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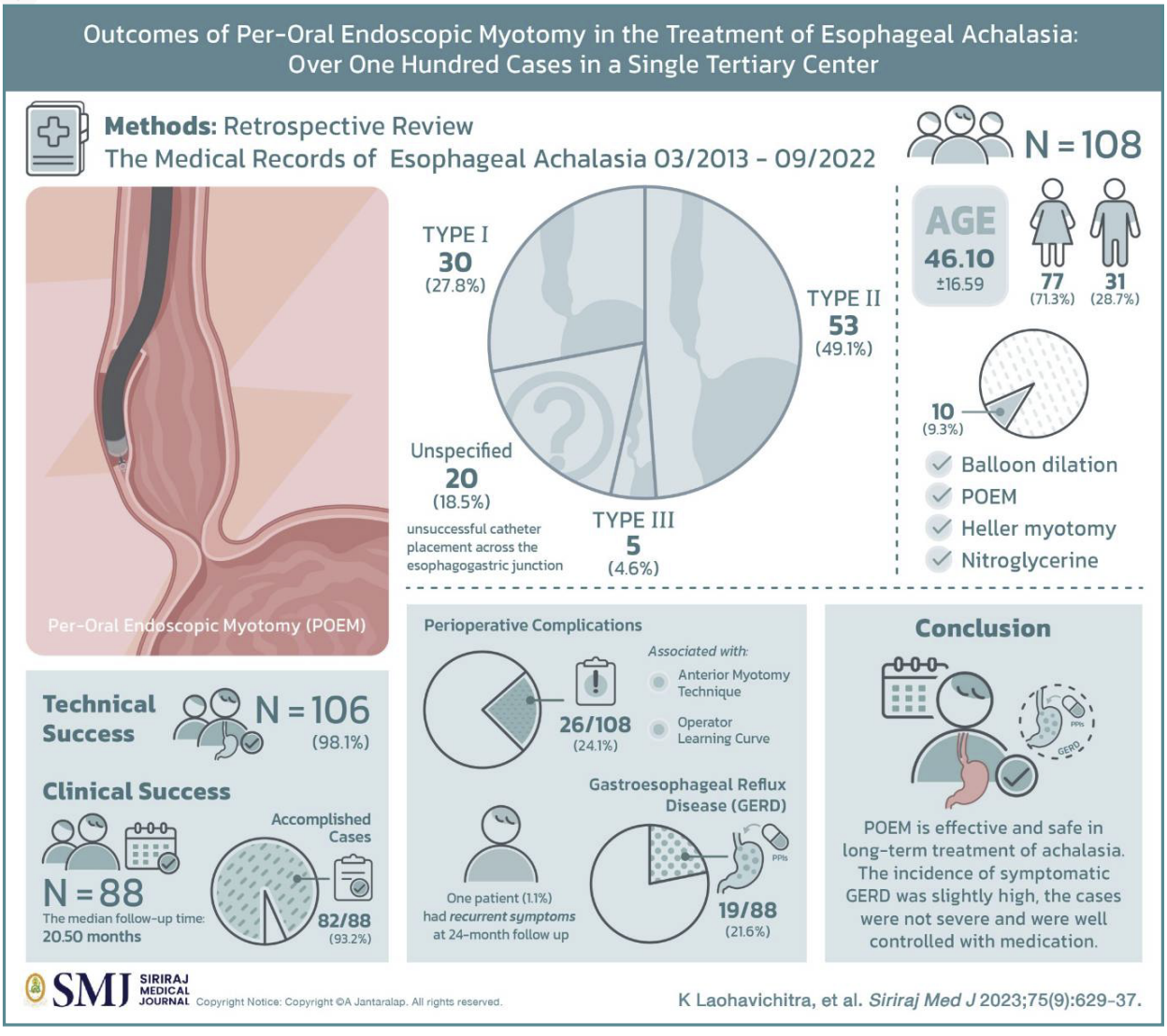

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Influence of Online Dating Apps on Sexual Risk Behaviors among Homosexual and Bisexual Adolescents and Youths in Thailand: An Online Cross-sectional Survey

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ABSTRACT

Objective: The internet and social media enhance communication, education, and social connection among users; however, some adverse effects on health are notable, particularly sexual risk engagement and mood problems. Mobile dating applications (apps)/websites facilitate high sexual-risk access, particularly among lesbian, gay, bisexual, transgender, and queer (LGBTQ) individuals. Recognition of the characteristics of using these platforms and identifying factors related to high sexual risk among LGBTQ youths will facilitate both targeting of those at risk and subsequent intervention.

Materials and Methods: Adolescents and youths were invited to voluntarily join this study, scan the QR code, and anonymously complete the questionnaires. These validated questionnaires were launched online via a popular platform among LGBTQs during 2017-2018. Multiple logistic regression was employed to identify factors independently associated with high sexual risk among study subjects.

Results: Of 360 participants (mean age: 21±2.8 years, range: 11-25), 60.8% self-reported as homosexual, and the rest were bisexual. Median dating app/website usage was 2 (range 1-10). Two-thirds (62.8%) met partners from those e-platforms, and most (79.6%) developed a sexual relationship. Over half (52.2%) did not use a condom, and one-third (30.6%) abused substances during sex. Poor condom compliance, multiple partners, and substance use were strongly associated with individuals who used >2 apps for longer than 3 years. Depression susceptibility was 32.2%, and was related to condom-use failure (p=0.01).

Conclusion: Among LGBTQs, the greater the number and longer time exposed to dating apps/websites, the higher the number of sexual risk behaviors. Moreover, unsafe sex increased among individuals at risk for depression.

Keywords: Bisexual; dating apps; homosexual; men who have sex with men (MSM); social media (Siriraj Med J 2023; 75: 612-621)

INTRODUCTION

Social media offers numerous benefits and perceived advantages for adolescents, including improved health literacy and communication skills. However, its excessive use can lead to undeniable social and medical problems,[1] such as cyberbullying, internet addiction, sleep problems, depression,[2] and increasing exposure to pornography and sexual risk behaviors.[1] In particular, social network dating in which individuals met online resulted in increased possibility of random, impromptu sexual encounters,

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which, in turn, led to unplanned, unprotected, and undiscerned sexual intercourse and sexual behaviors. Among men who have sex with men (MSM), high-risk sexual activity is frequently linked to substance abuse. Notably, misuse of prescription analgesic pills and muscle relaxants was significantly associated with engaging in receptive unprotected anal intercourse.[3] Other substances were used to enhance sexual stamina while performing anal sex, such as phosphodiesterase type 5 inhibitor.[4] Extensive social media use correlated with high-risk sexual activities. Smith LW et al. found a growing association between exposure to sexually explicit websites or "sexting" by young people and condomless sexual intercourse (SI), recent sexual activity, alcohol and drug use prior to SI, and having multiple recent sexual partners.[5] Furthermore, adolescents who shared sexual photos were more likely to have low self-esteem than their demographically similar peers.[6]

Sexting posed a specific risk to the MSM and bisexual population, as they extensively used geo-social mobile dating apps, granting greater access to potential sexual partners who lived nearby or were currently in close proximity. Previous research found that men who used online dating apps were more likely to seek sexual encounters rather than romantic relationships.[7] Moreover, the length of use of these dating apps was associated with increased likelihood of high-risk condomless anal intercourse.[8] Therefore, individuals who used geo-social apps for finding sexual partners were at greater risk for sexually transmitted infections, such as gonorrhea and chlamydia infection, when compared to individuals who met their partners in person.[9]

Sexual risk behaviors were also associated with patterns of geo-social dating app usage. Men who reported using 3 or more websites or apps to meet sex partners were significantly more likely to report anal intercourse and condomless anal sex within the past 3 months.[10] Finally, the use of such technology was also associated with increased likelihood of having sex exchanged for food, drugs, or a place to stay within the past 3 months.[11]

In Thailand, the use of online social networking has become increasingly popular over the past decade. The use of social media apps also increased from 33.2% to 86.8% in 2013 and 2016, respectively.[12,13] At the same time, increased sexual health risks were well-reported, especially among sexual minorities. It was estimated that there are 185,000 MSMs living in metropolitan Bangkok, and more than 75,600 transgenders living in Thailand. The median HIV prevalence among these two groups was estimated at 9.15% and 12.7%, respectively. A 2015 study by UNICEF found that 39% of young transgender people had commercial sex. Moreover, although condom use among MSMs and transgenders remained high at 82-84%, new infections had not declined[14], and the rate of HIV transmission in young MSMs aged less than 25-years-old remained 12.1%.[4] As such, the impact of mobile dating apps on this particular phenomenon remain unknown.

The study aimed to assess the association between mobile dating app usage and sexual risk behaviors among Thai homosexual and bisexual adolescents and youths. It also evaluated the links between sexual risk behaviors, self-esteem, and depression in the participants.

MATERIALS AND METHODS

Participants

We conducted a cross-sectional survey among adolescents and youths aged 11 – 25 years who identified themselves as homosexual, bisexual, or queer. Survey data was obtained during 17 May 2017 to 16 May 2018. Research posters were placed in large medical care centers in Bangkok, including the Adolescent Clinics at Siriraj Hospital and Ramathibodi Hospital, the Gender Variation Clinic at Ramathibodi Hospital, the Silom clinic at the Hospital for Tropical Diseases, the MSM Clinic at Bangrak Hospital, the Tangerine Clinic at the Thai Red Cross AIDS Research Center, and at the Rainbow Sky Association of Thailand Health Center. Study participants were also recruited via an advertisement in a popular online forum (www.pantip.com), and in an online chat room (www.lovecarestation.com). Those who were interested could voluntarily access the survey via a conspicuously visible QR code. Once logged in, the study information was visible, and participants were asked to complete a 62-item electronic questionnaire (provided in Thai), which took about 15-20 minutes to complete. Participants could decide whether they wanted to continue or not. Study consent was automatically obtained by way of a participant's voluntary decision to response the survey. Due to the anonymous log-in process, parental consent for participants aged less than 18 years was not required. Upon completion of the survey, a gift of 100 Thai baht in the form of a LINE pre-paid card (US$ 3.2) was sent to the email address provided by each participant. For sample size calculation, no previous study had reported the correlation coefficient value for this population. Considering other similar studies with 90-350 participants, the sample size for this study was set to at least 350.

The research methodology for this study was approved by the Ethical Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand [COA no. Si 264/2017] prior to initiation of the study.

Measurement

Survey questions were designed to collect demographic and lifestyle data, apps or website usage patterns, and sexual risk behaviors. Collected data included age, sexual orientation, marital status, education, occupation, and household income. Dating apps or website usage patterns within the previous 12 months were obtained using the number of apps or websites (multiple selectable choices with spaces for naming all dating apps or websites used), onset and duration of knowing apps, purpose of use, online day(s), online time(s), duration of use on weekdays, and duration of use on weekends. Sexual risk behaviors included inconsistent condom use, number of partners within the previous one and twelve months, number of previous partners, history of sexual transmitted infections (STIs), and history of substance use during sexual intercourse (SI). The developed questions were then tested for content validity by three experts (a child and adolescent psychiatrist, a gynecologist, and an adolescent medicine physician). The questions were then put to 33 unidentified participants to check for reliability and internal validity. The Cronbach's alpha coefficient was 0.95. Rosenberg Self-Esteem Scale, Thai version[15] with 10 items was used to assess the self-esteem of all participants (Cronbach's alpha: 0.86), with a higher score indicating higher self-esteem. Groups with low, moderate, and high self-esteem were classified by mean score. For depression screening, the 20-item self-report Center for Epidemiologic Studies-Depression Scale (CES-D), Thai version[16] was used. A score higher than 22 indicated a person at risk for depression (Cronbach's alpha: 0.86). The completed questionnaires were analyzed.

Statistical analysis

The descriptive data were shown as mean plus/minus standard deviation, median and range, or number and percentage. Chi-square and independent *t*-tests were used to test differences between two groups, and statistical significance was defined as *p*-value less than or equal to 0.05. To identify association between mobile dating apps or website usage patterns and sexual risk behaviors, we used Spearman's correlation coefficient (*r*). The factors associated with sexual risk behaviors were reported as crude and adjusted odds ratio with their respective 95% confidence interval (CI). Multiple logistic regression models were constructed for each exposure of interest, including age, biological sex, sexual orientation, education, occupation, and income, which were all previously found to be associated with sexual risk behaviors. The statistical analyses were conducted using SPSS version 18™ (licensed to Mahidol University).

RESULTS

Targeted recruitment

Out of 401 respondents, 360 completed the survey, resulting in an 89.7% response rate. Of those, 219 (60.8%) self-identified as homosexuals, 110 (30.6%) as bisexuals, and the remaining 31 (8.6%) as queer or not sure about their sexual orientation. Table 1 showed the demographic and lifestyle characteristics of study participants. The mean age was 21 years. The homosexual group was significantly older than the bisexual group (21.3±2.6 vs. 20.6±2.9, respectively; p=0.03). Most participants (75%) were in a relationship prior to the initiation of this study. Over half were studying (55.3%), and 62.8% had low income (<15,000 Thai baht/month).

Dating app or website usage patterns

The median number of dating- apps/websites used by study participants was 2 (range: 1-10). The most popular website for finding sex-partners was Google. The dating apps and websites reported by participants were shown in Fig 1. Weekends were the most common online days, and during 5 to 10 pm was the most popular time period for searching out dating partners (Fig 2). The majority of participants (78.1%) used dating apps to find friends, whereas one-third used them to find sexual partners. Subgroup analysis revealed homosexual males to be significantly more likely than homosexual females to use dating apps to find sex partners (p<0.001). In addition, bisexual males were significantly more likely to use dating apps to find sex partners than homosexual males (p=0.037), while homosexual females were significantly more likely to use these apps to find a partner for a long-term relationship than bisexual females (X^2 5.42, p=0.02).

Sexual risk behavior

In our study population, the mean age at first SI was 17.6±2.8 years. About two-thirds (62.8%) of subjects met with persons they found via dating apps, and most of those (79.6%) had SI with their apps partner. Among the homosexual group, males were significantly more likely to meet (p<0.001) and have SI (p<0.001) with an app partners than females. About half (52.2%) reported no condom use during SI with apps partners. About one-third (30.6%) of participants used substances during SI. The most common substance used was alcohol (83.6%). The median number of previous apps partners within 12 months was 4, and the median number of concomitant apps partners (within the previous 30 days) was 1 with a range of 0 to 22. Duration of familiarity with the dating apps was strongly associated with duration of dating

TABLE 1. Demographic and lifestyle characteristics of adolescents and youths aged 11-25 years grouped by sexual orientation.

Characteristics		All (n=360)	Sexual orientation: Homosexual (n=219)	Bisexual (n=110)	Queer (n=31)
Age (years old)	Mean ± sd	21.0 ± 2.8	21.3 ± 2.6	20.6 ± 2.9	19.8 ± 3.5
Previously in a relationship	n (%)	270 (75.0)	163 (74.4)	84 (76.4)	23 (74.2)
Educational status	n (%)				
High school		81 (22.5)	40 (18.2)	27 (24.5)	14 (45.2)
Vocational school		24 (6.7)	12 (5.5)	6 (5.5)	6 (19.4)
Bachelor degree		231 (64.2)	147 (67.1)	74 (67.3)	10 (32.3)
Master degree or higher		20 (5.6)	18 (8.2)	1 (0.9)	1 (3.1)
Others		4 (1.0)	2 (1.0)	2 (1.8)	0 (0.0)
Occupation	n (%)				
Student		199 (55.3)	116 (53.0)	66 (60.0)	17 (54.8)
Employed		142 (39.4)	91 (41.5)	39 (35.5)	12 (38.7)
Unemployed		19 (5.3)	12 (5.5)	5 (4.5)	2 (6.5)
Marital status	n (%)				
Single		249 (69.2)	143 (65.3)	81 (73.6)	25 (80.6)
In a relationship		103 (28.6)	72 (32.9)	25 (22.7)	6 (19.4)
Married/stay together/divorced		8 (2.2)	4 (1.8)	4 (3.6)	0 (0.0)
Income per month*	n (%)				
< 15,000 Baht		226 (62.8)	127 (58.0)	77 (70.0)	22 (71.0)
15,001-30,000 Baht		101 (28.1)	68 (31.1)	27 (24.5)	6 (19.4)
30,001-50,000 Baht		24 (6.7)	19 (8.7)	4 (3.6)	1 (3.2)
> 50,000 Baht		9 (2.5)	5 (2.3)	2 (1.8)	2 (6.5)
Dating apps/ websites usage pattern					
Number of dating apps/websites used	Median (range)	2.0 (1-10)	3.0 (1-10)	2.0 (1-10)	2.0 (1-7)
Duration of using dating app/ website (years)	Median (range)	3.0 (0.5-12.0)	3.0 (0.5-12.0)	3.0 (0.5-10.0)	2.0 (1.0-11.0)
Duration of use on weekdays (hours)	Median (range)	2.0 (0-16.0)	1.0 (0-14.0)	2.0 (0-16.0)	2.0 (1.0-10.0)
Duration of use on the weekend	Median (range)	2.0 (0-24.0)	2.0 (0.1-24.0	3.0 (0-24.0)	4.0 (1.0-15.0)
Purpose of using apps/websites	n (%)				
Find friends		281 (78.1)	167 (76.3)	87 (79.1)	27 (87.1)
Find long-term relationship		232 (64.4)	146 (66.7)	67 (60.9)	19 (61.3)
Find sex partner		117 (32.5)	75 (34.2)	33 (30.0)	9 (29.0)
Sex workers		17 (4.7)	7 (3.2)	8 (7.3)	2 (6.5)

TABLE 1. Demographic and lifestyle characteristics of adolescents and youths aged 11-25 years grouped by sexual orientation. (Continue)

Characteristics		All (n=360)	Sexual orientation: Homosexual (n=219)	Bisexual (n=110)	Queer (n=31)
Sexual practice					
Age at sexual debut (years) (n=233)	Mean ± sd	17.6 ± 2.8	17.5 ± 2.8	17.6 ± 2.8	17.8 ± 2.8
Met partner from a dating app/website,	n (%)	226 (62.8)	145 (66.2)	63 (57.3)	18 (58.1)
Having SI with apps-partner, n (%)	(n=226)	180 (79.6)	122 (84.1)	48 (76.2)	10 (55.6)
Previous apps sex-partners within 12 months (n=179)	Median (range)	4.0 (0-100)	3.0 (0-100)	5.0 (0-48)	10.0 (1-20)
Previous apps sex-partners in a month, (n=179)	Median (range)	1 (0-22)	1 (0-22)	1 (0-7)	1 (0-5)
Number of times having group sex (n=56)	Median (range)	3 (1-10)	3 (1-10)	3 (1-6)	3 (2-10)
No condom used with app-partners (n=180)	n (%)	94 (52.2)	61 (50.0)	25 (52.1)	8 (80.0)
Always ask the number of sex-partners from current apps-partner (n = 180)	n (%)	50 (27.8)	34 (27.9)	15 (31.2)	1 (10.0)
Always ask history of previous STD (n=180)	n (%)	46 (25.6)	27 (22.1)	16 (33.3)	3 (30.0)
Type of substances used while having sex					
Substance use during SI	n (%)	55 (30.6)	30 (24.6)	22 (45.8)	3 (30.0)
Alcohol		46 (83.6)	22 (73.3)	21 (95.5)	3 (100)
Vasodilator (sildenafil)		21 (38.2)	13 (43.3)	6 (27.3)	2 (66.7)
Methamphetamine & its derivatives		9 (16.4)	7 (23.3)	1 (4.5)	1 (33.3)
Cannabis		7 (12.7)	3 (10.0)	3 (13.6)	1 (33.3)
Mental health issues					
Rosenberg's self-esteem score	Mean ± sd	28.9 ± 4.8	28.7 ± 4.9	29.3 ± 4.4	29.0 ± 4.9
Level of self-esteem					
Low	n (%)	65 (18.1)	46 (21.0)	16 (14.5)	3 (9.7)
Moderate to high	n (%)	295 (81.9)	173 (79.0)	94 (85.5)	28 (90.3)
CES-D score,	Median (range)	17.4 ± 9.6	17.5 ± 9.2	16.9 ± 10.0	18.4 ± 11.3
Positive depression screening	n (%)	116 (32.2)	72 (32.9)	35 (31.8)	9 (29.0)

* 1 USD = 32.507 Thai baht (2017)

Abbreviations: SD, standard deviation; USD, United States dollars; App(s), application(s); SI, sexual intercourse; STD, sexually transmitted disease; CES-D, Center for Epidemiologic Studies Depression Scale

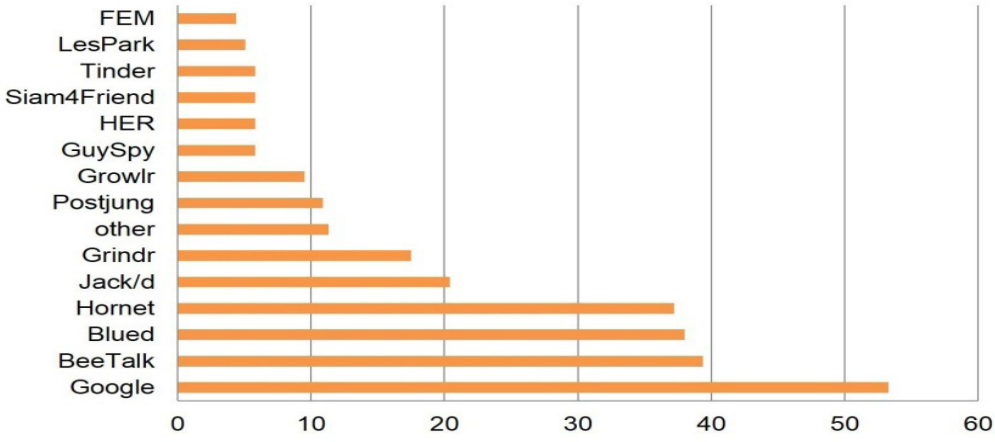

Fig 1. Dating apps/websites accessed among study adolescents and youths.

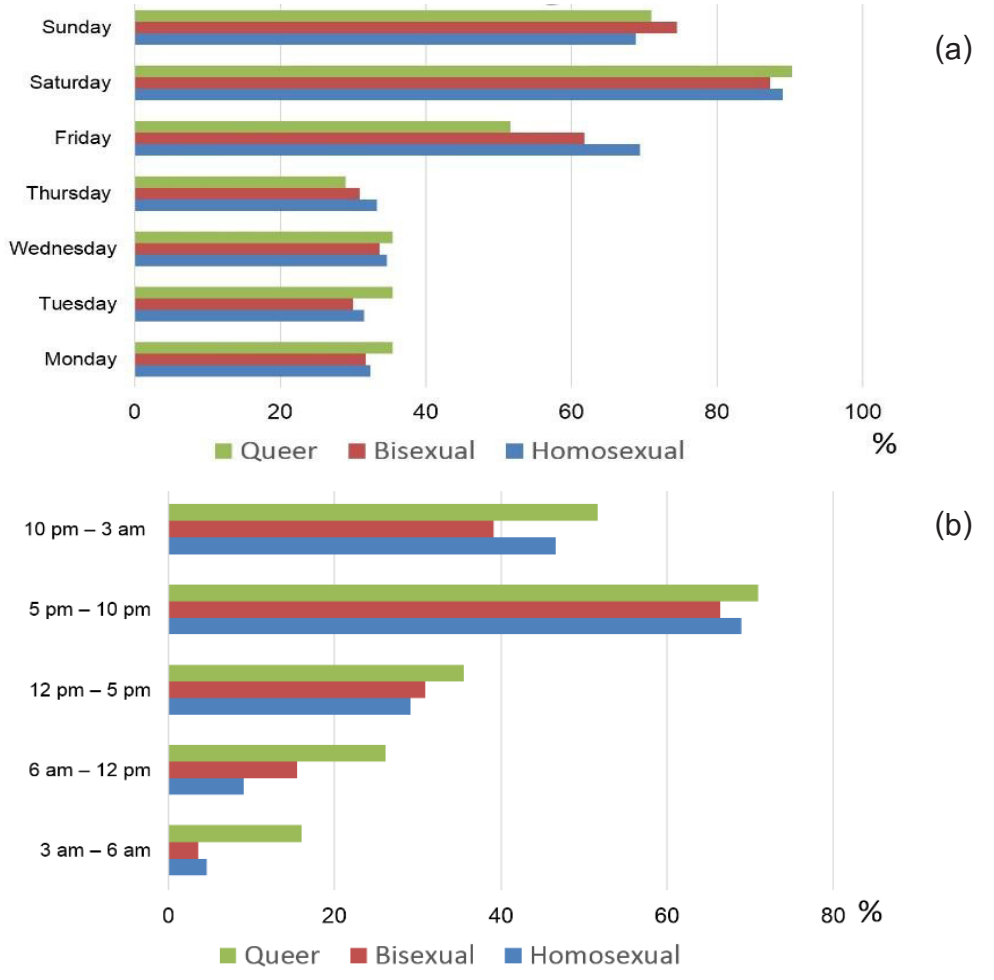

Fig 2. Days (a) and times (b) online among subgroup participants.

platform use during the weekdays and weekend ($p<0.001$). Moreover, those who used dating apps during the weekday were also more likely to use them during the weekend ($r=0.80$, $p<0.05$) (Table 2). In addition, if a study subject currently had sex partners that they became acquainted with via dating apps, they were significantly more likely to have had app-partners before within that year ($r=0.67$, $p<0.001$).

Table 3 showed the factors significantly associated with specific sexual risk behaviors (inconsistent condom use, recent multiple apps sex-partners, and substance use during SI). After adjusting for age, biological sex, sexual orientation, education, occupation, and income, participants who used ≥2 apps/websites were twice as likely to have inconsistent condom use [OR: 2.131, 95% CI: 1.047-4.334], and 2.8 times more likely to use drug

TABLE 2. Spearman's correlation coefficient of dating app/website usage patterns.

Dating app usage patterns	Age	Number of dating apps being used	Duration of knowing dating apps	Duration of dating app use on weekdays	Duration of dating app use on weekends	Previous app partner within 12 months
Number of dating apps being used	*0.18***					
Duration of knowing dating apps	*0.56***	-0.03				
Duration using dating app use on weekdays	*0.10**	*0.29**	*0.26***			
Duration of dating app use on weekends	*0.10**	*0.13**	*0.24***	*0.80**		
Previous app partner within 12 months	0.015	*0.28***	-0.04	0.10	0.14	
Recent app partner	-0.002	0.06	-0.14	0.136	0.13	*0.67***

A p-value<0.05 indicates statistical significance* and p<0.01 indicated strongly statistical significance**

TABLE 3. Factors associated with various sexual risk behaviors.

Factors	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)*	*P*	B	SE
Inconsistent condom use						
Duration of knowing apps >3 years	1.984 (1.086 - 3.623)	0.026	1.975 (0.998 - 3.907)	0.051	0.680	0.348
Number of apps/websites used >2 apps	1.466 (0.792 - 2.711)	0.223	2.131 (1.047 - 4.334)	*0.037*	0.756	0.362
Previous history of no condom use	74.408 (24.155 - 229.210)	*<0.001*	90.348 (26.373 - 309.509)	*<0.001*	4.504	0.628
Recent sex partners from apps ≥2 partners	2.212 (1.198 - 4.081)	*0.011*	2.212 (1.159 - 4.219)	*0.016*	0.794	0.330
Positive depression screening	2.612 (1.359 - 5.020)	*0.004*	2.436 (1.231 - 4.821)	*0.011*	0.890	0.348
Recent multiple sex partners from apps						
Duration of knowing apps >3 years	2.381 (1.263 - 4.489)	*0.007*	2.633 (1.248 - 5.552)	*0.011*	0.968	0.381
No condom use with apps sex partner	2.212 (1.198 - 4.081)	*0.011*	2.267 (1.149 - 4.475)	*0.018*	0.818	0.347
Substance use during SI	2.646 (1.381 - 5.073)	*0.003*	3.080 (1.467 - 6.464)	*0.003*	1.125	0.378
Substance use during SI						
Number of apps/websites used >2 apps	2.154 (1.051 - 4.415)	*0.036*	2.807 (1.172 - 6.725)	*0.021*	1.032	0.446
Recent sex partners from apps ≥2 partners	2.646 (1.381 - 5.073)	*0.003*	3.144 (1.487 - 6.646)	*0.003*	1.145	0.382

*Adjusted for age, biological sex, gender orientation, education, occupation, and income
A p-value<0.05 indicates statistical significance* and p<0.01 indicated strongly statistical significance**
Abbreviations: OR, odds ratio; CI, confidence interval; SE, standard error; App(s), application(s); SI, sexual intercourse

during SI [OR: 2.807, 95% CI: 1.172-6.725]. History of no-condom use [OR: 90.348, 95% CI: 26.373-309.509] and having positive depression screening [OR: 2.436, 95% CI: 1.231-4.821] were factors that had higher odds that a study subject would have sex without barrier method. Moreover, those who used dating apps for a long time and those who practiced unsafe sex (no condom use or use of substances while having sex) also had a higher chance of having multiple sex partners. Lastly, participants who regularly had a minimum of 2 sex partners had a greater probability of taking any substance while having SI [OR: 3.144, 95% CI: 1.487-6.646]. These results strongly confirm that duration of use these kinds of dating apps/websites, and the number of dating apps used strongly significantly associated with high sexual risk behaviors among homosexual and bisexual adolescents and youths.

Self-esteem and depression

The mean score of the Rosenberg self-esteem scale was 28.9±4.8. Sixty-eight participants (18.1%) showed low self-esteem (scores less than 25) with no statistical difference among the homosexual, bisexual, and queer groups. No association between low self-esteem and sexual risk behaviors was found. Around one-third of each group had positive depression screening. Those at risk for depression were associated with inconsistent condom use (X^2 9.05, $p<0.01$), and were twice as likely to use no condom when compared to the group without depression (OR: 2.61, 95% CI: 1.36-5.02; $p<0.01$) (Table 3).

DISCUSSION

This paper described the patterns and relationships specific to geo-social mobile dating apps among the homosexual, bisexual, and queer adolescents and youths in Thailand. Our findings demonstrated that these populations have used several dating apps/websites for a few years, that they spent twice as much time during the weekend compared to during the week, and that they accessed these platforms mostly at night. Interestingly, most of the dating apps/websites used were originally created in English, which suggests that these populations were well-educated or that at least they understood English. This hypothesis was supported by the fact that over 80% of our participants completed at least high school. Extensively use of geo-social mobile dating apps provided greater access to nearby potential sexual partners, which was found to pose a special sexual risk to the MSM, lesbian and bisexual populations. More than three-fourths of our target populations already had a sexual relationship and had their sexual debut by the end of middle adolescence (at age 17.5-17.8 years). Most participants used mobile dating apps to search for sexual partners, which is similar to previous research. People used online dating apps to seek sexual relationships, and men were more likely to seek out a sexual encounter rather than a romantic relationship.[7] However, the Thai youths in this study tended to seek friends and romantic relationships from dating apps more than finding sexual partners when compared to previous study.[6] The data from our study showed that the more study participants used these dating apps, the more likely they were to engage in sexual risk behaviors. In addition to inconsistent condom use and unawareness of their partner's sexual risk, our study identified other high-risk sexual behaviors, such as group sex or 'sex party or swinging sex', substance use when having sex, and a large number of sex partners (22 partners in a month or a hundred in a year). Consistent with previous study, we found condomless anal intercourse to be more common among low-education people who spent more time using dating apps.[8] In addition, a small number of bisexual and homosexual females reported no condom use during sex, which may be due to a lack of education, unawareness of sexual transmitted disease, or misunderstanding that condom is only for males.[17]

Compatible with another report[18], one-third of our study participants reported using substances while having sex, and alcohol was the most common substance used followed by vasodilator medication (sildenafil), methamphetamine, and cannabis, sequentially. It's worth noting that cannabis was not legally declared "free" during the study. Access to alcohol was not difficult, but sildenafil required a physician specialist's prescription, and amphetamine and cannabis were illegal in Thailand, which suggested illegitimate sourcing for all (including under age for alcohol) or most substances. Those using substances were more likely to be employed, bisexual, using many dating apps for a long time, spending more time online, and currently having multiple partners from dating apps. Generally similar to other previous reports[19,20], individuals who had positive screening for depression were more likely to demonstrate condom noncompliance. Depression was also shown to increase sexual risk and diminish self-efficacy towards condom use among MSM population.[21] In addition to having sex to cope with sadness, when feeling depressed, people had less concentration, which could reduce sexual risk perception that could lead to forgetting to use a condom.[22,23]

Our study demonstrated association between the use of dating apps/websites and sexual risk behaviors among bisexual and homosexual adolescents and youths population. The more exposure they had to these dating

platforms, the more sexual risk they experienced. Therefore, sexual risk prevention that specifically focuses on dating apps/ websites is suggested. First, exposure to dating apps or sexually explicit websites should be delayed in children and adolescent population. Second, educate children and adolescents to postpone their sexual debut until the appropriate age or relationship, and emphasize the important of a 'no condom, no sex' approach to SI decision-making. In addition to family, school was shown to be another effective environment for helping students develop the confidence to say "No" to sex, to understand the consequences of unplanned sex, and how to minimize sexual risk, including substance use.[24] Legal mandating of pop-up messages, such as a warning to engage in safe sex, should be considered for dating apps/websites. Finally, early detection of depression and treatment may help to reduce possible future sexual risk.

Limitations

This study has some mentionable limitations. Firstly, since this was a self-report questionnaire-based study, certain recall bias among study participants was possible. Secondly, the authors provided a LINE pre-paid card to participants who provided their email addresses as a token of gratitude for their cooperation. However, this could be seen as a biased incentive favoring a specific group. Thirdly, the authors acknowledged the delayed timing of publication but emphasized that the study's uniqueness and relevance persist for Thailand and neighboring countries with similar social and cultural norms, contrasting to developed countries where "sexual health/sexuality or gender minorities" issues are more advanced. Lastly, recruiting participants from specific locations serving sexual-minority adolescents and youths may introduce bias towards mental health and substance use issues, potentially inflating their prevalence in the study. In addition to the valuable findings from this study, an additional strength of this study is proof of the effectiveness of the study design. For researchers who set forth to study these same or similar objectives in their respective country (especially in the developing world), we recommend an anonymous online approach that is user-friendly, and the use of an attractive premium that can be rapidly and easily redeemed as a thank you gift to the respondent.

CONCLUSION

The patterns of use of online dating apps/websites was found to be significantly related to high sexual risk behaviors among homosexual and bisexual adolescents and youths. The longer they used and the more they were exposed to these kinds of apps/websites, the higher the likelihood that they would present sexual risk behaviors, particularly having recent multiple partners, inconsistent condom use, and using substance while having sex. In addition, almost one-fifth of this population had low self-esteem, and around one-third were at-risk for depression, and depression would increase the risk of unsafe sex practices.

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Conflict of interest declaration

The authors hereby declare no personal or professional conflicts of interest regarding any aspect of this study.

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Increased Serum Neutrophil Lymphocyte Ratio Raises the Risk for Peripheral Diabetic Neuropathy in Type 2 Diabetes Mellitus Patients

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ABSTRACT

Objective: Peripheral diabetic neuropathy (PDN) is among the most prevalent diabetes mellitus (DM) sequelae. PDN is a severe health issue that represents a huge social and economic burden worldwide, is associated with long-term morbidity, and diminishes the quality of life of those affected. The neutrophil-lymphocyte ratio (NLR) is a mixture of the two primary components of chronic inflammatory diseases (high neutrophils and low lymphocytes) that contribute to the production of PDN. This study aimed to demonstrate high serum NRL levels enhance the risk of PDN in type 2 DM patients.

Materials and Methods: This study employed a case-control design, collecting data from the registers and outpatient medical records of Prof. Dr. IGNG Ngoerah General Hospital type 2 DM patients who satisfied the inclusion and exclusion criteria between January 2018 and December 2019. Based on clinical neuropathy and abnormal electrodiagnostic testing, the PDN diagnosis was established. Serum NLR was collected from laboratory tests recorded by a computer.

Results: The Receiver Operating Characteristic (ROC) curve approach determined the NLR cut-off value of 2.18. High NLR substantially increased the incidence of PDN (OR 10.36; 95% CI 3.69-29.07; p≤0.001). Other characteristics evaluated, including duration of diabetes, usage of anti-diabetic medications, uncontrolled diabetes, obesity, hypertension, and dyslipidemia, were not significantly associated with the incidence of PDN. High serum NLR was an independent risk factor for PDN in type 2 DM patients (adjusted OR=10.36; 95% CI: 3.57-29.07; p≤0.001).

Conclusion: Based on the findings of this investigation, it was determined that elevated serum NLR increases the risk of PDN events in patients with type 2 DM.

Keywords: Diabetes mellitus; neutrophil-lymphocyte ratio; peripheral diabetic neuropathy; risk factors (Siriraj Med J 2023; 75: 622-628)

INTRODUCTION

One of the most prevalent consequences of diabetes mellitus is peripheral diabetic neuropathy (PDN). PDN is a serious health issue representing a large social and economic burden worldwide, causing long-term morbidity and diminished quality of life for those affected. The prevalence of diabetes globally is predicted to be around 382 million people, with the number of diabetics expected to reach 629 million by 2045.[1] PDN was found in about 10% of DM patients within the first year after diagnosis, rosed to 50% after 25 years. Approximately fifty percent of DM patients experience PDN, thirty

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percent of diabetic patients suffer PDN pain (PDNP), and thirty-nine percent do not obtain treatment or disregard the PDN complaint.[2,3] A lack of understanding of the pathophysiology of neuropathy impedes the management of PDN, resulting in suboptimal therapy that leads to long-term morbidity and diminishes the quality of life for patients.[4] Peripheral diabetic neuropathy causes balance disturbances and increases the risk of falls, especially in the elderly.[5] Foot ulcers are the leading cause of lower limb amputation, affecting around fifty percent of those with neuropathy.[3]

The neutrophil-lymphocyte ratio (NLR) combines the two primary components of chronic inflammatory disorders (high neutrophils and low lymphocytes). An increased neutrophil count indicates a continuous, nonspecific, damaging inflammatory activity, whereas a low lymphocyte count suggests comparatively insufficient immunological control and dormant immune pathways. Elevated NLR can show the immune system's functioning during chronic inflammatory events.[6] NLR as an inflammatory biomarker in type 2 complications involving the macrovascular and microvascular systems Diabetes mellitus is an independent predictor of carotid artery intima-media thickening, and albuminuria compared to other cardiovascular risks factors such as age, male sex, smoking history, duration of diabetes, estimated glomerular filtration rate (eGFR), LDL, albuminuria-creatinine ratio, and HbA1c. NLR is also believed to be indicative of an autonomic vascular imbalance. The sympathetic nerves stimulate granulocyte release, whereas the parasympathetic nerves stimulate lymphocyte release. A greater NLR may imply a greater ratio of sympathetic to parasympathetic activity. In addition to increasing oxygen consumption and releasing proinflammatory cytokines such as IL-6 and TNF-, the sympathetic tone also stimulates smooth muscle and interstitial cell proliferation, accelerating the progression of atherosclerosis.[7,8]

According to a literature search undertaken by researchers, there is a lack of domestic literature and study examining the association between NLR and the increased risk of microvascular complications of DM, particularly in PDN instances. NLR examination is simple, non-invasive, available in nearly all level one healthcare institutions, and affordable. Based on this and the reviewed theoretical background, a study on a high NLR is recommended to evaluate an increase in the risk of diabetic neuropathy in type 2 diabetes patients at Prof. Dr. IGNG Ngoerah General Hospital, Denpasar.

MATERIALS AND METHODS

This study used a case-control design. Aim of this study was to prove high NLR as the risk factor of diabetic neuropathy in type 2 diabetes patients. The odds ratio was determined by comparing two groups of subjects with type 2 DM (T2DM) who had PDN (cases) and those without PDN (controls) and then examining the serum NLR in the blood (high or low) recorded in the medical record of neuro polyclinic and internal medicine polyclinic (diabetes center) Prof. Dr. IGNG Ngoerah General Hospital, Denpasar. NLR was measured by dividing the absolute number of neutrophils by the absolute number of lymphocytes. Patients treated from January 2018 to December 2019 were the subjects of the collected data. The study included 85 types 2 DM participants who fulfilled the eligibility requirements and were divided into groups with (42 subjects) and without PDN (43 subjects). This study's sample size fulfilled the minimal sample size requirements, with 39 people in each group.

Inclusion criteria in this research included: (1) patients were diagnosed with type 2 diabetes for under five years, (2) patients were diagnosed with PDN, (3) patients were between 40 and 80 years old, (4) gender, length of DM, type of diabetic therapy, duration of diabetes treatment, diabetes control status, nutritional status, medical history, connected full blood laboratory test, HbA1c examination, and lipid profile were included in the patient's medical record, (5) patients underwent an electrophysiological evaluation at the electro neuro-myography (ENMG) neuro polyclinic, with data indicating a PDN. The exclusion criteria for cases and controls were: (1) patients had history of chronic kidney disease, HIV infection, morbus hansen, systemic lupus erythematosus, cancer, entrapment neuropathy (carpal tunnel syndrome/CTS, cervical root syndrome/CRS), history of the spinal cord and peripheral nerve trauma, blood disease (myeloproliferative and leukemia), coronary heart disease, cerebrovascular disease, diabetic retinopathy, (2) patients had severe illness and were bleeding profusely, (3) antiretroviral, chemotherapeutic, traditional analgesic, anti-inflammatory, and anti-tuberculosis medicines were administered to individuals with neuropathy, (4) patients had history of hazardous exposure, including alcohol, pesticides, mercury, and organophosphates, are at risk for lead poisoning.

Purposive sampling was used to determine research subjects, with the researcher selecting topics based on subjective and practical considerations. Subjects in medical records that met the eligibility criteria were included in the study until the required number of samples was obtained and homogenous. The age and gender matching procedure was conducted in both groups. The Chi-Square test has

been used to test the null hypothesis in bivariate analyses involving categorical nominal independent variables and unpaired dependent variables. If the requirements for the Chi-Square test are not met, Fisher's test will be conducted. The logistic regression method has been used to examine other categorical variables that may have affected the study's results. Variables included in the multivariate analysis are those with a *p*-value≤0.25 in the bivariate analysis. The study data will be statistically examined using Windows SPSS version 20.

RESULTS

The case group included 42 subjects with a mean age of 59.9±1.44 years, while the control group had a mean age of 61.37±1.59 years. In both groups, men predominated, with 69% males in the case group. In the control group, the mean HbA1c was greater than in the case group (8.32±0.38 vs 7.90±0.31%). The case group had a higher median NLR value than the control group (2.99 vs 1.94) (Table 1).

TABLE 1. Fundamental characteristics of research participants.

Variables	Case (42 samples) N (%)	Control (43 samples) N (%)	*P*-value
Age mean ± SD (tahun)	59.9 ± 1.44	61.37 ± 1.59	0.490
Sex			
Male	29 (69.0)	31 (72.1)	0.760
Female	13 (31.0)	12 (27.9)	
Level of education			
Elementary	2 (4.8)	6 (14.0)	0.270
Junior high school	12 (28.6)	5 (11.6)	
Senior high school	15 (35.7)	18 (41.9)	
Undergraduate/Diploma	8 (19.0)	9 (20.9)	
Job			
Government employees	10 (23.8)	8 (18.6)	0.270
Private employees	7 (16.7)	15 (34.9)	
Self-employed	12 (28.6)	11 (25.6)	
Farm workers	6 (14.3)	2 (4.7)	
Etc	7 (16.7)	7 (16.3)	
HbA1C levels			
Mean ± SD (%)	7.90 ± 0.31	8.32 ± 0.38	0.220
Neutrophil levels			
Median (103/µL)	6.27	5.01	0.007*
Lymphocyte levels			
Mean ± SD (103/µL)	1.97 ± 0.15	2.57 ± 0.11	0.002*
NLR			
Median	2.99	1.94	<0.001*

Note: *statistically significant $p \leq 0.05$

The total NLR yielded value data with a range of 0.86 to 26.83 and a median of 2.39. The ROC curve demonstrates that the NLR value has a relatively high diagnostic value, as the curve is above the 50% line. The ROC method yielded an AUC value of 77.9% (95% CI: 0.68 - 0.88; p = 0.001). The AUC value of 77.9% indicates appropriate diagnostic capacity from a statistical point of view. The ROC coordinates indicate that the NLR cutoff value of 2.18 utilized in this investigation has a sensitivity of 83.3%, specificity of 67.4%, positive predictive value (PPV) of 71.4%, and negative predictive value (NPV) of 80.5%. The research data were separated into two groups: those with serum NLR levels greater than 2.18 and those lower than 2.18.

Using an NLR cutoff value of 2.18, the relationship between elevated serum NLR as the independent variable and PDN in T2DM patients as the dependent variable was evaluated. The analysis revealed a significant association between high serum NLR and PDN in T2DM patients, with an odds ratio of 10.357 (95%CI = 3.69 – 29.07; $p \leq 0.001$), indicating that high serum NLR in T2DM patients increases the risk of PDN by 10.36 times relative to DM patients with low serum NLR in Table 2. The analysis of each component of NLR (neutrophils and lymphocytes) revealed that lymphocytes significantly increased the risk of PDN events in T2DM patients (OR = 9.07; 95%CI=2.31-34.11; $p \leq 0.001$).

A bivariate analysis was performed between PDN in patients with T2DM and duration of DM, types of anti-diabetic drugs (ADD), uncontrolled DM, obesity, hypertension, dyslipidemia, neutrophil levels, and lymphocyte levels. Of all the variables, no significant relationship was found between other variables and PDN in T2DM patients (Table 3).

Multivariate analysis included serum NLR, dyslipidemia, neutrophil levels, and lymphocyte levels with $p \leq 0.25$ in bivariate analysis. Serum NLR was an independent risk factor for PDN in DM patients, with an odds ratio of 10.36 (95% CI: 3.57-29.07; $p \leq 0.001$) (Table 4).

DISCUSSION

This study performed an age-matching procedure at the outset of the study. However, due to data limitations, an age difference of fewer than 2 years was still included, resulting in a relatively small difference in the mean age between the two groups. This study's findings are consistent with a study by Karki et al.[9] and an investigation by Suwannaphant et al.[10] which found that the prevalence of PDN was highest among individuals aged 51 to 60. The prevalence and incidence of PDN increased and were directly proportional to age, with the prevalence rising by 3.2% in the 20-30 age group, 11.5% in the 40-59 age group, and 20.4% in the over-60 age group.[11,12] It is related to the vascular characteristics of the peripheral nervous system that the prevalence of PDN increases with the age and duration of DM. The peripheral nervous system's reliance on vascular supply makes it susceptible to disruption.[13] In this analysis, the average age of DM patients with PDN was 59-60 years, presumably owing to the significant number of patients over 60 with other comorbid diseases. They were excluded at the outset.

In this survey, it was discovered that men predominated in both categories. In China, the prevalence of PDN among women was greater than among men.[6] Males are four years more likely than females to develop PDN as a complication of T2DM.[14] Compared to previous studies, the variance in this study's proportion of males and females may result from demographic differences

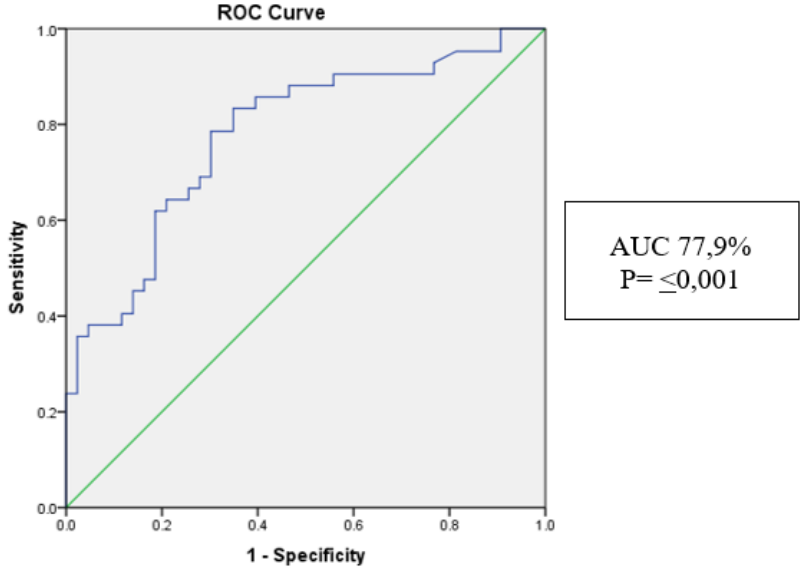

Fig 1. ROC of serum NLR to PDN values.

TABLE 2. Bivariate analysis of NLR, neutrophils, and serum lymphocytes with PDN in DMT2.

Variables		PDN Case N (%)	Control N (%)	OR (CI 95%)	*P*-value
NLR	High	35 (83.3)	14 (32.6)	10.36 (3.69-29.07)	<0.001*
	Low	7 (16.7)	29 (67.4)		
Neutrophil	High (≥7.5)	15 (35.7)	6 (14.0)	3.43 (1.18-9.98)	0.200
	Low-Normal (<7.5)	27 (64.3)	37 (86.0)		
Lymphocyte	Low (<1.5)	17 (40.5)	3 (7.0)	9.07 (2.31-34.11)	<0.001*
	Normal-High (≥1.5)	25 (59.5)	40 (93.0)		

Note: *statically significant $p \leq 0.05$

TABLE 3. Bivariate analysis of other variables and PDN in patients with DMT2.

Variables	PDN Case N (%)	Control N (%)	OR (CI 95%)	*p*-value
Length of diabetes				
3-5 years	13 (72.2)	21 (48.8)	2.72 (0.83-8.97)	0.090
< 3 years	5 (27.8)	22 (51.2)		
Type of diabetics drugs				
Insulin	21 (50.0)	19 (44.2)	1.26 (0.54-2.96)	0.590
Oral	21 (50.0)	24 (55.8)		
Uncontrolled DMT2				
Yes	26 (61.9)	28 (65.1)	0.87 (0.36-2.1)	0.760
No	16 (38.1)	15 (34.9)		
Obesity				
Yes	6 (14.3)	6 (14.0)	1.03 (0.30-3.48)	0.960
No	36 (85.7)	37 (86.0)		
Hypertension				
Yes	22 (52.4)	23 (53.3)	0.96 (0.41-2.24)	0.920
No	20 (47.6)	20 (46.5)		
Dyslipidemia				
Yes	28 (66.7)	34 (79.1)	0.53 (0.2-1.4)	0.198
No	14 (33.3)	9 (20.9)		

Note: DMT2: diabetes mellitus type 2

TABLE 4. Logistic regression multivariate analysis.

Variable	OR	CI 95%	*P*-value
Step 1			
NLR	9.83	3.47-27.88	<0.001*
Length of diabetes	1.65	0.59-4.58	0.330
Dyslipidemia	0.73	0.23-2.30	0.590
Step 2			
NLR	10.11	3.58-28.59	<0.001*
Length of diabetes	1.72	0.63-4.72	0.290
Step 3			
NLR	10.36	3.69-29.07	<0.001*

Note: *statically significant p<0.05

in the sampling location. The same was discovered for education in secondary school in our study. The difference in results may be because most subjects in this study reside in urban areas and generally have at least a high school education. Those with a high level of education are more aware of complications of DM, such as a PDN, and therefore are more likely to seek medical attention. Work and education are not directly related to the incidence of diabetes mellitus or neurodegenerative disease but rather to the existence of urban residents, the majority of whom are urban residents who have a lifestyle-related association.[15] PDN severity correlates linearly with age, body mass index (BMI), and duration of DM, but not with HbA1c in our study.[16] In this study, obesity was determined by BMI values and the results did not indicate a statistically significant increase in the risk of adverse events. In previous studies, the BMI had no statistically significant effect on the incidence of PDN in T2DM patients.[17,18] Similarly, precise results were obtained for hypertension, possibly due to the large number of DM patients with hypertension at our hospital who had other complicating conditions and thus did not satisfy the criteria for sample collection.

Neutrophils are integrally connected to chronic inflammation, whereas lymphocytes reflect immune regulation pathways. The literature explaining the direct relationship between lymphocytes and the formation of PDN is scarce. Chronic hyperglycemia in DM will increase the release of reactive oxygen species (ROS) from neutrophils and decrease lymphocyte levels. Chronic hyperglycemia also directly causes diminished lymphocyte proliferation. In patients with uncontrolled type 2 diabetes, decreased lymphocyte proliferation is more prevalent. In type 2 diabetes, the decrease in lymphocyte proliferation is due to the low expression of IL-2 receptors. CD25 deficiency is the cause of the reduced level of IL-2 receptor expression. CD25 is crucial for stimulating the IL-2 receptor to produce T cells. CD25 serves a vital role in expanding T cell cloning after antigen discovery. Antigen stimulation increases IL-2 expression because T cells are the primary proliferating cells in specific immune responses. Low levels of IL-2 inhibit lymphocyte proliferation and differentiation.[10] NLR is an independent risk factor for PDN associated with diabetic microangiopathy, which impairs the nutrient supply to neuronal and Schwann cells, resulting in peripheral neuropathy due to nerve degeneration. NLR combines the two primary components of chronic inflammatory disorders (high neutrophils and low lymphocytes).[6] High neutrophils were more prevalent in the PDN group, but there was no significant association with an increased risk of PDN.

In contrast, low lymphocytes substantially increased the risk of a PDN incident. Similar lymphopenia has been observed in numerous clinical and experimental studies of people with diabetes with microvascular, macrovascular, and other complications. It may be the result of increased oxidative DNA damage and lymphocyte apoptosis. Diabetes patients exhibited decreased lymphocyte proliferation due to lower IL-2 receptor expression levels. It causes a decrease in lymphocytes and an increase in neutrophils, thereby increasing the NLR.[6]

This study's strength is the lack of prior research on NLR and the incidence of PDN. NLR has extensively

studied DM microvascular complications such as peripheral arterial disease (PAD), diabetic retinopathy, and diabetic nephropathy.[18] Still, its relationship to PDN has not been extensively studied, particularly in Indonesia so this study will add future research references. This study was also conducted by matching by design on confounding variables so that other factors contributing to the incidence of PDN can be controlled and the results of high serum NLR as an independent risk factor for PDN in patients with T2DM can be strengthened. Blood assays for evaluating NLR (a marker of ongoing destructive nonspecific inflammatory processes) or lymphocytes (relatively inactive or insufficient immune regulation) alone are less stable indicators of the functional status of the immune system than the ratio.

The limitation of this study is there were differences in treatment between the two groups, with ENMG examination not being performed in the control group, so a diagnosis of subcutaneous PDN (no visible signs of neuropathy but abnormalities in nerve conduction velocity or abnormal small fiber neuropathy examination) could not be ruled out (no visible symptoms of neuropathy but irregularities in nerve conduction velocity or abnormal small fiber neuropathy examination). In addition, the sample size is limited to a single region, so it cannot be used to characterize the population as a whole. Large-scale research is required to further evaluate the implementation of NLR in predicting PDN.

CONCLUSION

Neutrophil-lymphocyte ratio can be one of the predictors of high risk PDN in T2DM patients. Compared to T2DM patients with low serum NLR, T2DM patients with high blood NLR levels (2.18 mg/dL) had a 10-fold greater chance of developing PDN.

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Outcomes of Per-Oral Endoscopic Myotomy in the Treatment of Esophageal Achalasia: Over One Hundred Cases in a Single Tertiary Center

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ABSTRACT

Objective: To study the outcomes and complications of per-oral endoscopic myotomy (POEM) in patients with esophageal achalasia.

Materials and Methods: This retrospective observational study reviewed the medical records of esophageal achalasia patients who underwent POEM between March 2013 and September 2022. One hundred and eight cases were included.

Results: A total of 108 consecutive patients were included in this study and classified into 4 groups: 30 (27.8%) as type I; 53 (49.1%) as type II; 5 (4.6%) as type III; and 20 (18.5%) as unspecified due to unsuccessful catheter placement across the esophagogastric junction. The mean patient age was 46.10±16.59, 77 (71.3%) patients were female. Ten (9.3%) of the patients had undergone prior treatment, including balloon dilation, POEM, Heller myotomy, and nitroglycerine. Technical success was achieved in 106 (98.1%) cases, clinical success was evaluated only in 88 patients who follow up more than 6 month and the median follow-up time was 20.50 months (range 6-110 months). The clinical success was accomplished in 82 (93.2%), and 26 (24.1%) patients experienced perioperative complications which were significantly associated with anterior myotomy and probably operator learning curve. One patient (1.1%) had recurrent symptoms at 24-month follow up. Gastroesophageal reflux disease (GERD) was found in 19 (21.6%) patients, all of whom responded well to proton pump inhibitors (PPIs).

Conclusion: POEM is effective and safe in long-term treatment of achalasia. Although the incidence of symptomatic GERD was slightly high, the cases were not severe and were well controlled with medication.

Keywords: Per-oral esophageal myotomy; POEM; achalasia; outcomes; complication. (Siriraj Med J 2023; 75: 629-637)

INTRODUCTION

Esophageal achalasia is an esophageal motility disorder characterized by incomplete relaxation of the lower esophageal sphincter (LES), increased LES pressure and lack of normal peristalsis of the esophagus causing symptoms of dysphagia, chest pain, regurgitation and weight loss. Diagnosis and pre-operative evaluations include esophagogastroduodenoscopy (EGD), high-resolution esophageal manometry (HREM) and barium/time-barium esophagography (BE/TBE). Various treatments are available for lowering LES pressure, such as nitroglycerine, balloon dilation, and botulinum toxin injection, Heller myotomy and also per-oral endoscopic myotomy (POEM), which was first performed in 2008 by Professor Haruhiro Inoue, who later published his first case series of 17 patients in 2010.[1] Since then, many

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POEM studies, including retrospective single- and multi-center reviews, systematic reviews and meta-analyses, have reported its good clinical outcomes and safety.[2-7]

Our center first performed POEM in March 2013 and had conducted 108 of these operations by September 2022. In the early period, all procedures were performed by two experienced endoscopists, who later supervised operations conducted by a further 2 experienced endoscopists. This retrospective observational study aims to analyze the outcomes of our 9-year experience in a single tertiary center in terms of technical and clinical success, as well as perioperative and long-term complications, such as gastroesophageal reflux disease (GERD).

MATERIALS AND METHODS

This study was approved by Institutional Review Board (code: 66054). Medical records were retrospectively reviewed of 108 patients who underwent POEM between March 2013 and September 2022. The study included patients who had undergone the procedure after being diagnosed with achalasia from EGD, BE/TBE and/or HREM results.[8-12] The exclusion criteria were factors which identified individuals as unsuitable candidates for POEM, such as those with end-stage achalasia with massive dilated and tortuous esophagus; severe heart or pulmonary disease; coagulopathy; cirrhosis with portal hypertension; and history of previous endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), or radiofrequency ablation (RFA) of esophagus.[13,14]

The data used for pre-operative evaluation included gender, age, duration of symptoms, prior treatment, pre-operative Eckardt score, barium column height and width recorded at 5 minutes post-swallow from TBE, and integrated relaxation pressure (IRP) from HREM. Achalasia patients were classified into 4 groups: types I, II and III (by manometric patterns characterized with the Chicago Classification), and an unspecified group (patients whose esophageal manometry failed due to unsuccessful catheter placement across the esophagogastric junction). Further subtypes were classified as non-sigmoid and sigmoid type based on BE/TBE findings.

The procedure began with EGD for esophageal irrigation to eliminate the contents of the esophagus. Mucosal injection and incision were performed to create a submucosal tunnel appropriate for the myotomy technique and planned approach. Two different myotomy approaches were used in our department: anterior, in which the myotomy is performed at 12-1 o'clock; and posterior, at 5-6 o'clock. The choice of operative technique varied in accordance with operator preference or whether a previous myotomy by POEM or Heller technique had been performed, in which case the opposite approach was utilized. The length of myotomy in the esophagus varied according to the type of achalasia and manometry patterns, plus 2-3 cm in the gastric site. At the end of the procedure, the mucosal incision was closed with clips.[1]

Technical success was defined as complete performance of all steps.[15] Perioperative complications such as hypercarbia, pneumoperitoneum, subcutaneous emphysema, pneumothorax, pleural effusion, mucosal injury, perforation, or bleeding, were recorded. EGD with or without esophagogram was performed the following morning. If all mucosal clips were correctly placed and no leakage was observed, then the patients were allowed a clear liquid diet followed by a full liquid diet on the following day. The patients were discharged when they could tolerate a liquid diet, and they were advised to resume a soft diet the following week.

Postoperative clinical evaluation was performed using Eckardt score at 1, 3, and 6 months, and then once annually.[15] A score of over 3 within 6 months indicated clinical failure, while this score after 6 months was classified as recurrence.[16] Testing of HREM and TBE was performed in some patients who had questionable clinical evaluation but no time specific. GERD as a long-term complication was recorded if patients presented with reflux symptoms which were relieved by taking proton pump inhibitors (PPI) or when the results of 24 hours of pH monitoring confirmed acid exposure with pH levels below 4 for over 80 minutes/day or when EGD showed evidence of reflux esophagitis or Barrett's esophagus.[17]

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc. Chicago IL, USA), Descriptive statistics were used to characterize populations, categorical variables were presented as number and percentage, and continuous variables were represented by mean ± standard deviation (SD) or median (range) when the data are skewed. Differences in qualitative variables between two groups were analyzed using Chi-squared test or Fisher's exact test, while either Student's t-test or Mann-Whitney U test was used to compare continuous variables between two groups. Multivariate analysis was performed with logistic regression model in the "Enter" method.[18] Adjusted by surgical technique and subtype of achalasia and a p-value less than 0.05 was considered to be statistically significant.

RESULTS

A total of 108 consecutive patients underwent POEM. Their mean age was 46.10±16.59 years, and the majority were female (77/108, 71.3%). Twenty-nine (26.9%) had

underlying diseases such as hypertension, diabetes mellitus, reactive airway disease (asthma/COPD), hyperthyroid, cardiac arrhythmia (atrial fibrillation, sinus bradycardia, PVC), and others. All conditions were well controlled preoperatively. Thirty patients (27.8%) had achalasia type I, 53 (49.1%) had type II, 5 (4.6%) were type III, and 20 (18.5%) were unspecified type. With regard to subtype classification, 14 (13.0%) were sigmoid and 94 (87.0%) were non-sigmoid type. Median duration of symptoms was 12 months (range 2-240 months). Ninety-eight (90.7%) had had no prior treatment, while 10 patients (9.3%) had undergone previous modalities (2 pneumatic balloon dilations, 5 POEMs (3 POEMs from our hospital who were clinical failure from the first POEMs and 2 POEMs from outside hospital), 1 laparoscopic Heller myotomy, 1 open Heller myotomy, and 1 nitroglycerine). Median Eckardt score was 6 (range 0-10), and median IRP was 31.4 (range 11.5-83.6) mmHg. Preoperative TBE was conducted in 26 patients (24.07%) with median barium height 129.3 (range 34.6-242.7) mm, and median width 36.7 (range 22.8-76.4) mm as shown in Table 1.

With regard to surgical techniques and perioperative outcomes, about the myotomy technique, 26 patients (24.1%) underwent the myotomy technique using anterior approach and 80 patients (74.1%) had the posterior approach, while 2 patients' operative reports were missing (1.9%). Median myotomy length was 9 (range 2-17) cm, and median operative time was 120 minutes (range 45-295). Technical success was achieved in 106 patients (98.1%), while 2 patients (1.9%) had severe inflammation and fibrosis of esophageal mucosa resulting in failure to create a submucosal tunnel and, therefore, an unsuccessful operation. Perioperative complications occurred in 26 patients (24.1%) as follows: pneumoperitoneum needing intraoperative needle decompression (13), subcutaneous emphysema (4), pneumothorax (2), hypercarbia (4), perforation (2), mucosal injury (6), hypotension (1), hypoxia (1), pleural effusion (2) and bleeding (1). All complications were resolved with symptomatic and supportive treatment, except one case of pleural effusion, which required intercostal tube drain insertion. Median length of hospital stay was 9 days (range 4-41).

TABLE 1. Preoperative demographic and clinical characteristics of the study patients.

Characteristics	Total (n=108) n (%)
Gender	
Male	31 (28.7)
Female	77 (71.3)
Age (mean±SD)	46.10±16.59
Underlying Disease	
Yes	29 (26.9)
No	79 (73.1)
Type of achalasia	
Unspecified	20 (18.5)
Achalasia type I/II/III	30 (27.8)/ 53 (49.1)/ 5 (4.6)
Subtype of achalasia	
Non-sigmoid	94 (87.0)
Sigmoid	14 (13.0)
Duration of symptoms (month)	12 (2-240)
Prior treatment	
No	98 (90.7)
Yes	10 (9.3)
Pre-operative IRP (mmHg) (median (min-max))	31.4 (11.5-83.6)
Pre-operative Eckardt score	6 (0-10)
Pre-operative time barium swallowing	
Barium height at 5 min. (mm)	129.3 (34.6-242.7)
Barium width at 5 min. (mm)	36.7 (22.8-76.4)

Twenty patients (18.5%) were excluded from clinical outcomes due to follow up period less than 6 months, only the remaining 88 patients were evaluated in clinical outcomes. Median follow-up time was 20.50 months (range 6-110), median post-operative IRP decreased to 17.2 mmHg (range 0.7-73.5), median barium height fell to 30.0 mm (range 0.0-245.8), and median barium width went down to 24.8 (1.7-134.7) mm. Eighty-two patients (93.2%) had improvement of symptoms and Eckhardt score ≤ 3 and were classified as clinical successes, while 6 (6.8%) were categorized as clinical failures, as they developed symptoms and had Eckhardt score > 3 within 6 months. Three of these patients underwent laparoscopic Heller myotomy, while another 3 received POEM (which were included in the analysis as 3 patients who had prior treatment by POEM), and all 6 eventually achieved clinical improvement. Nineteen patients (21.6%) developed GERD, and all of these improved with daily PPI use. One patient (1.1%) who developed symptoms at 24 months was classified as a case of recurrence and successfully underwent laparoscopic Heller myotomy.

According to very low number of technical failure, there was no factor associated with technical success (Table 2). The patients without perioperative complication achieved clinical success higher than the patients with perioperative complication significantly on univariate analysis (p=0.027) as shown in Table 3 but it was not necessary to perform multivariate analysis due to small number of clinical failure. The perioperative complications were significantly associated with the use of the anterior myotomy technique on uni-and multivariate analysis as shown in Table 4 and Table 5.

TABLE 2. Factors associate with technical success.

Characteristics	Technical success Success (n=106) n (%)	 Failure (n=2) n (%)	P-value
Gender			0.494
Male	30 (96.8)	1 (3.2)	
Female	76 (98.7)	1 (1.3)	
Age	46(16-88)	44(44-44)	0.191
Co-morbidities			0.467
Yes	28 (96.6)	1 (3.4)	
No	78 (98.7)	1 (1.3)	
Type of achalasia			0.078
Unspecified	18 (90.0)	2 (10.0)	
Type I	30 (100.0)	0 (0.0)	
Type II	53 (100.0)	0 (0.0)	
Type III	5 (100.0)	0 (0.0)	
Subtype of achalasia			0.244
Non-sigmoid	93 (98.9)	1 (1.1)	
Sigmoid	13 (92.9)	1 (7.1)	
Duration of symptoms (month)	12 (2-240)	126 (12-240)	0.545
Prior treatment			1.000
None	96 (98.0)	2 (2.0)	
Yes	10 (100.0)	0 (0.0)	
Pre-operative Eckard	6(0-10)	4.5 (1-8)	0.726
Complications (early postoperative)			1.000
Yes	26 (100.0)	0 (0.0)	
No	80 (97.6)	2 (2.4)	

*Values were represented as n (%), mean+SD and median (min-max). The p-value from independent samples t-test and chi-square test with significant at p<0.05

**Factors associated with technical success could not be computed in pre-operative IRP, pre-operative time barium swallowing, myotomy site, myotomy length because failure group data was missing.

TABLE 3. Factors associate with clinical success.

Characteristics	Clinical success		P-value
	Success (n=82) n (%)	Failure (n=6) n (%)	
Gender			0.665
Male	25 (96.2)	1 (3.8)	
Female	57 (91.9)	5 (8.1)	
Age	47.2±16.96	45.5±2.81	0.444
Co-morbidities			0.339
Yes	21 (87.5)	3 (12.5)	
No	61 (95.3)	3 (4.7)	
Type of achalasia			0.808
Unspecified	17 (89.5)	2 (10.5)	
Type I	22 (95.7)	1 (4.3)	
Type II	39 (92.9)	3 (7.1)	
Type III	4 (100.0)	0 (0.0)	
Subtype of achalasia			1.000
Non-sigmoid	70 (93.3)	5 (6.7)	
Sigmoid	12 (92.3)	1 (7.7)	
Duration of symptoms (month)	12.5 (2-240)	33 (12-240)	0.309
Prior treatment			1.000
None	72 (92.3)	6 (7.7)	
Yes	8 (100.0)	0 (0.0)	
Pre-operative IRP	33.35±15.63	51.25±4.88	0.115
Pre-operative Eckard	6.11±1.92	6.17±3.06	0.947
Myotomy length (cm)	8.99±2.47	8.75±0.96	0.850
Operative time	120 (50-295)	80 (60-120)	0.113
Complications (early postoperative)			0.027*
Yes	17 (81.0)	4 (19.0)	
No	65 (97.0)	2 (3.0)	

*Values were represented as n (%), mean+SD and median (min-max). The p-value from independent samples t-test and chi-square test with significant at $p<0.05$

TABLE 4. Factors associate with complications.

Characteristics	Complications		P-value
	Yes (n=26) n (%)	No (n=82) n (%)	
Gender			0.818
Male	7 (22.6)	24 (77.4)	
Female	19 (24.7)	58 (75.3)	
Age	46.04±14.62	46.12±17.26	0.982
Co-morbidities			0.125
Yes	10 (34.5)	19 (65.5)	
No	16 (20.3)	63 (79.7)	
Type of achalasia			0.870
Unspecified	4 (20.0)	16 (80.0)	
Type I	6 (20.0)	24 (80.0)	
Type II	15 (28.3)	38 (71.7)	
Type III	1 (20.0)	4 (80.0)	
Subtype of achalasia			0.511
Non-sigmoid	24 (25.5)	70 (74.5)	
Sigmoid	2 (14.3)	12 (85.7)	
Duration of symptoms (month)	19(4-156)	12(2-240)	0.448
Prior treatment			0.696
None	25 (26.0)	71 (74.0)	
Yes	8 (80.0)	2 (20.0)	
Pre-operative IRP	33.42±15.88	32.68±15.09	0.861
Pre-operative Eckard	6.08±2.19	6.07±1.88	0.993
Pre-operative time barium swallowing			
Barium high (mm)	178.7(87.3-242.7)	120.8(34.6-235.3)	0.088
Barium wide (mm)	35.0(29.7-51.4)	38.6(22.8-76.4)	0.377
Technique			0.001*
Anterior approach	13 (50.0)	13 (50.0)	
Posterior approach	13 (16.3)	67 (83.8)	
Myotomy length (cm)	9.71±2.44	8.92±2.29	0.152
Operative time (min.)	120 (60-150)	120 (45-295)	0.688
LOS (days)	9 (4-15)	9 (5-41)	0.893

*Values were represented as n (%), mean+SD and median (min-max). The p-value from independent samples t-test and chi-square test with significant at $p<0.05$

TABLE 5. Multivariate analysis of factors associated with Complication.

Factors	Crude OR	95% CI	P-value	Adj. OR	95%CI	P-value
Surgical technique						
(Anterior approach)	5.154	1.951-13.616	0.001	5.194	1.955-13.798	0.001
(Posterior approach)	1			1		

On multivariable analysis by logistic regression model in the "Enter" method. Adjusted by Surgical technique and Subtype of achalasia, *significance at p<0.05.

DISCUSSION

After the excellent outcomes of the first POEM case series were reported by Professor Inoue in 2010[1], this procedure became accepted as a good treatment choice for achalasia. In our institute, 108 consecutive cases have been carried out with a good technical success rate of 106/108 (98.1%). The two technical failures, resulting from severe submucosal fibrosis, were unspecified type, one sigmoid and one non-sigmoid subtype. A recently published retrospective review showed that the majority of cases of submucosal fibrosis occur in type I achalasia and proposed a double tunnel method to effectively and safely reduce technical failure during POEM, improving the technical success rate from 68.3% to 98.4%.[19]

The short-term clinical success rate at 6-month follow up was 82/88(93.2%) patients. There was only one incidence of recurrence which was identified at the 24-month long-term follow up. At the maximum follow-up time of 110 months, the long-term clinical success rate was 92.0%, similar to the findings of two previous systematic reviews, one of which reported clinical success rates at 6-12 months, at 24 months, and at 36 months of 93.2%, 91.5% and 93.1% respectively.[7] The other review found pooled clinical success at 30 to 60 months and >60 months of 87% and 84% respectively.[6] This suggests that POEM is an effective treatment which yields very good results that can be maintained beyond 5 years.

Concerning about achalasia patients diagnosed despite normal IRP and outcome of treatment, Sanagapalli et al.[20] suggested that, to diagnosed a subset of achalasia patients with normal IRP, but impaired LES relaxation can demonstrated by additional provocative tests using rapid drink challenge (RDC), solid swallows during HREM, and/or barium esophagogram, and the outcome of treatment exhibited equivalent to achalasia diagnosed in the conventional fashion. There are 5 patients demonstrated normal IRP in this study, one patient loss follow up and 4 patients had clinical success with a 9-103 month- follow up period.

Even though the median of post-POEM IRP was higher than 15 mmHg (17.2 mmHg) but Eckardt score was lower than 3 can be explained by a multicenter, observational cohort study reported by Hata Y et al.[21] studied the associations between post-POEM HREM and the outcomes of POEM. 7% (151 of 2,171 patients) showed residual high post-POEM IRP (≥ 26 mmHg; Starlet [Starmedical Ltd, Tokyo, Japan]) still have comparable clinical outcome with low post-POEM IRP patients. The high pre-POEM IRP and gastric myotomy of ≤ 2 cm were predictive of residual of high post POEM IRP values, and a residual high post-POEM IRP not necessarily mean clinical failure and routine HREM follow-up is not recommended after POEM.

Another factor which may influence the outcome was "prior treatment". A retrospectively study reported the effect of prior treatment on clinical outcomes with a low rate of major adverse events but increase the risk of clinical failure after POEM.[22] In this study, 8 of 10 patients with prior treatment (5 POEM, 2 heller myotomy and 1 nitroglycerine) had minor perioperative complication but not statistically significant (p=0.696) and there was no technical failure and clinical failure in this group which probably due to small number of patients.

Regarding perioperative complications associated with myotomy techniques and practices used in our center, we performed POEM using the anterior approach in the first 16 cases routinely, and then moved on to the posterior approach which was then adopted as the normal technique, where technically feasible, over the next 3 years. Adverse events occurred in a total of 26 cases (24.1%), half of which resulted from use of the anterior approach, 13/26 cases (50.0%) and the majority of these (10) occurred in the first 16 cases. A randomized pilot study and a narrative review supported the correlation between anterior myotomy and increased risk of mucosal injuries due to its need for greater scope tip angulation[23,24], but the majority of findings of randomized clinical trials and systematic reviews have reported comparable outcomes

for the two approaches.[25-27] In our study, the significant complications from anterior approach might be from early period of learning curve.[28] The minimum threshold number of cases required for an expert interventional endoscopist to reach this plateau was around 13. Another study focusing on training 4 surgeons in the use of POEM found that the number of operations required to reach this plateau was 12 cases, after which significant reductions in dissection speed and perforation were achieved.[29]

GERD occurred in 19 of 88 patients (21.6%), all of whom were in the clinical success group. Some studies have claimed that the posterior approach probably has a higher incidence of GERD because it involves severance of both the circular and sling or oblique fiber, but the difference has been found to be of only borderline significance in some systematic reviews and meta-analysis.[30] In our study, the incidence of GERD was also higher with the posterior (15/67, 22.4%) compared to the anterior approach (4/21, 19.0%), but this difference was also not significant (p=1.00).

Limitation of this study was retrospective study and the small number of patients.

CONCLUSION

POEM is effective and safe as a long-term treatment for achalasia. While perioperative adverse events were associated with anterior myotomy and probably surgeons' insufficient experience in the use of the technique, these complications responded well to conservative management. Although the incidence of symptomatic GERD was slightly high at 21%, the cases were not severe and were successfully treated with to PPI.

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Bedaquiline Effect Towards QT Interval in Drug Resistant Tuberculosis (DR-TB): A Systematic Review

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ABSTRACT

Objective: Bedaquiline is recommended by World Health Organization (WHO) to treat Drug-Resistant Tuberculosis (DR-TB). Bedaquiline is chosen due to its efficacy and safety in numerous studies. One adverse event that could happen is QT interval prolongation, which increases the risk of Torsade de Pointes (TdP) and leads to death. This study aimed to discuss the knowledge on the effect of bedaquiline on before-after and changes of QT interval.

Materials and Methods: This systematic review based on PRISMA guidelines through PubMed, Cochrane, Science Direct, ProQuest, Google Scholar, and Epistemonikos until April 10, 2023. The keywords used was ("Bedaquiline" AND "QT Interval"). We implemented inclusion and exclusion criteria by PICOS framework then assessed the studies by Joanna Briggs Institute (JBI) critical appraisal checklist tools.

Results: From 1.170 articles, eleven articles met the criteria. In total 2,449 patients assessed in this study. Most of the studies carried out treatment duration of 6 months. There was a change in the mean QT interval between 11ms to 52.5ms in patients using bedaquiline from the beginning to the end of treatment. The mean QT interval after treatment ranges from 409.7ms – 464.5ms.

Conclusion: The use of bedaquiline requires attention to the ECG before and during therapy. Regular monitoring is necessary to prevent QT prolongation.

Keywords: Bedaquiline; Drug-Resistant Tuberculosis; QT Interval (Siriraj Med J 2023; 75: 638-645)

INTRODUCTION

Bedaquiline is an anti-tuberculosis drug that is still recommended by the World Health Organization (WHO) today for Multi Drug-Resistant Tuberculosis (MDR-TB).[1] MDR-TB is a difficult case to treat and the incidence is increasing. Not only that, the genes of resistant TB that can mutate and present various variants of resistant mutations pose a potential ineffectiveness of current drugs in the future.[2] However, Bedaquiline is used because of its good efficacy in treating DR-TB and is better than kanamycin and bedaquiline could reduce the median time to culture conversion.[3,4] Result from clinical trial phase 2 in 2015 showed bedaquiline containing regimen considered well tolerated and led to good outcomes for DR-TB patients.[5] But behind a therapy with its efficacy, certainly has side effects that need to be considered in the provision of therapy. Meta-analysis by Lan *et al* in 2020 revealed the least amount of adverse events leading to long-term drug cessation occurred with bedaquiline (1.7% [0.7 – 4.2]),[6] However

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the QT interval prolongation, skin rash, hyperlactatemia, peripheral neuropathy, electrolyte depletion, and hearing loss are some adverse effects that need to be dealt with.[7,8]

The side effect of QT interval prolongation needs to be a concern for clinicians before giving the drug to patients. Issues arising from QT interval prolongation will progress to Torsade de Pointes (TdP), a heart arrhythmia that could be fatal and cause the patient to pass away. TdP is a distinctive polymorphic ventricular arrhythmia that is linked to delayed ventricular repolarization as shown by a prolonged QT interval on the surface electrocardiogram.[9] A retrospective cohort study by Darmayani *et al* showed 37.1% patients experienced clinically significant QTcF prolongation from 105 observed subjects.[10] Darmayani *et al*'s suggestion for therapy with bedaquiline is that patients require intensive cardiac monitoring during therapy period.[10]

The clinical question that will continue to arise is how much change in QT interval can be considered safe during Bedaquiline therapy? It has not yet been established exactly what is the limit or value that clinicians should be concerned about that can be considered "safe". Some opinions use the limitation that if the QT interval is above 500mm then the patient is stopped on treatment. We argue that this is potentially dangerous. This is due the risk of arrythmic events increases by 5% for every 10ms increase in the QT interval (normal QTc invervals are approximately 450ms for men and 460ms for women.[11] If 500mm is taken as the limit, men have a risk of arrythmia of 25% and 20% in women. Thus, this systematic review aims to discuss the knowledge on the effect of bedaquiline on before-after and changes of QT interval.

MATERIAL AND METHODS

Data sources and search strategy

For reporting in systematic reviews, we used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and synthesis without meta-analysis. PubMed, Science Direct, Epistemonikos, Cochrane, ProQuest and Google Scholar were all searched for papers. Keywords like "Bedaquiline" AND "QT Interval" were utilized. We incorporate all research: (1) full text, (2) English or Indonesian Language, (3) Display the QT Interval value in numeric form, and (5) last 10 years. The search strategies are described in full in Fig 1. Unpublished data, duplicate research and reviews were disregarded. This systematic review registered at PROSPERO with number: CRD42023393217.

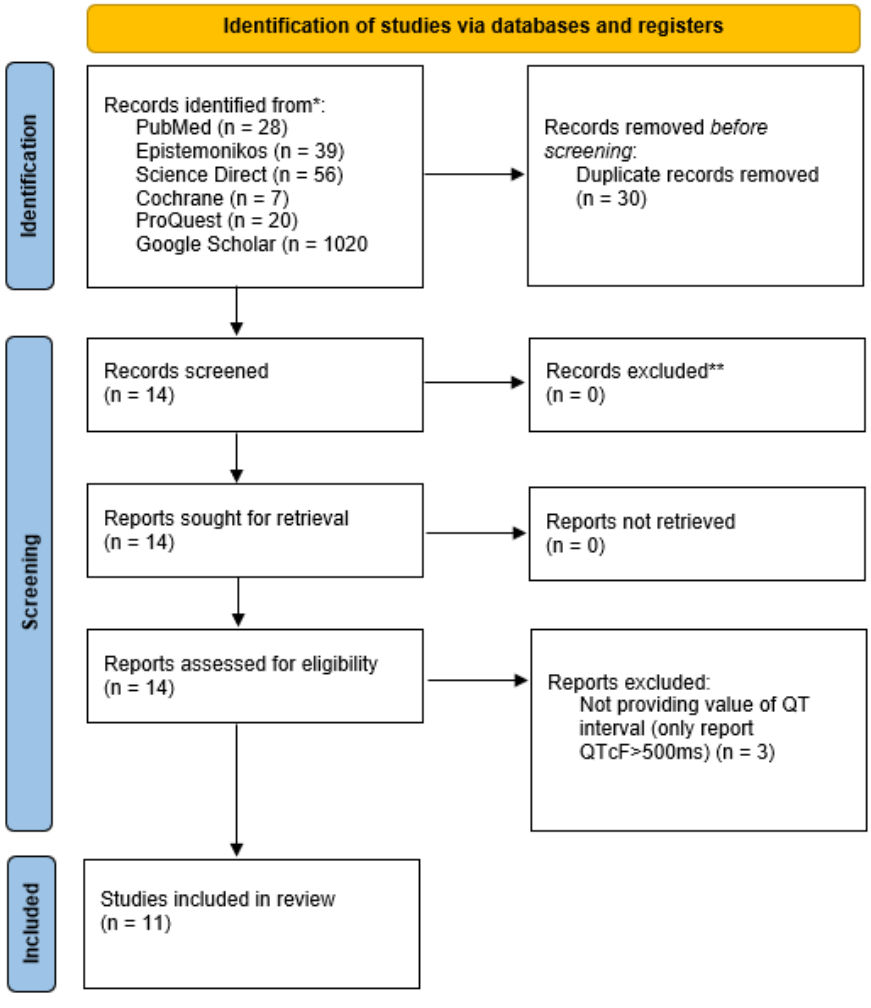

Fig 1. Flow diagram of included studies based on PRISMA flow chart.

Study Selection

Four researchers (AMS, RA, DTB, and RDH) independently evaluated eligibility based on titles and abstracts using the PICO framework (Population = DR-TB; Intervention = Bedaquiline; Compare = Not Specified; Outcome = QT interval). The consensus was reached between investigators to resolve disagreements, or supervisors (IY) were involved when consensus could not be reached.

Data extraction and risk of bias

From each included study, data were taken on: (1) country, (2) study design, (3) population, (4) study size, (5) Intervention, (6) time on treatment, (7) Regimen, (8) QT Interval before and after, and (9) QT interval changes. The primary outcome to determine QT interval changes after take Bedaquiline during obervation.

According to the type of articles received, AMS, RA, DTB and RDH examined full-text articles using the Joanna Briggs Institute Critical Appraisal Tool (jbi.global/critical-appraisal-tools). Consensus was reached to resolve the disagreements, or when consensus could not be established, supervisors (IY) were involved.

RESULTS

Study selection

A total of 1.170 studies were identified from the research database (Fig 1). After removing the duplicate records, 14 records were screened and assessed for eligibility. 11 studies were included in the review, after excluding three studies due to out of scope based on inclusion criteria. There are three articles that provide the effects of Bedaquiline in QT Interval but the form of QT interval they provided in categorical form, either >500ms or <500ms. Therefore we exclude those three articles.

Characteristics of included studies

A total of 1.170 studies were identified from the research database (Fig 1). After removing the duplicate records, and analyze the article based on title, abstract then proceed with full-text, we include 11 studies with 2,449 patients included. The studies we included have various types of study designs such as cohort and clinical trials originating from various countries such as Indonesia, South Africa, America, China, and so on. Patients included in this study were all patients with DR-TB and in some articles were specified according to findings such as Rifampicin-Resistant Tuberculosis (RR-TB), Multi Drug Resistant Tuberculosis (MDR-TB), and others. All studies conducted observations with a duration of six (6) months and there are some notes from several articles as compiled in Table 1.

QT interval changes in the use of bedaquiline

Of the patients included in this study, 405 out of 2,449 patients (16.5%) had QT Interval problems either QT interval ≥500ms or an increase in QT interval from baseline ≥60ms. Table 2 summarizes the results of each study included in this study including the QT interval values before therapy, after therapy, and the change in QT interval from baseline. The mean QT interval value after treatment with Bedaquiline in each article was rated as safe at <450ms. Only one article by Vandu et al.[12], 2022 which in their research found a mean QT interval value of 458.4ms, this according to the degree of QT interval display is considered as QT prolongation degree 1. When looking at the column of QT Interval changes from baseline also in each study can be said to be safe, no study found a mean increase in QT interval from baseline ≥60ms. The highest value of change in QT interval from baseline was 44.5 (23.8 - 63.8) from the study of Lee et al[13], 2021. Although on average both the change in QT interval after Bedaquiline therapy and the change in QT interval were said to be good, there were several cases of QT interval prolongation and some had to be discontinued. This shows that Bedaquiline can indeed increase the QT interval, but the number of cases can be said to be small, so it is necessary to monitor the QT interval of patients who are on therapy using Bedaquiline.

Risk of bias

All authors analyze risk-of-bias for every included study based on study design. The cutoff value we set has a risk of bias if it is less than 65%. The mean score of all articles was 89.9% with a lowest score of 84%. Fig 2 displays the JBI score of each article that has been analyzed.

DISCUSSION

Summary and interpretation of findings

This systematic review seeks to analyze the impact of Bedaquiline on QT Interval prolongation in patients with DR-TB. Of the various studies that have been included, the average QT Interval value after six months of observation with Bedaquiline is below 450ms, only two studies report the average post-treatment QT interval is above 450ms, namely Vandu et al., 2022 ranging from 458.4 (SD, 23.7) and Lee et al., 2021 with a median value of 462 (IQR, 443.3 - 492.0). Based on the degree of the average value of the two studies, it is categorized as QT

TABLE 1. Characteristics of the included studies.

Authors	Country	Design	Population	Study size	Intervention	Time on Treatment	Notes
Vandu, *et al.*[12], 2022	Indonesia	Retrospective Cohort	DR-TB	46	BDQ Regiment	6 Months	
Darmayani, *et al.*[10], 2022	Indonesia	Retrospective Cohort	DR-TB	105	BDQ Regiment	6 Months	52 Patients were not completed the BDQ's treatment
Dooley, *et al.*[16], 2021	South Africa and Peru	RCT	RR-TB/MDR-TB	50	BDQ Regiment (400mg for 14 days + 200mg thrice-weekly) BDQ+DLM Regimen	6.5 Months	Clofazimine was not allowes Moxifloxacin switched to levofloxacin
Katrak, *et al.*[17], 2021	America Cohort	Prospective	MDR-TB	37	BDQ Regiment	6 Months	
Isralls, *et al.*[18], 2021	South Africa Cohort	Retrospective	DR-TB	420	BDQ Regiment	6 Months	
Gao, *et al.*[19], 2021	China	Prospective Cohort	MDR-TB/XDR -TB	1162	BDQ Regiment	6 Months	
Brust, *et al.*[20], 2021	South Africa	Prospective Cohort	RR-TB/XDR-TB	195	BDQ Regiment	6 Months	
Lee, *et al.*[13], 2020	South Korea	Retrospective Cohort	MDR-TB	74	BDQ+DLM Regiment	6 Months	
Ndjeka, *et al.*[21], 2022	South Africa	Retrospective Cohort	XDR-TB	200	BDQ Regiment	6 Months	
Ferlazzo, *et al.*[22], 2018	Armenia, India, and South Africa	Retrospective Cohort	DR-TB	28	BDQ Regiment	6 Months	
Diacon, *et al.*[23], 2014	Brazil, India, Latvia, Peru, the Philippines, Russia, South Africa, and Thailand	RCT	MDR-TB	132	BDQ Regiment	6 Months	66 Patients are placebo

TABLE 2. Result of selected studies.

Authors	Regimen	n	QT Interval (Before), ms	QT Interval (After), ms	QT Interval Changes, ms	Notes
Vandu, *et al*.[12], 2022	BDQ Regiment	46	443.8 (SD, 10.2)	458.4 (SD,23.7)	NA	
Darmayani, *et al*.[10], 2022	BDQ Regiment	53	414.52 (SD, 33.74)	NA	23.97 (SD, 52.82)	1. 7 Patients had persistent QT Prolongation 2. 39 patients had clinically significant QTcF prolongation
Dooley, *et al*.[16], 2021	BDQ Regiment	26	397.4 (389.3 – 405.6)	409 (402.5 – 416.8)	12.3 (7.8 – 16.7)	1. Grade I QTC Prolongation: 9 (32.1%) 2. Grade 2 QTc Prolongation: 1 (3.6%)
	BDQ+DLM Regiment	24	391.7 (383.2 – 400.2)	412.4 (405 – 419.9)	20.7 (16.1 - 25.3)	1. Grade I QTC Prolongation: 10 (37%) 2. Grade 2 QTc Prolongation: 2 (7.4%)
Katrak, *et al*.[17], 2021	BDQ Regiment	37	Med, 428 (IQR, 414 – 458)	Med, 388 (IQR,376 – 400)	Med, 23 (IQR,12 - 41)	1.7 Patients had QTc Prolongation ≥500ms. 2. 3/7 had an increase of QTc interval from pre-drug baseline >60ms
Isralls, *et al*.[18], 2021	BDQ Regiment	420	Med, 406.4 (IQR, 389.1 – 421.3)	Med, 434.0 (IQR, 419 – 447.9)	Med, 29.5 (IQR, 9.6 – 47.2)	1. 2 Patients (11%) had QTcF >500ms 2. during 6 months, 18 patients (4.3%) experience QTc F >500ms 3. During 6 months, 110 patients (26.2%) had change of >60ms from base line
Gao, *et al*.[19], 2021	BDQ Regiment	1162	Med, 413 (IQR, 398 – 429)	NA	Med, 16 (IQR, -3 – 35)	32 patients experienced QTcF ≥500ms and 123 (15.7%) experienced QTcF ≥60ms from baseline 4 (2%) Patients

TABLE 2. Result of selected studies. (Continue)

Authors	Regimen	n	QT Interval (Before), ms	QT Interval (After), ms	QT Interval Changes, ms	Notes
Brust, *et al*.[20], 2021	BDQ Regiment	195	404.6 (SD, 22.2)	427.6 (SD,22.1)	23.7 (SD, 22.7)	experienced QTcF >500ms and 8 (4.4%) experience QTcF >60ms from baseline.
Lee, *et al*.[13], 2020	BDQ+DLM Regiment	74	420.8 (SD,24.7)	462 (SD,443.3 – 492.0)	44.5 (23.8 – 63.8)	23 (31.1%) patient had significant QT Prolongation and 1 (1.4%) patient discontinued due to QTcF Prolongation
Ndjeka, *et al*.[21], 2022	BDQ Regiment	200	Med, 403 (IQR, 389 – 422)	NA	Med, 11 (IQR, -6 – 27)	1 (6.3%) stopped because QTcF Prolongation. 5 Patients has QTcF >500ms
Ferlazzo, *et al*.[22], 2018	BDQ Regiment	28	Med, 401 (IQR,381 – 432)	Med, 434 (IQR, 408 – 446)	Med, 16 (IQR, -13 – 31)	No patients had QTcF >500ms.
Diacon, *et al*.[23], 2014	BDQ Regiment	66	NA	NA	15.4	

Abbreviations: DR-TB: Drug-Resistance Tuberculosis, MDR-TB: Multi Drug Resistance Tuberculosis, RR-TB: Rifampicin Resistance Tuberculosis, XDR-TB: Extensively drug-resistant Tuberculosis, BDQ: Bedaquiline, DLM: Delamanid, Med: Median, IQR: Interquartile Range, SD: Standard Deviation, NA: Not Available, QTcF : QT Interval Friderica Formula

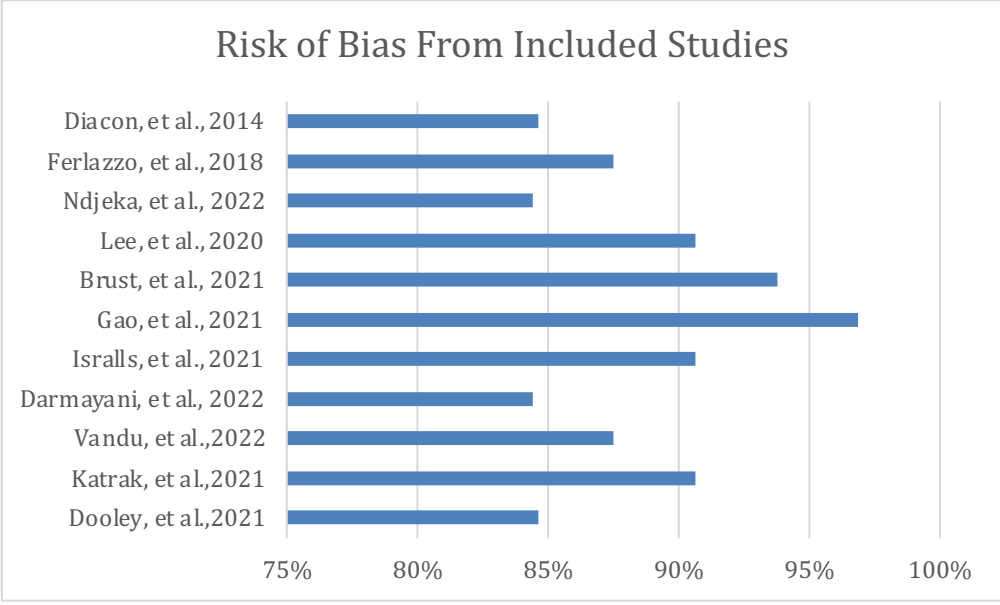

Fig 2. JBI scores of articles included in the study

interval Prolongation grade 1. Based on the change in QT Interval from the baseline, all studies assessed the average and there was no average value above 60ms. However, 405 out of 2,449 patients (16.5%) included in this study had QT interval problems ≥500ms or an increase in QT interval from baseline ≥60ms and some of them had to be discontinued.

As a result of this systematic review, it can be interpreted that the use of Bedaquiline may affect the QT Interval in its users, although few of these events have occurred or been reported. However, the use of Bedaquiline should still be cautioned in patients who have cardiovascular system problems, especially arrhythmias. The small number of cases does not mean that no patient will experience it, so clinician care in treating DR-TB patients is needed to ensure patient safety during therapy. Routine evaluation of the patient's ECG can be a good solution, especially in patients who are suspected of potentially facing adverse effects on the QT interval.

Bedaquiline mechanism on prolonging QT interval

A diarylquinoline called bedaquiline is an excellent treatment for DR-TB. This medication works by specifically inhibiting the mycobacterial ATP synthase enzyme.[14] The heart's hERG potassium channel can be blocked by bedaquiline, which can also influence the incidence of QT interval prolongation.[15] According to recent research, the QT interval is also accompanied with lower serum potassium levels and higher serum sodium levels, which may indicate a connection between the cardiac hERG channel and sodium currents and QT interval lengthening.[15]

Limitation, strength and future research direction

The limitation of this systematic review is that we did an analysis without using any statistics (without meta-analysis) so that a stratification or overall conclusion of the combined research was not obtained. Strength of this study. We summarize the characteristics of this systematic review of the use of Bedaquiline in DR-TB patients for changes in the current QT interval, which can be said to be safe and only a few cases have reported significant problems with the QT interval of its users. So with this systematic review providing evidence of the safety of using Bedaquiline in DR-TB while clinically careful in the condition before the patient received treatment. For future research, it is hoped that it will continue to report if QT interval prolongation occurs when using Bedaquiline and it is expected to be able to carry out a meta-analysis to determine the impact of using Bedaquiline on the QT interval in a combined manner from all existing data.

CONCLUSION

Of all the patients included, 16.5% had problems with the QT interval when using Bedaquiline and some of them had to stop treatment. The use of Bedaquiline is safe for the QT interval but requires the clinician's attention to the patient before giving the treatment with ECG both before and during therapy. Regular monitoring is important to prevent before QT prolongation occurs so that DR-TB treatment can be safer for patients.

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Evaluating Risk Factors for Cumulative Life Course Impairment in Psoriasis using Patient-Acceptable Symptom State and European Quality of Life 5 Dimensions (EQ-5D)

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ABSTRACT

Objective: To evaluated the health-utility values and risk factors for cumulative life course impairment (CLCI) using Patient Acceptable Symptom State (PASS) and European Quality of Life 5 Dimensions (EQ-5D).

Materials and Methods: This cross-sectional investigation enrolled patients with psoriasis. Patients were asked PASS questions about their overall self-perceived health state, adaptation, and expectations for current, future, and lifelong conditions. The patients also completed EQ-5D.

Results: The mean age of 139 enrolled patients was 45.8 ± 14.4 years, and 57.6% were women. Most cases had chronic plaque psoriasis 121 (87.1%). For current PASS, satisfaction was significantly associated with older age, being married, and lower disease severity. The mean health-utility value and visual analog scale of the 139 patients were 0.89 ± 0.12 and 77.0 ± 17.4, respectively. Patients would not accept their disease if they had moderate to extreme problems in usual activities and depression/anxiety for the future and lifelong. Univariate analysis revealed that depression and usual activities were significantly associated with satisfaction for current PASS, future PASS, and lifelong PASS.

Conclusion: Disease severity, age, marital status, problems with usual activities, and depression/anxiety were significantly related to CLCI. These findings may allow physicians to identify psychosocial and psychological aspects of psoriatic patients at high risk for developing CLCI. Early and adequate treatment, good coping strategies, and good social support can prevent a negative impact on CLCI and major life-changing decisions.

Keywords: Cumulative life course impairment; EQ-5D; Patient-acceptable symptom state; Psoriasis; Quality of life (Siriraj Med J 2023; 75: 646-654)

INTRODUCTION

Psoriasis is a common chronic inflammatory skin disease characterized by thick scaly erythematous plaques on the skin, especially in trauma-prone areas.[1,2] The condition substantially affects patients' health-related quality of life (HRQoL) since it can affect daily activities, social functioning, and psychological well-being.[3] The level of HRQoL impairment in psoriasis has been shown to be comparable to some serious medical conditions, such as ischemic heart disease, diabetes, depression, and cancer.[4] Furthermore, it has a cumulative impact on a patient's life course, which sometimes cannot be detected by measuring HRQoL at a specific time point.[5]

The term "cumulative life course impairment"

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(CLCI) was proposed more than a decade ago. It was intended to reflect the overall effects of psoriasis that result in an altered or impaired life potential during the life course of a patient. The dimension of the future is embedded in the CLCI concept, which is considered a key element in the management of lifelong conditions. Understanding the adaptations of patients and their future expectations may allow physicians to provide high-quality patient care. However, this dimension has not been extensively studied in psoriasis.[6]

Patient Acceptable Symptom State (PASS) is a simple questionnaire that captures the overall self-perceived health state, adaptation, and expectations of individual patients. Three questions are asked:

1. Considering the ways that skin psoriasis affects your functioning, is your current condition satisfactory? ("Current PASS").
2. Considering the ways that your skin psoriasis is affecting you, if you were to remain in this state for the next few months, would this be satisfactory? ("Future PASS").
3. If you were to remain for the rest of your life as you were during the last 48 hours, would this be satisfactory? ("Lifelong PASS").

The answers are recorded as "Yes" or "No," indicating "satisfaction" and "dissatisfaction," respectively.[7,8]

This study aimed to evaluate health-utility (HU) values and risk factors for CLCI using PASS and European Quality of Life 5 Dimensions (EQ-5D).

MATERIALS AND METHODS

This cross-sectional investigation included psoriasis patients with and without psoriatic arthritis (PsA) who attended the Psoriasis Clinic, Outpatient Dermatology Unit, in a tertiary hospital in Thailand. The diagnoses of PsA were confirmed by an expert rheumatologist and were based on the classification criteria for PsA.[9] For this study, the inclusion criteria were patients who (i) were 18 years or older; (ii) could read, write, and speak Thai; and (iii) were willing to participate in the study. Patients with psychiatric conditions were excluded. This study was approved by the Institutional Review Board (COA no. Si 156/2020). All methods were performed in accordance with the relevant guidelines and regulations. All patients gave their written informed consent. Details of the following were recorded: demographic and clinical data of patients; the severity of psoriasis (PASI; Psoriasis Area and Severity Index); and treatments. HU values were derived from European Quality of Life-5 Dimensions – 5 Levels (EQ-5D-5L). The completion of EQ-5D-5L, patient global assessment severity (PtGA), and self-assessment Simplified Psoriasis Index (saSPI-s)[10] was carried out by each patient or with the help of a research assistant. The overall health state, adaptation, and expectations of individual patients were investigated using the PASS questions.

EQ-5D-5L

The EuroQoL group introduced EQ-5D-5L in 2009. The Thai version of EQ-5D-5L was validated in 2014.[11] EQ-5D-5L consists of a descriptive system and a visual analog scale (EQ-5D VAS).[12] The descriptive system has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and depression/anxiety. In turn, each dimension has 5 levels of impairment: no problems, slight problems, moderate problems, severe problems, and extreme problems.[13] The selected levels for each of the 5 dimensions of the descriptive system are combined to derive the HU value for a patient.[14] Thai HU values range from -0.28 to 1, with values of 0 and 1 indicating "dead" and "perfect" health, respectively.[14] A negative value indicates a state of health that is perceived by a patient as "worse than death".[14] In relation to EQ-5D VAS, it uses a 20-cm vertical numerical scale ranging from 0 to 100, with 0 and 100 representing "the worst" and "the best" imaginable health states, respectively.[11]

Statistical analysis

Descriptive statistics (frequency, percentage, mean, standard deviation, median, minimum, and maximum) were used to analyze patient characteristics and the variables studied. Fisher's exact test was used to compare categorical variables. Normally and non-normally distributed data were analyzed using an independent t-test and the Mann–Whitney U test, respectively. The 5 domains of EQ-5D-5L were divided into 2 groups: no to slight problems, and moderate to extreme problems. Subsequently, binary logistic regression with the enter method was used to determine the factors associated with HRQoL for each EQ-5D-5L domain, as well as satisfied PASS. Variables with P values of < 0.2 in a univariate analysis were included in a multivariate analysis. A P value of ≤ 0.05 was considered statistically significant. All statistical analyses were performed using PASW Statistics for Windows (version 18.0; SPSS, Chicago, IL, USA).

RESULTS

A total of 139 patients were involved. Their overall mean age was 45.8 ± 14.4 years, and 57.6% were women (Table 1). Patients who were employed and patients with a bachelor's or higher degree represented 86.2% and

TABLE 1. Clinical characteristics and EuroQol-5 Dimension-5 Levels (EQ-5D-5L) for current Patient Acceptable Symptom State (PASS), future PASS, and lifelong PASS.

Characteristics	Total (N=139)	Current PASS		*P* values	Future PASS		*P* values	Lifelong PASS		*P* values
		Dissatisfied (n=36)	Satisfied (n=103)		Dissatisfied (n=42)	Satisfied (n=97)		Dissatisfied (n=20)	Satisfied (n=119)	
Male gender, n (%)	59 (42.4)	12 (33.3)	47 (45.6)	0.199	16 (38.1)	43 (44.3)	0.495	9 (45.0)	50 (42.0)	0.803
Age (years), mean±SD	45.8±14.4	41.6±13.9	47.2±14.3	**0.046**	42.8±13.9	47.0±14.4	0.112	37.7±12.8	47.1±14.2	0.006
Being married, n (%)	92 (66.2)	19 (52.8)	73 (70.9)	**0.048**	24 (57.1)	68 (70.1)	0.138	11 (55.0)	81 (68.1)	0.253
Education level (n=137) ≥ Bachelor's degree†, n (%)	75 (54.7)	20 (57.1)	55 (53.9)	0.741	24 (58.5)	51 (53.1)	0.560	12 (60.0)	63 (53.8)	0.609
Occupation (n=138) Employed status, n (%)	119 (86.2)	28 (77.8)	91 (89.2)	0.098	34 (81.0)	85 (88.5)	0.234	16 (80.0)	103 (87.3)	0.480
Alcohol consumption, n (%), (n=138)	36 (26.1)	10 (27.8)	26 (25.5)	0.788	11 (26.2)	25 (26.0)	0.985	7 (35.0)	29 (24.6)	0.326
Meditation, n (%) (n=135)	49 (36.3)	14 (40.0)	35 (35.0)	0.596	12 (29.3)	37 (39.4)	0.262	4 (20.0)	45 (39.1)	0.101
Co-morbidities, n (%)	74 (53.2)	20 (55.6)	54 (52.4)	0.746	25 (59.5)	49 (50.5)	0.328	8 (40.0)	66 (55.5)	0.200
Psoriatic arthritis, n (%)	40 (28.8)	11 (30.6)	29 (28.2)	0.784	14 (33.3)	26 (26.8)	0.435	5 (25.0)	35 (29.4)	0.687
Psoriasis duration (years), median (min,max)	15.0 (0.3,54.0)	10.5 (0.3,54.0)	17.0 (1.0,49.0)	0.119	12.5 (0.3,54.0)	16.0 (1.0,49.0)	0.127	10.0 (0.3,30.0)	16.0 (1.0,54.0)	0.104
Family history of psoriasis, n (%)	33 (23.7)	8 (22.2)	25 (24.3)	0.804	9 (21.4)	24 (24.7)	0.673	4 (20.0)	29 (24.4)	0.783
Body Surface Area, median (min, max) (n=126)	5.0 (0,80.0)	8.5 (0,50.0)	5.0 (0,80.0)	**0.009**	8.0 (0,80.0)	5.0 (0,80.0)	**0.013**	10.0 (2.0,80.0)	5.0 (0,80.0)	**0.031**
PASI score, median (min, max) (n=133)	4.8 (0,33.3)	5.8 (0,27.5)	4.3 (0,33.3)	**0.013**	5.8 (0.5, 33.3)	4.2 (0,30.2)	**0.004**	5.8 (0.5,33.3)	4.4 (0,30.2)	0.071
saSPI-s score, median (min, max)	5.0 (0,45.0)	8.5 (0,45.0)	4.0 (0,32.0)	**<0.001**	10.0 (0.5,45.0)	4.0 (0,32.0)	**<0.001**	10.0 (1.5,20.0)	5.0 (0,45.0)	0.033
EQ-5D-5L										
Health utility, mean±SD	0.89±0.12	0.82±0.14	0.92±0.10	**<0.001**	0.83±0.15	0.92±0.09	**<0.001**	0.85±0.13	0.90±0.11	0.057
EQ-VAS, mean±SD	77.0±17.4	65.2±19.3	81.1±14.7	**<0.001**	70.1±19.1	80.1±15.7	**0.002**	68.8±18.1	78.4±17.0	**0.026**

TABLE 1. Clinical characteristics and EuroQol-5 Dimension-5 Levels (EQ-5D-5L) for current Patient Acceptable Symptom State (PASS), future PASS, and lifelong PASS. (Continue)

Characteristics	Total (N=139)	Current PASS		*P* values	Future PASS		*P* values	Lifelong PASS		*P* values
		Dissatisfied (n=36)	Satisfied (n=103)		Dissatisfied (n=42)	Satisfied (n=97)		Dissatisfied (n=20)	Satisfied (n=119)	
Mobility, n (%)										
No to slight problems	125 (89.9)	32 (88.9)	93 (90.3)	0.757	36 (85.7)	89 (91.8)	0.357	18 (90.0)	107 (89.9)	1.000
Moderate to extreme problems	14 (10.1)	4 (11.1)	10 (9.7)		6 (14.3)	8 (8.2)		2 (10.0)	12 (10.1)	
Self-care, n (%)										
No to slight problems	133 (95.7)	33 (91.7)	100 (97.1)	0.180	39 (92.9)	94 (96.9)	0.615	20 (100.0)	113 (95.0)	0.593
Moderate to extreme problems	6 (4.3)	3 (8.3)	3 (2.9)		3 (7.1)	3 (3.1)		0	6 (5.0)	
Usual activities, n (%)										
No to slight problems	131 (94.2)	30 (83.3)	101 (98.1)	**0.004**	36 (85.7)	95 (97.9)	**0.010**	15 (75.0)	116 (97.5)	**0.002**
Moderate to extreme problems	8 (5.8)	6 (16.7)	2 (1.9)		6 (14.3)	2 (2.1)		5 (25.0)	3 (2.5)	
Pain/discomfort, n (%)										
No to slight problems	111 (79.9)	24 (66.7)	87 (84.5)	0.022	29 (69.0)	82 (84.5)	**0.037**	15 (75.0)	96 (80.7)	0.554
Moderate to extreme problems	28 (20.1)	12 (33.3)	16 (15.5)		13 (31.0)	15 (15.5)		5 (25.0)	23 (19.3)	
Depression/anxiety, n (%)										
No to slight problems	118 (84.9)	24 (66.7)	94 (91.3)	**<0.001**	30 (71.4)	88 (90.7)	**0.004**	12 (60.0)	106 (89.1)	**0.003**
Moderate to extreme problems	21 (15.1)	12 (33.3)	9 (8.7)		12 (28.6)	9 (9.3)		8 (40.0)	13 (10.9)	

Abbreviations: EQ-VAS, EuroQol-visual analog scale; PASI, Psoriasis Area and Severity Index; PtGA, Patient Global Assessment; saSPI, self-assessment Simplified Psoriasis Index
Bold indicates a statistical significance.

54.7% of the cohort, respectively. In all, there were 121 (87.1%) cases of chronic plaque psoriasis, 9 (6.5%) of guttate psoriasis, 4 (2.9%) of erythrodermic psoriasis, 3 (2.2%) of pustular psoriasis, and 2 (1.4%) of acrodermatitis continua of Hallopeau. For current PASS, older age, being married, and a lower disease severity were significantly associated with satisfaction with the overall health state. Except for being married, these factors were also significant for future PASS and lifelong PASS.

The mean HU value and the mean EQ-VAS score of the study cohort were 0.89 ± 0.12 and 77.0 ± 17.4, respectively. Eighty-nine patients reported being satisfied for current PASS, future PASS, and lifelong PASS, whereas 13 patients reported dissatisfaction for all stages of PASS. The mean HU score and the mean EQ-VAS score of the 89 patients who reported being satisfied were 0.93 ± 0.09 and 81.2 ± 15, respectively. These were significantly higher than the corresponding values for patients who reported dissatisfaction (n = 13; mean HU score = 0.84 ± 0.14, P = 0.003; and mean EQ-VAS = 65.5 ± 19.1, P = 0.005). Among the 5 dimensions of EQ-5D, the highest percentage of reports of moderate to extreme problems was for pain/discomfort (20.1%), while the lowest percentage was for self-care (4.3%). Pain/discomfort, usual activities, and depression were significant problems that prevented patients from being able to accept their condition if they were still present in the future. Patients reported that they would not accept their disease if moderate to extreme problems in usual activities and depression/anxiety lasted for life.

Although the mean HU value and the mean EQ-VAS of patients without PsA were slightly higher than those of patients with PsA, the differences were not significant (P = 0.203 and P = 0.402, respectively; Table 2). However, the mean EQ-VAS score was significantly different for patients reporting satisfaction and dissatisfaction for current PASS for both the psoriasis and PsA groups. Pain/discomfort, followed by depression, was common among patients without PsA, but pain/discomfort and mobility were the most commonly experienced problems for patients with PsA. Among patients without PsA, those who reported being unhappy for current PASS had significantly lower HU and EQ-VAS scores and more difficulties with their usual activities and depression/anxiety than patients who stated that they were satisfied for current PASS.

Univariate logistic regression analysis showed that patients who were satisfied for current PASS and future PASS should have no or slight problems performing usual activities, or with pain/discomfort and depression/anxiety (Table 3). The analysis also revealed that having no to slight problems with usual activities and depression were significantly associated with satisfaction for current PASS, future PASS, and lifelong PASS. Subsequent multivariate analysis showed that no to slight problems with self-care were associated with satisfaction for current PASS. Furthermore, the multivariate analysis found that the EQ-5D-5L domains were not associated with satisfaction for future PASS and lifelong PASS.

DISCUSSION

The concept of CLCI was introduced in 2010. It referred to the cumulative results of the burdens of social stigmatization, physical comorbidities, and psychological comorbidities and their interaction with coping strategies and external factors.[5,15] The complex interaction of these key components explains the variations in how each patient experiences life with psoriasis.[5] A recent systematic review of the mapping of risk factors for CLCI was conducted in patients with chronic skin diseases such as psoriasis, atopic dermatitis, and hidradenitis suppurativa. The analysis found that such patients are at high risk of developing a lifelong negative impact from their disease.[16] Nine of the reviewed studies addressed patients with psoriasis. The severity and comorbidities of the disease were mentioned the most frequently, while only a few studies addressed psychosocial risk factors over time.[16]

In this study, we used PASS and EQ-5D-5L to assess psychosocial factors over time in patients with psoriasis. Our study showed that satisfaction for current PASS was significantly associated with lower disease severity, older age, and being married. Patients who could accept their disease for a lifetime were significantly older than those who could not. This may be because the coping strategies at different ages are not the same. Middle-aged adults (aged approximately 40 to 59 years) are more likely to use problem-focused coping rather than emotion-focused coping to solve problems.[17,18] Problem-focused coping can produce positive effects and minimize CLCI. Furthermore, it is generally accepted that good family and social support play a positive role even though they may not decrease the severity of the disease.[19] The results of our study highlight the need to promote problem-focused coping strategies for patients. Moreover, educational programs are needed for family members, friends, and the broad community so that they understand that psoriasis is not a contagious disease and are more accepting of individuals with the condition.

A systemic review and meta-analysis of EQ-5D for psoriatic patients showed that the mean utility scores of EQ-5D for psoriasis and PsA were 0.82 and 0.76, respectively.[20] This was in line with our study, which

TABLE 2. EuroQol-5 Dimension-5 Levels (EQ-5D-5L) and current Patient Acceptable Symptom State (PASS).

Characteristics	Patients without PsA (n=99)	Current PASS		*P* values	Patients with PsA (n=40)	Current PASS		*P* values
		Dissatisfied (n=25)	Satisfied (n=74)			Dissatisfied (n=11)	Satisfied (n=29)	
EQ-5D-5L								
Health utility, mean±SD	0.90±0.11	0.83±0.12	0.93±0.09	**<0.001**	0.87±0.14	0.81±0.19	0.89±0.10	0.175
EQ-VAS, mean±SD	77.8±17.0	67.5±18.0	81.3±15.3	**<0.001**	75.1±18.4	60.0±21.8	80.8±13.3	0.011
Mobility, n (%)								
No to slight problems	94 (94.9)	24 (96.0)	70 (94.6)	1.000	31 (77.5)	8 (72.7)	23 (79.3)	0.686
Moderate to extreme problems	5 (5.1)	1 (4.0)	4 (5.4)		9 (22.5)	3 (27.3)	6 (20.7)	
Self-care, n (%)								
No to slight problems	95 (96.0)	23 (92.0)	72 (97.3)	0.264	38 (95.0)	10 (90.9)	28 (96.6)	0.479
Moderate to extreme problems	4 (4.0)	2 (8.0)	2 (2.7)		2 (5.0)	1 (9.1)	1 (3.4)	
Usual activities, n (%)								
No to slight problems	94 (94.9)	21 (84.0)	73 (98.6)	**0.014**	37 (92.5)	9 (81.8)	28 (96.6)	0.178
Moderate to extreme problems	5 (5.1)	4 (16.0)	1 (1.4)		3 (7.5)	2 (18.2)	1 (3.4)	
Pain/discomfort, n (%)								
No to slight problems	80 (80.8)	17 (68.0)	63 (85.1)	0.079	31 (77.5)	7 (63.6)	24 (82.8)	0.227
Moderate to extreme problems	19 (19.2)	8 (32.0)	11 (14.9)		9 (22.5)	4 (36.4)	5 (17.2)	
Depression/anxiety, n (%)								
No to slight problems	81 (81.8)	14 (56.0)	67 (90.5)	**<0.001**	37 (92.5)	10 (90.9)	27 (93.1)	1.000
Moderate to extreme problems	18 (18.2)	11 (44.0)	7 (9.5)		3 (7.5)	1 (9.1)	2 (6.9)	

Abbreviations: EQ-VAS, EuroQol-visual analog scale; PsA, psoriatic arthritis
Bold indicates statistical significance.

TABLE 3. Univariate and multivariate analysis of factors associated with each domain of EuroQol-5 Dimension-5 Levels (EQ-5D-5L).

	Univariate analysis: Crude OR (95% CI), no to slight problems									
	Mobility	***P* values**	**Self-care**	***P* values**	**Usual activities**	***P* values**	**Pain/discomfort**	***P* values**	**Depression/anxiety**	***P* values**
Married	0.30 (0.06-1.38)	0.122	0.38 (0.04-3.34)	0.381	0.26 (0.03-2.21)	0.219	0.59 (0.23-1.51)	0.273	1.25 (0.48-3.26)	0.653
Employed	1.84 (0.46-7.32)	0.386	1.27 (0.14-11.48)	0.833	4.28 (0.93-19.63)	0.062	2.04 (0.70-5.95)	0.194	1.60 (0.47-5.40)	0.449
Age >40 years	1.13 (0.37-3.44)	0.836	0.73 (0.13-4.14)	0.724	2.61 (0.60-11.41)	0.201	2.37 (1.02-5.50)	0.045	2.24 (0.88-5.75)	0.093
High education	1.24 (0.41-3.74)	0.707	2.52 (0.45-14.23)	0.296	0.71 (0.16-3.10)	0.651	0.41 (0.17-1.00)	0.051	1.12 (0.44-2.84)	0.813
Comorbidities	0.84 (0.28-2.56)	0.758	0.56 (0.10-3.14)	0.506	3.66 (0.71-18.82)	0.120	1.69 (0.73-3.90)	0.221	2.06 (0.80-5.35)	0.136
Psoriasis duration	0.97 (0.92-1.01)	0.159	**0.91 (0.85-0.97)**	**0.006**	0.98 (0.92-1.04)	0.493	0.99 (0.96-1.03)	0.721	1.03 (0.98-1.08)	0.278
PASI	1.04 (0.91-1.18)	0.563	1.16 (0.86-1.57)	0.329	0.95 (0.86-1.06)	0.357	0.95 (0.89-1.02)	0.134	0.97 (0.90-1.05)	0.502
PtGA	0.92 (0.73-1.16)	0.502	0.96 (0.68-1.35)	0.803	**0.68 (0.49-0.95)**	**0.022**	**0.73 (0.61-0.89)**	**0.001**	**0.78 (0.64-0.96)**	**0.021**
saSPI-s	0.96 (0.92-1.02)	0.172	1.19 (0.94-1.49)	0.152	0.95 (0.89-1.01)	0.099	**0.92 (0.87-0.96)**	**<0.001**	**0.95 (0.91-1.00)**	**0.035**
Satisfaction for current PASS	1.16 (0.34-3.97)	0.810	3.03 (0.58-15.75)	0.187	**10.10 (1.94-52.66)**	**0.006**	**2.72 (1.13-6.52)**	**0.025**	**5.22 (1.97-13.83)**	**0.001**
Satisfaction for future PASS	1.85 (0.60-5.72)	0.283	2.41 (0.47-12.47)	0.294	**7.92 (1.53-41.04)**	**0.014**	**2.45 (1.04-5.76)**	**0.040**	**3.91 (1.50-10.20)**	**0.005**
Satisfaction for lifelong PASS	0.99 (0.20-4.80)	0.991	-	-	**12.89 (2.79-59.47)**	**0.001**	1.39 (0.46-4.22)	0.560	**5.44 (1.88-15.75)**	**0.002**

TABLE 3. Univariate and multivariate analysis of factors associated with each domain of EuroQol-5 Dimension-5 Levels (EQ-5D-5L). (Continue)

	Multivariate analysis: Adjusted OR (95% CI), no to slight problems									
	Mobility	***P* values**	**Self-care**	***P* values**	**Usual activities**	***P* values**	**Pain/discomfort**	***P* values**	**Depression/anxiety**	***P* values**
Married	0.27 (0.05-1.49)	0.132								
Employed					2.60 (0.20-33.05)	0.462	**5.20 (1.15-23.49)**	**0.032**		
Age >40 years							2.41 (0.75-7.73)	0.139	0.97 (0.28-3.38)	0.965
High education							0.39 (0.12-1.26)	0.117		
Comorbidities					9.64 (0.85-109.20)	0.067			2.23 (0.66-7.50)	0.197
Psoriasis duration	0.98 (0.92-1.04)	0.428	0.93 (0.86-1.01)	0.071						
PASI							1.06 (0.94-1.20)	0.325		
PtGA					0.70 (0.40-1.24)	0.223	0.97 (0.73-1.31)	0.858	0.87 (0.64-1.19)	0.375
saSPI-s	0.96 (0.89-1.02)	0.168	1.40 (0.97-2.03)	0.076	1.02 (0.92-1.14)	0.682	**0.91 (0.84-0.99)**	0.022	1.00 (0.93-1.07)	0.880
Satisfaction for current PASS			**13.67 (1.08-173.84)**	**0.044**	0.77 (0.06-10.29)	0.844	1.86 (0.37-9.31)	0.452	1.84 (0.36-9.53)	0.466
Satisfaction for future PASS					7.13 (0.24-210.58)	0.256	0.60 (0.12-2.98)	0.533	1.43 (0.24-8.69)	0.698
Satisfaction for lifelong PASS					3.40 (0.32-36.38)	0.312			1.95 (0.39-9.69)	0.412

Abbreviations: CI, confidence interval; OR, odds ratio; PASI, Psoriasis Area and Severity Index; PASS, Patient Acceptable Symptom State; PtGA, Patient Global Assessment; saSPI, self-assessment Simplified Psoriasis Index

Bold indicates statistical significance.

found that patients with PsA had a lower HRQoL than patients without PsA. Like the systemic review, our investigation also showed that of the 5 dimensions of EQ-5D, pain/discomfort and self-care presented the most and least problems, respectively.[20] However, our study added additional information. Specifically, problems with usual activities and depression/anxiety were the most significant for patients with PsA who could not accept those problems in the future (ie, the next few months) nor their lifetime. Depression/anxiety can occur in up to 30% of patients.[21] Some studies have shown that severe psoriasis significantly raises the risk of depression.[16,22] A connection between the brain and the skin (brain-skin axis) and increased inflammation in psoriasis may be directly related to pathophysiological pathways in depression.[23] Nevertheless, depression/anxiety and psychological effects can be severe regardless of disease severity if patients do not have appropriate coping strategies and good social support.[24]

In conclusion, our study evaluated risk factors for CLCI using the PASS and EQ-5D tools. It showed that a clinical characteristic (disease severity), sociodemographic factors (age and marital status), impaired general health (problems in usual activities), and depression/anxiety were significantly related to CLCI. These findings can help physicians identify psoriatic patients who are at high risk of developing CLCI. Early and adequate treatment, good coping strategies, and good social support can prevent negative impacts on CLCI and major life-changing decisions.

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The Efficacy of Preoperative Tamsulosin on Ureteroscopy Access in Pediatrics: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: The incidence of urolithiasis in pediatrics increases to 4-10% annually. One of the methods for treating urolithiasis is ureteroscopy (URS). The small anatomy in pediatrics often makes the initial URS unsuccessful. Alpha blockers, a drug that can relax the ureteral muscles, is a therapy that can be considered before URS is carried out. The objective of this study is to evaluate the efficacy of preoperative tamsulosin for URS access in pediatrics.

Materials and Methods: We conducted a search using four databases, including PubMed, EBSCO, Cochrane Library, and ProQuest. This study includes randomized controlled trials (RCTs), retrospective and prospective studies, which compared the efficacy of preoperative alpha blockers and placebo or non-placebo controls in pediatrics undergoing ureteroscopy. The outcome of interest was the success rate of URS access and the duration of surgery.

Results: A total of 120 studies were identified from a database search. There were 3 studies included in this review involving 235 patients. The meta-analysis was conducted using a random-effects model. The results of the meta-analysis showed that alpha blockers provided a successful rate of ureteroscopy access in pediatric patients (Odds ratio (OR) 2.73; 95% confidence interval (CI) 1.52 up to 4.91; p=0.0008). Duration of surgery did not show significant results (Mean difference (MD) 3.46; 95% CI -3.59 up to 10.50; p=0.34).

Conclusion: Preoperative administration of tamsulosin may increase the success rate of ureteroscopy access in pediatric patients.

Keywords: Alpha blockers; pediatric; systematic review; tamsulosin; ureteroscopy (Siriraj Med J 2023; 75: 655-664)

INTRODUCTION

The incidence of urolithiasis in children within the past twenty years continues to increase steadily every year with a ratio of 4-10% per year.[1] In children it will be difficult to determine the pain experienced, but the symptoms typically in the form of crying, anxiety, vomiting, hematuria, traces of blood or small stones on diapers, or recurrent urinary tract infections (UTI) with painful micturition.[2] 20% of kidney stones are found in the ureters which cause discomfort and can result in kidney damage.[3] The modality of treatment that can be given is influenced by the location and size of the stone, degree of back-pressure, as well as associated UTI.[4] The treatment is in the form of observation, medical expulsive therapy (MET), ureteroscopy (URS), and ureterolithotomy.[3] The AUA and the Endourological Society recommend URS and ESWL for patients who have failed MET and may require surgical intervention. URS has been evaluated

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as safe for both adults and children, although there is a risk of failure in the initial attempt.[1] However, failure rates are higher in children than in adults due to the smaller width of the ureter, making URS challenging in children.[1,3]

There is controversy regarding the risk of routine prestenting and dilation of balloons to gain ureteral access in children because of the risk of ureteral perforation and ureteral stricture. Ureteral access is often obstructed at the ureteral orifice or intramural ureter, where there are many α1-adrenergic receptors. The presence of alpha blockers can reduce muscle contractions around the ureteral orifice.[5] In addition, it can reduce basal tonicity, reduce peristaltic activity and intraluminal tone.[3] To our knowledge, there is not much literature about the use of tamsulosin for ureteroscopy in pediatrics. Thus, we conduct a systematic review and meta-analysis to find out the effectiveness of tamsulosin for ureteroscopy access in pediatrics.

MATERIALS AND METHODS

Data sources and literature search strategy

We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 2020.[6] Our search encompassed relevant literature from PubMed, Proquest, EBSCO, and the Cochrane Library databases. We utilized specific search terms such as "alpha blocker", "alpha adrenergic blocker", "tamsulosin", "silodosin", and "α-blocker" in conjunction with terms like "ureteroscopy", "ureteroscopic", and "retrograde intrarenal surgery". Furthermore, we included terms related to the target population, such as "children", "adolescence", "pediatric", and "school-age children". To ensure comprehensiveness, we manually examined the reference lists of selected manuscripts for potential articles that met our inclusion criteria.

Eligibility criteria

This systematic review incorporated a variety of study designs, including Randomized Control Trials (RCTs), case-control studies, retrospective cohorts, and prospective cohorts. To be included in this review, studies needed to fulfil specific criteria. Firstly, studies had to compare the use of perioperative alpha blockers with no alpha blockers in the context of ureteroscopy (URS) access. This comparison aimed to examine the potential effects of alpha blockers on the outcomes of interest. Secondly, the study population had to consist of patients who were under the age of 18. Lastly, the reported outcomes of interest included URS success in the initial attempt and surgical time. Those outcomes were chosen to assess the efficacy and efficiency of utilizing perioperative alpha blockers during URS procedures. To maintain the rigor of our review, we excluded certain types of articles that did not meet our criteria, including case reports, reviews, and conference abstracts, as they were not deemed suitable for inclusion in our analysis.

Data extraction

The data extraction process was carried out independently by 3 reviewers. The data extracted included first author, year of publication, country where the study was conducted, study design, sample sizes, age, sex, body mass index (BMI), stone size, duration of alpha blocker administration, surgical time, and success rate. The primary outcome was the success rate in the initial URS attempt. Secondary outcome was the length of surgical time. Disagreements or discrepancies were discussed by all authors.

Methodological quality and risk of bias assessment

Six reviewers contributed to assessing the quality of bias, with each study independently evaluated by two reviewers using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies. The NOS is a commonly used tool to assess the quality of non-randomized studies. The maximum score on the NOS is 9. Studies that received a score of 7-9 stars were considered to have a low risk of bias, studies scoring 4-6 stars were considered to have moderate risk, while studies scoring 3 or less stars were considered to have a high risk of bias.[7] This rigorous assessment process ensured a comprehensive evaluation of the included studies and provided valuable insights into their methodological quality and potential sources of bias.

Statistical analysis

For the analysis of primary outcomes with dichotomous data, we utilized an OR along with a 95% CI. A p-value below 0.05 was considered statistically significant. This approach allowed us to assess the association between the use of preoperative alpha blockers and the outcomes of interest in a binary manner. On the other hand, secondary outcomes, which involved continuous variables, were analyzed using weighted mean differences (WMD). This method enabled us to compare the differences in means between groups and quantify the effect sizes for these variables. To assess heterogeneity between studies, we calculated the I^2 index. If the I^2 value exceeded 50%, indicating substantial heterogeneity, we applied the random effects model for the meta-analysis. Conversely, if

the I^2 value was below 50%, indicating low heterogeneity, we employed the random-effect model. These models help account for differences across studies and provide a pooled estimate of the effect size. For the statistical analysis, we used RevMan 5.4. software on a Macbook platform. This widely used software facilitated the analysis and synthesis of the data, allowing us to generate forest plots and descriptive narratives to present the outcomes visually and concisely.

RESULTS

Literature search

The comprehensive flow diagram of study selection with subsequent exclusions is presented in Fig 1. A total of 120 studies were found using the search term in four databases. From the first screening, we excluded 42 articles because they did not meet our inclusion criteria from the screening of the title and the abstract. We included 3 suitable English publications in the meta-analysis after removing duplicates and examining the titles, abstracts, and full texts. Of these studies, two were published from the USA and one from Pakistan.

Result of literature extraction

Study characteristic

The baseline characteristics of the included studies are presented in Table 1. This study consisted of three articles, including two cohort studies and one case-control study, with a total of 235 participants.[1,3,5] The average age in each group ranged from 11.7 to 13.7 years old. The intervention groups received alpha blockers (specifically, tamsulosin), while the control groups did not receive alpha blockers. The duration of alpha blocker administration before the ureteroscopy procedure ranged from 2 to 7 days. All studies utilized tamsulosin as the alpha blocker intervention. The average body mass index

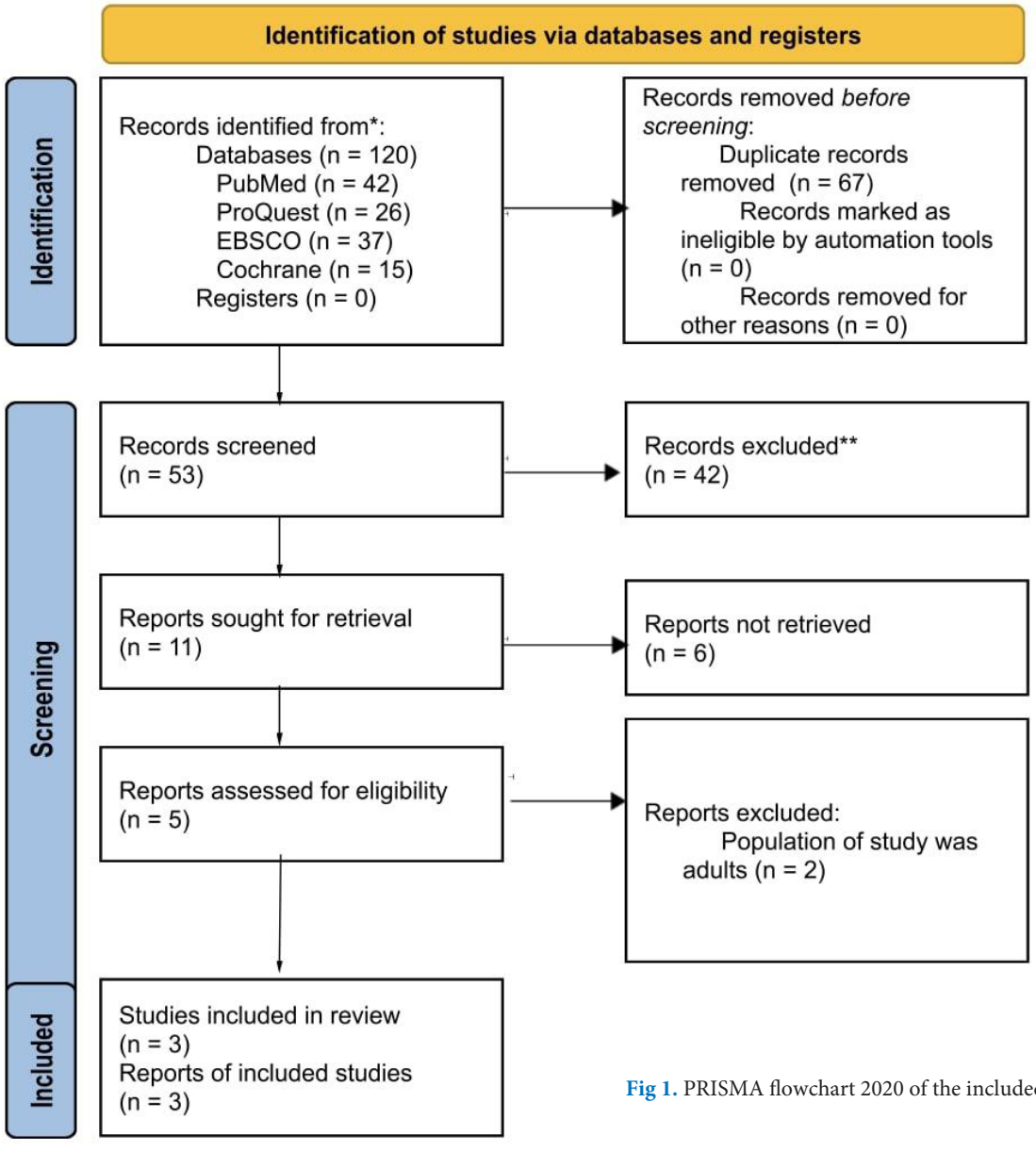

Fig 1. PRISMA flowchart 2020 of the included studies.

TABLE 1. Characteristics of included studies.

Author, year	Country	Study design	Group	Protocol	Duration of administration	Uretroscope	Age (year)	Body mass index (BMI)	Stone size (mm)	Length of surgery (min (SD))	Outcome	Success rate (%)	Stone free rate (%)
McGee LM, et al., 2021.[1]	USA	Retrospective	Intervention	Tamsulosin 0.4 mg	>=7 days	Olympus P6 Flexible URS	13.0	23.3	6.5	40.5 (26.2)	Success rate, stone free rate	62%	75%
			Control	No tamsulosin			13.7	23.2	6. 3	36.1 (16.0)	Success rate, stone free rate	39%	50%
Morley C, et al., 2020.[5]	USA	Retrospective	Intervention	Tamsulosin 0.4 mg	2 days	Semi rigid (wolf 4.5 Fr),	12.2	23.8	2	NA	Success rate	88%	NA
			Control	No tamsulosin		flexible URS (Storz 7.5 Fr)	11.7	21.2	3.25	NA	Success rate	65.40%	NA
Khan A, et al., 2022.[3]	Pakistan	Case control	Intervention	Tamsulosin 0.4 mg	7 days	NA	12.9	24.1	6.59	43.91 (20.11)	Success rate	72.73%	NA
			Control	No tamsulosin			12.9	25.2	7.44	40.70 (22.37)	Success rate	52.73%	NA

(BMI) ranged between 21.2 and 25.2. The average stone size, as reported in the studies, ranged between 2 and 7.44 mm. Based on the length of surgery, the administration of alpha blockers took longer compared to the absence of alpha blockers. The success rate of the three studies indicated that the administration of alpha blockers led to an increased success rate of ureteroscopy access in pediatric patients. There were significant differences of patients' age, stone and URS size between the two cohort studies.[1,5]

Quality assessment

Quality assessment was conducted to evaluate the risk of bias using the Newcastle-Ottawa Scale (NOS). The results revealed that the two retrospective studies included in this study obtained a mean total score of 7, while the case-control study obtained a mean total score of 7 as well. These scores indicate that the included studies were considered to be of good quality. The NOS is a widely recognized tool for assessing the quality of non-randomized studies, and its application in this study provides confidence in the reliability and validity of the findings. The high scores obtained by the included studies suggest that they had a low risk of bias and were methodologically robust.[7] The NOS assessment is presented in Table 2.

Meta analysis result on the success rate of ureteroscopy access

There was a significant difference in the success rate of ureteroscopy access between the alpha blockers group and the control group, with an odds ratio (OR) of 2.73 (1.52-4.91; 95% confidence interval; p=0.0008). Heterogeneity analysis among the studies yielded an I2 index of 0%. Therefore, a random-effects model was applied based on the collected study heterogeneity. The analysis of the success rate of ureteroscopy access was presented as a forest plot in Fig 2. This funnel plot showed that it is symmetrical, indicating a low risk of bias (Fig 3).

Meta analysis result on length of surgery

Among the 3 studies included, only 2 studies were measuring the length of surgery. Between the control group and the alpha blocker group, there was no significant difference in surgical time during the ureteroscopy surgery, with a mean difference of 3.46 (-3.59-10.50; 95% confidence interval; p=0.34). The heterogeneity analysis among the studies was low (P=0.79, I^2=0%), and a random effect model was used for data synthesis. The analysis of length surgery was presented as a forest plot in Fig 3. This funnel plot showed that it is symmetrical, indicating a low risk of bias (Fig 5).

DISCUSSION

Urolithiasis is a common case, even in children. Recently, several studies have reported an increase in the incidence of pediatric urolithiasis.[1,4,5] McGee LM, *et al.* described the incidence in the last 20 years has been estimated at 4-10%. The increasing incidence of urolithiasis in children has strengthened the evaluation of kidney stone management.[1] Pediatrics need a precise identification of the underlying cause and personalized treatments to prevent recurrences of stone formation. It is crucial to see the medical history, find out urinary and dietary habits, perform some tests such as urine and blood tests, as well as analyze urinary stone composition.[8] Disease recurrence can be prevented by dietary adjustment and pharmaceutical intervention. Acute management of the condition comprises monitoring with supportive care, medical expulsive therapy (MET), and surgical intervention.[9] In the past, treatment for urinary tract stone diseases was performed by open surgeries, but recently there has been a significant drive toward minimally invasive surgery (MIS), such as extracorporeal shockwave lithotripsy (ESWL), ureteroscopy (URS), retrograde intrarenal surgery (RIRS),

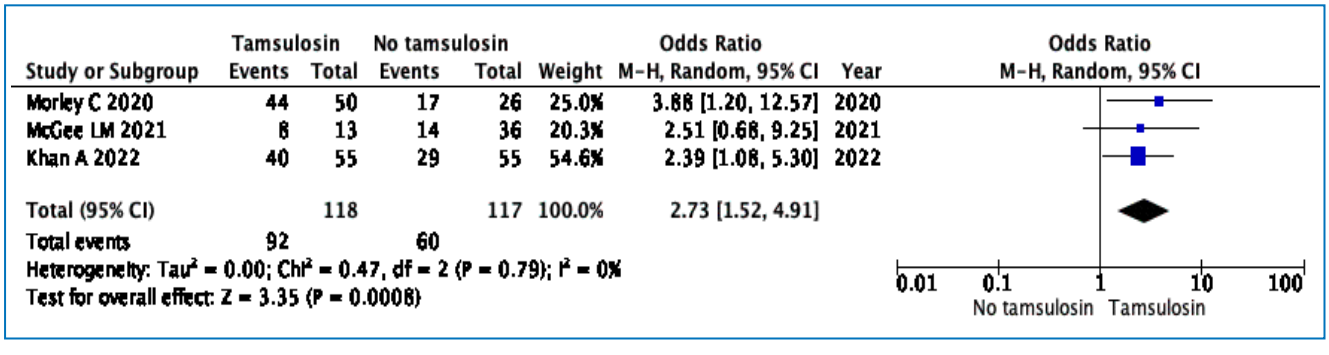

Fig 2. The success rate of ureteroscopy access. CI = Confidence Interval

TABLE 2. Newcastle Ottawa Scale for cohort.

No	Author, year	Selection				Comparability	Outcome			Total score
		Representative of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstrain that outcome of interest was not present at start of study	Comparability of cohort on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcome to occur	Adequacy of follow up cohort	
1	Morley, et al. (2020)	1	1	1	1	1	1	0	1	7
2	McGee et al. (2021)	1	1	1	1	1	1	0	1	7

TABLE 3. Newcastle Ottawa Scale for case control.

No	Author, year	Selection				Comparability	Outcome			Total score
		Is the case definition adequate	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
1	Khan et al. (2022)	0	1	1	1	1	1	1	1	7

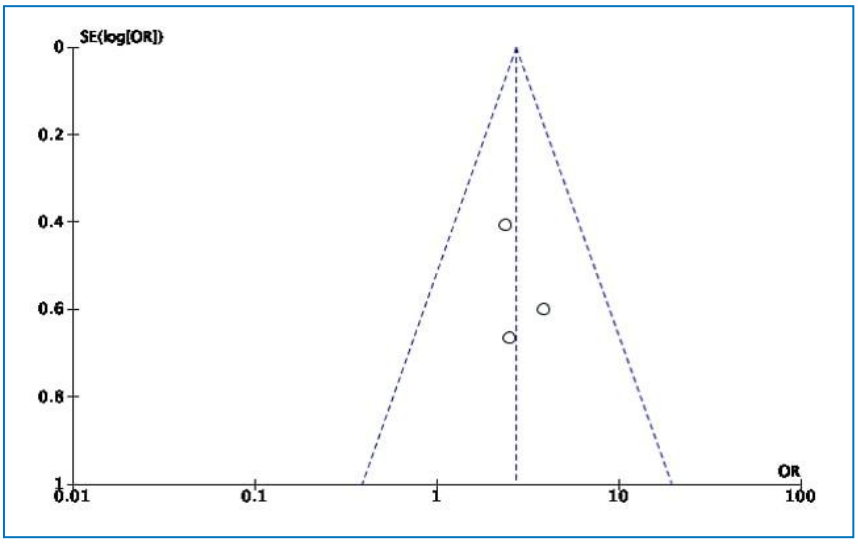

Fig 3. Funnel plot of success rate ureteroscopy access for publication bias. OR = Odds Ratio

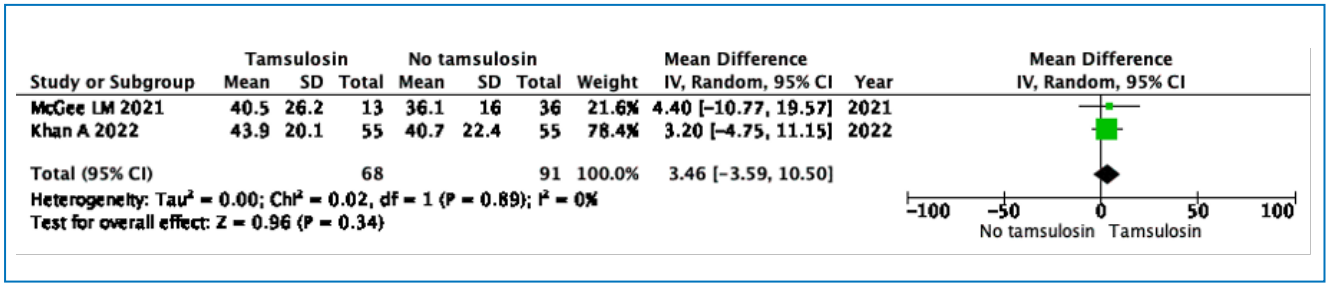

Fig 4. The surgical time during ureteroscopy procedures. CI = Confidence Interval

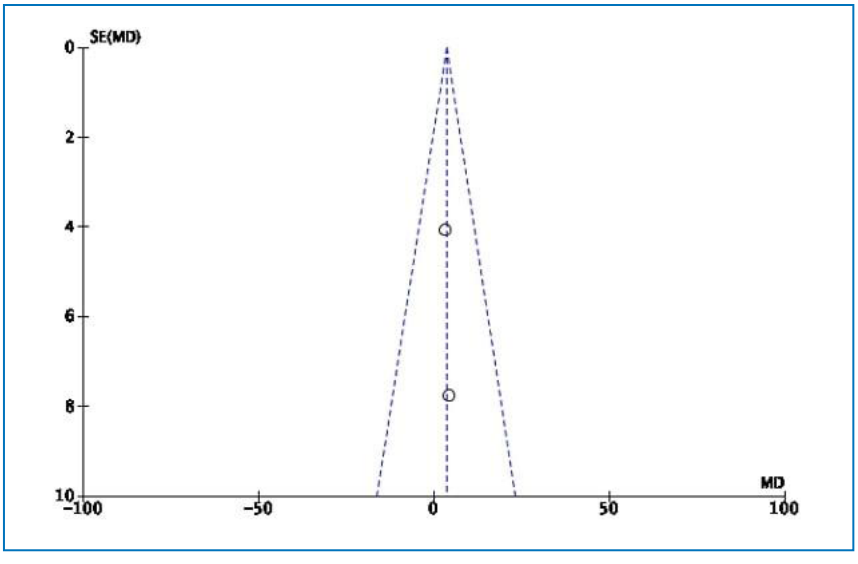

Fig 5. Funnel plot of surgical time during ureteroscopy procedures. MD = Mean Difference

and percutaneous nephrolithotomy (PCNL). According to the European Association of Urology (EAU) guidelines for the management of urinary stone disease in children, robotic-assisted laparoscopic surgery approaches are good alternatives in patients with a history of previous failed endoscopic procedures, complex renal anatomy (ectopic or retrorenal colon), concomitant ureteropelvic junction obstruction (UPJO) or calyceal diverticula, mega-ureter, or large impacted stones. Miniaturized instruments and new technological developments have led to many innovations in the surgical management of pediatric urolithiasis.[8]

The use of ureteroscopy for stone management in children can be a good option. Straub, *et al.* mentioned that the URS procedure is the most ideal procedure for stones in the mid and distal ureters.[9] In a study conducted by Whatley A, *et al.*, with an average age of 8.5 years showed that the use of ureteroscopy in the

treatment of urolithiasis resulted in an 87% stone-free rate with an average operating time of 62 minutes.[11] Another research according to Nerli, *et al*. found that the use of ureteroscopy as therapy in children under 60 months of age proved effective and safe in ureteral and renal pelvic stones. However, in this study, before the ureteroscopy procedure, dilatation of the ureter was required first.[12] It is challenging and risky to advance a ureteroscope into the non-dilated ureter; failure to do might result in the procedure's failure.[13] A systematic review by Rob S, *et al*. showed equally high SFRs and safety profiles of URS in pediatrics may be attained by medium-volume centers as well as large-volume centers, hence encouraging expanded URS use in facilities that do fewer operations annually.[14]

According to meta analysis from Ziaeefar, using medical compulsive therapy (MET) enhances stone expulsive rate while decreasing stone expulsive time.[15] The use of alpha-blockers such as tamsulosin is generally used for medical compulsive treatment (MET) of distal ureteral stones in adults and children.[1] Alpha-1 adrenergic receptors are the most common adrenoceptors in prostate and bladder neck tissue. The drug also has the ability to relax, dilate the intramural distal ureter, and is predicted to be able to lower ureteral peristalsis and intraluminal pressure due to the presence of alpha-1 receptors in the distal ureter. Alpha-1 adrenergic receptors are the most common adrenoceptors in the urinary tract, including the ureters.[16] In the ureters, alpha-1 adrenergic receptors are distributed more distally than in the middle and proximal portions, especially the α1D subtype.[17] Stimulation of α receptors increases the strength of ureteric contractions and the frequency of ureteral peristalsis. Meanwhile, the mechanism of α-antagonists includes reducing ureteral spasm, increasing proximal stone pressure, relaxing the ureter in the distal area, and reducing the tone and frequency of contractions.[18-20] Due to the relaxing effect of distal ureteral tone, the preoperative use of tamsulosin may increase the successful insertion of ureteral access in children.[5]

A meta-analysis was prepared by Alshaikhan A, *et al*. on the use of pre-ureteroscopy alpha-blockers. In this study, it was concluded that the use of preoperative alpha blockers provides a high success rate of ureteroscopic access and reduces the need for ureteral dilation. In this study, there was no age limit between children and adults.[21] Another study by Ahmed AF, *et al*. who studied the use of adjunctive tamsulosin therapy before ureteroscopy procedures in adult patients, showed that tamsulosin decreased the failure rate of ureteroscopic access, shortened the duration of surgery, and reduced the rate of complications.[22] A pooled analysis by Tan H, *et al*. described false lumen development, perforation, and mucosal hemorrhage as complications that may result from ureteroscopy. When compared to the placebo group, the adjunctive alpha-blocker medication was linked to a considerably reduced risk of all these complications.[13] A meta analysis by Sesari SS, *et al*. showed that administration of adjunctive alpha blocker also minimizes colic episodes.[23] In children, the lumens of the ureters are narrow, making ureteroscopy has many failures compared to adults, thus providing a more complex challenge.[1,3]

In the present systematic review and meta analysis study, we attempted to provide a comprehensive summary of the evidence available to assess the use of alpha blocker on the success of ureteroscopy access in pediatrics. The findings of this study may have important implications for the management of urolithiasis in pediatrics and may guide clinical decision-making regarding the use of alpha blocker preoperative in this population. In our included studies, the alpha blocker used was all tamsulosin. The studies compared patient outcomes who received tamsulosin preoperative and those who did not. There were two outcomes analyzed, the success of the initial URS attempt and the surgery length.

The meta-analysis was conducted on 3 studies involving 235 participants, comparing preoperative administration of alpha-blockers with no use of alpha-blockers showing that preoperative administration of alpha-blockers increased the success rate of ureteroscopic access. In these studies, the alpha blocker used was tamsulosin 0.4 mg with an average dose of 2-7 days before the URS procedure because tamsulosin was found to have a rapid onset of action after 8 hours when used for benign prostatic hyperplasia.[3,5] Meanwhile, another research stated that administration of alpha-blockers takes at least 5 days to achieve a stable dose.[16] Tamsulosin, a highly selective 1d adrenoceptor antagonist, has been shown to boost stone ejection rates for distal ureteral calculi in several studies.[24] Side effects that arise as a result of the administration of tamsulosin in children can occur in the form of hypotension, asthenia, syncope, palpitations, somnolence, nausea, vomiting, headache, nasal congestion, and dizziness. Sun K, *et al* stated the side effects of alpha blockers were 2.3 times higher than placebo. According to further subgroup analysis, the use of tamsulosin was positively connected with adverse drug reactions (ADRs) in children with ureteral calculi, but doxazosin and silodosin had no statistically significant impact on the likelihood of treatment-emergent adverse events (TEAEs).[25]

Meta-analysis conducted in 2 studies showed

that preoperative administration of alpha blockers did not have a significant effect on the duration of surgery compared to without alpha blockers. Research by Demir M, *et al.* demonstrated that preoperative administration of tamsulosin in patients over 18 years of age resulted in a shorter operating time than those who did not receive tamsulosin.[26] Other studies in populations under 18 years stated that the administration of tamsulosin before surgery did not provide significant results.[1,3] The factors that can affect the duration of surgery in ureteroscopy procedures can vary. Some factors that can influence the surgery duration include stone complexity, stone size, patient's anatomical condition, surgeon's experience, techniques used, and available equipment. A retrospective study by Whitehurst L, *et al.* showed that operative times are longer while treating large, multiple stones.[27] Another retrospective study by Katafigiotis I, *et al.* described that total stones volume, type of ureteroscope used, stone number, main surgeon experience, radio-opacity on KUB X-ray, nurse's experience, operating room type, and having a nephrostomy tube prior to surgery were several important preoperative predicting factors that affect total operative time.[28] The duration of ureteroscopy surgery can be influenced by the complexity of the stone being treated. Stones with high complexity, such as larger size or additional complications like infection or obstruction, may require a longer operating time. Additionally, stone size can also affect the surgery duration. Larger stones typically require more time to be fragmented or removed.[29] A single center analysis by Ito H, *et al.* resulted larger stone volume, a surgeon with less expertise, higher HUs, and a lack of preoperative stenting were all shown to extend the length of the flexible URS procedure in general and the period after fragmentation begins in particular. However, it was more challenging to estimate the amount of time that would be needed to locate the stone via ureteroscopy and place the access sheath before beginning fragmentation.[30] The patient's anatomical condition can also impact the surgery duration. If the patient has anatomical abnormalities or challenging structures to access, the ureteroscopy procedure may take longer.[31,32] Experienced surgeons may be more skilled in performing the procedure quickly and efficiently, thereby reducing the operating time.[33-36]

There are several limitations to this systematic review and meta analysis study. First, the number of studies on preoperative alpha blockers in children were small. Second, the study design was non-RCT. Third, this study only provides one type of alpha blocker, namely tamsulosin, therefore cannot analyze the effects of other alpha blockers. Fourth, the duration of administration of alpha blockers was varied, giving rise to the potential of bias. Fifth, studies were done in only two countries which may not be representative of the general population of urolithiasis in pediatrics. Our suggestions for further research are to conduct research with a large study population with RCT study design along with preoperative alpha blockers other than tamsulosin such as silodosin and doxazosin. In addition, we suggest outcomes such as side effects, and postoperative pain reduction effects of alpha blockers in the pediatric population. Lastly, further study suggested using URS with a smaller size.

CONCLUSION

Preoperative administration of tamsulosin increases the success of ureteroscopy access in pediatrics. For the length of surgery, there was no significant difference between the use of tamsulosin as an alpha blocker with the control group.

Ethical approval

This research did not involve human subjects; therefore, it was exempt from ethical clearance

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Integrative Health Promotion Model in Leprosy Prevention and Control Programs to Improve Quality of Life for Leprosy Survivors

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ABSTRACT

Objective: Leprosy is an infectious disease that causes highly complex problems from the medical aspect to social, economic, cultural, security, and national defence issues. This research aimed to develop and analyse the effect of an integrative model on leprosy prevention and control programs to improve the life quality of leprosy survivors.

Materials and Methods: This research was conducted in Madura, East Java, Indonesia. The study consists of 360 leprosy survivors. The exposed group in this study was a group of leprosy survivors living within the areas of the Ministry of Health's leprosy program, a total of 180 leprosy survivors. The unexposed groups were leprosy survivors living around the areas with the absence of Ministry of Health leprosy program, a total of 180 leprosy survivors.

Results: The quality of life has a direct and positive relationship with health status (b= 0.56 ; 95% CI = 0.14 to 1.00; p=0.010), health status has a direct and positive relationship with healthy behavior (b= 0.55 ; 95% CI = 0.10 to 1.00; p=0.016), healthy behavior has a direct and positive relationship with self-efficacy (b= 0.91 ; 95% CI = 0.38 to 1.44; p=0.001), healthy behavior has a direct and positive relationship with family support (b= 0.54; 95% CI = 0.06 to 1.03; p=0.029), healthy behavior has a direct and positive relationship with attitude (b= 0.56 ; 95% CI = 0.05 to 1.09; p=0.032).

Conclusion: Health status, healthy behavior, self-efficacy, family support, attitude and community support related to improving quality of life for leprosy survivors.

Keywords: Leprosy survivors; quality of life; prevention and control (Siriraj Med J 2023; 75: 665-673)

INTRODUCTION

Leprosy is an infectious disease that causes extremely complex problems in not only a medical aspect but also social, economic, cultural, security and national security issues.[1,2] The cases of leprosy worldwide are still profound. Based on data from the World Health Organization (WHO), about 0.2 per 10,000 population, with 208,619 new patients throughout 2018 were recorded. To date, there are still three countries severely fighting against leprosy, which are India, Brazil, and Indonesia.[3]

At present, Indonesia levels in the third place in terms of the number of leprosy patients worldwide, while East Java Province ranks the first across Indonesia.[4] Based on data from the Directorate General of Disease Prevention and Control of the Ministry of Health of the Republic of Indonesia, the highest prevalence of leprosy in Indonesia happens in East Java. This province is the largest contributor of leprosy patients in Indonesia with 3,857 cases (28.44%). The province with the second highest leprosy cases is West Java with 2,612 cases (19.26%), and

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the third highest is Papua, with 1,582 cases (11.66%). Following are several provinces in Indonesia with the lowest number of cases, including Banten with 1,116 cases (8.23%), South Sulawesi with 1,086 cases (8.00%), West Papua with 978 cases (7.21%) %), Central Java 710 cases (5.23%), North Maluku 621 cases (4.57%), North Sulawesi with 507 cases (3.73%), and the lowest leprosy cases were in East Nusa Tenggara, with only 490 cases (3.61%).

Nationally, in 2014, there were 16,131 new cases of leprosy, consisting of 13,509 cases of the multibacillary type (83.74%) and 2,622 cases of paucibacillary type (16.25%), and the proportion of grade 2 disorder was 9.45 percent. This condition requires leprosy efforts for not only prevention but also integration of patients with society so that the life quality of the survivors does not go lower due to the various, a part from social resistance.[5]

East Java is an area with a high leprosy case in 2013-2020 which has achieved leprosy elimination in 2017 (the morbidity rate is 0.93 per 10,000), but there are still 10 regencies or cities that have not yet eliminated leprosy, which are Sumenep, Sampang, Pamekasan, Bangkalan, Probolinggi, Lumajang, Situbondo, Tuban, Jember, and Pasuruan. The highest cases happen around Madura and the north sea coast of East Java. Leprosy control in East Java is found in two areas, the east and west areas. It the end of 2020, Jember is expected to also reach leprosy elimination because the morbidity rate is approaching less than 1 per 10,000 population.

According to the strategic plan of the Indonesian Ministry of Health, all regencies or cities are targeted to have achieved leprosy elimination by 2024. The incidence of leprosy in East Java in 2013-2020 shows fluctuating data, due to changing individual and environmental health conditions. In 2013-2016, it exhibited a sloping curve. Then, in 2017 it increased up to the highest number of leprosy cases with 4,668 survivors. The curve decreased in 2017 to 2020 with 2,319 survivors.

Management of leprosy cases prioritizes early case and active case finding methods while prioritizing voluntary self-report. Community advocacy and mobilization, production of health promotion materials, health promotion campaigns, and self-reporting as well as examination of family members should be carried out. The number of leprosy cases covered has not yet reached the target. So far, information about leprosy is not widely understood.[6] The clinical symptoms of leprosy are mostly perceived as white patches of numbness. Even though this information is a symptom of dry leprosy, early detection with other clinical signs needs to be made, not only on the symptoms of anaesthesia in the white spots. In addition, it is necessary to provide proper information to the public about leprosy. In addition, the definition of contact adopted by officers is still limited to contact that occurs between family members in a single house. Furthermore, officers' understanding is fundamental, for example contact with neighbours (4-5 houses to the front, side, and back), social (school friends, work, and so on).[7]

The participation of the community is required to provide an appropriate management of leprosy. For example, health personnel in villages can be trained to provide education and health promotion about leprosy. The leprosy prevention and control program is still constrained due to limited competence of the health resources. Therefore, improvement in training for the health workers is on high demand.[8] Coordination with other programs and other stakeholders also needs to be encouraged. Political commitment at the district/city level is still lacking, as represented from the lack of funds for the strategy implementation program to achieve the targeted coverage. Thus, it is necessary to create an integrated Neglected Tropical Diseases (NTD) program, for example in the aspects of advocacy and education to the community, drug distribution and case detection. Program planning needs to be made at the district/city level.[9]

Based on the background, the current health promotion for leprosy survivors is deemed to be ineffective. Therefore, it is necessary to change the strategy in the implementation of health promotion through policy revisions to ongoing health promotion programs to improve the life quality of leprosy survivors.

MATERIALS AND METHODS

This research was conducted in Madura, East Java, Indonesia. It employed a mixed method design in stages (sequential mixed methods). This was a cohort retrospective study, which aimed to examine the factors that influence healthy behavior, health status, and quality of life of leprosy survivors. Respondents in phase 1 used a 1:1 ratio between the exposed group and the unexposed groups. The exposed group in this study was a group of leprosy survivors living within the areas of the Ministry of Health's leprosy program, a total of 180 leprosy survivors. The Ministry of Health's leprosy program such as health promotion, surveillance, chemoprophylaxis; and management of leprosy. Health promotion for empower people to be able to play an active role in supporting behavior and environmental change as well as maintaining and improving health for leprosy prevention and control. Surveillance for the discovery of

leprosy survivors and early treatment and knowledge the magnitude of the problem in an area. Chemoprophylaxis to prevent transmission leprosy in people who have contact with leprosy survivors. Management of leprosy for treat leprosy survivors early and prevent disability due to leprosy. The unexposed groups were leprosy survivors living around the areas with the absence of Ministry of Health leprosy program, a total of 180 leprosy survivors. The independent variables in the study were health status, healthy behavior, family support, community support, attitudes and self-efficacy. The dependent one was the life quality of leprosy survivors. The data analysis adopted univariate analysis, bivariate analysis, and path analysis. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. The study was conducted according to the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia (NO.: 80/UN27.06.6.1/KEP/EC/2021), and informed consent was obtained from all individual participants.

RESULTS

The results of the study involved the exposed and unexposed groups. The participants of this study were 360 respondents, divided into two groups: those who were exposed to the leprosy program and those who were not.

Table 1 shows the personal characteristics of the participants including the age of the respondents, gender, education and family income, knowledge. The results of the univariate analysis demonstrated that either the exposed or the unexposed group to the leprosy program was mostly aged before 34 years, 126 respondents (70.00%) and 95 (52.78%) respectively. Correspondingly, in the gender variable, they were mostly male, 115 respondents (63.89%) in the exposed group and 94 respondents (52.22%) in the unexposed one.

In terms of education level, most of them, either in the exposed or unexposed group, are high school graduates, namely 125 respondents (69.44%) and 125 respondents (69.44%) respectively. The majority of the family income was below the regional minimum wage, 102 respondents (56.67%) and 107 (59.44%).

Table 2 shows the survivors in the group unexposed to the program mostly, 133 respondents (73.89%), had a negative attitudes (below the average value), while most of the exposed group, 104 respondents (57.78%), exhibited a positive knowledge (over the average value). In terms of self-efficacy, most of the unexposed group, 125 respondents (69.44%), showed a low self-efficacy, while most of the exposed one, 117 respondents (65.00%), had a high self-efficacy.

In the variable of family support, most of the families in the unexposed group, 150 respondents (83.33%), belonged to the weak category while that in the exposed one, majority of them, 111 respondents (61.67%), belonged to the strong category. Meanwhile, most of the community support variables in the unexposed group were weak, with 121 respondents (67.22%), while those in the exposed group, 114 respondents (63.33%), had a strong category.

In the healthy behavior variable, most of those in the unexposed group, 123 respondents (68.33%), belonged to the bad category, while in those in exposed group mostly had a good category, with 101 respondents

TABLE 1. Characteristics of the sample

No	Characteristics	Criteria	Not Exposed to Programs		Exposed Program	
			N	%	n	%
1	Age	< mean (34)	126	70.00	95	52.78
		≥ mean (34)	54	30.00	85	47.22
2	Gender	Male	115	63.89	94	52.22
		Female	65	36.11	85	47.78
3	Education	< Senior High School	125	69.44	125	69.44
		≥ Senior High School	55	30.56	55	30.56
4	Family income	< Regional minimum wage	102	56.67	73	40.56
		≥ Regional minimum wage	78	43.33	107	59.44

TABLE 2. Characteristics of the variable.

No	Characteristics	Criteria	Not Exposed to Programs		Exposed Program	
			n	%	n	%
1	Attitude	negative	133	73.89	76	42.22
		positive	47	26.11	104	57.78
2	Self-efficacy	low	125	69.44	63	35.00
		high	55	30.56	117	65.00
3	Family support	weak	150	83.33	69	38.33
		strong	30	16.67	111	61.67
4	Community support	weak	121	67.22	66	36.67
		strong	59	32.78	114	63.33
5	Healthy behavior	poor	123	68.33	79	43.89
		good	57	31.67	101	56.11
6	Health status	Very bad	114	63.33	100	55.56
		Good	66	36.67	80	44.44
7	Quality of life	< mean	143	79.44	76	42.22
		≥ average	37	20.56	104	57.78

(56.11%). Most of the health status variables in the both group, 114 respondents (63.33%) and 100 respondents (55.56%), were in a very bad category. In the quality-of-life variable, most of the participants, 143 respondents (79.44%), in the first group had a below average score while most of the participants, 104 respondents (57, 78%), in the second group belonged to the good category.

Path analysis was intended to identify the number of measured variables, the number of endogenous variables, exogenous variables, and estimated parameters. At this stage, the degree of freedom (df) was calculated, which defined that path analysis could be carried out under the following conditions:

a. Number of measured variables: 7

b. Endogenous variables: 5 (attitude, self-efficacy, family support, community support, and healthy behavior)

c. Exogenous variables: 2 (quality of life and health status)

d. Number of parameters: 7

The degree of freedom formula is as follows:

df = (number of measured variables x (number of measured variables + 1) / 2 – (endogenous variables + exogenous variables + number of parameters) = (7 x (7+1)/ 2 – (5 + 2 + 7) = (56 / 2) – 14 = 28 – 14 = 14.

Path analysis can be done if df ≥ 0, and in the model identification, the value of df was 14, and it was called over identified path analysis. Therefore, path analysis could be obviously conducted.

Table 3 shows the results of calculations using the STATA 13 computer program software. Quality of life had a direct and positive relationship with health status. Leprosy survivors with good health status had a log odd of increasing quality of life 0.56 units higher than the leprosy survivors with very poor health status (b= 0.56; 95% CI = 0.14 to 1.00; p=0.010).

Health status had a direct and positive relationship with healthy behavior. Leprosy survivors with good health behavior had a log odd of improving health status 0.55 units higher than the leprosy survivors with poor health behavior (b= 0.55; 95% CI = 0.10 to 1.00; p=0.016).

Healthy behavior had a direct and positive relationship with self-efficacy. Leprosy survivors with high self-efficacy had a log odd of increasing healthy behavior 0.91 units higher than leprosy survivors with low self-efficacy (b= 0.91; 95% CI = 0.38 to 1.44; p=0.001).

Healthy behavior had a direct and positive relationship with family support. Leprosy survivors with strong family support had a log odd of increasing healthy behavior 0.54 units higher than leprosy survivors with weak family support (b= 0.54; 95% CI = 0.06 to 1.03; p=0.029).

Healthy behavior had a direct and positive relationship with attitude. Leprosy survivors with a positive attitude had a log odd of increasing healthy behavior 0.56 units

TABLE 3. Results of path analysis of integrative model influence on leprosy prevention and control to improve the quality of life of leprosy survivors.

Relationship of dependent and independent variables		Coefficient line	CI 95% Lower limit	Upper limit	p
Direct Effect					
Quality of life	←				
health status		0.56	0.14	1.00	0.010
Health status	←				
Healthy behavior		0.55	0.10	1.00	0.016
Healthy behavior	←				
self-efficacy		0.91	0.38	1.44	0.001
Family support		0.54	0.06	1.03	0.029
Attitude		0.56	0.05	1.09	0.032
Indirect Effect					
Family support	←				
Community support		0.96	0.53	1.40	<0.001
Attitude	←				
Community support		1.57	1.06	2.09	<0.001
N Observation = 360		description:			
df = 14		← = be connected			

* Signification $p \leq 0.05$

higher than leprosy survivors with a negative attitude (b= 0.56; 95% CI = 0.05 to 1.09; p=0.032).

Community support was indirectly related to quality of life through family support. Leprosy survivors with strong community support had a log odd of having strong family support of 0.96 units higher than leprosy survivors who had a weak community support (b= 0.96; 95% CI = 0.53 to 1.40; p=<0.001).

Community support was indirectly related to quality of life through attitudes. Leprosy survivors with a strong community support had a log odd of having a positive attitude of 1.57 units higher than leprosy survivors with a weak community support (b= 0.57; 95% CI = 1.06 to 2.09; p=<0.001).

DISCUSSION

Based on the results, this study reveals that health status has a direct effect with quality of life. Leprosy and the physical deformities become sources of stigma and social isolation for patients and their families among society. The disability and stigma suffered by the patients play a major role in the decrease of life quality. In addition, the negative stigma of leprosy can hinder community health programs related to the prevention, early diagnosis, therapy, and adherence to treatment of leprosy patients.[10] People Affected by Leprosy in their lives experience physical health problems, psychological well-being disorders, social relationship disorders, and environmental problems. It can have a negative impact on the quality of life, such as mobility, interpersonal relationships, and other social activities.[11]

Based on the research results, health status is a very complex point. It can be achieved optimally when the four factors - heredity, environment, behavior, and health services - are optimal. Once a single of them is disturbed (nonoptimal), the health status will be below optimal. For this reason, leprosy sufferers are expected to achieve good health status through internal and external factors, so they can improve their quality of life.

The result shows that healthy behavior has an indirect effect with quality of life through health status. Leprosy is a chronic disease caused by Mycobacterium leprae (M. leprae) infection, which first attacks the peripheral nerves, then attack the skin, oral mucosa, upper respiratory tract, reticuloendothelial system, eyes, muscles, bones, and testes except the central nervous system.[12] Health can be

achieved through behavioral change from unhealthy to the healthy behavior and creating a healthy environment in the family. According to Becker, the concept of healthy behavior is an extension of the behavioral concept developed by Bloom, which describes health behavior into three domains, which are health knowledge, health attitude, and health practice.

Healthy behavior affects one's physical, mental, and spiritual health. Mental health is a determinant of one's quality of life. One's mental health is good if he or she feels peaceful, calm, and happy with his life, and it will obviously affect the quality of life as well.[13] A good mental health will improve the quality of life. Health workers are expected to be more optimal in conveying health promotion related to leprosy, such as by holding outreach about leprosy. The information obtained by the community can support the healthy behavior of leprosy survivors.[14]

The results show that self-efficacy has an indirect effect to quality of life through behavior and health status. Good self-efficacy can improve problem solving, reduce fear of failure, and promote enthusiasm.[15] One's self-efficacy can be seen from several sources, from one's own experience, the experience of others, verbal persuasion, and physiological conditions. Self-efficacy can refer to the belief in improving the life quality of the survivors in dealing with the disease.[16] The higher the self-efficacy, the stronger the coping in leprosy survivors.

The study result indicates that efficacy with all the aspects therein can improve the life quality of leprosy survivors through their behavior and health status. Therefore, self-efficacy is positively related to the quality of life of leprosy survivors. The higher the self-efficacy, the better the quality of life; the lower the self-efficacy, the worse the quality of life.

The result shows that family support has an indirect effect to the quality of life through healthy behavior. Family support is all assistance provided by family members to provide a sense of physical and psychological comfort to individuals who are depressed or stressed due to certain problems.[17] A good family support for the leprosy survivors can reduce the stress and depression so that they feel a better quality of life. In a family, there are several functions to fulfil, one of which is a family care, taking care of the family members who are sick.[18]

The family support is expected to provide benefits or a stimulus for leprosy survivors in carrying out routine treatment. Leprosy patients whose families are not supportive might have a worse prognosis. Therefore, family plays a highly crucial role because their support can improve the life quality of leprosy survivors.[19] Family support consists of 4 indicators examined in this study, which include informational support, appraisal support, instrumental support, and emotional support. All aspects of family support are closely related one another.[20]

Family support is a function of social ties that describe the level and quality of individuals that protect individuals from the consequences of stress.[21] It can make them feel calm, cared for, increase self-confidence and competence. Health behavior can be formed due to the internal and external factors that play a role. These external factors include experience, facilities, and socio-culture, while internal factors include perceptions, knowledge, beliefs, desires, motivations, intentions, and attitudes.[29,30]

The result of the study shows that attitude has an indirect effect with quality of life through healthy behavior. Leprosy sufferers who experience disabilities or (PCK) tend to live alone and reduce social activities with the surrounding environment. The disability problems due to leprosy will ultimately affect the life quality of the lepers.[24] The defects that occur affect the decrease in self-confidence of leprosy survivors, so they feel that they are not worthy among society. It causes withdrawal behavior from the surrounding environment, so that it affects the life quality of the lepers.[25]

In this case, everyone has a set of standards within a person to judge what other people see or think. Although a former leper patient is medically considered cured, society remains considering him a leper. Even former lepers themselves often see the permanent physical disabilities they experience as a sign that they really have leprosy.[26] This condition affects the daily activities of leprosy sufferers to be disrupted, so it affect the life quality of lepers, such as physical health problems, psychological problems, social relations problems, and the environment. Negative attitudes and behavior of the community towards leprosy sufferers often cause leprosy sufferers to feel they do not have a place in their families and the community environment for the stigma and leprophobia which are heavily influenced by various understandings and misinformation from the community about leprosy, so this problem causes lepers.[27]

The study results show that community support has an indirect effect to the quality of life through family support. Community support as a source of emotion, information or assistance provided by people around to deal with any problems encountered daily in life.[28] Community support comes from other people, such as friends, neighbours, co-workers, and others.[29,30]

There is a feeling of anxiety experienced by leprosy survivors in the productive age group, which can limit daily activities such as meeting other people, gathering

with friends, and even working. Leprosy is a chronic disease that attacks any part of the body except the central nervous system. People who suffer from leprosy will certainly experience functional disorders of their bodies. It can lead to the lack of self-confidence due to the physical disabilities, so it can reduce their quality of life. For this reason, social support is vital to improve the life quality of leprosy survivors.[31]

The purpose of this study is to offer a conceptual model for developing a health promotion model, to improve the quality of life of leprosy survivors. The final model is a scheme of the health promotion model to reach the goal. This model is not only oriented to program performance for a moment. Sustainability of changes that can improve the quality of life at individual, family, and community levels, is way more important. This model is also community development, the process of which involves community support (cross-sectors). Each program involves a few institutions relevant to the issues by optimizing social capital through efforts to increase their active role in preventing and controlling the quality of life of leprosy survivors. Accordingly, this program is designed in the form of preventive promotion.

The efforts that can be designed to achieve the goal can be in the form of promotion and socialization, as well as communication about the quality of life of leprosy survivors. At the community level, high social capital plays an active role in supporting the quality of life of leprosy survivors. Through social capital, social support is further enhanced, so they feel stronger support and are able to improve the quality of life of leprosy survivors. The support is in the form of material support, informational support, and instrumental support. The higher the community support for leprosy survivors, the faster the change in healthy behavior of leprosy survivors.[32]

With advances in technology in the areas of promotion, prevention, treatment, and health restoration including medical rehabilitation and socio-economic rehabilitation, treatment becomes more effective through an integrated approach, one of which is the collaboration model.[33] The mission of the leprosy control program is to cure and improve the quality of life of leprosy survivors. One's quality of life is not only measured from the aspect of his health, but also from other aspects such as social, economic, emotional, and human rights, so it is necessary to be integrated with related sectors.[34]

The poor quality of life will affect the daily lives of leprosy survivors as well.[35] Leprosy survivors have a lot of roles, especially related to their role in society that experiences a change because leprosy survivors find difficulty in socialization. Therefore, support at the community level is significant to help them adapt to themselves.[36]

At the individual level, it is about how the individual can adapt and accept his disease to achieve a good quality of life. Leprosy affects all ages, male and female, and the most common age is young adults, those in the productive age. Leprosy, especially if it happens with disability, will create a bad stigma for the patient and their family. Thus, leprosy patients often experience difficulties in social interactions, going to school, working, and even having a family, which can reduce the patient's quality of life.[37]

Continuous support from health workers and especially from the family is fundamental to restore self-confidence and at least erode self-stigma, so their quality of life becomes better. On the other hand, the group with low education is generally more indifferent to their illness or may be helpless and forced to accept the situation. The group is more closed and difficult to interview. They have a lot of other things to prioritize, such as working for a living. Thus, this group can pursue their lives, even though not optimal, and choose to avoid the environment. Self-stigma can be reduced, but social stigma remains attached to all subjects. There is still a need for continuous socialization of leprosy to the community so that social stigma can be eliminated so that the quality of life for leprosy patients will be even better.[38,39]

CONCLUSION

Health status, healthy behavior, self-efficacy, family support, attitude and community support related to improving quality of life for leprosy survivors. The level of a one's quality of life is influenced by two factors, environmental and personal factors. Someone who lives around the depressed environment, coops up in a limited home environment, and has the opportunity to play a narrow social role will have a low quality of life, but if he or she can control the situation, he or she can participate in community life and various social interactions.

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Validity and Reliability of a Thai Behavioral and Emotional Screening Tool for Children with Enuresis (TBEST-E)

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ABSTRACT

Objective: Psychological comorbidity in children with enuresis is common and its screening is recommended. A brief validated screening instrument is needed for a busy medical practice. This study focused on the development of the Thai Behavioral and Emotional Screening Tool for children with Enuresis (TBEST-E) and aimed to examine its psychometric properties.

Materials and Methods: Using the Short Screening Instrument for Psychological Problems in Enuresis (SSIPPE) as a template, the 15-item with a yes/no answer format of the TBEST-E was developed for the screening of emotional problems (7 items), attention and hyperactivity/impulsivity problems (3 items each), and oppositional defiant symptoms (2 items). The parents of the children with enuresis completed the TBEST-E and the behavioral rating scale "Thai Youth Checklist" (TYC). The optimal cut-off for further assessment, the sensitivity, and the specificity the TBEST-E were identified using receiver operating characteristic (ROC) curves.

Results: After an adaptation following comments from three child psychiatrists, the TBEST-E showed a content validity of 0.9, an internal consistency of 0.71. A total of 33 children with enuresis (median age = 9, interquartile range = 6.5-11 years) were recruited. Further assessment was indicated when one of the following occurred; at least 3 emotional problems; 3 attention problems; or 2 hyperactivity/impulsivity together with 2 oppositional defiant symptoms. The overall sensitivity and specificity were 0.88 and 0.71 respectively with the accuracy of 0.84 (95% CI = 0.68-0.95).

Conclusion: The TBEST-E is time-efficient and has acceptable psychometric properties in early detection of common psychological problems in children with enuresis.

Keywords: Enuresis; emotion; behavior; psychological; questionnaire; SSIPPE (Siriraj Med J 2023; 75: 674-679)

INTRODUCTION

Enuresis is the intermittent involuntary leakage of urine during sleep and is a heterogenous disorder consisting of different subgroups. With and without the presence of lower urinary tract symptoms (LUTs), enuresis is classified as non-monosymptomatic and monosymptomatic, respectively. It is also categorized as primary when the longest period of dryness is less than 6 months, and secondary if there is relapse after more than 6 months of dryness. The majority of enuresis cases are primary, with genetic predisposition, biological factors, and developmental variations, contributing to its multifactorial etiology.[1,2] The essence of its pathogenesis is a mismatch between nocturnal urine production and nocturnal functional bladder capacity in combination with deficient arousal and/or sleep disorders. In some

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children, sleep-disordered breathing may perpetuate the problem due to an increase in arousal thresholds while sleeping.[2] Primary enuresis is also considered a maturational disorder of the central nervous system, considering that its prevalence decreases with increasing age: 5–10% in 7-year-olds, 3% in adolescents, and 0.5–1% in adults. A study in Thailand found a similar trend of decreasing prevalence with increasing age: 10% in 5-year-olds, 5.3% in 7-year-olds, 3% in 10-year-olds, and 1.2% in 12-year-olds.[3]

Psychological and psychiatric comorbidities in children with enuresis are common and well documented; 20%-30% of children with enuresis have clinically relevant comorbid disorders.[4,5] ADHD is the most common comorbid disorder in enuresis; individuals with ADHD have a 2-3 times greater risk of enuresis than those without it.[6] Other neurodevelopmental conditions, i.e., autism spectrum disorder and intellectual disability, neurological "soft signs", and motor deficits are also associated with incontinence.[7] Moreover, more recent previous studies reported association of enuresis with a range of externalizing and internalizing problems, including ADHD, oppositional defiant disorder, conduct disorder, anxiety and depression.[8] Enuresis also affects children's socialization, self-esteem, interpersonal relationships, and emotional health. These behavioral and emotional problems lead to poor quality of life not only for the children, but also their families. More importantly, if these behavioral and emotional problems are not screened and treated properly, the effective treatment of enuresis may not be possible.[9]

Emotional and behavioral screening is recommended as part of a comprehensive assessment of enuresis. Although available broadband behavioral questionnaires in Thai language exist, they are usually long and can be time-consuming in terms of completing, scoring and interpretation. A brief validated screening instrument in Thai language is needed. Therefore, we aimed to develop and validate a brief screening tool in Thai language for use in busy medical settings.

MATERIALS AND METHODS

The study was approved by Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital (COA no. Si 926/2020). This is a cross-sectional study. The study population included children aged 6-18 years who reportedly had enuresis at least once a month. The participants with enuresis were recruited from specialized pediatric clinics i.e., the nephrology clinic, child psychiatric-consultation-liaison service, developmental behavioral and continuity of care clinics, at the Faculty of Medicine Siriraj Hospital from December 2020 to September 2021. Candidates with a diagnosis of intellectual disability or a neurological disorder resulting in mental age less than 6 years old were excluded. A set of 33 enuretic children with positive screening of psychosocial problems is needed for the TBEST-E to achieve a sensitivity of at least 0.75 with both type I and Type II error of 0.05, and 0.15, respectively.[10] A sample size of 55 was calculated assuming a rate of psychological comorbidity at 60% among enuretic children presenting to a specialize pediatric service.[4]

Guided by the Short Screening Instrument for Psychological Problems in Enuresis (SSIPPE), the 15-item Thai Behavioral and Emotional Screening Tool for children with Enuresis (TBEST-E) was developed. SSIPPE is a validated parent-report questionnaire, mentioned by the International Society for Continence in Children (ICCS).[2] Its construct is based on the items with the highest scores on the Dutch version of the Child Behavior Checklist (CBCL). The construct features three scales in the form of 13 questions in a yes/no answer format: emotional problems, attention problems, and hyperactivity symptoms.[11] The SSIPE has acceptable psychometric properties for early screening of psychosocial problems in children with enuresis and has been used in many studies.[8,12-14] The TBEST-E is also a parent-report questionnaire for the screening of common psychological comorbidities i.e., anxiety, depression, ADHD, and oppositional defiant disorder, in children aged 6-18 years with enuresis. There were 4 scales in the form of 15 questions in a yes/no answer format: 7 items of internalizing problems (anxiety and depression), 3 items of attention problems, 3 items of hyperactivity/impulsivity symptoms, and 2 items of oppositional defiant symptoms (APPENDIX 1). All 15 TBEST-E items were examined for relevance, clarity, and simplicity by three child and adolescent psychiatrists experienced in the evaluation of enuresis. The content validity and the internal consistency were calculated using the Index of Item-Objective Congruence (IOC) test and the kappa coefficient test, respectively. The final version of the TBEST-E was subsequently validated against the standard behavioral screening rating scale: Thai Youth Checklist (TYC)

The TYC is the Thai version of the Child Behavioral Checklist (CBCL). The CBCL was originally developed by Achenbach and Ruffle (2000) to identify problem behaviors over the preceding 6 months. We used the parent version, school-age form for children aged 6-18 years of the TYC, which has been validated in Thai children and adolescents with adequate psychometric properties.[15] The TYC is a broadband behavioral rating

scale which comprises 135 problem items subdivided into several subscales; anxiety, somatic complaints, depression, immaturity, hyperactivity/impulsivity and social problems, aggressive behavior, delinquency, attention problems, and thought problems. To complete TYC, parents were asked to evaluate their and child's behavior during the preceding 6 months on a 3-point likert scale for each item (0 = "Absent", 1 = "Occurs sometimes", 2 = "Occurs often"). Raw scores for each scale are converted to norm-referenced T-scores, with separate norms provided for each gender within the 6–11 and 12–18-year age ranges. According to the Thai normative data, a T-score < 67.5 indicates non-clinical symptoms, a T-score between 67.5 and 70 indicates that the child is at risk for clinical symptoms (borderline clinical range), and a T-score > 70 indicates clinical symptoms (clinical range). These qualitative categories reflect symptom severity, and scores falling within clinical range suggests the need for a more comprehensive diagnostic assessment.[15,16] Moreover, scores on internalizing, externalizing, and total problems can be analyzed. The internalizing domain is a broad measure of emotional problems including anxiety and depressive symptoms that incorporates 3 subscales: anxiety, somatic complaints, and depression. The externalizing domain includes 4 subscales: immaturity, hyperactivity/impulsivity and social problems, aggressive behavior, and delinquency. The total problems score sums all TYC items including those on the remaining subscales: attention problems and thought problems.

In this study scores on total, internalizing and externalizing problems falling within clinical range and were used to an estimate of behavioral and emotional problems and indicate a positive TYC result. After obtaining informed consent, the demographic and enuresis history questionnaire, TYC and TBEST-E were given to 40 parents of eligible participants; of these, 33 completed adequate questionnaire items.

Statistical analysis

Descriptive statistics were used to illustrate the children's demographics and characteristics concerning the frequency of and symptoms related to enuresis. The TBEST-E responses were rated on a 0-and-1 binary scale for each item ("no" = 0, "yes" = 1). Each TYC response was classified as positive when at least one of the 3 T-scores; internalizing, externalizing or total problem scores were in clinical range. The TBEST-E was validated using receiver operating characteristic (ROC) curves to indicate the optimum cut-off to achieve acceptable sensitivity and specificity.

RESULTS

There were 33 children whose parents completed adequate items of TBEST-E and TYC: of these, 22 (66.7%) were boys, 20 (60.6%) were younger than 10, with a median age of 9 years old, and 19 (57.6%) had non-monosymptomatic enuresis (NMNE). Other associated medical conditions were constipation and snoring, found in 12 (36.4%) and 16 (48.5%) participants, respectively. Demographic data, characteristics of enuresis and associated medical conditions are reported in Table 1.

With T-scores in clinical range, the TYC identified 26 (78.8%) children who had significant clinical symptoms in at least one domain of emotional or behavioral problems (internalizing, externalizing, or total problems): of these, 16 (48.5%) had significant internalizing problems, 22 (66.7%) had significant externalizing problems, and 15 (45.5%) had the overall extent of total problems including attention problems. This suggested that 26 children were in need of a more comprehensive diagnostic assessment, particularly for common psychiatric comorbidities in children with enuresis such as ADHD, anxiety, and depression.

Regarding the psychometric properties, TBEST-E demonstrated the content validity of 0.9 and strong internal consistency with a Cronbach's alpha coefficient of 0.71. Using the ROC curves, the optimal cut-offs for the TBEST-E were three or more internalizing problems, three attention problems, or two or more hyperactivity/impulsivity problems together with two oppositional defiant problems. Fig 1 shows the ROC curves for TYC internalizing, externalizing, or total problem scales as predicted by TBEST-E emotional problem items (A), TBEST-E attention problem items (B), TBEST-E hyperactivity/impulsivity items (C), and TBEST-E oppositional defiant symptoms items (D). Using the above criteria, the TBEST-E predicted a positive result of TYC with sensitivity and specificity of 88.46% and 71.43%, respectively (Table 2).

DISCUSSION

Enuresis is a common problem with significant psychosocial comorbidities. Early screening for emotional and behavioral problems can facilitate effective treatment and optimize outcomes.

Based on the demographics of this study, all participants were younger than 12 and the majority were younger than 9. More than half of the participants had non-monosymptomatic enuresis and almost half were frequent bed-wetter with the frequency of more than 4 times/week.

TABLE 1. Demographic data and detail regarding the enuresis history of the participants (N=33)

Demographic characteristics	Number (%)
Gender: male	22 (66.7)
Age[a]	9 (6.5-11)
Education	
Kindergarten	4 (12.1)
Grade 1-3	15 (45.5)
Grade 4-6	11 (33.3)
Grade 7-9	3 (9.1)
Frequency of enuresis	
1 time/month	11 (33.3)
More than 2 times/week	5 (15.2)
More than 4 times/week	16 (48.5)
Have a symptom related with enuresis	
Frequent urination more than 8 times/day	9 (27.3)
Frequent urination less than 3 times/day	4 (12.1)
Urge incontinence	5 (15.2)
Daytime enuresis	7 (21.2)
Staining	-
Voiding intermittency	2 (6.1)
Dysuria	2 (6.1)
Postmicturition dribble	3 (9.1)
Hesitancy	7 (21.2)
Associated symptom	
Constipation	12 (36.4)
Snoring	16 (48.5)

[a]Data presented as median (IQR)

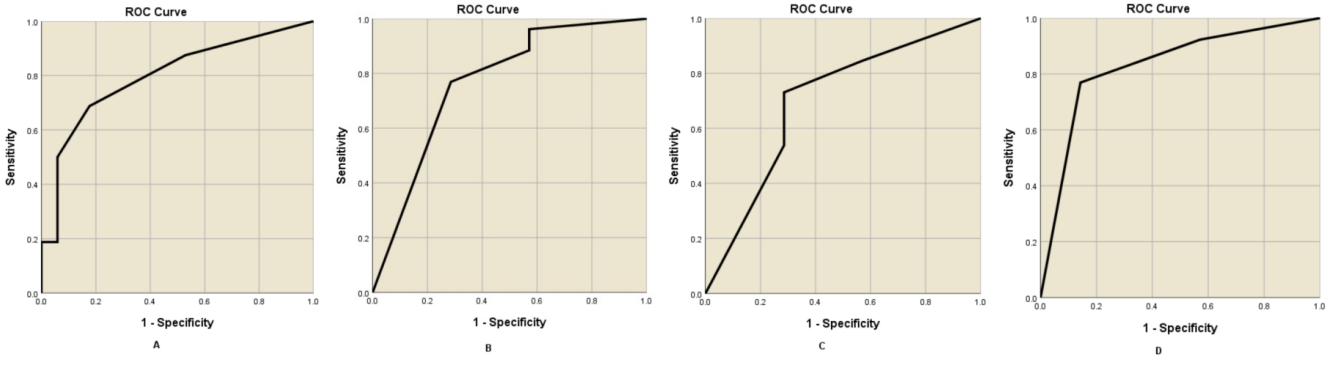

Fig 1. ROC curves for TYC internalizing, externalizing, or total problem scales as predicted by TBEST-E emotional items (A), TBEST-E inattention items (B), TBEST-E hyperactivity/impulsivity items (C), and TBEST-E oppositional defiant items (D).

TABLE 2. Screening test: sensitivity, specificity, positive predictive value, negative predictive value, and accuracy, according to criteria A and criteria B

Criteria	TP[1]	FP[2]	FN[3]	TN[4]	Sensitivity	Specificity	PPV	NPV	Accuracy
Criteria A Positive for one of the emotional problems or inattention problems or hyperactive problems	24	3	2	4	92.31% (74.87% to 99.05%)	57.14% (18.41% to 90.10%)	88.88% (77.14% to 94.99%)	66.68% (31.34% to 89.77%)	84.85%
Criteria B Positive for one of the emotional problems or inattention problems, or positive for both a hyperactivity problem and an opposition problem	23	2	3	5	88.46% (69.85% to 97.55%)	71.43% (29.04% to 96.33%)	92.00% (77.94% to 97.40%)	62.51% (34.26% to 84.21%)	84.85%

[1]TP: True positive, [2]FP: False positive, [3]FN: False negative, [4]TN: True negative

Constipation and snoring were associated with enuresis in significant numbers of children. Other studies also demonstrated higher prevalence in younger children and decreasing rates with increasing age.[4] Association between LUTs i.e., detrusor overactivity in NMNE and constipation is also common.[11,13]

There was an extremely high rate of the clinical range of the TYC in the study population (78.8%) compared to those of other studies of children with enuresis (20-40%). However, the rate was similar to that of studies in tertiary care sample with ADHD being the most common psychiatric disorder among enuretic children.[4,17] This study also revealed higher rate of significant externalizing problems which included symptoms of ADHD. Although several participants from our child psychiatric clinic might have a diagnosis of ADHD and its treatment[18], we did not collect any of the psychiatric diagnosis in our sample. The TYC T-scores in clinical range were an estimate of significant behavioral and emotional problems justified for a referral to further diagnostic assessment.

Compared to the SSIPPE, the TBEST-T has a lower specificity (71.43% vs. 91-99%) but higher sensitivity (88.46% vs. 29-75%).[11,13] Overall, the TBEST-E has acceptable psychometric properties in the early screening of psychological problems in children with enuresis. Moreover, a questionnaire with a yes/no answer format is easy for parents to complete and practical for primary care professionals to interpret.

Our study has some limitations. Firstly, the sample size was small. In addition, our population consists of children receiving medical services in Siriraj Hospital, who are often more susceptible to behavioral and emotional issues than the community population. Thus, the sensitivity and specificity obtained from the study can be different in other populations with low prevalence of emotional or behavioral comorbidities. A large sample size of participants should be surveyed for the TBEST-E psychometric properties to be representative of cases managed in community or primary care. Secondly, this study did not assess psychiatric diagnoses and its validity was evaluated against symptoms of significant psychological/psychiatric problems. So, the TBEST-E only offers initial screening and by no means replace a psychiatric/psychological assessment. The cut-off is to help practitioners decide which patients would need a referral to a more comprehensive diagnostic assessment of psychiatric comorbidities.

CONCLUSION

The TBEST-E has acceptable psychometric properties for the screening of common psychological problems in patients with enuresis. It is suitable for use as a first-line screening tool in a busy pediatric practice.

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Predicting Progression to Hypervascular HCC in Hypovascular Hypointense Nodules in Gadoxetic Acid-enhanced MR Images in Patients with Chronic Liver Disease

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ABSTRACT

Objective: To identify patient characteristics and MR imaging features of hypovascular hypointense nodules in the hepatobiliary phase (HBP) of gadoxetic acid-enhanced MR imaging in patients with chronic liver disease associated with progression to hypervascular hepatocellular carcinoma (HCC).

Materials and Methods: The institutional review board approved this retrospective review of 40 patients with 60 hypovascular hypointense nodules in the HBP of gadoxetic acid-enhanced MR imaging. Univariate and multivariate Cox regression analyses for hypervascular HCC development were used to define variables, including initial nodule size, cause of cirrhosis, history of locoregional therapy of HCC, fat-containing, signal intensity on T1W, T2W, portal and equilibrium phases of dynamic phase, and DW images. The cumulative percentage incidence of hypervascularity and growth rate were calculated using the receiver operating characteristic (ROC) curve.

Results: The prevalence of progression to hypervascular HCC was 45% (27 out of 60). The Multivariable Cox analysis of developing hypervascularization was an initial nodule diameter more than 1 cm. (P=0.027; HR 2.52; 95% CI: 1.11,5.74) The mean growth rate was significantly higher in subsequent hypervascular nodules than in those without hypervascularization (P < 0.001). The cumulative risk incidence of hypervascularization at 3, 6, 12, 24 months was 5%, 20%, 35%, 44 %, respectively.

Conclusion: An initial nodule diameter of more than 1 cm and nodules with higher growth rates are significant predictive factors for hypervascular transformation of hypovascular hypointense nodules in the HBP of gadoxetic acid-enhanced MR imaging.

Keywords: Gadoxetic acid-enhanced MRI; hypovascular hypointense nodule in hepatobiliary phase; HCC imaging
(Siriraj Med J 2023; 75: 680-687)

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common primary liver cancers in patients with chronic liver disease. The concept of multistep carcinogenesis in chronic liver disease or a cirrhotic liver involves regenerating nodules, dysplastic nodules and finally HCC.[1-3] Surveillance via an ultrasound every six months is recommended for early detection.[4-7] Further cross-sectional imaging, including multiphasic computed tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging (MRI) of the liver should be performed for lesion characterization. Nowadays, HCC diagnosis is made

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through evidence of typical enhancement patterns that show arterial phase hyperenhancement with washout in portovenous and/or delayed phases, without any requirement of pathological confirmation.[4-7] However, some small HCC does not show this typical enhancement pattern.[8]

Currently, gadoxetic acid disodium, a combined extracellular and hepatocyte-specific MR contrast agent is being increasingly used and improving the diagnostic accuracy of HCC.[9] This agent has uptake in the normal hepatocyte in the hepatobiliary phase (HBP), and is seen with hypersignal intensity, whereas HCC cannot uptake it and results in hyposignal intensity.[10] The feature of a hypointense nodule in HBP combined with hypervascularity in the arterial phase is indicative of HCC. Meanwhile, some hypointense nodules in HBP with no appearance of hypervascularity in the arterial phase are borderline nodules.[11,12] These borderline nodules require close follow-up since they can convert into hypervascular HCC in follow-up imaging.[13]

The purpose of this study was to identify patient characteristics and MR imaging features of hypovascular hypointense nodules in HBP from gadoxetic acid-enhanced MRI in patients with chronic liver disease associated with progression to hypervascular HCC.

MATERIALS AND METHODS

Patients

This retrospective study was approved by our institutional review board (COA no. Si 507/2016). Our hospital picture archiving and communication system (PACS) database was searched for gadoxetic acid-enhanced MRI performed on patients with liver cirrhosis or chronic liver disease between 2012 to 2014.

The inclusion criteria included: patients with chronic liver disease aged above 18 who had hypovascular hypointense nodules in HBP from gadoxetic acid-enhanced MRI. These patients were required to undergo follow up either with gadoxetic acid-enhanced MRI, extracellular gadolinium-based MRI, or dynamic multiphase CT scans of the liver. Nodules which had characteristics of cyst, cystic tumor, hemangioma or hypovascular liver tumor such as cholangiocarcinoma or lymphoma were excluded from the study. Patients who had a history of transarterial chemoembolization (TACE) treatment before their initial MR imaging and last follow-up were not included. Any nodules with a history of post radiofrequency ablation (RFA) treatment were not included. However, patients who had a history of HCC with locoregional treatment such as surgery and RFA at other location were also included (Fig 1).

Baseline clinical data, cause of liver cirrhosis or chronic liver disease, Child-Pugh class and serum alpha-fetoprotein (AFP) level at the time of the initial MR image examination of each patients was also recorded.

MR examinations

The MR images were acquired using a whole body MR system Achieva 1.5-T; Philips Healthcare, Best, the Netherlands and two 3.0-T whole body MR systems (Ingenia 3.0-T and Achieva 3.0-T); Philips Healthcare, Best, the Netherlands.

The conventional MRI protocol consisted of axial T1-weighted dual fast field echo in-phase and opposed phase sequences, axial T2-weighted with fat suppression, axial T2 weighted turbo spin echo, and coronal single shot T2-weighted sequence. DWI was obtained before gadoxetic acid administration by using a respiratory-

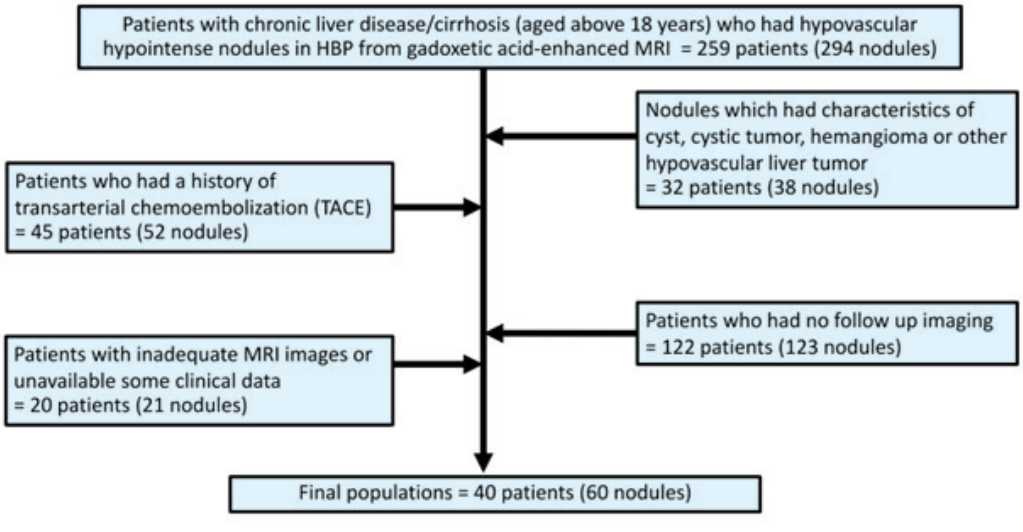

Fig 1. Final population of this study

triggered single-shot echo-planar imaging sequence with b values of 0, 50 or 150, 600 or 750 or 800 sec/mm^2. A spectral attenuated inversion-recovery technique was used for fat suppression on DWI. The apparent diffusion coefficient (ADC) map was generated by using b values of 0, 50 or 150, 600 or 750 or 800 sec/mm^2.

The MR contrast agent used was gadoxetic acid disodium (Primovist®; Bayer-Schering Healthcare, Berlin, Germany) which was administered at 0.1 mL/kg bodyweight (equivalent to 25 μmol/kg bodyweight). All injections were performed by a power injector at a rate of 1.5 mL/s through an antecubital vein and flushed with 30 mL saline administered at the same rate.

The dynamic study looked at suspended respiration at 30 seconds (arterial phase), 70 seconds (portovenous phase),120 seconds and 5 minutes (transitional phase) after intravenous contrast administration. The hepatobiliary phase images were done at 20 and 30 minutes after contrast injection.

Image analysis

The initial MR images were evaluated with consensus by two abdominal radiologists; observer 1 (V.S., with 5 years of experience) and observer 2 (R.T., with 16 years of experience). Both were blinded to the clinical information, follow up MRI interpretations and the final diagnosis.

All lesions were preselected for review by a third abdominal radiologist (W.T., with 10 years of experience) who noted the image numbers, the segmental location of the lesion and marked them on the MR images.

All MR images were evaluated using PACS. Both observers were given the initial gadoxetic acid-enhanced MRI set (unenhanced T1 and T2-weighted images, gadoxetic acid-enhanced dynamic phase, hepatobiliary phase and DW images). The nodule size, presence of fat component, signal intensity on T1W, T2W, portal and transition phases of dynamic study, including hypersignal intensity in a high b-value DWI were investigated. The lesion sizes were measured as the longest diameter in hepatobiliary phase images. The presence of fat component was determined by decreased signal intensity of nodules on opposed phase T1W compared to in-phase T1W images. The signal intensity of the nodule surrounding the liver parenchyma was recorded relatively on T1W and T2W images and with high b values of DWI which can be described as hypointense, isointense and hyperintense. We evaluated the ADC for each nodule at the initial DWI. The b values of 0 and 600 or 800 sec/mm^3 were used to generate the ADC map.

The third radiologist was given the last follow up image which could be either a gadoxetic acid-enhanced MR image, extracellular gadolinium-based enhanced MR image, or dynamic CT scan to define the transformation to hypervascular HCC. If the nodules showed signs of enhancement in the arterial phase, wash out on portal or transition phases with consistent hypointensity in the hepatobiliary phase, a diagnosis of "hypervascular HCC" was made.[4-7] Meanwhile, nodules with no arterial enhancement and no progression in size were classified as "non-hypervascularization group". The time between the initial to last images and the nodules' sizes in the last follow up images were also recorded.

Statistical analysis

The clinical data was compared for hypervascular HCC and non-hypervascularization group. A two-sample t–test, Mann-Whitney U test were used to determine the difference in quantitative variables with (i.e., age, and duration of time between the first and the last imaging) and without normal distribution (serum AFP) between the HCC and non-HCC group. A Pearson's chi-square test was used to compare qualitative variables between the two groups.

The time to HCC development was calculated from the date of initial MR imaging to the final follow-up. A Kaplan-Meier survival curve was constructed for qualitative variables (e.g., T2W image and DW image). The univariate Cox regression analysis was used to determine the effect of each factor towards the time of HCC development. A forward multivariate Cox regression analysis was performed to identify predictive variables for HCC after adjusting for other characteristics. The adjusted hazard ratio and 95% confidence intervals (CIs) were also calculated.

The growth rate was computed as the difference between the initial and final diameter of nodules (millimeters), divided by duration (days) in initial and final MR imaging. The difference in growth rate between the two groups was compared using a Mann-Whitney U test. The prognostic value of the growth rate was evaluated using the receiver operating characteristic (ROC) curve.

All tests were two sided, and a p-value of less than 0.05 was considered statistically different. All statistical analyses were performed using PASW version 18.

RESULTS

Baseline clinical data was collected from a total of 40 patients (30 men and 10 women). The age range of male patients was 42-81, with a mean age of 60.9; while the range of female patients was 50-81, with a mean age of 64.09.

The cause of liver cirrhosis or chronic liver disease was also obtained and the results were as follows: chronic hepatitis B viral infection (n=25), chronic hepatitis C viral infection (n=8), alcoholic cirrhosis (n=3), non-alcoholic steatohepatitis (NASH) (n=2), hemochromatosis (n=1), and cryptogenic cirrhosis (n=1). Almost all patients were classified in Child-Pugh class A except one who was classified as Child-Pugh class C. The serum alpha-fetoprotein (AFP) level at the time of the initial MR image examination was also recorded.

A total of 60 hypovascular hypointense nodules in HBP of gadoxetic acid-enhanced MRI were identified in 40 patients; 28 had a single nodule, seven had two nodules, three had three nodules, one had four nodules, and 1 other had five nodules. Of these, 27 nodules showed progression to hypervascular HCC upon follow-up imaging (Group 1) while 33 nodules did not change to hypervascular HCC in a follow-up MRI (Group 2). All Group 1 nodules were underwent the specific treatment of HCC, including TACE (14/27 nodules = 51.85%, RFA 12/27 nodules = 44.45%, surgery 1/27 nodule = 3.7%). All patients in Group 2 underwent a follow-up MRI and there was no evidence of hypervascular HCC.

A mean follow-up time of 674.63±407.87 days (range 62-1341 days), hypervascular HCC was seen in 27 out of 60 nodules (45%) while 33 out of 60 nodules (55%) did not show progression to hypervascular HCC. All nodules were diagnosed on the basis of gadoxetic acid-enhanced MRI. The cumulative incidence of hypervascular transformation at 3, 6, 12 and 24 months was as follows: 5%, 20%, 35%, and 44%, respectively (Fig 2). Hypovascular hypointense nodules in HBP combined with hyperintensity in T2W images had median time to hypervascular HCC of 118 days. Hypovascular hypointense nodules in HBP combined with hyperintensity DW images had a median time to hypervascular HCC of 137 days and was statistically significant ($P < 0.001$).

The baseline clinical data between two groups, including age, sex and serum AFP of patients show no statistically significant difference between the two groups.

MR imaging features of both groups are summarized in Table 1. A Univariate Cox regression analysis (Table 1) revealed that hyperintensity on T2W images, hypersignal intensity on DWI, and history of previous HCC were statistically significant and associated with progression to hypervascular HCC. These variables were entered into the multivariate Cox analysis, which included the initial size of the nodules (Table 2). Only initial sizes of nodules greater than 1 centimeter were statistically significant and associated with progression to hypervascular HCC (Adjusted HR 2.52; 95% CI: 1.11, 5.74) (Fig 3).

Hyperintensity on T2W images seemed to increase the risk of progression to hypervascular HCC but this was not statistically significant (P=0.308; Adjusted HR 4.77; 95%CI: 0.24, 95.95). Hyperintensity on DW images also tended to increase the risk of hypervascular HCC but this was also not statistically significant (P = 0.597; Adjusted HR 1.93; 95%CI: 0.17, 22.22). However, most hypervascular HCC groups (19 out of 27 nodules, 70.4%) did not show hyperintensity on T2W images and/or hyperintensity on DW images in initial MR imaging. The history of locoregional treatment for HCC is associated with progression to hypervascular HCC (P = 0.059; adjusted HR 2.27; 95%CI: 0.97, 5.34).

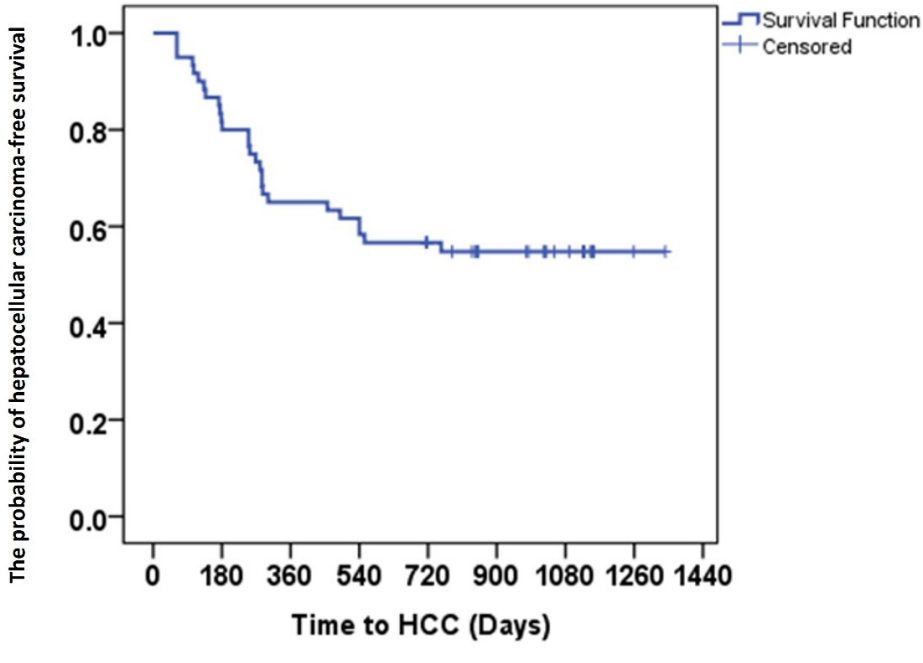

Fig 2. The probability of hepatocellular carcinoma-free survival for all hypovascular hypointense nodules in the hepatobiliary phase.

TABLE 1. Characteristics and Univariate Cox analysis for developing hypervascular HCC

Parameter	Number of patients (%)		Univariate Cox Model	
	HCC	Non-Hypervascularization	HR (95%CI)	P-value
Fat containing				
Yes	6 (46.2)	7 (53.8)	0.96 (0.39,2.37)	0.956
No	21 (48.8)	22 (51.2)	1.00	
T1W				
Hyperintensity	4 (40.0)	6 (60)	0.703(0.2,2.5)	0.586
Isointensity	17 (45.9)	20 (54.1)	0.75 (0.3,1.91)	0.545
Hypointensity	6 (46.2)	7 (53.6)	1.00	
T2W				
Hyperintensity	8 (88.9)	1 (11.8)	16.03(1.98,129.88)	0.009
Isointensity	18 (40.9)	26 (59.1)	2.99 (0.40,22.40)	0.287
Hypointensity	1 (14.3)	6 (85.1)	1.00	
Portal				
Isointensity	11 (44.0)	14 (56)	1.00	
Hypointensity	16 (45.7)	19 (54.1)	1.11(0.52,2.4)	0.789
Equilibrium				
Isointensity	3 (37.5)	5 (62.3)	1.00	
Hypointensity	24 (46.2)	28 (53.2)	1.36 (0.41,4.53)	0.612
DW image				
Hyperintensity	8 (88.9)	1 (11.8)	5.75 (2.46,13.44)	<0.001
Isointensity	19 (37.8)	32 (62.1)	1.00	
History of local therapy for HCC				
Yes	16 (61.5)	10 (38.1)	2.44(1.13,5.27)	0.023
No	11 (32.4)	23 (67.1)	1.00	
Initial diameter				
>1 cm	12 (60.0)	8 (40)	2.01 (0.94,4.31)	0.071
≤ 1 cm	15 (37.5)	25 (62.1)	1.00	
Cirrhosis				
HBV	17 (54.8)	14 (45.1)	1.21 (0.47,3.07)	0.694
HCV	4 (25)	12 (75)	0.42(0.12,1.47)	0.173
Non HBV/HCV	6 (46.2)	7 (53.6)	1.00	

TABLE 2. Multivariate analysis by Cox regression model for hypovascular hypointense nodules in HBP using gadoxetic acid-enhanced MRI to transform into hypervascular HCC

Characteristics	P-value	Adjusted HR	95%CI
T2W			
Hyperintense	0.308	4.77	(0.24,95.95)
Isointense	0.549	1.89	(0.24,15.03)
Restricted Diffusion	0.597	1.93	(0.17,22.22)
History of local therapy for HCC	0.059	2.27	(0.97,5.34)
Size > 1 cm	**0.027**	2.52	(1.11,5.74)

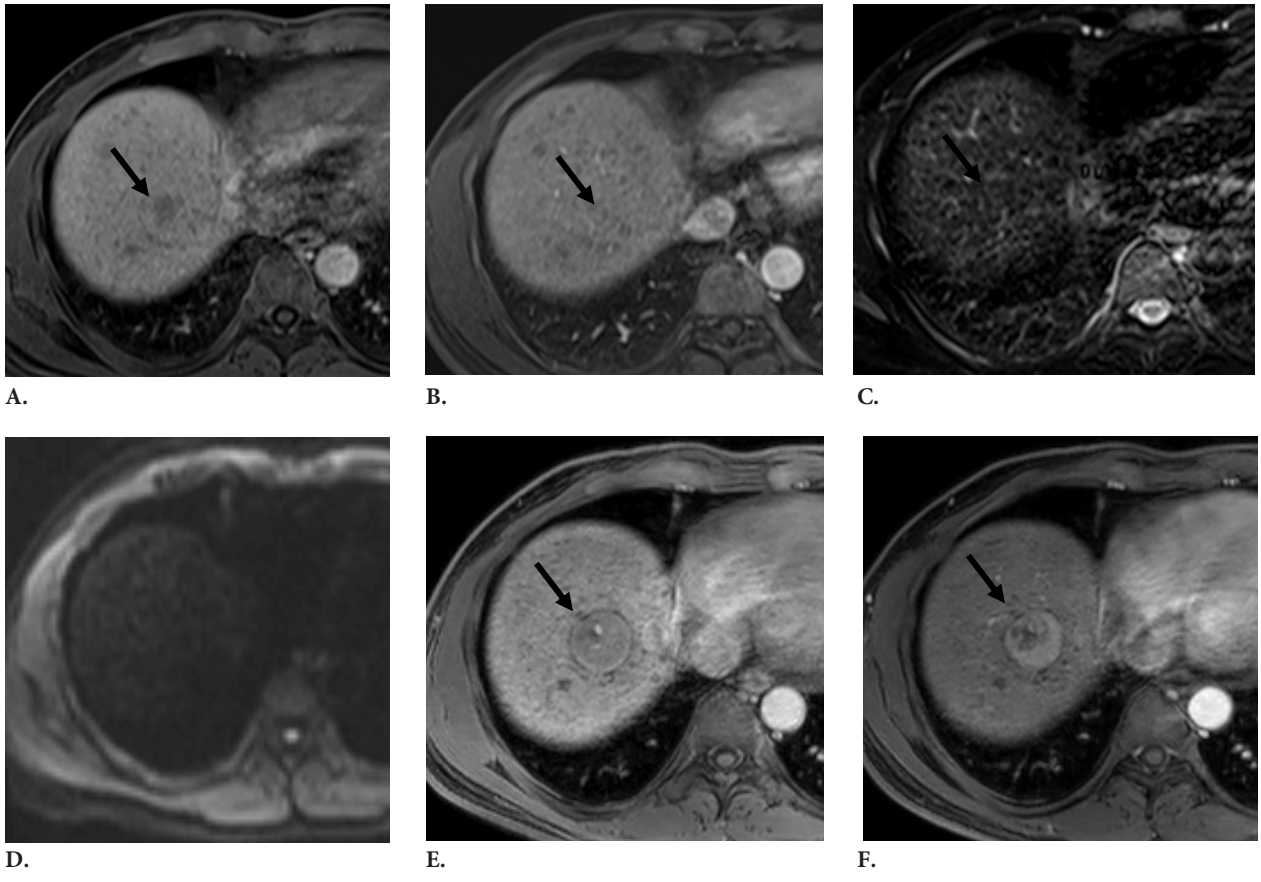

Fig 3. A 53-year-old male with HCV cirrhosis. (A) Axial gadoxetic acid-enhanced 20 minute HBP image showing a hypointense nodule, initial diameter of about 1.7 cm. (B) Axial arterial phase showing no arterial enhancing nodule at the same location. (C) Axial T2W image and (D) DW image (b = 800 sec/mm^2) observed no hypersignal intensity. (E,F) Axial gadoxetic acid-enhanced MRI obtain later 9 months, the same nodule showed increased in diameter to 3.1 cm. measured in (E) hepatobiliary phase image. (F) Arterial phase showing hypervascularization.

Growth analysis of the two groups was also recorded. Twenty-seven nodules in the hypervascular HCC group (initial diameter 10.4 mm ± 4.5) (range, 5-21 mm) and thirty-three nodules in the non-hypervascularization group (initial diameter 8.2 mm ± 3.5) (range, 4-16 mm) were evaluated. The median time of observation was 269.7 ± 178.21 days (range 62-754) in the hypervascular HCC group and 1005.94 ± 171.37 days (range 716-1341) in the non-hypervascularization group.

In the hypervascular HCC group, 26 nodules increased in size and one nodule remained stable during follow-up imaging. The median growth rate in the hypervascular HCC group was 19.4 x 10^{-3}/day. In the non-hypervascularization group, the median growth rate was -0.8 x 10^{-3}/day. By using the Mann-Whitney U test, the mean growth rate of hypervascular HCC group was higher than the non-hypervascularization group ($p<0.001$). The ROC analysis (area under the curve, 0.985) had a growth rate cutoff value of 3.1x10^{-3} per day, sensitivity of 92.59% and specificity of 96.97%, positive predictive value (PPV) of 96.15% (25 of 26 nodules) and negative predictive value (NPV) of 94.12% (32 out of 34 nodules).

DISCUSSION

Due to the multistep hepatocarcinogenesis concept, the hypovascular hypointense nodule in HBP can progress to hypervascular HCC in serial follow-up MR imaging. [14-16] This recent study showed that the cumulative percentage incidence of hypervascular transformation at 6 months, 1 and 2 years were 20%, 35%, and 44%, respectively. These results are apparently more than the cumulative incidence rates from a meta-analysis[16] which found a pooled 1 and 2-year cumulative incidence rate of 18.3% and 25.2%, respectively. This difference is reflected in the high prevalence of HCC in our region, which requires strict interval follow-up of these nodules.

This study found that a initial nodule size (more than 1 centimeter) is the only significant predictive factor for hypervascular transformation of hypovascular hypointense nodules in HBP, similar to the previous report.[15-17] Moreover, the mean growth rate of nodules that progress to hypervascular HCC was significantly higher than the non-hypervascularization group. According to the receiver operating characteristic (ROC) curve, a cut-off growth rate of 3.1x10^{-3} per day in this study is higher

than a previous report.[18] Nodules with a growth rate of more than $3.1x10^{-3}$ per day are related to subsequent hypervascular HCC. The authors suggest that hypovascular hypointense nodules in HBP larger than 1 cm in diameter with a fast growth rate be closely follow up.

Nevertheless, the Univariate Cox analysis from this study revealed hypersignal intensity on T2W and DW images and a history of local therapy for HCC associated with progression to hypervascular HCC. These results are in accordance with previous studies.[17-21] *Kim YK et al.*[20] reported that hypersignal intensity on DW images strongly associated with progression to hypervascular HCC. *Hyodo et al.*[18] also noted that hyperintensity on T2W images was a strong risk factor for subsequent hypervascularization. Although these MRI features and patient characteristics were not statistically significant when using a Multivariate Cox regression analysis in this study, it tended to increase the risk of development of hypervascular HCC. The authors also suggest that hypovascular hypointense nodules with these suspicious imaging features or a history of local therapy for HCC with higher growth rates should be closely followed-up for the development of hypervascular HCC in the future.

This study had several limitations. First, the number of patients included in this single-center study was small. Second, this was a retrospective study, and therefore there may have been selection bias. Third, our MR imaging protocols had various b-values for DW imaging which may have had an effect on interpretation of signal intensity of the nodules. Fourth, there was no pathological result correlation, and thus the ability to identify the exact stage of these nodules in multistep carcinogenesis was not available.

In conclusion, hypovascular hypointense nodules in the HPB of gadoxetic acid-enhanced MRI can potentially progress to hypervascular HCC in the future. A initial nodule diameter of more than 1 cm and nodules with higher growth rate are significant predictive factors for hypervascular transformation.

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Radiopharmaceuticals for Positron Emission Tomography Imaging of Amyloid: Research and Clinical Applications in Thailand

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ABSTRACT

In the past two decades, the research community has focused on defining reliable molecular biomarkers for the early diagnosis of Alzheimer's disease (AD). Several positron emission tomography (PET) radiopharmaceuticals have been developed and gained regulatory approval for the non-invasive detection of amyloid-β (Aβ) amyloid deposits in the brain. Nowadays, there are several PET imaging radiopharmaceuticals available in Thailand for amyloid imaging including [^{11}C]-labeled Pittsburgh compound B ([^{11}C]PiB), [^{18}F]Florbetapir, and [^{18}F]Florbetaben. This review provides a summary of commonly used amyloid PET radiopharmaceuticals, focusing on the available radiopharmaceuticals in Thailand and the experiences of using amyloid PET radiopharmaceuticals and imaging for clinical and research applications at Siriraj Hospital.

Keywords: Positron emission tomography; radiopharmaceuticals; Alzheimer's disease; amyloid-β; plaque; molecular imaging; dementia; amyloid; brain (Siriraj Med J 2023; 75: 688-698)

INTRODUCTION

Alzheimer's disease (AD) is a significant cause of dementia in persons older than 65 years.[1] Cognitive deficiencies in those with AD manifest as a progressive neurodegenerative disorder that is clinically characterized to lead to loss of memory, cognitive decline[2], difficulty finding the right words or difficulty in interpreting what people say, difficulty performing previously routine tasks, and mood swings.[3] Progressive cognitive decline negatively impacts daily life activities, resulting in the person needing assistance to undertake even simple activities such as shopping or managing finances[4], leading eventually to death, normally about seven to ten years after diagnosis.[5] Therefore, an early and accurate diagnosis is very important in patients with AD.

Approximately 48% of the world's population with dementia lives in Asia and this percentage is evaluated to grow to 59% within 2050.[6] The prevalence of dementia in the elderly in Thailand ranges from 18% to 33%.[7,8] Several biomarker screening tests have been used in clinical studies for the early detection of AD, including apolipoprotein E gene status[9,10], total Tau, phosphorylated Tau levels in cerebrospinal fluid[11], Aβ 1-42, and reduced platelet amyloid precursor protein ratio.[12]

In the past two decades, several PET radiopharmaceuticals have been developed for the non-invasive detection of specific molecular biomarkers involved in the pathophysiology and pathomorphology of AD, such as amyloid- plaques including [^{11}C]-labeled Pittsburgh compound B [^{11}C]PiB, [^{18}F]Flobetapir (Amyvid®, Avid radiopharmaceuticals &

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Eli Lilly and Company), [18F]Florbetaben (Neuraceq®, Bayer Healthcare), [18F]Flutemetamol (Vizamyl®, GE Healthcare), [18F]Flutafuranol (Astra-Zeneca and Navidea) and [18F]FIBT.

To date, [18F]Flobetapir, [18F]Flutemetamol and [18F]Florbetaben have been approved for clinical applications by the Food and Drug Administration (FDA: April 2012) and the European Medicines Agency (EMA: January 2013).

A brief history of radiopharmaceuticals for Aβ imaging

The development of PET radiopharmaceuticals for Aβ imaging started in 1984 with the radiolabeling of derivatives of dyes used for histopathological staining of amyloid plaques and neurofibrillary tangles (NFTs), such as thioflavin-S, thioflavin-T[26], Congo red[27], and chrysamine-G[28] (Fig. 1).

The first Aβ radiopharmaceutical for imaging cerebral Aβ deposits, [18F]FDDNP, was developed in 1999 by Barrio et al.[29] at the University of California Los Angeles. The [18F]FDDNP was able to bind with non-selectively extracellular Aβ plaques and intracellular NFTs.[30]

After the [18F]FDDNP was developed, the [11C]PIB was the first generation of radiopharmaceuticals for selective in vivo imaging of Aβ plaques in AD patients. [11C]PIB has been developed from thioflavin-T[31] which binds with high affinity and selectivity to fibrillar Aβ plaques. Currently, [11C]PIB is a widely used PET radiopharmaceutical and remains the gold standard for imaging Aβ plaques in the brain. Despite this, the short half-life of [11C] nuclide (about 20 mins) limits the centralized commercial production and distribution of [11C]PIB for routine clinical use. These limitations can be overcome by [18F] labeled Aβ radiopharmaceuticals because the half-life of [18F] is 109.77 mins. Furthermore, the longer half-life of radioactive decay [18F] allows a longer time for washout of the non-bound radiopharmaceutical from the brain and lower non-specific brain tissue background activity, and more precise quantitation of cerebral Aβ accumulation sites during the initial phases AD. In general, the [18F] labeled radiopharmaceuticals generate more specific images of the location and magnitude of Aβ plaques and allow for better visual interpretation and quantitative analysis of the results.[32]

The improvement of [18F]-labeled radiopharmaceuticals for PET imaging Aβ plaques in the brain was a notable step. The next generation of radiopharmaceuticals with Aβ-specific binding included [18F]Florbetaben[33], [18F]Flutemetamol[34], and [18F]Florbetapir.[35] Presently, all three radiopharmaceuticals in this generation have been approved for clinical diagnosis by the EMA and the FDA.

The [18F]Florbetapir is a [18F] labeled PET radiopharmaceutical that specifically binds to Aβ peptide in amyloid plaques. The detection of Aβ is one of the diagnostic hallmarks of AD and accumulation of the Aβ in the brain is the most significant factor associated with the development of AD.[13] In clinical applications, it helps to assess the efficacy of disease-modifying therapies and future treatments to slow down the progression of AD if administered during the early stages of the disease. However, the mere presence of amyloid plaques alone does not correlate with the magnitude of neurodegeneration, disease severity, and cognitive decline.[14,15] Moreover, it should be noted that cerebral Aβ deposits could be found in other categories of dementia, including dementia with Lewy bodies, in patients with cerebrovascular disease,

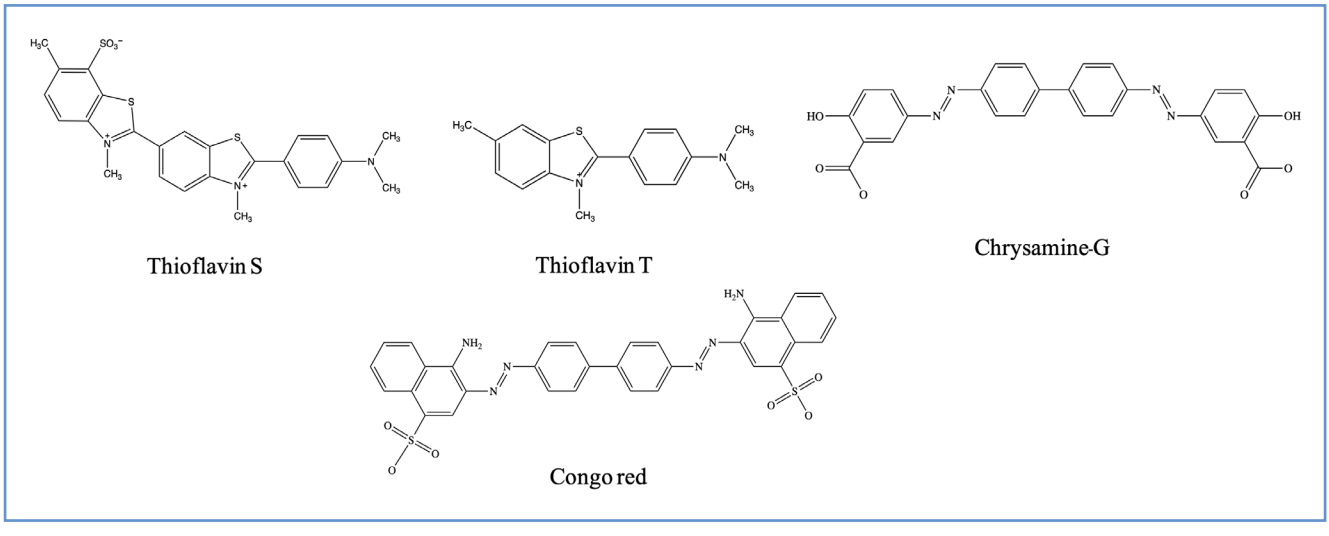


Fig 1. The chemical structure of derivatives of dyes used for histopathological staining of amyloid plaques and NFTs.

corticobasal degeneration, frontotemporal dementia, cortical amyloid angiopathy[16], and Parkinson's disease (PD) with dementia.[17] The absence of Aβ deposits can be anticipated in frontotemporal lobe dementia[18], Creutzfeldt–Jakob disease[19], and cognitively intact PD.[20]

The spatial distribution of accumulation of [^{18}F] Florbetapir is highly correlated with that of the [^{11}C]PiB[21] and is useful for primary and differential diagnosis of AD.[22] A recent Phase III trial has demonstrated that [^{18}F] Florbetapir has 92% sensitivity and 100% specificity for Aβ pathology.[23] Meanwhile, in anpther phase III multicenter trial, [^{18}F]Florbetaben PET detected cortical fibrillar Aβ plaques with 98% sensitivity and 89% specificity as compared to histopathology.[24] Additionally, the retention of [^{18}F]Florbetaben at global and regional levels is highly correlated with the retention of [^{11}C]PiB.[25] The results of the standard centiloid analysis showed a little higher Aβ binding and slightly lower variance than [^{11}C]PIB, significant properties for detecting the early stages of Aβ deposition.[36] However, the second generation of radiopharmaceuticals do not bind well to NFTs, and the true extent of cortical retention of [^{18}F]Florbetapir and [^{18}F]Florbetaben is below [^{11}C]PIB.[25]

For this reason, [^{18}F]NAV4694 (AKA [^{18}F]AZD4694) was recently developed and is now used in phase III clinical trials[37] as [^{18}F]Flutafuranol (Navidea Biopharmaceuticals). [18F]Flutafuranol exhibits rapid pharmacokinetics, strong binding to Aβ plaques, and slightly lower non-specific binding in the cerebral white matter.

Table 1 provides a summary of PET radiopharmaceuticals for imaging Aβ amyloid plaques, including their current chemical abbreviation, chemical structure, trade name, parent molecule, mechanism of binding to amyloid plaque, limitations, and the approval status.

Radiopharmaceuticals employed for imaging Alzheimer's patients in Thailand

At present, three cyclotron centers in Bangkok, Thailand, are producing PET radiopharmaceuticals for the detection of Aβ plaques in the brains of AD patients. The Wattanosoth Hospital in Bangkok was the first center in Thailand to start developing [^{11}C]PIB in November, 2012.[45] The National Cyclotron and PET Centre at the Chulabhorn Hospital, Chulabhorn Royal Academy, Bangkok, started producing [^{11}C]PIB in 2017[46] and [^{18}F] Florbetaben in 2019. The Siriraj Hospital in Bangkok started producing [^{18}F]Florbetapir in 2015.

Clinical and research applications at the Wattanosoth Hospital.

The [^{11}C]PiB at Wattanosoth Hospital was produced by TR-19 PET cyclotron using iPHASE [^{11}C] PRO-2 automated radiosynthesizer module (iPHASE technologies). The [^{11}C]CO_2 was produced via ^{14}N(p,α)^{11}C nuclear reaction. The radiosynthesis of [^{11}C]PiB was started with [^{11}C]CO_2 delivered from the cyclotron to the [^{11}C] PRO-2 automated synthesis module. It was synthesized via the Grignard reaction using 6-OH-BTA-0 precursor (2-(4'-aminophenyl)-6-hydroxybenzothiazole). The specific activity of [^{11}C]PiB was 2.5 Ci/μmol. The radiochemical purity was about 18%-20% (delay corrected) with a total synthesis time of 30 minutes.[45]

The current [^{11}C]PiB production at Wattanosoth Hospital can service 2-3 dementia patients a day requiring amyloid PET scan for an early diagnosis to allow a better chance of benefiting from treatment, participating in clinical drug trials, and allowing more time to plan for the future. Nevertheless, to our knowledge, there has been no available published data on clinical performance of [^{11}C]PiB PET scan.

Clinical and research applications at the National Cyclotron and PET centre.

In 2017, The National Cyclotron and PET Centre at Chulabhorn Hospital developed [^{11}C]PIB and studied the determination of the preliminary optimal cutoff points for SUVRs in amyloid using [^{11}C]PIB. The results showed that the [^{11}C]PIB accumulation pattern in healthy control subjects was used to confirm the early onset AD of a limited or no accumulation in cortical brain regions. This indicates that 10%–30% of normal elderly participants could show significant [^{11}C]PIB retention.[50] [^{11}C]PIB was uptake in the gray matter of neocortical regions, including the frontal lobes, parietal lobes, temporal lobes, and posterior cingulate cortex. The study of clinical performance of [^{11}C]PiB in AD patients and normal controls in the Thai population found significantly higher mean SUVR in AD patients than that of normal controls ($P < 0.05$), with distinctly elevated [^{11}C]PiB deposition in the anterior and posterior cingulate in AD. The proposed [^{11}C]PiB cut-off for regional SUVR was approximately 1.46-1.81 in their study yielded sensitivity ranging from 81.25% to 93.75%, and specificity of 100% (CI 0.82-1.00).[64] Another study on the additional diagnostic value of molecular imaging using [^{11}C]PiB amyloid PET together with [^{18}F] FDG metabolic PET and [^{18}F]THK5351 Tau PET on the diagnosis of dementia subtypes found primary diagnosis change in 60% of patients and the combined PET scan information was able to solve 95.2% pre-PET diagnostic dilemmas.[65] To the best of our knowledge, the clinical performance of [^{18}F]Florbetaben PET scan at The National Cyclotron and PET Centre has not been published yet.

TABLE 1. Examples of commonly used [^{18}F]-labeled radiopharmaceuticals for Aβ imaging.

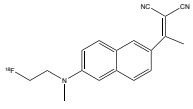
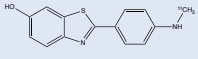
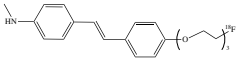
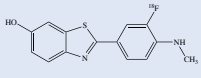
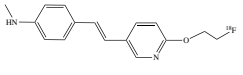
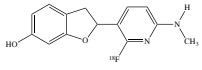
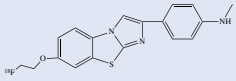
Radiopharmaceuticals	Chemical structure	Trade name / company	Parent molecule	Mechanism of binding to amyloid plaque	Limitation	Approval status and approval organization
[^{18}F]FDDNP[30,38]		-	Amyloid dyes such as thioflavin-S, thioflavin-T, Congo red and	Bind non-selectivity to both of extracellular Aβ plaques and intracellular chrysamine-G	Limited binding to both Aβ plaques and NFTs NFTs	-
[^{11}C]PIB[31,39]		- (Research use)	Benzothiazole	High affinity and selectivity for fibrillar Aβ plaques and in another Aβ containing lesion	Short radioactive half-life	- (Research use)
[^{18}F]Florbetaben [33,40] ([^{18}F]AV-1, [^{18}F]BAY-94-9172)		Neuraceq®/ Piramal Imaging, Berlin, Germany	Stilbene	High level of non-specific white matter retention	May not be useful for correct mapping of Aβ plaque load in low-density regions and in prodromal phases of AD.	The FDA and the EMA in 2014
[^{18}F]Flutemetamol[34] ([^{18}F]GE-067)		Vizamyl®/ GE Healthcare, Milwaukee, Wisconsin, USA	Benzothiazole	High specificity and sensitivity for the in vivo detection of brain Aβ density	-	The FDA in 2013 and the EMA in 2014
[^{18}F]Flobetapir[35] ([^{18}F]AV45)		(Amyvid; Avid Radiopharma-ceuticals, Eli Lilly and Company, USA)	Styrylpyridine	Higher non-specific white matter uptake	-	The FDA in 2012 and the EMA in 2013

TABLE 1. Examples of commonly used [^{18}F]-labeled radiopharmaceuticals for Aβ imaging. (Continue)

Radiopharmaceuticals	Chemical structure	Trade name / company	Parent molecule	Mechanism of binding to amyloid plaque	Limitation	Approval status and approval organization
[^{18}F]Flutafuranol[41-42] ([^{18}F]NAV4694 or ([^{18}F]AZD4694)		- (Phase 3 clinical trial) / AstraZeneca; Cambridge, England)	Benzothiazole	Fast kinetics reaching apparent steady state and very low non-specific white matter binding.	May not be useful for correct mapping of Aβ plaque load in low-density regions and in prodromal phases of AD.	- (Under clinical trials)
[^{18}F]FIBT[43-44]		- (Clinical trial)	Imidazobenzo-thiazole	High contrast Aβ imaging agent, excellent pharmacokinetics and high binding affinity to Aβ fibrils in vitro and in vivo	-	- (Under clinical trial)

Clinical and research applications of brain PET scans using [^{18}F]Florbetapir at the Siriraj Hospital

Since 2015, the research team from the Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine, Siriraj Hospital, started a research project entitled [^{18}F]Florbetapir PET to evaluate brain amyloid deposition in patients with AD, mild cognitive impairment, and regular aging. The project was initially funded by the National Research Council of Thailand via the Health System Research Institute. In 2016, another research project entitled "Evaluation of multimodal imaging in the assessment and diagnosis of early-stage AD with and without comorbidities" was initiated; it was funded by the International Atomic Energy Agency as a part of an international multi-center coordinated research project. These clinical research projects were ethically permitted by the institutional review board and co-funded by the Faculty of Medicine, Siriraj Hospital, Mahidol University in 2018 under the departmental project entitled "Research and technology development of PET scans for the assessment of brain amyloid deposition in patients with Alzheimer's dementia".

The routine production of [^{18}F]Florbetapir has been established at the Siriraj Cyclotron Centre following the Good Manufacturing Practice standards, as described in detail in previous publications[31,48] using the cyclotron model HM20S (Sumitomo Heavy Industries Ltd., Japan) and two CFN-MPS200 automated radiosynthesis modules (Fig 2) (Sumitomo Heavy Industries Ltd., Japan).[47] Briedly, the [^{18}F] radionuclide was produced using ^{18}O(p,n)^{18}F nuclear reaction using [^{18}O]H_2O. Then, [^{18}F-] was combined with the AV-105 precursor via substitution of the tosylate leaving group in the fluorination process. Then, the boxylic protecting group was hydrolytically removed by adding 1M of hydrochloric acid, and neutralized with 1M sodium hydroxide. Purification of [^{18}F]Florbetapir was accomplished using semi-preparative HPLC; the [^{18}F]Florbetapir product was diluted with 20 ml of 0.5% sodium ascorbate/ultra-pure water and purified with a tC18 cartridge. The purified [^{18}F] Florbetapir was transferred

into the reactor vial, then dried up to remove the residual solvent, diluted with normal saline, and then the final product was sterilized by passing through the 0.22 µm GV filter (Merck Millex™). [^{18}F]Florbetapir quality control was in accordance with US Pharmacopeia Standards Chapter 823. The total synthesis time was about 60 minutes; the radiochemical yield was about 14% and the radiochemical purity was more than 98%. The quality control results of the produced [^{18}F]Florbetapir were similar to those reported previously.[33,49] The amount of produced [^{18}F]Florbetapir radioactivity could support PET imaging of about 5 patients per production run.

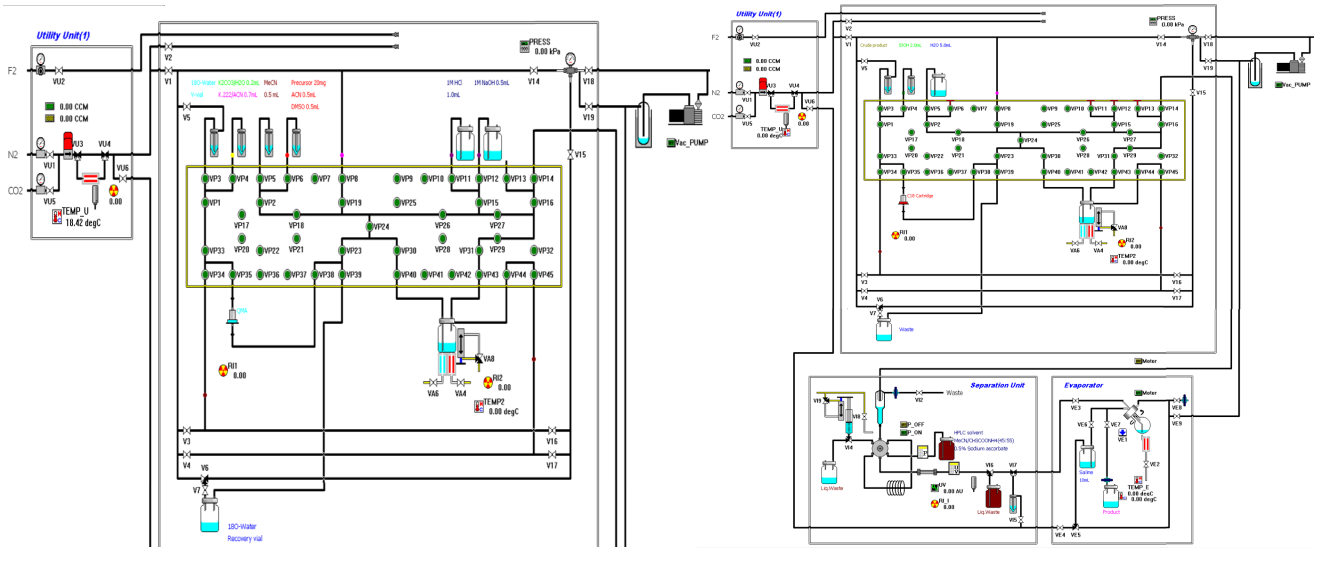
After gaining experience from these research projects, PET imaging with [^{18}F]Florbetapir has been utilized to support the clinical management of patients with neurocognitive impairment and suspected AD. The current clinical applications are following the appropriate use criteria which were recommended in previous publications.[62,63] The application of amyloid PET scans is considered most likely helpful for improving diagnostic certainty or for adjusting the clinical management plan of patients with confirmed cognitive impairment of an uncertain cause after a comprehensive evaluation by a dementia expert, where AD is considered in the differential diagnosis. In order to conduct an amyloid PET scan, the following acceptance criteria are used: 1) patients who have persistent or progressive unexplained MCI; 2) the core clinical criteria for possible AD are complacent but there is an ambiguous clinical presentation (atypical clinical course or mixed presentation); 3) patients who have progressive dementia with an unusually early onset age (< 65 years). The update of the appropriate use criteria to include the potential role of amyloid PET, for example, in selecting candidates for amyloid-targeting therapy, is still ongoing.

[^{18}F]Florbetapir PET imaging protocols

The quality of images obtained with PET/CT scanners (Discovery STE and Discovery MI; GE Healthcare) were qualified using a Hoffman brain phantom. All research volunteers underwent PET/CT imaging 50-70 min after IV injection of 10 mCi (370 MBq) of [^{18}F] Florbetapir using a 20 min acquisition (acquired in 4 x 5 min-frames), following the protocols in ADNIGO[51] and ADNI2.[52] The full description of amyloid PET image acquisition and reconstruction protocols and the image quality obtained from the Hoffman brain phantom were described in our previous publications.[47,53-55] In some clinical cases when patients had significantly poor cooperation, we reduced the acquisition time to the standard 10 minutes acquisition (acquired in 2 x 5 min-frames), in line with the manufacturer's recommendations.[53]

PET image analysis and interpretation

All PET images underwent quality control before further visual interpretation and analysis. The visual interpretation was carried out by nuclear medicine specialists and was categorized as either 'positive' or 'negative' following the standard guidelines.[56] The semi-quantitative analysis to determine the localization and dimensions of Aβ depositions in the brain was also



Schematic diagram of [^{18}F]Florbetapir synthesis

Schematic diagram of [^{18}F]Florbetapir purification

Fig 2. Schematic diagram of the [^{18}F]Florbetapir synthesis and purification process

accomplished using software packages. The DICOM image files of each PET scan were further processed using specialized software packages: either the Neurological Statistical Image Analysis Program (NEUROSTAT / 3D-SSP software, University of Utah, SLC, USA), Pneuro PMOD image analysis software (PMOD Technologies; Zurich, Switzerland)[57], FreeSurfer[58], or Statistical Parametric Mapping (SPM) version 12 (The Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, UK).[57] The results from our research using these software packages have been reported in previous publications.[47,53,54,59] The NEUROSTAT software was used to spatially normalize the amyloid PET scans obtained in cognitively-normal volunteers (age 60-82 years), whose original scans were interpreted as negative for both glucose hypometabolism and Aβ deposition, and who provided a normal database for the calculation of z-scores and generation of images of z-score maps. The Pneuro, FreeSurfer, and SPM software packages were used to analyze the T1-weighted MRI images from individual patients for segmentation and volumetric analyses of brain structures, co-registration with corresponding PET images, and measurements of the regional brain uptake values [standardized uptake value (SUVs)] and standardized SUV ratios, as well as the volume of the corresponding brain regions. Figs 3 & 4 provide examples of [^{18}F]Florbetapir brain PET images in the evaluated patients for both visual and quantitative analyses.

Clinical studies conducted at the Siriraj Hospital using [^{18}F]florbetapir PET and visual assessment of images demonstrated a sensitivity of 86.7% and specificity of 95.0% for differentiating patients with AD from normal control subjects. When using the global SUVR cut-off of 1.15 obtained from 3D-SSP NEUROSTAT Software, we found a sensitivity of 83.3% and a specificity of 90%.[54] Moreover, we found that high amyloid uptake in occipital region is associated with clinically advanced AD and may be useful for evaluating AD severity.[53] Therefore, [^{18}F] Florbetapir amyloid PET scan may be feasible for both diagnostic and prognostic applications. Furthermore, our results from combining imaging information from amyloid PET, FDG PET, and MRI volumetry to create the specific AV45/FDG/NVol index found significant correlation with clinical neurocognitive status and higher than using amyloid PET, FDG PET, or MRI alone. We expected this combined molecular imaging index may facilitate more accurate diagnosis, staging, and prognosis of AD.[47]

Future directions of brain PET radiopharmaceuticals and imaging development in Siriraj Hospital

The cyclotron-radiochemistry core facility team at Siriraj Hospital is currently working on setting up the production of the latest generation of radiopharmaceuticals for PET imaging of amyloid beta deposits in the brain, such as [^{18}F]Flutafuranol. Another radiopharmaceutical in development is [^{18}F]MK-6240, which binds to tau protein fibrils and provides an advantage in terms of detecting early tau pathologies. The evaluation of amyloid beta and tau proteinopathies, along with A-T-(N) criteria[60,61], and the potential roles of PET imaging biomarkers in selecting suitable candidates for clinical

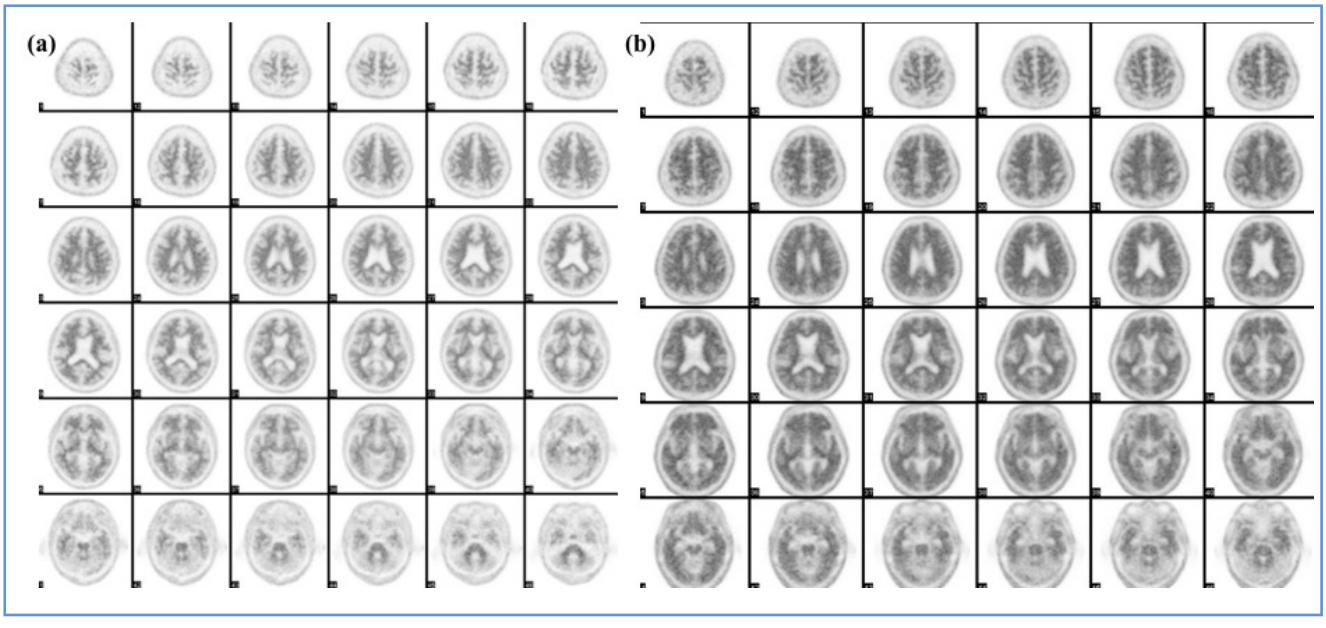


Fig 3. Examples of [^{18}F]Florbetapir brain PET images: (a) amyloid-negative in an elderly individual with normal cognition, and (b) amyloid-positive in a patient with AD.

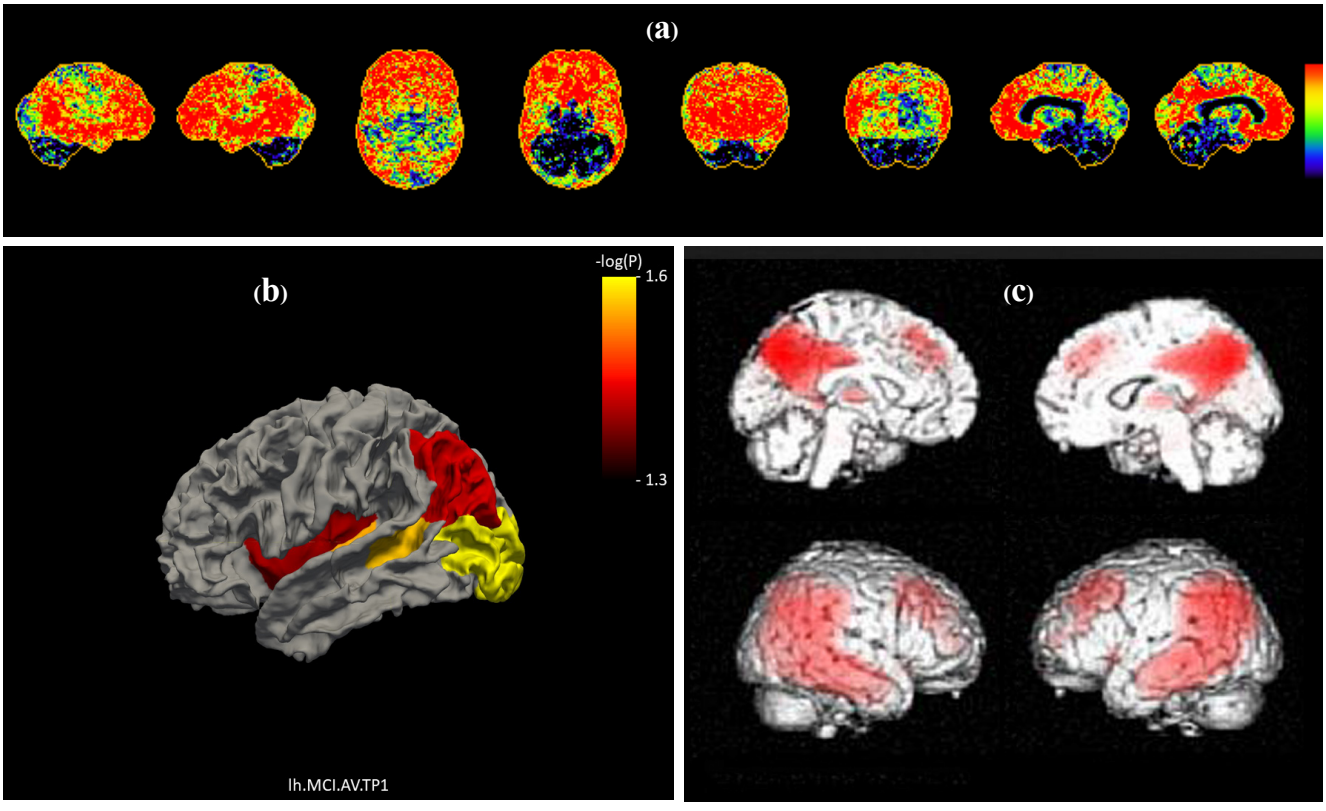


Fig 4. Examples of quantitative and semi-quantitative analyses using software packages with NEUROSTAT (a), FreeSurfer (b), and SPM (c).

trials or monoclonal antibody therapy have been recently discussed. Moreover, the ongoing longitudinal clinical studies are aimed to elucidate the dynamic changes in brain amyloid deposition, glucose metabolism, and morphological changes (neurodegeneration) in relation with neurocognitive performance tests and other biomarkers of AD. The focus of these ongoing studies is to develop and translate these PET imaging biomarkers into routine clinical practice.

CONCLUSION

In Thailand, amyloid PET neuroimaging has been confirmed as a helpful technique for the detection of the Aβ plaques in the primary and differential diagnosis of AD and possibly for the evaluation disease progression. So far, the use of amyloid PET radiopharmaceuticals in Thailand including at Siriraj Hospital has been successfully implemented without any complications or side effects. The available reported clinical performance and impact of amyloid PET in Thailand are similar to those reported from other countries. Larger scale clinical research involving patients with different types of dementia-associated neurodegenerative diseases should be conducted to provide more information on the diagnostic, prognostic, and therapeutic values of PET imaging of amyloid in the brain.

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Conflict of interest

All authors declare there is no competing interest.

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