anonymous and distributed by the unit of student affairs, faculty of Medicine, Prince of Songkla university, Thailand.

Measurements

Literature regrading undergraduate medical education, and the medical curriculum on sexual health was reviewed by all authors as per the core concept of the primary aims, before the rest of the co-authors reviewed studies on practices, attitude toward sexual history taking and medical students' perceptions or perspectives on their undergraduate training, regarding the issue of sexual health for the main objectives of this study.

The self-reported questionnaire consists of 4 parts as below:

1) Participants' characteristics; gender, sexual orientation, age, ethnicity, religion, grade point average (GPA), and romantic relationship status

2) Attitude toward sexual history taking consisted of 5 questions (five-point scales: 1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, 5 = strongly agree):

2.1 Importance of sexual history taking in general practice

2.2 Impact of sexual history taking on clinical management

2.3 Preference of patients to discuss on their sexual history from physician's question

2.4 Importance of confidentiality of patients 'sexual history

2.5 Preference of medical students on duration of time taking sexual history

The Likert scale was the grouped attitude toward sexual history taking into three groups by using Best's criterion: good (high level, score = 19-25), fair (moderate level, score = 12-18) and poor (low level, score = 5-11) attitude.

3) Practice on sexual history taking consisted of 15 questions (five-frequency scale: always [100%], usually [75-99%], often [50-75%], rarely [<50%] and never [0%])

4) Perceptions about the undergraduate medical training on taking a sexual history consisted of 9 questions about their knowledge, skills in sexual history taking and confidence on their communication skill. (There were five-rating scales: very high, high, moderate, low, and very low). The first draft of the questionnaire was tested for content validity by three experts in sexual health. The Item Objective Congruence Index (IOC) was calculated for each question and re-adjusted until the IOC value > 0.5. Then, the questionnaire was re-tested for its reliability by 30 final-year medical students in other medical schools in southern Thailand. The Cronbach's alpha coefficient were 0.71 for the second part, 0.90 for the third part, and 0.91 for the last part of questionnaire.

Statistical analysis

All data were analyzed by the R program. Descriptive analysis was used to analyzed baseline characteristics, practice on sexual history taking and perception on undergraduate medical training of sexual history taking. The mentioned parts were presented as frequency and percentages, while multiple logistic regression was used to analyze factors associate with practice, attitude toward sexual history taking and perceptions on undergraduate medical training. A p-value =< 0.05 is considered statistically significant.

RESULTS

Demographic data

Of 91 medical students who participated in the study, most of participants were male (54.9%), with a median age of 23.0 years old (23.0, 24.0). Most of them were Thai, Buddhist and identified that their sexual orientation is heterosexual (96.7%, 87.9% and 78.0%). 72.5% of the students stated their grade point average (GPA) as between 3.01 and 4.00. More than half of the participants were single, without a current romantic relationship (63.7%) (Table 1).

Attitudes towards sexual history taking among Thai medical students

Approximately two-thirds of our participants had a high level of attitude toward sexual history taking (68.1%) and no one had a low level of attitude. Most of the participants had a strong-to-very strong agreement that sexual history taking is important for general practice (83.4%) and it significantly affected medical care (64.9%). In addition, confidentiality about the patient's sexual history was the most critical issue (94.5%). However, 74.7% of them moderately-to-highly agreed that it took time for them to take sexual history in general, in an unpredictable manner. (Fig 1)

Practice on sexual history taking among medical students

To survey on the clinical practice, the questionnaire asked how many percent of patient consultations incorporated the taking of sexual history. Contraceptive methods were the most frequently incorporated questions asked of patients with any chief complaints (36.3% in female patients and 17.6% in male patients). During visits for annual checkups and patients with suspected sexually transmitted diseases (STDs), the most frequently asked question was about preventive methods for sexually transmitted infections. (27.5% and 49.5% respectively However, approximately half of medical students rarely-to-never asked about their partner's gender (48.2%) and sexual activity patterns for patients who were suspected STDs (57.2%). Whereas sexual dysfunction symptoms had rarely-to-never been asked by the medical students for general patients who came with other chief complaints (61.6%) (Table 2).

Overall, most medical students assessed their ability to conduct sexual history taking as moderate-to-good in all areas, including communication skills. Approximately two-thirds of the participants perceived that, they had skills which were well-to-very-well trained and good-to-very good knowledge in discussing and advising on

TABLE 1. Participants' demographic data.

Characteristic	Number (%)
Age [Median (Q1, Q3)]	23 (23,24)
Sex assigned at birth	
Male	50 (54.9)
Female	41 (45.1)
Sexual orientation	
Heterosexual	71 (78.0)
Non-heterosexual[a]	17 (18.7)
Non specified	3 (3.3)
Race	
Thai	88 (96.7)
Cambodian/Chinese	3 (3.3)
Religion	
Buddhism	80 (87.9)
Muslim, Christian, Irreligious	10 (11.0)
Non specified	1 (1.1)
GPA	
3.01-4.00	66 (72.5)
2.01-3.00	18 (19.8)
Non specified	7 (7.7)
Marital status	
Single	58 (63.7)
In relationship	28 (30.8)
Non specified	5 (5.5)

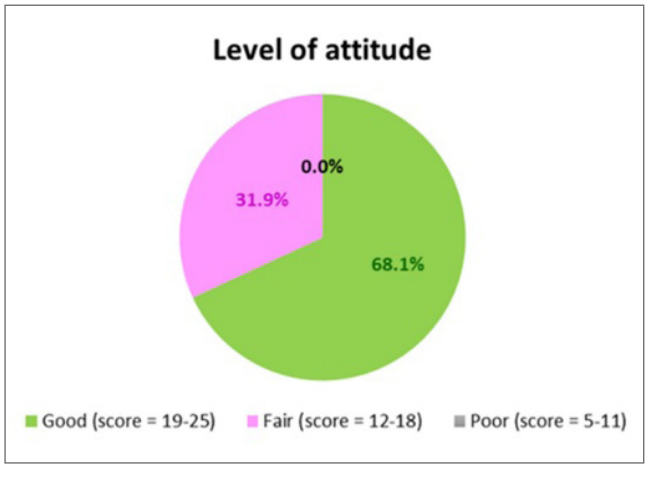

Fig 1. Attitude toward sexual history taking among Thai medical students.

contraception (64.9% and 67.1% respectively), while sexual dysfunction was the topic most perceived having a moderate-to-poor skill and knowledge as (69.3% and 70.4%) However, 57.2% of them perceived their own communication skill on sexual history which were good-to-very good. (Table 3).

Factors associated practice and attitude toward sexual history taking in an undergraduate medical curriculum

This part of questionnaire asked participants directly for the perception of all skills trained under the curriculum of undergraduate medical education. According to the attitude toward sexual history taking, no significant associated factor was found. However, males and students who perceived good-to-very good knowledge and skills as well-to-very well-trained; were statistically significantly associated with usually-to-always sexual history taking in patients with symptoms leading to the suspicion of STDs {[adjusted OR (95%CI) = 4.51 (1.19-17.11)] and [adjusted OR (95%CI) =5.3 (1.51-18.65)]}. In addition, a perception of good-to-very good skill and knowledge on sexual history taking and sexual health also was associated with more regular sexual history taking in general patients with any chief complaint [adjusted OR (95%CI) = 4.85 (1.43-16.41)] (Table 4).

Regarding perceived knowledge and skills of sexual history taking among medical students, perception of well-to-very well-trained skills regarding the curriculum, and perceived good-to-very good communication skill were statistically significant associated factors. [adjusted OR (95%CI) = 4.93 (1.5-16.22) and 3.45 (1.22-9.73), respectively (Table 5).

DISCUSSION

To take sexual history must involve questions of sexual behavior, sexual function, sexual orientation, gender identity, sexual health risks, contraceptive uses and protection of transmitted diseases.[1,10] This study covered the questions that should be asked in most general practices and inquired regarding the confidence of medical students about their trained skills and knowledge, in the context of feedback to the Thai curriculum of medical degrees (M.D.). Moreover, this survey is the first study to precisely examine sexual history taking among Thai medical students, particularly those studying in southern Thailand, in the past 10 years.

Compared with a Malaysian study, agreement on the importance of sexual history taking and patients' confidentiality were found to be similar.[6] In addition, they also showed the same opinion of hesitancy due

TABLE 2. Sexual history taking practice among medical students.

Sexual history topic	Frequency of asking patients [number (%)]				
	Always (100%)	Usually (75-99%)	Often (50-75%)	Rarely (<50%)	Never (0%)
Visit for annual examination					
Number of partners in the previous year	7 (7.7)	9 (9.9)	14 (15.4)	37 (40.7)	24 (26.4)
Sex assigned at the birth of patient's partner	6 (6.6)	8 (8.8)	18 (19.8)	28 (30.8)	31 (34.1)
Preventive method of sexually transmitted infection	25 (27.5)	16 (17.6)	20 (22.0)	17 (18.7)	13 (14.3)
Visit with symptoms of suspected sexually transmitted infection					
Sexual orientation	13 (14.3)	11 (12.1)	23 (25.3)	23 (25.3)	21 (23.1)
Number of partners in the previous year	20 (22.0)	20 (22.0)	18 (19.8)	19 (20.9)	14 (15.4)
Frequency of having sexual intercourse	19 (20.9)	15 (16.5)	27 (29.7)	18 (19.8)	12 (13.2)
Sex assigned at the birth of patient's partner	11 (12.1)	17 (18.7)	19 (20.9)	23 (25.3)	21 (23.1)
Patient's sexual activity patterns such as vaginal, anal, oral	10 (11.0)	16 (17.6)	13 (14.3)	24 (26.4)	28 (30.8)
Preventive method of sexually transmitted infection	45 (49.5)	21 (23.1)	11 (12.1)	9 (9.9)	5 (5.5)
History of having sexually transmitted infection	45 (49.5)	19 (20.9)	12 (13.2)	10 (11.0)	5 (5.5)
History of having sexual abuse	4 (4.4)	10 (11.0)	16 (17.6)	24 (26.4)	37 (40.7)
Visit with any chief complaint					
Methods of contraception in the female of reproductive age	33 (36.3)	31 (34.1)	11 (12.1)	14 (15.4)	2 (2.2)
Methods of contraception in the male of reproductive age	16 (17.6)	16 (17.6)	12 (13.2)	28 (30.7)	19 (20.9)
Problems of sexual dysfunction	4 (4.4)	13 (14.3)	18 (19.8)	27 (29.7)	29 (31.9)
Current medications used which may impact sexual dysfunction	8 (8.8)	14 (15.4)	20 (22.0)	23 (25.3)	26 (28.6)

to time-consuming process of sexual history taking, which may be a part of normal Asian culture, regarding discussing sensitive issues such as sexual function.[6] For these reasons, socio-cultural context should be embedded into not only sexual history taking skill, but other sensitive topics such as taking the history of psychiatric symptoms. In addition, sexual health should be embedded in both preventive care and medical treatment.[1,4] However, less than half of medical students regularly took a sexual history during annual check-up visits, whereas most of them regularly asked the patients with suspected sexually transmitted diseases. Approximately half of the medical students did not ask about the history of sexual abuse and related behaviors in these patients. While contraception is a common topic in doctor-patient discussions, the students tended to discuss it more with female patients than with male patients. These results may give feedback on the undergraduate curriculum of preventive medicine to enhance sexual health into the Thai medical education. Even though no factor associated with attitudes toward sexual history taking was found, male gender and perception on knowledge and skill regarding trained curriculum of Thai M.D. were associated factors of such practices. We can imply that the results showed the significance of appropriate teaching and training on sexual health in Thailand. Most of Thai medical students perceived their knowledge and skill on sexual history taking as fair-to-poor. Thus, further

TABLE 2. Perception of knowledge and skills of sexual history taking regarding medical curriculum.

	Perception of knowledge and skills [number (%)]				
	Very good	Good	Fair	Poor	Very poor
Perception of knowledge					
Knowledge of sexual history taking adequate for diagnosis and treatment of disease	8 (8.8)	36 (39.6)	41 (45.1)	6 (6.6)	0 (0.0)
Knowledge in screening, diagnosis, and treatment of sexually transmitted infection	8 (8.8)	41 (45.1)	38 (41.8)	4 (4.4)	0 (0.0)
Knowledge of diagnosis and treatment of sexual dysfunction	4 (4.4)	23 (25.3)	39 (42.9)	18 (19.8)	7 (7.7)
Knowledge of contraception	20 (22.0)	41 (45.1)	27 (29.7)	3 (3.3)	0 (0.0)
Perception of trained skills					
Skill in sexual history taking adequate for diagnosis and treatment of disease	9 (9.9)	28 (30.8)	39 (42.9)	14 (15.4)	1 (1.1)
Skill in screening, diagnosis, and treatment of sexually transmitted infection	7 (7.7)	42 (46.2)	33 (36.3)	9 (9.9)	0 (0.0)
Skill in diagnosis and treatment of sexual dysfunction	6 (6.6)	22 (24.2)	34 (37.4)	19 (20.9)	10 (11.0)
Skill in advising contraception	14 (15.4)	45 (49.5)	25 (27.5)	7 (7.7)	0 (0.0)
Perception of Communication skills	9 (9.9)	43 (47.3)	32 (35.2)	7 (7.7)	0 (0.0)

development on sexual health and associated clinical skills regarding the undergraduate medical curriculum should be more focused on this. Furthermore, 42.8% of medical students perceived their communication skills as fair-to-poor, and this perception was significantly associated to knowledge and skills of sexual history taking.

Communication skills themselves are critical for medical practice because it is essential for building trust and rapport with patients who are often anxious and stressed, especially when they visit health care providers for sensitive issues such as psychological and sexual-related problems.[11] Moreover, providing high-quality care needs good-to-very good communication skills for gathering accurate and complete patients' information. Medical doctors must be able to communicate effectively with patients to obtain their health information, as well as clearly communicate with them for proper self-care.[12] Thus, this skill may not influence only the skill of sexual history taking but may influence the general skills of medical practices.

However, these medical students have studied their clinical practice during the COVID-19 pandemic (the fourth-to sixth years regarding the curriculum). This globally challenging situation has presented a struggle in regard to communication in general. Medical students faced challenges communicating with patients, colleagues, and medical instructors. The uses of tele-medicine and other remote teachings for undergraduate medical education may assist them for more effective communication skill. A previous study on history taking among medical students at the same medical school reported that 91% of them showed confidence on history taking in psychiatric practice in 2017-2018, whilst this study found only 42.8% reported self-assurance on the same topic.[11,12] Although they engage in history taking on different issues, both are vulnerable, and their dissimilarities of prevalence could reveal the communication skill struggles during the pandemic.[13] For these reasons, medical educators should provide more training and resources, such as remote classroom, case-based learning, and simulation, to help the students to improve their communication skills in the context of the COVID-19 pandemic and beyond.[14]

TABLE 4. Factor associated with practice and attitude toward sexual history taking among medical students.

Factor	High level of attitude toward sexual history taking			Usually to always in practice in sexual history taking								
				Visiting for annual examination			Visiting with suspected STDs			Visiting for any chief complaint		
	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value
Sex assigned at birth												
Female	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Male	0.8 (0.33-1.96)	0.67 (0.25-1.81)	0.425	0.66 (0.2-2.15)	0.31 (0.07-1.42)	0.131	3.39 (1.12-10.26)	4.51 (1.19-17.11)	**0.027***	0.87 (0.33-2.32)	0.8 (0.24-2.64)	0.715
Sexual orientation												
Non-heterosexual[a]	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Heterosexual	0.87 (0.27-2.76)	0.73 (0.21-2.55)	0.624 (0.35-24.44)	2.93	4.02 (0.35-46.88)	0.266	0.64 (0.2-2.11)	0.39 (0.1-1.55)	0.181	1.36 (0.35-5.32)	1.4 (0.28-7.07)	0.682
Non specified	0.83 (0.06-11.42)	0.59 (0.02-17.03)	0.757	8 (0.35-184.36)	477955878. 01 (0-Inf)	0.993	1.2 (0.09-16.44)	0.69 (0.02-22.76)	0.835	9.33 (0.62-139.57)	12038553 9.03 (0-Inf)	0.992
Race												
Thai	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Cambodian/ Chinese	0.93 (0.08-10.73)	1.81 (0.13-25.98)	0.663	0 (0-Inf)	0 (0-Inf)	0.996	1.7 (0.15-19.73)	3.24 (0.23-45.51)	0.383	0 (0-Inf)	0 (0-Inf)	0.994
Religion												
Buddhism	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Others[b]	0.51 (0.14-1.85)	0.44 (0.1-1.87)	0.268 (0.07-4.84)	0.57	0.46 (0.04-5.69)	0.542	0.71 (0.14-3.59)	1.84 (0.27-12.54)	0.534	1.29 (0.31-5.38)	2.43 (0.39-15.10)	0.341
GPA												
3.01-4.00	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
2.01-3.00	0.68 (0.23-2.02)	0.69 (0.21-2.33)	0.551	1.45 (0.34-6.14)	1.34 (0.23-7.82)	0.747 (0.28-3.4)	0.97	0.61 (0.13-2.78)	0.524	1.06 (0.3-3.73)	0.79 (0.17-3.61)	0.766
Non specified	1.09 (0.19-6.08)	1.31 (0.19-9.12)	0.783	2.9 (0.48-17.52)	1.37 (0.17-11.32)	0.772	1.36 (0.24-7.73)	1.18 (0.14-10.01)	0.88	2.79 (0.56-13.92)	0.82 (0.12-5.62)	0.836

TABLE 4. Factor associated with practice and attitude toward sexual history taking among medical students. (Continue)

Factor	High level of attitude toward sexual history taking			Usually to always in practice in sexual history taking								
				Visiting for annual examination			Visiting with suspected STDs			Visiting for any chief complaint		
	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value
Marital status												
Single	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
In a relationship	0.59 (0.23-1.53)	0.49 (0.17-1.4)	0.18	2.89 (0.87-9.61)	4.45 (0.95-20.96)	0.059	1.15 (0.4-3.31)	1.04 (0.31-3.49)	0.956	2.67 (0.95-7.47)	3.61 (1.00-13.02)	0.05
Non specified	0.57 (0.09-3.74)	0.62 (0.06-6.29)	0.689	0 (0-Inf)	0 (0-Inf)	0.992	0.87 (0.09-8.43)	0.82 (0.06-11.51)	0.88	1.2 (0.12-11.91)	0 (0-Inf)	0.993
Attitude toward sexual history taking												
Low-to-moderate				Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
High				1.67 (0.42-6.58)	1.82 (0.35,9.56)	0.481	1.67 (0.55-5.11)	1.45 (0.41-5.13)	0.562 (0.55-5.11)	1.67	1.75 (0.47-6.53)	0.407
Perception of received knowledge and skills of sexual history taking												
Very low to moderate	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
High to very high	2.76 (0.84-9.04)	3.48 (0.97-12.52)	0.056	4.52 (1.33-15.33)	3.01 (0.74,12.24)	0.123	3.99 (1.4-11.36)	5.3 (1.51-18.65)	**0.009***	5.32 (1.85-15.32)	4.85 (1.43-16.41)	**0.011***

[a]Non-heterosexual = Homosexual, Bisexual, and Pansexual

[b]Religion: others = Muslim, Christian, Irreligious, and Non specified

TABLE 5. Factor associated with the perception of knowledge and skills of sexual history taking regard to medical curriculum.

Factor	Perception of good-to-very good knowledge in sexual history taking			Perception of well-to-very well trained skills in sexual history taking			Perception of good to very good communication skills		
	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value
Sex assigned at birth									
Female	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.53 (0.62-3.77)	1.46 (0.52-4.14)	0.476	1.67 (0.62-4.54)	1.73 (0.53-5.69)	0.365	2.25 (0.96-5.25)	1.89 (0.72-4.92)	0.195
Sexual orientation									
Non- heterosexual[a]	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Heterosexual	4.08 (0.86-19.28)	3.93 (0.77-20.11)	0.101	3.12 (1.00-9.74)	3.4 (0.88-13.06)	0.075	1.54 (0.53-4.45)	1.33 (0.40-4.41)	0.645
Non specified	15 (0.90-251.05)	30.92 (0.88-1082.66)	0.059	10955952.55 (0-Inf)	95485553.51 (0-Inf)	0.993	17607780.88 (0-Inf)	6597424.74 (0-Inf)	0.994
Race									
Thai	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Cambodian/ Chinese	0 (0-Inf)	0 (0-Inf)	0.989	4603341.41 (0-Inf)	9492087.19 (0-Inf)	0.994	1.52 (0.13-17.39)	1.58 (0.12-20.98)	0.78
Religion									
Buddhism	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Others[b]	0.78 (0.19-3.18)	1.07 (0.2-5.72)	0.935	0.44 (0.11-1.68)	0.58 (0.1-3.23)	0.533	0.38 (0.10-1.41)	0.46 (0.09-2.22)	0.331
GPA									
3.01-4.00	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
2.01-3.00	3.12 (1.06-9.22)	3.23 (0.95-10.94)	0.06	2.78 (0.58-13.34)	2.82 (0.5-15.84)	0.238	2.3 (0.74-7.19)	3.1 (0.82-11.73)	0.096
Non specified	4.17 (0.84-20.62)	1.96 (0.32-11.98)	0.467	2.08 (0.23-18.56)	1.1 (0.09-13.51)	0.941	1.18 (0.24-5.69)	0.97 (0.14-6.71)	0.974
Marital status									
Single	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
In a relationship	2.15 (0.83-5.57)	2.4 (0.75-7.63)	0.138	1.46 (0.47-4.57)	1.89 (0.47-7.5)	0.367	1.16 (0.47-2.88)	1.23 (0.43-3.55)	0.701
Non specified	1.91 (0.29-12.57)	0.58 (0.04-7.58)	0.677	1.27 (0.13-12.35)	0.34 (0.02-6.21)	0.47	13631830.37 (0-Inf)	14890688.05 (0-Inf)	0.991
Attitude toward sexual history taking									
Low-to-moderate	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
High	1.73 (0.64-4.68)	2.61 (0.82-8.27)	0.104	3.6 (1.28-10.09)	4.93 (1.5-16.22)	**0.009***	2.58 (1.04-6.36)	3.45 (1.22-9.73)	**0.019***

[a]Non-heterosexual = Homosexual, Bisexual, and Pansexual
[b]Religion: others = Muslim, Christian, Irreli¬gious, and Non specific

Limitations and suggestions

This study has a cross-sectional design. It is useful for gathering information on specific topics such as the sexual history taking on medical students in southern Thailand. Even though more than half of medical students in southern Thailand have studied at the Prince of Songkla university, this study was conducted at a single centre. Thus, this study may not be representative for all Southern-Thai medical students. Another limitation is the temporal sequence of events because all data was collected at a single point in time. So, it was difficult to establishing a cause-and-effect relationship, especially when the survey was done during the COVID-19 pandemic. The first recommendation for further studies should be to conduct multi-center surveys that include all clinics, such as those that offer rehabilitation services.[15] In addition, a time-series study may be beneficial in following the outcomes of curriculum development.

CONCLUSION

This study on medical education aimed to examine the perception of practice, attitude toward sexual history taking and their associated factors among the final year medical students in southern Thailand. Most participants were male and Buddhists. Most of them showed a good attitude towards sexual history taking and reported that contraception was the primary topic discussed with patients. The prevention of sexually transmitted diseases (STDs) was the most common issue for both annual examinations and patients with suspected STDs. Male medical students who perceived good-to-very good knowledge and well-to-very well-trained skills in sexual history taking were significantly associated with more regular sexual history taking. Additionally, Thai medical students with a positive attitude towards sexual history taking were significantly associated with good training of their skills in both history taking and communication.

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Efficacy of Atropine Eye Drops for Suppressing Myopia Progression in Thai Children

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ABSTRACT

Objective: This retrospective cohort study aimed to assess the efficacy and safety of low-dose atropine eye drops in retarding myopic progression among school-age children at Siriraj Hospital.

Materials and Methods: The medical records of 247 myopia-diagnosed patients were reviewed. All patients were received low-dose atropine eye drops and had at least one follow-up visit within 1 year after the treatment initiation. Spherical equivalent (SE) measurements were collected at pre- and post-treatment visits, as well as any reported side effects. Comparing the SE changes observed between the pre- and post-treatment periods, as well as between the two different concentrations of atropine was analyzed.

Results: A total of 493 eyes were analyzed, with 461 eyes receiving 0.01% atropine eye drops and 32 eyes being administered 0.05%. The demographic data between two groups showed no significant difference. The comparison of SE change one year prior to and one year after treatment in the 0.01% and 0.05% group yielded a p-value of less than 0.001 and 0.003, respectively, (SE change were -0.38 D (-0.75-0.00 D) and -0.25 D (-0.72-(-0.25 D)) in the 0.01% and 0.05% group, respectively). However, the between-group comparison of SE change at 6 months and 1 year showed no significant difference. Regarding side effects, one-third of the eyes (12 eyes) in the 0.05% group (37.5%) experienced adverse effects while only eight eyes (1.7%) in the 0.01% group reported side effects.

Conclusion: This research contributes support to the effectiveness of employing low-dose atropine for the treatment of myopia in Thai children. However, the use of 0.05% atropine was associated with a higher incidence of side effects.

Keywords: Myopia; Atropine Eye Drops (Siriraj Med J 2023; 75: 794-799)

INTRODUCTION

Myopia, or nearsightedness, is a visual condition resulting in blurred distance vision. Holden and colleagues estimated a prevalence of myopia in 1.4 billion individuals worldwide in 2000 (22.9%), with a predicted increase to 4.8 billion by 2050.[1] The prevalence of myopia has been on the rise globally, particularly in Asian populations, and reportedly dramatically increased during the COVID-19 pandemic period.[2-6] Multiple factors have been attributed to the development of myopia, including genetic, environmental, and lifestyle factors, such as increased screen time on electronic devices, decreased outdoor exposure, and prolonged reading and studying.[7] Myopia usually occurs and progresses during the school-age period.[7] High myopia (-5.0 diopters or more), which can develop during the school-age period, can potentially extend beyond just affecting a person's daily activities and can lead to subsequent complications, such as retinal detachment, glaucoma, cataract, or macular pathologies.[8-10] Therefore, proactive practice to prevent and mitigate its progression should be taken into consideration.

The treatment approaches for myopia encompass

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various strategies, including environmental modifications, optical interventions, and medical treatment. Among the treatment options, atropine, which is a liquid medication that comes in the form of eye drops, has gained significant attention in recent years due to its ability to suppress the elongation of the eyeball and slow the progression of myopia.[11] Although the exact mechanism by which atropine slows myopia is not fully understood, it is believed to involve non-selective antimuscarinic, mydriatic, and cycloplegic effects, which block accommodation of the eye.[12] Other mechanisms, such as dopamine release, increased choroidal thickness, remodeling of scleral fibroblasts, and the inhibition of glycosaminoglycan in eye growth, are still not well elucidated.[12-16] However, the optimal concentration of atropine that strikes a balance between its efficacy and limiting its side effects remains uncertain. Several randomized controlled trials have been conducted to observe the outcomes and side effects of different atropine concentrations, ranging from 0.01% to 1%, in school-age children with myopia.

The ATOM 1[17] and ATOM 2[18] studies conducted in Singapore found that 0.01% atropine was the most effective concentration in suppressing axial length elongation with minimal side effects. Similarly, a retrospective study from Tiana et al.[19] and a prospective study in Japan[20] reported similar results. However, in a Hong Kong study, 0.05% was reported to be the most effective concentration among the 0.01%, 0.025%, 0.05% tested concentrations, and a placebo, with no serious side effects observed in any of the groups.[21,22] These results highlight the variability in the optimal concentration, even among school-age Asian populations.[23] Additionally, no study has yet been conducted in a Thai population to determine the appropriate concentration and potential side effects of atropine, despite started using 0.01% atropine since 2016 and 0.05% since 2019 in Siriraj Hospital in concentrations of 0.05% and. 0.01%. Therefore, we conducted this study to provide information specific to a Thai population to aid in clinical practice.

MATERIALS AND METHODS

This study was approved by the the International Review Board of Faculty of Medicine Siriraj Hospital (COA no. Si 650/2022). Following the approval, patients diagnosed with ICD-10 codes referring to myopia (H25.1) were identified. This retrospective comparative cohort study consisted of school-age patients aged 5–18 years old who were diagnosed with myopia with a spherical equivalent (SE) higher than -1.00 diopter (D) for more than 1 year. All the included patients were receiving atropine as the treatment at Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, between January 2017 and December 2022. The inclusion criteria encompass the following conditions: individuals aged between 5 and 18 years old, myopic children with spherical equivalent (SE) greater than -1.0 D, who have been diagnosed with myopia for over one year and exhibit evidence of progression (indicated by changes in SE) and have not undergone any other forms of treatment aside from wearing eyeglasses prior to the prescription of atropine. Patients with concomitant ocular conditions that could potentially impact visual acuity, such as corneal pathologies, cataracts, and glaucoma, were excluded from the study. Additionally, individuals who were diagnosed with myopia subsequent to ophthalmic surgery or were lost to follow-up within the first year after initiating treatment were also excluded.

The required sample size was calculated with an alpha of 0.05, mean difference from a previous study of 0.220[21], power of 80%, and ratio of 6:1 between the 0.01% and 0.05% concentration atropine treatments. The required sample sizes according to the calculations were 71 and 426 in the 0.05% and 0.01% groups, respectively.

Evaluation method

The patient's demographic data, clinical features, and ocular examination data were retrospectively reviewed. Age at myopia diagnosis, age at starting atropine eye drops, sex, coexisting ocular diseases, best-corrected visual acuity (BCVA) before treatment, and autorefraction were recorded. At post-treatment visits, the spherical equivalent refractive errors were measured, and the side effects of the atropine eye drops at 6 months and 1 year were recorded.

Descriptive statistics were utilized to summarize the demographic data and clinical characteristics of the patients. Categorical data were presented as frequencies and percentages, while continuous variables were presented as median values and interquartile ranges (IQR) or as the mean and standard deviation (SD). Comparisons between the two groups were evaluated using Fisher exact or Mann–Whitney U test according to the distributive nature. The visual acuity data were transformed logarithmically to the minimum angle of resolution (logMAR) equivalents for statistical analysis. Changes in BCVA, spherical values, and spherical equivalent (SE) after treatment were evaluated using the Wilcoxon signed-rank test. A p-value of less than 0.05 was considered statistically significant. All the analyses were conducted using SPSS Statistics version 28.0 (SPSS, Inc, Chicago, IL, USA).

RESULTS

Overall, 247 cases (493 eyes) were enrolled in the study, among which 461 eyes received 0.01% atropine eye drops, while 32 eyes received 0.05% atropine eye drops. Table 1 presents all the relevant demographic data of the patients. The mean age of the patients in the 0.01% atropine group was 10.70 years old (SD ± 2.85), while in the 0.05% atropine group, the mean age was 10.06 years old (SD ± 3.67). No significant differences were observed in the demographic data between the patients receiving 0.01% atropine and those receiving 0.05% atropine.

Before treatment, myopic progression (spherical equivalent change) over one year in the 0.01% atropine group was -0.87 D (-1.37 to -0.5 D), while in the 0.05% atropine group, was -0.5 D (-1.09 to 0 D) (P-value 0.010). Following the initiation of atropine treatment, at the 6-month mark, myopic progression in the 0.01% atropine group (spherical equivalent) was -0.13 D (-0.38 to 0.13 D), whereas in the 0.05% atropine group was 0 D (-0.22 to 0.22 D) (P-value 0.053). After one year of treatment, myopic progression in the 0.01% atropine group (spherical equivalent) was -0.38 D (-0.75 to 0 D), and in the 0.05% atropine group, was -0.25 D (-0.75 to

TABLE 1. Demographic data and clinical findings.

	0.01% N = 461 (231 patients)	**0.05%** N = 32 (16 patients)	P-value
Study population			
Age at start treatment (years); mean (SD)	10.70 (± 2.85)	10.06 (± 3.67)	0.223†
Sex (Male/Female)	116/115	8/8	1.000*
Family History of myopia; n (%)			N/A
No	12 (2.6%)	4 (12.5%)	
Yes	122 (26.6%)	12 (37.5%)	
Unknown	325 (70.8%)	16 (50.0%)	
Study eyes			
Side (Right/Left)	231/230	16/16	N/A
BCVA at start treatment logMAR); median (IQR)	0.12 (0.04-0.30)	0.15 (0.05-0.30)	0.677#
Spherical change 1 year prior (D); median (IQR)	-0.75 (-1.25-(-0.5))	-0.38 (-1.00-0.00)	**0.007#**
SE change 1 year prior (D); median (IQR)	-0.87 (-1.37-(-0.5))	-0.50 (-1.09-0.00)	**0.010#**
At start treatment			
Spherical equivalent (SE) (D); median (IQR)	-5.37 (-7.25-(-4.13))	-5.31 (-8.00-(-4.66))	0.541#
Six months after treatment			
SE change (D); median (IQR)	-0.13 (-0.38-0.13)	0.00 (-0.22-0.22)	0.053#
BCVA at 6 months; median (IQR)	0.12 (0.04-0.20)	0.10 (0.04-0.28)	0.860#
Side effects; n (%)	8 (1.7%)	12 (37.5%)	0.001*
	Headache 2: Continue **Blurred near vision 4:** Stop **Irritation 2:** Continue	**Photophobia 4:** switch to 0.01% **Pupil sluggish react 2:** Continue. **Blurred near vision 6:** switch to 0.01%	
One year after treatment			
SE change (D); median (IQR)	-0.38 (-0.75-0.00)	-0.25 (-0.72-(-0.25))	0.799#
BCVA at 1 year; median (IQR)	0.10 (0.02-0.19)	0.12 (0.07-0.36)	0.066#

Abbreviations: IQR = interquartile range, SD = standard deviation, BCVA = Best-corrected visual acuity, logMAR = logarithmic minimum angle of resolution, SE = spherical equivalent.
*p-values were obtained by chi-square test.
†p-values were obtained by independent t test.
#p-values were obtained by Mann Whitney U test.

-0.25 D) (p-value 0.799). When comparing the efficacy within each atropine group before and after one year of treatment, both concentrations demonstrated a significant ability to slow myopic progression (p-value < 0.001 for the 0.01% atropine group and p-value = 0.003 for the 0.05% atropine group). However, when comparing the efficacy between the two groups at the one-year mark, no significant difference was observed (p-value = 0.799) (Fig 1).

In the 0.01% atropine group, four cases (8 eyes) (1.7%) experienced adverse drug reactions, with blurred near vision reported in two cases, headache in one case, and eye irritation in one case. Conversely, in the 0.05% atropine group, six cases (12 eyes) (37.5%) exhibited adverse drug reactions, including two cases of photophobia, one case of pupil dilatation, and three cases of blurred near vision (P-value 0.001).

DISCUSSION

Since 1966[24], atropine has been utilized as a mean to decelerate the progression of myopia and is widely regarded as the most effective medication available today.[11] Topical atropine, available in varying concentrations ranging from 0.01% to 1%, has been employed to effectively delay the progression of myopia[18,24-28] Numerous studies have indicated that 0.01% atropine may be the most suitable concentration for managing myopia progression.[17,18,29-33] However, it is important to note that no specific concentration of atropine has yet received approval from the US Food and Drug Administration (FDA) for the treatment of myopia.

At our institution, the hospital pharmacy unit has been preparing 0.01% atropine eye drops for clinical use since 2016, followed by the introduction of 0.05% atropine in 2019. Consequently, the sample size in our study consisted of more eyes in the 0.01% atropine group (461 eyes) than in the 0.05% atropine group (32 eyes), with the latter group number being lower than the expected sample size calculated statistically (71 eyes). Furthermore, in the 0.05% group, the change in spherical equivalent (SE) prior to treatment initiation showed a smaller shift. This observation might be attributed to the smaller sample size and a proclivity to prescribe a higher concentration of atropine, likely driven by the younger age of the participants and a higher incidence of family history of myopia (37.5% and 26.6% in the 0.05% and 0.01% groups, respectively). The results of our study demonstrated statistically significant efficacy in myopia retardation during the one-year follow-up period in both the 0.01% and 0.05% atropine groups, consistent with findings from similar studies conducted worldwide. However, although the 0.05% atropine group

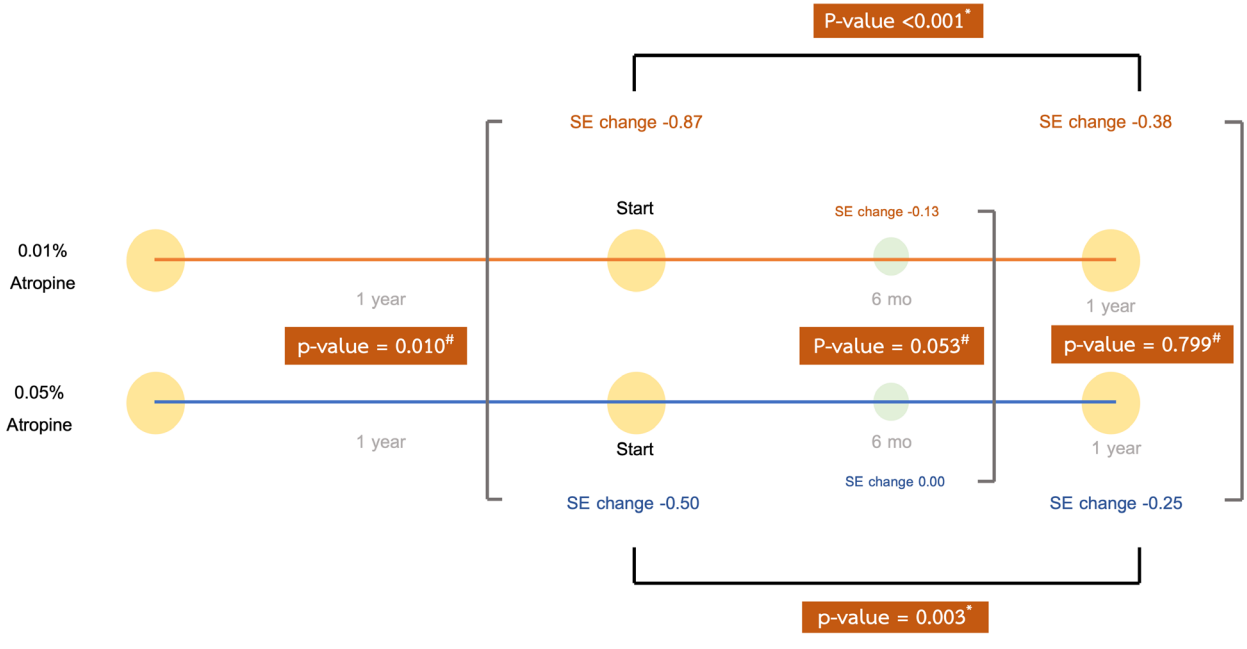

Fig 1. Comparison of SE change between before and after starting treatment and between atropine groups.
- 0.01% atropine group (N = 461): SE change -0.87 D (1-year before treatment), SE change -0.38 D (1-year after treatment) (p value < 0.001)
- 0.05% atropine group (N = 32): SE change -0.50 D (1-year before treatment), SE change -0.25 D (1-year after treatment) (p value = 0.003)
- Green circle = 6 months after treatment (SE change -0.13 D (0.01% atropine) vs 0.00 D (0.05% atropine) p value = 0.053)
- Yellow circle = 1 year after treatment (SE change -0.38 D (0.01% atropine) vs -0.25 D (0.05% atropine) p value = 0.799)

* = Comparison was done by using Wilcoxon signed-rank test.
# = Comparison was done by using Mann Whitney-U test.
Abbreviation: SE = spherical equivalent

exhibited a tendency toward a smaller change in spherical equivalent compared to the 0.01% atropine group, this difference did not reach statistical significance. This lack of statistical significance may be attributed to the discrepancy in the sample size between our two groups.

There are known to be some possible adverse drug reactions associated with topical atropine, which are dependent on its concentration[23], with higher concentrations being associated with an increased likelihood of side effects. In the present study, a small number of patients in the 0.01% atropine group (1.7%) reported experiencing side effects. These side effects included one case of headache, two cases of blurred near vision, and one case of eye irritation. Conversely, approximately one-third of the patients in the 0.05% atropine group experienced side effects. These side effects included two cases of photophobia, one case of pupil dilatation, and three cases of blurred near vision.

The present study has several limitations that need to be acknowledged. First, the small sample size, particularly within the 0.05% atropine group, restricted the statistical power and may have affected the ability to establish significant differences in clinical outcomes between the two atropine concentrations. Therefore, caution should be exercised when interpreting the results. Additionally, the relatively short one-year follow-up period may not have captured the long-term effects of atropine treatment for myopia management. The efficacy and safety profiles of 0.05% and 0.01% atropine concentrations may evolve over an extended period, highlighting the importance of conducting studies with longer follow-up durations. Furthermore, the present study only explored the comparative effectiveness of two atropine concentrations (0.05% and 0.01%).

To overcome these limitations and provide more robust and conclusive results, future studies should aim to include larger sample sizes to enhance the statistical power and improve the generalizability. Moreover, extending the follow-up period to multiple years would offer insights into the sustainability of the observed outcomes and potential long-term effects. Lastly, investigating additional concentrations of atropine would help elucidate the dose–response relationship and aid optimizing treatment strategies.

CONCLUSION

In conclusion, this preliminary study had shown that both 0.01% and 0.05% atropine concentrations are effective in delaying myopic progression among Thai school-age children. However, the higher incidence of adverse drug reactions in the 0.05% atropine group suggests the need for careful consideration when choosing the optimal concentration for myopia management in this specific population.

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Smartphone Addiction, Daytime Sleepiness and Depression among Undergraduate Medical Students: A Cross-sectional Study in a Medical College of Kolkata, India

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ABSTRACT

Objective: Smartphone addiction has become an emerging problem among the youth, especially among medical students in India. It has the potential to hamper their sleep quality as well act as a precipitating factor for depression. This study thus assessed the magnitude of smartphone addiction, excessive daytime sleepiness and depression among undergraduate medical students in Kolkata and elicited its determinants.

Materials and Methods: This cross-sectional study was conducted among 204 undergraduate medical students in a selected medical college of Kolkata from March to June 2023. Smartphone addiction, daytime sleepiness and depression were assessed using the SAS-SV, EPSS and PHQ-9 questionnaires. Logistic regression analysis was undertaken to determine the associated factors of smartphone addiction, while Spearman's correlation coefficient was estimated to find the relationship of smartphone addiction with depression and daytime sleepiness.

Results: Approximately 29.4% participants were addicted to smartphone, 45.5% were suffering from excessive daytime sleepiness. The depression scores on the PHQ-9 scale showed a mean value of 8.15 (±4.72). Factors significantly associated with smartphone addiction were increasing age (AOR=1.23, 95%CI=1.12-2.21), male gender (AOR=2.12, 95% CI=1.36-3.45) and duration of smart phone usage >6 hours per day (AOR=1.92, 95%CI=1.23-2.45). Smartphone addiction showed positive correlation with both daytime sleepiness (ρ =0.5, p-value<0.05) and depression (ρ=0.23, p-value=0.001)

Conclusion: Utmost care should be taken for promoting good mental health and wellbeing among medical students. Motivation and counselling sessions along with peer support groups can help in combating this addictive behaviour and depressive symptoms.

Keywords: Depression; excessive sleepiness; medical students; smartphone addiction (Siriraj Med J 2023; 75: 800-808)

INTRODUCTION

With the advancement of artificial intelligence and technology over the past decade, smartphones have become an indispensable entity in our daily life. A smartphone is characterized not only by its conventional utilities of communication but also consists of sophisticated software, internet, and multimedia functionality. The Telecom Regulatory Authority of India has reported the wireless telephone density to be 82.57% as on 31st December 2022.[1] Recent trends in smartphone market analysis predicts a growth of smartphone market size from 1.45 in the year 2023 to 1.78 in 2028[2] The rapid escalation in India has been boosted by "Digital India" initiative launched by the government to ensure the availability of government's services electronically via smartphone and internet to its citizens.[3]

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Gambling addiction has been classified under "substance-related and addictive disorders." as per the latest version of Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[4,5] Smartphone addiction is often characterized by the presence of the following elements: functional impairment, compulsive behavior, withdrawal, and tolerance. These characteristics bear quite similarities with the DSM-5 criteria of substance use and addictive disorders.[6] Thus, psychologists often opine an irrational overuse of smartphones to be denoted as smartphone addiction which has high propensity in becoming one of the most prevalent forms of addictions.[7]

A major proportion of smartphone users comprises college-going young adults; especially medical students, who utilize their smartphone not only for communication and recreational purposes, but also as an educational tool in their vast medical curriculum. Research work suggests that smartphone has become such a significant part in a student's life that they do not necessarily realize their level of dependence on it.[8] Smartphone addiction can have adverse effects on the health and well-being of an individual as it can precipitate physical ailments (neck and wrist pain and accidents) as well as behavioral problems (depression).[9] It can also interfere with academic performances, reduce social interactions, cause negligence in personal life and form an important environmental factor disturbing quality sleep, thus leading to lethargy and excessive sleepiness during daytime working hours. Sleep restoration has shown a strong relationship with better physical, cognitive, and psychological well-being in adults, adolescents, as well as in children. Good quality sleep is thus an essential entity in a student's life as poor sleep quality increases the risk of physical and mental disorders.[10-12]

Unfortunately, medical students are exposed to high levels of stress right from the beginning of their course, and this makes them highly vulnerable to sleep deprivation. Smartphone addiction if present in these students might aggravate this problem and have impact on their sleep quality. Lack of sufficient sleep often leads to undesired consequences like medical errors, job burnout and depression.[13] In addition, the emergence of the COVID-19 pandemic has shown an increase in the mode of virtual learning which has the potential to initiate a vicious cycle of smartphone addiction, sleep deprivation and mental distress. Moreover, previous studies in Asia have opined smartphone addiction acting as a defense mechanism to compensate for sadness, boredom and other mental health disorders.[14] A previous study among medical students in Thailand have demonstrated 11.1% of participants suffering from depression which highlighted the relationship between smartphone addiction and depression among medical students.[15] There is dearth of literature in this domain among undergraduate medical students in the city of Kolkata, especially after the emergence of the pandemic. With this backdrop, this study envisaged to assess the magnitude of smartphone addiction, excessive daytime sleepiness, and depression among undergraduate medical students of a medical college in Kolkata and elicit its associated determinants.

MATERIALS AND METHODS

This cross-sectional study was conducted from March to June 2023 among undergraduate medical students of Medical College and Hospital, Kolkata. Data were collected from the study participants from April to May 2023. The study was conducted after taking clearance from Institutional Ethics Committee for Human Research of Medical College and Hospital, Kolkata (Approval ID: MC/KOL/IEC/NON-SPON/1832/04/2023 dated: 05/04/2023). Participants who did not give written informed consent or were absent during the data collection phase were excluded from the study.

Sampling

A previous study conducted by Nowreen N et al[4] among undergraduate medical students of SKIMS Medical College, Srinagar, India showed the prevalence of smartphone addiction to be 34.4% Considering P=0.344 (34.4%), $Z_{1-\alpha}$=1.96, Q=1-P and absolute error of precision (L) to be 8% (0.08), the minimum sample size was estimated using the $(Z_{1-\alpha})^2PQ/L^2$, which comes to be 135.[16] Since simple random sampling was not done, a design effect of 1.5 was added and the final sample size came to be 204.

Multistage probabilistic sampling technique was used to select the study participants. Students were distributed into 5 groups according to their academic year of study. (1st year, 2nd year, 3rd year, 4th year and internship period). Data regarding total number of students present in each of the academic years was collected from the college registers and line listing was done. At first, the total number of students required from each academic year was calculated according to proportionate allocation as per the sample size. Then after calculating the requisite number of participants from each year, in the 2nd stage, participants from each year were selected through simple random sampling by computer generated random number tables

Data collection, study tools and parameters used

On the day of data collection, the investigators explained the purpose & procedure of the study elaborately

to the participants and written informed consent was taken from them. They were assured of the confidentiality of the data. The study was conducted via face-to-face interview with the study participants with the help of a pre-designed pre-tested self-administered questionnaire. Pre-testing of the questionnaire was done among 30 students of a different medical college who were not included in the study. Reliability of the questionnaire was checked by estimating Cronbach's alpha coefficient while face and content validity of the questionnaire were checked by public health experts. The questionnaire consisted of the following domains:

a) Socio-demographic characteristics like age in completed years, gender, per-capita monthly family income, place of residence
b) Smartphone usage characteristics like duration of usage in completed years, average hours used per day, number of apps present in smartphone, purpose of use of smartphones.
c) Presence of smartphone addiction was assessed by the validated Smartphone Addiction Scale-Short Version (SAS-SV) consisting of 10-items. This 10-item self-report instrument addressed the following 5 content areas: Daily-life disturbance, withdrawal, cyberspace-oriented relationship, overuse, and tolerance. For each item, participants expressed their opinion on a 6-point Likert scale ranging from '1' for 'strongly disagree' to '6' for 'strongly agree'. Total scores range from 6 to 60 with increasing scores indicating increasing addiction. Males were considered to be addicted to smartphones if scores were higher than 31 while females were addicted if scores were higher than 33.[17,18]
d) Presence of excessive daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) consisting of 8-items. Participants could give their response in a 4-point Likert scaling pattern ranging from 'would never nod off' as '0' to 'high chance of nodding off' as 3. Total scores thus range from 0 to 24, higher scores indicating increasing chances of excessive daytime sleepiness. Moreover, if a person scored 11 or more out of 24, he/she was considered as having excessive daytime sleepiness.[19,20]
e) Presence of depression among the study participants was assessed by the Patient Health Questionnaire-9 (PHQ-9) which consisted of 9-items. Participants gave their responses in a 4-point Likert scaling pattern ranging from '0' for 'Not at all' to '3' for 'Nearly every day'. Total scores thus ranged from 0 to 27 with higher scores indicating increasing depression. The scores were also categorized as follows: 0-4 as minimal depression, 5-9 as mild depression, 10-14 as moderate, 15-19 as moderately severe and 20-27 as severe depression.[21]

Data analysis

Data were analyzed using Microsoft Excel (v.2019) and SPSS (version 16.0 IBM Corp. USA). Continuous data were denoted as mean (±standard deviation) or as median with interquartile range, whereas categorical data were expressed as number with percentages. Kolmogorov-Smirnov and Shapiro-Wilk test were performed to test the normal distribution of the data. Multicollinearity among the variables was excluded by estimating variance inflation factor (VIF>10). Factors associated with smartphone addiction were analyzed using univariate and multivariable binary logistic regression models. Only the biologically plausible significant variables in the univariate analysis (p-value<0.05 at 95% confidence interval) were included in the final multivariable model. Pearson's or Spearman correlation coefficient (whichever applicable) was estimated to find out the relationship between excessive sleepiness and depression with smartphone addiction among the study participants.

RESULTS

Socio-demographic characteristics of the study participants

Among 204 study participants, the median age was 20 years (IQR=19-21 years). Approximately 72% of the participants were males, 141 (69.1%) resided in urban areas while 148 (72.5%) participants lived in hostel premises of the institute. The median per-capita income of the study participants was ₹12500 (IQR= ₹6250-₹22500). A major proportion (65.2%) of participants belonged to Class I socio-economic status as per modified BG Prasad scale 2022.[22] Other socio-demographic characteristics have been described in detail in Table 1.

Smartphone usage characteristics of the study participants

Approximately 38% of the participants have used a smartphone for a duration of 3-5 years, 90 (44.1%) participants utilize their smartphones for 4-6 hours duration per day. Approximately 46% of the participants had 11-20 apps in their smartphones. Other smartphone usage characteristics of the participants have been described in detail in Table 1.

Smartphone addiction, daytime sleepiness, and depression among the study participants

The total scores of the SAS-SV scale had a median value of 27 (IQR=21-34), 60 (29.4%) participants were found to be addicted to their smartphones (Table 2).

TABLE 1. Socio-demographic and smartphone usage characteristics of the study participants (n=204).

Variables	Categories	Frequency (%)
Gender	Male	147 (72.1)
	Female	57 (27.9)
Type of residence	Urban	141 (69.1)
	Rural	63 (30.9)
Living in hostel premises	Yes	148 (72.5)
	No	56 (27.5)
Socio-economic status (as per modified BG Prasad scale 2022)	Class I	133 (65.2)
	Class II	39 (19.1)
	Class III	12 (5.9)
	Class IV	14 (6.9)
	Class V	6 (2.9)
Duration of smartphone usage (in completed years)	< 3 years	57 (27.9)
	3-5 years	78 (38.2)
	6-8 years	41 (20.1)
	> 8 years	28 (13.7)
Average hours of smartphone usage per day	< 4 hours	57 (27.9)
	4-6 hours	90 (44.1)
	7-9 hours	36 (17.6)
	>9 hours	21 (10.3)
Purpose of smart phone usage*	Educational tool	183 (89.7)
	Playing games	72 (35.3)
	Using social media	140 (68.6)
	Watching movies	99 (48.5)
	Taking photos	112 (54.9)

*multiple response

The daytime sleepiness scale scores showed a median value of 10 (IQR=7.25-13), 45.6% (n=93) participants were found to have excessive daytime sleepiness. The depression scores on the PHQ-9 scale showed a mean value of 8.15 (±4.72). 53(26%) had moderate levels of depression, 15(7.4%) had moderately severe depression and 5(2.5%) were having severe levels of depression. (Fig 1)

Factors associated with smartphone addiction among the study participants

Multivariable logistic regression analysis showed that increasing age (AOR=1.23, 95%CI=1.12-2.21), male gender (AOR=2.12, 95% CI=1.36-3.45) and duration of smart phone usage >6 hours per day (AOR=1.92, 95%CI=1.23-2.45) were significantly associated with the presence of smartphone addiction among the study participants. The non-significant Hosmer-Lemeshow test (p-value>0.05) indicated goodness of fit of the multivariable model, while 26-38% of the variance of the outcome variable could be explained by this multivariable model. (Table 3)

Correlation between smartphone addiction with daytime sleepiness and depression scores

Spearman's correlation coefficient (ρ) was estimated to find the relationship of smartphone addiction with daytime sleepiness and depression scores. Smartphone addiction and sleepiness scores showed moderate positive correlation between them which was found to be statistically significant (ρ=0.5, p-value <0.001) (Fig 2). However, there was mild significant positive correlation between smartphone addiction and depression scores (ρ=0.23, p-value=0.001) (Fig 3).

DISCUSSION

Medical students are the future backbone of the healthcare infrastructure of any country, thus care of their

TABLE 2. Responses of the study participants on the SAS-SV questionnaire (n=204).

Statements	Strongly disagree N (%)	Disagree N (%)	Weakly disagree N (%)	Weakly agree N (%)	Agree N (%)	Strongly agree N (%)
I have missed a planned work due to smartphone use	33 (16.2)	44 (21.6)	20 (9.8)	50 (24.5)	38 (18.6)	19 (9.3)
I am having a hard time concentrating in class, while doing assignments, or while working due to smartphone use	27 (13.2)	61 (29.9)	37 (18.1)	30 (14.7)	28 (13.7)	21 (10.3)
Feeling pain in the wrists or at the back of the neck while using a smartphone	55 (27.0)	68 (33.3)	25 (12.3)	29 (14.2)	20 (9.8)	7 (3.4)
I won't be able to stand not having a smartphone	48 (23.5)	57 (27.9)	25 (12.3)	23 (11.3)	32 (15.7)	19 (9.3)
I feel impatient and fretful when I am not holding my smartphone	66 (32.4)	69 (33.8)	27 (13.2)	26 (12.7)	10 (4.9)	6 (2.9)
I have my smartphone in my mind even when I am not using it	73 (35.8)	64 (31.4)	39 (19.1)	20 (9.8)	4 (2.0)	4 (2.0)
I will never give up using my smartphone even when my daily life is already greatly affected by it.	66 (32.4)	64 (31.4)	26 (12.7)	23 (11.3)	19 (9.3)	6 (2.9)
I constantly check my smartphone so as not to miss conversations between other people on Twitter or Facebook	66 (32.4)	56 (27.5)	26 (12.7)	22 (10.8)	20 (9.8)	14 (6.9)
I use my smartphone longer than I had intended	19 (9.3)	35 (17.2)	14 (6.9)	42 (20.6)	64 (31.4)	30 (14.7)
The people around me tell me that I use my smartphone too much.	36 (17.6)	58 (28.4)	30 (14.7)	28 (13.7	32 (15.7)	20 (9.8)

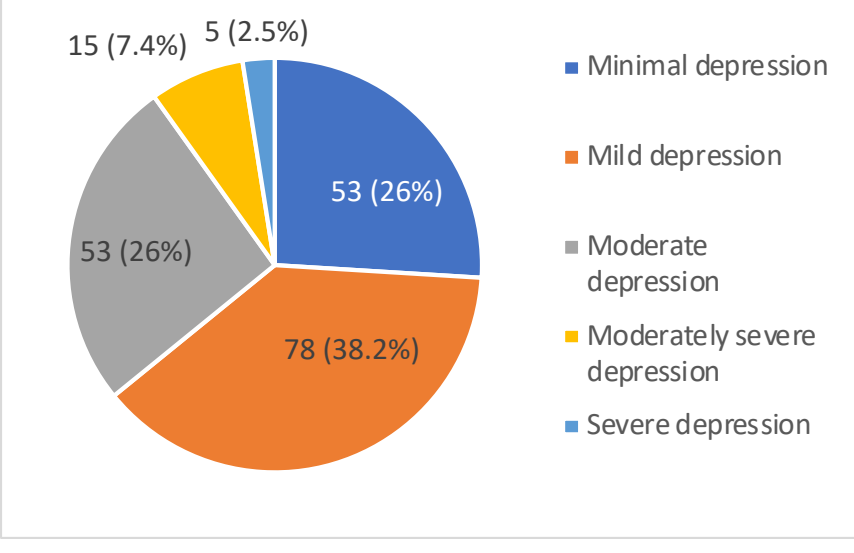
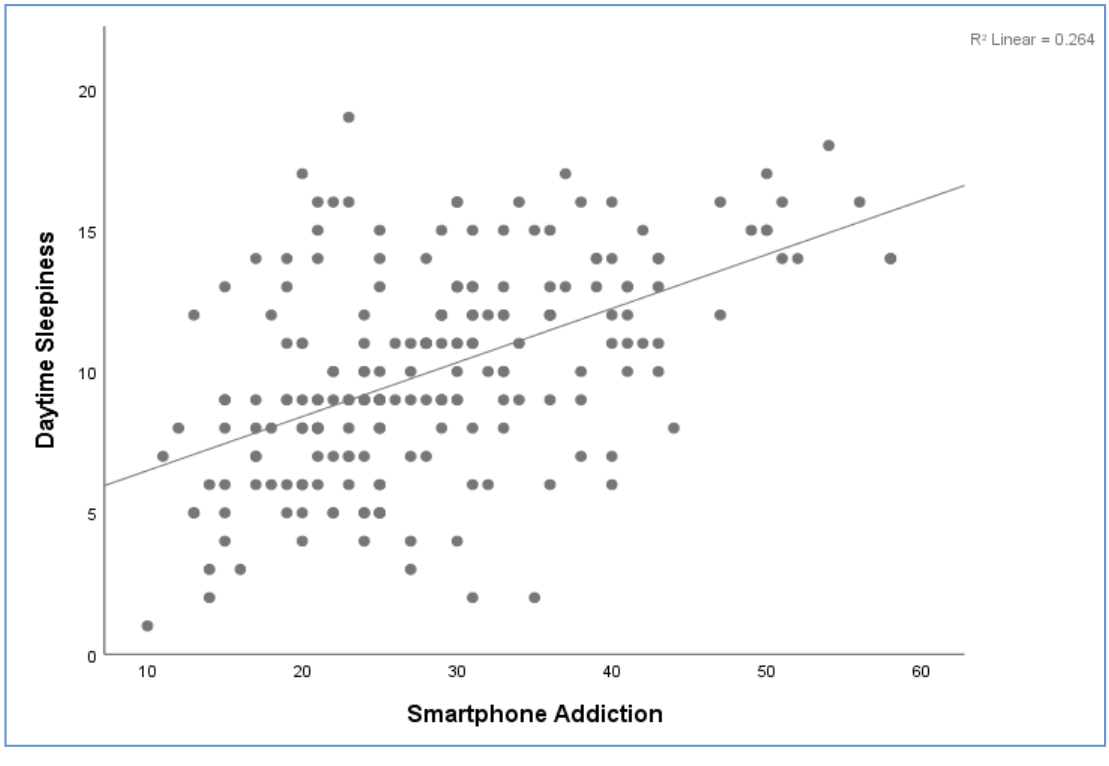


Fig 1. Pie Diagram showing pattern of depression among the study participants (n=204).

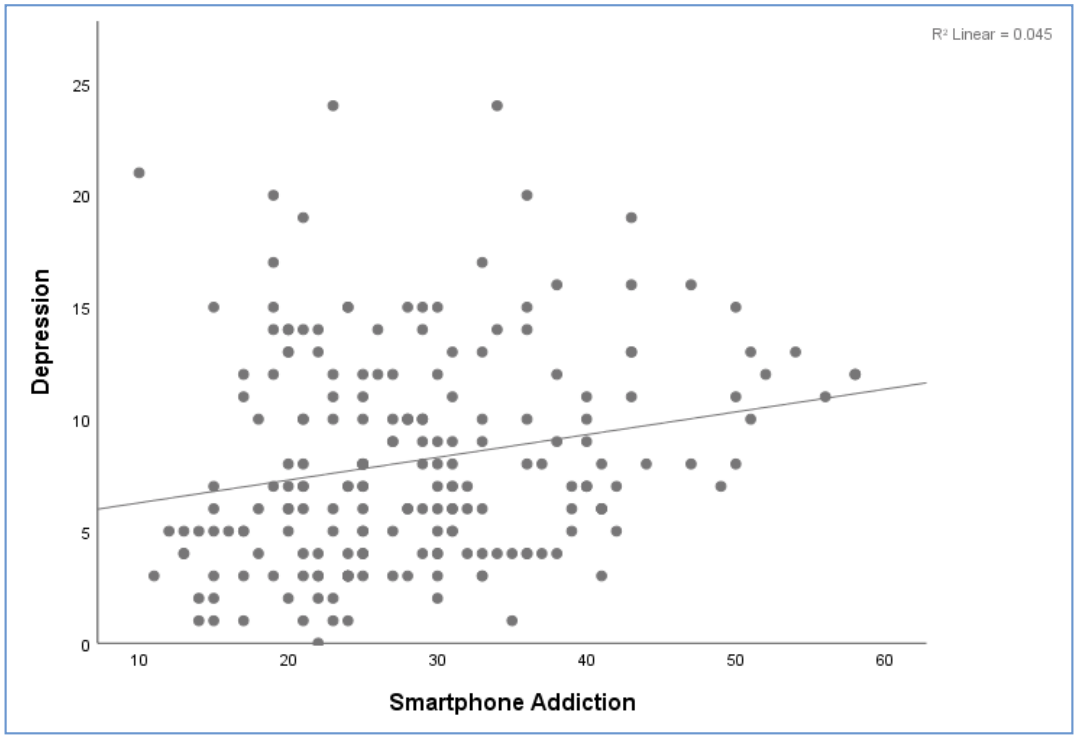
TABLE 3. Factors associated with presence of smartphone addiction among the study participants: Univariate and multivariable binary logistic regression analysis (n=204).

Variables	Categories	OR (95% CI)	P-value	AOR (95% CI)	P-value
Increasing age*		1.46 (1.23-2.45)	<0.001	1.23 (1.12-2.21)	0.012
Gender	Male	2.63 (1.95-4.23)	<0.001	2.12 (1.36-3.45)	0.023
	Female	1 (Ref)		1 (Ref)	
Residence	Urban	1.23 (0.88-1.63)	0.231	--	--
	Rural	1(Ref)		--	--
Socio-economic status (as per modified BG Prasad scale 2022)	Class I	2.12 (1.21-3.14)	0.005	1.82 (0.92-2.41)	0.091
	Below Class I	1 (Ref)		1 (Ref)	
Duration of smartphone usage in years	≤5 years	2.1 (1.32-2.82)	0.001	1.56 (0.8-2.11)	0.102
	> 5 years	1 (Ref)		1 (Ref)	
Hours of smartphone usage per day	≤6 hours	1 (Ref)	<0.001	1 (Ref)	0.012
	> 6 hours	2.65 (1.92-3.65)		1.92 (1.23-2.45)	

*continuous variables
OR=Odds Ratio, CI=Confidence interval
Hosmer-Lemeshow test of significance = 0.12
Cox and Snell R^2=0.26 and Nagelkerke's R^2=0.38



ρ=0.5, p-value<0.001
Fig 2. Scatter plot showing correlation between smartphone addiction and daytime sleepiness among the study participants [n=204].



ρ=0.233, p-value=0.001

Fig 3. Scatter plot showing relationship between smartphone addiction and depression among the study participants [n=204].

mental health and wellbeing is of utmost importance. This study made a unique attempt in the state of West Bengal by determining the levels of smartphone addiction, daytime sleepiness, and depression among undergraduate medical students of a selected medical college in Kolkata. Moreover, a novel aspect was explored by determining the relationship between smartphone addiction with daytime sleepiness and depression among the study participants. Almost one-third of participants were found to have smartphone addiction which is quite alarming and shows the increasing levels of dependency on internet, technology, and artificial intelligence in the current scenario.

A study was conducted in a medical college of Durgapur, West Bengal by Choudhury S et al where 19.4% of males and 11.1% of females were found to be addicted to smartphones.[23] Another study among nursing students in Nadia, West Bengal by Ghosh T et al found approximately 50% of their participants having smartphone addiction.[24] A study conducted by Senthuraman AR et al among undergraduate students pursuing medical education in Andaman and Nicobar Islands found an alarming proportion of 85.4% of students to be addicted to their smartphones.[25] However, in contrast, the current study utilized the validated SAS-SV questionnaire for assessing addiction to smartphones and determined 29.4% of medical students having smartphone addiction.

Age was found to be a significant predictor of smartphone addiction as older participants were found to have high risk of smartphone addiction as compared to their younger counterparts. Age and year of academic year of medical curriculum were found to be multicollinear, hence academic year was excluded from the multivariable regression model to reduce confounding. Students in finals years of the MBBS curriculum generally comprise the older age group of the participants There is increased burden of subjects in the final years which often requires increased amount of studying not only from textbooks but also from the internet. Moreover, students in final years and internship periods often concentrate on preparing for postgraduate entrance examinations which often compels them to spend large hours on their smartphones. This predisposes them to develop dependency on these devices. However, discordant findings were found from a study conducted in Jammu and Kashmir, India by Nowreen N et al where younger participants were found to have increasing smartphone addiction.[4]

Male gender emerged as an important factor associated with the presence of smartphone addiction among the study participants. Concordant findings were found in a study conducted by Chatterjee S et al among medical students of a north Indian medical college where approximately 46% males were found to be addicted to their smartphones in comparison to 33% of females.[26]

Another predictor for the presence of smartphone addiction was also elicited in the current study in the form of hours of smartphone usage per day. The study conducted by Choudhury S et al in West Bengal also demonstrated total hours of smartphone usage to be associated with presence of smartphone dependence among medical students.[23]

Depression among medical students has gained increasing importance nowadays which often gets precipitated by the burden of the vast medical curriculum. A systematic review and metanalysis by Dutta G et al demonstrated the pooled prevalence of depression among undergraduate medical students in India to be 50%.[27] However, the current study detected approximately 74% of the participants suffering from some amount of depression ranging from mild to severe levels. Similar findings were reported in a study conducted by Santander-Hernanadez FM et al in Peru among medical students during the COVID-19 pandemic where 78.4% students were suffering from depression. They also demonstrated addictive smartphone usage to be significantly associated with the presence of depressive symptoms among medical students.[28] Concordance was also detected in the current study as smartphone addiction was found to have positive relationship with the presence of depression among the study participants.

Smartphone addiction often compels students to spend long hours on their devices due to which they often remain awake for long hours during night-time. This hampers their sleep quality which often precipitates lethargy and sleepiness during daytime working hours. The current study also assessed for the presence of excessive daytime sleepiness among the study participants by which 45.6% were found to have excessive daytime sleepiness. A study conducted by Dagnew B et al among medical students in Ethiopia showed slightly less proportion (31%) of excessive daytime sleepiness among the participants as compared to the current study.[20] Mild positive correlation between smartphone addiction and daytime sleepiness was found in the current study. The study conducted in Jammu and Kashmir, India by Nowreen N et al showed concordant findings where positive correlation was found between smartphone addiction and sleep quality.[4]

Limitations

Since this study was cross-sectional in nature, establishment of causality between the different factors and the outcome variable could not be achieved. Moreover, as this was a single institution-based study, the results might not generalizable to the community, thus compromising the external validity of the results. Some of the responses were recall-based, hence bias might be possible.

Conclusion and recommendations

A significant proportion of participants were found to have smartphone addiction which nowadays has become an important public health issue. Sleep quality often gets hampered leading to excessive lethargy and sleepiness during working hours. Nearly half of the participants were found to be suffering from excessive daytime sleepiness which is quite alarming. Thus, medical students need to be motivated and counselled regarding the adverse effects of smartphone over usage. Dissemination of appropriate information through faculty and peer groups will also help in the long run. Peer group support systems can help in reducing the burden of depression and addictive smartphone usage which in turn will help in promoting good mental health and wellbeing among them. Further research through qualitative exploration in multicentric settings is needed on this domain which can help in improve the mental health and well being of the future Indian medical fraternity.

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None

Conflict of interest

The authors declare no conflict of interests

Data availability statement

All the data supporting the results reported in the current study are available upon reasonable request to the corresponding author.

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Clinical Efficacy of *Andrographis paniculata* Extracted Scrub Compared With 4% Chlorhexidine Scrub in Burn Wounds: A Prospective Randomized Controlled Trial

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ABSTRACT

Objective: The primary objective of this study is to compare the healing rate between AP soap and 4% Chlorhexidine solution in superficial second-degree burn wounds. The secondary objectives include the analgesic effect and moisturization of these two products.

Materials and Methods: Data was collected between 2019 and 2021. Patients aged 18 years and above, with superficial second-degree burns including at least 20% of TBSA, and admitted to the Burn Unit within 24 hours of injury were included. They were randomly assigned to two groups: *Andrographis paniculata* with Perilla oil liquid soap group (AP group) and 4% Chlorhexidine group (control group). The measurements included percentage of epithelialization, pain score during wound cleansing, itching score after wound cleansing, and dry skin specified symptoms. All patients received standard care for burn wound treatment.

Results: A total enrollment was 23 patients in this study (12 in the AP group and 11 in the control group). The median age was 38.5 years. There were no statistically significant differences in age, %TBSA, and initial wound size between both groups ($p > 0.05$). Although the healing time was similar in both groups, (18.5 vs. 20.1, p=0.347), the AP group had a significantly lower pain score than the control group (4.7 vs. 5.4, p=0.020). Moreover, the AP group demonstrated significant improvements in itching score and SRRC score at 14 days compared to the control group (5.1 vs. 6.0, p 0.039 and 1.08 vs. 1.55, p 0.020, respectively). There were no adverse effects during this study.

Conclusion: Patients treated with *Andrographis paniculata* with Perilla oil liquid soap experienced less pain and better moisturization compared to those treated with the standard 4% chlorhexidine solution, while achieving a comparable healing rate. A future large-scale prospective trial is recommended.

Keywords: *Andrographis paniculata*; wound cleansing; second degree burn (Siriraj Med J 2023; 75: 809-816)

INTRODUCTION

Superficial second-degree burn wounds primarily affect the epidermis and superficial dermis.[1] The dermal layer has the ability to produce epithelial cells in order to replace the lost ones, leading to complete epithelialization of wounds within 3 weeks[2] without any surgical intervention. The primary objective of burn wound care is to achieve rapid wound closure. The treatment involves wound cleansing for optimal wound bed preparation and application of temporary dressings, and infection prevention to create

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a protective environment that facilitates the normal wound healing process.[3-5]

Wound bed preparation plays a crucial role in wound management as it enables assessment and treatment of patients with wounds. Wound cleansing is an integral component of wound bed preparation as it leads to an optimized wound environment by removing debris, reducing bacterial load, preventing biofilm activity and maintaining wound moisturization.[6] The standard cleansing treatment for burn wounds has been the use of 4% Chlorhexidine solution. It has a wide range spectrum of anti-bacterial effects and serves as a prophylactic agent against infections of burn wounds - serious problem that can lead to conversion of partial-thickness to full-thickness burn wounds. Literature recommends the use of Chlorhexidine to maintain wound disinfection[6], and two publications suggesting its use only for superficial burns wounds.[7,8] However, the disadvantages of Chlorhexidine solution include pain during wound cleansing and tissue irritation in individuals with dry skin that can potentially delay the wound healing process.[9,10]

Andrographis paniculata known as Fa-Ta-Lai-Jone, is a medicinal plant listed on the World Health Organization's (WHO) 2002 catalogue.[11] It has anti-oxidant properties[12] and exhibits antimicrobial and anti-inflammatory effects[13,14] Phytochemical analysis of extracted *A. paniculata* has revealed that it has several bioactive molecules, for example, andrographolides and flavonoids.[15] These phytochemical constituents may contribute to the plant's wound-healing activity. Andrographolide - the main compound of *Andrographis paniculata* has been reported to decrease inflammation[14,16] caused by dimethyl benzene, histamine, and adrenaline.[17,18] It also demonstrates significant antibacterial activity in its extracted solution.[19,20] Flavonoids, which are known for their antimicrobial properties, have been found to promote the wound-healing process by enhancing wound contraction and epithelialization.[21]

Perilla oil has been shown to suppress production of chemical mediators involved in allergic pathways and inflammatory responses. Essential fatty acids present in Perilla oil offer a wide range of benefits, including anti-inflammatory, antimicrobial, and anticancer properties. In vivo, polyunsaturated omega-3 fatty acids are primarily metabolized into docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are incorporated into cell membranes throughout the body. These specific omega-3 fatty acid metabolites play a role in preventing abnormal clotting, reducing inflammation, relaxing blood vessels, and improving ventilatory parameters.[22]

Therefore, *Andrographis paniculata* with Perilla oil liquid soap (AP soap) is a novel product used for wound cleansing and moisturizer, with potential pain-relieving properties. However, there is a lack of published data regarding its effectiveness in treating burn patients. The objective of this study is to assess the clinical efficacy of AP soap in promoting the healing of superficial second-degree burns, in comparison to the standard cleansing, 4% Chlorhexidine solution.

MATERIALS AND METHODS

A prospective, randomized controlled trial was designed, involving 23 patients who were admitted to the Burn unit at Siriraj Hospital between June 2019 and February 2021. Ethical approval for this study was obtained from the Siriraj Institutional Ethical Review Board (SIRB) (COA no. Si 684/2019). Written consent was obtained from all participating patients after providing them with detailed information. The inclusion criteria was patients between 18 and 60 years of age, presenting with superficial second degree burns within 24 hours of sustaining the injury. The burn wounds covered areas at least 20% of the total body surface area (TBSA). Patients who have underlying medical conditions that could affect the wound healing process such as diabetes mellitus, end-stage renal disease, post-radiation therapy, immunosuppressive drug use, or immunocompromised diseases were excluded, as were pregnant or lactating individuals and those with known hypersensitivity to herbal products. The patients were randomly assigned to one of two treatment groups: the Andrographis and Perilla oil liquid soap (AP soap) group (12 patients) and 4% Chlorhexidine-treated group (11 patients). Demographic data including gender, age, causes of burn, %TBSA, and initial wound area were collected. All patients received initial treatment and underwent wound examination by experienced burn surgeons and nurses who were blinded to the assigned treatment group. The patients were treated following standard burn wound care treatment protocol and wound cleansing procedure as flow chart described in Fig 1 below.

1. Wound bed preparation

The wounds were cleansed using sterile normal saline solution and wrapped to remove excessive discharge from the wound.

2. Wound assessment

The wounds were evaluated. Unfavorable clinical symptoms, complications, or side effects were reported to burn surgeon. A nurse, who was not part of the treatment team, obtained the wound size by placing a sterile transparent

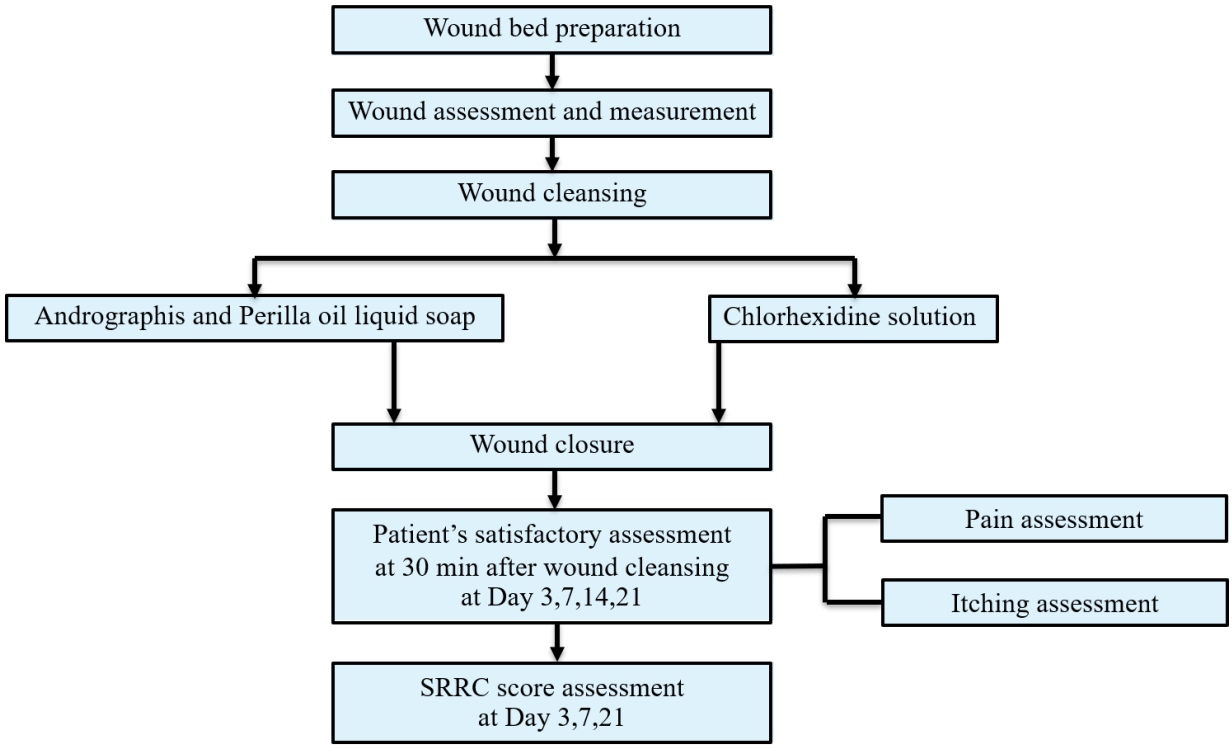


Fig 1. Study protocol.

film on the wound base and measuring its dimensions using a 0.4 mm pinpoint marker. The wound size was recorded. Wound healing was quantified as a percentage of epithelialization, following a previously established protocol[23] using the formula below

$$\%\text{Epithelialization} = \frac{(\textit{Area of initial wound} - \textit{Area of wound at examination date})}{\textit{Area of initial wound}} \times 100$$

3. Wound cleansing

Wound cleansing was performed using either AP soap or a 4% Chlorhexidine solution, based on the assigned treatment group.

4. Wound closure

Sterile gauze was applied to the wound and secured with adhesive tape as per the standard treatment.

5. Pain assessment

Patients were asked to rate their pain levels at thirty minutes after wound dressing using the "Pain Numeric Rating Scale 0-10" on Days 3, 7, 14, 21 of treatment.

6. Itching assessment

Patients were asked to rate their itching score at 30 minutes after wound dressing using the "Itching Visual Analog Scale 0-10" on Days 3, 7, 14, 21 of treatment.

7. SRRC score assessment

Experienced burn surgeons and nurses evaluated the specified symptoms of dry skin at Days 3, 7, 14 of the treatment.

Critically ill-patient treatments, such as volume resuscitation, nutrition, and analgesia were same administered in both groups following standard approach.

The primary outcome of this study was to compare the treatment outcomes of *Andrographis paniculata* extract scrub and 4% Chlorehexidine scrub in the healing of superficial second-degree burn wounds, specifically in terms of healing time and the percentage of gross epithelialization. The secondary outcomes were as follows:

- To compare pain between the two treatments: as rated by patients using the "Pain Numeric Rating Scale 0-10" (scaling on a straight line from 0 to 10 where 0 = no pain, 5 = moderate pain, and 10 = worst possible pain).
- To compare wound moisturization after wound cleansing, assessed using the "Itching Visual Analog Scale 0-10" (scaling on a straight line from 0 to 10 where 0 = no itching; 1-3 = mild itching, 4-6 = moderate itching, and 7-10 = severe itching) and SRRC rating score (assess dry skin-specific symptoms such as scaling, roughness, redness and cracks after wound cleansing).

Statistical analysis

Statistical data analysis was conducted using SPSS version 18.0. Student's t-test was used to assess the difference in means, while the $\chi 2$ test was utilized to determine relationships between parameters. All p values were two-sided. Statistically significant was considered as p values less than 0.05. Kaplan-Meier analysis was performed to compare the healing time between two groups.

RESULTS

A total of twenty-three patients were included in this study, with random allocation into two groups: the AP group consisting of 12 patients, and the control group comprising 11 patients. The median age of all patients was 38.5 years. In the AP group, 66.7% of patients were male, while in the control group, the percentage was 63.6%. Scald burns were the predominant cause in both groups, accounting for 75% in the AP group and 63% in the control group. The mean total body surface area (TBSA) affected was 33% and 35% in the AP and control groups respectively. The mean initial wound size was 171 and 157 square meters in the AP and control groups, respectively. There were no statistically significant differences in sex, age, cause of burn, %TBSA, and initial wound area between the AP and control groups ($p > 0.05$). The demographic data is shown in Table 1 below.

The mean healing time in the AP soap-treated group was 18.5 days, while it was 20.1 days in the control group. There was no statistically significant difference in healing time between these two groups (p 0.347). All patients in this study achieved complete epithelialization of their wounds within 4 weeks after injury. The percentage of gross wound epithelialization on day 14 was statistically significantly higher in the AP soap-treated group compared to the control group, with values of 87% and 82%, respectively (p-value of 0.027). On day 21, the percentage of gross wound epithelialization was 97.8% in the AP soap-treated group and 96.77% in the control group, with a p-value of 0.58. Tables 2 provides details on the percentage of epithelialization. Kaplan-Meier analysis demonstrated no statistically significant difference in wound epithelialization between the two groups as shown in Fig 2. The healing time after treatment was 18 and 20 days, respectively, with no statistically significant difference. Hospital stay did not significantly differ between the two groups (46.7 and 50.5 days, p-value = 0.64). There was no instance of burn wound infection among the patients.

TABLE 1. Demographic data.

	AP soap group (n=12)	Control group (n=11)	P-value
Male patient (%)	8 (66.7)	7 (63.6)	0.879
Age (years ± SD)	40.33 ± 14.69	36.55 ± 12.93	0.520
Cause of burn			0.554
Frame burn (%)	3 (25.0)	4 (36.4)	
Scald burn (%)	9 (75.0)	7 (63.6)	
%TBSA (percent ± SD)	33.8±14.3	35.6±15.2	0.762
Initial wound area (cm^2± SD)	171.0 ± 29.6	157.2 ± 36.7	0.331

TABLE 2. Percent epithelialization at days 3, 7, 14, 21 after treatment, healing time, and length of stay.

	AP soap group	Control group	P-value
% Epithelialization			
Day 3	3.68±1.42	3.05±1.10	0.256
Day 7	28.65±4.69	26.75±5.06	0.361
Day 14	87.39±4.65	82.55±5.14	0.027
Day 21	97.80±4.06	96.77±4.73	0.581
Healing time	18.5 ± 4.0	20.1 ± 3.9	0.347
Length of stay (Days)	46.7±18.8	50.5±20.8	0.643

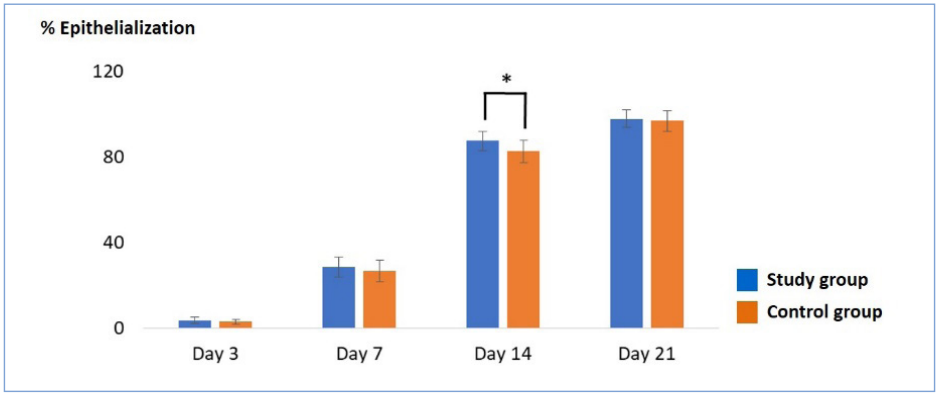


Fig 2. Percent Epithelialization on days 3, 7, 14, 21 after treatment

Pain assessment during wound cleansing

The mean of pain analog scores assessed between the AP soap-treated group and the control group during the initial treatment period (days 1-3) showed no significant differences. However, the pain score was significantly lower in the AP soap-treated group at 7 days (4.7 vs. 5.4, p=0.020), and 14 days (2.6 vs. 3.5, p=0.011) after treatment, as shown in Table 3.

Wound moisture after wound cleansing

The AP soap-treated group demonstrated a significant improvement in itching score, indicating enhanced wound moisturization at 14 days compared to the control group (5.1 vs. 6.0, p=0.039). Although the SRRC score could not be evaluated during the first 3 days after treatment due to excessive wound discharge, the, the AP soap group exhibited a significantly lower SRRC score than the control group at 14 days post-treatment treatment (1.08 vs. 1.55, p=0.020). Table 3 presents the pain score, itching score, and SRRC score.

Cases demonstration

Patients received standard care for burn wound treatment, with the exception of the cleansing process which depended on the assigned treatment group. The procedure for wound cleansing using AP soap is demonstrated in Fig 3. An example of wound healing progression using AP soap is shown in Fig 4.

TABLE 3. Percent epithelialization at days 3, 7, 14, 21 after treatment, healing time, and length of stay.

	AP soap group	Control group	P-value
Pain score			
Day 0	6.0±1.1	5.9±1.4	0.864
Day 3	6.0±0.9	6.0±1.1	1.00
Day 7	4.7±0.5	5.4±0.8	0.020
Day 14	2.6±0.7	3.5±0.8	0.011
Itching score			
Day 0	2.9±1.0	3.1±1.1	0.850
Day 3	3.1±0.9	3.3±1.1	0.655
Day 7	4.5±0.7	4.8±0.9	0.337
Day 14	5.1±1.0	6.0±1.0	0.039
SRRC score			
Day 0	N/A	N/A	N/A
Day 3	N/A	N/A	N/A
Day 7	1.33±0.49	1.45±0.52	0.573
Day 14	1.08±0.29	1.55±0.52	0.020

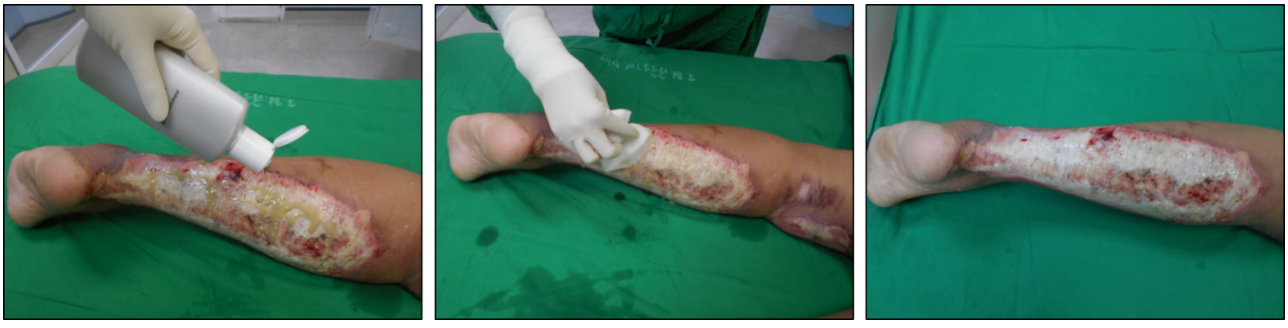
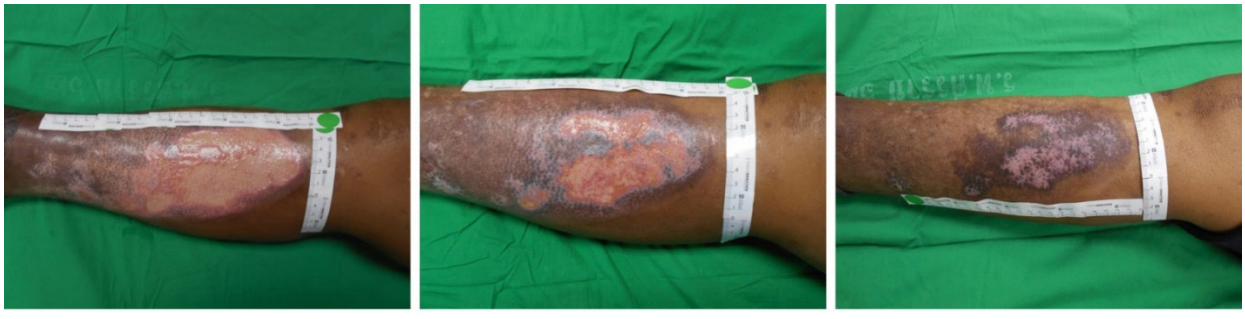


Fig 3. The application of AP-soap started with rinsing AP soap. Wet gauze was used for scrubbing and then the wound was cleaned.



A. Day3 B. Day7 C. Day14

Fig 4. Example of an AP soap treatment group patient.

DISCUSSION

The use of Chlorhexidine solution as a standard topical wound cleansing treatment for partial thickness burns has been established for decades. However, there are some disadvantages such as wound base tissue irritation and pain during wound cleansing.[10,24] This study aimed to evaluate the clinical efficacy of *Andrographis paniculata* and Perilla oil liquid soap (AP soap) in the healing of superficial second-degree burn wounds. The results demonstrated comparable wound healing outcomes with reduced pain during wound cleansing, and more moisturization compared to the standard cleansing Chlorhexidine solution. Thus, AP soap appeared to address the disadvantages associated with Chlorhexidine solution. *Al-Bayaty et al*, reported the effects of topically applied *A. paniculata* leaf extract on wound healing in rat models. The macroscopic examination revealed the significantly faster wound healing rate in rats with extracted *A. paniculata* dressing compared to placebo.[25] This study showed no significant differences in time required to complete gross epithelialization, representing the healing time of burn wounds, between the AP soap-treated group and 4% Chlorhexidine-treated group (control group), which were 18.5 days and 20.1 days, respectively (p=0.347). However, on day 14 of treatment, the epithelialization rate was higher, suggesting that AP soap may accelerate the wound healing process. No significant difference was found on day 21, as wounds tended to heal naturally, and the small sample size may have contributed to the lack of statistical significance. Significant differences may be identified in a randomized controlled trials with larger number of enrolled patients. This study also reported no significant differences in the length of stay between the groups (AP soap 46.7 ± 18.8 vs. Control group 50.5 ± 20.8, p= 0.643). No adverse side effects of AP soap were observed in this study.

Pain management remains a challenging aspect in burn patient care. Recurrent pain exposures in burn patients can lead to secondary hyperalgesia and contribute to chronic pain issues, significantly affecting quality of life.[26] Wound cleansing, in particular, is a procedure that can produce severe pain, as patients often have to endure it more frequently compared to other treatments. Previous studies have explored several of methods and wound cleansing products to address this problem. Although achieving completely pain-free wound cleansing products remains elusive, advancements in dressing material have shown promise in reducing pain and discomfort during wound dressing changes. Our study demonstrated that pain during wound cleansing was significantly lower in the AP soap treated group compared to the 4% Chlorhexidine–treated group at 7 days and 14 days after treatment, during the period when wounds had not fully epithelialized. This finding was supported by

patient experiences and the numeric pain score ratings, indicating that AP soap was less painful and provided a more comfortable experienced for patients.

For optimal wound healing, a moist environment is known to facilitate faster and less painful hearing compared to a dry environment, which can lead to cell dehydration and death. This often results in the formation of a scab or crust over the wound, hindering healing. By maintaining proper hydration with a moisture-retentive dressing, migration of epidermal cells is enhanced, encouraging epithelialization.[9] The itching visual analog scale, as suggested by *Reich, et al*[27] is an appropriate parameter for evaluating skin conditions. In this study, the itching visual analog scale demonstrated significantly lower scores in the AP soap-treated group compared to the control group at 14 days after treatment (5.1 vs. 6.0, p=0.039), indicating improved moisturization with AP soap.

The specified symptom sum score (SRRC) system, acknowledged by the European group on Efficacy Measurement of Cosmetics and other topical products (EEMCO), assesses skin-specific symptoms such as scaling, roughness, redness, and cracks or SRRC; to evaluate the effects of topical products.[28,29] In this study, statistically significant improvements in the SRRC rating score were observed in the AP soap-treated group at 14 days after treatment (p-value 0.020).

This research was conducted in randomized controlled trial design to reduce bias. However, the small sample size limited the ability to detect significant differences in certain measurements. These findings highlight the need for well-designed studies to further investigate the efficacy of the *Andrographis paniculata* and Perilla oil liquid soap as a wound cleansing agent for partial thickness burn wounds. A future large prospective study is warranted.

CONCLUSION

Andrographis paniculata and Perilla oil liquid soap, a novel natural product for epithelialization of wounds demonstrated comparable wound healing rates to chlorhexidine solution, with the added benefits of reduced pain and better moisturization.

Declaration of conflicting interests

The author(s) declare no potential conflicts of interest according to the research, authorship, and/or publication of this article.

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Hepatocellular Carcinoma's Characteristics in an Endemic Country: A Closer Examination of Tumor Grade and Microvascular Invasion

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ABSTRACT

Objective: Although histological grade and microvascular invasion are known predictors for patient survival and recurrence in hepatocellular carcinoma (HCC), their relationship with various clinical and histomorphological features of HCC remains unclear.

Materials and Methods: Medical records were retrieved from 61 patients who were diagnosed with HCC from 2008-2018. Clinical and histomorphological variables that were hypothesized to be associated with histological grade and microvascular invasion were analyzed statistically using the Chi-square test or the Fisher's exact test as alternatives. Multivariate analysis was performed with logistic regression model.

Results: The majority of the patients had well to moderately-differentiated HCC (67.2%) with some of them presenting microvascular invasion (57.4%). Alpha-fetoprotein level (AFP) ≥100 ng/ml (p=0.036), tumor size >7cm (p=0.031) and mitotic index ≥5 per 10 high power field (p=0.009) were significantly correlated with poorly-differentiated HCC. Mitotic Index ≥5 per 10 high power field was an independent factor for poorly differentiated HCC. Meanwhile BCLC stage B and mitotic index were also an independent factor for the presence of microvascular invasion.

Conclusion: Larger tumor size and higher mitotic index was significantly correlated and independent factors for poorly differentiated HCC and microvascular invasion. In biopsy specimens for which the microvascular invasion is difficult to assess, histological grade, tumor size and mitotic index may be beneficial to depict the prognosis of patients with HCC.

Keywords: Hepatocellular carcinoma; tumor grade; microvascular invasion; Indonesia (Siriraj Med J 2023; 75: 817-826)

INTRODUCTION

Hepatocellular carcinoma (HCC) is the second most frequent cancer in Asia and the second leading cause of cancer-related deaths in East Asia and Sub-Saharan Africa. Moreover, China, Southeast Asia, Japan and Sub-Saharan Africa are areas with a high incidence of HCC with an incidence >20/100,000.[1,2]

The current HCC diagnostic approach relies on radiologic imaging and the use of histopathology biopsy is limited to specific cases.[1,3] Surveillance through ultrasonography (US) examination and alpha-fetoprotein (AFP) measurement should be carried out every 6 months in individuals with a high risk of HCC to achieve early diagnosis.[4] When nodules are found on the liver US with increased AFP level, a computed tomography (CT) scan or three-phase magnetic resonance imaging (MRI) should be performed. Typical features of HCC on CT scan or three-phase MRI are sufficient for diagnosis of

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HCC, otherwise, tumor biopsy should be carried out for diagnostic purposes.[4]

Although various therapeutic modalities are available, HCC is generally diagnosed at an advanced stage when curative therapy is not possible. Therefore, at present, the prognosis of HCC remains poor.[5] Histopathological examination is involved in determining therapy and prognosis through the assessment of histological parameters which cannot be replaced by radiologic examinations.[3] The present study aimed to provide data on the clinical and histomorphology characteristics of HCC and clarify how these relate to important prognostic factors of HCC, particularly histologic grade and microvascular invasion.

MATERIALS AND METHODS

Medical records of 61 patients were retrieved from 2008-2018 archives for consecutive evaluation. Inclusion criteria were all resection cases with a diagnosis of HCC in the Department of Anatomic Pathology, FKUI/RSCM. Exclusion criteria were biopsy cases, cases with unrepresentative slide and cases with a final diagnosis of non-HCC. The clinical variables assessed were sex, age, hepatitis infection, AFP level, cirrhosis status and Barcelona Clinic Liver Cancer (BCLC) staging. Triphasic CT and additional MRI with contrast for patients with inconclusive CT were performed on all patients and yielded inconclusive radiologic results. Hepatitis infection involves positive serological markers for hepatitis B or C virus (HBV and HCV, respectively) before or during HCC diagnosis. AFP levels were measured at the time of HCC diagnosis. Cirrhosis status was determined radiologically with a US Fibroscan from Echosans and confirmed through histopathological analysis. The BCLC criteria classify clinical stages as 0, A, B, and C.[6]

Two independent pathologists evaluated the pathology reports and histologic specimens of all patients. The histomorphology variables assessed were tumor size, histological pattern, mitotic index, special type carcinomas, histological grade and microvascular invasion. Tumor size was defined as the largest dimension from resection or radiologic findings and was categorized based on the Milan criteria.[7] The histological patterns that were identified included macrotrabecular, microtrabecular, solid and pseudoglandular. Mitotic index was categorized as low or high and defined as <5 per 10 high power field (HPF) and ≥5 per 10 HPF respectively according to a study by Ha *et al.*[8] Special type carcinomas that were identified included fibrolamellar, scirrhous, undifferentiated carcinoma, lymphoepithelial, sarcomatous, steatohepatitic and macrotrabecular massive. HCC was categorized into good-to-moderate or poor differentiation based on histological grade. The cells of HCC with well-to-moderate differentiation display mildly to moderately atypical nuclei, often with nucleoli, and copious eosinophilic to basophilic cytoplasm. Meanwhile, the cells of HCC with poor differentiation were anaplastic with pleomorphic and atypical nuclei, and sparse basophilic cytoplasm.[9] Malignant cells in peritumoral blood vessels indicate microvascular invasion.

The Statistical Package for Social Sciences software (version 25.0; IBM Corp.) was used for analysis. Variables hypothesized to be associated with histological grade or microvascular invasion were analyzed with the Chi-square test or its alternatives Fisher's exact test. Multivariate analysis was performed with logistic regression to draw significant factors associated with features of HCC, the variables were selected from bivariate analysis with p-value ≤0.25.

The Ethics Committee of the Faculty of Medicine Universitas Indonesia and Dr. Cipto Mangunkusumo Hospital have granted ethical approval for this study (protocol number 23-01-0066) under the decision number KET-84/UN2.F1/ETIK/PPM.00.02/2023.

RESULTS

Data from 61 patients with HCC were retrieved. Of these, 80% were male with a mean age of 51.8 years ± 15.643, 20% of them were <40 years old and the youngest patient was 17 years old. Most patients had hepatitis infection. Most patients had stage B HCC according to the BCLC staging system (91.8%). Tumor size ranged from 2.5-25 cm. A similar proportion of cirrhotic and non-cirrhotic patients was found. The median AFP level was 113.5 ng/ml. The mean mitosis count was 6.72 over 10 HPF. The most common histological pattern was the microtrabecular pattern (72.1%). Only 5 patients (8.1%) were found to have steatohepatitic HCC. Most patients had well to moderately-differentiated HCC (67.2%). The microvascular invasion was observed in most cases (57.4%). Clinical and histological characteristics of HCC can be seen in Table 1. Representative microscopic images of the HCC found in the current patients can be seen in Fig 1.

Statistical tests examined the association between sex, age, AFP level, hepatitis infection, BCLC staging, cirrhosis status, tumor size and mitotic index with histological grade, microvascular invasion, and well-differentiated with no microvascular invasion. There was a significant association between AFP level, tumor size and mitotic index with histological grade. AFP level ≥100 ng/ml (p=0.036), tumor size >7cm (p=0.031) and mitotic index ≥5 per 10 HPF (p=0.009) were significantly

TABLE 1. Clinical and histological characteristics of HCC (n=61).

Characteristics	n (%)
Sex	
Male	49 (80.3)
Female	12 (19.7)
Age in years, mean (SD)	51.80 ± 15.643
Hepatitis infection, n (%)	
Non-hepatitis	13 (15.9)
Hepatitis	42 (58.5)
BCLC staging	
Stage 0	0 (0)
Stage A	5 (8.2)
Stage B	56 (91.8)
Stage C	0 (0)
Tumor size in cm, median (minimum-maximum)	10.9 (2.0-25)
Tumor size	
≤7 cm	24 (39.3)
>7 cm	37 (60.7)
Cirrhosis status	
Non-cirrhotic	29 (47.5)
Cirrhotic	32 (52.5)
Median (minimum-maximum) AFP level, ng/ml	113.5 (1.5 – 3898)
Mitosis count in 10 HPF, mean (SD)	6.72 (5.16)
Histological grading	
Well-moderate differentiation	41 (67.2)
Poor differentiation	20 (32.8)
Microvascular invasion	
Positive	35 (57.4)
Negative	26 (42.6)
Histological pattern*	
Macrotrabecular	16 (26.2)
Microtrabecular	44 (72.1)
Solid	31 (50.8)
Pseudoglandular	14 (22.9)
Special type carcinoma	
Fibrolamellar	0 (0)
Scirrhous	0 (0)
Undifferentiated	0 (0)
Lymphoepithelioma-like	0 (0)
Sarcomatoid	0 (0)
Steatohepatitis	5 (8.1%)
Macrotrabecular massive	0(0)

* More than one pattern can be observed in one tumor.
Abbreviations: SD - standard deviation, BCLC - Barcelona Clinic Liver Cancer, AFP - alpha-fetoprotein, HPF - high power field

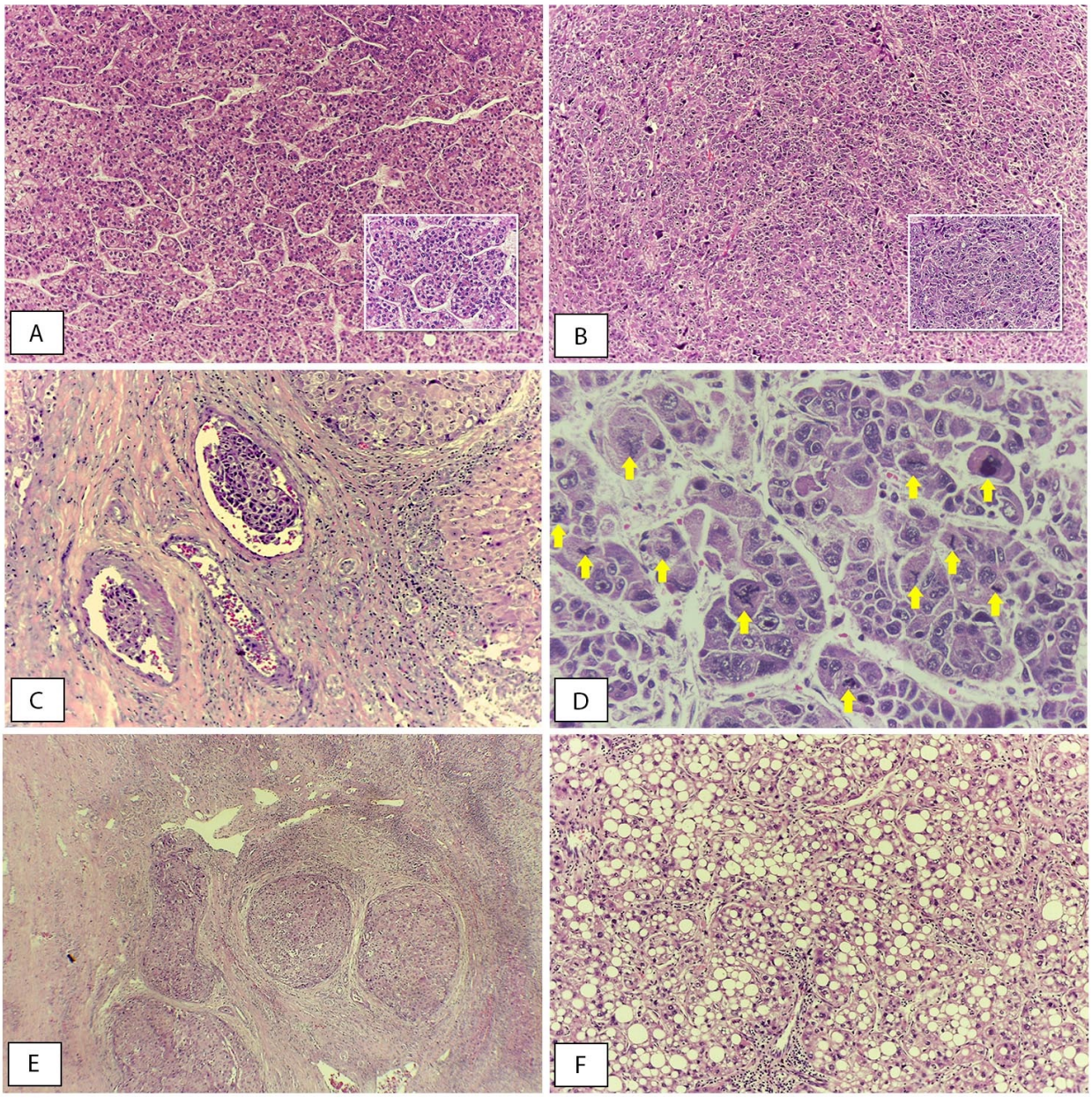

Fig 1. Histomorphology features of HCC. A) Well-moderate differentiation with microtrabecular and pseudoglandular patterns (HE, 100x and 400x). B) Poor differentiation with solid patterns (HE, 100x and 400x). C) Microvascular invasion (HE, 100x). D) Mitosis in poorly-differentiated HCC (HE, 400x). E) Non-tumor liver tissue showing cirrhosis with bridging fibrosis and regenerative nodules (HE, 100x). F) Steatohepatitic HCC with diffuse microvesicular and macrovesicular steatosis (HE, 400x).

correlated with poorly-differentiated HCC. Significant correlations were found between BCLC staging, tumor size and mitotic index with microvascular invasion. BCLC stage B (p=0.011), tumor size >7cm (p=0.046) and mitotic index ≥5 per 10 HPF (p=0.001) were significantly correlated with the presence of microvascular invasion. Significant correlations were also found between age, AFP level, BCLC staging, tumor size, and mitotic index with well-differentiated and no microvascular invasion. Age ≤60 (p=0.022), AFP level < 100 (p=0.000), BCLC stage A (p=0.015), tumor size ≤7 (p=0.001), and mitotic index <5 (p=0.000). Multivariate analysis was conducted from factors with p ≤ 0.25 in bivariate analysis. Mitotic Index ≥ 5 per 10 HPF were independent risk factors for poorly differentiated tumor, with an odds ratio of mitotic index (95% CI: 1.781-64.671; p≤0.005). Mitotic Index ≥ 5 per 10 HPF (95% CI: 1.934-25.853; p≤0.005) was an independent risk for microvascular invasion. On the other hand, AFP level <100 and mitotic index < 5 per 10 HPF were independent risk factors for well-differentiated with no microvascular invasion. Data are presented in Table 2, Table 3 and Table 4.

TABLE 2. Association clinicopathological features with histological grading (n=61).

Factors	Histological Grading			Univariate		Multivariate		
	Poor differentiation, n (%)	Well-moderate differentiation, n (%)	P-value	OR	95% CI	P-value	OR	95% CI
Sex								
Male	16 (26.2)	33 (54.1)						
Female	4 (6.6)	8 (13.1)	1.000[2]	1.031	0.270-3.3941			
Age, years								
≤60	15 (24.6)	29 (47.5)						
>60	5 (8.2)	12 (19.7)	0.727[1]	0.806	0.239-2.716			
AFP level, ng/ml								
≥100	14 (23)	17 (27.9)						
<100	6 (9.8)	24 (39.3)	**0.036**[1]	3.294	1.053-10.305	0.783	1.208	0.315-4.625
Hepatitis infection								
Non-hepatitis	2 (3.3)	11 (18)	Reference					
Hepatitis	18 (29.5)	30 (49.2)	0.189[2]	3.300	0.656-16.608			
BCLC staging								
Stage A	1 (1.6)	4 (6.6)						
Stage B	19 (31.1)	37 (60.7)	1.000[2]	2.054	0.214-19.685			
Tumor size, cm								
>7	16 (26.2)	21 (24.4)						
≤7	4 (6.6)	20 (32.8)	**0.031**[1]	3.810	1.086-13.365	0.460	1.690	0.420-6.804
Cirrhosis status								
Non-cirrhotic	9 (14.8)	20 (32.8)						
Cirrhotic	11 (18)	21 (34.4)	0.781[1]	1.164	0.398-3.403			
Mitotic index, per 10 HPF								
≥ 5	15 (27.8)	19 (35.2)						
< 5	2 (3.7)	18 (33.3)	**0.009**[1]	7.105	1.420-35.550	**0.017**	7.105	1.420-35.550

Abbreviations: OR – odd ratio, CI – Confident Interval, AFP - alpha-fetoprotein, BCLC - Barcelona Clinic Liver Cancer, HPF - high power field. [1]Chi-square test, [2]Fischer's exact test

TABLE 3. Association between clinicopathological features with microvascular invasion (n=61).

Factors	Microvascular Invasion			Multivariate				
	Positive, n (%)	Negative, n (%)	P-value	OR	95% CI	P-value	OR	95% CI
Sex								
Male	30 (49.2)	19 (31.1)						
Female	5 (8.2)	7 (11.5)	0.219[1]	0.452	0.125-1.633	0.234	0.382	0.078-1.864
Age, years								
≤60	27 (44.3)	17 (27.9)						
>60	8 (13.1)	9 (14.8)	0.313[1]	0.560	0.181-1731			
AFP level, ng/ml								
≥100	15 (24.6)	15 (24.6)						
<100	20 (32.8)	11 (18.0)	0.252[1]	1.818	0.651-5.075			
Hepatitis infection								
Non-hepatitis	9 (14.8)	4 (6.6)	Ref					
Hepatitis	26 (42.6)	22 (36.1)	0.330[2]	0.525	0.142-1942			
BCLC staging								
Stage A	0 (0)	5 (8.2)						
Stage B	35 (57.4)	21 (34.4)	**0.011**[2]	n/a[a]	n/a[a]	0.999	2700265285	0.000-.
Tumor size, cm								
>7	25 (41)	12 (19.7)						
≤7	10 (16.4)	14 (23)	**0.046**[1]	2.917	1.006-8.453	0.458	1.673	0.429-6.515
Cirrhosis status								
Non-cirrhotic	18 (29.5)	11 (18)						
Cirrhotic	17 (27.9)	15 (24.6)	0.481[1]	0.693	0.249-1.925			
Mitotic index, per 10 HPF								
≥ 5	27 (50)	7 (13)						
< 5	7 (13)	13 (24.1)	**0.001**[1]	7.163	2.075-24.731	**0.003**	7.071	1.934-25.853

Abbreviations: OR – odd ratio, CI – Confident Interval, AFP - alpha-fetoprotein, Ref - reference value, BCLC - Barcelona Clinic Liver Cancer, HPF - high power field.

[1]Chi-square test, [2]Fisher's exact test, [a]No positive cases of stage A in BCLC Staging, therefore the analysis of OR estimate could not be done.

TABLE 4. Association between clinicopathological features with well-differentiated and no microvascular invasion (n=61).

Factors	Histological Grading		Multivariate					
	Poor differentiation, n (%)	Well-moderate differentiation, n (%)	P-value	OR	95% CI	P-value	OR	95% CI
Sex								
Male	4 (6.6)	37 (60.7)						
Female	12 (4.9)	8 (13.1)	0.715[2]	1.542	0.394-6.040			
Age, years								
≤60	8 (13.1)	36 (59.0)						
>60	8 (13.1)	9 (14.8)	**0.048**[2]	4.000	1.178-13.579	0.787	1.418	0.112-17.925
AFP level, ng/ml								
≥100	15 (24.6)	15 (24.6)						
<100	1 (1.6)	30 (49.2)	**0.000**[1]	0.33	0.004-0.277	**0.014**	0.056	0.006-0.552
Hepatitis infection								
Non-hepatitis	4 (6.6)	9 (14.8)	Ref					
Hepatitis	12 (19.7)	36 (59.0)	0.728[2]	0.750	0.195-2.884			
BCLC staging								
Stage A	4 (6.6)	1 (1.6)						
Stage B	12 (19.7)	44 (72.1)	**0.015**[2]	0.068	0.007-0.668	0.492	0.178	0.001-24.575
Tumor size, cm								
>7	4 (6.6)	33 (54.1)						
≤7	12 (19.7)	12 (19.7)	**0.001**[1]	0.121	0.033-0.449	0.213	0.324	0.55-1.914
Cirrhosis status								
Non-cirrhotic	7 (11.5)	22 (36.1)						
Cirrhotic	9 (14.8)	23 (37.7)	0.727[1]	1.230	0.390-3875			
Mitotic index, per 10 HPF								
≥ 5	2 (3.7)	32 (59.3)						
< 5	11 (20.4)	9 (16.7)	**0.000**[2]	0.051	0.010-0.274	**0.003**	0.065	0.010-0.406

Abbreviations: OR – odd ratio, CI – Confident Interval AFP - alpha-fetoprotein, Ref - reference value, BCLC - Barcelona Clinic Liver Cancer, HPF - high power field.

[1]Chi-square test, [2]Fisher's exact test

DISCUSSION

The average age of patients diagnosed with HCC in areas with high HCC frequency is found to be 10-20 years lower than that in areas with low HCC frequency. This is likely caused by risk factors and age when exposed. HBV is the most common risk factor for HCC and is usually acquired at birth or in childhood.[10] In agreement with the findings of Xiao *et al*, the mean age of the patients in the present study was 51.80 ± 15.643 years and the age was not associated with both histological grade and microvascular invasion.[11] Being an endemic country, the frequency of young patients with HCC (>40 years old) is quite high in the present study (20%).

About 70-90% of patients had a history of chronic liver disease due to HBV and/or HCV infection, alcoholic liver disease or non-alcoholic steatohepatitis (NASH).[12] Atisook *et al* also reported the most common precursor are cirrhosis and chronic hepatitis due to HBV and HCV.[13] The present study showed a similar result in which hepatitis infection was predominantly present in patients with HCC. However, hepatitis infection status was not associated with histological grading, microvascular invasion, and well-differentiated and no microvascular invasion.

Epidemiologically, HCC is more common in males, with male/female ratio ranging from 2:1-4:1.[14] Males are more susceptible to high-risk chronic diseases (HCC) due to exposure to risk factors like alcohol use and Hepatitis infections. In addition, androgens promote DNA damage and oxidative stress, while estrogens suppress tumor by reducing the effect of interleukin-6.[14] Accordingly, the present study showed a higher prevalence of HCC in men. Histological grade and microvascular invasion are associated prognosis and survival in patients with HCC.[9,15] HCC is a heterogeneous tumor due to the gradual dedifferentiation of cells during hepatocarcinogenesis. The histological grade may predict HCC's biological nature.[16] Sasaki *et al*, concluded that any poorly-differentiated components within a tumor increase its degree of malignancy.[9] Tumor recurrence is associated with poor prognosis. According to a study by Lim *et al*, microvascular invasion is a reliable indicator of disease recurrence and poor overall survival.[17] Moreover, it causes frequent recurrence within 30 months of resection because of its role in intrahepatic metastases.[17]

In the present study, tumor size and mitotic index linked to histologic grade and microvascular invasion. Dai *et al* and Nagano *et al* also showed that larger tumor size links to microvascular invasion and higher histological grade.[18,19] In the current study, tumors size >7 cm was associated with poorly-differentiated HCC and positive microvascular invasion. Vascular endothelial growth factor (VEGF) overexpression was found in tumors >5 cm in size. VEGF promotes endothelial cell proliferation, migration and increased vascular permeability.[20] Following this study, Pawlik *et al* found that the larger the size of the tumor, the higher the histological grade.[21] Tumor growth gradually changes its pathobiological nature. In a study about DNA ploidy, the majority of HCC with tumors <3 cm had diploid DNA with a relatively more benign nature and an improved postoperative prognosis. By contrast, HCCs with tumors ≥3 cm were shown to have aneuploid DNA and presented a more aggressive nature and worse survival.[22]

A high proliferation rate is a hallmark of a malignant process; this occurs because of the ability of malignant cells to produce growth factors, insensitivity to anti-growth factors and a high potential for replication.[8] The mitotic index in HCC is associated with early recurrence and a worse prognosis.[23] Concordance with the present study, a higher mitotic rate is more common in tumors with poorly-differentiated components and tumors with microvascular invasion. Meantime, lower mitotic rate is an independent factor for well-differentiated and no microvascular invasion. Ha *et al* and Osorio *et al* concluded that a higher mitotic index was correlated with microvascular invasion and high-grade tumors.[8,23] The mitotic index should be reported in the histopathological report of patients with HCC.

AFP is normally secreted by the yolk sac and fetal hepatocyte cells. The level of AFP decreases from 40 ng/ml in neonates to 20 ng/ml in children of 1 year of age, remaining constant until adulthood. However, in cases of cirrhosis, malignancy and other liver pathologies, the AFP level rises.[24] Increased AFP levels before surgery impact overall and disease-free survival.[25] Tateishi *et al*, found that an AFP level >100 ng/ml significantly predicts tumor progression and recurrence.[26] The present study indicated a significant association between poorly-differentiated HCC and AFP levels ≥100 ng/ml. Meanwhile, survival rate with normal to moderate AFP levels were longer than people with elevated AFP levels>400 ng/ml.[17] This study found that AFP level <100 ng/ml was an independent factor for well-differentiated with no microvascular invasion.

The BCLC staging system is one of the earliest staging systems developed for HCC and has been validated in cohort studies for prognostic stratification.[6] The present study demonstrated a significant difference in the proportion of patients with stage A and B HCC, with and without microvascular invasion, with stage B HCC patients associated with the presence of microvascular

invasion. In contrast to the present study, Huitzil-Malendez *et al* demonstrated that the BCLC staging lacks prognostic significance.[27] The present study had some limitations, including a small sample and lack of patients survival data.

CONCLUSION

Higher mitotic index was significantly associated and independent factor for poorly-differentiated HCC and microvascular invasion suggesting that these factors might influence patients prognosis. In biopsy specimens in which microvascular invasion is difficult to assess, histological grade, tumor size and mitotic index may be beneficial to depict the prognosis of patients with HCC. In approaching patients with HCC, pathologists should carefully assess and report histopathologic features associated with unfavorable prognosis. Physicians should also be aware of these histopathologic features.

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All contributors complied with the authorship criteria.

Conflicts of interest

All authors declare no potential conflicts of interest in this study.

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The Impact of Retro-apical Urethral Dissection Approach Technique on Positive Surgical Margins in Robotic-assisted Laparoscopic Radical Prostatectomy: A Study in Thailand

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ABSTRACT

Objective: Among the various postoperative outcomes following robotic-assisted laparoscopic radical prostatectomy (RARP), positive surgical margins (PSMs) are a significant prognostic factor associated with biochemical recurrence (BCR). Many surgical techniques are available for RARP; however, the technique proposed in this study may improve surgical outcomes. This study aims to evaluate the incidence of post-operative PSMs in patients diagnosed with clinically localized prostate cancer at Siriraj Hospital using the retro-apical urethral dissection approach with a 30-degree-lens flip-up technique.

Materials and Methods: A retrospective review of 2,114 consecutive patients who underwent RARP with the conventional technique was conducted using Siriraj Hospital's database, from January 2007 to June 2022. Propensity score matching was employed to select a group of 284 men from the total cohort of 2,114 patients who underwent conventional radical prostatectomy (Group 1) for comparison against another group of 284 patients who underwent the retro-apical dissection technique (Group 2). The incidence of PSMs was then evaluated in each group.

Results: Of the 568 patients, PSMs were observed in 219 patients. The overall incidence of PSMs decreased from 128 cases (45.1%) in Group 1 to 91 cases (32.0%) in Group 2 (p-value <0.01). Similar results were seen in the subgroup of patients with pT2 staging who had PSMs (52 cases vs 24 cases, p-value <0.01). PSMs occurred mostly at the apex with a total of 112 cases (52.1%).

Conclusion: The retro-apical urethral dissection approach with a 30-degree-lens flip-up technique is associated with a lower risk of overall PSMs and the trend of apical PSMs, indicating its clinical significance.

Keywords: Positive surgical margins; retro-apical urethral dissection approach technique; prostate cancer; radical prostatectomy (Siriraj Med J 2023; 75: 827-834)

INTRODUCTION

Prostate cancer is the fourth most common cancer among men in Thailand.[1-3] Patients diagnosed with prostate cancer are informed about and provided with multiple treatment options, including active surveillance, surgery, hormonal therapy, and radiotherapy.[4-6]

Recently, various surgical techniques have become available for prostatectomy, such as open retropubic radical prostatectomy (RRP), laparoscopic radical prostatectomy (LRP), and robotic-assisted laparoscopic radical prostatectomy (RARP). RARP, which is known for its better postoperative outcomes compared to other techniques, has become increasingly popular.[7-10]

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During RARP, urethral transection is one of the most significant steps that needs to be meticulously performed because the remaining urethral length helps maintain the continence mechanism. Therefore, it is crucial to secure the apical margin while preserving an adequate urethral length during the surgery to prevent complications such as positive surgical margins (PSMs) and urinary incontinence.[11,12]

Despite various modifications in surgical techniques over the decades[13-19], PSMs remain a challenging problem for urologists, as they are strongly associated with biochemical recurrence (BCR).[20-25] Failure to completely remove the tumors may occur due to various anatomical details and different surgical procedures.[26-30]

PSMs commonly occur at the prostatic apex, including in our institution.[30,31] This study aims to demonstrate the advantages of the retro-apical dissection technique, introduced by *Tewari et al.*, in reducing the incidence of PSMs in patients undergoing radical prostatectomy (RP). The technique helps improve the visualization of the prostatic apex for surgeons during the operation.[32]

MATERIALS AND METHODS

Patient population

Between January 2007 and June 2022, a retrospective review of medical records was conducted on patients diagnosed with localized prostate cancer who underwent radical prostatectomy (RP) at Siriraj Hospital. Based on the surgical technique used, the patients were classified into two groups: Patients who underwent the conventional urethral dissection technique (Group 1), while patients who underwent the retro-apical urethral dissection technique (Group 2) were included in the study.

A total of 2,114 men underwent RARP using the conventional urethral dissection technique. From this group, a statistical selection of 284 patients was made through propensity score matching. Several factors were taken into consideration to calculate the propensity score, including age, body mass index (BMI), American Society of Anesthesiologist (ASA) physical status classification, prostate-specific antigen (PSA), neurovascular bundle (NVB) sparing technique, operative time, estimated blood loss (EBL), prostatic weight, pathologic tumor stage (pT), Gleason score (GS), and the effect of androgen deprivation therapy (ADT).

Group 2 comprised 284 men who underwent RARP using retro-apical urethral dissection technique and were included in the study.

The operations were performed by experienced surgeons at Siriraj Hospital, each having conducted more than 100 cases of the procedure, and informed consent was obtained individually for surgical procedures. Patients with incomplete data or other types of cancer apart from prostate cancer were excluded from the study.

Demographic data, surgical technique, operative time, estimated blood loss, and pathological reports were collected through a review of electronic medical record review, and tumors were staged according to the 2002 TNM classification.

Surgical techniques

At our center, RARP was performed using the transperitoneal approach. The patient was positioned in the lithotomy or supine position with split legs and placed in the Trendelenburg position using the Da Vinci S, Si or Xi Surgical System (Intuitive Surgical, Sunnyvale, CA, USA) as preferred by the surgeons. A small incision was made above the umbilicus for the insertion of the camera, followed by three robotic ports and two assistant ports (5 mm and 12 mm). The placement of the three robotic ports depended on the system used, either in a dome or straight fashion. Both 0-degree and 30-degree lenses were used for the procedure, as depicted in Fig 1. The bladder was dropped to access the Retzius space. The endopelvic fascia was incised, and the prostate was freed from the levator ani muscle. A bladder neck transection was performed, and the anterior bladder wall was incised at the prostate-vesical junction until reaching the Foley catheter. The Foley catheter was then grasped and held anteriorly with the fourth arm. The posterior bladder neck was dissected until reaching the vas deferens and seminal vesicles. Once the seminal vesicles were mobilized freely, they were lifted anteriorly using the fourth arm. As the prostate was lifted, Denonvilliers' fascia was incised. The lateral pedicle of the prostate was divided with a Hem-O-Lok clip or electrocauterization. At this stage, the prostate was freed. To dissect the posterior and the apex of the prostate, two optional methods were available at our center. The first method (Group 1) involved dissecting from anterior to posterior until the urethra was dissected. The second method (Group 2) involved dissecting from the posterior aspect of the prostate anterogradely toward the urethra, using a flip-up 30-degree lens, as displayed in Fig 1, to identify the posterior prostate-urethral junction, before dissecting from both anterior and posterior approaches. Bladder neck reconstruction was performed if necessary, and urethra-vesical anastomosis was done.

Statistical analysis

Propensity scores were constructed based on known confounders, including age, BMI, ASA physical status

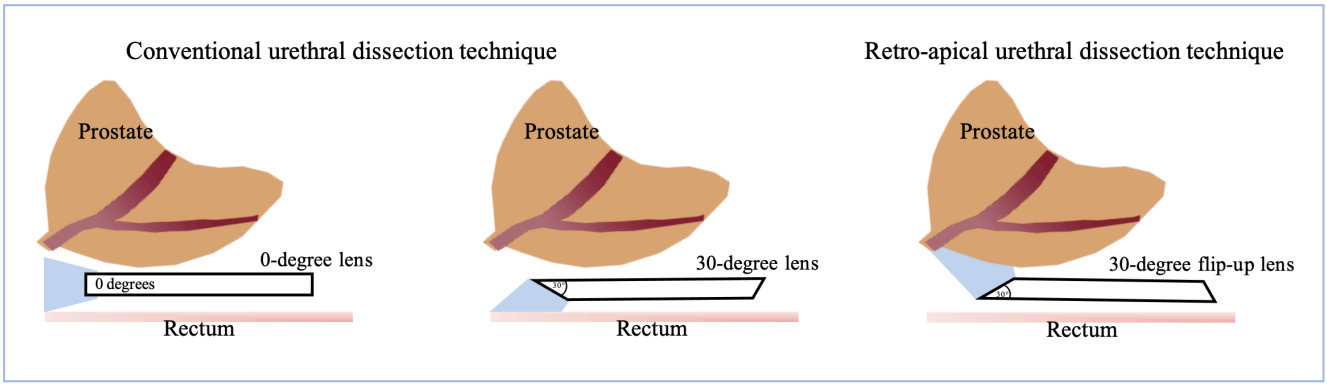

Fig 1. Comparison of Visualization Techniques
Conventional Technique: Utilizing either a 0-degree or 30-degree lens for dissection.
Retro-apical Technique: Employing a "flip-up" 30-degree lens, enhancing visibility of the prostatic apex.

classification, PSA level, operative time, EBL, prostatic weight, pT stage, GS, and ADT effect.

Demographic data were reported as mean and standard deviation for age and operative time, while median and interquartile ranges were used for BMI, PSA level, EBL, and prostatic weight. Independent t-tests were used to compare continuous data with a normal distribution, while the Mann-Whitney U test was used for non-normal distribution data. Chi-square and Fisher's exact tests were used for qualitative data.

Propensity score matching was performed using Python (Python Software Foundation, Wilmington, DE, USA) with the assistance of the following statistical packages: SciPy version 1.5.2 and Matplotlib version 3.3.2. Stata statistical software for Mac version 17.0 (StataCorp. 2021, College Station, TX, USA) and RStudio version 2023.06.2+561 (Posit Software. 2023, PBC, Boston, MA) were used for other statistical analyses. Statistical significance was defined as a p-value less than 0.05. Standardized mean differences of less than 0.1 was considered as covariate balance.

RESULTS

The results indicate that out of the 568 patients diagnosed with clinically localized prostate cancer, 284 underwent RARP using conventional techniques, while the other 284 underwent the retro-apical urethral dissection approach technique. Baseline characteristics between two groups were matched.

Patient characteristics

As shown in Table 1, the mean ages of 284 patients in Group 1 and 284 patients in Group 2 were 67.6 (±7.3) and 67.6 (±7.2) years, respectively. The median BMI was 24.15 in Group 1 and 24.24 in Group 2. Regarding the ASA classification, the majority of patients in both Group 1 and Group 2 were classified as ASA class II, with 190 (66.9%) and 192 (67.6%) patients, respectively. The median preoperative PSA level was 10.13 (range, 1.09-137.50) ng/dL in Group 1 and 9.50 (range, 0.70-267.00) ng/dL in Group 2. The mean operative time was 185.5 (±55.76) minutes for Group 1 and 182 (±55.6) minutes for Group 2. The median intraoperative blood loss was 300 (range, 20-1300) mL in Group 1 and 250 (range, 25-2100) mL in Group 2. The median prostatic weight was about 40 grams in both groups. The standardized mean difference of each covariate was less than 0.1.

Pathological outcome of patients

According to Table 2, the majority of patients in both groups had a GS of 3+4, with 108 (38.0%) in Group 1 and 115 (40.5%) in Group 2. The least common GS was 5+5 with 9 (3.2%) in Group 1 and 7 (2.5%) in Group 2. Additionally, some patients received preoperative ADT, which affected the ability to conclude the final GS. The proportion of patients with ADT effect was 16 (5.6%) in Group 1 and 13 (4.6%) in Group 2. The PSA levels at 1 year after surgery predominantly indicated undetectable PSA levels, with a total of 291 cases, comprising 138 (53.7%) out of 257 cases in Group 1 and 153 (61.9%) out of 232 cases in Group 2.

Among the 284 patients in each group, PSMs confirmed by the pathological report were found in 128 (45.1%) patients from Group 1 and 91 (32.0%) patients from Group 2. The rate of positive margins was significantly lower in Group 2 compared to Group 1 (p-value <0.01). The majority of patients in both groups were classified as pT2 stage, with 61.6% in the conventional group and 61.3% in the retro-apical group.

TABLE 1. Preoperative characteristics of patients diagnosed with clinically localized prostate cancer who underwent RARP.

Characteristics	Conventional dissection (N = 284)	Retro-apical dissection (N = 284)	p-value	SMD
Age[a], years	67.6 (±7.3)	67.6 (±7.2)	0.88	0.01
BMI[b], kg/m^2	24.15 (22.01, 26.33)	24.24 (22.31, 26.48)	0.46	<0.01
ASA[c]			0.98	<0.01
Class I	23 (8.1)	22 (7.7)		
Class II	190 (66.9)	192 (67.6)		
Class III	71 (25.0)	70 (24.6)		
PSA[b], ng/mL	10.13 (6.50, 16.00)	9.5 (6.00, 16.79)	0.11	0.03
NVB sparing technique[c]			0.70	0.05
None	213 (75.0)	22 (7.7)		
Unilateral	31 (10.9)	192 (67.6)		
Bilateral	40 (14.1)	70 (24.6)		
Operative time[a], minutes	185.5 (±55.76)	182.00 (±55.60)	0.46	0.06
EBL[b], mL	300 (150, 450)	250 (150, 400)	0.27	0.01
Prostatic weight[b], g	39.65 (30.72, 50.93)	39.70 (31.67, 50.00)	0.78	0.06

Abbreviations: RARP = Robotic-assisted Laparoscopic Radical Prostatectomy; SMD = Standardized mean differences; BMI = Body mass index; ASA = American Society of Anesthesiologist physical status classification; PSA = prostate-specific antigen; NVB = neurovascular bundle; EBL = estimated blood loss.

[a] Data are presented as mean ± standard deviation and p-value is calculated by independent samples T-test.

[b] Data are presented as median (interquartile range) and p-value is calculated by Mann-Whitney U test.

[c] Data are presented as n (%) and p-value is calculated by Chi-square or Fisher's exact test.

In terms of the location of PSMs, as shown in Table 3, a total of 215 out of 219 patients with PSMs were eligible for location analysis. PSMs were predominantly observed at the apex in both groups, with 71 (22%) out of a total of 323 sites in Group 1 and 41 (16.7%) out of a total of 246 sites in Group 2 (p-value 0.11).

From Table 4, in pT2 patients with PSMs, the retro-apical technique was also associated with a significantly lower overall PSMs rate compared to the conventional technique. Out of 175 cases in Group 1, 52 (29.7%) had PSMs, while in Group 2, out of 174 cases, only 24 (13.8%) had PSMs (p-value <0.01). Among patients staged as pT2 with PSMs, the majority had multiple PSMs, with 44 out of 52 patients (84.6%) in Group 1 and 22 out of 24 patients (91.7%) in Group 2 (p-value 0.49). Furthermore, the rate of apical PSMs decreased from 33 (30.6%) out of a total of 108 sites in Group 1 to 13 (22.4%) out of a total of 58 sites in Group 2 (p-value 0.26).

Similarly, as shown in Table 5, the retro-apical technique group exhibited a decrease in the overall rate of PSMs for pT3 patients with PSMs. In Group 1, out of 109 patients, 75 (68.8%) had PSMs, while in Group 2, out of 110 patients, 64 (58.2%) had PSMs (p-value 0.16). The rate of apical PSMs also decreased from 38 out of a total of 210 (18.1%) sites in Group 1 to 28 out of a total of 193 (14.5%) sites in Group 2 (p-value 0.33).

DISCUSSION

In the pursuit of performing RP, urologists strive to achieve complete tumor removal while preserving urinary and sexual function. PSMs are recognized as significant prognostic factors that can lead to early biochemical failure and tumor recurrence.[20-25] Consequently, numerous studies have been conducted to address these challenges.

In Thailand, several studies have explored the occurrence of PSMs in relation to pre-operative Magnetic Resonance Imaging (MRI) evaluation and clinicopathological characteristics of patients, with no significant differences observed among different surgical approaches RRP, LRP and RARP. In addition, PSMs are most commonly observed at the prostatic apex.[10,30,31]

TABLE 2. Pathological report and the rate of postoperative PSA level of patients with clinically localized prostate cancer who underwent RARP.

Characteristics	Conventional dissection (N = 284)	Retro-apical dissection (N = 284)	p-value	SMD
pT[c]			0.93	0.01
2	175 (61.6)	174 (61.3)		
3	109 (38.4)	110 (38.7)		
Gleason score[c]			0.97	0.08
3+3	54 (19.0)	49 (17.3)		
3+4	108 (38.0)	115 (40.5)		
4+3	45 (15.8)	48 (16.9)		
4+4	15 (5.3)	11 (3.9)		
4+5	35 (12.3)	35 (12.3)		
5+5	9 (3.2)	7 (2.5)		
ADT effect	16 (5.6)	13 (4.6)		
Surgical margin[c]			<0.01	
Positive	128 (45.1)	91 (32)		
Negative	156 (54.9)	193 (68)		
Post-operative PSA level[c,d]			<0.01	
Undetectable	138 (53.7)	153 (61.9)		
Low detectable	89 (34.6)	52 (21.1)		
Persistent	30 (11.7)	27 (10.9)		

Abbreviations: RARP = Robotic-assisted Laparoscopic Radical Prostatectomy; pT = pathologic tumor stage; GS = Gleason score; ADT = androgen deprivation therapy; PSA = prostate-specific antigen.
[a] Data are presented as mean ± standard deviation and the p-value is calculated by independent samples T-test.
[b] Data are presented as median (interquartile range) and the p-value is calculated by Mann-Whitney U test.
[c] Data are presented as *n* (%) and the p-value is calculated either by Chi-square or Fisher's exact test.
[d] The PSA level was assessed within 3 months after surgery. An undetectable PSA level is defined as a PSA level of less than 0.006 ng/ml. A low detectable PSA level is defined as a PSA level of 0.006 ng/ml and less than 0.1 ng/ml. A persistent PSA level is defined as a PSA level of 0.1 ng/ml or greater.

TABLE 3. Overall location and frequency of PSMs in 215 eligible patients with PSMs.

	Total	Conventional technique	Retro-apical technique	p-value
PSMs cases (n, %)	215	127 (59.1)	88 (40.9)	0.04
PSMs locations and frequency (n, %)				0.11
Apical	112 (19.7)	71 (22)	41 (16.7)	
Non-apical	457 (80.3)	252 (78)	205 (83.3)	
Total sites	569	323	246	

Abbreviation: PSMs = Positive surgical margins.
This table presents the number of overall patients with PSMs and the proportion of PSMs and their location in 215 eligible patients. The proportion of subgroups in "PSMs locations and frequency" is calculated based on the total number of sites (569 sites) where positive margins were found in each patient. For Group 1, there were a total of 323 positive margin sites, while for Group 2, there were a total of 246 positive margin sites. P-value was calculated using Chi-square test.

TABLE 4. Locations and frequency of PSMs in pT2 patients with PSMs.

	Total	Conventional technique	Retro-apical technique	p-value
Cases (n, %)				
pT2 patients	349	175 (50.1)	174 (49.9)	
pT2 patients with PSMs	76 (21.8)	52 (29.7)	24 (13.8)	<0.01
PSMs locations and frequency (n, %)				0.26
Apical	46 (27.7)	33 (30.6)	13 (22.4)	
Non-apical	120 (73.6)	75 (69.4)	45 (77.6)	
Total sites	166	108	58	

Abbreviations: pT = pathologic tumor stage; PSMs = Positive surgical margins.
This table presents the number and proportion of patients having pT2 disease and PSMs (out of 175 patients in Group 1 and out of 174 patients in Group 2). The table also provides the proportion of PSMs and their locations in a group of 76 patients diagnosed with PSMs and pT2 stage. The proportion of subgroups in "PSMs locations and frequency" is calculated based on the total number of sites (166 sites) where positive margins were found in each patient. For Group 1, there were a total of 108 positive margin sites, while for Group 2, there were a total of 58 positive margin sites. P-value was calculated using Chi-square test.

TABLE 5. Locations and frequency of PSMs in pT3 patients with PSMs.

	Total	Conventional technique	Retro-apical technique	p-value
Cases (n, %)				
pT3 patients	218	109 (49.5)	110 (50.5)	
pT3 patients with PSMs	139 (63.8)	75 (68.8)	64 (58.2)	0.16
PSMs locations and frequency (n, %)				0.33
Apical	66 (16.4)	38 (18.1)	28 (14.5)	
Non-apical	337 (83.6)	172 (81.9)	165 (85.5)	
Total sites	403	210	193	

Abbreviations: pT = pathologic tumor stage; PSMs = Positive surgical margins.
This table presents the number of patients having pT3 disease and PSMs (out of 109 patients in Group 1 and out of 109 patients in Group 2). The table also provides the proportion of PSMs and their locations in a group of 139 patients diagnosed with PSMs and pT3 stage. The proportion of subgroups in "PSMs locations and frequency" is calculated based on the total number of sites (403 sites) where positive margins were found in each patient. For Group 1, there were a total of 210 positive margin sites, while for Group 2, there were a total of 193 positive margin sites. P-value was calculated using Chi-square test.

The retro-apical technique shows a promising trend in reducing both overall PSMs and apical PSMs rate. At our institution, two techniques were used depending on surgeons' preferences: the conventional and retro-apical techniques. According to *Tewari et el.*, the retro-apical urethral dissection technique with RARP significantly lowered the rate of overall PSMs and apical PSMs.[7,32] Similarly, in our present study, we observed a substantial decline in both overall and apical PSMs rate within the retro-apical group. This improvement can be attributed to the enhanced visibility provided by a flip-up 30-degree lens, which offers a clearer view of the prostatic apex and enables more thorough removal of apical tumors.

Despite the observed trend not being statistically significant, concerning the rate of apical positive margins, a noticeable downward trend was observed in both pT2 and pT3 groups (8.2% and 10.6% decrease). However, the statistical insignificant may result from the rate which was determined as the proportion of positive margin sites, rather than the number of cases. The increase in

the percentages of PSMs at other sites may have also contributed to the lack of statistical significance in our findings.

The high rate of PSMs in our study may be attributed to the combined prevalence of pT2 and pT3 cases. However, when we compared the conventional and retro-apical techniques while controlling for confounding factors, the PSMs rate in pT2 patients fell within the typical range (29.7% and 13.8%), while a higher rate was observed in pT3 patients (68.8% and 58.2%), according to a previous study.[33]

Known by unfavorable consequences following PSMs, there are numerous treatment options available, including active surveillance, hormonal therapy, radiation, and chemotherapy. Early post-operative PSA levels, assessed within 3 months after surgery, is one of the strong predictors for BCR, and is classified into 3 groups: undetectable, low detectable, and persistent.[34-36] In the current study, it was observed that the retro-apical techniques yield a higher rate of undetectable PSA levels, leading to a more favorable outcome.

Limitations

Our findings should be considered in the context of study's limitations. Firstly, it's worth acknowledging that, as a retrospective study, the visualization provided by different versions of the DaVinci system across different time periods may have a minor impact on surgical margins. Among the Da Vinci versions used, Da Vinci version S may offer slightly lower resolution compared to the other two versions, but no substantial impact on the surgical procedure was observed. Furthermore, no difference in visualization was noted between Da Vinci version Si and Xi.

Secondly, our initial sample size calculation was based on an analysis of overall PSMs, and it may not have provided sufficient statistical power to detect differences in subgroups related to the specific sites of PSMs. Therefore, it is advisable to recruit a larger sample size to improve the statistical robustness in future study. Additionally, it is important to note that other potential confounding factors, such as PSA density (PSAD), was not included in matching process of this study. Since both PSA and prostate volume were matched, presuming that PSAD would not significantly alter the outcomes.

Thirdly, our study was conducted at a single tertiary center, which restricts the generalizability of our results to a broader population. Furthermore, it's crucial to consider the learning curve of surgeons in interpreting our findings. Further studies should be conducted to enhance the validity and generalizability.

CONCLUSION

The retro-apical dissection technique in RARP provides better visualization of the apical aspect on the posterior side of the prostate, enabling surgeons to achieve more complete tumor removal. This technique has demonstrated a reduction in the incidence of both overall PSMs and potentially at the apical area when compared to conventional techniques.

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Efficacy and Safety of Combination 308-nm Excimer Laser and Intralesional Corticosteroid versus Intralesional Corticosteroid Monotherapy in the Treatment of Frontal Fibrosing Alopecia: A Pilot Study

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To the Editor: A standard treatment regimen for frontal fibrosing alopecia (FFA) has not been established.[1] We compared the efficacy and safety of the combination of a 308-nm excimer laser with intralesional corticosteroid (ILC) versus ILC alone to treat FFA.

This was a randomized, controlled, split-scalp pilot study that recruited FFA patients with clinical and/or histopathological manifestations of active disease (burning sensation, pain, redness, scaling, and papules).

Each side of the scalp was randomly assigned to each treatment group. One side received combination therapy of a 308-nm excimer laser (Ra Medical Systems Inc. Carlsbad, CA, USA) and ILC (Triamcinolone, L.B.S. Laboratory Ltd, Bangkok, Thailand), while the other received ILC monotherapy. The treatment lasted 12 weeks, and the results were eventually assessed after 16 weeks. The ILC dosage was 10 mg/ml (0.1 ml/cm^2) monthly. The affected area of the combination-therapy side was additionally treated twice weekly with a 308-nm excimer laser. The initial laser dose was 200 mJ/cm^2; after every second session, it was increased by 50 mJ/cm^2. If patients exhibited a significant adverse reaction (moderate to severe erythema, discomfort, numbness, and/or bullous), the laser dose was reduced by 50 mJ/cm^2 from the previous treatment. During the trial, no oral or topical medications were permitted.

The Frontal Fibrosing Alopecia Severity Index (FFASI) was used to evaluate therapy response at baseline and week 16.[2] Two dermatologists reviewed photographs taken at baseline, weeks 4, 8, 12, and 16 to establish the global improvement score. The patients were also asked to rate the percentage of improvement on each side of their scalp at week 16. During each visit, side effects were noted.

The five FFA patients were all female, with a mean age of 56.2 years. The average disease duration was 6.4 years, with an active disease duration of 13.2 months prior to recruitment. One patient (20%) had FFA confirmed by biopsy. The respective FFASI scores for combination and monotherapy groups were 29.6 ± 5.2 *vs.* 30.0 ± 5.7 at baseline (P = 0.374) and 29.2 ± 5.8 *vs.* 29.6 ± 6.3 at week 16 (P = 0.374). Blinded dermatologists classified two patients (40%) as having minimal improvement (< 25%) on both sides of the scalp at week 16. Regarding patients' assessments, three patients (60%) reported no improvement on either side of the scalp, whereas two patients (40%) reported mild to moderate improvements (10%-40%) with no difference between sides of scalp. The most common side effects from the combination therapy were erythema (60%) and burning sensation (20%). Representative pictures of pre-and post-treatment are shown in Fig 1.

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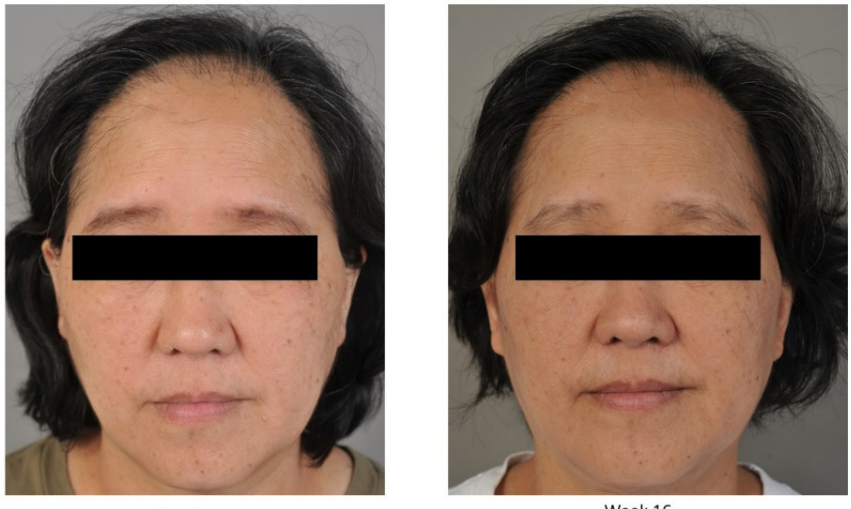

Fig 1. FFA patient who was rated as minimal improvement on both sides by dermatologists. (Right side, ILC alone; left side, combination therapy with 308-nm excimer laser and ILC).

Few studies have been conducted to assess the efficacy of excimer lasers in the treatment of FFA.[3-5] In FFA patients with active disease, Fertig et al. found that oral finasteride combined with an excimer laser successfully reduced inflammation and peripilar casts.[3] Zhang *et al.* reported a 100% treatment response in 3 patients treated with an excimer laser alone.[4] Another study discovered that an excimer laser dramatically reduced scalp inflammation and improved hair loss in 13 patients with lichen planopilaris.[5] The excimer laser's hypothesized mechanism for FFA treatment is to diminish T cells and change cytokine expression throughout the disease's inflammatory process.[5]

Our initial excimer laser dose (200 mJ/cm^2) was lower than that of another study (250 mJ/cm^2). However, our study's mean treatment time (23.4) was longer than the prior study's (11.0), resulting in a greater mean total dosage (11 800 vs. 4300 mJ/cm^2).[5] Nonetheless, our findings show that combining a 308-nm excimer laser with ILC is not superior to ILC alone. The FFASI scores and improvements assessed by physicians and patients in both groups were not substantially different.

The limitation of this study is the small sample size; however, this was a pilot study. Further studies in a larger study population, and with different combinations of laser power, laser frequency, ILC dose, and ILC frequency are needed to evaluate whether there is clinical benefit in treating FFA with an excimer laser and ILC.

In conclusion, the combination of a 308-nm excimer laser with ILC for treating FFA was not superior to ILC alone. Furthermore, the combination group experienced adverse effects (erythema and a burning feeling).

Conflict-of-interest declaration

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

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Author contribution statement

Conceptualization: Rattapon Thuangtong; Methodology: Chadakan Yan; Formal analysis and investigation: Supisara Wongdama; Writing - original draft preparation: Supisara Wongdama; Writing - review and editing: Rattapon Thuangtong, Daranporn Triwongwaranat, Kanchalit Thanomkitti; Funding acquisition: Nuttagarn Jantanapornchai; Resources: Nuttagarn Jantanapornchai; Supervision: Rattapon

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Compliance with Ethical Standards

The protocol for this pilot study was approved by the Siriraj Institutional Review Board (COA no. Si 672/2017), and all included patients gave written informed consent to participate.

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