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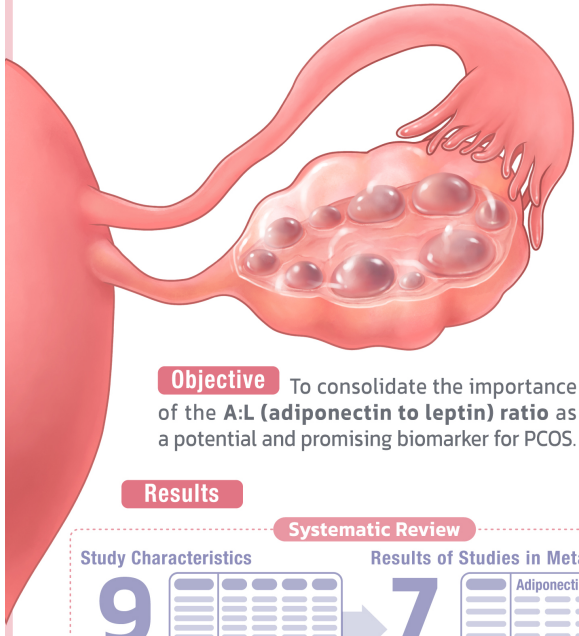
ORIGINAL ARTICLE REVIEW ARTICLE

Systematic Review and Meta-Analysis on Role of Adiponectin to Leptin Ratio in Women with Polycystic Ovarian Syndrome



Objective To consolidate the importance of the **A:L (adiponectin to leptin) ratio** as a potential and promising biomarker for PCOS.

Methods

The method followed the PRISMA 2020 guidelines, and the databases were used to obtain eligible studies published up to February 2023.

PRISMA

PROSPERO
April 2, 2023
CRD42023411754

Databases

MEDLINE
ProQuest
EBSCO*host*

ESHRE ASRM Rotterdam Guideline

I2 statistic
Cochran's Q test
Examine
The studies' heterogeneity

The evaluation on publication bias
Egger's test
Rank correlation test

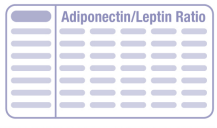
Data analysis was conducted with JASP 0.17.1, and statistical significance was characterized as a p-value below 0.05.

Results

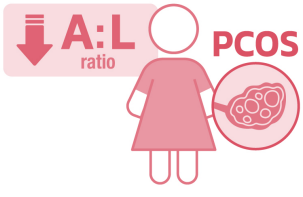
Systematic Review

Study Characteristics: 9 studies

Results of Studies in Meta-Analysis: 7 studies



Each paper showed a reduced A:L ratio in women with PCOS.



A standardized mean difference (SMD) among PCOS and control groups of 0.49 (CI: 0.37-0.61).

The residual heterogeneity test

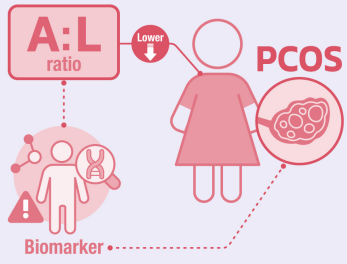
p-value = 0.069

No publication bias indication

Pre and post intervention

p-value = 0.002

Conclusion



The A:L ratio was notably lower in PCOS patients. Consequently, the A:L ratio holds promise as a novel and potential biomarker for PCOS.

A Iskandar, et al. *Siriraj Med J* 2023;75:838-850.

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Systematic Review and Meta-Analysis on Role of Adiponectin to Leptin Ratio in Women with Polycystic Ovarian Syndrome

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ABSTRACT

Objective: PCOS or Polycystic Ovarian Syndrome, a multifaceted disorder marked by disruptions in endocrine and metabolic processes, influences reproductive age women. The most commonly used criteria for diagnosing this condition are the Rotterdam 2003 and the National Institutes of Health Consensus 1990 guidelines. Recent studies are currently focusing on novel biomarkers, such as adiponectin and leptin to gain deeper insights on the intricate pathophysiology of PCOS. Therefore, this review aimed to consolidate the importance of the A:L (adiponectin to leptin) ratio as a potential and promising biomarker for PCOS.

Materials and Methods: The method followed the PRISMA 2020 guidelines. Furthermore, MEDLINE, Proquest, and EBSCOhost databases were used to obtain eligible studies published up to February 2023. This study was registered in PROSPERO on April 2, 2023 with registration number CRD42023411754. ESHRE/ASRM or Rotterdam Guideline was used as the diagnosis criteria for women with PCOS. To examine the studies' heterogeneity, the I^2 statistic and Cochran's Q test were utilized. Meanwhile, the evaluation on publication bias visually employed a funnel plot and was confirmed through Egger's test and rank correlation test. Data analysis was conducted with JASP 0.17.1, and statistical significance was characterized as a p-value below 0.05.

Results: In the systematic review, a total of nine studies were incorporated, and seven studies were used in the subsequent meta-analysis. Each paper showcased a reduced A:L ratio in women with PCOS, with a standardized mean difference (SMD) among PCOS and control groups of 0.49 (CI: 0.37 - 0.61). The residual heterogeneity test yielded a p-value of 0.069, and no publication bias indication both pre and post intervention (p=0.002).

Conclusion: Referring to the findings, the A:L ratio was notably lower in PCOS patients. Consequently, the A:L ratio holds promise as a novel and potential biomarker for PCOS.

Keywords: Polycystic ovarian syndrome; adiponectin to leptin ratio; biomarker (Siriraj Med J 2023; 75: 838-850)

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) stands as a familiar and diverse endocrine disruption that impacts reproductive age women. This condition significantly impacts the endocrine, reproductive, and metabolic systems.[1] In numerous studies, the occurrence differs based on the particular used criteria for diagnosis. The worldwide prevalence can vary, spanning from 4% to 21% when considering the Rotterdam 2003 criteria and the National Institutes of Health Consensus 1990 criteria.[2] Over the years, PCOS has shown a rapidly increasing trend and is frequently associated with abdominal adiposity, infertility, obstetrical problems, and cardiovascular disease, leading to a deprived life quality.[3]

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Recent analysis revealed that this disease is linked to a range of metabolic disorders, emphasizing the need for further in-depth investigation to explore the relationship between the two entities.[4] This field of study aims to uncover novel biomarkers to provide enhanced comprehension of the intricate pathophysiological mechanisms at play in PCOS, including factors like adiponectin (A) and leptin (L).[5] These adipokines have been associated to a variety of metabolic disorders, such as obesity, insulin resistance, hyperandrogenism, as well as dyslipidemia.[6]

Leptin, originating from adipose tissue, serves as an indicator of body fat levels and plays role in energy homeostasis and insulin resistance.[7] Adiponectin is additionally generated by adipocytes, controlling lipid metabolism and glucose uptake. Furthermore, it functions by increasing hepatic glycolysis and fatty acid oxidation, as well as decreasing gluconeogenesis.[8] Numerous investigations have documented the connection between leptin and adiponectin and their relevance to cardiometabolic conditions, suggesting that the A:L ratio could act as a predictor of metabolic risk factors.[9] A:L ratio also has better diagnostic accuracy in identifying the risk of insulin resistance compared to these adipokines alone.[10] In PCOS patients, it has shown potential as a promising biomarker for diagnosis, as PCOS shares several common metabolic disturbances.[11] Despite previous reports have investigated the connection between the A:L ratio and PCOS, a better understanding of these adipokines in the course of disease is still needed. Findings also show fewer studies on the significance of the A:L ratio as a biomarker, thus we performed a meta-analysis to synthesize its magnitude and obtain the effect size (ES). Therefore, this article summarizes the final results of the A:L ratio as a promising reliable biomarker for PCOS.

MATERIALS AND METHODS

The design was planned and executed as the guideline in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 protocol.[12]

Variable of interest and aim of the study

This study examines the differences in the A:L ratio between PCOS and non-PCOS groups as a novel diagnosis biomarker.

Eligibility criteria

This article encompassed all previously published observational studies that examined the A:L ratio's role in marking inflammation and insulin resistance in PCOS cases.

All articles published dating up to 2023 were also included. Furthermore, the 2003 European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine (ESHRE/ASRM or Rotterdam Guideline)[13,14] were used as diagnosis criteria for women with PCOS. Studies falling under categories, such as review, case reports, case series, conference abstracts, book sections, commentaries/editorials, and studies consisting of non-human subjects were omitted. Articles lacking complete text and those unrelated to the relevant subject matter were also disregarded.

Literature search and information sources

The PRISMA 2020 guidelines were used during the literature search. MEDLINE, Proquest, and EBSCOhost search engines were used to find relevant cases, dating up to February 2023. All studies obtained were screened for duplicates, while the titles and abstracts were independently reviewed by the authors. Furthermore, the studies were omitted from consideration if the titles and/or abstracts did not align with the focus of this review. The full text was read by three authors and the eligible papers were included in this review. Conflicts were solved by consensus and the opinion of all reviewers.

Data collection process

Six reviewers individually carried out the process of data extraction. Any disagreements that arose were resolved through common consent among the reviewers and, when necessary, by seeking the input of the sixth reviewer. Comprehensive data was documented concerning the name of the primary author, study year, the country, the study's type, demographic characteristic of the patients (number of participants and their age), PCOS diagnosis criteria, population matching, adjusted confounding factors/exclusion criteria, and their outcome of interest. For bivariate data extraction, yielded studies were further classified based on the L:A or A:L ratio from each group (PCOS and non-PCOS). This primary outcome was measured by mean difference (MD) as the parameter of ES.

Data and outcome measures

Adiponectin and leptin serum level was presented as μg/L or ng/mL, consecutively. Values were displayed as mean ± standard deviation (SD) for normally distributed data, or as median (interquartile range) for not normally distributed data. A:L ratio was reported or calculated by dividing the amount of adiponectin by the amount of leptin, leading to a single numerical value of ratio. When the study reported the L:A ratio, the value was reversed to obtain the A:L ratio.

Synthesis of result and summary measures

The main outcomes were tabulated in univariate and bivariate results. Data regarding the number of participants and patient's age were included as demographic characteristics in each study. The types of study, PCOS diagnosis criteria, population matching, and other possible outcome biases were also presented in an univariate table. These baseline characteristics were further discussed to elaborate on the confounding factors that could interfere with the results of the A:L ratio. The bivariate table presents the A:L ratio for each group, and also a *p-value* and 95% Confidence Interval (CI).

Quality assessment

Each article underwent evaluation utilizing the Newcastle-Ottawa Scale (NOS) for case-control studies, and an adjusted version of NOS was employed for cross-sectional studies.[15,16] These tools consisted of three main domains, namely (a) Selection, (b) Comparability, (c) Outcome/exposure. According to the NOS for case-control studies, the quality was classified as follows: (1) Good (3-4 stars in the selection domain, 1-2 stars in comparability, and 2-3 stars in exposure), (2) Fair (2 stars in selection, 1-2 stars in comparability, and 2-3 stars in exposure), and (3) Poor (0-1 star in selection or 0 stars in comparability or 0-1 stars in exposure). In relation to the modified NOS for cross-sectional studies, the categorization of study quality was conducted as outlined below: (1) Very good (9-10 stars), (2) Good (7-8), (3) Satisfactory (5-6), (4) Unsatisfactory (0-4). Each study was independently assessed by two authors. Any discrepancies were resolved through deliberation among all the authors until an unanimous agreement was achieved. The findings of the assessment of study quality are displayed in Table 1.

Data synthesis and statistical analysis

The standardized mean difference (SMD) and the 95% CI of the A:L ratio in participants of all included studies was calculated using the "Meta-Analysis Effect Size Calculator".[17] The standard error (SE) was obtained by dividing the length of the CI by 3.92. The ES and SE were then entered into a Microsoft Excel spreadsheet and used to perform meta-analysis. I^2 statistic and Cochran's Q test were employed to examine the heterogeneity among articles. In cases where heterogeneity was identified ($p < 0.10$ or $I^2 > 75\%$)[18,19], It was used the random effects model for the analysis, and generated a forest plot to illustrate the combined effect size. Subsequently, a visual assessment on the publication bias was performed through a funnel plot. The statistical confirmation was accomplished by conducting a rank correlation and Egger's tests. The trim and fill method[16] was employed to correct the bias found. However, it was unable to ascertain the presence of publication bias when the total number of included studies was fewer than 10. All analyses were conducted using JASP 0.17.1 and p <0,05 was assumed as statistically significant.

RESULTS

Literature search

Fig 1 presents a flowchart summarizing the study selection process and its outcomes. Furthermore, the searches strategy yielded 561 potentially relevant studies. Following the specified criteria for selection, a total of 12 studies were pinpointed for a more thorough full-text evaluation, one was considered not suitable, and another two had no control group for comparison. In total, nine papers were involved in systematic review and seven studies eligible for data extraction were used in meta-analysis. The PCOS groups exhibited sample sizes that spanned from 31 to 241, while the control groups had sample sizes ranging from 22 to 216.

Characteristics of included studies

A total of nine studies, consisting of 1,598 women (865 PCOS and 733 non-PCOS) met the inclusion criteria. The characteristics, including the number of participants (N), age (years), population matching, exclusion criteria, and area under the curve (AUC) represented the sensitivity and specificity of A:L ratio were extracted from each study and reported in Table 1. Furthermore, six of them were case-control studies[5,20–24] and the other three were cross-sectional studies.[11,25,26] All the papers used the Rotterdam ESHRE/ASRM 2003 criteria for diagnosing PCOS. The mean ages of PCOS and non-PCOS populations ranged from 23.4 ± 6.1 to 32.85 ± 4.25 years and 23.9 ± 3.6 to 32.5 ± 4.9 years, respectively. The results showed that only five studies[5,11,20,22,26] had carried out age population matching and two studies[11,26] had performed BMI-matching population. Among the nine studies, two came from India[5,11], one from Bangladesh[24], one from Ghana[21], two from Bahrain[22,23], one from Australia[25], one from Italy[26] and one from Brazil.[20]

Quality Assessment

Quality assessment for obtained studies were performed using the NOS for case-control (Table 2A) and cross-sectional studies (Table 2B). A total of three, five, and one papers were in the very good,[11,25,26] good,[5,20–23] and fair quality categories, respectively.[24]

In the nine studies included in the qualitative

TABLE 1. Study Characteristics.

Author, Year, Country	Types of Study	N		Age (Mean ± SD)		Population matching	Exclusion Criteria	Sensitivity/ Specificity of A:L ratio AUC*
		PCOS	Non PCOS	PCOS	Non PCOS			
Mishra et al., 2022, India[11]	Cross-Sectional Study	60	60	27.5 ± 2.83	27.83 ± 3.03	Age and BMI	Pregnant, liver disease, lactating and women with diabetes, glucocorticoids, Cushing syndrome, late onset of CAH or other serious medical condition, history of intake of oral contraceptives in the last 3 months, antiandrogens, antidiabetic, ovulation induction agents, antipsychotic, or antihypertensive or hormone replacement therapy.	0.7873 (cut off ≤0.1154)
Mohana et al., 2021, Bangladesh[24]	Case-Control Study	20	20	27.30 ± 1.29	26.45 ± 0.91	N/A	N/A	0.868* (cut off 4.35); P<0.001
Obirikorang et al., 2019, Ghana[21]	Case Control Study	BMI <30: 54 BMI ≥30: 50	52	32.85 ± 4.25	31.63 ± 4.88	N/A	Women with Cushing syndrome, androgen-producing tumors, hyperprolactinemia, non-classic adrenal hyperplasia, diabetes, and active thyroid disease.	0.83
Sarray et al., 2015, Bahrain[22]	Case-Control Study	241	216	28.6 ± 6.1	27.5 ± 7	Age and Ethnic	Androgen-producing tumors, nonclassic adrenal hyperplasia, 21-hydroxylase deficiency, hyperprolactinemia, Cushing disease, and active thyroid disease.	0.650 Cut-off 0.039 P<.001
Shorakae et al., 2018, Australia[25]	Cross-Sectional Study	46	22	30 ± 6	29 ± 8	N/A	Pregnancy, use of any medication that could interfere with SNS activity, diabetes, insulin resistance within 3 months before recruitment, history of secondary hypertension, cardiovascular, cerebrovascular, renal, liver, thyroid, or lung disease, or severe mental illness.	N/A

TABLE 1. Study Characteristics. (Continue)

Author, Year, Country	Types of Study	N		Age (Mean ± SD)		Population matching	Exclusion Criteria	Sensitivity/ Specificity of A:L ratio
		PCOS	Non PCOS	PCOS	Non PCOS			AUC*
Gupta et al., 2017, India[5]	Case-Control Study	223	216	25 ± 10	25 ± 10	Age	Pregnant, lactating, and women with any kind of gynecological or obstetrical problems, women on medication including hormone replacement therapy, with any viral, bacterial, allergy, and inflammatory disease.	N/A
Golbahar et al., 2012, Bahrain[23]	Case-Control Study	50	50	29.5 ± 2.9	28.5 ± 5.9	N/A	History of insulin resistance, ovarian failure, or any other endocrine or major organ disorders.	0.861 (95%CI 0.786 –0.936)
Savastano et al., 2011, Italy[26]	Cross-Sectional Study	BMI <25: 42 BMI ≥25: 48	BMI <25: 20 BMI ≥25: 20	BMI <25: 24.1 ± 4.6 BMI ≥25: 24.8 ± 4.0	BMI <25: 23.9 ± 3.6 BMI ≥25: 25.4 ± 4.6	Age and BMI	The presence of T2DM or abnormal glucose tolerance was excluded by the oral glucose tolerance test (OGTT), Smoking or alcohol consumption, pregnancy, hypothyroidism, hyperprolactinemia, Cushing's disease, non-classical congenital adrenal hyperplasia; previous (within the last 6 months) use of oral contraceptives, glucocorticoids, anti-androgens, ovulation induction agents, anti-obesity drugs, or other hormonal drugs.	N/A
Lecke et al., 2011, Brazil[20]	Case-Control Study	BMI <25: 8 BMI ≥25: 23	BMI <25: 19 BMI ≥25: 38	BMI <25: 25.4 ± 5.3 BMI ≥25: 23.4 ± 6.1	BMI <25 :29.3 ± 5.9 BMI ≥25: 32.5 ± 4.9	Age	Pregnant women with diabetes, thyroid dysfunction, liver or renal disease, and have received drugs known to interfere with hormonal levels for at least 3 months.	N/A

*Area Under the Curve

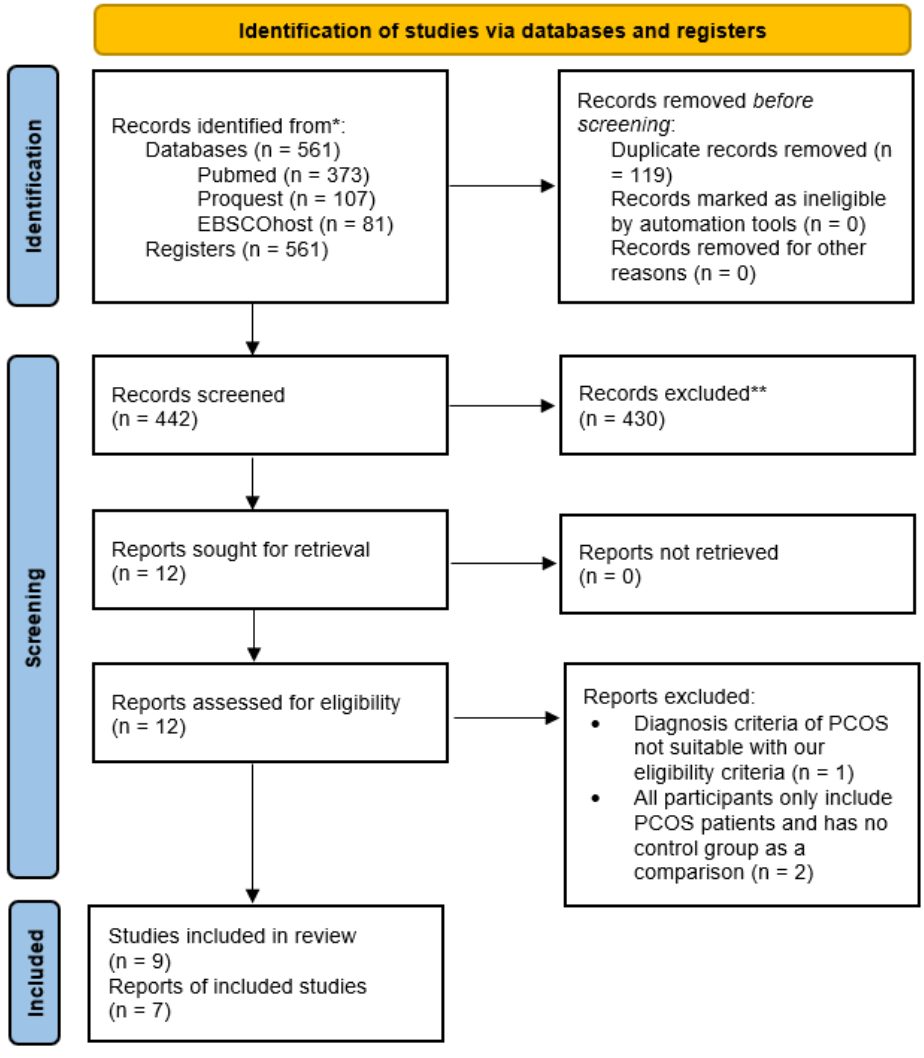

Fig 1. PRISMA flow diagram of involved studies.

TABLE 2A. Risk of bias assessment for case-control studies.

Author, year	Selection				Comparability	Exposure			Conclusion
	S1	S2	S3	S4	C1	E1	E2	E3	
Lecke et al., 2011	☆	☆	☆	☆	☆	☆	☆	☆	Good
Golbahar et al., 2012	☆	☆	☆	☆	☆	☆	☆	☆	Good
Sarray et al., 2015	☆	☆	☆	☆	☆☆	☆	☆	☆	Good
Gupta et al., 2017	☆	☆	-	☆	☆	☆	☆	☆	Good
Obirikorang et al., 2019	☆	☆	-	☆	☆	☆	☆	☆	Good
Mohana et al., 2021	☆	-	-	☆	☆☆	☆	☆	☆	Fair

Note: S1: adequate case definition, S2: case representativeness, S3: control selection, S4: control definition, C1: Comparability, E1: Exposure Ascertainment, E2: identical method of ascertainment for cases and controls, and E3: non-Response Rate.

TABLE 2B. Bias assessment risk for cross-sectional studies.

Author, year	Selection				Comparability	Outcome		Conclusion
	S1	S2	S3	S4	C1	O1	O2	
Savastano et al., 2011	☆	☆	☆	☆	☆☆	☆☆	☆	Very Good
Shorakae et al., 2018	☆	☆	☆	☆☆	☆☆	☆☆	☆	Very Good
Mishra et al., 2022	☆	☆	☆	☆☆	☆☆	☆☆	☆	Very Good

Note: S1: sample representativeness, S2: sample size, S3: non-respondents, S4: exposure ascertainment, C1: comparability, O1: assessment of outcome, and O2: statistical test.

synthesis, the A:L ratio exhibited a significant decrease in PCOS patients, with p-values of <0.0001 to 0.05. The meta-analysis findings from the seven incorporated studies were visualized in both forest and funnel plots (Figs 2A and 2B). The accumulation diagrams of forest plots showed the SMD in each study and the ultimate ES derived from the amalgamation of all the studies. As displayed by the figure, the ultimate weighting of the combined value was depicted in the form of a rhombus shape, while a square shape indicated a weight for each study. The dimensions of each square were determined based on the study's weight in the meta-analysis and calculated referring to the population samples.

Sarray et al.,[22] constituted the larger proportion of samples (N= 457) and Mohana et al.,[24] accounted for the smallest proportion (N=40). All studies had an ES favoring PCOS groups, which was marked by the positive ES on the right side of the plot. A study by Shorakae et al.,[25] had a 95% CI border coinciding with the vertical axis on the left. Based on meta-analysis results, SMD between PCOS and non-PCOS groups was 0.49 (CI: 0.37 - 0.61). Table 5 showed the model for meta-analysis with each Q-statistics and their p-values.

The test results of residual heterogeneity showed a p-value of 0.069. This indicated that the heterogeneity for all studies was not statistically affecting the result, leading to the selection of the fixed effect model. When heterogeneity was attributed to random variation, the random effects model was employed, and it could not be explained because the model presupposed that the

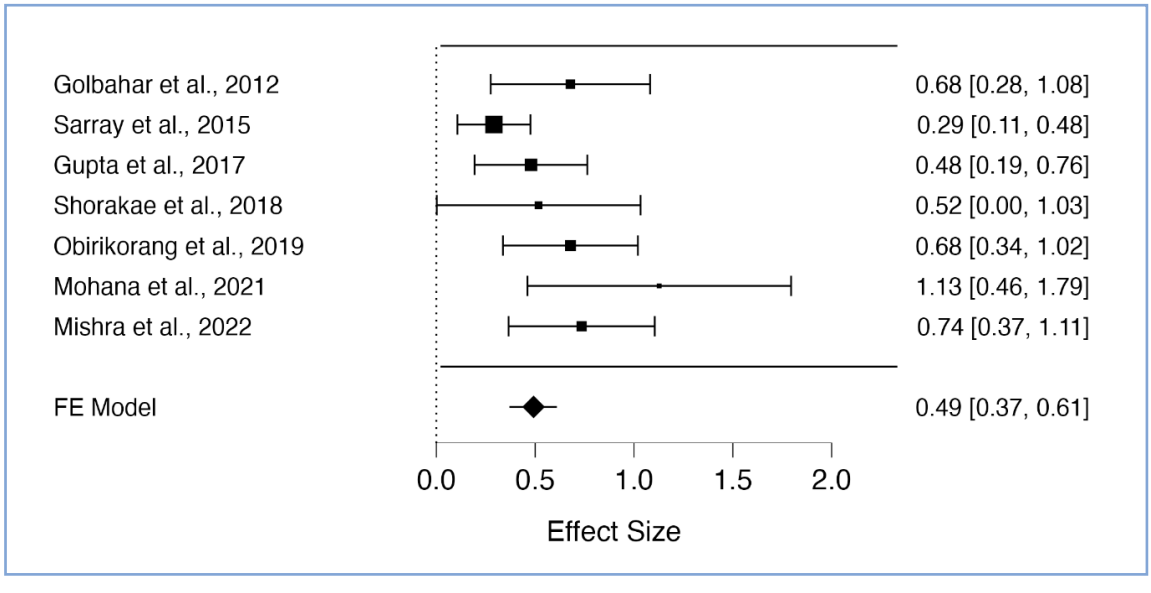

Fig 2A. Meta-analysis results for A:L Ratio (Forest Plot)

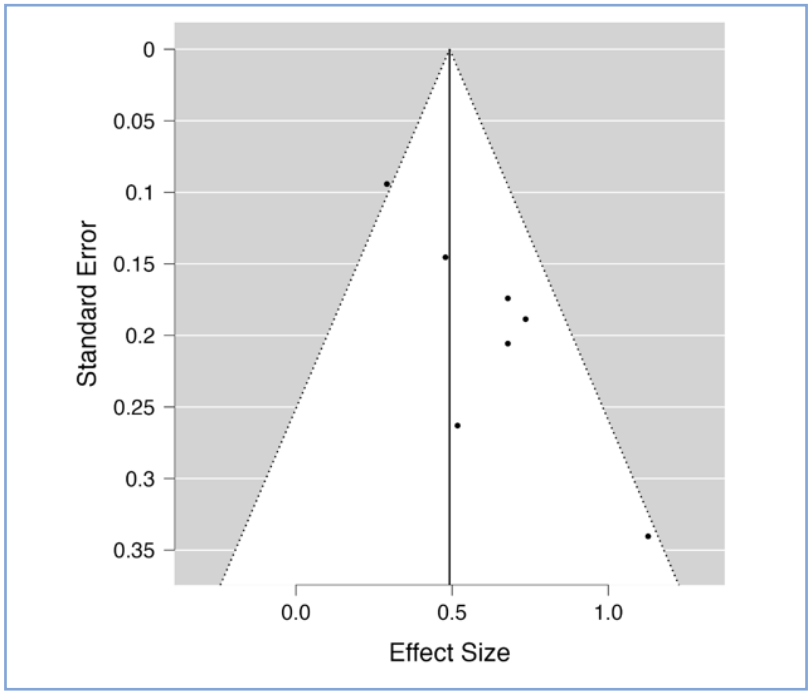

Fig 2B. Meta-analysis results for A:L Ratio (Funnel Plot).

TABLE 3. Results of studies in meta-analysis.

No	Author, Year	Adiponectin/Leptin Ratio				
	PCOS*	PCOS	Non PCOS*	p-value**	SE	SMD
1.	Golbahar et al., 2012[23]	0.25 ± 0.08	0.50 ± 0.15	< 0.001	0.2057	0.6785
2.	Sarray et al., 2015[22]	2.6 (0.2–99.0)	4.8 (0.4–116.9)	0.002	0.0942	0.2912
3.	Gupta et al., 2017[5]	0.53 ± 0.625	0.66 ± 0.68	0.012	0.1454	0.4789
4.	Shorakae et al., 2018[25]	0.07 (0.1)	0.13 (0.1)	0.05	0.2630	0.5175
5.	Obirikorang et al., 2019[21]	0.60 (0.35–0.88)	1.19 (0.92–1.37)	< 0.0001	0.1741	0.6785
6.	Mohana et al., 2021[24]	0.17 (0.12, 0.22)	0.47 (0.29, 0.74)	<0.001	1.1276	0.3404
7.	Mishra et al., 2022[11]	0.15±0.24	3.03±15.04	< 0.0001	0.1886	0.7354

treatment impact was distributed over certain populations and gave each study a more equal weighting. Furthermore, these effects were varying but connected to each other. The results of the I^2 test showed an estimate of 46.287% (<75%), indicating that the random effect model was not considerable.

Results for the Omnibus test of Model Coefficients showed a p-value of <0.001, and the association of the A:L ratio was considered significant. Furthermore, significant results were observed between SMD in PCOS and non-PCOS groups (with intercept result of p<0.001), as shown in Table 4B.

The Egger test was used to assess the bias observed and the results showed no publication bias before and after the intervention (p=0.002). Regarding the correlation test for detecting asymmetry in the funnel plot, Kendall's T value was 0.524, but this correlation did not reach statistical significance (p = 0.136), as detailed in Table 4C.

TABLE 4A. Test for fixed and random effects model.

Test	Q	Df	p-value
Omnibus test of Model Coefficients	64.839	1	<0.001
Residual Heterogeneity Test	11.683	6	0.069

TABLE 4B. Coefficient and residual heterogeneity estimates.

Test	Estimate	95% CI		SE	p-value
		Lower	Upper		
Intercept	0.492	0.372	0.612	0.061	< 0.001

TABLE 4C. Rank correlation test and regression test for funnel plot asymmetry (Egger's test).

Test	Kendall's T / z	p-value
Rank test	0.524	0.136
sei	3.034	0.002

Calculation on SE for both groups from all included studies was performed employing the formula below: SE = (upper CI limit – lower CI limit) / 3.92, or by calculating the square root of the calculated error variance (v). A total of six studies were inside the 95% confidence triangle, with five being located near the vertical axis with 0.49 as the symmetrical line, and one located far from the triangle at the right side of the bottom. Furthermore, only one study was located outside the triangle area. The funnels plot diagram showed that the distribution of studies was asymmetry, with 1 study lying outside the triangle area with SE between 0.05 to 0.1. Others were plotted inside the triangle area, with three studies having an SE between 0.1 to 0.2, two had values between 0.2 to 0.3, and one was between 0.3 to 0.35. The higher the SE, the lower the position of the papers in the inverted funnel, indicating low power compared to others. Accompanying the plot was the 'Rank Correlation Test' for assessing funnel plot asymmetry, and the results showed non-significance with a p-value of 0.136.

DISCUSSION

Meta-analysis results suggested that PCOS patients had a lower A:L ratio, with a statistically significant ES (MD=0.49, 95%CI: 0.37 -0.61, p<0.001). Similarly, Lin et al.,[27] found that in patients with PCOS, adiponectin levels fell statistically significant, but leptin levels rose significantly. Leptin was a hormone derived from adipocytes and encoded by the human obese (ob) gene, which regulated glucose homeostasis. Several studies had recognized its role in several metabolic and endocrine disorders, including PCOS. Prolonged elevation of circulating leptin levels in obese individuals can lead to the development of resistance and decreased receptor sensitivity to leptin.[28] Decreased leptin sensitivity could lead to excessive triglyceride accumulation in multiple

organs and impaired insulin sensitivity.[29] Moreover, the expression of leptin receptors had also been documented in granulosa cells, indicating that it had direct regulatory action in maintaining ovarian folliculogenesis. Leptin resistance could alter the process and this explained the contribution of leptin in PCOS pathophysiology.[30]

Based on two previous meta-analyses,[31,32] increased concentrations of leptin were linked with an increased probability of developing PCOS compared to control participants. According to previous studies, higher levels were also linked to an increased risk of insulin resistance, metabolic disturbance, and cardiovascular disease, all of which could contribute to the development of PCOS. Leptin was assumed to have a stimulatory impact on LH secretion while exerting an inhibitory influence on the actions of FSH and insulin-like growth factor (IGF)-1.[33] Moreover, hyperleptinemia conditions can inhibit ovarian response to gonadotropin stimulation. Based on these findings, raised leptin levels could potentially disrupt hormonal balance and ovarian function in women, elucidating its contribution to PCOS pathophysiology.[34] As analyzed by Zheng et al.,[32] hormone levels were somewhat elevated in non-obese PCOS patients than controls with matching BMI, but this difference was not statistically significant. Hence, leptin levels were elevated in individuals with PCOS, regardless of their BMI.

Adiponectin hormone released by adipose tissue contributes to mitigating atherogenic harm and insulin resistance, and it also has an effect on other tissues. Given adiponectin's insulin-sensitizing properties, its reduced levels in obesity, and the capacity of testosterone to diminish adiponectin levels,[34] one could hypothesize that women with PCOS might have lower concentrations.[34] Among non-PCOS women, the levels exhibited a decline as BMI increased.[36] Meanwhile, in women with PCOS, there was an independent impact on insulin sensitivity, which was not associated with obesity and had been observed in lean individuals as well (BMI < 25 kg/m^2).[37] Adiponectin receptor 1 (adipoR1) and adiponectin receptor 2 (adipoR2) have been discovered as the membrane receptors responsible for mediating its glucose-lowering and anti-inflammatory actions. Previous research indicated that the expression of these receptors was diminished in individuals with obesity. Nevertheless, in women with PCOS, there was an upregulation observed in both visceral fat and subcutaneous tissue.[35]

According to meta-analysis by Toulis et al.,[38] adiponectin was reduced in PCOS women in contrast with control group with a comparable BMI. The levels were descending in obese individuals with PCOS than those without. Also, it was related to insulin sensitivity, where patients with higher insulin resistance had more inferior amounts of the hormone.

The A:L ratio has been considered as an indication of adipose tissue malfunction and a potentially valuable biomarker for metabolic disorders.[39] Insulin resistance (IR) had been associated with a decrease in A:L ratio. Even though IR is considered an intrinsic feature to PCOS, yet it is not included in most established diagnostic criteria. Therefore, A/L ratio come up as a promising novel biomarker for IR in PCOS patients, regarding their independent association with PCOS. Besides, it might help to identify PCOS women who are at risk of developing IR, which marked by an alteration in the A:L ratio and subsequently be used as a screening tools for the risk factor of IR in PCOS.[11]

Several studies showed that A:L ratio considered as the best predictor of IR in PCOS, compared to other adipokines (adiponectin (A) alone, leptin (L) alone, resistin (R) alone, or L:R ratio).[22,39,40] Supported by its AUC values in the ROC curve, the A:L ratio exhibited superior sensitivity and specificity in five studies (with AUC values of 0.787[11], 0.868,[24] 0.830[21], 0.861,[23] and 0.650[22]). An AUC between 0.8 and 0.9 as reported in three of the studies[21,23,24] indicated a good diagnostic performance.[41] The ROC curve was unaffected by disease prevalence since it depended on the sensitivity and specificity. Therefore, samples could be calculated independent of the incidence of disease among the general population.[42]

For decades, IR is considered as a major factor for the development of the metabolic syndrome.[43] With the purpose to prevent further metabolic and cardiovascular complications, A:L ratio emerge as a propitious biomarker of IR, thus generate a requirement of an accurate and personalized clinical assessment. Treatment plans should be customized for each PCOS woman based on her risk profile for metabolic disease, as well as any complaints she may have regarding infertility, hirsutism, or menstruation disturbances.[44]

Heterogeneity and publication bias analysis

The I^2 test for heterogeneity showed a value of 46.287%, which could be classified as *"represent moderate heterogeneity"*.[45] Considering the low to moderate heterogeneity of this result, further subgroup analyses were not necessary. The heterogeneity of the result could be observed from clinical, methodological, or statistical perspectives. From a clinical perspective, the differences in participants or outcomes could lead to high levels. This study involved 40 to 457 women as participants. The larger the sample, the more likely or unlikely the ES could occur. From a methodological

perspective, the differences in study design and population matching could lead to high heterogeneity. Apart from the matching effort, all studies excluded those with pregnancy, diabetes, liver disease, renal dysfunction, history of oral contraceptives, hormonal imbalance (Cushing syndrome, androgen deficiency), and all medical history encompassing the use of medications such as hormone replacement therapy, as well as any history of viral, bacterial, allergic, or inflammatory conditions. Considering the possibility of controlling the confounding factors at the beginning of the study, heterogeneity from methodological perspectives was unlikely. Ultimately, from a statistical perspective, variation in intervention effects or results contributed to increased heterogeneity. In this systematic review, three studies reported the L/A ratio and four other studies reported the A:L ratio. Four studies reported ratio in median and interquartile range values,[21,22,25] and three other papers reported in mean and SD values. Despite the various reporting results, all studies were calculated using SMD in meta-analysis, thus minimizing the statistical heterogeneity.

The source of potential bias in this study included publication bias, where there was a tendency among authors and publishers to predominantly release papers that showcased significant results. In this systematic review, results for the A:L ratio driven from all papers were reportedly significant. Other sources of bias included data variances among methodological designs, where two and five studies had cross-sectional and case-control designs.

Strengths and limitations of the study

Our review had several strengths, including being the first meta-analysis that investigated the potential role of the A:L ratio in determining the presence of inflammation in PCOS. This review also included all studies that either reported an A:L ratio or an inverted L:A ratio. All studies were considered to have good quality, implying more reliable conclusions. The results varied based on the difference in the A:L ratio in PCOS and non-PCOS groups, with several papers being reported in mean and median. These varying results could be solved by normalizing the data distributions to obtain more parametric findings. Several confounding variables, particularly insulin resistance and BMI could not be adjusted. This condition could potentially influence the outcome and exposure relationship, leading to a discrepancy in the summary ES.

Future directions

A threshold for A:L ratio had been proposed, with values of >1.0, 0.5-1, and <0.5 being deemed normal, moderately increased risk, and severe increase in cardiometabolic risk, respectively.[39] Furthermore, there was no established cut-off value for the A:L ratio as a biomarker for PCOS. Future studies with larger populations and interventional study designs are advised to depict the appropriate values of the A:L ratio limit in PCOS patients.

CONCLUSION

The findings revealed a significant reduction in the A:L ratio among PCOS patients than non-PCOS individuals. Consequently, the A:L ratio holds promise as a potential novel biomarker for PCOS in the forthcoming.

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Conflict of interest

No conflict of interest in this study.

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Registration of review protocol

This review was registered in PROSPERO on April 2nd, 2023 with the registration number CRD42023411754.

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A Systematic Review and Meta Analysis of Non-Randomized Interventional Studies on the Pamidronate Treatment Efficacy for Patients with Bone Fibrous Dysplasia

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ABSTRACT

Objective: Pamidronate is one of the main therapies for Fibrous Dysplasia (FD), with documented enhancements in patients' clinical characteristics. Nevertheless, its usage has yielded inconclusive results. Therefore, this review aimed to investigate pamidronate's impact on several clinical and biochemical outcomes in FD patients.

Materials and Methods: This review was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. MEDLINE, ProQuest, Wiley, and EBSCO search databases were used to search the literature. Risk of Bias In Non-Randomized Studies of Interventions (ROBINS-I) was applied for quality assessment of the included studies and Review Manager (RevMan) 5.4 was employed in performing the meta-analysis.

Results: There are eight and seven studies used in the meta-analysis and systematic review, respectively. The results showed there are two studies with a low risk of bias and six with a moderate category. All papers included in this meta-analysis showed significant differences in the reduction of bone pain ($p<0.00001$) and serum alkaline phosphatase (SAP) ($p=0.04$) after pamidronate treatment compared to the before-treatment groups.

Conclusion: The findings of this study indicated that pamidronate therapy had been proven to significantly reduce bone pain and increase SAP in FD patients. However, trials with more age-specific samples and a lower risk of bias should be carried out to determine the statistical significance of overall results.

Keywords: Fibrous dysplasia; pamidronate; bone pain; serum alkaline phosphatase; bone mineral density (Siriraj Med J 2023; 75: 851-863)

INTRODUCTION

Fibrous Dysplasia (FD) is a rare skeletal disorder characterized by an abnormal fibrous tissue development within bone which leads to deformities and functional impairments. This condition exhibits an estimated prevalence of approximately 1 in 20,000 individuals worldwide.[1] Furthermore, FD typically manifests during childhood or adolescence, with the majority of cases being diagnosed before the age of 30.[2] The common manifestations are bone pain, skeletal deformities, and an increased propensity for fractures. Craniofacial FD can lead to facial asymmetry and vision/hearing impairments, while long bone involvement often causes limb-length discrepancies and pathologic fractures.[3] This indicates that early intervention is essential in managing FD-related complications and preventing functional disabilities. Several studies have also identified various timely treatment strategies, such as surgical interventions

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and pharmacological therapies, which aim to alleviate pain, mitigate bone deformities, and enhance the overall quality of life for affected individuals.[4]

Bisphosphonates are therapeutically valuable analogs of naturally occurring pyrophosphate. These compounds find utility in conditions related to accelerated bone resorption, like Paget's disease, bone metastases, osteoporosis, and FD. Furthermore, previous reports have shown that chemical alterations on their side chain can substantially increase their efficacy.[5] Bisphosphonates have a complex molecular structure for their action, with a cumulative inhibitory impact on pathologic bone loss. These compounds prevent bone resorption by being absorbed and transported to the mineral surfaces which interferes with osteoclast function. Bisphosphonates also exert an anti-osteoclast effect by inducing osteoblasts to create an osteoclast inhibitory factor, thereby inhibiting bone resorption and stimulating formation.[6]

Pamidronate, a biphosphonate, was derived from inorganic pyrophosphate (PPi) and exhibits a strong affinity for hydroxyapatite crystals found in bone remodeling zones. Furthermore, pamidronate as a second-generation bisphosphonate includes R-2 side chains that contain nitrogen, compared to early variants. The key distinction lies in the farnesyl pyrophosphate synthase inhibition, an enzyme that is expressed in mammalian cells and is essential for the formation of lipids. This indicates that cellular apoptosis only appears in osteoclasts, due to the capacity of the compound to be maintained in bone before endocytosis during osteoclast-mediated matrix digestion and bone mineral breakdown.[7] Pamidronate also has intravenous (IV) preparations, thereby reducing the number of doses as well as gastrointestinal side effects experienced by certain patients treated with oral bisphosphonates.[8]

Pamidronate as one of the primary therapy for FD, has been shown to develop the patients' clinical features by reducing pain, bone turnover markers, and raising bone mineral density (BMD). Furthermore, its intravenous administration for polyostotic and monostotic FD has also been proven to be effective in reducing fracture rates in the afflicted regions.[9] BMD increase was observed after pamidronate treatment, but the response varied among patients.[10] This treatment also has an initial pain-relieving effect from its direct analgesic properties, but the exact pain-relieving mechanism is still being searched for.[11] The use of pamidronate contributes to the reduction of serum alkaline phosphatase (SAP). SAP level is a vital laboratory finding correlated with osteoblastic activity which is often applied as an important prognostic marker for FD and bone-related malignant tumors, such as osteosarcoma.[12] A study by Park et al., showed high SAP is related to the recurrence and progression into a more severe condition of FD, indicating that the marker can be used as a reliable predictor for the disease evolvement.[13]

Individualized pamidronate administration for FD management has shown inconclusive results.[14] Hence, this review aims to analyze the pamidronate treatment effect on several clinical and biochemical parameters in patients with FD.

MATERIALS AND METHODS

This review was completed under the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement.[15]

Variable of interest

This study aimed to evaluate the pamidronate treatment effect on bone pain, serum alkaline phosphatase (SAP), and bone mineral density (BMD) in patients suffering from FD.

Eligibility Criteria

Types

This review consisted of both published and unpublished studies examining the impact of pamidronate treatment on patients diagnosed with bone FD. Meanwhile, studies falling under the categories of reviews, cross-sectional analyses, cohort investigations, case reports, case series, conference abstracts, book sections, commentaries/editorials, and papers entailing non-human subjects were omitted. Articles lacking complete text and those unrelated to the relevant subject matter were disregarded.

Participants

Inclusion criteria were polyostatic or monostatic FD patients with normal renal and hepatic function, who were not taking drugs that affect bone metabolism. The FD diagnosis was according to clinical history, biochemical examination, and radiographic findings. Furthermore, there were no limitations for age, gender, and race.

Outcome of interest

The interest outcome of this study was the bone pain assessment for patients receiving pamidronate treatment, which was measured and reported as proportion (%) data, while SAP and BMD z-scores were measured and reported in numerical (continuous) data.

Search strategy and study selection

MEDLINE, EBSCO-Host, Wiley, and ProQuest electronic databases were used to search for eligible

studies by the year 2023. Furthermore, EBSCO-Host and ProQuest databases were screened for grey literature to identify potential unpublished studies with suitable PICO criteria. Papers were identified by three independent authors by using the following keywords: *(("polyostotic fibrous dysplasia"[All Fields] OR "bone fibrous dysplasia" [All Fields] OR "bone dysplasia"[All Fields]) AND ("pamidronate"[All Fields]) AND ("bone mineral density"[All Fields] OR "bone pain"[All Fields] OR "serum alkaline phosphatase"[All Fields]))*.

All acquired studies were imported into the Mendeley reference manager program. They were then checked for duplication, followed by titles and abstracts screening. The papers were assessed separately by the authors and eliminated if the title and/or abstract were not appropriate for this review. The selected papers were reviewed in full-text assessment using the aforementioned eligibility criteria, and suitable articles were included in the review. The differences observed were settled among the review team members.

Data collection process

The included studies were analyzed and the data extracted were first author, country, design, sample size, baseline characteristics (age and sex), FD diagnosis criteria, FD severity assessment, Pamidronate treatment protocol, Pamidronate regimen follow-up duration, and pamidronate treatment side effects.

Summary measures

The numerical data were in the form of mean ± standard deviation (SD) for normally distributed, or median (interquartile range) for non-normally distributed. The p-value and 95% Confidence Interval (CI) were also included for each item to show the results' significance. A p-value less than or equal to 0.05 was statistically significant.

Assessment of risk bias/ Quality assessment

Each study was evaluated using the Cochrane Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) for non-randomized controlled trials. The tool consisted of seven main domains, which were divided into 3 main categories: (1) Pre-intervention, consisting of (a) Bias because of confounding, (b) Bias in the participants' selection, (2) intervention, consisting of (c) Bias in interventions classification, (3) Post-intervention, comprising (d) Bias because intended interventions deviations, (e) Bias because of missing data, (f) Bias in outcomes measurement, and (g) Bias in reported result selection. From each domain, the bias risk was considered as low, moderate, serious, critical risk, and no information. Each trial's overall quality was divided into five groups based on the degree of bias present: (1) low risk of bias (low for all domains), (2) moderate risk of bias (low or moderate for all domains), (3) serious risk (serious at least one domain, but not at critical risk in any domain), (4) critical risk (critical in at least one domain), (5) no information (lack of information in one or more key domains where judgment was needed). All authors separately evaluated each article, and any disagreements were addressed among the whole review team until agreement was obtained.

Synthesis of results and Statistical analysis

For all outcomes, the odds ratios (ORs) for bone pain and the standardized mean differences (SMDs) for SAP and BMD were calculated as the effect size. The ORs were computed based on the proportion differences between the two groups, and the SMDs were computed based on the mean changes from baseline to the end of each group. Statistical analyses were carried out for between-group comparison, before and after pamidronate treatment. For some studies, the SAP values from individual patients were added to obtain the mean value, and the SD was calculated using the SD Calculator.[16] Considering that some showed primary results applying different methods, the meta-analyses were performed using a random effect model. This model presupposed that the treatment impact was distributed over certain populations and gave each study a more equal weighting. The combined effect measures of the direct comparisons from an individual intervention were compared using the inverse variance method for continuous data and the Cochran Mantel Haenszel test (CMH) for proportional data.

Heterogeneity across trials was assessed using the I^2 statistic. An I^2 value of < 25%, 25-50%, and >50 was placed in the low, moderate substantial, and high categories, respectively. When heterogeneity was present, possible causes were investigated through sensitivity analyses. A proportional result was obtained as weighted ORs and a continuous result as weighted SMDs. Differences across studies were calculated based on population sample sizes. Furthermore, publication bias was analyzed visually through a funnel plot, where each trial impact was plotted with its inversed SE. All studies were conducted using RevMan software version 5.4.

RESULTS

PRISMA

Fig 1 provides a selection process overview of the study and its outcomes. The initial search strategy yielded 269

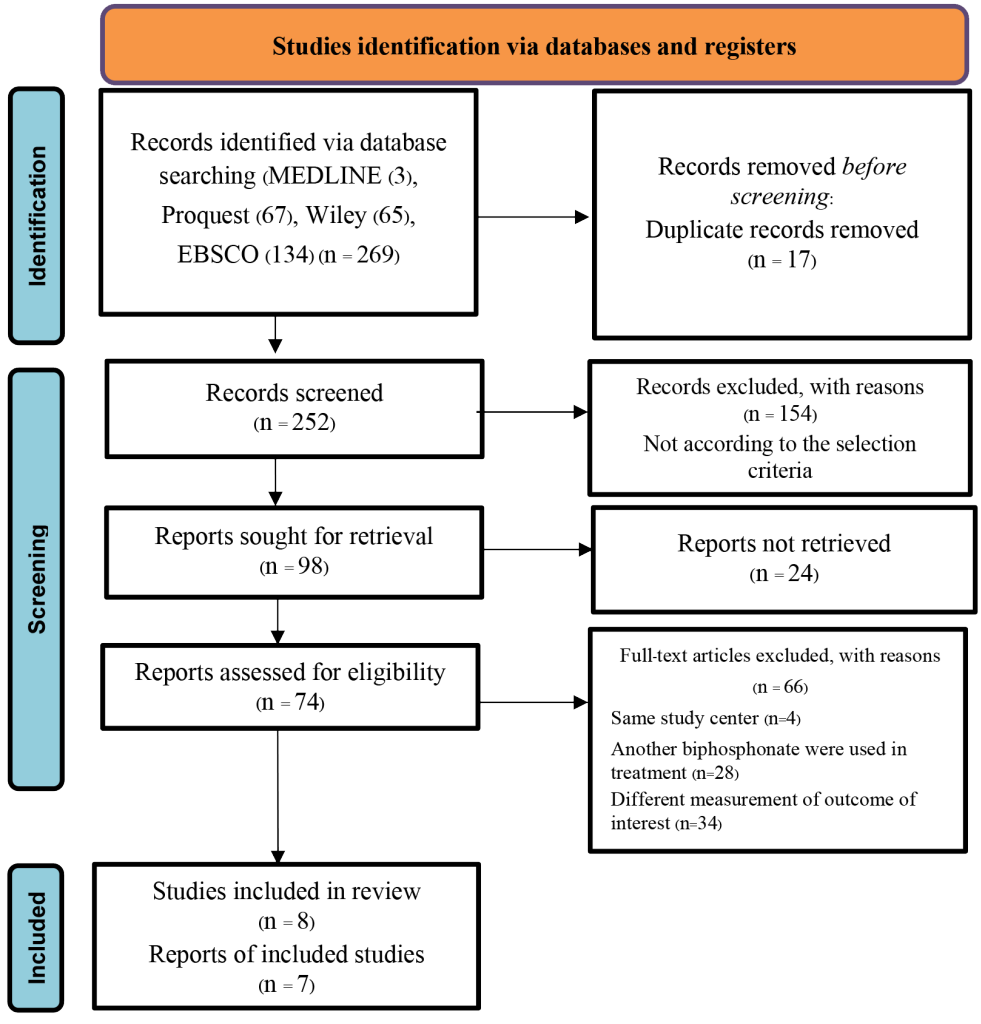

Fig 1. PRISMA 2020 flow diagram of included studies.

potentially relevant studies from the keywords searching using the Medical Subject Heading (MeSH). Among these papers, 252 were selected for comprehensive full-text evaluation, and only 74 full-access articles were retrieved. Furthermore, 62 studies were excluded according to the predefined criteria, namely the same study center (n=4), the combination of other bisphosphonate treatments (n=28), and different measurements for the outcome of interest (n=34). Eight studies were included in the systematic review and seven were included in the meta-analysis which was eligible for data extraction. Among the included papers, there was no specific publication date. Unpublished studies with appropriate inclusion criteria were not found, indicating that it was likely not to affect the conclusions of the review.

Quality assessment

Among the eight studies that were evaluated using ROBINS-I, six of them[6,14,17–20] had a low risk of bias, while two[21,22] had a high risk. A study by Chapurlat et al., 2004[14] was the continuation of Chapurlat et al., 1997[17] with a larger population number. According to Cochrane's recommendations, the Robvis tool was used to summarize the bias risk (Figs 2A and 2B), which was rated as "low", "moderate", "serious" and "critical" across various domains.[23]

A total of eight studies consisting of 143 children and adults with FD fulfill the criteria. The included studies' characteristics comprised of number of participants (N), mean age (years), sex (%), FD diagnosis criteria, FD severity assessment, treatment protocol, follow-up duration, and pamidronate treatment side effects, as shown in Table 1. All the papers were open trials with non-randomized study designs. At the time of diagnosis, the youngest age of the participant was one year and the oldest aged 63 years. Meanwhile, at the treatment onset, the youngest aged three years and the oldest was 69 years. Seven studies[6,14,17,19–22] utilized clinical evaluation as the basis of FD diagnosis, and one study[18] relied on radiologic findings to uphold the FD diagnosis. All papers administered pamidronate via an intravenous route with

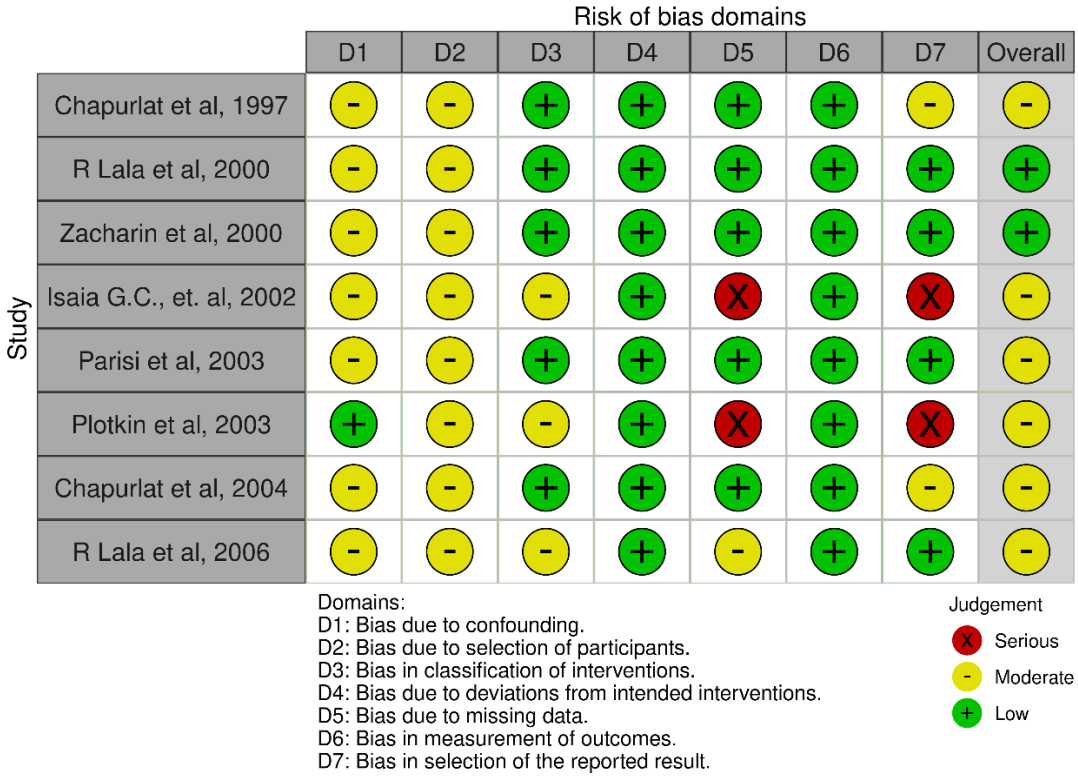

Fig 2A. Results of risk of bias assessment within studies illustrated with the Robvis tool.

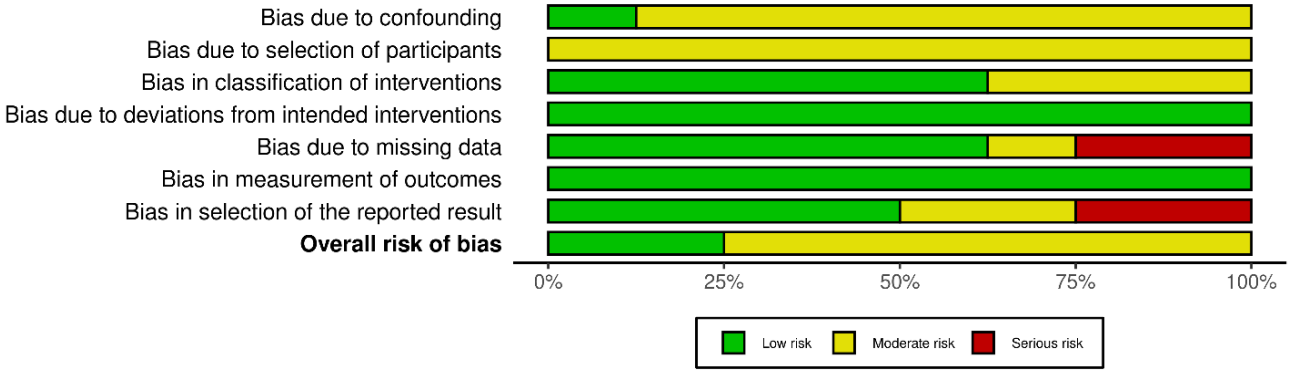

Fig 2B. Risk of bias domains summary in included studies.

a standard dose of 60mg/day or 0.5–1 mg/kgBW/day for three consecutive days. The regimen intervals ranged from four months to one year, with most of them having 6-month intervals for two years of treatment duration. The most common reported side effects included fever (hyperthermia/hyperpyrexia),[6,14,17–22] bone pain,[6,17–21] hypocalcemia,[6,17,19–21] and osteomalacia.[14,17]

Final Results

The seven studies included in the quantitative synthesis showed that bone pain and SAP were lower in the after-treatment group than in the before-treatment group, with a p-value ranging from 0.001 to 0.05. The meta-analysis results were described as a forest plot (Figs 3A and 3B) and the subsequent publication bias as a funnel plot (Figs 4A and 4B). The accumulation diagrams of forest plots showed the pooled OR for bone pain and SMD for SAP, as the final effect size obtained from the combination of all papers. Furthermore, the final weight of the combined value was shown in a rhombus shape, and a square shape indicated a weight for each study. The size of each square was determined by its weight in the meta-analysis, which was calculated based on the study population samples.

TABLE 1. Study Characteristics.

No.	Author, Publication Year, Country	Types of Study	Total population (n)	Mean/ Median Age (range) (years)	Sex (n) (%)	Fibrous Dysplasia Diagnosis Criteria	Bone Fibrous Dysplasia Severity Assessment	Pamidronate Treatment Protocol	Pamidronate Regimen Follow up Duration	Pamidronate Treatment Side Effects (%)
1	Chapurlat et al, 1997, France[17]	Open Trial, Non-Randomized Trial	20	At the time of diagnosis: 18 (1.5– 46) At the onset of treatment: 31 (13-69)	9 Females (81.81%) 11 Males (55%)	Diagnosed clinically, with support of biochemical and X-Rays examination	N/A	IV pamidronate over 3 days with 180 mg/course (60 mg/day). The drug was given in normal saline or glucose solution (1 l/day), as a 4-h infusion on 3 consecutive days. Two patients aged 13 years old were given pamidronate 1 mg/kg/day.	39 months	- Transient fever (40%). - Hypocalcemia. - Stiffness. - Bone pain (20%). - Osteomalacia (5%).
2	R Lala et al, 2000, Italy[21]	Non-Randomized Interventional Studies	9	At the onset of treatment: 9.63 (5.7 – 14.6)	7 Females (77.7%) 2 Males (22.2%)	Diagnosed clinically	Feuillan's Score (mild/moderate/ severe)	Pamidronnate was given at 0.5 mg iv/kg/day for 2 consecutive days with 1-year interval (from 1993 to 1994) and increased to 1 mg/kg/day for 3 consecutive days because clinical improvement with 6 months interval Dose was limited to 180 mg (over 3 days).	30 months	- Short term hypocalcemia - Pain and fever during at the end of pamidronate infusion
3	Zacharin et al, 2000, Italy[22]	Open Trial, Non-Randomized Trial	5	At the onset of treatment: 14.4 ± 9.79 (3.0-11.0)	3 Females (33.33%) 6 Males (66.67%)	Diagnosed clinically	N/A	Pamidronate was given by intravenous infusion 1 mg/ kg/d for 3 days every 6 months for 2 years.	24 months	- Mild acute reaction on first exposure to bisphosphonate with 38.5C fever for 24 hours in older children and young adults. - No child younger than 5 years was febrile.
4	Isaia G.C., et. al, 2002, Italy[19]	Non-Randomized Interventional Studies	11	At the time of diagnosis: 13.4 (6.9-19.9)	8 Females (72.7%) 3 Males (27.3%)	Diagnosed clinically	Feuillan's Score (mild/ moderate/ severe)	Pamidronate was given by intravenous infusion at 0.5 mg/kg/daily for 3 consecutive days at 12-month interval from 1994 - 1995. Pamidronate at 1 mg/kg/daily for 3 consecutive days at 6-month intervals from 1995 - 1997, and thereafter with the same dose every 4 months.	72 months	- Transient pain of the affected bones in 8 patients (72,7%). - Hyperpyrexia. - Transient hypocalcemia.

TABLE 1. Study Characteristics. (Continue)

No.	Author, Publication Year, Country	Types of Study	Total population (n)	Mean/ Median Age (range) (years)	Sex (n) (%)	Fibrous Dysplasia Diagnosis Criteria	Bone Fibrous Dysplasia Severity Assessment	Pamidronate Treatment Protocol	Pamidronate Regimen Follow up Duration	Pamidronate Treatment Side Effects (%)
5	Parisi et al, 2003, Argentina[6]	Open Trial, Non-Randomized Trial	8	At the time of diagnosis: 16 (4–30) At the onset of treatment: 26 (15–43)	7 Females (87.5%) 1 Males (12.5%)	Clinical history, radiographic fingdings, and bone biopsy	N/A	IV pamidronate infusion of 180 mg (60 mg/day over 3 consecutive days) every 6 months. Two patients did not receive the second pamidronate due to personal decision.	12 months	- Transient fever (28.57%). - Transient bone pain (28.57%). - Hypocalcemia (14.28%). - Ocular inflammation (28.57%).
6	Plotkin et al, 2003, Canada[18]	Non-Randomized Interventional Studies	18	At the onset of treatment: 9.83 (6.2 – 17.5)	8 Females (44%) 10 Males (56%)	The presence of radiologically detectable bone lesions at two or more sites plus genetic studies confirmed a FD-specific heterozygous mutations in codon 201 of the Gs gene.	N/A	Pamidronate was given on 3 consecutive days (the first 3-d cycle include 0.5 mg/kg on day 1 and 1 mg/kg on d 2 and 3). In subsequent cycles, 1–1.5 mg/kg daily for 3 days and repeated every 4 months. Each dose was diluted in 0.9% saline solution and given slowly over 4 hours.	24 months.	- An acute phase reaction in the form of a flu-like syndrome during the first treatment cycle, lasted for 24–48 h and resolved without complications.
7	Chapurlat et al, 2004, France[14]	Open Trial, Non-Randomized Trial	58	At the time of diagnosis: 18 (1 – 63) At the onset of treatment: 28 (5 – 63).	30 Females (51.72%) 28 Males (48.27%)	Diagnosed clinically, with the support of biochemical analysis, X-Rays examination, and bone biopsy	N/A	IV pamidronate 60 mg during 3 consecutive days, every 6 months. Cycles were repeated for 2 years, after 2 years, pamidronate was given only once a year in patients with excellent response. In children, the dose was 1 mg/kg/day during 3 days, every 6 months	50 months.	- Fever in 23% patients. -Venous irritation in 3 patients. - Venous thrombosis in 1 patient. - osteomalacia in 1 patient.
8	R Lala et al, 2006, Italy[20]	Non-Randomized Interventional Studies	14	At the onset of treatment: 11.4 (5.3 – 18.7)	10 Females (71.42%) 4 Males (28.58%)	Diagnosed clinically	Feuillan's Score (mild/ moderate/ severe)	Pamidronate was given by intravenous infusion at 0.5 mg/ kg/day for 3 consecutive days at 12-month intervals from 1994-1995 Pamidronate at 1 mg/ kg/day for 3 consecutive days at a 6-month interval from 1995-1998, after that every 4 months with the same dosage.	64 months	- Transient pain of the affected bones in 3 patients. - Transient hyperpyrexia during the first Pamidronate infusion in 11 patients. - Transient hypocalcemia (180-220 mMol/1).

TABLE 2A. Bone Pain.

Author Year, Country	Bone Pain (Number of patients with bone pain/number of total patients)		
	Before treatment	After treatment	P-value
R Lala et al, 2000, Italy[21]	5/9	1/9	<0.06**
Isaia G.C., et. al, 2002, Italy[19]	8/11	3/11	N/A*
Parisi et al, 2003, Argentina[6]	7/7	4/7	N/A*
Chapurlat et al, 2004, France[14]	44/58	23/58	0.001
R Lala et al, 2006, Italy[20]	8/14	0/14	N/A*

*N/A: Not available.
**considered as significant

TABLE 2B. Serum Alkaline Phosphatase (SAP).

Author Year, Country	SAP values (mean ± SD)		
	Before treatment	After treatment	P-value
Zacharin et al, 2000, Italy[22]	818.5 ± 181.7	654.0 ± 171	NS**
Parisi et al, 2003, Argentina[6]	315 ± 184	194 ± 150	0.05
Chapurlat et al, 2004, France[14]	185 ± 176	151.7 ± 460.6	0.015
R Lala et al, 2006, Italy[20]	1745.6 ± 1454.1	1018.5 ± 872.6	N/A*

*N/A: Not available.
**NS: Not significant.

TABLE 2C. Bone Mineral Density (BMD).

Author Year, Country	BMD Z-score (mean ± SD)		
	Before treatment	After treatment	P-value
Zacharin et al, 2000, Italy[22]	0.82 ± 0.06	0.94 ± 0.07	<0.05
Isaia G.C., et. al, 2002, Italy[19]	-2.77 ± 1.38	N/A	0.003
Parisi et al, 2003, Argentina[6]	-0.5 ± 0.7	N/A	0.02 (FDa)*
	(-1.4 ± 0.3)	N/A	0.05 (CL)**
Chapurlat et al, 2004, France[14]	0.831	0.973	0.003

*FDa = Fibrous Dysplasia Areas
**CL = Contralateral Side

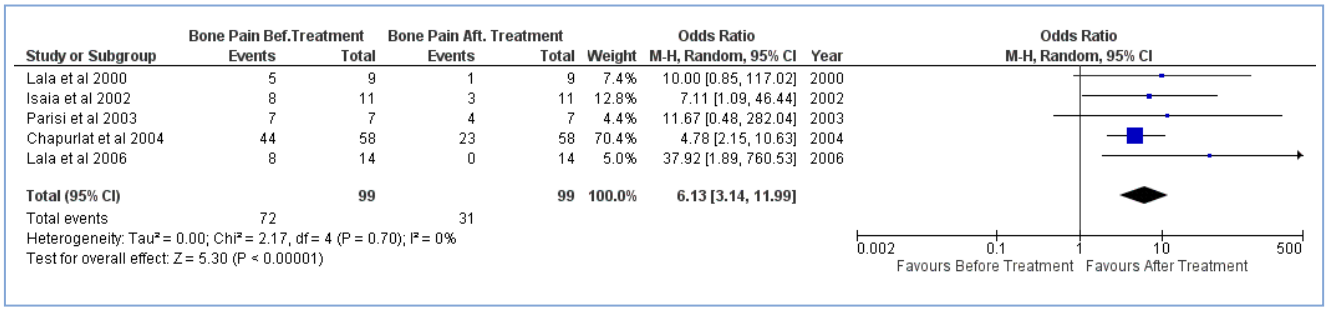

Fig 3A. Data Results in the Meta Analysis (Forest Plot) for Bone Pain Before and After Treatment of Pamidronate.

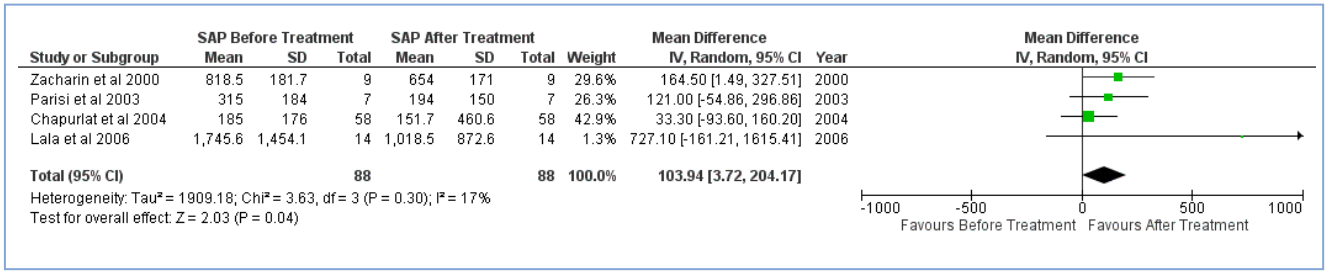

Fig 3B. Data Results in the Meta Analysis (Forest Plot) for Serum Alkaline Phosphatase (SAP) Before and After Treatment of Pamidronate.

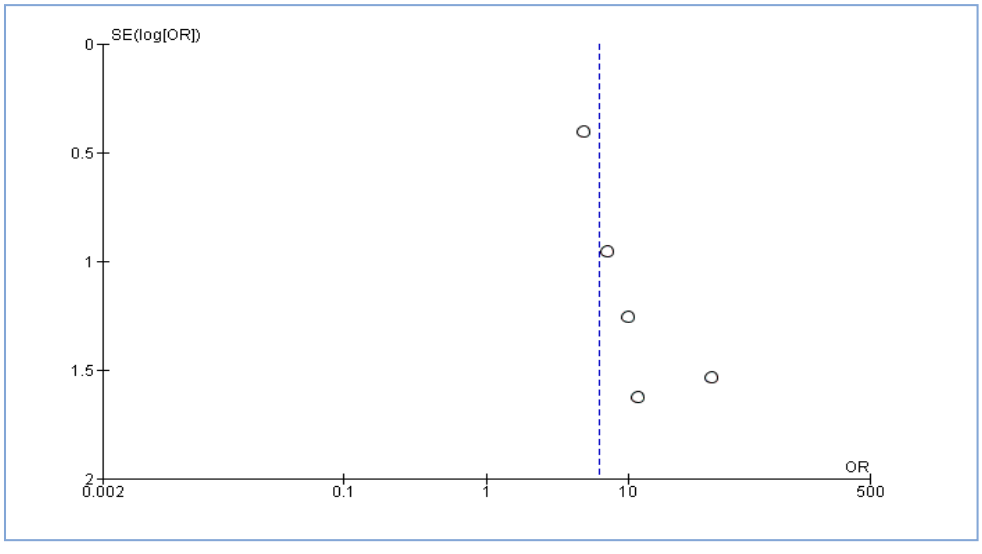

Fig 4A. Publication Bias as Funnel Plot Diagram for Bone Pain Assessment Before and After Treatment of Pamidronate in Patients with FD.

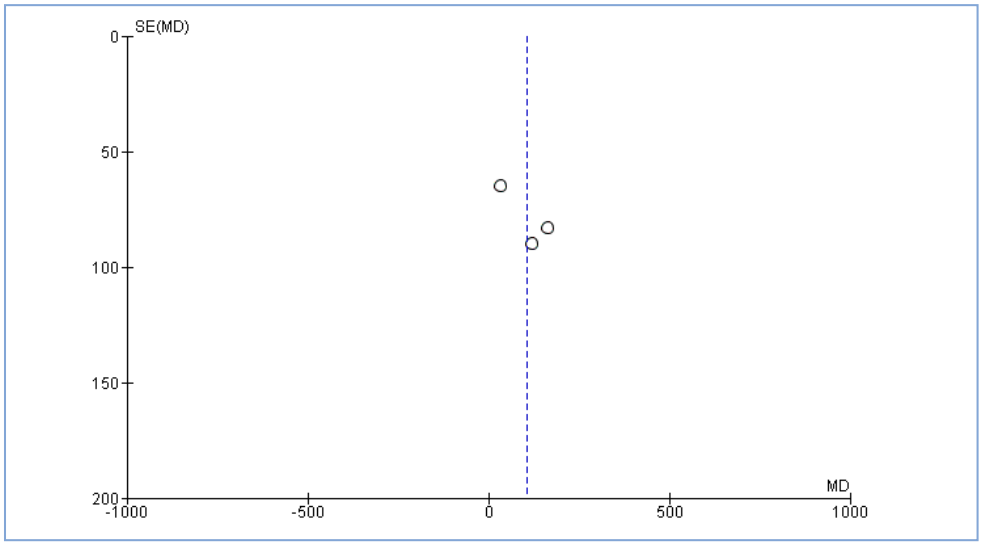

Fig 4B. Publication Bias as Funnel Plot Diagram for Serum Alkaline Phosphatase (SAP) Before and After Treatment of Pamidronate in Patients with FD.

All data in this meta-analysis showed significant differences in bone pain and SAP reduction after pamidronate treatment compared to the before-treatment groups, as shown in Figs 3A and 3B, with a p-value of <0.00001 and 0.04 respectively. The two outcomes were considered to have a low heterogeneity, with I^2 results of 0% and 17%, respectively. The publication bias represented as a Funnel Plot Diagram was shown in Figs 4A and 4B for bone pain reduction and SAP, respectively.

DISCUSSION

FD was a benign bone lesion characterized by altered osteogenesis, leading to intramedullary fibro osseous proliferation. The excessive fibro osseous tissue subsequently replaced the normal bone tissue. This phenomenon could lead to an increased risk of fracture, leading to pathologic fracture, specifically in weight-bearing bones on the lower extremities. Along with the poor FD bone quality, this could cause deformities and increased severity of pain.[24] Notwithstanding, McCune Albright syndrome (MAS) was a condition, where FD simultaneously occurred with endocrine dysfunction and skin pigmentation.[25]

Pamidronate was a second-generation bisphosphonate that inhibited osteoclast-mediated bone resorption and was widely used as a treatment among patients with FD, osteogenesis imperfecta, cerebral palsy, and chronic neuropathy.[26] The outcomes typically included clinical, radiological, and biochemical measurements for FD diagnosis. Bone pain, SAP, and BMD were the most reported outcomes to be analyzed.

An FD lesion could precipitate normal bone resorption and create a phosphaturic factor, leading to a deficiency of phosphate and consequent osteomalacia. This condition then led to lower BMD values, particularly in the trabecular-predominant bone locations.[27] Treatment with bisphosphonates could prevent the process, thereby enabling rapid restoration of BMD in the affected regions. The efficacy of pamidronate to increase BMD was proven by Lee et al. when the BMD Z-scores and lumbar spine (mg/cm^2) from the pamidronate group increased after the therapy during their follow-up (both p<0.001). All patients also experienced improvements in bone pain after the use of pamidronate.[28] These findings were consistent with the results of this current study. Zacharin et al.,[22] reported a significant increase in BMD z-score (0.82 ± 0.06 to 0.94 ± 0.07, p=<0.05), and Chapurlat et al.,[14] showed a significant elevation of BMD z-score (0.831 to 0.973, p=0.003) after several cycles of Pamidronate treatments.

Pain was one of the major complaints in patients with FD. Furthermore, thinly myelinated sensory nerve fibers (A-delta) and CGRP+ nerve fibers, which were rich in peptides, were the main nerve fibers found in innervate bone. The periosteum, mineralized bone, and marrow all exhibited this pattern of innervation. Patients with FD experienced excessive bone growth, pathological bone remodeling, and ectopic sensory plus sympathetic nerve fiber sprouting in the marrow and mineralized bone. These conditions led to alterations in the sensory nerve fibers, thereby causing bone pain formation.[29] Majoor et al. stated that pain was the most frequent complaint in FD patients regardless of age, bone involvement, and types of FD (monostotic or polyostotic).[30]

Compared to other forms of pain, FD pain could be well managed to retain functional status and life quality. The cumulative OR of 6.13 and the I^2 value of 0% from the meta-analysis indicated a substantial impact of pamidronate in reducing bone pain, with no significant heterogeneity among the included studies. This suggested that the results of this study were consistent and similar, thereby increasing the reliability of the meta-analysis findings.[6,14,19–21] After the first round of pamidronate therapy, pain intensity was decreased, and an additive effect was shown after numerous cycles of therapy. Lala et al., (2000) reported a gradual decrease alongside pamidronate treatment cycles. Furthermore, low pain (1–3) gone after the first therapeutic cycle, and moderate or severe pain (4–9) gone after the third cycle.[21] Isaia et al. observed that only 1/11 individuals had the sensation at the end of treatment (2000), down from 3/11 patients two years before (1998), and 8/11 patients at the start of treatment cycles in 1994.[19] These findings suggested that cumulative doses of pamidronate could reduce bone resorption and increase bone formation, leading to pain depletion.

Serum alkaline phosphatase (SAP) was a plasma membrane enzyme as a marker for bone formation and as a predictor for disease activity in metabolic bone diseases.[31] Adenyl cyclase in FD patients was constantly active due to the GNAS 1 mutation, and this led to elevated cAMP activity, which promoted aberrant osteoblasts and hyperfunction of skeletal progenitor cells.[32] Ma et al., revealed that the increase in ALP level was due to elevated levels of calcitonin through the action of cAMP.[33] Bone SAP was directly inhibited by three BPs that contained nitrogen atoms in their structure (Pamidronate, Alendronate, and Zolendronate), in a time- and dose-dependent manner. SAP activity was enhanced by low dosages of BPs (10^{-10}-10^{-5} M), but it was inhibited by high doses (10^{-4} M). Since SAP was a metalloenzyme that was dependent on zinc and magnesium, the BP-induced SAP

inhibition could be the consequence of metal chelation by the drug's phosphonate groups. This hypothesis was supported by the findings that an increase of Zn^{2+} or Mg^{2+} could reverse SAP inhibition.[34]

Decreased levels of SAP indicated a decline in bone turnover during the use of Pamidronate, indicating that the enzyme could be used to monitor the treatment response.[35] Based on the forest plot results, pamidronate treatment significantly and positively affects SAP levels among the included studies (95%CI: 3.72 – 204.17, p=0.04). The pooled mean difference of 103.94, along with a low to moderate heterogeneity suggested a consistent treatment effect. Studies from Parisi et al., and Chapurlat et al., showed a significant reduction of SAP levels after pamidronate treatment, from 315±184 to 194±150 (p=0.05)[27] and 185±176 to 151.7±460.6 (p=0.015), respectively.[14] Although a marked reduction of the enzyme levels was observed in Zacharin et al., (818.5 ± 181.7 to 654.0 ± 171), the result was not significant. This occurred in some patients six months after the second pamidronate therapy round, which indicated time between pamidronate infusions needed to be shorter in more severe cases, leading to a more notable SAP reduction.[22]

Pamidronate treatment was associated with a variety of side effects, including acute phase response, musculoskeletal discomfort, jaw osteonecrosis, hypocalcemia, and various ophthalmic events,[36] as reported in most of the included studies. However, all side effects were relieved by supportive therapies, only limited to the initial treatment, and did not persist after the second cycle of pamidronate infusion. The safety of Pamidronate treatment was also supported by Jjuszczak et al., who found that 39 out of 42 (93%) patients agreed Pamidronate is effective for NSAIDs-refractory chronic recurrent multifocal osteomyelitis in children, without reported prominent side effects.[37]

Demographic characteristics from each study significantly differed from others. The age in some studies varied greatly, while those in others varied considerably. The majority of cases were identified in children, while some studies focused on pediatric populations,[14,17,27] and others included a wider range of ages.[18–22] However, it was challenging to determine the extent of the correlation between age and FD. Hart et al, reported that clinically significant bone lesions often became visible by the age of five, and nearly no substantial lesions were developed after the age of fifteen. Adult FD lesions could become less active, due to the apoptosis of bone marrow mesenchymal stromal cells (BMSCs) carrying mutations.[38] In terms of ethnicity, the correlation between FD and the patient's race from different countries (France,[14,17] Italy,[19–22] Argentina,[27] Canada[18]) was not readily evident, taking into account that FD was generally considered to be unrelated to a specific race or ethnicity. This diversity could represent various racial groups, thereby allowing the conclusions to be generalized to broader populations.

Although GNAS mutation testing was the "gold standard" for FD diagnosis, it could be complicated by the sensitivity of the procedure and the degree of mosaicism in the afflicted tissue.[39] Other diagnostic methods were standard PCR and NGS, but both had limited value for evaluating mutations.[40] Therefore, several knowledgeable medical professionals could frequently rely on clinical findings and specific FD characteristics on a radiographic exam (ground-glass appearance),[41] making a diagnosis without the necessity for biopsy or molecular approach, as mentioned in most of the included studies.

Some studies had adjusted confounding factors, such as disease severity by classifying using Feuillan's score.[19–21] Patients with varying degrees of disease severity could respond differently to treatment. This indicated that including disease severity as a covariate in analyses could help account for this. The variation in gender distribution across studies showed that there might be differences in the proportion of females and males among participants, but FD had an equal sex distribution throughout all populations.[42]

Strengths and limitations of the study

Based on previous findings, this was the first systematic review and meta-analysis on pamidronate treatment in FD of the bone, both in children and adult populations. Our research comprised several primary studies that follow the development of Pamidronate usage from time to time, from the first published study in 1997 until the latest in 2006. Thus, we have exhibited a broad view regarding this matter. An additional novelty of our studies found that SAP, aside from BMD, was proven to be significantly reduced following Pamidronate treatment, furthermore demonstrating that this enzyme might be used to surveil the effectiveness of the treatment in the future. The grey literature was also included to minimize the potential publication bias.

All studies were open and non-randomized trials. While these could provide initial insights into the potential effectiveness of pamidronate for FD, their findings were considered to be less robust compared to randomized controlled trials (RCTs). Therefore, further RCTs were required to enhance the evidence and better understand the outcomes. The small sample size and the absence of a control group can potentially undermine the robustness of our findings, as it may not have provided adequate statistical power to detect more subtle effects.

CONCLUSION

In conclusion, the reduction in bone pain and the decrease in SAP levels appeared to be favorable treatment outcomes associated with Pamidronate treatment in individuals with FD. The meta-analysis results supported the conclusion that Pamidronate was effective in improving these conditions.

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Conflict of interest

No conflict of interest.

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Plasma Alpha Synuclein as a Potent Biomarker of Diseases with Synucleinopathies

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ABSTRACT

Objective: We explored whether plasma α-syn be used as a potential biomarker for synucleinopathies.

Materials and Methods: α-syn levels in plasma from 54 Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) patents, 31 Alzheimer's disease dementia (AD), and 29 controls were measured by enzyme-linked immunosorbent assay (ELISA).

Results: The mean age of the synucleinopathies group, the AD group, and the normal controls was 72.70, 74.26, and 62 years old. The median plasma α-syn levels in the synucleinopathies group, AD group and controls were 9.72 (4.41-25.30), 16.78 (7.68-51.41) and 16.65 (10.37-32.72) ng/ml, respectively (Independent-Samples Kruskal-Wallis test, $p = 0.026$). The α-syn levels in the synucleinopathies group were lower than those of AD and controls. There was a fair correlation between plasma α-syn levels and the sum of the Unified Parkinson's Disease Rating Scale (UPDRS) part 3 (spearman correlation coefficient $r = -0.261$, $p = 0.021$) but not with cognition measured by Thai Mental Status Examination (TMSE). The area under the receiver operating characteristic curve (ROC) was 0.710 between the PDD and DLB vs non synucleinopathies group (AD and normal controls) (SE = 0.052, $p \leq 0.001$). At the cut-off levels of 11.4 ng/ml indicated a sensitivity of 58% (95% CI 43.21-71.81%), specificity of 84.78% (95% CI 71.13-93.66%), positive predictive value (PPV) of 80.56%, a negative predictive value (NPV) of 65% and a precision of 70.83%.

Conclusion: The present results suggest that plasma α-syn could be a potential biomarker to differentiate synucleinopathies from Alzheimer's disease and the elderly with normal cognition.

Keywords: Alpha synuclein; biomarker; plasma; Parkinson's disease dementia; Lewy body dementia; Alzheimer's disease (Siriraj Med J 2023; 75: 864-870)

INTRODUCTION

Alpha-synuclein (α-synuclein) is a presynaptic neuronal protein that is neuropathologically related to synucleinopathies, including Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA).[1,2] This protein had been explored as a diagnostic biomarker for synucleinopathies in cerebrospinal fluid (CSF), blood plasma, serum, and skin.[3-10] Many studies have shown that CSF alpha-synuclein can be used to differentiate between synucleinopathies and Alzheimer's disease, the most common neurodegenerative disease.[6,7,11-12] However, fewer studies have investigated alpha-synuclein in peripheral blood and its utility to differentiate between synucleinopathies and other diseases.[13-16] Furthermore, data on the plasma alpha-synuclein level in patients with PD are still inconclusive because previous studies had

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shown that blood alpha-synuclein level in patients with PD can be higher[7,17] or lower[18,19] compared to normal control subjects. Some studies have also found that there is no difference in the blood level of alpha-synuclein between PD patients and control.[13,20-22] Therefore, we investigated whether plasma alpha-synuclein levels can be used to differentiate between synucleinopathies, Alzheimer's disease, and control.

MATERIALS AND METHODS

Study design and population

The patients were recruited from the memory clinic at Siriraj Hospital, Mahidol University. The diagnosis of PD and Parkinson's disease dementia (PDD) was based on the clinical diagnostic criteria of the Movement Disorder Society for Parkinson's disease[23] and the recommendations of the MDS Task Force for the diagnosis of PDD.[24] Dementia with Lewy bodies (DLB) was diagnosed by using consensus criteria for clinical diagnosis developed by the DLB Consortium[25], and probable Alzheimer's disease (AD) was defined using the criteria of the National Institute on Aging and the Alzheimer's Association (NIA-AA).[26]

The sample size was calculated using the mean ± standard deviation (SD) from the reference literature.[27] Inclusion criteria were individuals whose age was more than 40 years, without a minimum year of education and diagnosed with Alzheimer's disease, synucleinopathies, or normal cognition. Exclusion criteria were individuals who were less than 40 years old or did not meet criteria for the diagnosis of AD or synucleinopathies. We also excluded patients currently using medications that can cause parkinsonism, such as antipsychotic medications. Acetylcholine esterase inhibitor and Parkinson medications (e.g., levodopa, dopamine agonist) were allowed. Therefore, we recruited 114 patients, consisting of 54 PDD and DLB patents, 31 AD patients, and 29 control participants.

We collected clinical information including age, sex, diagnosis, Thai version Mental Status Examination (TMSE) score, Addenbrooke's Cognitive Examination-Revised (ACE-R), Thai Activities of Daily Living Scale (ADL)[28], Unified Parkinson's Disease Rating Scale (UPDRS), and result of dopamine transporter scan (using ^{99m}Tc-TRODAT-1 SPECT image).

Blood sample and measurement of plasma alpha-synuclein concentration

Venous blood (5 ml) was drawn from the participants in the morning, 9.00 to 12.00 am, and the samples were processed within 30 minutes of collection. Plasma was prepared after collection of whole blood in an ethylenediaminetetraacetic acid treated tube. The processed samples were treated by centrifugation for 15 minutes at 1,500 g at room temperature. Following centrifugation, plasma was immediately transferred into clean and low residue polypropylene tube using a low residue tip. Plasma was stored at -80°C for less than 3 months prior to examination. No hemolyzed, icteric, or lipemic samples used. The levels of alpha-synuclein in the blood were tested by immunosorbent assay (ELISA) using the Human Phosphorylated Alpha Synuclein (PSNCA) ELISA Kit of MyBioSource, Inc, United States. The test was performed concurrently after 8-10 samples had been collected.

Statistics

For the statistical analyses, IBM SPSS Statistics 18 software was used. The blood α-synuclein data was not normally distributed and assessed by the Kolmogorov-Smirnov test. Mann-Whitney U was used to compare the results between two groups and the Kruskal-Wallis test was used to compare the results between more than two groups with adequate correction for multiple comparisons (Bonferroni). To analyze frequency difference of dichotomous variables, the chi-square test was used. The Spearman rank-order correlation coefficient was used to assess the correlations between variables. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) were used to determine the cutoff value for α-synuclein.

RESULTS

Of the 114 participants in our study, there were 28 men (51.85%) in the synucleinopathies group, 15 men (45.45%) in the AD group and 3 men (11.11%) in the control group. The median age of all participants was 70.4 ± 10.463 years. Age frequencies showed median synucleinopathies (IQR) = 74 (66-77), AD = 75 (64-81), NC 61 (54.5-67.0); Independent-Samples Kruskal-Wallis Test $p<0.001$. The pairwise comparison of group diagnosis found that between synucleinopathies vs control: test statistic 32.987, standard error (SE) 7.604, standard deviation (SD) 4.338, $p<0.0001$; between AD vs control: test statistic 36.503, SE 8.533, SD 4.278, $p<0.0001$; between synucleinopathies vs AD: test statistic 3.516, SE 7.443, SD 0.472, $p=0.637$. The score of TMSE and ACE-R was lower in both disease groups compared to control and the ADL score in both disease groups was higher. The details of the score in each group are shown in Table 1.

TABLE 1. Patient's characteristics.

	Control	AD	Synucleinopathies (PDD and DLB)	
No patients	29	31	54	
Gender (Male, %)	3 (11.11%)	15 (45.45%)	28 (51.85%)	
Age (years)	61 (54.5-67.0)	75 (64-81)	74 (66-77)	p<0.001*
Education (years)	15.57 ± 6.53	10.35 ± 5.51	9.98 ± 6.09	0.07
TMSE	28.5 (27-30)	18 (14.5-23)	19.5 (13.25-24)	p<0.001*
ACE-R	90 (86.5-96)	37 (29-51.75)	40 (21.75-52)	p<0.001*
ADL score	0.54 ± 2.65	11.62 ± 7.66	10.20 ± 7.82	p<0.001*
UPDRS part 3	0	0 (0-1)	36 (20-44)	p<0.001¥

*p<0.001 between AD vs control, and between synucleinopathies vs control.
¥p<0.001 between synucleinopathies vs control, and synucleinopathies vs AD.
Data are presented as n (%), mean ± standard deviation, or median (interquartile range).
p-value corresponds to one-way and Kruskal-Wallis

For plasma alpha-synuclein level, median in synucleinopathies groups, AD groups, and controls was 9.72 (4.41-25.30), 16.78 (7.68-51.41), and 16.65 (10.37-32.72) ng/ml, respectively (Independent-Samples Kruskal-Wallis test, p = 0.026). Pairwise comparisons of group diagnosis in plasma α-syn levels revealed that between PDD and DLB vs control: test statistic -15.99, Standard Error (SE) 7.61, SD -2.10, p = 0.036; between PDD and DLB vs AD: test statistic 17.39, SE 7.45, SD 2.34, p = 0.02; and between controls vs AD: test statistic 1.407, SE 8.54, SD 0.17, p = 0.869. The plasma level of alpha-synuclein in the synucleinopathies group was significantly lower than in both the AD and the control group. We look for correlation between plasma alpha-synuclein and other factors, such as age, education, cognitive score (TMSE) and UPDRS score, but found a fair correlation only between plasma α-syn levels and the sum of UPDRS part 3 (spearman correlation coefficient r = -0.261, p = 0.021). Data on the correlation of other factors are shown in Table 2. The area under the receiver operating characteristic curve (ROC) was 0.710 between the PDD and DLB group vs. non-synucleinopathies (AD and normal controls)(SE = 0.052, p ≤ 0.001) as shown in Fig 1.

At the cutoff levels of 11.4 ng/ml indicated a sensitivity of 58% (95% CI 43.21-71.81%), specificity of 84.78% (95% CI 71.13-93.66%), positive predictive value (PPV) of 80.56%, a negative predictive value (NPV) of 65% and a precision of 70.83%.

In our study, 15 participants were scanned using ^{99m}Tc-TRODAT-1 SPECT imaging. Eleven participants had a positive scan, five of whom were in the synucleinopathies group and six were in the AD group. Comparing the positive and negative groups in age, blood alpha-synuclein, UPDRS part 3, or cognitive score, did not show any significant differences.

DISCUSSION

In synucleinopathies (PD, DLB and MSA), we diagnosed mainly by clinical criteria while neuroimaging biomarkers, structural and functional, were used only to support and exclude other possible causes.[1,29] Previous studies have shown the potential of cerebrospinal fluid (CSF) alpha-synuclein to differentiate synucleinopathies

TABLE 2. Spearman's rank correlation coefficient between each factor.

Variables	Correlation coefficient	Alphasynuclein (ng/mL)	Age	Education	TMSE	UPDRS
Alphasynuclein (ng/mL)	Spearman's Rho[a]	1				
	p-value	NA				
Age	Spearman's Rho[a]	-0.018	1			
	p-value	0.848	NA			
Education	Spearman's Rho[a]	-0.110	-0.275*	1		
	p-value	0.321	0.011	NA		
TMSE	Spearman's Rho[a]	-0.040	-0.293**	0.230*	1	
	p-value	0.686	0.003	0.038	NA	
UPDRS	Spearman's Rho[a]	-0.261*	0.235	-0.122	-0.460**	1
	p-value	0.021	0.039	0.379	<0.001	NA

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

[a] Spearman's rank correlation coefficient

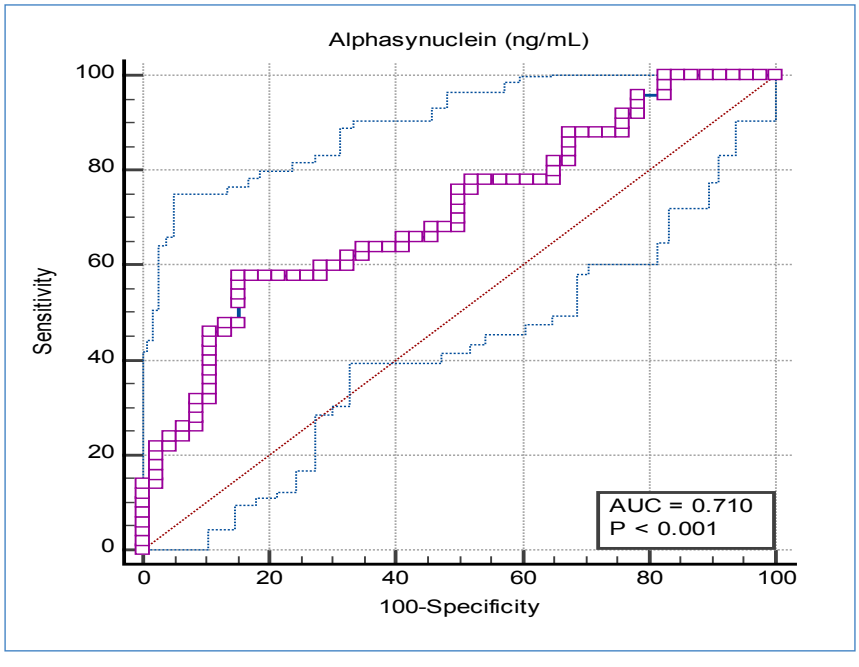

Fig 1. Receiver operating characteristic (ROC) curve for plasma α-synuclein levels to detect synucleinopathies (PDD and DLB). ROC curve of plasma α-synuclein levels for distinguishing synucleinopathies group from non-synucleinopathies group. AUC, area under ROC curve. Cut-off value = 11.4 ng/ml

from AD or normal cognitive control.[12, 30-31] However, due to difficult, invasive and costly of CSF collection compared to blood draws, so blood-based biomarkers are promising methods to use in clinical practice for the evaluation of neurodegenerative disease.[32-34]

Plasma alpha-synuclein in a previous study shows that it can be used to differentiate PD from AD or normal control[13-16], and most of the study found that plasma level of alpha-synuclein is higher than AD or control.[7,16-17] But in our study, plasma level of alpha-synuclein in synucleinopathies was lower than AD or control, and there are some other studies that reported similar results.[18-19] These conflicting results could be due to the different assay or method used to measure plasma alpha-synuclein[35] or because the main source of alpha-synuclein is red blood cells (RBC), so even low RBC contamination could affect the results.[36] Therefore, the handling method and the preparation of the sample are other factors that cause

inconsistency in the plasma alpha-synuclein level. In addition, disease severity and disease duration, which are different in each study, can also affect the results.[13]

According to published data, commonly used technologies for evaluation included the bead-based multiplexed immunoassay system (Luminex), sandwiched ELISA or ImmunoMagnetic Reduction (IMR).[16] If we look studies that use the same technique that we used[7,13,20-21,37-38], sandwiched ELISA, most had either higher or equal of plasma alpha-synuclein in the disease group compare to the control. It may be that, first, our studies inclusion criteria were synucleinopathies disease group, not just Parkinson's disease, which is different from previous research. Synucleinopathies consist of Parkinson's disease, Dementia with Lewy Body, and Multisystem Atrophy, which each of them had clinically and pathologically heterogeneous. For example, pathological hallmark of MSA was glial cytoplasmic inclusions (GCIs) predominantly in striatum, midbrain, pons, medulla, and cerebellum whereas for DLB, pathological hallmark was widespread of Lewy bodies or Lewy neurites in cerebral cortex and limbic system.[39-41] Due to different pathological seeding locations of alpha synuclein, clinical manifestations, criteria diagnosis, and prognosis of disease also different and that's explained why cut off value of blood alpha synuclein in our study different diagnosis of patient from previous studies, show different results. Second, our recruiting population was in an earlier stage and less severe than others with respect to the UPDRS score. Normally, plasma alpha-synuclein levels will increase over time along with disease severity[13] so our studies that patient were still in early stage, which mean alpha synuclein still didn't spread that much in central nervous system, measurement of alpha synuclein will be lower compare to other studies.

Plasma alpha-synuclein alone may not be suitable to differentiate parkinsonism from other neurodegenerations or controls and may need other biomarkers to increase accuracy. There are many recent studies that use multiple biomarkers, in CSF or blood, to produce greater sensitivity, specificity, and precision to differentiate between parkinsonism and control.[42-48] The most recent published studies[48] found that using combination of α-synuclein, Aβ42, Aβ40, Aβ42/40, and NfL could achieve a best diagnostic value in differentiating parkinsonian syndrome from healthy control with AUC 0.98. In future research, we may need to use multiple biomarkers, including plasma alpha-synuclein, to discriminate parkinsonism from other neurodegenerative diseases.

For imaging modality, we know for a long time that brain perfusion single photon emission computed tomography (SPECT) can be used for aiding diagnosis of Alzheimer's disease in early stage.[49] Because of difference abnormal perfusion area in each type of dementia, brain SPECT can help in differential diagnosis of dementia.[50] More specific type of SPECT, ^{99m}Tc-TRODAT-1 SPECT (TRODAT), is dopamine transporter imaging that can be used for differential diagnosis of Parkinsonism, between synucleinopathies and secondary Parkinsonisms.[51] It can also differentiate between Dementia with Lewy Bodies and Alzheimer's disease, which scan should be positive if patient had DLB.[52] We tried to analyze data between the positive and negative TRODAT SPECT group or between the positive TRODAT SPECT group in synucleinopathies and AD groups, but small sample sizes prevented us from detecting significance differences when comparing between them.

CONCLUSION

Plasma α-synuclein is a new biomarker for the diagnosis of Parkinson's disease and other synucleinopathies that may be useful to distinguish them from other diseases. Our study showed that the plasma level of α-synuclein is lower in synucleinopathies compared to Alzheimer's disease and normal control participants. At the cutoff levels of 11.4 ng/ml indicated a sensitivity of 58% (95% CI 43.21-71.81%), specificity of 84.78% (95% CI 71.13-93.66%), positive predictive value (PPV) of 80.56%, a negative predictive value (NPV) of 65% and a precision of 70.83%. The area under ROC was 0.710 between the PDD and DLB vs. the group without synucleinopathies (AD and normal controls) (SE = 0.052, $p \leq 0.001$). Plasma α-synuclein level correlates well with the motor sign of parkinsonism, measured by the sum score of UPDRS part 3, but not with cognition, evaluated using the TMSE score. Using multiple biomarkers, both fluid and imaging, will give more benefit to differentiate synucleinopathies from Alzheimer's disease.

Statement of Ethics

The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (COA no. Si 667/2018). Written informed consent was obtained from all participants in this study. All authors confirm that the research was conducted in accordance with the Declaration of Helsinki. Abstract and some content of this article was presented as Poster at Alzheimer's Association International Conference in 2020, Chicago but only abstract and figure was published online in supplementary issue of Alzheimer's & Dementia Journal. Content and figure in this article were all different from previous publication to avoid issue of plagiarism.

Conflict of interest statement

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

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This was an unfunded study.

Author contributions

CD was involved in data and statistical analysis, interpretation of data, and manuscript writing. LW was involved in taking blood samples and processing them. SU was involved in data and statistical analysis. CR and PS participated in data collection. VS participated in design of study, interpretation of data, and manuscript revision. All authors approved the protocol.

Data availability statement

All data generated for this study are included in the article. There are no other datasets generated during the current study.

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Mobile Device Digital Photography for Teledermatology Consultation: Real-Life Situations

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ABSTRACT

Objective: The use of mobile phones for teledermatology consultations is increasing. In this study, we aimed to describe photographic problems in teledermatology performed via mobile phones and their effects on diagnostic decision-making.
Materials and Methods: Three dermatologists independently reviewed the medical histories and photographs of patients taken by primary-care physicians for teledermatology between January 2018 and August 2020. The consensus of the dermatologists' decision-making was categorized into "definite diagnoses given," "probable diagnoses given," and "unable to provide any diagnosis." Relationships between photographic errors and dermatologist decision-making were investigated. Factors related to photographic problems were evaluated.
Results: In all, 899 images from 220 patients were reviewed. The most common purpose of teledermatology was to make a diagnosis. The most frequent diagnoses were eczema, infection, and autoimmune diseases. Consultants gave definite diagnoses for 63.2% of patients and probable diagnoses for another 29.5%. However, diagnoses were not made in 7.3% of cases. Defocusing and non-eczematous lesions were significantly associated with the inability to give diagnoses (P = 0.002 and 0.037, respectively). Pictures from peripheral areas showed higher frequencies of distortion errors, improper framing, wasted space, and improper background, while truncal regions tended to have lighting problems. The outpatient department setting was associated with a lack of overview and defocusing.
Conclusion: Focusing was the central factor for making diagnoses in teledermatology. Lighting should be more concerned in truncal regions. While using smartphone cameras, distortion should be aware. These factors should be considered to improve the effectiveness of teledermatology.

Keywords: Consult; dermatology; smartphone; teledermatology; telemedicine (Siriraj Med J 2023; 75: 871-879)

INTRODUCTION

Telemedicine is increasingly being used in dermatology. Diagnoses are based mainly on inspection, with additional information from palpation and patient history.[1] Two types of teledermatology are currently in use: (1) store and forward techniques, in which clinical data are sent electronically to dermatologists for evaluation; and (2) live interaction techniques, involving real-time synchronous communication between the patient and dermatologist, typically facilitated through videoconferencing technology, enabling direct visual and audio communication.[2] In the store and forward technique, high-quality images can replace primary-care physician descriptions of skin lesions, which are susceptible to describer bias.[1]

It is undisputed that clinical photographs are beneficial for educational purposes, research, and the management of dermatological conditions, especially in healthcare facilities without dermatologists.[1-4] Moreover, teledermatology in outpatient settings enables the immediate diagnosis of complicated cases by general physicians

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consulting with dermatologists located elsewhere. This joint approach avoids the referral delays and travel costs that would otherwise be incurred if patients have to visit dermatologists for in-person examinations. These benefits were demonstrated by Zakaria et al. (2010) and S. Paradela de la Morena et al. (2015), who found that approximately two-thirds of patients could be treated without a clinic-based evaluation after the implementation of teledermatology.[5,6] The diagnostic accuracy reported for teledermatology was approximately 80%, compared with face-to-face diagnoses.[3,7-9]

In addition to the complex nature of certain diseases, the evolution of lesions, and incomplete clinical data, poor image quality negatively affects the accuracy and reliability of teledermatological diagnoses.[6,7,10] Inadequate pictures result from the photographic techniques used rather than any shortcomings of the technology or the camera options.[1] The photographic technique standard mainly comprises light and shadow, background, the field of view, orientation and framing, distortion, focus and resolution, scale, color calibration, and patient confidentiality.[1,11-13] From previous studies, approximately 80% to 90% of images obtained with store-and-forward teledermatology were considered adequate or excellent.[6,8,14]

Smartphones are used daily for dermatological consultations. Advancements in related camera technologies have resulted in a tool that can capture high-quality images and is easy to use.[15] Nevertheless, few articles have discussed the quality of pictures obtained from mobile phones in practice. Thus, this study evaluated photographic problems in mobile-phone teledermatology, the factors associated with inadequate photographs, and their effects of the various shortcomings on diagnostic decision-making. Therefore, these findings could be beneficial for physicians seeking consultations in teledermatology.

MATERIALS AND METHODS

Ethics consideration

This retrospective study was conducted at the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. Before the research began, its protocol was approved by the Siriraj Institutional Review Board (COA no. Si 801/2020).

Data collection and evaluation

Photographs of patients taken by primary-care physicians between January 2018 and August 2020 were collected from a private social-media group for dermatology teleconsultation. The clinical information collected from the group consisted of baseline characteristics, consultation setting, and purpose of consultation. Three independent board-certified dermatologists, each with over a decade of teaching and consulting experience, including their roles as committee members of monthly dermatologic photographic assessment conferences, reviewed the patient histories and images to describe lesion morphology and provide diagnoses. For each patient, the dermatologists' diagnoses were categorized into "definite diagnoses given," "probable diagnoses given," and "unable to provide any diagnosis." In terms of image quality assessment, photographs of the same body area of the patients were compiled and placed into a corresponding body-region group. We further evaluated these groupings by drawing upon an image-quality checklist we had adapted from various established recommendations[11,12,16] and adjusted to suit mobile phone photography (Supplementary Table 1). Assessments were made of the domains of photographic techniques (the presence of overview photographs and close-up views, focus, lighting, background, framing, orientation, wasted space, perspective distortion, color saturation, and white balance). Any disagreements on clinical diagnoses and photographic assessments were resolved through discussion and consensus. Data related to patient confidentiality issues were also evaluated.

Statistical analysis

Data analyses were performed using PASW Statistics for Windows, version 18 (SPSS Inc., Chicago, IL, USA). With each patient, we selected photographs that had the best quality of photographic technique from representative regions. Subsequently, these were used to evaluate the relationships between image quality and dermatologist diagnostic decisions. As appropriate, Chi^2 tests or Fisher's exact tests were used. In addition, the worst quality photographs from each body region were chosen to identify factors associated with inadequate images.

RESULTS

We collected 899 images from 220 patients and grouped them into 385 body regions. As shown in Table 1, most patients were older than 18 years (81.6%). The primary source of consultation was an outpatient department (OPD; 82.3%), with 17.7% consulted in an inpatient department (IPD) setting. In most of the cases (55%), general physicians were seeking the diagnosis of a skin condition. In another 25% of the cases, general physicians required advice on diagnosing and managing the presenting condition. In the remaining cases (20%), general physicians had formed a diagnosis and were only seeking advice on managing the condition. Most skin lesions were erythematous and eczematous (31.8% and 24.5% of the patients, respectively). In 42 cases (19.1%),

TABLE 1. Patient demographic data.

Demographic data	Number of patients n = 220 (%)
Mean age at the onset ± SD (years)	41.64 ± 22.47
Age group	
0–5 years	15/207 (7.2)
6–17 years	23/207 (11.1)
18–64 years	134/207 (64.7)
> 65 years	35/207 (16.9)
Median duration of disease (IQR; months)	1.00 (0.22–3.00)
Gender	
Male	105/209 (50.2)
Female	104/209 (49.8)
Consultation setting	
Outpatient	181/220 (82.3)
Inpatient	39/220 (17.7)
Purpose of consultation	
For diagnosis	122/220 (55.5)
For proper management	42/220 (19.1)
For diagnosis and proper management	56/220 (25.5)
Provided data in teleconsultation	
Disease duration	186/220 (84.5)
Underlying disease	148/220 (67.3)
Previous treatment	134/220 (60.9)
Current medication	133/220 (60.5)
Occupation	33/220 (15.0)
Pet or animal exposure	4/220 (1.8)
Drug allergy	1/220 (0.5)
Family history	1/220 (0.5)
Environmental exposure	0/220 (0.0)
Diagnosis category	
Definite diagnosis given (spot diagnosis)	116/220 (52.7)
Definite diagnosis given (requiring provided history)	23/220 (10.5)
Probable diagnoses given along with proper management	65/220 (29.5)
Unable to provide any diagnosis	16/220 (7.3)
Disease morphology	
Erythematous lesions	70/220 (31.8)
Eczematous lesions	54/220 (24.5)
Tumor, nodules, and plaques	29/220 (13.2)
Vesiculobullous lesions	17/220 (7.7)
Pustular lesions	14/220 (6.4)
Hair and nail lesions	11/220 (5.0)
Ulcer and erosion	9/220 (4.1)
Papulosquamous lesions	8/220 (3.6)
Hyperpigmentation	8/220 (3.6)
Concurrent skin disease	34/216 (15.7)

Abbreviations: IQR, interquartile range; SD, standard deviation

a lack of patient confidentiality was an issue. Specifically, hospital names or logos, patient faces, patient tattoos, and name tags were visible in images associated with 29, 8, 5, and 4 cases, respectively. Patient consent for photography from referring general practitioners was explicitly mentioned in only 11 of the 220 cases (5%), while the verbal consent was obtained in the remaining cases. The scale measurement was found in only 1 patient.

The diagnostic concordance rate between the three consultant dermatologists was 184 of 220 cases (83.6%). No significant associated factors with the discordance were found, including sex, age, lesion type, location of the lesion, and image quality. Nevertheless, for the final diagnosis, disagreements were resolved through discussions and consensus among three experienced dermatologists. In 63.2% of all cases, the three consulting dermatologists could provide definite diagnoses. With 29.5% of cases, a definitive diagnosis could not be determined, but lists of probable diagnoses were given and case management plans were given. The three consultant dermatologists could not provide diagnoses for only 7.3% of the patients.

The diseases of the patients receiving definite diagnoses are listed in Supplementary Table 2. Eczema was the most common disorder in 33.8% of the cases, followed by cutaneous infection (14.5%) and autoimmune and connective tissue diseases (8.6%). The main reason given by the dermatologists for not making a diagnosis (Table 2) was problems with the photographic technique used. Predominant were the lack of a close-up shot (31.3%) and defocusing (25.0%).

As shown in Table 3, there were no statistically significant differences in the age at onset, duration of symptoms, or consultation setting of the different dermatologist decision-making groups. However, in terms of disease morphology, eczematous lesions were significantly more frequent in patients with a definitive diagnosis (30.2%) than in those with probable (15.4%) and no (12.5%) diagnoses (probability value [P] = 0.037). Additionally, we demonstrated a statistically significant difference between the focus of images and the decision-making of the dermatologists. Defocus was found in 37.5% of the cases without any diagnosis, 24.6% of the probable diagnosis group, and 10.1% of the definite diagnosis group (P = 0.002).

According to Table 4, we evaluated 385 body region images captured by primary-care physicians. The common technical errors with the photographs were the lack of a close-up view (61.3%) and inadequate lighting (55.6%). Relative to the other areas of the body, the photographs of peripheral areas had a significantly higher proportion with distortion (P < 0.001), improper framing (P < 0.001), wasted space (P < 0.001), and improper background (P = 0.005). However, photographs from the truncal region had a significantly higher proportion with poor lighting than those from other regions (P < 0.001). Head and neck photographs lacked an overview shot (P = 0.049). Moreover, defocusing and lack of overview photographs were more common in the OPD setting than the inpatient setting (37.8% versus 25.9% [P = 0.046]; and 14.8% versus 4.9% [P = 0.018]). The photographs of patients under 5 years of age tended to have more wasted space than those of children over 5 (61.5% versus 38.0 %; P = 0.018).

TABLE 2. Reason for inability to provide diagnosis, as given by the dermatologists.

Reason for ambiguous diagnosis[†]	Number of patients n = 16 (%)
Photographic techniques	11/16 (68.8)
No close-up shot	5/16 (31.3)
Defocusing	4/16 (25.0)
Need additional photos from specific area	3/16 (18.8)
Distortion	2/16 (12.5)
Inadequate lighting	1/16 (6.3)
Disease-related factors	7/16 (43.8)
Evolution of the lesions	5/16 (31.3)
Need more physical examination	2/16 (12.5)

[†]One case could have more than one cause of ambiguous diagnosis.

TABLE 3. Factors effecting dermatologists' decision-making to give diagnoses.

	Definite diagnosis n = 139 (%)	Probable diagnoses n = 65 (%)	Unable to provide diagnosis n = 16 (%)	*P*
Mean age ± SD (years)	42.89 ± 22.22	40.02 ± 24.17	37.29 ± 18.47	0.482
Median duration of disease (IQR; months)	1.00 (0.22 – 3.00)	0.75 (0.22 – 6.00)	1.75 (0.22 – 10.50)	0.709
Consultation setting				
Outpatient	118 (84.9)	50 (76.9)	13 (81.3)	0.379
Inpatient	21 (15.1)	15 (23.1)	3 (18.8)	
Disease morphology				
Eczematous lesions	42 (30.2)	10 (15.4)	2 (12.5)	0.037*
Erythematous lesions	41 (29.5)	23 (35.4)	6 (37.5)	0.617
Tumor, nodule, and plaque	16 (11.5)	10 (15.4)	3 (18.8)	0.592
Vesiculobullous lesions	11 (7.9)	4 (6.2)	2 (12.5)	0.689
Pustular lesions	10 (7.2)	3 (4.6)	1 (6.3)	0.905
Hair and nail lesions	7 (5.0)	4 (6.2)	0 (0.0)	0.787
Papulosquamous lesions	5 (3.6)	3 (4.6)	0 (0.0)	0.844
Ulcer and erosion	4 (2.9)	4 (6.2)	1 (6.3)	0.305
Hyperpigmentation	3 (2.2)	4 (6.2)	1 (6.3)	0.243
Photographic techniques of the representative images				
Defocusing	14 (10.1)	16 (24.6)	6 (37.5)	0.002*
No close-up photo	71 (51.1)	31 (47.7)	9 (56.3)	0.805
Inadequate lighting	60 (43.2)	31 (47.7)	7 (43.8)	0.830
Improper background	54 (38.8)	27 (41.5)	4 (25.0)	0.475
Wasted space	37 (26.6)	15 (23.1)	6 (37.5)	0.499
Improper framing	20 (14.4)	13 (20.0)	3 (18.8)	0.580
No overview photo	20 (14.4)	13 (20.0)	2 (12.5)	0.551
Improper white balance	9 (6.5)	6 (9.2)	0 (0.0)	0.566
Inadequate color saturation	6 (4.3)	5 (7.7)	1 (6.3)	0.480
Distortion	4 (2.9)	1 (1.5)	2 (12.5)	0.132

* $P < 0.05$ indicates statistical significance, Chi^2 test.

Abbreviations: IQR, interquartile range; SD, standard deviation

TABLE 4. Factors associated with photographic technical errors.

Photographic techniques	Total	Body regions			*P*	Consultation setting		*P*-value	Age group (years)		*P*
		Head /neck n (%)	Trunk n (%)	Peri pheral n (%)		OPD n (%)	IPD n (%)		0–5 n (%)	≥ 6 n (%)	
	385	**99**	**98**	**188**		**304**	**81**		**26**	**342**	
Inadequate lighting	214 (55.6)	50 (50.5)	73 (74.5)	91 (48.4)	<0.001*	169 (55.6)	45 (55.6)	0.955	18 (69.2)	186 (54.4)	0.142
Wasted space	154 (40.0)	28 (28.3)	12 (12.2)	114 (60.6)	<0.001*	121 (39.8)	33 (40.7)	0.878	16 (61.5)	130 (38.0)	0.018*
Improper framing	97 (25.2)	11 (11.1)	10 (10.2)	76 (40.4)	<0.001*	76 (25.0)	21 (25.9)	0.865	9 (34.6)	86 (25.1)	0.287
Distortion	25 (6.5)	0 (0.0)	1 (1.0)	24 (12.8)	<0.001*	21 (6.9)	4 (4.9)	0.523	0 (0.0)	25 (7.3)	0.239
Improper background	163 (42.3)	37 (37.4)	31 (31.6)	95 (50.5)	0.005*	121 (39.8)	42 (51.9)	0.051	12 (46.2)	147 (43.0)	0.753
No overview photos	49 (12.7)	19 (19.2)	13 (13.3)	17 (9.0)	0.049*	45 (14.8)	4 (4.9)	0.018*	3 (11.5)	43 (12.6)	1.000
Out of focus	136 (35.3)	28 (28.3)	35 (35.7)	73 (38.8)	0.205	115 (37.8)	21 (25.9)	0.046*	12 (46.2)	123 (36.0)	0.299
No close-up view	236 (61.3)	58 (58.6)	61 (62.2)	117 (62.2)	0.813	190 (62.5)	46 (56.8)	0.348	18 (69.2)	207 (60.5)	0.380
Improper white balance	34 (8.8)	12 (12.1)	6 (6.1)	16 (8.5)	0.325	26 (8.6)	8 (9.9)	0.709	1 (3.8)	31 (9.1)	0.714
Inadequate color saturation	23 (6.0)	6 (6.1)	6 (6.1)	11 (5.9)	0.995	15 (4.9)	8 (9.9)	0.113	2 (7.7)	20 (5.8)	0.662

* $P < 0.05$ indicates statistical significance, Chi^2 test.

Abbreviations: IPD, inpatient department; OPD, outpatient department

DISCUSSION

In the situation of a limited number of dermatologists, waiting times for face-to-face consultations are likely to become extended. Moreover, with a steadily growing population, dermatologists will likely face pressure to expand their services.[9] Teleconsultation is a promising solution in these scenarios. Our data confirmed its benefits as our three consulting dermatologists could provide definite or probable diagnoses and management plans in most cases.

From our literature review, the quality of photographs affects the accuracy of diagnoses.[6,7] We found that focus was the most critical factor since good focus was the only domain significantly associated with the ability to make a definitive diagnosis in our study. This finding underscores the need to have high-quality images for teleconsultation. It is recommended to use the flash function to avoid shadows, improve exposure, and obtain better focused and more detailed photographs than otherwise. The need for the flash function is especially critical in low-light areas such as the oral cavity (Fig 1).[12,16,17] However, a loss of morphological features could occur if the flashlight is placed too close to lesions.[16-18] Furthermore, photographs should reveal the distribution of the lesions and their associated anatomical structures. The morphological details of the lesions should also be obtained through a well-lit and focused close-up shot.[16,17]

Other techniques that should be considered are lighting, background, wasted space, framing, distortion, white balance, and color saturation. Diffused and broad-spectrum lighting is appropriate, and the light source should be oblique to the skin surface.[11,16] Natural light can vary in intensity and color. While the light from a camera flash is more consistent, it can cause reflection, especially in scalp and nail photographs.[11,19] Regarding background, patient-identifiable objects and distracting elements such as jewelry should be removed, and solid non-reflective backgrounds are preferable.[11,12,16-18] In terms of framing, an orientation following the direction of the body area is recommended to eliminate wasted space in the background (i.e., horizontal and vertical orientation for the chin and legs, respectively).[12] To take a picture of fingernails, we suggest that patients flex all fingers to bring the fingertips together (Fig 2).[20] Next, distortion is expected in the photograph from a mobile phone due to the automatic wide-angle camera setting. To prevent distortion, it is recommended to zoom in slightly and move backward until the image fits the frame, with the camera placed perpendicular to the photographic plane.[12] For color temperature, the skin tone might appear red in warm light, whereas a cool tone will decrease redness. Therefore, a non-neutral white balance can interfere with the diagnosis of erythematous lesions. Finally, a preset filter that affects color tone and saturation should be avoided.

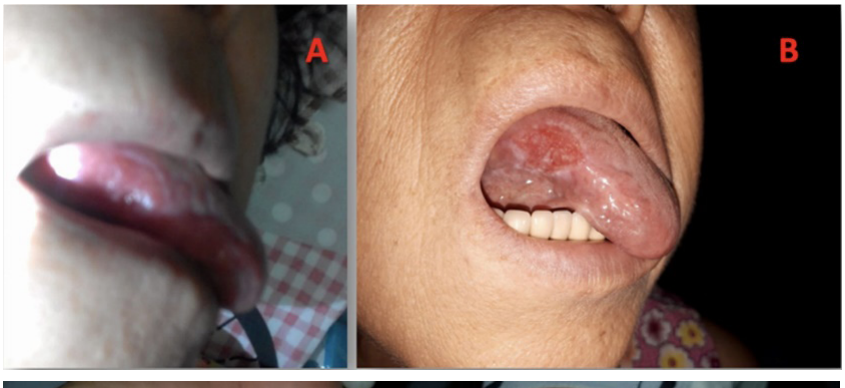

Fig 1. Using a camera flash for the photographs avoids shadows and provides improved exposure results in more detailed photos, especially in low-light areas such as the oral cavity. Fig 1A demonstrates a blurry photo with poor light exposure, in which the lesion could not be identified. Fig 1B shows a focused and appropriately exposed image with the use of the camera flash.

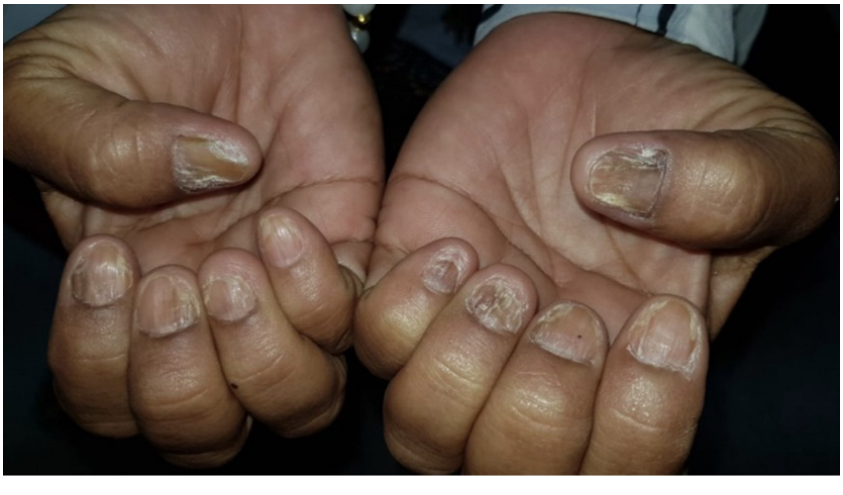

Fig 2. Nail photography. Flexing the fingers at the proximal interphalangeal joints in order to bring all of the fingertips toward the palm will demonstrate the distribution of lesions in nail disorders.

We also analyzed factors associated with poor photographic techniques. Body regions seemed to have the most effect on photographic quality. The peripheral areas were more likely to have distortion, improper framing, wasted space, and improper background. On the other hand, truncal regions tended to have lighting problems. The photographs from the inpatient consultations frequently had inappropriate backgrounds. This finding was partly because of the more distracting elements found in the inpatient setting versus the OPD setting. However, the difference was nonsignificant. The OPD setting was associated with a lack of overview and defocusing. Possibly, this was due to the enormous number of patients visiting the OPD of primary care hospitals in Thailand, making it challenging to take high-quality images. Finally, wasted space was more frequent in pictures of patients under 5 years of age than in older patients. This finding would have resulted from the smaller body sizes of the younger patients. All of the factors above should be considered when taking photographs for teledermatology.

Finally, previous studies reported dermatitis, psoriasis, tumors, and onychomycosis as common consultation problems, with a lower frequency of cases with erythematous morphology (such as urticarial lesions).[21-23] However, the typical morphology in our subjects was erythematous, followed by eczematous and tumoral or nodular lesions. As a result, more education on eczematous, tumoral, and especially erythematous lesions would be advantageous.

In terms of patient confidentiality, patient consent for photography from referring general practitioners was mentioned in only 5% of cases. In most Thai hospitals, there were no standardized forms for obtaining patient consent for photography. Given the existence of the Personal Data Protection Act in Thailand, physicians should be more conscientious about obtaining documented consent for photography.

The main limitation of this study was related to the image-quality checklist. Even though we based it on various established guidelines, there was a lack of standardized criteria for assessing photographic quality. More specifically, there were no prescribed criteria to determine whether individual photographs are acceptable for each domain (overview photographs, close-ups, focus, lighting, background, framing, and orientation, wasted space, perspective distortion, color saturation, and white balance). Another limitation was the broad spectrum of the information with various dermatologic conditions. Consultant experience also was a factor influencing the success of teledermatology but this study faced challenges in collecting relevant data. Collecting such data could prove beneficial in future research.

In conclusion, teleconsultation can increase patient access to dermatologists, especially in facilities without specialists. When mobile phones are used for teledermatology, good camera focus is the most important photographic technique. An acceptable image quality can enhance the diagnostic accuracy of dermatologists.

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Conflict of Interest

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Effect of Wearing a Face Mask on the 6-Minute Walk Test in Healthy Volunteers

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ABSTRACT

Objective: This study aimed to examine the influence of wearing different types of face masks on the results of the 6-Minute Walk Test (6MWT) in a cohort of healthy volunteers.

Materials and Methods: Volunteers were partitioned into three groups (each comprising 36 individuals) with different mask-wearing conditions: NIOSH-approved N95 mask, and double-mask scenarios featuring two layers of surgical mask, and a combination of a surgical mask covered by a cloth face mask. Each participant performed two rounds of the 6MWT, one while wearing a mask and another without. Various metrics, such as the six-minute walk distance (6MWD), oxygen saturation (SpO_2), and dyspnea and fatigue scores, were measured.

Results: No significant differences were found in the 6MWD results between the mask-wearing and non-mask-wearing scenarios across all the mask types. Strong positive correlations were also established between the 6MWD results in the mask-wearing and non-mask-wearing conditions. However, a small cohort experienced dyspnea significantly more when wearing double surgical masks compared to not wearing a mask. Additionally, there were no major deviations in SpO_2 levels or fatigue scores regardless of the type of mask used.

Conclusion: The study indicated that wearing an N95 mask, or double surgical masks, or cloth-over-surgical face masks did not significantly influence the outcomes of the 6MWT in healthy individuals. However, caution is advised in the case of wearing double surgical masks, as this may induce a greater sense of dyspnea. This suggests that face masks can be worn safely during physical fitness and pulmonary function assessments, aligning with their essential role in viral spread prevention in daily life.

Keywords: 6-Minute walk test; face mask; oxygen saturation; dyspnea; fatigue (Siriraj Med J 2023; 75: 880-886)

INTRODUCTION

The 6-Minute Walk Test (6MWT) is a method used to assess functional capacity[1] and illness severity. It is often used for comparative purposes before and after various treatments, such as lung transplantation and lung surgery, pulmonary rehabilitation, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, heart failure, peripheral arterial disease, and fibromyalgia, and to assess elderly patients' functional capacity. In the test, the distance walked in 6 minutes (6-minute walk distance, 6MWD), oxygen saturation in the blood (SpO_2), heart rate (HR), respiratory rate (RR), blood pressure (BP), dyspnea score, and fatigue score are measured. The test is easy to perform utilizing simple equipment and technology, and is cost-effective, making it popular in healthcare settings.

Since the beginning of the COVID-19 pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2

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(SARS-CoV-2), the World Health Organization (WHO) has recommended wearing face masks as a preventive measure in public places.[2] This measure has been effective in helping prevent the transmission and spread of the virus.[3] However, the use of a face mask may have an impact on the 6-Minute Walk Distance (6MWD), but there is currently no established testing protocol for the 6-Minute Walk Test (6MWT) to be performed during a pandemic situation according to the standards set by the American Thoracic Society[4] or the European Respiratory Society.[5] Existing studies have only explored the effects of wearing face masks on the 6MWD results during the 6MWT in sample groups, considering various types of masks, such as surgical masks or N95 masks, for individuals who have previously been infected with COVID-19[6], while wearing the oronasal surgical mask for patients with end-stage lung diseases[7], and the use of surgical masks with healthy volunteers[8], as well as the effects of wearing multiple layers of masks, such as the double-mask technique[9] involving the use of two surgical masks or a combination of a surgical mask as the first layer and a cloth face mask as the second layer. These studies aimed to provide supplementary information for developing testing guidelines to be used during the COVID-19 pandemic and for other respiratory conditions.

Therefore, this research aimed to add to the field by investigating the impact of wearing a single layer N95 standard face mask, the double-mask technique involving two surgical masks or a combination of a surgical mask and a cloth face mask on the 6MWD during the 6MWT. The study also involved healthy volunteers to provide additional reference test data for walking assessments during a pandemic situation and for other respiratory conditions.

MATERIALS AND METHODS

Healthy volunteers were included in the study who were aged over 18-years old, with a body mass index (BMI) between 18.5–22.90, non-smokers, and without a history of tuberculosis, coronavirus disease (COVID-19), asthma, chronic obstructive pulmonary disease, cystic fibrosis, and no contraindications to perform the 6MWT). The sample size calculation involved randomizing volunteers into six groups, each with 18 individuals. The calculation was based on data from a literature review, specifically from Swiatek et al.[8] study on the Healthy group. The average 6MWD before wearing a mask was 610.45 meters, and after wearing it, it was 605.36 meters. Since the standard deviation of the difference was unavailable, it was set to 39.62 meters to maximize the sample size, with a maximum expected difference of 30 meters.[10] The highest expected average 6MWD without a mask was 635.36 meters. An independent comparison of means between two population groups was planned using a paired t-test, with a significance level of 5% (standard value = 1.96) and a test power of 80%.

$$\text{n/group} = \frac{\sigma_d^2 (Z_{\alpha/2} + Z_{\beta})^2}{\mu_d^2}$$

$$\text{n} = \frac{(1.96+0.84)^2(39.62)^2}{(605.36-635.36)^2}$$

$$\text{n} = 16$$

The quantitative analysis conducted necessitated careful consideration of the sample size for non-inferiority assessment. Initially, a sample size of 16 was contemplated, but subsequently augmented to mitigate potential data loss. This augmentation constitutes a 10% increment relative to the originally computed sample size, equating to an additional two participants. Consequently, the revised sample size now stands at 18. It is imperative to elucidate that this research encompasses a comparative investigation involving two distinct cohorts: individuals who initially abstained from mask usage and subsequently commenced wearing masks, and those who initially donned masks but subsequently ceased usage. In both groups, a standardized resting period of 30 minutes was observed before mask alteration. Notably, during testing, no masks were worn by participants in accordance with the testing protocols prescribed by the American Thoracic Society/European Respiratory Society.

In the first group, volunteers were equipped with NIOSH-approved N95 masks devoid of valves, specifically the 3M™ 1860S model. Group 2 participants utilized a double-layer medical mask, with each layer comprising 3-sublayers. Group 3, wore a 3-tiered medical surgical mask covered by a cloth face mask. The cloth masks, known as Siri Masks, were tested for dust filtration according to the Thai Industrial Standards Institute (TISI) 2424-2552 / EN143:2000 (European Union Personal Protective Equipment: EU PPE) standards.

This study was approved by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital (COA no. Si 1015/2021).

Statistical analysis

The study findings were reported using descriptive statistics, including frequency, percentage, standard deviation, maximum, minimum, mean and median values. The study explored various health variables, such

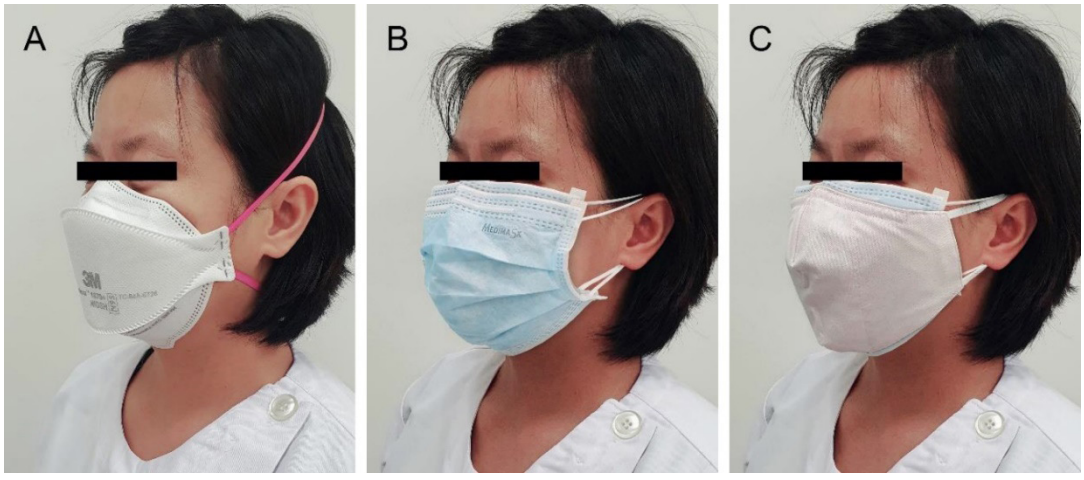

Fig 1. Three mask wearing scenarios tested: (A) NIOSH-approved N95 mask without a valve, specifically the 3M™ 1860S, (B) medical surgical mask, double-layered, and (C) three-tiered medical surgical mask covered by a cloth face mask.

as age, gender, weight, BMI, 6MWD, SpO_2, HR, dyspnea score, and fatigue score. The statistical software SPSS® Version 18 was employed to analyze the data, utilizing inferential statistics to investigate the relationships between variables or factors, including the independent t-test and Pearson correlation coefficient. Statistical significance was determined using a p-value threshold of less than 0.05.

RESULTS

Table 1 presents the volunteer characteristics. In total, 108 individuals were included in the study, comprising 13 males and 95 females, with an average age of 37 (±9.08) years old, mean weight of 52.97 (±5.49) kg, average height of 158.70 (±6.08) cm, and mean body mass index (BMI) of 21.0 (±1.29) kg/m^2.

From Table 2 and Fig 2, it can be found that the 6MWD in the sample group wearing masks and not wearing masks during the three types of tests did not show statistically significant differences at a significance level of 0.05. Additionally, the 6MWD results when wearing masks and not wearing masks showed a strong positive correlation (r_{sp} = 0.95, p < 0.001) in the same direction. The mean difference in walking distance was 1.431 (±16.64) meters, and the concordance correlation coefficient (CCC) between the meters walked during the 6MWT with and without masks was 0.98. Furthermore, the difference in walking distance was not dependent on the type of mask used (p = 0.252). It was also found that the sample group did not have a difference in the 6MWD greater than 30 meters when wearing masks versus not wearing masks for all types of masks in all the groups.

TABLE 1. General characteristics of the study participants.

	N95 face mask (*n*=36)	Double surgical face masks (*n*=36)	Cloth mask over a surgical face mask (*n*=36)
Age, y	34.8 (8.71)	36.4 (8.31)	37.3 (10.22)
Sex, M, n (%)	3 (8.33)	4 (11.11)	6 (16.67)
Sex, WM, n (%)	33 (91.67%)	32 (88.89%)	30 (83.33%)
Weight, kg	52.6 (5.87)	52.5 (4.45)	53.8 (6.16)
Height, cm	158.4 (6.56)	158.1 (5.14)	159.6 (6.53)
BMI, kg m^2	20.9 (1.31)	21.0 (1.22)	21.0 (1.33)

TABLE 2. 6MWT differences with or without an N95 face mask, double surgical face mask, or cloth mask over a surgical face mask.

	N95 face mask (n=36)			Double surgical face mask (n=36)			Cloth mask over a surgical face mask (n=36)		
	w	w/o	*p*	w	w/o	*p*	w	w/o	*p*
6MWD, m	462.7±58.0	460.5±57.4	0.874	454.8±52.22	457.4±48.66	0.823	462.2±59.12	463.1±55.98	0.945
Basal SpO_2, %	98.4±1.05	98.7±1.00	0.139	98.8±0.90	99.1±0.85	0.111	98.8±1.02	99.1±0.89	0.222
1-min SpO_2, %	97.5±1.46	97.8±1.70	0.417	97.9±1.47	98.0±1.28	0.670	97.9±1.31	98.5±1.21	0.053
3-min SpO_2, %	97.3±1.62	97.8±1.44	0.253	98.0±1.56	97.9±1.47	0.757	97.7±1.61	98.1±1.30	0.265
Final SpO_2, %	97.8±1.26	98.3±1.30	0.145	98.3±0.98	98.4±1.08	0.570	98.2±1.04	98.4±1.13	0.332
After 1-min SpO_2, %	97.5±1.25	97.9±1.16	0.122	98.2±1.08	98.5±1.13	0.246	98.1±1.25	98.4±1.13	0.280
After 3-min SpO_2, %	97.8±1.05	98.1±1.20	0.254	98.1±1.08	98.3±1.01	0.370	98.1±1.17	98.2±1.02	0.521
Basal HR, bpm	79.6±10.13	78.0±9.12	0.488	83.8±9.56	83.9±9.50	0.980	79.1±11.3	77.5±10.83	0.525
1-min HR, bpm	105.9±15.82	106.1±16.00	0.965	111.0±14.98	109.1±15.06	0.656	104.4±18.54	104.4±15.73	0.989
3-min HR, bpm	110.7±16.72	109.8±16.97	0.807	113.5±15.59	113.4±16.18	0.977	106.8±22.42	107.1±19.38	0.955
Final HR, bpm	117.4±15.73	114.8±13.03	0.441	119.2±13.85	116.4±15.13	0.433	112.8±16.72	110.3±17.29	0.539
After 1-min HR, bpm	95.6±14.61	91.6±12.73	0.220	99.9±13.11	94.9±13.20	0.104	91.3±16.17	87.9±17.60	0.402
After 3-min HR, bpm	87.6±12.34	86.4±11.74	0.661	93.4±12.26	90.8±12.53	0.345	84.0±14.78	82.3±14.98	0.619
Dyspnea basal score	0.0 (0-2)	0.0 (0-2)	0.582	0.0 (0-0.5)	0.0 (0-0.5)	1.000	0.0 (0-2)	0.0 (0-1)	0.451
Dyspnea 1-min score	0.0 (0-3)	0.0 (0-4)	0.599	0.5 (0-1)	0.0 (0-1)	0.080	0.0 (0-2)	0.0 (0-1)	0.366
Dyspnea 3-min score	0.5 (0-4)	0.5 (0-4)	0.441	1.0 (0-2)	0.5 (0-3)	0.077	0.5 (0-3)	0.5 (0-2)	0.145
Dyspnea final score	2.0 (0-6)	1.0 (0-6)	0.166	2.0 (0-5)	1.0 (0-5)	0.010*	1.0 (0-4)	1.0 (0-3)	0.064
After dyspnea 1-min score	1.0 (0-6)	0.5 (0-4)	0.140	1.5 (0-4)	0.5 (0-5)	0.016*	0.5 (0-4)	0.5 (0-2)	0.053
After dyspnea 3-min score	0.5 (0-4)	0.0 (0-4)	0.159	0.5 (0-3)	0.0 (0-2)	0.036*	0.0 (0-2)	0.0 (0-2)	0.320
Fatigue basal score	0.0 (0-2)	0.0 (0-2)	0.519	0.0 (0-0.5)	0.0 (0-2)	0.067	0.0 (0-2)	0.0 (0-2)	1.000
Fatigue 1-min score	0.0 (0-5)	0.0 (0-2)	0.298	0.0 (0-2)	0.0 (0-1)	0.750	0.0 (0-2)	0.0 (0-2)	0.514
Fatigue 3-min score	0.5 (0-6)	0.5 (0-5)	0.680	0.5 (0-3)	0.5 (0-5)	0.748	0.5 (0-5)	0.0 (0-4)	0.605
Fatigue final score	1.0 (0-7)	0.5 (0-7)	0.942	0.5 (0-4)	0.5 (0-5)	0.626	0.5 (0-5)	0.5 (0-4)	0.518
After fatigue 1-min score	0.5 (0-6)	0.5 (0-7)	0.542	0.5 (0-4)	0.5 (0-4)	0.361	0.5 (0-4)	0.0 (0-2)	0.189
After fatigue 3-min score	0.0 (0-5)	0.0 (0-4)	0.476	0.0 (0-3)	0.0 (0-2)	0.176	0.0 (0-3)	0.0 (0-2)	0.356

w = With face mask; w/o = Without face mask; 6MWD = 6-minute walking distance; 6MWT = 6-minute walking test; HR = Heart rate; SpO_2 = Oxygen saturation measured by pulse fingertip oximeter, Mean±SD or median(Minimum–Maximum); 1-minute and 3-minute scores correspond with measurements at 1 minute and 3 minutes after the 6MWT. Dyspnea and fatigue scores were measured with the Borg scale.

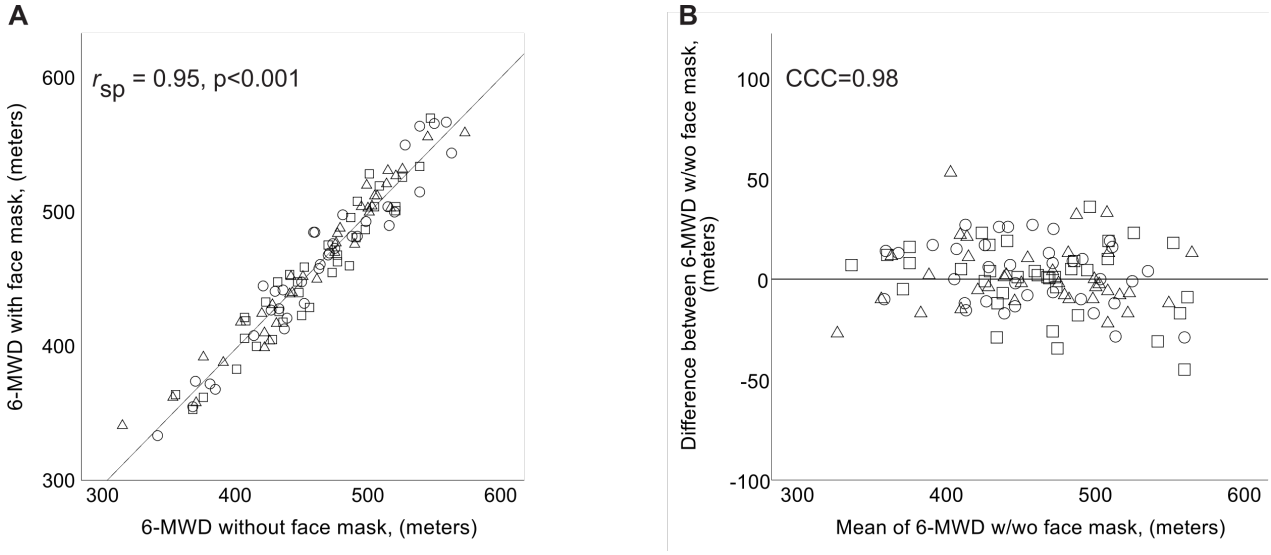

Fig 2. (A) Spearman correlation (r_{sp} = 0.95, p < 0.001) and (B) concordance correlation coefficient (CCC) between the meters walked during the 6-minute walking test (6MWT) with and without a face mask (CCC = 0.98).
w/wo = with/without masks. △ = N95 face mask, ○ = Double surgical face masks, □ = Cloth mask over a surgical face mask (n = 36).

No significant decrease in SpO_2 of more than 4% was found. However, among the sample group of 34 individuals (62.03%), there was a difference in SpO_2 levels when wearing masks versus not wearing masks, with a mean difference of 0.07% (±0.92) after completing the test.

There was no significant difference between wearing masks and not wearing masks in terms of the SpO_2, and dyspnea and fatigue scores for the N95 masks and the combination of a cloth face mask over a medical surgical mask. However, among the sample group wearing the double-surgical masks, featuring a 3-layer surgical mask (medical face mask) with two overlapping layers, and not wearing the masks, a significant difference was found in dyspnea after completion of the test (p = 0.010) and at 1 minute (p = 0.016) and 3 minutes (p = 0.036) after completion of the test.

DISCUSSION

Six-minute walk distance

There was no significant difference in the 6MWD when wearing the N95, double surgical face masks, or cloth mask over a surgical face mask combination during the 6MWT test (p = 0.932, 0.806, and 0.990, respectively). There was also a strong positive correlation in the same direction (r_{sp} = 0.937, p < 0.001) between the 6MWD results and the use of any of the three mask-type scenarios. These findings are consistent with other studies that showed there were no statistically significant differences in the 6MWD when wearing an N95[10-13], surgical face mask[11-15], or cloth mask.[11,13] Furthermore, it was found that wearing or not wearing a mask did not result in a difference of more than 30 meters in the 6MWD, which is clinically significant for diagnosing, predicting, and monitoring individuals with chronic lung diseases.[10,16-17]

Oxygen saturation

There was no significant difference in the SpO_2 levels when wearing the N95, double surgical face masks, or cloth mask over a surgical face mask combination during the 6MWT test. These findings align with the study conducted by Fukushi et al.[18], who found that mask-wearing does not impact oxygen saturation levels in red blood cells during any level of exercise load.[19] It is possible that there may be a temporary decrease in blood oxygen saturation after performing activities or exercise, but this effect is short term and clinically insignificant.

Dyspnea and fatigue

The sample group who wore the double surgical face masks experienced significantly higher levels of dyspnea compared to when not wearing a mask during the test and after completing the test, at a statistically significant level of 0.05 (p = 0.010) one minute after the test (p = 0.016), and three minutes after the test (p = 0.036). These findings are consistent with the study conducted by Person et al.[15], who found that wearing a surgical mask resulted in greater dyspnea compared to not wearing one, and with the study conducted by Kusalin et al.[11], who found that surgical masks caused more dyspnea compared to N95 cloth PM2.5 masks. However, Cabanillas-Barea et al.[20] found that N95 masks

resulted in more dyspnea compared to surgical masks. Additionally, Fukushi et al.[18] found that wearing surgical masks or cloth masks did not worsen dyspnea during light to moderate exercise but worsened dyspnea during strenuous exercise. No significant difference in fatigue was observed between wearing or not wearing any of the three types of masks in the present study.

Limitations

This study primarily included middle-aged, healthy individuals with normal BMI and a female predominance. As such, our findings may not be readily extrapolated to diverse populations with varying demographics, obesity levels, and comorbidities, particularly pulmonary and cardiovascular disorders. Moreover, our results are specifically relevant to healthy individuals without underlying cardiac conditions. Additionally, the study's focus was on short-term mask effects, and long-term implications were not explored. Future research should consider these limitations and investigate broader demographic profiles and long-term outcomes.

CONCLUSION

This study provides valuable insights into the impact of various mask types on 6MWT in healthy individuals. It is important to emphasize that the safety considerations related to different masking strategies discussed herein primarily apply to a cohort of healthy participants without underlying cardiopulmonary diseases.

The findings underscore that, for individuals without pre-existing cardiac or pulmonary conditions, wearing N95 masks, double surgical masks, or a cloth mask over a surgical mask during the 6MWT does not appear to significantly affect the distance walked in six minutes (6MWD), oxygen saturation (SpO_2) levels, or fatigue. These results offer reassurance regarding the continued use of face masks as a crucial measure in mitigating the spread of viral infections during daily life and within the context of physical fitness and pulmonary function assessments.

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Efficacy and Safety of Topical 5% Azelaic Acid Solution Versus 2% Minoxidil Solution in the Treatment of Female Pattern Hair Loss

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ABSTRACT

Objective: To determine the efficacy and safety of 5% azelaic acid solution in comparison with 2% minoxidil solution in the treatment of FPHL.

Materials and Methods: Twenty-six FPHL patients with Ludwig grade I or II were randomly treated with 5% azelaic acid solution or 2% minoxidil solution twice daily for 6 months. At baseline, 2, 4, and 6 months, hair density and hair shaft diameter were assessed at the targeted fixed area. At 6 months, patient and investigator assessments of hair growth were performed using a 7-point scale.

Results: Hair density and hair shaft diameter in the patients treated with 5% azelaic acid and 2% minoxidil solution were significantly increased compared to the baseline in all cases and visits ($P < 0.05$). There were no statistically significant differences in hair density and hair shaft diameter changes between both groups ($P > 0.05$). Both the investigator and patient assessments were comparable between both groups at 6 months. Pruritus was the major adverse effect reported in both groups, but only mild and all could be tolerated.

Conclusion: 5% Azelaic acid solution might be an effective treatment for FPHL, comparable with 2% minoxidil, and could be an alternative treatment for FPHL in minoxidil-allergic patients and pregnant women.

Keywords: Androgenetic alopecia; azelaic acid; female pattern hair loss; minoxidil allergy; pregnancy (Siriraj Med J 2023; 75: 887-893)

INTRODUCTION

Androgenetic alopecia (AGA), also known as pattern hair loss, is the most common form of nonscarring alopecia, affecting up to 80% of men and 50% of women throughout their lifetime.[1] It is characterized by progressive hair loss due to miniaturization of the hair follicles, resulting in vellus transformation of the terminal hairs.[2] Androgens and genetic predisposition appear to play important roles in etiopathogenesis.[2,3] Current treatments of AGA that are approved by the US Food and Drug Administration (FDA) consist of oral finasteride (5α-reductase inhibitor) in men, and topical minoxidil and low-level light therapy (LLLT) in both men and women.[4,5]

Concerning female pattern hair loss (FPHL), the treatment options are limited. Although the roles of androgens and genetic susceptibility are less apparent than in male AGA, oral finasteride and other antiandrogens appear to be helpful in FPHL. However, these medications are

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off-label and restricted, especially in women of childbearing age due to their teratogenicity and the increase in risk of breast cancer.[4] Therefore, topical minoxidil is the only FDA-approved first-line medication for FPHL prescribed in general practice. However, concern has been raised in FPHL patients with pregnancy, and so minoxidil should be avoided for pregnant women.[4,6] There have been reports of neonatal hypertrichosis and fetal malformations (heart, brain, and vascular) related to topical minoxidil use during pregnancy.[7,8] Although topical minoxidil usage by mothers offers no harm to breastfed children according to expert consensus, minoxidil-induced hypertrichosis in a breastfed infant was recently reported.[9] Therefore, minoxidil should be prescribed under supervision, especially when a substantial maternal dosage is part of the therapy and while nursing a premature baby.[9]

Elevated estrogen levels during pregnancy slow down the hair follicles' normal cycle of shedding. As a result, most pregnant women with FPHL can actually have less hair loss.[10] However, some of them might also suffer from ongoing hair loss during the gestational period, which may happen as a result of iron deficiency anemia, stopping the oral contraceptive pill, stress, or an imbalance of essential vitamins.[11,12] Further hair thinning usually has a negative impact on quality of life and self-esteem.

Azelaic acid is an effective topical treatment for various dermatologic conditions, such as rosacea, acne, and hyperpigmentation, owing to its anti-inflammatory, antioxidant, and antibacterial properties.[13] In addition, azelaic acid is also an inhibitor of 5α-reductase, which is a key enzyme in the pathogenesis of AGA.[14] A recent study also showed that azelaic acid could protect hair bulge cells from ultraviolet B damage via an increase in catalase activity, and upregulate *Gli1* and *Gli2* expression, which could enhance telogen to anagen transition and promote hair growth.[15] Therefore, azelaic acid is believed to be beneficial in the treatment of AGA, and there are many commercial topical preparations containing minoxidil solutions in combination with 5% azelaic acid. Moreover, topical azelaic acid is considered to be safe to apply during pregnancy (pregnancy category B) and breastfeeding.[16] However to the best of our knowledge, there has been no previous study on the efficacy of azelaic acid topical solution monotherapy or a controlled study comparing the efficacy of azelaic acid topical solution and the standard treatment of AGA. Thus, the objective of this study was to determine the efficacy and safety of 5% azelaic acid solution in comparison with 2% minoxidil solution in the treatment of FPHL.

MATERIALS AND METHODS

Study design

This prospective, randomized, double-blinded comparative study was conducted at the Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University. The study was approved by the Siriraj Institutional Review Board and informed consent was obtained from all participants. Overall, 26 FPHL women were enrolled and randomized to receive 5% azelaic acid topical solution or 2% minoxidil topical solution by block randomization (1:1 allocation ratio). The patients were instructed to apply the solution all over their thinning scalp twice daily. The patients were evaluated at months 0 (baseline), 2, 4, and 6.

Participants

FPHL patients aged ≥ 18 years, with a Ludwig classification grade I or II, were recruited in the study. They must not have received any topical or systemic hair loss treatment for at least 6 months prior to the enrollment. The exclusion criteria included patients who had other scalp, systemic, or psychiatric conditions that could be the cause of alopecia. Pregnant or breastfeeding women were also excluded.

Azelaic acid and minoxidil solution

Both 5% azelaic acid and 2% minoxidil solution were formulated by the Pharmacy Department, Faculty of Medicine Siriraj Hospital, Mahidol University. Both solutions used the same vehicles, consisting of 50% ethyl alcohol, 25% propylene glycol, and 25% purified water.

Outcome assessment

Hair density and diameter

On the day of enrollment, each patient was tattooed with 4 dots forming a 1x1 cm square on the vertex area of the scalp, using a brown cosmetic tattoo ink (Micro Pigments, Biotouch Inc., Los Angeles, CA, USA) that would gradually disappear after 6 months. At each visit, hairs in the target area were cut to approximately 1 mm in length and collected. Macrophotographs of the target area on the scalp were taken using a dermoscopic device (Dino-Lite DermaScope®, Dino-Lite, Naarden, the Netherlands) and DinoCapture software. All hairs in the target area were manually counted and reported as the total hair and terminal hair counts. The hair diameter at each visit was calculated by the mean hair diameter of ten representative hairs from the target area. Each hair was measured using an electronic external micrometer (RS PRO External Micrometer, RS Components Ltd., Corby, UK). Both the hair density and hair diameter at

each visit of all the participants were evaluated by the same author (C.P.), who was blinded to the treatment.

Global photographic review (GPR)

Standardized photographs were taken using a digital camera (Digital Canon PowerShot G15, Canon Inc., Tokyo, Japan) at baseline and 6 months. All the photographs at baseline and 6 months were evaluated by two blinded expert dermatologists (K.T. and D.T.) for assessing the improvement in the patient's global hair volume using a 7-point scale (-3 = significant worsening; -2 = moderate worsening; -1 = slight worsening; 0 = no change; +1 = mild improvement; +2 = moderate improvement; +3 = significant improvement).

Patient's own evaluation

After 6 months, patients evaluated their improvement of FPHL compared with the baseline using a 7-point scale, as in the GPR assessment.

Safety assessments

At every patient visit, safety evaluations of 5% azelaic acid solution and 2% minoxidil solution were conducted utilizing the combined information from the history taking, physical examination, and photoimaging. The majority of recorded adverse events were related to scalp irritation, including erythema, itching, scaling, and pruritus. Subjects rated the severity as none, mild, moderate, or severe. Inspection of the returned container of the designated preparation allowed for the assessment of patient drug compliance.

Statistical analysis

All the data were analyzed using PASW Statistics, version 18.0 (SPSS Inc, Chicago, IL, USA). Descriptive statistics were demonstrated as the frequency, percentage, mean ± standard deviation (SD), median, and range. All the continuous data were evaluated for normality by the Shapiro–Wilk test. The paired t-test and repeated measured ANOVA were used to compare the mean hair density and hair diameter of each visit. The independent t-test was used to compare the means of the two groups. Nonparametric data were compared using the Mann–Whitney U test. Pearson chi-square test and Fisher's exact test were used to compare the categorical data between the two groups. A P-value of <0.05 was considered to be statistically significant.

RESULTS

Demographic data of the patients

This trial enrolled a total of 26 FPHL patients with a mean age of 38.7 years. At baseline, the patients' demographics and hair loss characteristics were similar between both treatment groups (Table 1). Most of them had grade I hair loss severity on the basis of the Ludwig classification.

TABLE 1. Demographic data of patients with female pattern hair loss treated with 5% azelaic acid and 2% minoxidil topical solution.

	5% Azelaic acid solution (n = 13)	2% Minoxidil solution (n = 13)	P-value
Age, y, mean (SD)	40.1 (6.6)	37.3 (4.2)	0.216
Family history of AGA, n (%)	8 (61.5)	5 (38.5)	0.239
Age of onset, y, mean (SD)	33.5 (7.9)	31.5 (6.0)	0.473
Duration of hair loss, months, median (range)	84 (5 to156)	60 (24 to 156)	0.638
Ludwig classification, n (%)			1.000
Grade I	11 (84.6)	10 (76.9)	
Grade II	2 (15.4)	3 (23.1)	
Baseline hair density, per cm^2, mean (SD)			
Total hair	139.1 (34.3)	158.1 (36.9)	0.419
Terminal hair	109.2 (31.6)	127.7 (34.2)	0.644
Baseline hair diameter, μm, mean (SD)	66.0 (7.7)	65.5 (9.3)	0.548

Hair density and hair diameter

The hair density and hair diameter of the participants treated with 5% azelaic acid and 2% minoxidil solution at each follow-up visit are shown in Table 2. Compared to the baseline, the hair density and hair diameter of both groups significantly increased after two months of treatment. There were no significant differences in the mean percentage of improvement in hair density and diameter between both groups during six months. At the end of the study, the hair density of the 5% azelaic acid solution group and 2% minoxidil solution group increased by 20.4% and 21.1%, respectively. The diameter of the hair improved by 5.3% in the group receiving 5% azelaic acid solution and 7.6% in the group receiving 2% minoxidil solution.

Global photographic review

The investigators assessment of both groups at six months were comparable. Five patients (38.5%) treated with 5% azelaic acid solution showed a mild to moderate improvement in their FPHL (4 mild improvement, 1 moderate improvement), compared with four patients (30.8%) treated with 2% minoxidil solution (1 mild improvement, 3 moderate improvement). Clinical photographs demonstrating the treatment responses after a 6-month period of using 5% azelaic acid solution and 2% minoxidil solution are shown in Fig 1 and Fig 2, respectively.

Patient's own assessment

Regarding the patient's own assessment, 12 patients (92.3%) treated with 5% azelaic acid solution reported an improvement in their hair loss (5 mild improvement, 7 moderate improvement), while 11 patients (84.6%) treated with 2% minoxidil solution reported an improvement (3 mild improvement, 4 moderate improvement, 4 significant improvement) at the end of the study.

Adverse effects

The major reported adverse effect of both 5% azelaic acid and 2% minoxidil topical solution was pruritus, comprising 46.2% of patients in the azelaic acid group and 23.1% in the minoxidil group (Table 3). Most patients in both groups rated only a mild degree of pruritus, which tended to improve over time. One patient treated with 2% minoxidil solution complained of dryness, while one patient treated with 5% azelaic acid solution reported scaling. No patients reported erythema, or a burning or stinging sensation.

TABLE 2. Comparison of hair density and hair diameter at each follow-up visit after treatment with 5% azelaic acid and 2% minoxidil topical solution

	5% Azelaic acid solution (n = 13)		**2% Minoxidil solution (n = 13)**		**Azelaic acid vs. Minoxidil**	**Difference in percentage of improvement between both groups**	
	Mean (SD)	P-value (compared to baseline)	Mean (SD)	P-value (compared to baseline)	P-value	Mean difference	P-value
Total hair density, per cm^2							
Baseline	139.1 (34.3)		158.1 (36.9)		0.186		
2 months	154.7 (37.1)	**0.001**	180.5 (45.9)	**0.001**	0.129	-2.4	0.592
4 months	161.2 (35.5)	**<0.001**	187.0 (45.0)	**<0.001**	0.118	-2.1	0.718
6 months	167.5 (35.0)	**<0.001**	191.5 (39.6)	**<0.001**	0.115	-0.4	0.947
Hair diameter, μm							
Baseline	66.0 (7.7)		65.5 (9.3)				
2 months	68.0 (9.3)	**0.017**	68.1 (8.4)	**0.043**	0.968	-1.5	0.475
4 months	69.4 (7.9)	**0.001**	69.1 (8.0)	**0.010**	0.939	-0.8	0.735
6 months	69.5 (7.9)	**<0.001**	70.5 (9.3)	**0.004**	0.760	-2.6	0.282

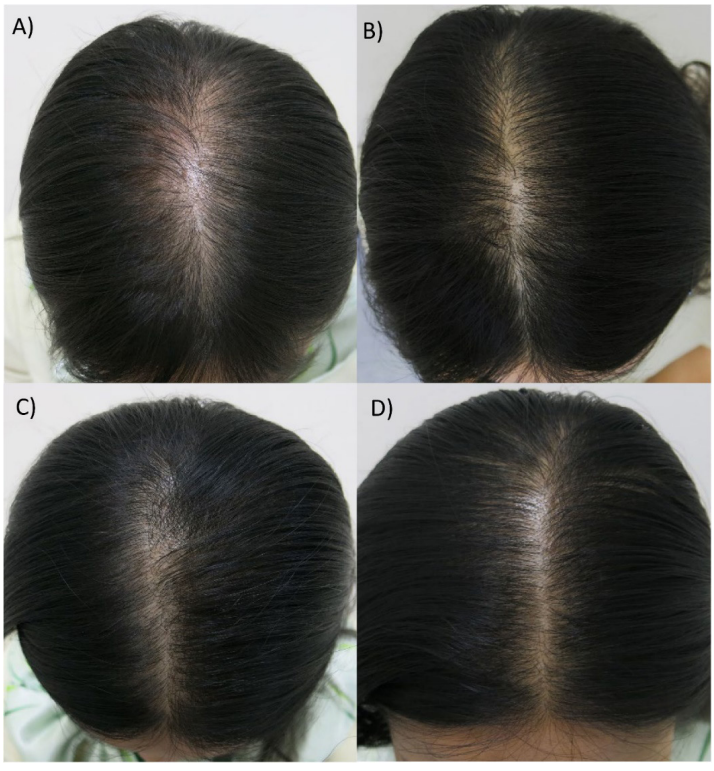

Fig 1. Female pattern hair loss patients (Ludwig grade I) who received 5% azelaic acid solution twice daily for 6 months. Patient No. 1 (**A** baseline, **B** 6 months) and patient No. 2 (**C** baseline, **D** 6months).

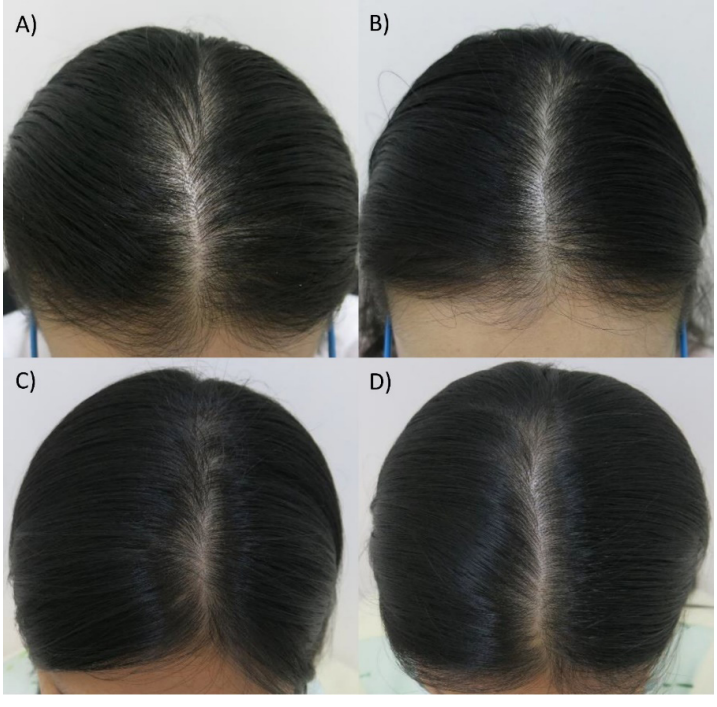

Fig 2. Female pattern hair loss patients (Ludwig grade I) who received 2% minoxidil solution twice daily for 6 months. Patient No. 3 (**A** baseline, **B** 6 months) and patient No. 4 (**C** baseline, **D** 6 months).

TABLE 3. Reported adverse effects from 5% azelaic acid and 2% minoxidil topical solution.

	5% Azelaic acid solution (n = 13)	2% Minoxidil solution (n = 13)
Dryness, n (%)	0 (0)	1 (7.7)
Pruritus, n (%)	6 (46.2)	3 (23.1)
Scaling, n (%)	1 (7.7)	0 (0)

DISCUSSION

According to Stamatiadis et al.'s study, azelaic acid was proved to be a potent inhibitor of 5α-reductase.[14] Moreover, a recent study also demonstrated that azelaic acid could improve telogen to anagen transition and promote hair growth by upregulating *Gli1* and *Gli2* expression and protecting hair bulge cells from ultraviolet B damage.[15] Therefore, azelaic acid might be an effective treatment for AGA. There are many commercial topical preparations containing various concentrations of minoxidil in combination with 5% azelaic acid. A previous randomized controlled study on the efficacy of 5% minoxidil topical solution monotherapy and a combination of 12.5% minoxidil, 5% azelaic acid, and 0.025% betamethasone-17-valerate showed a similar outcome in increasing hair growth between both treatments, but the combination solution significantly decreased hair shedding compared to 5% minoxidil monotherapy.[17] However, evidence of the efficacy of azelaic acid topical solution as a monotherapy for AGA is lacking. Our study was the first randomized clinical study of the efficacy and safety of 5% azelaic acid topical solution in comparison with 2% minoxidil solution in the treatment of FPHL.

Both 5% azelaic acid and 2% minoxidil topical solution significantly increased both hair density and hair diameter at 2, 4, and 6 months of treatment. There were no statistically significant differences between both solutions in every follow-up visit (Table 2). Nonetheless, the increases in hair density and the hair diameter of FPHL patients treated with 5% azelaic acid solution were slightly lower than those with 2% minoxidil solution, which is one of the standard treatments for FPHL. The investigators and patient's own assessments also correlated with both clinical parameters. Regarding GPR, slightly more FPHL patients treated with 5% azelaic acid solution than 2% minoxidil solution were considered to demonstrate mild to moderate improvement at the end of the study. More than half of the patients in both groups rated themselves at least showing a moderate improvement from the baseline condition.

The azelaic acid concentration in commercially available hair formulations, combined with minoxidil solution, varies between 1.5% to 5%. However, the 5% azelaic acid used in our study was lower than typical concentrations used for other dermatologic conditions, such as rosacea, acne, and melasma, which range from 10% to 20%.[13] A higher concentration of azelaic acid might be more effective in improving hair thinning but may also incur an increased risk of adverse events, like pruritus, dryness, stinging, and burning sensation. Further investigations are needed to establish the optimal concentration of azelaic acid for the treatment of FPHL. As mentioned above, the possible mechanisms of azelaic acid in the improvement of FPHL could be that azelaic acid may inhibit 5α-reductase[14] and promote telogen to anagen transition.[15] Its anti-inflammatory property might also be another explanation. In a recent study, it was reported that the pathophysiology of both male pattern hair loss (MPHL) and FPHL may be influenced by the presence of perifollicular inflammation.[18] Azelaic acid could reduce the synthesis of pro-inflammatory cytokines and reactive oxygen species, thus it might be capable of improving PHL.[13]

The US Food and Drug Administration (FDA) has classified azelaic acid as pregnancy category B and can be used in pregnant and breastfeeding women, whereas minoxidil is not recommended due to several reports of fetal abnormalities.[16] According to our study, azelaic acid could be a treatment option for pregnant women with pre-existing FPHL, particularly in patients who have previously received anti-hair loss treatments, in particular, because discontinuation of those treatments in patients who were trying to conceive could further result in a deterioration of hair thinning and finally lead to a negative impact on their quality of life and self-esteem. Thus, 5% azelaic acid topical solution might be a valuable alternative to 2% minoxidil solution for the treatment of FPHL in pregnancy, as not only would it improve FPHL, but it would also relieve stress and be beneficial to the quality of life of patients during pregnancy, as minoxidil is restricted in these patients.

Topical minoxidil could cause transient telogen hair shedding in some patients in the first 8 weeks of treatment.[2] In this study, we expected to find no change or perhaps a slightly worsening in hair density in patients treated with 2% minoxidil at 2 months after treatment. However, our study showed that the hair density in patients treated with 2% minoxidil increased at 2 months and continued increasing throughout the study, similar to a previous study.[19] This suggested that hair shedding following minoxidil therapy might actually resolve before 8 weeks, or the quantity of hair growth might outnumber hair shedding.

In our study, the most common adverse effect was pruritus in both groups of patients. The explanation for this might be due to the inclusion of propylene glycol in both solutions or the active ingredient itself. Propylene glycol is a well-known allergen and irritant that can cause contact dermatitis.[20] Other vehicles or solvents may be used instead of propylene glycol to avoid skin irritation. A previous study showed that the rates of pruritus and dandruff were significantly lower in patients treated

with 5% minoxidil topical foam (propylene glycol-free preparation) than in those treated with 2% minoxidil topical solution.[21] Further investigations are needed to assess the efficacy and safety of different vehicles used in azelaic acid topical preparations in the treatment of FPHL. In our study, pruritus was more commonly observed in patients treated with 5% azelaic acid solution than in those treated with 2% minoxidil solution. This might be because azelaic acid is also a skin irritant and probably causes additional pruritus.

Even though this study was a randomized, double-blind, comparative study, our sample size of 26 patients can be regarded as being relatively small. To accurately determine the effectiveness and long-term safety of topical azelaic acid for the treatment of both MPHL and FPHL patients, a larger sample size with longer research periods is needed in the future.

In conclusion, 5% azelaic acid topical solution might be an effective treatment for FPHL, comparable to 2% minoxidil solution. Furthermore, it could be an alternative treatment for FPHL in pregnant and breastfeeding women. More research on azelaic acid solution is needed to determine the optimal concentration of azelaic acid and the proper vehicles to use in FPHL preparations.

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Factors Related Pain Catastrophizing in Hospitalized Patients with Trauma

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ABSTRACT

Objective: This study aimed to explore the factors related to pain catastrophizing (PC) in hospitalized patients with trauma within 72 hours of injury.

Materials and Methods: The study was a cross-sectional correlation study. The sample was 109 patients who were admitted to ICU Trauma or General Trauma Unit within 72 hours after injury and were aged 18 years and over. They were diagnosed with at least one or multiple organs of injury with a Glasgow Coma Scale (GCS) between 13 and 15. Pearson's product-moment correlation coefficient, spearman rank correlation, point-biserial correlation, and linear multiple regression were used to analyze the data.

Results: The results showed that more than half of the sample was male (67.0%) with the age range from 18 to 91 years. During admission, the subjects complained about pain at moderate to severe levels (68.5%). The prevalence of PC was 11.9%. A few participants (2.8%) experienced anxiety. Also, more than half of them (63.3%) had ADLs in independent to absolutely independent levels. Almost 50.5% of the participants experienced poor sleep quality. Lastly, 49.5% of them were in frailty and pre-frailty conditions. There was a positive relationship between PC and anxiety ($r = .439$, $p < .01$). Finally, anxiety could explain the variance of PC by 19.3% ($F_{1,107} = 25.571$, $P < .001$).

Conclusion: Based on the study findings, the predictor of PC was anxiety. Thus, healthcare providers should assess this factor, in order to provide interventions to reduce high levels of anxiety leading to the prevention of PC occurrences in hospitalized trauma within 72 hours after injury.

Keywords: Pain catastrophizing; theory of unpleasant symptoms; hospitalized patients with trauma (Siriraj Med J 2023; 75: 894-901)

INTRODUCTION

Trauma has become a highly prevalent and leading cause of mortality and morbidity around the world, especially in developing countries. Therefore, it has drawn international attention. As a result of trauma, incidents have become multi-dimensional, affecting health problems in both physical and mental health well-being.[1]

Mainly, trauma even causes pain which is defined as "An upset sensory and emotional experience associated with potential damage".[2] Moderate to severe acute pain occurs due to the tissue injury, particularly pain within 72 hours after trauma events because of the physiological changes.[3]

However, the standard for pain assessment and management has been developed for trauma patients specifically. The remaining severe acute pain during hospital admission through hospital discharge was evidenced.[4] Thus, the predictors or correlated factors of pain severity (PS) were explored commonly to prevent the influencing

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of PS. The interesting factor is pain catastrophizing (PC) because it is defined as a common problem to increase a patient's risk for high PS experience in a wide group of hospitalized trauma patients.[5-7]

PC is defined as a maladaptive cognitive for pain stimulation. It turns the patients to feel negative and induces more PS, including emotional distress.[8] PC was identified as a significant predictor of PS in hospitalized trauma, but studies of PC in Thailand are rare. Theory of Unpleasant Symptoms (TOUS) classifies unpleasant symptoms into four dimensions: distress, severity, quality, and timing and their interaction. Also, the related factors in the dimension of physiological, psychological, situational, and performance factors are defined as the influencing factors of unpleasant symptoms.[9] When studying the unpleasant symptoms of pain among other domains by using TOUS, a significant gap in knowledge was seen.

Previous studies reported the association between PS and severity of injury[4], sex and age[10], frailty[11], sleep quality[5], anxiety[6], and activities of daily living (ADLs).[12] However, the relationship between those variables and PC has been not demonstrated clearly in hospitalized trauma patients in Thailand. Thus, this study aimed to explore the predictors of PC among unpleasant symptoms of severity of injury, frailty, sex, age, sleep quality, anxiety, and ADLs in hospitalized patients with trauma within 72 hours of injury.

MATERIALS AND METHODS

Researchers selected the participants based on the purposive sampling method. The sample size was calculated by the G*power program.[13] The researchers specified effect size as medium ($f^2 = 0.15$), alpha (α) equal to .05 and level of power (β) of .80. The minimal sample size was 103 sample. The participants were admitted to ICU trauma or General Trauma Unit within 72 hours after injury in a university hospital in the metropolitan area of Bangkok, Thailand. They were aged over 18 years and were diagnosed with at least one or multiple organs of injury with a GCS between 13 and 15. The researchers excluded patients who were unable to communicate in Thai, experienced chronic pain, had diagnoses of mental health disorders, or who had critical conditions such as an altered level of consciousness, hemodynamic unstable including oxygen supplement needed with invasive mechanical ventilator requirements.

Instruments

The data collection comprised 6 parts as follows:

1) Demographic data and general information: Researchers collected the demographic data which consisted of age, sex, severity of injury, pain severity, places and times of admission, diagnosis, operation type, and surgery history.

The severity of injury was calculated by the Injury Severity Score (ISS). The overall of ISS is 75 points, and the score is ranked to 4 levels of severity: 1-8 = "minor injury", 9-15 = "moderate injury", 16-24 = "serious injury", and 25-75 = "severe injury".[14]

The Numeric Rating Scale (NRS) was used for pain severity assessment. NRS is a pain screening tool that uses a 0-10 scale with 0 meaning "no pain", 5 meaning "moderate pain", and 10 meaning "the worst pain imaginable". NRC evaluates pain into 4 levels; no pain (0), mild (1-3), moderate (4-6), and severe (7-10).

2) PC was measured by the Pain Catastrophizing Scale (PCS). The total score ranges from 0 to 52, and a total score of 30 and over indicates a clinically significant level of catastrophizing. PCS was translated into the Thai version by Youngcharoen et al. (2017).[15] Cronbach's alpha coefficient was revealed at 0.876.

3) Anxiety symptoms were measured by the Hospital Anxiety Depression Scale (HADS), in part of the Anxiety Sub-scale, which includes 7 items. The total score ranges from 0-21. The cut point is 11; an increase in score indicates a rise in psychological problems. HADS was translated into Thai version by Ninchaikowit et al. (1996).[16] In this study, Cronbach's alpha coefficient level of HADS was seen at 0.70.

4) ADLs was measured by the Barthel Index (BI). The summation of BI is 100, which interprets into 5 levels of daily activity abilities: absolutely dependent to absolutely independent. The instrument was translated into the Thai version by Laohaprasitiporn et al. (2017).[17] Cronbach's alpha coefficient was shown at 0.84.

5) Sleep quality was measured by the Pittsburgh Sleep Quality Index (PSQI). The summation of the PSQI global score ranges from 0-21. The cut-point of sleep problems is greater than 5. An increase in score indicates a high level of sleep problems. The Thai version of the PSQI (T-PSQI) was translated by Tawanchai et al. (1997).[18] T-PSQI had Cronbach's alpha coefficient at 0.70.

6) The researchers used the SHARE (Survey of Health, Ageing and Retirement in Europe) Frailty Instrument (SHARE-FI) to measure frailty condition. There is an SPSS program to calculate frailty automatically. A high overall score means increasing the severity of frailty (Romero-Ortuno et al., 2010). The SHARE-FI question was translated into many languages, including the Thai version. All of those have been provided on the online website.[19,20] The Thai version of SHARE-FI had Cronbach's alpha at 0.74.[21]

Ethical considerations

This research was conducted with proper consideration of human subjects' provision and ethical issues in nursing research. Researchers conducted the data collection under the approval of the Institutional Review Board (IRB), Faculty of Nursing, Mahidol University, and the Siriraj Institution Review Board (SIRB), Faculty of Medicine Siriraj Hospital (MU-MOU-IRB-NS 2022/92.1011). This research had a protocol for pain management. Only 30-40 minutes were requested to complete the questionnaires.

Statistical analysis

All data were analyzed by the Statistical Package for Social Science (SPSS). Demographic data were analyzed by descriptive statistics. Pearson's product-moment correlation coefficient, spearman rank correlation, point-biserial correlation, and linear multiple regression were used to analyze the relationship between PC among related variables.

RESULTS

All trauma admission, there were 109 patients included in this study. Almost all of the sample was male (67.0%). The rest of the patients (33.0%) were female. The average age was 53.9 (SD = 21.33). In detail, almost half (42.2%) of the participants represented older aged adults. The majority of hospitalized trauma patients (88.1%) were admitted to the General Trauma Unit, and the rest of them (11.9%) were included in the Intensive Care Unit of Trauma (Table 1). The period of admission was categorized into 3 categories. Most patients (60.6 %) participated in the research within 24 hours after injury. The organ of injury was described as the top five diseases presented to hospitalized trauma patients including the following: 1) Multiple organs of injuries (24.8%); 2) Orthopedic injuries (22.9%); 3) Head-spine injuries (17.4%); 4) Chest injuries (8.2%); 5) Abdominal injuries (3.7%); 6) Vascular injuries (2.8%), as well as the other injuries (20.2%) (i.e., facial fractures, animal bites, and cut wounds). The mean score of ISS was 10.81 (SD = 7.60). More than half of the patients (56.0%) received conservative treatment for close observation in the hospital. All hospitalized trauma patients presented pain with at least 1 score of PS. The average PS indicated at around 4.9 (SD = 2.54) (Table 2).

Most of the sample (88.1%) had no PC. However, the rest of them (11.9%) experienced PC during hospitalization. The mean score of PCS was 15.84 (SD = 10.72). The ratio of 13 patients who had PC was described as 23.1 % in neurological and orthopedic patients; 15.4% in

TABLE 1. The demographic characteristics of the sample.

Characteristics	Frequency	Percentage (%)
Sex		
Male	73	67
Female	36	33
Year (age)		
Young adults (18-30)	21	19.3
Middle- age adults (31-60)	42	38.5
Older adults (> 60)	46	42.2
Mean = 53.95, SD = 21.32		
Glasgow Coma Score (GCS)		
GCS 15	108	99.08
GCS 13-14	1	0.92
Places of admission		
The ICU	13	11.9
The General Unit	96	88.1
Times of admission		
Within 24 hours	66	60.6
Within 36 hours	37	33.9
Within 72 hours	6	5.5
Mean = 1.45, SD =.601		

TABLE 2. The injury characteristics and treatments of the sample.

Characteristics	Frequency	Percentage (%)
The organ of injuries		
Head-spine injuries	19	17.4
Chest injuries	9	8.2
Orthopedic injuries	25	22.9
Abdominal injuries	4	3.7
Vascular injuries	3	2.8
Other injuries	22	20.2
Multiple organ injuries	27	24.8
Injury Severity Score (ISS)		
Minor injury	37	33.9
Moderate injury	41	37.7
Serious injury	21	19.2
Severe injury	10	9.2
Mean = 10.81, SD = 7.60		
Major treatments		
Non-Operation (Conservative treatment)	61	56.0
Operative treatment	48	44.0
Pain Severity (PS)		
Mild pain	34	31.2
Moderate pain	44	40.4
Severe pain	31	28.4
Mean = 4.99, SD = 2.54		

multiple injuries, chest injuries, and other injuries such as bee sting; as well as the remaining 7.7% in abdominal injured patients. Nonetheless, PC was found mostly in the patients who presented with moderate levels of injury (61.50%) and severe pain (53.80%) (Table 3). A few of the participants (2.8%) reported anxiety experiences with a mean HADS score of 3.63 (SD = 2.97). Participants reported a mean ADLs score of 72.34 (SD = 21.24). Most of the participants (37.8%) reported an independent status of ADLs followed by moderate dependence on the functional status by almost 27.5%. The mean score of PSQI was 5.74 (SD = 2.99). Half of the participants (50.5%) reported sleep problems. The mean score of frail condition was 1.42 (SD = 2.04). Some of the participants (29.4%) indicated frailty.

There was a similarity between PC, anxiety level, sleep quality, and ADLs among the patients in the ICU and the General Trauma Unit. However, the difference was seen when comparing the ISS in both groups of patients. The average score of ISS in ICU patients (mean = 17.47, SD = 11.005), and the General Trauma Unit (mean = 9.91, SD = 6.597) was shown a bit difference (P=.005) (Table 4).

Pearson's Product Moment Correlation, Spearman Rank Correlation, and Point-Biserial Correlation were performed for exploring the association between PC and age, sex, ISS, sleep quality, anxiety, frailty, and ADLs. PC was associated with anxiety positively (r = .439, p < .01).

The model summary by an enter model of linear multiple regressions showed that anxiety could explain the variance of PC by 19.3% (R^2= .193, $F_{(1,107)}$= 25.571, P < .001). In conclusion of the results, when all variables were put into steps in the equation; PC increased by 1.465 points with each 1 score rise in anxiety mood when adjusting for age, sex, frailty, ISS, sleep quality, and ADLs (B = 1.465, P < .001) (Table 5).

TABLE 3. The information of Pain Catastrophizing in each sample's characteristic and treatment.

Characteristics	Frequency	Percentage (%)
Pain Catastrophizing in each injury type (N=13)		
Head-spine injuries	3	23.10
Chest injuries	2	15.40
Orthopedic injuries	3	23.10
Abdominal injuries	1	7.70
Vascular injuries	0	0
Other injuries	2	15.40
Multiple organ injuries	2	15.40
Pain Catastrophizing in each Injury Severity Score (ISS)		
Minor injury	1	7.70
Moderate injury	8	61.50
Serious injury	3	23.10
Severe injury	1	7.70
Pain Catastrophizing in each Major treatment		
Non-Operation (Conservative treatment)	8	61.50
Operative treatment	5	38.50
Pain Catastrophizing in each Pain Severity (PS)		
Mild pain	1	7.70
Moderate pain	2	15.40
Severe pain	10	76.90

TABLE 4. The comparison of ISS, PC, anxiety, sleep quality, and ADLs between the Intensive Care Unit and General Trauma Unit

Variables	ICU Mean (SD)	General Unit p-value	
ISS	17.47(11.005)	9.91(6.597)	.005
PC	16.92 (12.537)	15.70(1.073)	.481
Anxiety	3.85(.750)	3.06 (.308)	.308
Sleep quality	6.31(3.401)	5.67 (2.947)	.547
ADLs	47.31(24.033)	75.73(1.889)	.159

PC mean to Pain Catastrophizing
ISS mean to The Injury Severity Score
ADLs mean to Activities of Daily Living

TABLE 5. The predictors of PC among age, sex, frailty, ISS, sleep quality, anxiety, and ADLs in hospitalized patients with trauma.

Variables	b	Std.Error	Beta	t	Sig
Constant	10.258	6.326		1.621	.108
Age	-.074	.055	-.147	-1.334	.185
Sex	1.941	2.145	.086	.905	.368
ISS	.964	1.042	.088	.925	.357
Sleep quality	.206	.322	.057	.638	.525
Frailty	.406	.555	.077	.732	.466
Anxiety	1.465	.326	.406	4.491	.000
ADLs	-.029	.048	-.057	-.592	.555

ISS mean to The Injury Severity Score
ADLs mean to Activities of Daily Living
R=.439, R^2=.193, Adjust R^2=.185, df (1,107), F=25.571, Sig=P<.001

DISCUSSION

Most results were found to be congruent with previous research findings. For example, the majority group of hospitalized patients with trauma was male, and the characteristics of injury indicated in the injury of multiple organs (multiple injuries).[22] The Injury Severity Score (ISS) was average at a moderate level.[4,23] By following the low to moderate injury, most samples were admitted to the General Trauma Unit more than to the ICU. However, incongruent results were indicated in the mean age. In this study, the average age was older adults, which was not in line with previous studies.[4,5] It can be explained that, globally, society is becoming an aging society, which is related to rising in the geriatric trauma.[24] Also, a higher number of hospitalized traumas received conservative methods as their major treatments; this is opposite to the study result of Yaowares et al. (2020) who showed that the number of at least one-time receiving surgery had higher than conservative treatment.[23] However, there are many antecedents of studies that can offer explanations that support this study's results, in that physicians' considerations nowadays for each organ of injury are becoming conservative strategies.[25-29]

The average PS indicated around 4.99 (SD = 2.54), and more than half of the sample who received operative treatments complained about moderate to severe levels (4-10) of pain experiences. This result is supported by Edgley et al. (2019) who stated that severe pain was related to post-operative procedures in trauma patients.[30,31] Following surgical incisions, patterns of pain behavior showed that both peripheral and central sensitization are stimulated. The mediators, such as prostaglandins, interleukins, cytokines, and neurotrophies are released locally and systemically during and after surgery contribute to the nociceptor sensitization.[32,33]

A few samples experienced anxiety. This psychological problem occurs possibly due to trauma consequences suddenly, which impact a patient's physical health and mental health outcomes.[34] Pre-frailty and frailty were seen at 20.3%, and 29.3%, respectively. This condition was found mostly in the aging population. Its outcome was confirmed by previous studies, which stated that frailty is mostly evident in the aging group.[35,36] More than half of the participants indicated poor sleep quality; there was no significant difference between sleep quality in the two settings bacause the patients may have received care from healthcare providers with similar activities, which may interrupt their sleep time.[37] Most patients were able to perform ADLs independent to moderate dependent ADLs because their severity of injury was at a low to moderate level in the injury severity score.[38,39]

The research hypothesis was supported partially; predicting factors of PC in trauma patients during hospitalization was anxiety. Anxiety was associated with PC.[6,40] Also, it could predict PC significantly. Thus, phenomena could be explained by the following linked

model: Anxiety episodes are accompanied by emotional, cognitive, and physiological changes; these may be linked to the mechanism of PC, which is related to the Behavior Inhibition and Activation System (BIS/BAS) in emotion regulation and cognition control systems. Thus, anxiety occurring may lead to a maladaptive cognitive of pain perception manifestation.[41-43]

CONCLUSION

Based on the study findings by TOUS, the unpleasant symptoms of pain catastrophizing could be predicted by psychological factors such as anxiety in hospitalized trauma within 72 hours after injury. Other factors related to physical impairment such as injury severity, frailty, and decreasing ADLs may not forecast PC. Thus, PC should be prevented in the clinical setting because it is a condition that is independent of physical injury. The nurse is supposed to assess PC and anxiety. The interventions of PC are requested for proper management. Moreover, nurses are supposed to screen anxiety mood as a risk factor and to conduct universal interventions in order to reduce high levels of anxiety in patients, leading to the prevention of PC occurrences.

LIMITATION

This research presented the benefit of identifying a factor related to PC in hospitalized trauma patients, however, a limitation was seen. According to the inclusion and exclusion criteria of the study, the eligible participants were specified only trauma patients without critical conditions such as hypotension, unconsciousness, or hypoxia. Hence, the sample selection processes may be difficult to define as an impartial method and it might impact the outcomes of injury severity and PC. As a result, the researchers suggest that future research should be studied on PC by using a random sampling method to avoid sampling bias.

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Conflict of interest

The authors have no conflict of interest.

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Assessing Low-Concentration Atropine in Myopia Progression: A Systematic Review

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ABSTRACT

Objective: Low-concentration atropine (LCA) eye drop is used as a promising treatment for the management of myopia but its effectiveness has not been widely evaluated. Therefore, this study aimed to analyze the efficacy of LCA eye drop for myopia progression.

Materials and Methods: This review was conducted following the PRISMA guidelines and a comprehensive literature search was performed on 3 online databases including PubMed, Cochrane, and ProQuest. The keywords used included 'Low-concentration atropine eye drop', 'Atropine', 'Eye Drop', 'Myopia', and their Mesh. All studies included were available in English and full-text format. Myopia progression rates were analyzed from all studies, and Rayyan, an online-based tool was used in the screening process.

Results: The results showed that 3 randomized control trials (RCT), 2 cohort studies, and 3 case reports with a total of 1389 participants were analyzed. The majority studies were conducted in Asia, while one RCT was performed in Australia. The participants ranged from 4-12 years old, while atropine eye drop concentrations used were 0.01%, 0.025%, 0.05%, 0.1%, 0.125%, and 0.2%. All studies showed a slower progression rate of myopia in the atropine group compared to the control (-0.31 D vs. -0.90 D; -0.05 D vs. -1.05 D; -0.27 D vs. -0.81 D; -0.28 D vs. -0.54 D; -0.36 D vs. -0.90 D;−0.31 D vs. −0.76 D; -0.31 vs. -0.53 D; -0.38 D vs. -0.55 D) with $P < 0.05$.

Conclusion: LCA eye drop showed promising effects in slowing myopia progression. However, further investigation is needed, particularly in non-Asian countries.

Keywords: Low-concentration atropine eye drop; myopia; children (Siriraj Med J 2023; 75: 902-908)

INTRODUCTION

Myopia is one of the most frequent refractive disorders and is expected to become increasingly prevalent globally, affecting nearly 5 billion people with 1 billion having high-severity cases.[1] The prevalence among 6-7-year-old children in Taiwan and Singapore ranges from 20% to 30%, reaching levels of 84% among high school students in Taiwan.[2] This growing incidence indicates a rising epidemic in developed regions of East and Southeast Asia,[3] making it a significant public health issue that should not be underestimated.

Myopia is characterized by abnormal elongation of the eyeball, even with the use of refractive lenses or surgical interventions. The severity can ultimately lead to blindness and significantly affect children's quality of life.[2] Several methods have been implemented to manage the progression of myopia, including progressive bifocal glasses, peripheral defocus and contact lenses, orthokeratology, multifocal contact lenses, and pharmacological agents.[4] Atropine, a nonselective muscarinic antagonist, has shown efficacy in inhibiting myopia progression, with several studies examining different concentrations, from the lowest (0.01%), to moderate (0.01%-0.5%), and high (1%).[5,6]

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Previous studies reported that the use of high-concentration atropine may result in adverse effects such as blurred vision, reduced accommodation, and glare. Optimal concentrations of low-concentration atropine (LCA) were proposed for inhibiting myopia progression, but the efficacy has not been widely evaluated. Therefore, this study aimed to analyze the efficacy of LCA eye drop in inhibiting myopia progression.

MATERIALS AND METHODS

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline.[7] A comprehensive literature search was performed on 3 online databases namely PubMed, Cochrane, and ProQuest. The inclusion criteria for studies included (1) the population focused on children with myopia, and (2) used LCA eye drop. Meanwhile, the exclusion criteria were: (1) studies not conducted written English language, (2) full publication was unavailable, and (3) reviews. Three independent reviewers conducted the search, and the keywords used were 'Low concentration atropine eye drop', 'Atropine', 'Eye Drop', 'Myopia', and their corresponding Mesh terms. The search, conducted up to March 17th, 2023, used terms adapted to fit the requirements of each database, without any publication year filter. The screening process was carried out with Rayyan, an online-based tool.[8] Blinding was maintained until each reviewer completed the screening process, and any disagreements were resolved by discussion.

The myopia progression in children was analyzed across all included studies. This condition was defined as spherical equivalent (SE) change after 12 months of treatments. The following data were extracted from each study: authors, year of publication, design, country, number of samples, patient demographics, intervention given, comparison, myopia progression rate, and side effects.

The risk of bias assessment was conducted by three reviewers using version 2 of the Cochrane risk of bias tool (RoB 2) for randomized controlled trial (RCT) included in this review.[9] The quality of the case-control and cohort studies was assessed using the Newcastle-Ottawa Scale.[10] All reviewers independently conducted the assessment and extracted the data.

RESULTS

The search identified 36 articles from the databases but after removing duplicates and conducting the screening process, this review included 8 studies consisting of 3 RCT, 3 case controls, and 2 cohort studies. A total of 23 irrelevant articles and 1 written in the Russian language were excluded (Fig 1). About 1389 samples of myopic children were included in this review. The studies were conducted in various locations, with the majority coming from Asia, and 1 RCT from Australia.

The characteristics presented in Table 1 showed that each study had a different age range, except for Wu PC et al., and Lee CY et al., which had the same range (6-12 years old). Jeon GS et al., and Lee SS et al., had a 10-year gap between the youngest and oldest patients.

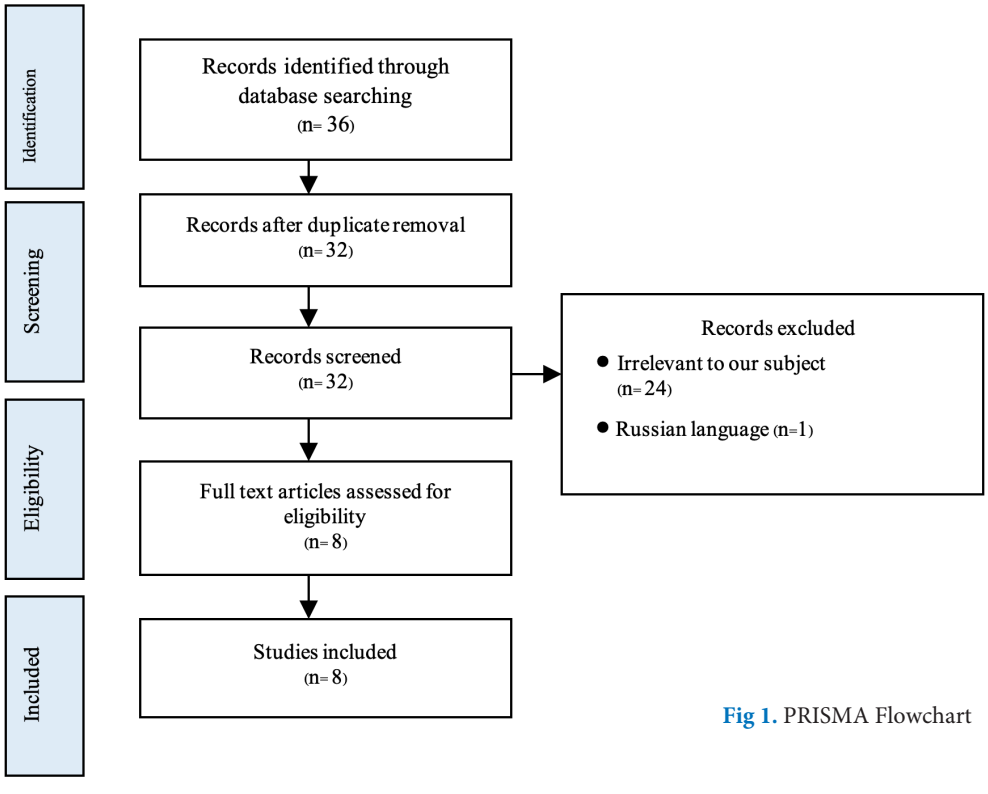

Fig 1. PRISMA Flowchart

TABLE 1. Study result.

Author	Year	Country	Study design	Follow up (yr)	Number of samples	Age	Intervention	Comparison/ Control	Mean Myopia Progression (D)		
									IG	CG	p-value
Wu PC, et al	2011	China	Case-control	≥ 3 years	117 • 97 IG • 20 CG	6-12	AED 0.05 -0.1%[a]	No treatment	-0.31 ± 0.26	-0.90 ± 0.30	*p* <0.001
Lee CY, et al	2016	Taiwan	Case-control	1 year	56 • 32 AED 0,125% • 12 AED 0,25% • 12 CG	6-12	- AED 0.125% - AED 0.25%	Spectacle	-0.05 0	-1.05	*p* >0.025
Yam JC, et al	2018	Hong Kong	RCT	1 year	438 • 109 AED 0,05% • 108 AED 0,025% • 110 AED 0,01% • 111 CG	4-12	- AED 0.01 % - AED 0.025% - AED 0.05%	Placebo ED (0.9% sodium chloride)	- 0.59 ± 0.61 - 0.46 ± 0.45 -0.27 ± 0.61	- 0.81± 0.53	*p* <0.001
Chuang MN, et al	2021	Taiwan	Cohort	10 years	23 • 15 IG • 8 CG	5-9	AED 0.05-0.1%	AED 0,25-0.5%	− 0.28 ± 0.43	-0.54 ± 0.58	*p* <0.001
Jeon GS, et al	2021	South Korea	Cohort	1 year	68 • 37 IG • 31 CG	5-15	AED 0.01%[b]	AED 0.01%[c]	-0.36 ± 0.17	-0.90 ± 0.22	*p* <0.001

TABLE 1. Study result. (Continue)

Author	Year	Country	Study design	Follow up (yr)	Number of samples	Age	Intervention	Comparison/ Control	Mean Myopia Progression (D) IG	CG	p-value
Jethani J	2021	India	Case-control	2 years	60 • 30 IG • 30 CG	4-12	AED 0.01%	No treatment	-0.31 ± 0.3	-0.76 ± 0.4	*p* <0.05
Lee SS, et al	2022	Australia	RCT	2 years	153 • 104 IG • 49 CG	6-16	AED 0.01%	Placebo ED	-0.31 (95% CI = -0.39 to -0.22)	-0.53 (95% CI = -0.66 to -0.40)	*p*= 0.004
Yam JC, et al	2023	Hong Kong	RCT	2 years	474 • 160 AED 0,05% • 159 AED 0,01% • 155 CG	4-9	AED 0.01% AED 0.05%	Placebo ED (0.9% sodium chloride)	- 0,38 (-0.46 to -0.30) -0.11 (-0.18 to -0.04)	-0.55 (-0.64 to -0.45)	*p* <0.001

Abbreviations: yr: year, D: diopter, IG: intervention group, CG: control group, AED: atropine eye drop, RCT: Randomized controlled trial

[a]If myopia progression was > -0.5 D at 6 months follow-up, the concentration was increased to 0.1% AED

[b]if SE progression ≤ 0.50 D after 12 months of treatment

[c]if SE progression > 0.50 D after 12 months of treatment

All studies stated there were no significant differences among groups in terms of demographics.[3,11-17] The follow-up period varied from 1 to 10 years and LCA eye drop was used within a range of 0.01% to 0.5%, specifically once daily at night. In the studies conducted by Chuang MN et al., and Jeon GS et al., the control group also received the atropine eye drop, either in a higher concentration or included a subgroup of poor responders (SE progression > 0.50 D after 12 months of treatment). However, others used a placebo eye drop, spectacles, or implemented no treatment at all within the control group.

The mean myopia progression rates presented in Table 1 showed that although some studies had a follow-up period of more than one year, only the first-year report was included, with all showing better outcomes in LCA group. In the case of Chuang MN et al., where both groups received LCA eye drop, the intervention group exhibited a significantly higher rate of myopia progression.

All studies reported minimal side and adverse effects, with Yam et al., (2018) showing photophobia in LCA 0.05%, 0.025%, and 0.01% groups at a rate of 7.8%, 6.6%, and 2.1%, while another study in 2023 found a similar case in LCA 0.05% and 0.01% groups at a rate of 20.6% and 20.9%, respectively. Lee SS et al. reported a total of 9 adverse events in the treatment group (8.7%), but none were classified as severe. Among these, only 3 were related to LCA including two cases of sore or heavy-feeling eyes and one case of blurred near vision.

The critical appraisal results for each study, based on their respective designs, are presented in Tables 2, 3, and 4. Table 2 shows the assessment results for RCT, all of which indicated a 'low risk' of bias, while Table 3 presents the quality assessment outcomes for the case-control. Two studies achieved high scores, with a total of 9 and 8, indicating good quality. However, the study by Jethani J was rated as 'fair quality,' receiving only 2 stars in the selection domain. Table 4 showcases the quality of the cohort studies, all of which received high scores of 9 and 8.

TABLE 2. Risk of bias assessment using RoB 2.0.

No	Study	Domain 1 (Risk of bias arising from the randomization process)	Domain 2 (Risk of bias due to deviations from the intended interventions)	Domain 3 (Missing outcome data)	Domain 4 (Risk of bias in the measurement of the outcome)	Domain 5 (Risk of bias in selection of the reported result)
1	Yam JC, et al	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
2	Lee SS, et al	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
3	Yam JC, et al	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

TABLE 3. Quality assessment using Newcastle-Ottawa Scale for Case-Control Studies.

No	Author	Selection				Comparability	Outcome			Total Quality
		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 controlled for confounders	Ascertainment of exposure	The same method of ascertainment for cases and controls	Non-response rate	
1	Wu PC, et al	★	★	★	★	★★	★	★	★	9
2	Lee CY, et al	★	★	★	★	★★	★	★	-	8
3	Jethani J	★	★	-	-	★★	★	★	★	7

TABLE 4. Quality assessment using Newcastle-Ottawa Scale for Cohort Studies.

No	Author	Selection				Comparability		Outcome		Total Quality
		Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up cohorts	
1	Chuang MN, et al	★	★	★	★	★★	★	★	★	9
2	Jeon GS, et al	★	★	★	-	★★	★	★	★	8

DISCUSSION

A recent healthcare breakthrough for myopia control, known as LCA, has been subjected to extensive investigations to optimize its effectiveness and safety. Despite some studies reporting p values > 0.001, the majority consistently showed promising results in slowing myopia progression. Lee CY et al. found that the use of LCA at 0.25% culminated in no significant myopia progression ($p > 0.025$). According to Wu PC et al., Chuang MN et al., and Yam JC et al., (2018 and 2023), the 0.05% concentration was more effective than 0.1% in myopia control. Chuang MN et al., and Jeon GS et al., also incorporated a control group receiving LCA.

The ATOM studies using the 1% atropine eye drop have shown its efficacy in slowing the progression of myopia in children. However, the use of high concentration was reportedly associated with side effects such as photophobia, glare,[18] and narrow-angle glaucoma resulting from its anticholinergic properties. Photophobia, mydriasis, blurred vision, and systemic side effects such as allergic dermatitis, dry mouth, difficulty swallowing, and warm or red skin have also been reported with high-concentration atropine use.[12,19] However, LCA treatment is both effective in slowing myopia progression and is associated with minimal side effects. The most commonly reported mild symptoms include glare and blurred vision. Compared to higher concentrations of atropine, such as the 0.5% used in the ATOM 2 study, low concentrations exhibit a lower incidence of side effects such as eye discomfort and photophobia.[20] The majority of studies in this review consistently reported that all concentrations of LCA were well-tolerated. The 0.05% and 0.1% concentrations induced only mild to moderate pupil dilation (mydriasis) compared to the full dilation by 1% atropine. LCA may induce less photophobia, thereby making it a more suitable option for long-term use in retarding myopia progression.

All included studies had varying follow-up durations, with some reaching over a period of one year, including Jeon GS et al., Lee CY et al., and Yam JC et al., (2018). Several others extended their evaluation to two years, such as Lee SS et al., and Jethani J, while some continued for more than two years, reaching four and ten years by Wu PC et al., and Chuang MN et al., respectively. Based on the results, the effects of LCA on myopia progression can be assessed early in the first year of medication. In studies with longer time spans, significant effects were observed in the first and fifth years.[14] To standardize the duration, only the mean myopia progression in the first year of treatment was considered. This pattern may also be affected by the mechanism of atropine action.

Atropine functions to slow myopia progression through non-accommodative mechanisms, including the regulation of muscarinic receptors in the retina, choroid, and sclera.[12] It increases choroidal thickness in children by regulating dopamine release, associated with reducing axial eye growth,[19] and may also have biochemical effects on the retina or sclera.[13] However, the anti-myopia mechanisms of atropine are not fully understood, necessitating the need for further studies.

Despite the widespread use of LCA in routine ophthalmological and optometric practices both in the United States and globally, the majority of the included studies were conducted in Asia, while 3 were from other continents. Lee SS et al. (Australia) and McCrann et al. (Ireland) reported significant reductions in myopia

progression with the use of LCA eye drop, while Repka et al. (USA) found that the treatment did not yield a significant result.[16,21,22] The limited representation from Western countries showed the necessity for further investigation to comprehensively evaluate the efficacy of LCA in these regions.

There are several limitations to this study, first, there was a lack of data on LCA from other regions outside Asia. This was attributed to the factors affecting myopia progression, such as sunlight exposure, environmental effects, and ethnicity, according to Lee SS et al. Some studies did not explore the potential effect of demographic differences, sunlight exposure, and activities on the effectiveness of LCA. Further investigation is also needed to understand the correlation between LCA and ethnicity. These factors may introduce bias in assessing the effectiveness of the used atropine concentration. The second limitation was the absence of control groups in some studies, limiting the extent of the evaluations conducted. Finally, half of the studies had a small sample size that did not fully represent the total results.

CONCLUSION

In conclusion, LCA eye drop showed high effectiveness in controlling myopia progression. Healthcare professionals should prioritize patient comfort and safety by minimizing the side effects. However, further investigation was needed, particularly in non-Asian countries.

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Efficacy of Pregabalin, Solifenacin, or Combination therapy for Ureteral Stent Related Symptoms: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: The Double-J (DJ) ureteral stent is essential in urology but can lead to Ureteral Stent-Related Symptoms (USRS), prompting research into various therapies to enhance patient comfort. The purpose of this study is to assess the efficacy of pregabalin, solifenacin, or combined therapy on ureteral stent-related symptoms.

Materials and Methods: We conducted thorough searches in four databases, which included PubMed, Cochrane, EBSCO, and ProQuest. PRISMA Guideline 2020 was applied in this study. The risk of bias was assessed using Newcastle-Ottawa Scale and Cochrane Risk of Bias 2.0.

Results: Ten studies consisting of 1477 participants were included in this study. Solifenacin monotherapy could significantly decrease total USSQ (mean difference (MD) -16.62; p=0.001), urinary symptoms (MD -9.16; p=0.002), and sexual matters (MD -0.81; p=0.002). Pregabalin monotherapy could significantly decrease pain (MD -7.29; p<0.00001). Compared to solifenacin monotherapy, combination therapy of pregabalin and solifenacin could significantly decrease total USSQ (MD -12.40; p <0.0001), urinary symptoms (MD -1.88; p=0.007), pain (MD -6.82; p<0.00001), sexual matters (MD -0.77; p <0.00001), and additional problems (MD -1.51; p=0.0007).

Conclusion: Combination therapy of pregabalin and solifenacin had the best advantages in lowering USRS, especially urinary symptoms, pain, sexual matters, and some other additional problems.

Keywords: Double-J ureteral stent; lower urinary tract symptoms; pregabalin, solifenacin; ureteral Stent related symptoms (Siriraj Med J 2023; 75: 909-923)

INTRODUCTION

Ureteral stents are utilized in more than 1.5 million people globally each year.[1,2] They are commonly employed in urological procedures and play a pivotal role in maintaining urinary flow while facilitating postoperative recovery.[3] They are implanted for a short period of time to ease ureteral obstruction, avoid ureteral strictures, encourage healing, and manage urine leakage.[4] However, they frequently introduce a range of discomforting symptoms, collectively referred to as Ureteral Stent-Related Symptoms (USRS). These symptoms, which encompass pain, urinary frequency, urgency, and hematuria, can significantly diminish patients' quality of life and impede their postoperative rehabilitation.[5]

While pregabalin is primarily recognized by the FDA as a gamma-aminobutyric acid (GABA) medication for diabetic neuropathy, central pain, and headaches, emerging research suggests it may also be effective in alleviating

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lower urinary tract symptoms (LUTS).[6] Solifenacin, an antimuscarinic medication, is licensed for the treatment of overactive bladder. Recent studies have indicated that USRS has improved and that it can be used to relieve symptoms after ureteroscopy and lithotripsy.[7]

This systematic review and meta-analysis aim to synthesize existing evidence, critically assess the strengths and limitations of individual studies, and provide a comprehensive overview of the current state of knowledge regarding these interventions.

MATERIALS AND METHODS

Protocol registration and literature search

This systematic review and meta-analysis have been registered in PROSPERO under the registration number CRD42023451928, and the study will strictly follow the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020.[8] A comprehensive literature search will be conducted in electronic databases such as PubMed, EBSCO, ProQuest, and the Cochrane Library, until agust 2023. The search strategy will involve a combination of medical subject headings (MeSH terms) and relevant keywords, including "ureteral stent", "stent-related symptoms", "Pregabalin","Solifenacin", "combination therapy", and "randomized controlled trial". The search will be limited to articles published in English.

Eligibility criteria

The inclusion criteria for this study were patients diagnosed with USRS, which involved pregabalin/solifenacin monotherapy or combination, randomized controlled trials, observational, cohort, and case control studies, and published in the English language. The exclusion criteria were insufficient data reporting or unavailable full-text articles, case reports, letters to the editor, and proceeding abstract conferences.

Data extraction

The data extraction process was independently conducted by 3 reviewers. The data extraction included the author's name, year of publication, the mean age of respondents, country of origin, provided intervention, number of respondents, outcomes (Ureteral Stent Symptom Questionnaire - USSQ), duration of follow-up, and conclusion. USSQ is a valid reliable multidimensional questionnaire to assess ureteral stent symptoms and their impact on quality of life.[3]

Quality assessment

Five reviewers were involved in assessing the biased quality of the studies. For cohort and case-control studies, we utilized the Newcastle-Ottawa Scale (NOS), a widely used tool for evaluating the quality of non-randomized studies. On the other hand, for randomized studies, we employed the Cochrane Risk of Bias Tool 2.0. This tool evaluates five domains, which include the randomization process, bias arising from deviations in the intervention, bias due to incomplete outcome data, bias from the methods of outcome measurement, and bias related to outcome selection and reporting.

Meta analysis

Quantitative data will be collected using the Cochrane Collaboration application called Review Manager 5.4. For the analysis of the primary outcome using continuous data, we included the mean difference (MD) and a 95% confidence interval (CI). A p-value below 0.05 was considered statistically significant. In this meta-analysis, heterogeneity among studies will be assessed using I^2 (I^2; Inconsistency). The heterogeneity will be considered high if I^2 >50%, moderate if I^2 26-50%, and low if <26%. A P-value of < 0.05 is considered statistically significant.

RESULTS

Literature search

Fig 1 provides a comprehensive flow diagram that outlines the study selection process, including subsequent exclusions made during the review. In four databases, the search keyword turned up a total of 101 studies. After deleting the duplicate records, 80 records were screened and 15 were evaluated for eligibility. In total, we included 10 full-text English studies from eight different countries (Saudi Arabia, Greece, Taiwan, Iran, Egypt, Korea, China, and India) in the systematic review, and of these studies, six were included in the meta analysis.

Data extraction

The design of the studies included one non randomized prospective study and nine randomized controlled trials (RCTs). This study consisted of 1477 participants. The mean age of participants in groups ranged from 29.5 to 53.8. Intervention groups were solifenacin, pregabalin, solifenacin and pregabalin, and control or placebo. Dosage of pregabalin was 75 mg twice a day. Dosage of solifenacin varied between 5 mg a day or 10 mg a day. The literature described no significant difference in dosage 5 mg and 10 mg for ureteral stent symptoms, thus we included both dosages in meta analysis.[9] Duration of intervention was within two to four weeks.

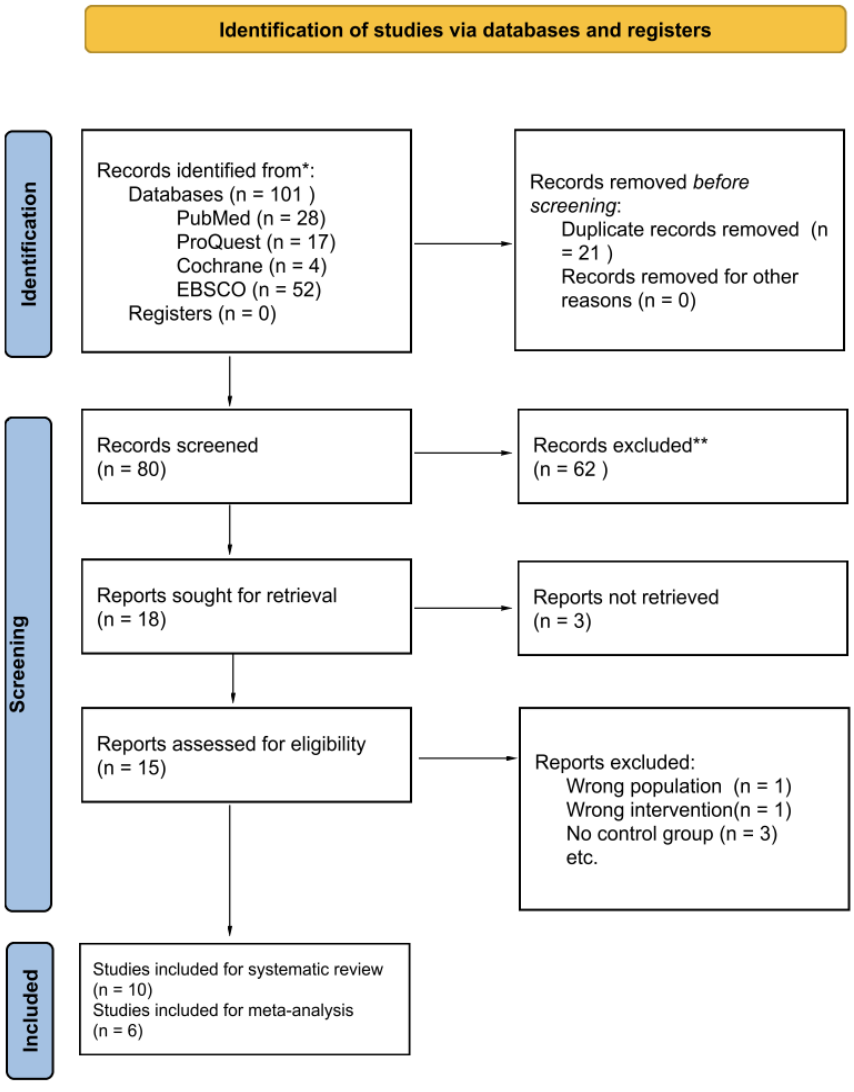

Fig 1. PRISMA flowchart 2020 of the included studies.

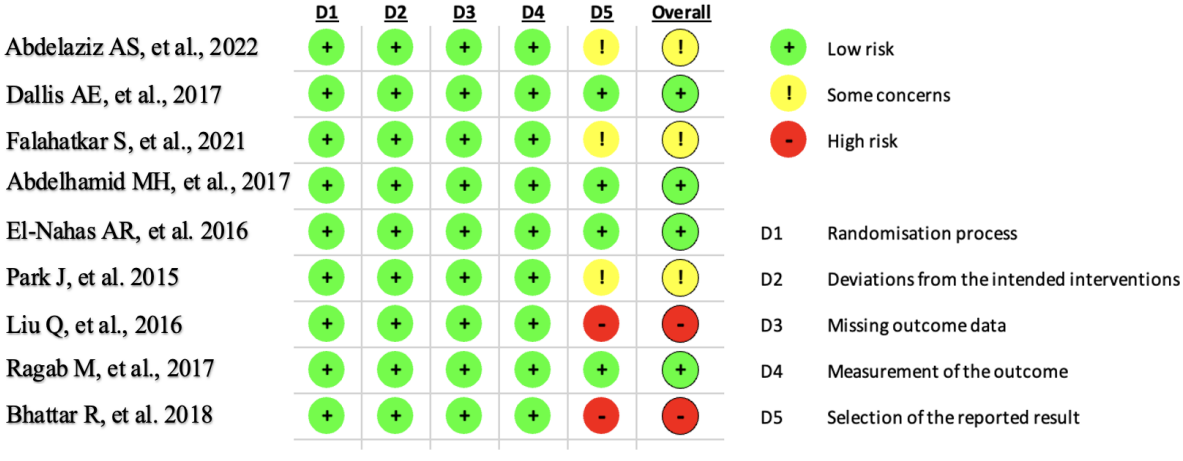

Fig 2. Cochrane risk of bias 2.0 for randomized controlled trial

Risk of bias assessment

The risk of bias assessment for randomized controlled trials (RCTs) is presented in Fig 2. Four studies indicated a low risk of bias, and 2 studies indicated a high risk of bias. The risk of bias assessment for non-RCT studies is presented in Table 2. According to the assessment using the Newcastle Ottawa Scale (NOS), it showed a low risk of bias.

TABLE 1. Baseline characteristic of included studies.

Author, year	Country	Design of Study	Drugs	Age (mean)	Total of Respon-dents	Diameter/Length of ureteral stent	Indication of the Ureteral Stent	Duration of Inter vention	Outcome	Side effect
Abdelaziz AS, et al., 2022.[10]	Saudi Arabia	RCT	Solife nacin 5 mg Well hydration	36.6 38.1	63	Diameter: 6 Fr, length: 24-28 cm (polyurethane DJ-stent)	Rigid URS, RIRS	2 weeks	USSQ	Consti pation, dry mouth
Dallis AE, et al., 2017.[11]	Greece	RCT	Solife nacin 5 mg Placebo	49.8 47.8	120	Diameter: 6F, length: 24-26 cm (Percuflex plus, Boston Scientific, Natick, MA)	ESWL, uretero scopy treatment, hydrone phrosis	4 weeks	USSQ	NA
Lee YJ, et al., 2013.[12]	Taiwan	Prospec tive non ran domized Control	Solife nacin 10 mg 53.4	53.8	140	Diameter: 6-7 Fr, length: 22-26 cm (Polyurethane by Cook Ireland Ltd)	URS lithotripsy	2 weeks	USSQ	Urinary retention, dry mouth, constipa tion, headache
Falahat kar S, et al., 2021.[13]	Iran	RCT	Prega balin 75 mg BID Solife nacin 5 mg Combi nation of pre gabalin and solife nacin Control	43.5	256	NA	URS	4 weeks	USSQ	Flushing, dry mouth, drowsi ness, dizziness, body pain, headache Dry mouth, drowsi ness, dizziness, body pain Flushing, dry mouth, drowsi ness, dizziness, headache
Abdelha mid MH, et al., 2017.[14]	Egypt	RCT	Solife nacin 10 mg Placebo	38 39.7	140	Diameter: 5-8 Fr, length 24-28 cm (polyurethane double-loop ureteral stent, Coloplast, Germany)	URS lithotripsy	2 weeks	USSQ	constipa tion, dry mouth, headache

TABLE 1. Baseline characteristic of included studies. (Continue)

Author, year	Country	Design of Study	Drugs	Age (mean)	Total of Respon-dents	Diameter/Length of ureteral stent	Indication of the Ureteral Stent	Duration of Inter vention	Outcome	Side effect
El-Nahas AR, et al., 2016.[15]	Egypt	RCT	Solifenacin 5 mg Placebo	39.6 40.8	87	Diameter: 6 F, length: 24-26 cm. (PercuflexÂ®, Boston Scientific, Marl-borough, MA, USA)	Calcular obstruction, post uretero scopy	2 weeks	USSQ	NA
Park J, et al., 2015.[16]	Korea	RCT	Solifenacin 5 mg Control	51.2 48.7	43	Diameter: 6F, length: 20-28 cm. (Percuflex®, Boston Scientific)	Post-uretero scopy	2 weeks	USSQ	NA
Liu Q, et al., 2016.[17]	China	RCT	Solifenacin 5 mg Control	41.6 40	54	Diameter: 4.7 Fr, length: 26 cm. (NLAY®, Bard Inc)	Before and after flexible uretero scopy	2 weeks	USSQ	Dry mouth
Ragab M, et al., 2017.[3]	Egypt	RCT	Solifenacin 5 mg Pregabalin 75 mg BID Combination of pregabalin and solifenacin Control	38.7 40.3 39.2 39.6	489	Diameter: 6 F, length: (Percuflex®, Boston Scientific)	Post URS	2 weeks	USSQ	Dry mouth, flushing, somnolence, headache Somnolence, headache, drowsiness dry mouth, flushing, somnolence, headache, drowsiness, body pain
Bhattar R, et al., 2018.[18]	India	RCT	Solifenacin 10 mg Placebo	29.9 29.5	85	Diameter: 6 F, length: not mentioned. (Polyurethane)	Patient underwent PCNL and URS	2 weeks lithotripsy	USSQ	NA

TABLE 2. Newcastle Ottawa Scale for Cohort (NOS).

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	Lee YJ, et al. (2013)	1	1	1	1	1	1	1	1	8

Meta analysis

Solifenacin monotherapy

Six studies are included in the meta analysis of solifenacin vs control. Total USSQ was significantly lower in the solifenacin group (MD -16.62; 95% CI, -26.59 to -6.66; p=0.001). Among all USSQ subgroup analyses, solifenacin could significantly decrease urinary symptoms (MD -9.16; 95% CI, -14.83 to - 3.49; p=0.002) and sexual matters (MD -0.81; 95% CI, -1.33 to -0.30; p=0.002). The heterogeneity was high in all subgroup studies. Detailed meta analysis of solifenacin vs control is presented in Fig 3. Solifenacin monotherapy funnel plots of bias are presented in Fig 4.

Pregabalin Monotherapy

Two studies are included in the meta analysis of pregabalin vs control. Total USSQ was lower in the pregabalin group but not significant (MD -10.78; 95% CI, -22.23 to 0.68; p=0.07). Among all USSQ subgroup analyses, pregabalin could significantly decrease pain (MD -7.29; 95% CI, -9.05 to -5.53; p<0.00001). The heterogeneity was high in subgroup studies of urinary symptoms, pain, general health, sexual matters, and additional problems. A detailed meta analysis of pregabalin vs control is presented in Fig 5. Pregabalin monotherapy funnel plots of bias are presented in Fig 6.

Combination therapy versus solifenacin monotherapy

Two studies are included in the meta analysis of pregabalin and solifenacin vs solifenacin monotherapy. Total USSQ was significantly lower in the combination group (MD -12.40; 95% CI, -18.58 to -6.23; p<0.0001). Among all USSQ subgroup analyses, combination therapy could significantly decrease urinary symptoms (MD -1.88; 95% CI, -3.25 to -0.52; p=0.007), pain (MD -6.82; 95% CI, -7.30 to -6.35; p<0.00001), sexual matters (MD -0.77; 95% CI, -0.99 to -0.55; p<0.00001), and additional problems (MD -1.51; 95% CI, -2.39 to -0.64; p=0.0007). The heterogeneity was high in subgroup studies of urinary symptoms, general health, work performances, and additional problems. A Detailed meta analysis of pregabalin and solifenacin vs solifenacin is presented in Fig 7. Combination therapy and solifenacin monotherapy funnel plots of bias are presented in Fig 8.

DISCUSSION

Numerous physio-pathological disorders or illnesses may block the upper urinary tract. The cause of blockage might be extramural, such as severe urological or non-urological neoplasia, or intraluminal, such as renal or ureteral stones, ureteral strictures, or papillary urothelial neoplasms.[1] An observational study described stenting and post-operative care could resolve post operative problems. Ureteral stent was introduced in the 1960s to bypass this blockage temporarily. It is a long tube device with a J-shaped (or known as a pigtail) on both sides to anchor in the kidney and bladder.[1]

The precise cause of USRS remains uncertain, but the prevailing understanding attributes it primarily to the stent's mechanical irritation of the ureter and bladder's trigonal area. This irritation leads to disturbances in ureteral peristalsis, detrusor spasms, inflammation of the bladder mucosa, and urine reflux into the kidney.[19,20] More than 80 percent of patients with USRS, including discomfort and storage symptoms can reduce their quality of life (QoL), despite the fact that most ureteral stents help patients improve drainage.[21]

In this meta analysis, solifenacin significantly reduces

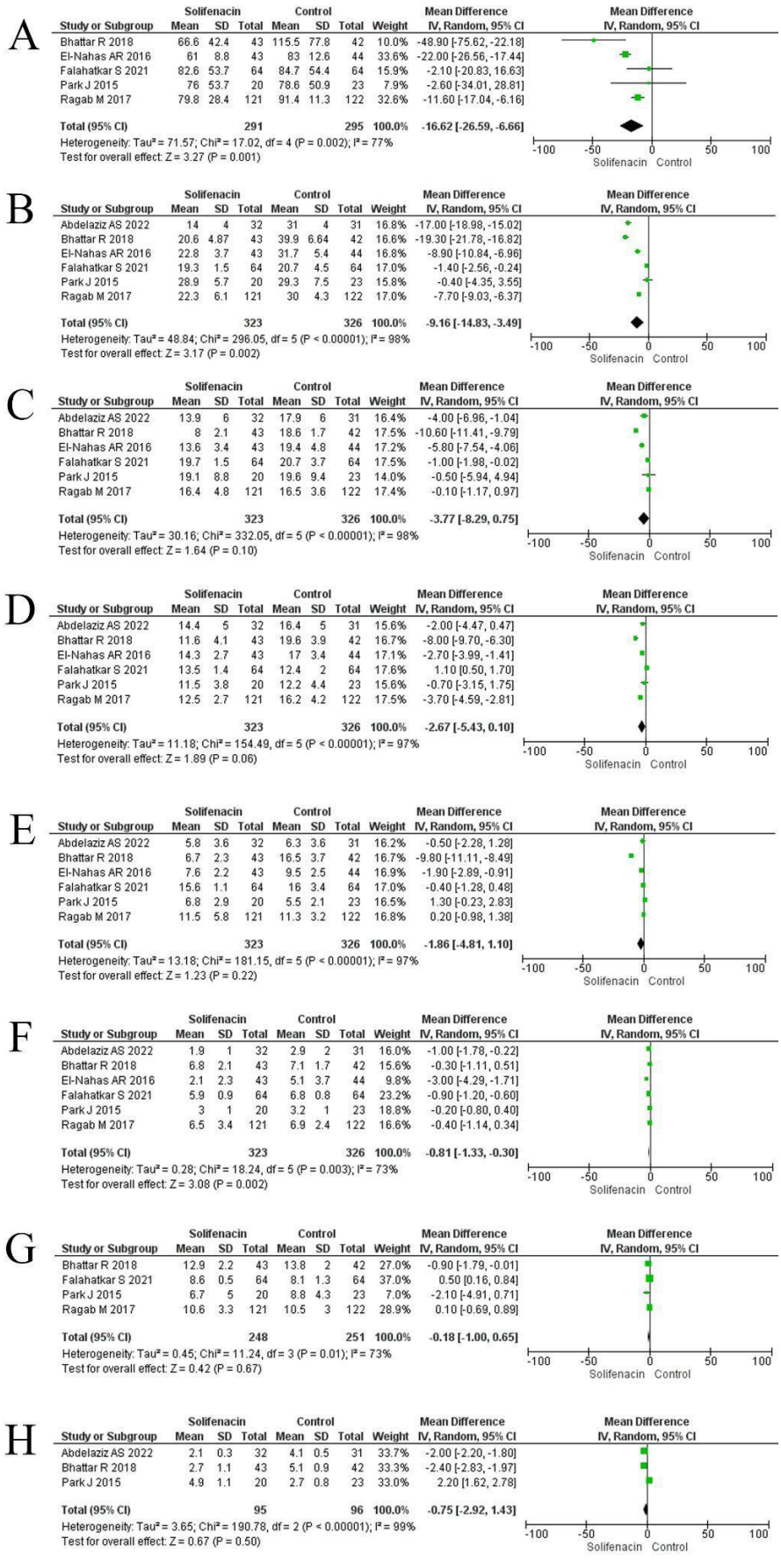

Fig 3. Forrest Plot Solifenacin vs Control. A: Total USSQ. B: Urinary Symptoms. C: Pain. D: General Health. E: Work Performance. F: Sexual Matters. G: Additional Problems.

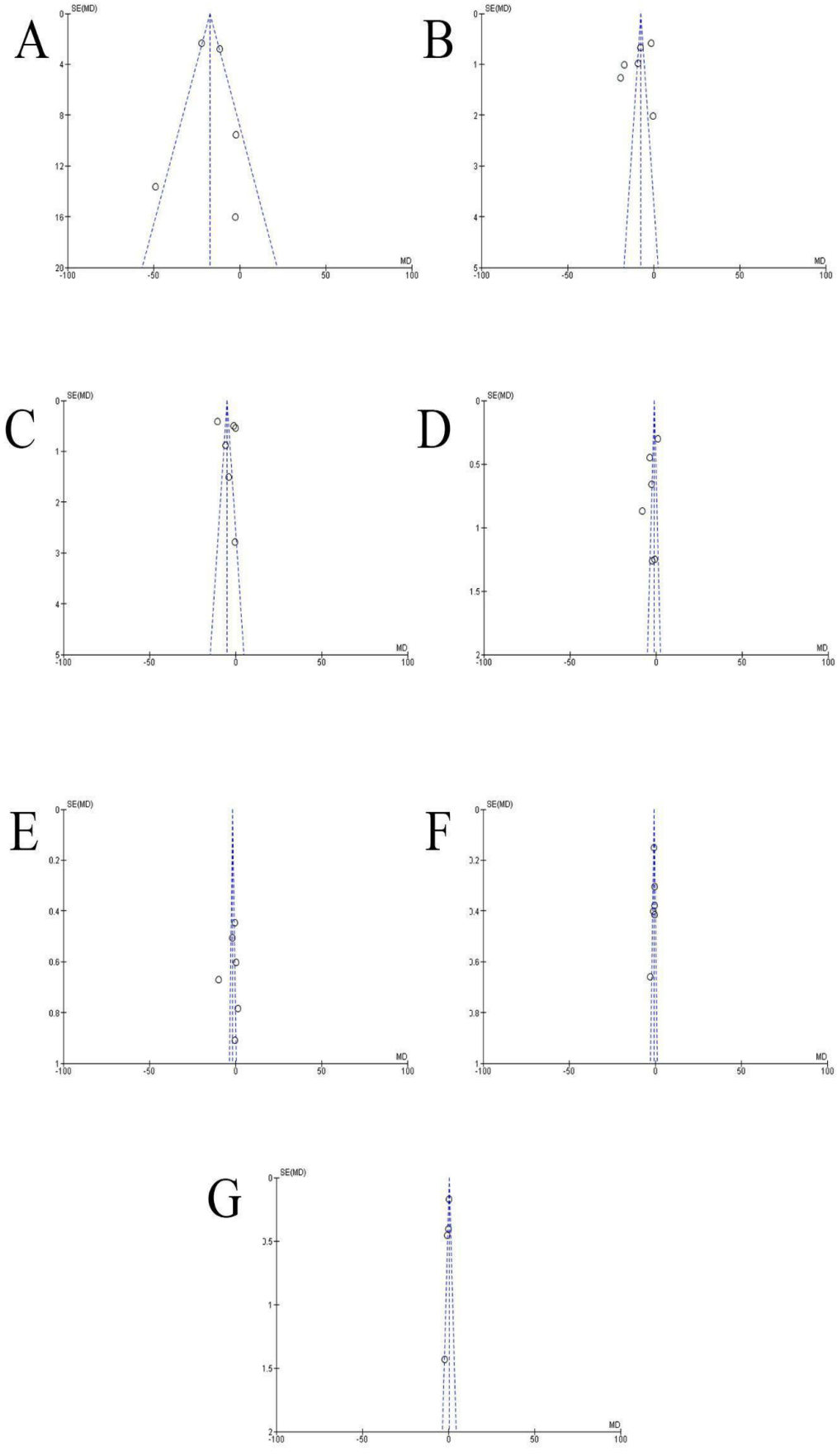

Fig 4. Funnel Plot Solifenacin vs Control. A: Total USSQ. B: Urinary Symptoms. C: Pain. D: General Health. E: Work Performance. F: Sexual Matters. G: Additional Problems.

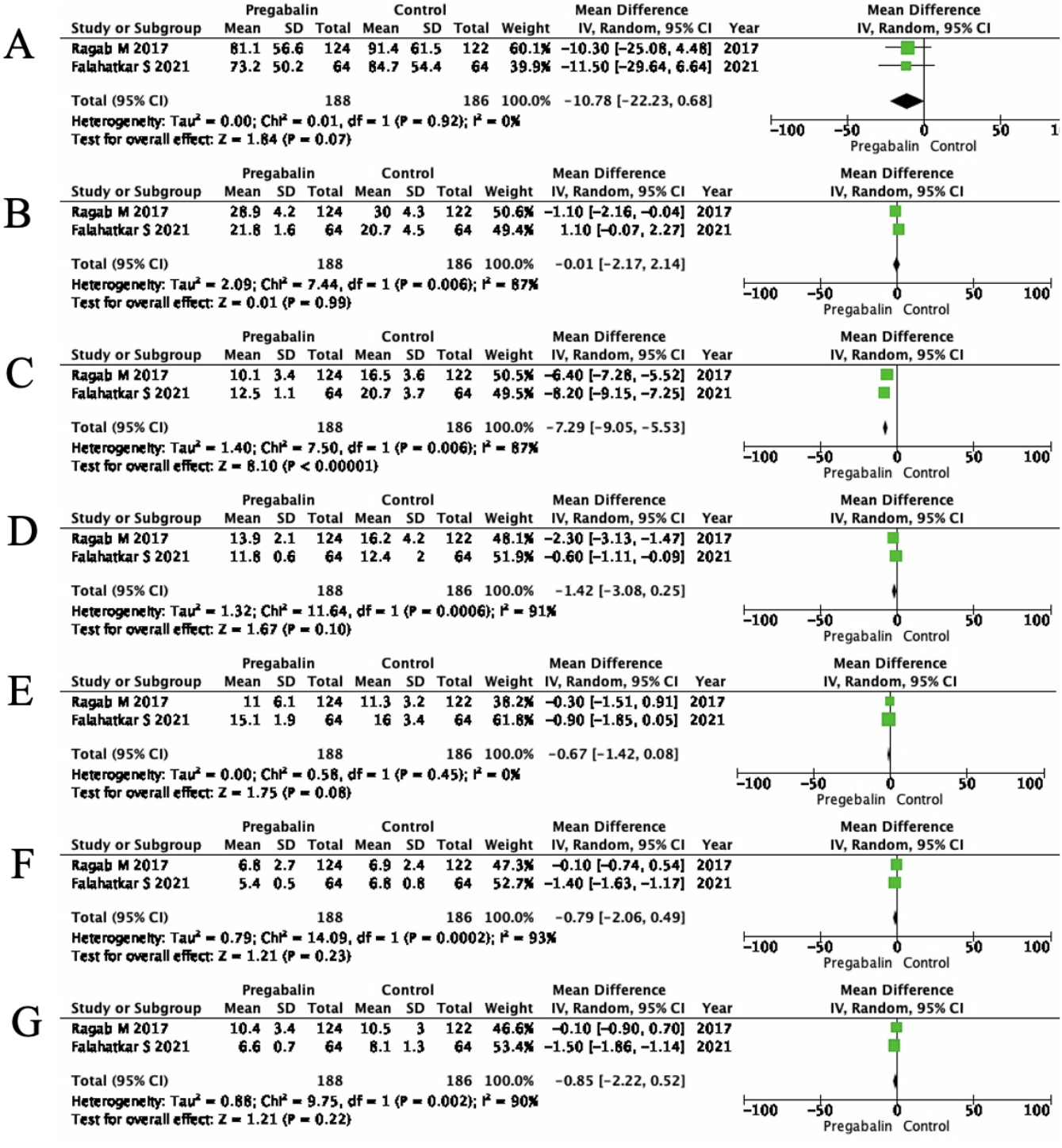

Fig 5. Forrest Plot Pregabalin vs Control. A: Total USSQ. B: Urinary Symptoms. C: Pain. D: General Health. E: Work Performance. F: Sexual Matters. G: Additional Problems.

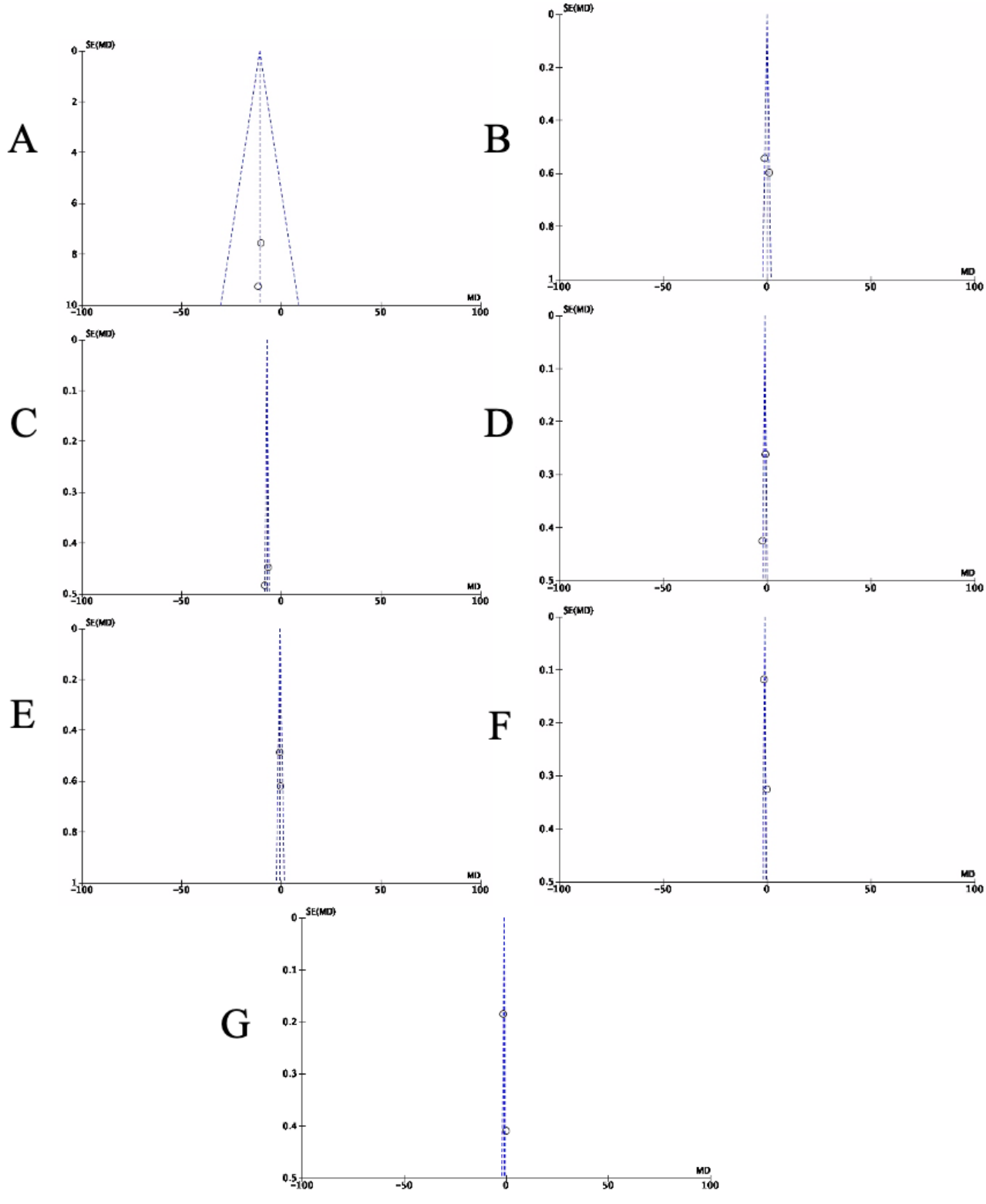

Fig 6. Funnel Plot Pregabalin vs Control. A: Total USSQ. B: Urinary Symptoms. C: Pain. D: General Health. E: Work Performance. F: Sexual Matters. G: Additional Problems.

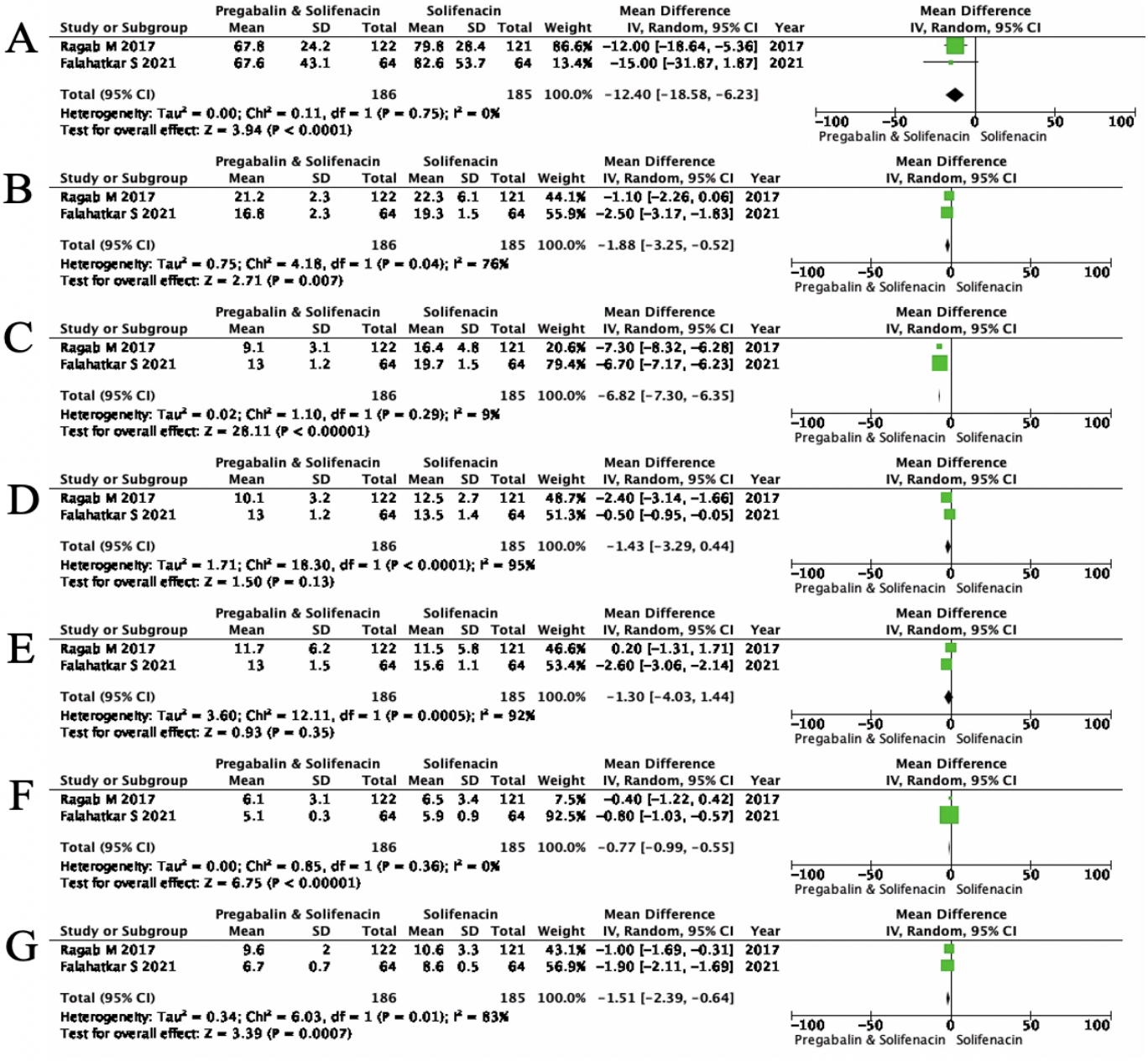

Fig 7. Forrest Plot Combination of pregabalin and solifenacin vs Solifenacin. A: Total USSQ. B: Urinary Symptoms. C: Pain. D: General Health. E: Work Performance. F: Sexual Matters. G: Additional Problems.

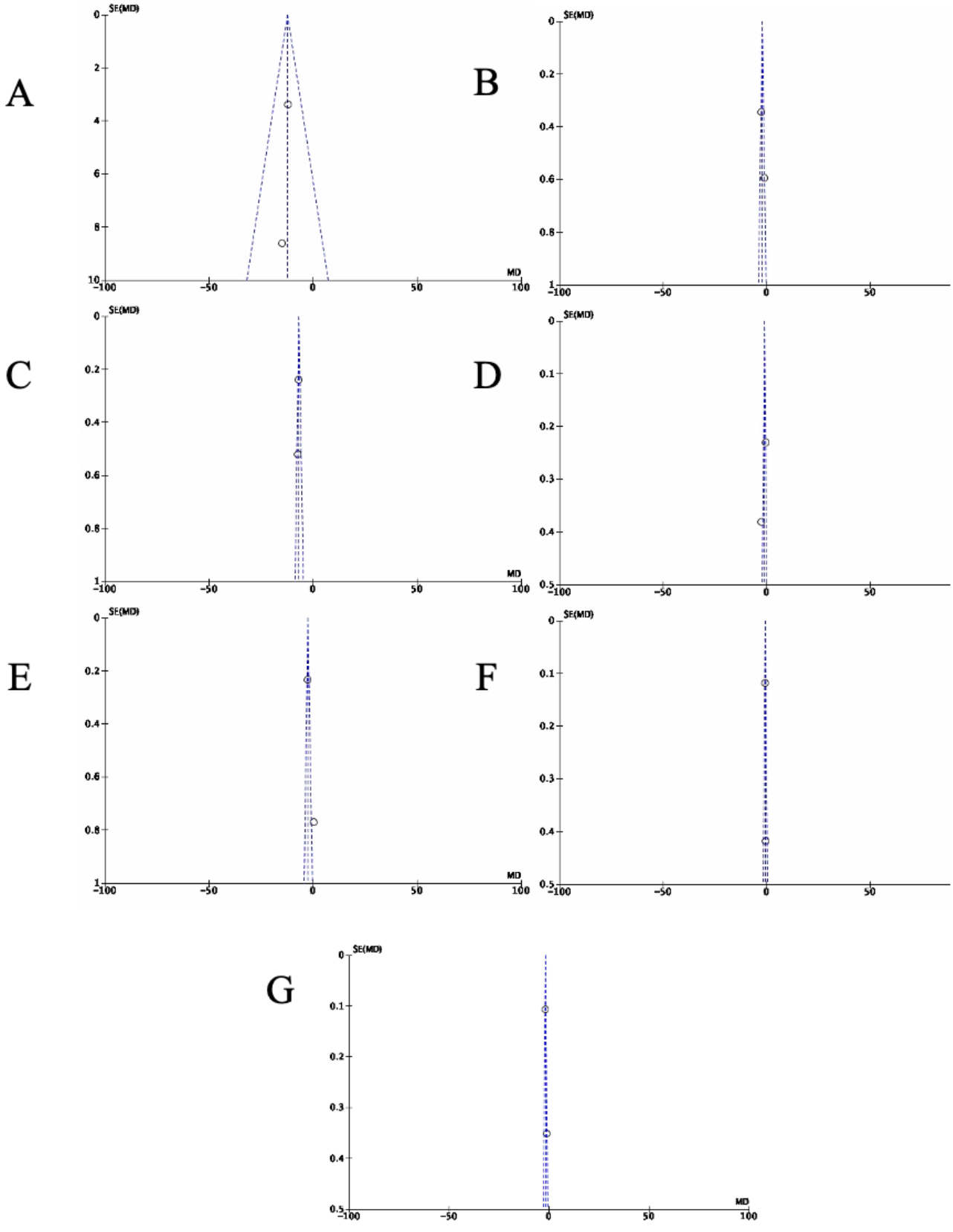

Fig 8. Funnel Plot Combination of pregabalin and solifenacin vs Solifenacin. A: Total USSQ. B: Urinary Symptoms. C: Pain. D: General Health. E: Work Performance. F: Sexual Matters. G: Additional Problems.

total USSQ. Specifically, it significantly reduces urinary symptoms and sexual matters compared to control. During urological surgery, bladder irritation causes the detrusor to contract involuntarily through the activation of muscarinic receptors (M2 and M3).[22] Being presented with favorable outcomes, solifenacin as an antimuscarinic drug, has been applied to treat symptoms brought on by the urinary bladder stent's distal end, which causes the bladder to contract involuntarily.[10,23]

Evrüke and Taş in their study showed that solifenacin therapy has demonstrated a favorable influence on the sexual functioning of premenopausal and postmenopausal women experiencing LUTS. As a result of solifenacin therapy leading to reduced urgency and urge incontinence (especially during intercourse), women might experience increased confidence and a greater willingness to engage in sexual activities with their partners, potentially elucidating the enhanced sexual functioning.[24,25] On the other hand, Kosilov K, et al. in their study showed that sexual satisfaction of BPH patients significantly increased with the administration of dutasteride and an increased dose of solifenacin (20mg/day). Their hypothesis posits that a higher dose of solifenacin may alleviate smooth muscle spasms in the detrusor and nearby pelvic organs, potentially improving microcirculation and enhancing tissue oxygenation. This effect could partially counteract the decrease in erectile function and stimulate afferent nerve structures, leading to improved orgasms. They also suggested that alleviated hyperactivity symptoms (urgency and nocturia) can give patients psychological comfort.[26]

A study by Lee YJ, et al. described solifenacin could lower USRS primarily urgency, urgent incontinence, bodily discomfort from stents, and hematuria in people of both sexes.[11] Several other combinations of medicines have been researched to reduce USRS, such as mirabegron and solifenacin, tamsulosin and solifenacin, silodosin and tadalafil, silodosin and solifenacin, solifenacin and tadalafil.[11,18,27] In comparison to solifenacin monotherapy, solifenacin with mirabegron significantly reduced OAB symptoms related to double-J stents and provided a superior quality of life without worsening undesirable side effects.[27] Combination of tamsulosin and solifenacin has a significant impact on urinary index score compared to each one of them and placebo.[11] In a study with 120 participants, mirabegron monotherapy had lower scores on the IPSS and OAB questionnaires compared to tamsulosin and solifenacin combination.[28] Silodosin and solifenacin were more effective in lowering USRS compared to either monotherapy or other combinations for silodosin, solifenacin, and tadalafil.[18]

In our research, pregabalin only significantly reduces the pain component of USSQ. Pregabalin, characterized by its chemical name (S)-3-(aminomethyl)-5-methylhexanoic acid, is recognized for its pharmacological effectiveness as the S-enantiomer of a racemic 3-isobutyl gamma amino butyric acid analogue, serving as a well-established anticonvulsant and analgesic agent.[29] It can inhibit the release of numerous neurotransmitters at synapses, which may explain why it decreases neuronal excitability and inhibits the inflammatory reactions elicited by afferent C nerve fiber. In addition, it benefits from central regulation of the dorsal horn neuron sensitization, which reduces postoperative pain associated with inflammation.[3,30] A randomized controlled study by Choppa S, et al. found that administering a single dose of 150 mg pregabalin 1 hour before percutaneous nephrolithotomy (PCNL) experienced less incidence and intensity of IID than those who received a placebo without experiencing any major side effects.[22] PCNL is the first-line management for stones larger than 20 mm.[31] A randomized controlled study by Rosen G, et al. found that preoperative pregabalin did not reduce pain after ureteroscopy compared to a placebo. Further study of pregabalin efficacy for post operative ureteroscopy is needed.[32] In our study, 75 mg of pregabalin was administered twice daily postoperatively with the aim of reducing USSQ (Ureteroscopy Stone Specific Questionnaire) scores.[3,13]

In our meta-analysis, the combination therapy of solifenacin and pregabalin versus solifenacin monotherapy has been statistically shown to reduce the total USSQ score, urinary symptoms, pain, sexual problems, and additional issues. These findings suggest that combination therapy has a more positive effect compared to monotherapy. This is in accordance with a study conducted by Falahatkar S, et al. that used a combination therapy of solifenacin and pregabalin for 4 weeks. The combination therapy successfully improved the scores of urinary symptoms, pain, sexual activity, overall condition, and work performance in the patient.[13] Solifenacin monotherapy alone does not reduce pain levels, but when combined with pregabalin, it can effectively reduce pain levels.[33]

Solifenacin is a medication that effectively and safely treats overactive bladder and has few adverse effects. In a prospective study comparing the dose of solifenacin, 5 mg solifenacin didn't show a significant number of side effects compared to placebo. On the other hand, 10 mg solifenacin showed a higher number of minor and self-limited side effects such as headache, constipation, and dry mouth.[9] In this review, most of the studies described headache, constipation, and dry mouth as side effects. Moreover, some studies also described urinary retention,

drowsiness, dizziness, and body pain. Pregabalin and gabapentin are two of the gabapentinoids that demonstrate opioid-sparing effects, are reasonably safe for individuals with renal or cardiac risk factors, do not prevent fusion during spinal surgery, and lessen the side effects of intravenous patient-controlled analgesia. Adverse effects, such as sedation, dizziness, and peripheral edema, are important considerations in the use of gabapentinoids, and they tend to become more pronounced with higher doses.[34] A systematic review and meta analysis studying the safety and efficacy of gabapentinoids for neuropathic pain described dizziness, somnolence, euphoria, constipation, dry mouth, peripheral oedema, and increased weight were several significant adverse effects of gabapentinoids use.[35] Two studies using pregabalin twice a day reported some side effects such as flushing, dry mouth, drowsiness, somnolence, dizziness, body pain, and headache.

Besides medicines, several stent characteristics have been studied to reduce USRS. The choice of stent material is something that can be considered to reduce USRS. A study by Gadzhiev N, et al. described silicone material for ureteral stents could lower body pain compared to polyurethane.[21] Silicone also has a lower potential for encrustation.[36] New stent shapes that might lessen tissue irritancy and urine reflux have lately received a lot of attention in the development of innovative stent designs.[1] "Pigtail suture stent" at the distal end can reduce USRS more than a J-shaped stent.[36] According to a meta analysis, urinary symptoms and pain are worse as the stent diameter gets bigger. As a result, smaller diameter stents ought to be chosen.[37] Materials used in the included studies were material of polyurethane, proprietary copolymer (Percuflex®), and proprietary polymer (InLay®), with a diameter of 4.7 to 8 Fr which has been adjusted to the patient's condition. Furthermore, a systematic review and meta analysis by Bao X, et al. reported that patients who had stents crossing the midline experienced more uncomfortable symptoms across subcategories such as urine symptoms, work performance, additional problems, overall health, storage symptoms, and quality of life. Urologists must make sure the ureteral stent is positioned correctly before implanting it.[38]

Postoperative follow up plays an important role in reducing USRS. According to statistics gathered from patients admitted to Thammasat University Hospital in the year 2020, 16 out of a total of 134 patients (8.9%) failed to show up on the scheduled day to have their stents changed or removed. Between the months of January and June of 2021, another 24 out of 121 patients (20%) neglected to show up for their appointments. Urinary tract infections, DJ stent mispositioning risk, ureteric stone development around the stents, and acute renal failure are all increased by indwelling ureteral stents. Some of these problems can lead to worsening USRS.[4]

In the systematic review and meta-analysis, several limitations were identified. First, the sample size for the combination of solifenacin and pregabalin in the population was still relatively small. Second, there was variability in the duration of follow-up among studies, which can potentially introduce bias. Third, there was variation in the dosages of solifenacin used in different studies. Fourth, this study still lacks a wide range of outcome measures. For future research, it is recommended to increase the sample size specifically for the combination of solifenacin and pregabalin, standardize the duration of follow-up across studies, and use consistent dosages of the medications. Additionally, it is advisable to include the size of ureteral stents and document any potential side effects associated with each drug.

CONCLUSION

Solifenacin monotherapy could decrease USRS especially urinary symptoms and sexual matters. Pregabalin monotherapy could only decrease pain related to USRS. Compared to solifenacin monotherapy, a combination therapy of pregabalin and solifenacin could significantly reduce the total USSQ score, especially in terms of decreasing urinary symptoms, pain, sexual matters, and additional problems.

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