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Editorial

Dear Reasearchers,

The July 2026 issue of *Medica Hospitalia: Journal of Clinical Medicine* presents a broad spectrum of clinical research, start moving from dermatology, autoimmune diseases, maternal health, surgery, cardiology, psychiatry and neurology, and infectious diseases. A common thread running through this issue is the effort to translate biological insights and therapeutic innovations into more precise clinical decision-making and improved patient outcomes.

This volume opens with a focus on dermatological conditions that substantially affect patients' quality of life. A study investigating the association between serum interleukin-6 levels and acne vulgaris severity in women highlights systemic inflammation as an important perspective in understanding acne, a condition traditionally regarded primarily as a localized skin disorder. Meanwhile, research on topical avocado oil for atopic dermatitis explores the potential of an adjunctive therapy aimed at restoring the skin barrier and improving hydration, both of which are fundamental components in the management of this chronic, relapsing disease.

Obstetrics and gynecology are prominently represented through an analysis of maternal mortality and maternal near miss associated with hypertensive disorders of pregnancy at Dr. Kariadi General Hospital throughout 2024. The study reinforces that hypertensive disorders of pregnancy remain a major priority in maternal health. Examining both maternal deaths and near-miss events provides valuable evidence to strengthen early detection, risk stratification, referral systems, and multidisciplinary management of severe obstetric complications.

Procedural innovation in obstetrics is highlighted in a meta-analysis evaluating the use of an episiotomy angle guide. The title, F*rom Eyeball to Exact*, aptly reflects the transition from visual estimation to a more standardized and precise surgical technique. This approach is particularly relevant to reducing severe perineal trauma during childbirth and illustrates how relatively simple innovations can yield meaningful clinical benefits.

Related with degenerative disease, a comparative study of etoricoxib and diclofenac sodium in patients with osteoarthritis emphasizes patient-reported quality of life as a primary outcome rather than focusing solely on pain relief. This reflects the contemporary clinical perspective that therapeutic success should be assessed through improvements in physical function, mobility, daily activities, and overall well-being.

Systemic disease and cardiovascular health are further explored in a study examining the relationships among C-reactive protein, the modified Rodnan Skin Score, and carotid intima-media thickness in systemic sclerosis. The findings illustrate the interplay between systemic inflammation, the extent of skin involvement, and subclinical vascular disease. They also reinforce the concept that systemic sclerosis is not merely a disorder of the skin and connective tissue but a multisystem disease with important cardiovascular implications that warrant early recognition.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2026; Vol 13 (2)
July 2026

Perioperative cardiology is represented by a study investigating increased P-wave dispersion as a risk factor for atrial fibrillation following coronary artery bypass grafting (CABG). Research of this nature has the potential to improve preoperative risk stratification, enabling earlier identification of high-risk patients who may benefit from closer monitoring and targeted preventive strategies.

This issue is complemented by two evidence-based case reports addressing challenging clinical scenarios. A report describing organic catatonia secondary to central nervous system infection reminds clinicians to avoid prematurely attributing catatonic symptoms to primary psychiatric disorders without first considering underlying medical causes. Another report explores the use of platelet-rich plasma in the management of leprosy ulcers, highlighting a regenerative therapeutic approach while emphasizing its role within the framework of evidence-based medicine and comprehensive wound care.

Taken together, the articles in this issue reflect the multidisciplinary, clinically oriented, and translational character of *Medica Hospitalia*. They demonstrate that improving health outcomes depends not on a single intervention but on earlier risk identification, deeper understanding of disease mechanisms, standardized clinical procedures, appropriate therapeutic selection, and sustained attention to patients' experiences and quality of life.

We hope that the studies presented in this issue will contribute to clinical practice, advance medical knowledge, and inspire future research.

We wish our readers an enjoyable and insightful reading experience, and we encourage you to continue advancing clinical research.

Editor

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Med Hosp 2026; vol 13 (2) : 102–111

OPEN ACCESS

Original Article

Benefits of Topical Avocado Oil in Improving Skin Moisture: A Study in Atopic Dermatitis Patients

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Abstract

Background : Atopic dermatitis is a chronic skin condition characterized by recurrent flare-ups that impair skin barrier function and significantly affect patients' quality of life. One of the key strategies in managing atopic dermatitis is to strengthen and maintain the skin's barrier function while reducing inflammation commonly achieved through the use of moisturizers such as petrolatum. However, petrolatum has several drawbacks, including a thick consistency that makes it difficult to apply, a greasy and shiny appearance, and the potential to cause follicular occlusion. As an alternative, avocado oil offers promising benefits due to its non-comedogenic properties and non-greasy finish.
Aim : To determine the difference in effectiveness between avocado oil and petrolatum in improving skin moisture.
Methods : This study is a single-blind randomized clinical trial using a two-parallel group pre- and post-test design. Samples were selected using consecutive sampling. The treatment was applied to the right and left forearms of patients with non flare-ups atopic dermatitis.
Results : The variable of user complaints was statistically significant in the general characteristics, with a *p*-value of <0.05. The TEWL (Transepidermal Water Loss) score for topical avocado oil showed a significant difference compared to petrolatum, with a *p*-value of <0.001.
Conclusion : A greater reduction in TEWL (indicating improved skin moisture) was observed with the application of 100% topical avocado oil in patients with non flare-ups atopic dermatitis, compared to the use of 100% topical petrolatum.

Keywords: atopic dermatitis, avocado oil, transepidermal water loss

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INTRODUCTION

Atopic dermatitis (AD) is a recurrent skin disease found in patients with a family history of atopy, characterized by intense itching. The highest incidence of AD occurs in infancy, but significant incidences have also been reported in adolescence and adulthood.[2] Data from the Indonesian Pediatric Dermatology Study Group indicates that the prevalence of AD in Indonesia has reached 23.7%.[3] The number of new cases of AD diagnosed between January 2012 to December 2013 at Kariadi Hospital was 121.[4] The large number of AD cases, coupled with recurrent attacks, means that AD does not only impact skin health but also triggers psychological distress, lowers patients' quality of life, and impose an economic burden.[1,2]

Atopic dermatitis is a complex skin disease that can occur due to the interaction of genetics, immune risk factors, impaired epithelial barrier function, and microbial imbalance. Interindividual variation adds to the heterogeneity of the causative mechanisms of AD.[5] Decreased skin barrier function is caused by mutations in the gene encoding filaggrin. This contributes to increased transepidermal water loss (TEWL), allergen absorption into the skin, and microbial colonization.[1,6] The TEWL score is an objective measure of skin integrity, measured as the amount of water lost in the stratum corneum. Transepidermal water loss can be measured using the Tewameter TM 300 (Courage & Khazaka, Cologne, Germany).[7]

Comprehensive AD management consists of five main pillars: patient and family education, modifying triggering factors such as irritants and allergens, strengthening and maintaining skin barrier function, reducing inflammation, and eliminating the itch-scratch cycle.[9] Skin barrier dysfunction occurs in all AD patients, whether experiencing a relapse or not, making the use of moisturizers a fundamental therapy in AD management. Clinical studies have shown that the use of moisturizers will repair the skin barrier, thereby reducing the risk of relapse through its primary effect of reducing TEWL. Moisturizers can be classified as occlusives, emollients, and humectants.[10,11]

Petrolatum is a classic occlusive moisturizer that effectively reduces TEWL by more than 98% and inhibits water vapor loss 170 times better than olive oil.[12,13] The main drawback of petrolatum is its very thick texture, making it difficult to apply to the skin and can cause follicular occlusion. Its texture also leaves a greasy, shiny residue, often causing discomfort and decreasing user compliance. Therefore, it is necessary to consider alternative moisturizers that are more comfortable and preferred by patients, thereby increasing patient compliance.[12–15]

Various plant oils have long been used on the skin for cosmetic and medical purposes due to their proven positive benefits. Avocado oil (Persea americana) is a plant oil obtained from avocados through various extraction methods, including cold pressing.[10] Avocado oil fills the gaps between corneocytes, resulting in more moisturized and smoother skin.[16] In addition, avocado oil can act as a skin protectant through its semi-occlusive effect, allowing the skin to retain moisture and resulting in a reduction in TEWL scores.[17] Avocado oil contains various fatty acids, squalene, lecithin, carotenoids, vitamins C and E (tocopherols), phytosterols, alkaloids, saponins, and quinones. These compounds demonstrate avocado oil's role in moisturizing and repairing the skin barrier, in addition to providing anti-inflammatory, antioxidant, and antimicrobial effects.[18-20] Due to the various components and benefits of avocado oil, it is suspected that avocado oil may play a role in treating skin diseases with barrier-disrupting pathogenesis, such as atopic dermatitis (AD). However, research on the effects of topical avocado oil on patients with AD has not been conducted.[18-20]

Although many studies on plant oil's role in improving skin moisture have been conducted, this research is the first to analyze the benefit of topical avocado in the context of lowering transepidermal water loss in atopic dermatitis patients in Indonesia. Compared to other plant oils, avocado oil is superior to olive oil in terms of its ability to repair the skin barrier. Avocado oil also has a role in wound healing by increasing collagen and reducing inflammatory cells, which is better than sunflower seed oil, safflower seed oil, soybean oil, peanut oil, sesame oil, oat oil, pomegranate seed oil, almond oil, apricot oil, rosehip oil, chamomile oil, and shea butter. Although both oil-based, avocado oil is also less comedogenic than other vegetable oils such as coconut oil or olive oil.[10]

METHODS

The study was conducted at the Dermatology and Venereology Clinic of Kariadi Hospital after obtaining ethical approval until the sample size was sufficient. This was a single-blind, randomized clinical trial with two-parallel groups pre- and post-test design.

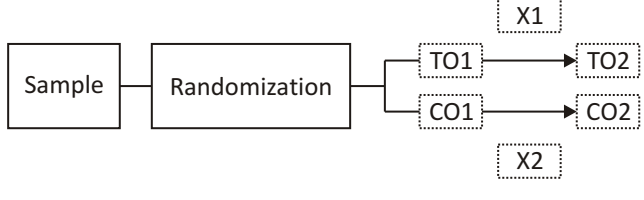

Figure 1. Research design

Description:
T : Treatment
C : Control
TO1 : Skin TEWL score before therapy in the treatment group
TO2 : Skin TEWL score after therapy in the treatment group
CO1 : Skin TEWL score before therapy in the control group
CO2 : Skin TEWL score after therapy in the control group
X1 : Topical 100% avocado oil for 4 weeks
X2 : Topical 100% petrolatum for 4 weeks

The target population was patients with non-flare-ups atopic dermatitis. Inclusion criteria included patients with AD, as defined by the Hanifin-Rajka criteria and no acute exacerbation in the body area to be treated with the test agent. Patients must be aged 18–45 years, willing to participate in the study and agree to receive therapy according to the agent used in the study.[1] Exclusion criteria include patients with a history of hypersensitivity to avocado extract and active skin infection or inflammation (such as AD exacerbation, psoriasis, scabies infestation, seborrheic dermatitis, or contact dermatitis) in the body area to be treated with the test agent, as determined by physical examination, taking medications that cause skin dryness such as antiandrogens, diuretics, chemotherapy, statins, cimetidine, or oral retinoids, and refusing to participate in the study or failing to attend the evaluation visit. [1,18,32,35]

The study sample was selected using consecutive sampling, based on patient attendance at the Dermatology and Venereology Clinic, Kariadi Hospital. The sample size was calculated using the sample size formula for two-parallel groups pre- and post-test design.

$$n_1 = n_2 = 2\left[\frac{(Z\alpha + Z\beta)SD}{X_1 - X_2}\right]^2$$

Annotation:
n1 = sample size in the treatment group
n2 = sample size in the control group
Za = level of significance (the value is set at 1,96)
Zb = power (the value is set at 0,842)
SD = standard deviation
X1–X2 = clinical difference *(clinical judgement)*.

The calculation results are as follows:

Variable	Za	Zb	X1	X2	SD	n	Annotation
TEWL	1.96	0.842	11.70	9.93	1.61	9.01	Patzelt A, *et al*[19]

When the research conducted by Patzelt is be added into the sample size formula calculation, the result is 9.01(rounded to 9). If it is estimated that there is a possibility of 10% dropout, then the sample size calculation with dropout correction is as follows:

$$ndo = \frac{n}{1 - do} = \frac{9}{1 - 0.1} = 10$$

From the calculation above, at least 10 patients were selected for the treatment group (100% topical avocado oil) and the control group (100% topical petrolatum), resulting in total number of samples not less than 20 patients. In this study, the researcher added 3 patients to both the treatment and control groups to anticipate any patients being excluded during the research process. Therefore, in this study the total number of samples was 26 people.

The moisturizer was coded A for 100% topical avocado oil and B for 100% topical petrolatum. The medication order was arranged using simple random sampling. The administration was determined by a staff who were not directly involved in the study sample observation. The order was stored in a sealed envelope and opened after the study was completed. A study sample was considered a dropout if an allergic reaction, such as itching, pain, a red rash, hives, or swelling, was observed after the therapy was administered.

Before data collection began, the assessing physician (resident doctor in the Dermatology, Venereology, and Aesthetics Program) received training on how to utilite a tewameter (Courage & Khazaka, Cologne, Germany) to examine the volar area of the left and right forearm. The volar area was chosen due to its ease for application, easily examined by researchers, has a quality level comparable to facial skin but is more ethically feasible for research in the event of adverse effects, and has the least bias compared to other skin areas. The average reading was then taken from the three evaluators.

Patients with a history of AD who visited to the Dermatology and Venereology Clinic of Kariadi Hospital were recorded and then interviewed using a screening questionnaire. Sampling was carried out sequentially until the sample size was reached. Each study sample underwent a one-week preconditioning period before participating in the study. During the week, the study subjects were advised against bathing with warm water, recommended to bathe twice daily and use the provided baby soap. They should not use any other soap or topical agent other than the one provided for the study. Each subject received a moisturizer consisting of 100% topical avocado oil or 100% topical petrolatum, according to randomization order, for a period of 4 weeks. The study subjects were randomly allocated to two groups: a control group and a treatment group.

Before participating in the study, each subject was

informed of the purpose of the study, its benefits, and potential risks. Those who understood and agreed to participate were asked to sign a consent form. The examining physician took a history of dry skin complaints in patients with AD, current medications, and history of skin care product used.

The physician explained how to use the topical agent. Patients in each test group applied the topical agent twice daily immediately after bathing. The topical agent was applied evenly to the volar aspect of the left and right forearm. During the first visit, the physician explained how to apply the topical agent, then patients applied the agent themselves at home. The physician then measured the skin moisture using a tewameter. This measurement was taken before any treatment was administered (day 0) and week 4 (day 28) after the start of test material administration. Upon arrival for a follow-up examination on the last measurement day, the subjects were asked not to use the topical agent on that day because the presence of topical materials on the skin surface would reduce the accuracy of TEWL measurements. Patient's compliance was assessed through a daily logbook and communication via WhatsApp. Objective parameters were evaluated by measuring TEWL. Prior to the study, the study protocol was submitted to the Health Research Ethics Committee of Kariadi Hospital with the registration number 16308/EC/KEPK-RSDK/2024 on December 16, 2024.

RESULTS

The characteristics of the research subjects in the avocado oil group and the petrolatum group are shown in Table 1.

The TEWL scores of the right and left legs of the study subjects at baseline (week 0) and week 4, as well as the difference in TEWL scores between the avocado oil

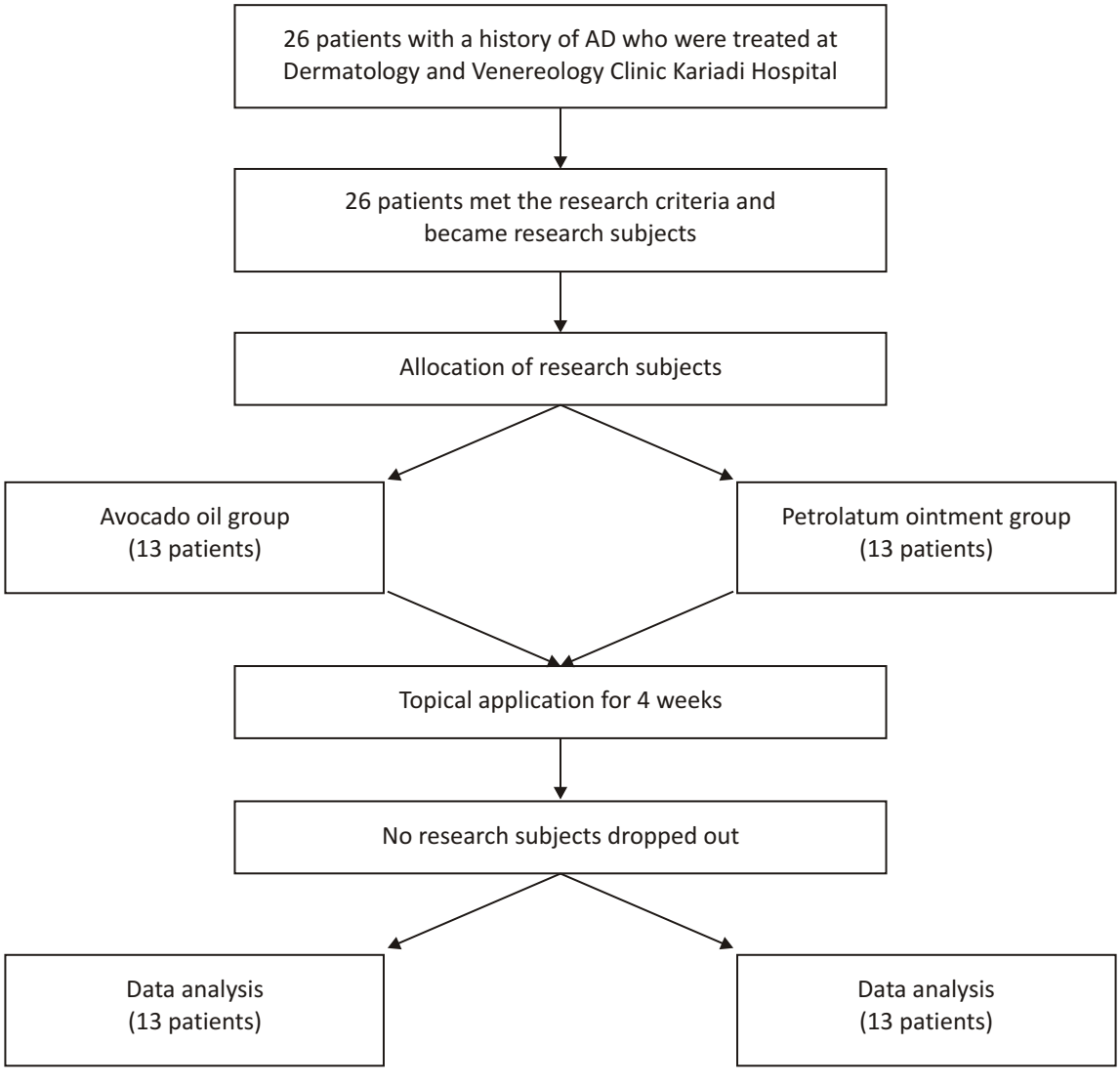

Figure 2.

TABLE 1
General characteristics of the study subjects in the groups receiving 100% avocado oil and 100% topical petrolatum

Variables	Group		*p*	Statistical test
	Avocado oil	Petrolatum		
Age	30.85 ± 3.81	30.15 ± 2.97	0.610	Levene
Gender			1.000	Chi-Square
Man	4 (30.8%)	4 (30.8%)	20 (52.6%)	
Woman	9 (69.2%)	9 (69.2%)		
Level of education			1.000	Chi-Square
Vocational school	1 (7.7%)	2 (15.4%)		
Bachelor	12 (92.3%)	11 (84.6%)		
Bathing frequency			1.000	Chi-Square
2x	10 (76.9%)	11 (84.6%)		
>2x	3 (23.1%)	2 (15.4%)		
Types of soap			1.000	Chi-Square
Antiseptic	11 (84.6%)	10 (76.9%)		
Non-Antiseptic	2 (15.4%)	3 (23.1%)		
Warm bath			0.673	Chi-Square
Yes	5 (38.5%)	3 (23.1%)		
No	8 (61.5%)	10 (76.9%)		
How to dry the body			1,000	Chi-Square
Wiped/patted	6 (46.2%)	5 (38.5%)		
Rubbed	7 (53.8%)	8 (61.5%)		
History of moisturizer use			0.378	Chi-Square
Always	5 (38.5%)	2 (15.4%)		
Seldom	6 (46.2%)	10 (76.9%)		
Never	2 (15.4%)	1 (7.7%)		
History of therapy			0.673	Chi-Square
Topical	8 (61.5%)	10 (76.9%)		
Topical + oral	5 (38.5%)	3 (23.1%)		
Initial complaint			1.000	Chi-Square
Dry skin	11 (84.6%)	10 (76.9%)		
Dry skin + Itchy	2 (15.4%)	3 (23.1%)		
Usage complaint			0.030	Chi-Square
Sticky	0 (0%)	7 (53.8%)		
Greasy	1 (7.7%)	0 (0%)		
No complaint	12 (92.3%)	6 (46.2%)		

TABLE 2
TEWL scores before and after topical application of 100% avocado oil and 100% petrolatum

Variables	Group		*p*	Statistical test
	Avocado oil	Petrolatum		
Right side TEWL				
Baseline	16.40 (15.01 – 20.06)	16.06 (15.22 – 21.62)	0.412	Mann-Whitney
Week 4	6.55 ± 0.73	9.40 ± 1.61	<0.001*	*Independent t-test*
p	<0.001*	<0.001*		
Statistical test	*Paired t-test*	*Paired t-test*		
Right side TEWL difference	-10.31 ± 1.38	-7.23 ± 1.59	<0.001*	*Independent t-test*
Left side TEWL				
Baseline	16.93 (16.34 – 22.60)	16.81 (15.25 – 20.65)	0.124	Mann-Whitney
Week 4	6.55 ± 1.04	9.24 ± 1.51	<0.001*	*Independent t-test*
p	<0.001*	<0.001*		
Statistical test	*Paired t-test*	*Paired t-test*		
Left side TEWL difference	-10.95 ± 1.55	-7.56 ± 1.27	<0.001*	*Independent t-test*

Notes : *Significant ($p < 0.05$)

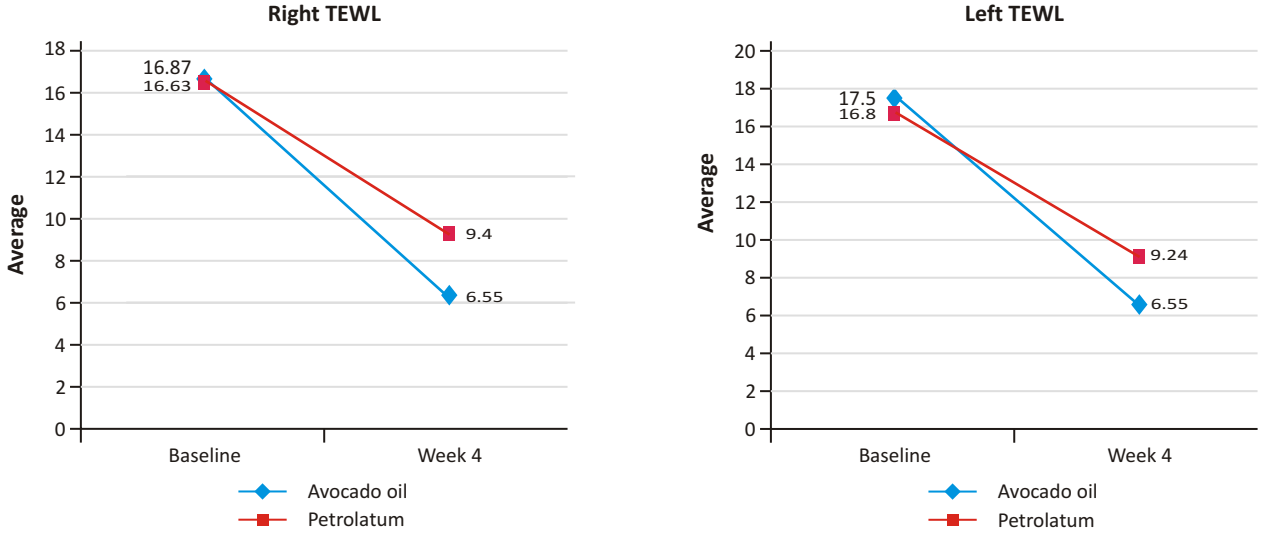

Figure 3. A. Right-sided TEWL scores at baseline and week 4 in the avocado oil and petrolatum group. **B.** Left-sided TEWL scores at baseline and week 4 in the avocado oil and petrolatum group.

and petrolatum groups, are shown in Table 2.

TEWL Scores Before and After Avocado Oil Use

The TEWL scores of the right and left legs of the study subjects at baseline (week 0) and week 4, as well as the difference in TEWL scores between the avocado oil and petrolatum groups, are shown in Table 2.

DISCUSSION

The research was a single-blind, randomized clinical trial with a two-group pre- and post-test control design. It assessed the effect of topical 100% avocado oil compared to topical 100% petrolatum on skin barrier repair (TEWL score) in patients with a history of atopic dermatitis (AD). This study was the first of its kind. The mean age in both

groups was 30.50 ± 3.36, with an age range of 24–36 years. Consistent with the literature, adult-onset AD itself occurs most often in individuals aged 20–40 years.[35] Research conducted by Wahnadian *et al*. at the Dermatology & Venereology Clinic, Waled Regional Hospital, Cirebon Regency, from November 2019 to December 2021 revealed that atopic dermatitis sufferers in the 26–45 year age range were the highest among all adult-onset AD patients.[36]

Gender in this study showed that the majority of subjects were female, representing 69.2% in each group, both the avocado oil and petrolatum groups. A study at the Dermatology & Venereology Clinic Dr. H. Abdul Moeloek Hospital found that of 96 AD patients, 41 (42.7%) were male and 55 (57.3%) were female. The Chi-Square statistical test results showed p=0.012 (p<0.05), indicating a significant association between gender and the incidence of AD. Emotional stress plays a significant role in the development of AD because sensory nerves release neuromediators that regulate inflammation, thus increasing inflammation in the skin. Stress itself is closely related to the hormone progesterone, which women experience as part of their biological functions. This results in women being more sensitive and susceptible to stress, especially during hormonal fluctuations, such as during the menstrual cycle and pregnancy, compared to men.[37]

The educational level of the study subjects in both the avocado oil and petrolatum groups was predominantly bachelor's degree. Individuals with lower levels of education often experience significant health disparities due to limited health literacy, which hinders understanding of skin care practices, medication adherence, and recognition of environmental triggers that can exacerbate AD.[38,39] A 2024 study by Nurapriyanti on the relationship between knowledge level and skin care behaviors in atopic dermatitis showed that patients with higher education demonstrated a better understanding of AD treatment, including AD-related skin care behaviors and needs.[40]

Most study subjects showered twice daily. Regular bathing can help cleanse the skin of bacteria, allergens, and irritants. However, a study involving 28 children with AD found no significant difference in symptoms whether they bathed daily or only twice a week. To date, there are no standards for the optimal frequency and duration of bathing.[41]

In avocado oil group 11 study subjects (84.6%) bathed with antiseptic soap. Meanwhile, in petrolatum group, 10 study subjects (76.9%) bathed with antiseptic soap. Antiseptic soap is commonly used for its ability to eliminate pathogenic bacteria and prevent skin infections. On the other hand, this type of soap can strip natural oils of the skin, causing increased dryness and irritation, especially in individuals with sensitive skin conditions such as AD.[42] However, this contradicts a study conducted by Baihaqi *et al*. on medical students at Diponegoro University regarding the relationship between antiseptic soap use and dry skin. The study showed no significant association.[43]

Five study subjects (38.5%) in the avocado oil group and three study subjects (23.1%) in the petrolatum group had a habit of bathing with warm water. Studies suggest that exposure to hot or warm water can remove the skin's natural oils, disrupting the skin's lipid matrix, leading to increased transepidermal water loss, worsening skin dryness and irritation.[44]

The drying method among study subjects was divided into patting (6 subjects) and rubbing (7 subjects) in the avocado oil group, while in the petrolatum group was divided into patting (5 subjects) and rubbing (8 subjects). For treating AD patients, rubbing should not be used because the mechanical friction that occurs during rubbing can damage the skin barrier and trigger the release of pro-inflammatory cytokines.[45,46]

The use of moisturizer in avocado oil group was detailed as follows: 5 study subjects (38.5%) regularly used moisturizer, 6 study subjects (46.2%) rarely used moisturizer, and 2 study subjects (15.4%) reported never used moisturizer. The history of moisturizer use in the petrolatum group was detailed as follows: 2 study subjects (15.4%) regularly used moisturizer, 10 study subjects (76.9%) rarely used moisturizer, and 1 study subject (7.7%) reported never used moisturizer. Regular use of moisturizer can prevent transepidermal water loss (TEWL) and maintain skin moisture.[2,12,28] Patzelt's research supports this statement, where transepidermal water loss (TEWL) before and after application of avocado oil moisturizer decreased from 11.70±1.61 to 9.93±2.22.[19]

Eight subjects in the avocado oil group (61.5%) had a history of topical treatment and five subjects (38.5%) had a history of topical treatment combined with oral treatment. Ten subjects in the petrolatum group (76.9%) had a history of topical treatment and three subjects (23.1%) had a history of topical treatment combined with oral treatment. The five main pillars of AD management are providing education about AD, avoiding and modifying trigger factors, strengthening and maintaining skin barrier function, reducing inflammation with anti-inflammatory medications, and controlling and eliminating the itch-scratch cycle.[9,30] A retrospective study conducted by Ratnaningtyas *et al*. regarding topical treatment in AD patients at Dr. Soetomo General Hospital Surabaya during 2013–2015 showed that 272 patients (83.2%) of 327 new AD patients received topical therapy: topical corticosteroids for 187 patients (23.6%), emollients for 183 patients (23.6%), and gents (23.1%), and topical antibiotics in 40 patients (5.1%).[47]

The majority of patients' initial complaints were dry skin. The literature indicates that patients with AD

experience decreased expression of epidermal differentiation proteins due to mutations in the filaggrin (FLG) gene. As a result, the skin becomes dry so that irritants and allergens are more easily absorbed, resulting in inflammation and pruritus.[23–25]

After using avocado oil for 4 weeks, no significant side effects were generally observed. The literature indicates that the main disadvantage of petrolatum is its oily texture and high viscosity which makes the skin surface sticky upon application and reducing compliance.[26,27] This is consistent with research conducted by Leo *et al*.[48]

This study found a decrease in TEWL scores before and after avocado oil application of -10.31±1.38 on the right side and -10.95±1.55 on the left side. These results indicate a statistically significant decrease in TEWL scores, with $p<0.001$ on the right side and $p<0.001$ on the left side. This aligns with the hypothesis that TEWL scores after avocado oil application on AD patients are lower than TEWL scores before treatment. The linoleic acid content in avocado oil makes it a potent moisturizing agent compared to other plant oils, helping to increase skin hydration and improve xerosis and pruritus.[30,33] The phospholipid lecithin component helps improve skin hydration and strengthens the skin barrier integrity. Meanwhile, squalene, a natural moisturizing component, can protect the skin by preventing environmental stressors and oxidative damage.[18,34] The results of this study align with those of Patzelt *et al*., who demonstrated a decrease in transepidermal water loss (TEWL) before and after avocado oil application in six healthy study samples.[19]

A statistically significant decrease was found in TEWL scores in the avocado oil group on the right side (-10.31±1.38) and left side (-10.95±1.55) compared to the decrease in TEWL scores in the petrolatum group on the right side (-7.23±1.59) and left side (-7.56±1.27). This finding aligns with the hypothesis that TEWL scores after avocado oil application are lower than those after petrolatum application in AD patients.

According to the literature, avocado oil and petrolatum effectively reduce TEWL. Both play a role in repairing the skin barrier and increasing skin moisture. The various essential fatty acids contained in avocado oil fill the intercorneocyte gaps in the skin, making avocado oil a good emollient.[26] Furthermore, avocado oil is said to have semi-occlusive properties due to its ability to form a hydrophobic layer to resist evaporation on the skin surface and the superficial interstitium of the stratum corneum.[10,12,13] The phospholipid component lecithin helps improve skin hydration and strengthens the integrity of the skin barrier. Meanwhile, squalene, a natural moisturizing component, can protect the skin by preventing environmental stressors and oxidative damage.[18,34] Vitamin E, vitamin C, carotenoids (lutein and beta-carotene), phenolics, and phytosterols are antioxidant components contained in avocado oil that can help neutralize free radicals and prevent cellular damage due to oxidation, thereby increasing resistance to factors that can exacerbate water loss and irritation.[30,34]

In addition to being a moisturizer and antioxidant, avocado oil can reduce skin inflammation by inhibiting the expression of inflammatory cytokines and the activation of NF-κB/caspase-1.[31] As an antibacterial, the alkaloids, saponins, and quinones in avocado oil can inhibit the growth of *Staphylococcus aureus* bacteria in AD patients, which occurs either primarily or secondary to epidermal barrier disruption and Th2-dominated immunity.[20,22,25] This reason is thought to be behind a more significant effect of avocado oil on reducing TEWL than petrolatum.

Previous research on the effects of avocado on skin hydration was not conducted in atopic dermatitis population, even though atopic dermatitis patients often experience recurring itching and require long-term use of moisturizer.[10,19]

CONCLUSION

This study that revealed topical 100% avocado oil is more effective in reducing TEWL scores in patients with AD compared to topical 100% petrolatum. Further research could use a larger sample size in a wider population to increase the generalizability of the results.

CONFLICT OF INTEREST

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the materials discussed in this manuscript.

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Original Article

Maternal Mortality and Near Misses in the Spectrum of Hypertensive Disorders in Pregnancy at Dr. Kariadi Hospital in 2024

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Abstract

Background : High maternal mortality from hypertension in pregnancy reflects poor early detection and management. Preeclampsia-eclampsia remains a major cause of severe outcomes.
Aims : To analyze the relationship between spectrum of hypertensive disorders in pregnancy and maternal near misses and mortality at Dr. Kariadi Hospital in 2024.
Methods : Cross-sectional study using medical records of pregnant women with hypertensive disorders. All cases were analyzed to assess the relationship between spectrum of hypertension and maternal near miss and maternal death using the chi-square test, in accordance with the ethical approval of KEPK Dr. Kariadi Hospital.
Results : Most pregnant women had preeclampsia/eclampsia (77.3%), followed by superimposed preeclampsia (14.2%). Maternal near miss occurred in 13.3% and mortality in 9.3% of cases, with 206 live births. Organ dysfunction was found in 22.7%, mainly cardiovascular (10.7%), followed by respiratory, coagulation (each 2.2%), and immunological (5.8%). Overall organ dysfunction, especially cardiovascular, respiratory, renal, and coagulation associate with maternal near miss ($p<0.05$). The highest risks were seen in cardiovascular (PR 19.54; CI95% 10.13–37.66), renal (PR 7.96; CI95% 5.63–11.26), respiratory (PR 6.76; CI95% 3.83–11.94), and coagulation dysfunction (PR 4.88; CI95% 2.20–10.86). Immunological dysfunction was strongly associated with maternal mortality and had the highest risk (PR 26.50; CI95% 13.42-52.29).
Conclusion : Preeclampsia/eclampsia is the dominant condition and correlates to maternal near miss and death. Organ dysfunction significantly worsens outcomes.

Keywords : Organ dysfunction, hypertension in pregnancy, maternal mortality, maternal near miss

INTRODUCTION

Maternal mortality remains a global and national challenge. The WHO reported 287,000 maternal deaths in 2020, with hypertension in pregnancy being the leading cause.[1] In Indonesia, the maternal mortality rate decreased from 346 per 100,000 live births (2010) to 189 per 100,000 live births in 2020, but the number of maternal deaths still reached more than 4,000 cases. Hypertension in pregnancy, including chronic hypertension, gestational hypertension, preeclampsia, and eclampsia, is the leading cause of maternal morbidity and mortality, mainly due to suboptimal early detection, inadequate management, and delayed referral.[2]

Near misses and maternal deaths generally occur due to severe complications such as placental abruption, HELLP syndrome, and pulmonary edema, which often arise due to delays in treatment at primary care facilities. An ineffective referral system also increases these risks. Various studies in Indonesia show that mothers with preeclampsia have a higher risk of adverse maternal and perinatal outcomes, and that the quality of antenatal care and the accuracy of referrals play a major role in preventing fatal complications. Optimization of maternal health services is still urgently needed to achieve the targets of the 2024 National Medium-Term Development Plan and the 2030 Sustainable Development Goals.[2,3]

In the city of Semarang, maternal mortality rates have fluctuated over the past three years, and hypertension during pregnancy remains the dominant cause of maternal mortality. Dr. Kariadi Hospital, as the tertiary referral hospital in Central Java, receives many referral cases with severe preeclampsia and records an average case fatality rate of 3.3% for these cases. Given the limited specific data on maternal outcomes in hypertension during pregnancy, an in-depth analysis of maternal near misses and maternal deaths in referral facilities is urgently needed.[4]

This study was conducted to assess the factors of hypertension in pregnancy that affect near misses and maternal mortality, using secondary data from medical records at Dr. Kariadi Hospital in Semarang in 2024 as a basis for evaluation and improvement of obstetric emergency services.

METHODS

The observational analytical design study with a cross-sectional approach was conducted at Dr. Kariadi Hospital in Semarang. The study employed secondary data from the medical records of pregnant women, women in labor, and postpartum women with a spectrum of hypertensive disorders in pregnancy in 2024.

The study population included all pregnant women, women who had given birth, and women in the postpartum period with hypertensive disorders. The sample was obtained using total sampling, covering all cases that met the inclusion criteria, namely patients with preeclampsia/eclampsia, superimposed preeclampsia, gestational hypertension, or chronic hypertension with complete medical records, both without complications and with near miss or maternal mortality. Exclusion criteria included patients with incomplete medical records, as well as patients who were referred out or discharged at their own request.

The independent variable of the study was the spectrum of hypertensive disorders in pregnancy, while the dependent variables were maternal near miss and maternal death. The intermediate variables of the study was the type of organ dysfunction and $MgSO_4$ therapy. Maternal near miss was defined as the occurrence of one or more adverse obstetric conditions such as hypertensive disorders (preeclampsia/eclampsia), hemorrhage, infection, pulmonary edema, shock, gestational diabetes, and critical laboratory values that arise during pregnancy, childbirth, or within 42 days after termination of pregnancy. Maternal death was defined as the death of a mother during pregnancy, childbirth, or within 42 days after termination of pregnancy, which might be caused by the pregnancy process or medical intervention, but not due to incidental events. The type of organ dysfunction, based on Mantell criteria, evaluated the presence of cardiovascular, respiratory, renal, coagulation, uterine, hepatic, neurological, and immunological dysfunctions. $MgSO_4$ therapy was administered in patients with severe preeclampsia, eclampsia, preeclampsia with neurological symptoms (severe headache or visual disturbances), severe gestational hypertension at risk of seizures, and women at risk of preterm delivery for fetal neuroprotection.

Data were collected from medical records using data extraction forms, then tabulated and analyzed. Analysis was performed using SPSS version 29 with Chi-square and Fisher exact tests. Results were considered significant if $p<0.05$.

Ethical approval was obtained from the Medical and Health Research Ethics Committee (KEPK) of Dr. Kariadi General Hospital, Semarang (Ethical Clearance No. 16630/EC/KEPK-RSDK/2025), issued on October 24, 2025.

RESULTS

An evaluation of 225 pregnant women, women who had given birth, and women in the postpartum period at Dr. Kariadi Hospital in Semarang in 2024 found that 174 mothers (77.3%) experienced preeclampsia/eclampsia, 32 mothers (14.2%) experienced superimposed preeclampsia, 7 mothers (3.1%) experienced chronic hypertension, and 12 mothers (5.3%) experienced gestational hypertension. Further analysis yielded the following results.

TABLE 1
Criteria for organ dysfunction based on Mantel

Diagnosis	Criteria
Organ dysfunction based on Mantell	a. Cardiac dysfunction (pulmonary edema or cardiac arrest) b. Vascular dysfunction (hypovolemia necessitating transfusion of ≥5 units of whole blood or packed red cells for resuscitation) c. Immunological dysfunction (requirement for intensive care due to sepsis or emergency hysterectomy secondary to sepsis) d. Respiratory dysfunction (intubation and mechanical ventilation for >60 minutes for reasons other than general anesthesia, oxygen saturation <90% on pulse oximetry persisting for >60 minutes, PaO_2/FiO_2 ratio <300) e. Renal dysfunction (oliguria, urea levels >15 mmol/L, or creatinine >400 mmol/L) f. Hepatic dysfunction (jaundice in the presence of preeclampsia) and metabolic dysfunction (diabetic ketoacidosis or thyroid storm) g. Coagulation dysfunction (acute thrombocytopenia requiring transfusion) h. Cerebral dysfunction (coma lasting >12 hours or subarachnoid/intracerebral hemorrhage) i. Management-based criteria (admission to intensive care, emergency hysterectomy, or anesthesia-related complications such as severe hypotension due to spinal/epidural anesthesia or failed tracheal intubation)

TABLE 2
The relationship between the spectrum of hypertensive disorders, MgSO4 therapy, and organ dysfunction with maternal near miss

Variables	Maternal *Near miss*		*p*	PR (CI95%)
	Yes	No		
Spectrum of hypertensive disorders			0.366[f]	NA
Preeclampsia/eclampsia	27 (90)	147 (75.4)		
Superimposed preeclampsia	3 (10)	29 (14.9)		
Chronic hypertension	0 (0)	7 (3.6)		
Gestational hypertension	0 (0)	12 (6.2)		
MgSO4 therapy			0.092[¶]	2.12 (0.84–5.30)
Yes	25 (83.3)	133 (68.2)		
No	5 (16.7)	62 (31.8)		
Organ dysfunction			<0.001[¶*]	NA
Yes	30 (100)	21 (10.8)		
No	0 (0)	174 (89.2)		
Cardiovascular dysfunction			<0.001[f*]	19.54 (10.13–37.66)
Yes	21 (70)	3 (1.5)		
No	9 (30)	192 (98.5)		
Respiratory dysfunction			<0.001[f*]	6.76 (3.83–11.94)
Yes	4 (13.3)	1 (0.5)		
No	26 (86.7)	194 (99.5)		

TABLE 2. *Continued.*

Variables	Maternal *Near miss*		*p*	PR (CI95%)
	Yes	No		
Renal dysfunction			0.017[f*]	7.96 (5.63–11.26)
Yes	2 (6.7)	0 (0)		
No	28 (93.3)	195 (100)		
Coagulation dysfunction			0.018[f*]	4.88 (2.20–10.86)
Yes	3 (10)	2 (1)		
No	27 (90)	193 (99)		
Uterine dysfunction			1.000[f]	NA
Yes	0 (0)	1 (0.5)		
No	30 (100)	194 (99.5)		
Liver dysfunction			1.000[f]	NA
Yes	0 (0)	0 (0)		
No	30 (100)	195 (100)		
Neurological dysfunction			1.000[f]	NA
Yes	0 (0)	1 (0.5)		
No	30 (100)	194 (99.5)		
Immunological dysfunction			0,225[f]	NA
Yes	0 (0)	13 (6.7)		
No	30 (100)	182 (93.3)		

[¶]Chi-square; [f]Fisher exact; [*]significant $p<0.05$
NA: Not applicable

TABLE 3
The relationship between the spectrum of hypertensive disorders, MgSO4 therapy, and organ dysfunction with maternal death

Variables	Maternal Death		*p*	PR (CI95%)
	Yes	No		
Spectrum of hypertensive disorders			0.127[f]	NA
Preeclampsia/eclampsia	18 (85.7)	156 (76.5)		
Superimposed preeclampsia	1 (4.8)	31 (15.2)		
Chronic hypertension	2 (9.5)	5 (2.5)		
Gestational hypertension	0 (0)	12 (5.9)		
MgSO4 therapy			0.060[¶]	0.46 (0.20–1.04)
Yes	11 (52.4)	133 (68.2)		
No	10 (47.6)	62 (31.8)		
Organ dysfunction			<0.001[f*]	NA
Yes	21 (100)	21 (10.8)		
No	0 (0)	174 (89.2)		

TABLE 3. *Continued.*

Variables	Maternal Death		*p*	PR (CI95%)
	Yes	No		
Cardiovascular dysfunction			0.476[f]	1.39 (0.44–4.39)
Yes	3 (14.3)	21 (10.3)		
No	18 (85.7)	183 (89.7)		
Respiratory dysfunction			0.390[f]	2.20 (0.36–13.33)
Yes	1 (4.8)	4 (2)		
No	20 (95.2)	200 (98)		
Renal dysfunction			1.000[f]	NA
Yes	0 (0)	2 (1)		
No	21 (100)	202 (99)		
Coagulation dysfunction			0.070[f]	4.63 (1.45–14.72)
Yes	2 (9.5)	3 (1.5)		
No	19 (90.5)	201 (98.5)		
Uterine dysfunction			0.093[f]	11.20 (7.37–17.01)
Yes	1 (4.8)	0 (0)		
No	20 (95.2)	204 (100)		
Liver dysfunction			1.000[f]	NA
Yes	0 (0)	0 (0)		
No	21 (100)	204 (100)		
Neurological dysfunction			0.093[f]	11.20 (7.37–17.01)
Yes	1 (4.8)	1 (0.5)		
No	20 (95.2)	204 (100)		
Immunological dysfunction			<0.001[f*]	26.50 (13.42–52.29)
Yes	13 (61.9)	13 (6.7)		
No	8 (38.1)	204 (100)		

[¶]Chi-square; [f]Fisher exact; [*]significant $p<0.05$
NA: Not applicable

The Mantell criteria based on intensive management interventions and organ dysfunction, including cardiovascular, respiratory, renal, coagulation, uterine, hepatic, neurological, and immunological dysfunctions.

The presence of any type of organ dysfunction ($p<0.001$), cardiovascular dysfunction ($p<0.001$), respiratory dysfunction ($p<0.001$), renal dysfunction ($p=0.017$), and coagulation dysfunction ($p=0.018$) significantly influenced the incidence of maternal near misses.

Maternal with cardiovascular dysfunction had a 19.54x higher risk (PR 19.54; CI95% 10.13–37.66) of experiencing maternal near miss events. Maternal respiratory dysfunction was associated with a 6.76-fold higher risk (PR 6.76; 95% CI 3.83–11.94) of maternal near miss events. Maternal with renal dysfunction had a 7.96 times higher risk (PR 7.96; 95% CI 5.63–11.26) of experiencing a maternal near miss event. Maternal with coagulation dysfunction has a 4.88x higher risk (PR 4.88; CI95% 2.20–10.86) of experiencing maternal near miss events.

However, these findings should be interpreted with caution due to the limited sample size and the inclusion of participants from a single healthcare center. This may restrict the external validity and generalizability of the results to broader populations. Therefore, the present study should be regarded as an

TABLE 4
Multivariate analysis of factors influencing maternal near miss

Variables		B	SE	Wald	df	*p*	Exp (B)	CI95%	
								Lower	Upper
Maternal near miss	MgSO4 therapy	-1.993	1.063	3.519	1	.061	.136	.017	1.093
	Organ dysfunction	-.025	4278.531	.000	1	1.000	.975	.000	–
	Cardiovascular dysfunction	23.451	4947.695	.000	1	.996	15299	.000	–
	Respiratory dysfunction	22.756	8765.907	.000	1	.998	76362	.000	–
	Renal dysfunction	43.304	30013.680	.000	1	.999	64105	.000	–
	Coagulation dysfunction	21.550	17070.412	.000	1	.999	22864	.000	–
	Immunological dysfunction	.038	35687.642	.000	1	1.000	1.038	.000	–
	Constant	-199.363	164312.036	.000	1	.999	.000	–	–

Binary logistic regression; *significant $p<0.05$

TABLE 5
Multivariate analysis of factors influencing maternal death

Variables		B	SE	Wald	df	*p*	Exp (B)	CI95%	
								Lower	Upper
Maternal death	Spectrum of hypertensive disorders	-.336	.601	.313	1	.576	.714	.220	2.320
	MgSO4 therapy	1.270	1.052	1.459	1	.227	3.562	.454	27.977
	Organ dysfunction	-1.613	.556	8.426	1	.004*	.199	.067	.592
	Coagulation dysfunction	-1.606	1.933	.690	1	.406	.201	.005	8.873
	Uterine dysfunction	16.710	40192.703	.000	1	1.000	18078	.000	–
	Neurological dysfunction	15.427	40192.934	.000	1	1.000	50082	.000	–
	Immunological dysfunction	13.361	10927.536	.000	1	.999	63462	.000	–
	Constant	-83.200	115763.837	.000	1	.999	.000	–	–

Binary logistic regression; *significant $p<0.05$

exploratory study that provides preliminary evidence of the relationships among the variables, which require confirmation through larger multicenter studies.

The presence of any type of organ dysfunction ($p<0.001$) and immunological dysfunction ($p<0.001$) associated with maternal mortality. Mothers with immunological dysfunction have a 26.50 times higher risk (PR 26.50; CI95% 13.42–52.29) of experiencing maternal mortality. Nevertheless, the results should be interpreted cautiously because the study was conducted in a relatively small sample drawn from a single healthcare institution. Such limitations may reduce the generalizability of the findings to other populations and clinical settings. Consequently, this study is best considered exploratory in nature, providing preliminary insights that warrant further validation in larger, multicenter investigations.

Multivariate logistic regression analysis showed that no variable was significantly associated with near-miss events. $MgSO_4$ therapy demonstrated a trend toward a protective effect against near-miss events (OR=0.136; 95% CI: 0.017–1.093; $p=0.061$), although statistical significance was not achieved. Organ dysfunction, cardiovascular dysfunction, respiratory dysfunction, renal dysfunction, coagulation dysfunction, and immunological dysfunction were not significant

predictors of near-miss events (all $p>0.05$).

Multivariate logistic regression analysis identified organ dysfunction as the only independent factor associated with maternal death (OR=0.199; 95% CI: 0.067–0.592; $p=0.004$). Spectrum of hypertensive disorders, $MgSO_4$ therapy, coagulation dysfunction, uterine dysfunction, neurological dysfunction, and immunological dysfunction were not significantly associated with maternal death after adjustment for other variables (all $p>0.05$). These findings indicated that organ dysfunction remained the most important factor related to maternal mortality in the study population.

DISCUSSION

The evaluation found that 77.3% of mothers experienced preeclampsia/eclampsia, 14.2% experienced superimposed preeclampsia, 3.1% experienced chronic hypertension, and 5.3% experienced gestational hypertension. Maternal near miss events were recorded in 30 subjects (13.3%), while maternal deaths occurred in 21 subjects (9.3%). Meanwhile, live births were found in 206 subjects (91.6%).

A maternal near miss is a pregnancy or delivery that threatens the mother's life but is successfully saved. A maternal near miss is preceded by potentially life-threatening conditions, in the end that can lead to a death, including various complications such as severe bleeding or eclampsia. Therefore, a near miss is the outcome of a serious condition that can be prevented, while potentially life-threatening conditions are the risk factors or causes. According to the WHO, potentially life-threatening conditions include bleeding disorders, placental abruption, and placenta accreta spectrum (accreta, increta, and percreta), as well as ectopic pregnancy, postpartum hemorrhage, uterine rupture, and other systemic conditions, along with complications such as endometritis, pulmonary edema, seizures, sepsis, shock, thrombocytopenia below 100,000, thyroid storm, and hypertensive disorders including severe preeclampsia, eclampsia, severe hypertension, hypertensive encephalopathy, and HELLP syndrome. In addition, the severity may be indicated by management-based criteria such as the need for blood transfusion, central venous access, hysterectomy, intensive care unit (ICU) admission, prolonged postpartum hospitalization exceeding 7 days, non-anesthetic intubation, return to the operating room, and other surgical interventions.[5] The WHO states that there are several conditions in which a mother is said to have experienced a near miss, including based on clinical criteria include acute cyanosis, gasping, respiratory rate >40 or <6 breaths per minute, shock, oliguria unresponsive to fluids or diuretics, coagulation failure, decreased consciousness lasting ≥12 hours, loss of consciousness with absence of pulse or cardiac activity, stroke, uncontrolled or complete paralysis, and jaundice in the presence of preeclampsia; laboratory criteria include oxygen saturation <90% for ≥60 minutes, PaO_2/FiO_2 <200 mmHg, creatinine >300 mmol/L or >3.5 mg/dL, bilirubin >100 mmol/L or >6.0 mg/dL, pH <7.1, lactate >5 mmol/L, loss of consciousness, and the presence of glucose and ketones in the urine; while management criteria include continuous use of vasoactive medications, uterine hemorrhage or infection requiring hysterectomy, transfusion of >5 units of red blood cells, intubation and mechanical ventilation for >60 minutes unrelated to anesthesia, dialysis for acute renal failure, or cardiopulmonary resuscitation.[6]

Eltigani A, *et al*., in a study involving 15,202 mothers, found 339 cases of near miss, 20 cases (5.9%) of preeclampsia, and 12 cases (3.5%) of eclampsia.[7] Tallapureddy S, *et al*., in a study at a tertiary hospital, found that 184 mothers had life-threatening pregnancy conditions, with severe preeclampsia occurring in 50.54% of subjects and eclampsia in 13.59% of subjects. SMO was reported in 38 subjects, consisting of 6 maternal deaths and 32 near-miss events. SMOR was reported at 10.04/1000 live births, MNMR was reported at 8.46/100 live births, maternal near miss mortality ratio was 5.34, and mortality index was 15.79%.[8] Dadhich R, *et al*. In an evaluation of 6,028 mothers, 5,713 live births were recorded. A total of 164 maternal near miss cases and 111 maternal deaths were recorded. The Maternal Near Miss Ratio (MNMR) was 28.70 per 1,000 live births, while the Maternal Near Miss to Maternal Mortality Ratio was 1.46, with a mortality index of 40.36%. The leading cause of near-miss events was pregnancy-induced hypertension (85 cases; 51.82%), followed by hemorrhage (39 cases; 23.78%).[9] Mawarti Y, *et al*., who conducted research at Dr. Sardjito Hospital in Yogyakarta involving 318 subjects, found that maternal deaths occurred in 28 subjects and near misses in 86 subjects. Eclampsia occurred in 30 subjects and severe preeclampsia in 99 subjects. Live births occurred in 303 subjects. The evaluation yielded an SMO of 114 cases, MNMR of 283.17/1000 live births, MMR of 9,240.25/100,000 live births, SMOR of 376.24/1,000 live births, MMI of 24.56%, and FR of 32.56%.[10] Laksana MAC, *et al*. in a study conducted at Dr. Soetomo General Hospital in Surabaya, there were 91 maternal deaths out of 926 deliveries in 2021 and 53 maternal deaths out of 912 deliveries in 2022.[11]

The most reported organ dysfunction in mothers was cardiovascular dysfunction (10.7%), followed by immunological dysfunction (5.8%), respiratory dysfunction (2.2%), and coagulation dysfunction (2.2%). Herklots T, *et al*., in a large-scale study involving 26,842 mothers, found that the most reported organ dysfunction in mothers with poor outcomes was hematological or coagulation dysfunction (52%), cardiovascular dysfunction (46%), and respiratory dysfunction (35%).[12] Drechsel KCE, *et al*., in a study

involving 447 pregnant women with hypertension, found 160 cases of maternal outcomes with poor results. The most commonly reported organ dysfunction was hematological or coagulation dysfunction and respiratory dysfunction, accounting for 59/160 [38.6%] and 23/160 [14.8%], respectively.[13] Eltigani A, *et al*. in a study involving 15,202 mothers found hepatic dysfunction in 9 subjects (2.7%), coagulation dysfunction in 9 subjects (2.7%), renal dysfunction in 8 subjects (2.4%), cardiovascular dysfunction in 4 subjects (1.2%), and respiratory dysfunction in 2 subjects (0.6%).[7]

Preeclampsia and gestational hypertension are among the most common hypertensive disorders in pregnancy, with preeclampsia notably linked to an elevated risk of future cardiovascular disease (CVD). Women who experience gestational hypertension during their first pregnancy have a 1.8-fold increased risk of developing CVD later in life (95% CI, 1.7–2.0) compared to those without pregnancy-related hypertension. This risk rises further, with a hazard ratio of 2.6 (95% CI, 2.3–3.0), when gestational hypertension is accompanied by small-for-gestational-age infants and/or preterm delivery.[14] Cardiovascular dysfunction characterized by pulmonary edema and cardiac arrest in pregnancy with hypertension (preeclampsia) is the result of a combination of endothelial dysfunction, increased systemic vascular resistance, fluid dynamics shifts, and direct cardiac damage.[15] Pulmonary edema, the most common cardiopulmonary complication of preeclampsia, is characterized by the excessive accumulation of fluid within the interstitial and alveolar spaces of the lungs.

Immunological dysfunction was assessed based on the presence of maternal sepsis, with an uncontrolled systemic inflammatory response playing a central role in the pathogenesis of preeclampsia. This condition is characterized by chronic inflammation, including oxidative stress, increased production of pro-inflammatory cytokines, and dysregulated T-cell function. Harrison RK *et al*. reported that the incidence of maternal peripartum infection was significantly higher in women with preeclampsia compared to those without (4.2% vs. 3.8%, p=0.026). Further analysis showed increased rates of wound infection (1.0% vs. 0.5%, p<0.001) and postpartum fever (8.2% vs. 4.4%, p<0.001) among women diagnosed with preeclampsia.[16] Inflammatory dysfunction occurs during preeclampsia, including excessive production of cytokines such as tumor necrosis factor alpha (TNF-a) and interleukin (IL)-6, decreased production of anti-inflammatory cytokines such as IL-4 and IL-10, worsening oxidative stress, and T cell dysregulation.[17,18] An exaggerated inflammatory response plays a key role in both preeclampsia and infection. During infection, similar inflammatory pathways are triggered, including elevated levels of TNF-α and IL-6. The body's physiological response to infection leads to fluid shifting into the interstitial space, resulting in tissue edema and potential organ dysfunction or failure, closely resembling the pathophysiological changes observed in preeclampsia.

Respiratory dysfunction in this study was evaluated based on the presence of respiratory distress/acute respiratory distress syndrome (ARDS), characterized by a PaO2/FiO2 ratio < 300. In this group of patients, intubation was generally required due to the risk of respiratory failure. ARDS is a clinical syndrome characterized by several clinical features and pathological responses that primarily involve the respiratory system. Severe inflammation occurs in the lungs, including injury to the alveolar-capillary barrier, surfactant deficiency, and loss of aerated lung tissue. These inflammatory processes contribute to the development of pulmonary edema, which may result in severe hypoxemia, reduced lung compliance, and increased intrapulmonary shunting and dead space ventilation.[19]

Coagulation dysfunction in pregnant women is assessed based on the presence of severe thrombocytopenia (<50,000) or the need for massive blood transfusions (>5 units of blood products). Thrombocytopenia during pregnancy may arise from obstetric conditions, such as gestational thrombocytopenia and preeclampsia/eclampsia, or occur secondary to systemic disorders, including thrombotic thrombocytopenic purpura and immune thrombocytopenia.[20] Mayama M, *et al*., in a study of 264 mothers, found that severe thrombocytopenia occurred in 24 patients. The estimated relative risk of severe thrombocytopenia was 4.46 [95% confidence interval, 2.59–7.68] for maternal organ damage except thrombocytopenia, 1.61 [1.06–2.45] for preterm delivery <34 weeks of gestation, and 1.35 [1.06–1.73] for admission to the neonatal intensive care unit.[21] Blood coagulation disorders, including thrombocytopenia, are signs of maternal organ damage. Therefore, the presence of thrombocytopenia alone is sufficient to classify a patient as having severe preeclampsia, even in the absence of other manifestations of maternal organ damage.

Mothers with cardiovascular dysfunction have a 19.54 times higher risk of experiencing a maternal near miss. Bashour H *et al*., in a multicenter study, reported that bleeding-related complications were the most frequent conditions among maternal near miss cases across the four hospitals evaluated. Coagulation dysfunction was identified as the most common organ dysfunction (76.1%), followed by cardiovascular dysfunction (33.8%).[22] Cardiovascular factors contribute significantly to severe maternal morbidity (SMM), including conditions such as cardiac arrest, arrhythmias, and acute myocardial infarction. The rising incidence of SMM and its cardiovascular components is associated with increasing maternal age, greater use of assisted

reproductive technologies––often resulting in higher-risk pregnancies––and overall shifts in cardiovascular health among women of reproductive age. Additionally, the growing prevalence of congenital heart disease, diabetes mellitus, pre-pregnancy obesity, and hypertension are key factors leading to obstetric intensive care unit admissions, while smoking, nulliparity, and a history of previous cesarean delivery further elevate the risk of SMM.[23,24] Coexisting metabolic conditions––such as obesity and diabetes mellitus––as well as cardiovascular disorders including hypertension, heart failure, arrhythmias, valvular heart disease, and congenital defects, are associated with an increased risk of severe maternal morbidity (SMM).[25,26]

Maternal patients with respiratory dysfunction have a 6.76 times higher risk of experiencing maternal near misses. Tonyali NV *et al*., in a study of 50 maternal patients treated in the ICU with near misses, found that pulmonary edema occurred in 12 subjects (24%) and ARDS in 4 subjects (8%). Clinical criteria related to respiration in establishing a diagnosis of near miss included acute cyanosis in 13 subjects (39%), gasping in 3 subjects (6%), and respiratory rate >40x or <6x/minute in 33 subjects (66%). Laboratory evaluations related to respiration in the diagnosis of near miss included SpO2 <90% for >60 minutes in 35 subjects (70%), PFR <200 mmHg in 11 subjects (22%), and lactate levels >45 mg/dL in 10 subjects (20%). The types of interventions received by patients included intubation and ventilation >60 minutes in 10 subjects (20%).[27] Acute Respiratory Distress Syndrome (ARDS) causes maternal near miss through severe inflammation and alveolar-capillary membrane disruption, resulting in organ dysfunction, particularly severe hypoxemia and multiple organ failure. ARDS is characterized by a systemic inflammatory response, which can be triggered by various obstetric and non-obstetric complications. The underlying causes (e.g., sepsis, aspiration pneumonia, preeclampsia, or massive transfusion) trigger massive release of inflammatory cytokines. This causes extensive injury to pulmonary endothelial and epithelial cells. The damage compromises the integrity of the alveolar-capillary barrier, leading to increased vascular permeability. Fluid, proteins, and inflammatory cells leak into the alveoli, causing non-cardiogenic pulmonary edema. Fluid accumulation in the alveoli disrupts gas exchange, causing severe hypoxemia (low blood oxygen levels) and an increase in physiological dead space. The lungs become stiff and less elastic (reduced compliance), making breathing difficult and often requiring mechanical ventilation. Ultimately, severe inflammation and hypoxia can lead to systemic inflammatory response syndrome (SIRS) and subsequent dysfunction in other organ systems, such as the kidneys, liver, and cardiovascular system. This multi-organ failure is a key indicator of a near-miss event, where a maternal life is threatened but she survives.[28,29]

Mothers with renal dysfunction have a 7.96 times higher risk of experiencing maternal near misses. Thakur G, *et al*. stated in their study that the incidence of maternal near misses was 43.04 per 1,000 live births. A total of 18.2% of mothers experienced acute kidney injury (AKI). A total of 51.1% experienced AKI during the postpartum period. The most common cause of AKI was bleeding, which occurred in 38.3% of women. The majority of women had serum creatinine levels between 2.1–5 mg/dl, and 44.68% required dialysis.[30] Other studies indicate that preeclampsia and eclampsia are the most common causes of AKI.[31] Renal dysfunction in cases of maternal near miss is mainly a consequence of major obstetric complications. The main mechanisms causing renal dysfunction include bleeding, preeclampsia, and sepsis, which cause AKI through decreased blood flow, direct damage to the kidneys, or systemic inflammatory response. Bleeding is the leading cause of AKI in women with maternal near miss. The mechanism is often prerenal renal failure due to massive blood loss, which causes volume depletion and hypotension, resulting in a significant reduction in blood flow to the kidneys (renal hypoperfusion). If blood flow is not restored promptly, this can lead to acute tubular necrosis and intrinsic renal damage.[30,32]

Mothers with coagulation dysfunction have a 4.88 times higher risk of experiencing maternal near misses. Oliveira LC *et al*., who evaluated 255 cases of maternal near misses in the ICU, found that patient diagnoses were predominantly hypertensive disorders (62.7%), with a substantial proportion complicated by HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) (41.2%). Laboratory-based criteria were the most frequently identified indicators of maternal near miss (59.6%), largely driven by the high incidence of acute thrombocytopenia (32.5%). Additionally, 19.2% of patients required transfusion of more than 5 units of blood products.[33] Among the various maternal near miss criteria, acute thrombocytopenia is the most frequently observed, likely reflecting the high prevalence of HELLP syndrome. Acute thrombocytopenia is associated with an increased risk of maternal mortality, and delayed recognition can place the mother in a life-threatening condition.[33] Thrombocytopenia can cause maternal near misses, mainly through severe postpartum hemorrhage (PPH) due to blood clotting disorders. Severe bleeding associated with low platelet counts can cause shock, organ failure (such as kidney failure), and the need for massive blood transfusions, all of which are clinical criteria and management decisions for maternal near misses.[34]

Mothers with immunological dysfunction have a 26.50 times higher risk of maternal mortality. Arora A *et al*. reported that sepsis was the leading cause of near-miss

morbidity, occurring in 54 out of 426 cases (12.7%). Obstetric sepsis was directly identified in 33 cases (61.1%), indirectly in 8 cases (14.8%), and not identified in 13 cases (24.1%). Peritonitis was the most common diagnosis at hospital admission, observed in 27 patients (50%), and 30 patients (55%) required immediate surgical intervention. Notably, approximately 69% of cases had residual morbidity at the time of discharge.[35] Near-miss maternal events due to sepsis involve a complex interaction between maternal infection and an inadequate bodily response, leading to life-threatening organ dysfunction. The main mechanisms include excessive inflammatory response, organ injury, and, often, delayed diagnosis and treatment. Sepsis often originates from bacterial infections, commonly in the uterus, urinary system, or lungs (pneumonia). Complications such as cesarean section wounds, chorioamnionitis, and post-abortion complications are often the entry points for infection. Pregnancy involves natural immunological changes that can mask the typical symptoms of infection, making early detection difficult. When infection occurs, the body's immune response can become overactive or disrupted, causing widespread inflammation that damages the body's own tissues and organs. This widespread inflammation disrupts blood flow and oxygen delivery to vital organs, causing injury or failure of the target organ. Organ dysfunction is the primary diagnostic criterion for severe sepsis and includes conditions such as kidney failure, respiratory distress, and cardiovascular collapse (septic shock).[36,37]

This study has several limitations. First, the cross-sectional design limits the ability to assess the causal relationship between the spectrum of hypertensive disorders in pregnancy, organ dysfunction, and maternal outcomes. Second, the use of secondary medical record data depends on the completeness and accuracy of the records, thus the possibility of misclassification and missing data cannot be avoided. Third, the relatively low number of maternal deaths reduces the power of the analysis to detect significant associations. Fourth, several confounding variables such as age, parity, comorbidities, referral delays, and quality of care cannot be fully controlled and may influence the relationship between the variables studied. Fifth, the evaluation of $MgSO_4$ therapy is also limited because it does not include dose compliance or timing of administration. Sixth, immunological dysfunction representing sepsis-related mechanisms was not supported by additional data, such as microbiological confirmation, source of infection, culture results, or sepsis severity classification. Seventh, the study did not evaluate longer-term neonatal outcomes, including preterm birth, fetal growth restriction, NICU admission, stillbirth, and neonatal mortality.

CONCLUSION

Mothers with cardiovascular dysfunction, respiratory dysfunction, renal dysfunction, or coagulation dysfunction should receive monitoring during more intensive care, such as care in the ICU, because this group is at high risk of maternal near miss.

Early identification of cardiovascular, respiratory, renal, and coagulation dysfunction should be integrated into standardized obstetric screening to enable timely referral and ICU care. Close monitoring and clear clinical protocols are essential to guide intensive management and reduce the risk of maternal near miss.

CONFLICT OF INTEREST

There is no conflict of interest in this research.

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Original Article

From Eyeball to Exact: A Meta-Analysis of an Innovation in Episiotomy with Angle-Guiding Devices

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Abstract

Background : Episiotomy is a surgical incision performed to enlarge the vaginal outlet during childbirth, but an inaccurate mediolateral angle may increase the risk of obstetric anal sphincter injury (OASIS).
Scope : This systematic review focused on randomized controlled trials evaluating dedicated angle-guiding devices for mediolateral episiotomy, including Episcissors-60, Episioguide, and the Episiometer.
Aims : To compare guided episiotomy devices with conventional eyeball technique in achieving appropriate episiotomy angles and reducing OASIS.
Methods : A systematic search of PubMed, ScienceDirect, and Wiley was conducted according to PRISMA 2020 principles. Eligible studies included women undergoing vaginal birth in whom a guided device was compared with conventional scissors or routine practice. The primary outcome was post-suture episiotomy angle. Secondary outcomes were OASIS incidence, incision characteristics, pain, practical limitations, and risk of bias.
Results : Four randomized controlled trials involving 543 participants were included. Guided devices produced higher post-suture episiotomy angles than conventional technique (standardized mean difference 0.88, 95% CI 0.69–1.06; Z = 9.33; *P*<0.00001), slthough heterogeneity was substantial (I^2=97%). Based on the pooled contingency table, OASIS was more frequent in the eyeball group than in guided group (OR 4.85, 95% CI 1.38–17.07; *P*-=0.0069)
Conclusion : Angle-guiding devices may improve episiotomy angle accuracy and may reduce OASIS risk, but the evidence remains limited by few trials, sparse OASIS event, indirect comparisons between devices, and substantial heterogeneity.

Keywords : Episiotomy angle, Guided Episiotomy, Mediolateral Episiotomy, Meta Analysis, Obstetric Anal sphincter injury

INTRODUCTION

Episiotomy is a surgical incision of the perineum performed to enlarge the vaginal opening and facilitate childbirth, particularly during the second stage of labor.[1] It is one of the most commonly performed obstetric procedures worldwide, with an estimated global prevalence of 56.3%.[2] The rates are significantly higher in some Asian countries, with reports indicating 100% in China and 92.6% in Cambodia.[3] In Indonesia, the prevalence of episiotomy is approximately 33%.[4]

Obstetric Anal Sphincter Injuries (OASIS) remain one of the most significant challenges in obstetric practice, despite the widespread use of episiotomy as a preventive measure. These injuries, which can result long-term complications such as fecal incontinence, sexual dysfunction, and chronic perineal pain, pose a substantial burden on women's health and quality of life. While the rate of OASIS has decreased in many countries due to improved delivery technique and perineal protection, its prevalence remains particularly in low-resource settings.[5,6] A variety of factors contribute to the risk of OASIS, including maternal age, parity, birth weight, and delivery technique. However, the angle and type of episiotomy incision are crucial determinants in reducing the incidence of these injuries.[7,8]

While episiotomy may reduce the duration of labour and prevent severe perineal trauma in selected cases, it is not without risks. One of the most significant complications associated with episiotomy is obstetric anal sphincter injuries (OASIS), which can lead to long-term morbidity such as fecal incontinence and chronic pain.[9–11] The risk of OASIS is influenced by several factors, including the type and angle of the episiotomy.[12]

Mediolateral episiotomy is generally preferred over a midline incision because it direct the cut away from the anal sphincter complex.[12] The biomechanical rationale is that the distended perineum at crowning changes the between the cutting angle and the final post-suture angle. An incision made too close to the midline may become more medial after repair, increasing the risk of extension into the anal sphincter, whereas an excessively lateral incision may increase bleeding, pain, or inadequate perineal support. Therefore, many authors recommend a cutting angle approximately 30–60 degrees or 40–60 degrees depending on the definition used.[13–15]

To address this issue, several innovations on angle-guiding devices have been developed to assist healthcare providers in performing episiotomies within the recommended safe zone.[14,16] Among the most widely used devices are Episcissors 60®, Episioguide, and Episiometer. Episcissors 60® features an integrated guide that aligns at a 60° angle, supported by a stiff but movable spring.[14] The Episioguide, made of stainless steel, is placed on the perineum during crowning to guide an accurate incision angle.[16] The Episiometer is a horseshoe-shaped transparent template made of vellum paper, marked with angular measurements from 0° to 60°.[17,15,18]

Previous studies have evaluated these devices separately, but comparative evidence remains limited.[14,16–18] Existing trials differ in device type, clinical setting, operator experience, episiotomy indication, and outcome reporting. Moreover, the available evidence has rarely been synthesized in a way that clearly separates episiotomy angle accuracy from clinical outcomes such as OASIS. This creates a practical evidence gap. First, it is important to determine if these tolls reliably optimize the post-suture angle. Second, evidence must show whether this change translates into fewer OASIS events. Finally, clinicians need to know if any single device outperforms the others.

This systematic review and meta-analysis aimed to evaluate randomized controlled trials comparing dedicated angle-guiding devices with conventional eyeball mediolateral episiotomy. The novelty of this review is its focused synthesis of Episcissors-60, Episioguide, and Episiometer as a group of angle-standardization innovations.

METHODS

This systematic review and meta-analysis was designed and reported in accordance with the PRISMA 2020 statement.[19] The protocol was not prospectively registered before study selection and data extraction. The author have submitted this review to PROSPERO for registration, and the registration number will be included in the manuscript as soon as it becomes available.

Studies were selected according to a PICOS framework. The population included women undergoing vaginal delivery in whom mediolateral episiotomy was performed or indicated. The intervention was any dedicated angle-guiding device for episiotomy, including Episcissors-60, Episioguide, or Episiometer. The comparator was conventional scissors, routine practice or eyeball technique without a dedicated angle guide. Eligible studies were randomized controlled trials reporting at least one prespecified outcome. Non-randomized studies, non-English articles, conference-only report without full text, duplicate publications, and articles with unavailable full text were excluded.

A systematic article search was conducted in PubMed, ScienceDirect, and Wiley. The core search strategy combined device terms and outcome term: "((((Episiometer) OR (Episioguide)) OR (Episcissors)) AND (episiotomy)) AND (((Obstetric anal sphincter injuries) OR (OASIS)) OR (Perineal Trauma))". In PubMed, Medical Subject Headings and free-text terms were combined where applicable, including "episiotomy", "obstetric anal sphincter injuries", "perineal trauma", "mediolateral episiotomy", and the device names. The same Boolean logic was adapted for

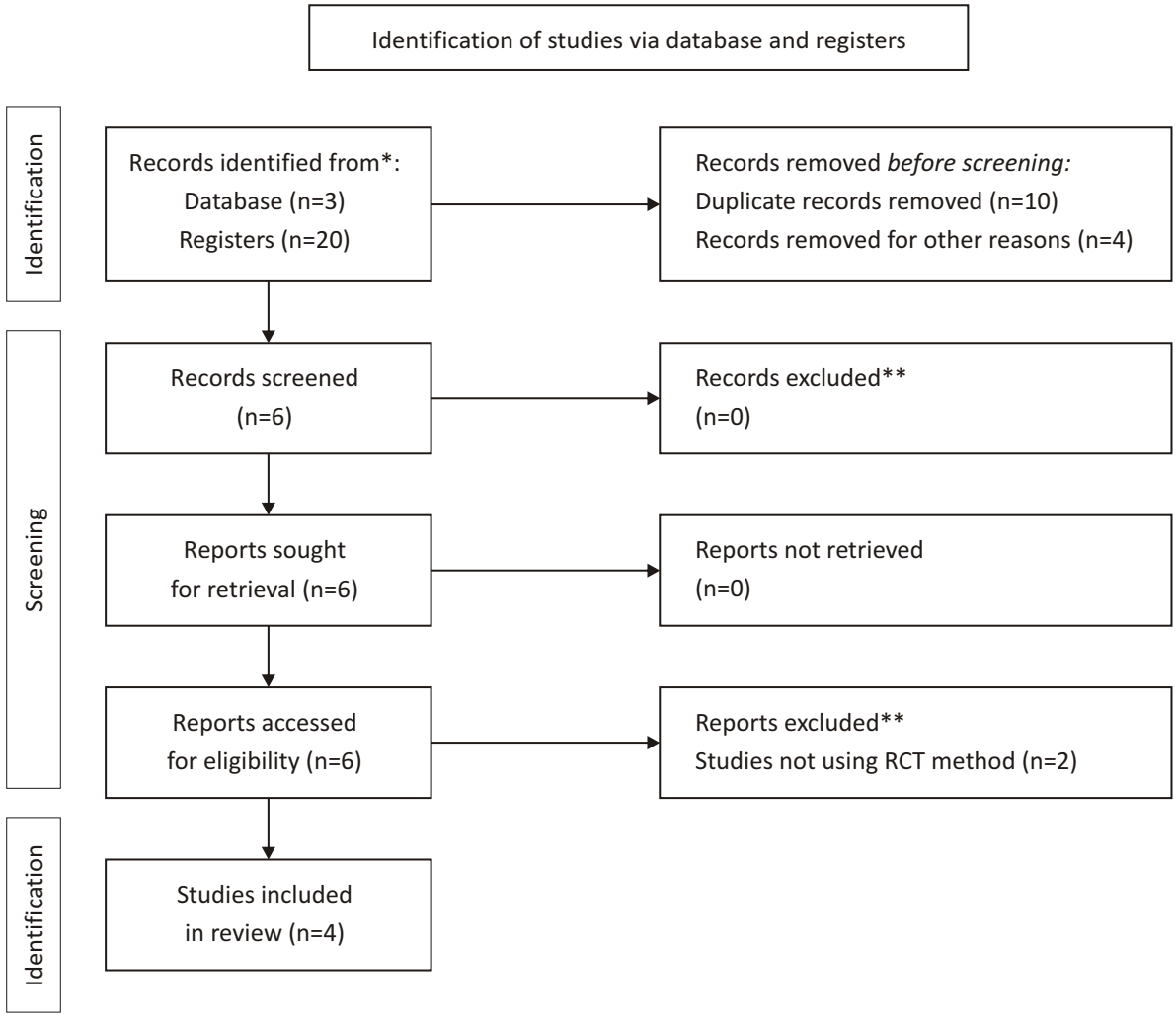

Figure 1. Flowchart of Article search

ScienceDirect and Wiley.

Titles and abstracts were screened independently by three reviewers. Full text of potentially eligible articles were assessed using the inclusion and exclusion criteria. Disagreements were resolved by discussion and, when consensus was not achieved, by consultation with the lead author. Extracted data included author, year, country, study design, sample size, device type, comparator, episiotomy angle, OASIS events, perineal pain, incision-related characteristics, device limitations, and study-level risk of bias.

The primary outcome was post-suture episiotomy angle because it directly reflects whether the incision achieved the desired mediolateral direction after tissue recoil and repair. Secondary outcomes were OASIS incidence, incision length or other incision characteristics, perineal pain, device-related limitations, and risk of bias. Device comparison was considered indirect because no included trial directly randomized participants between two different guided devices.

Risk of bias was assessed using the Cochrane Rob2 domains for randomized trial, bias arising from the randomization process, deviations from intended intervention, missing outcome data, outcome measurement, and selection of the reported result. Each domain was judged as low risk, some concerns, or high risk, and an overall judgment was assigned for each study.

Twenty articles were retrieved from three database. Ten duplicates were removed, and 4 articles were excluded due to not meeting inclusion criteria. A total of 6 titles and abstracts were screened. Among these, 2 were excluded because they were not using RCT. Finally, 4 articles met the inclusion criteria. A flowchart of the article selection process can be seen in Figure 1.

The four included randomized controlled trials were conducted in Iran, India, and Thailand and involved 543 participants. The interventions included Episcissors-60, Episioguide, and Episiometer. The comparators were conventional scissors, routine practice, or non-guided

TABLE 1
Study characteristics in the selected studies

Author, year	Study design	Country	Sample Size (n)	Devices	Key Findings
Hajhashemi M, *et al*. (2023)	RCT	Iran	64	Episcissors-60	• Episcissors had significantly higher episiotomy angles. No cases of OASIS in the Episcissors group.
Sawant G, et al. (2015)	RCT	India	63	Episcissors-60	• Episcissors produced episiotomies angled 12° more laterally. No OASIS in the Episcissors group and one evenet in control.
Thanapongpibul C, *et al.* (2022)	RCT	Thailand	88	Episioguide	• Higher post-suture angle compared with conventional scissors.
Sriram SN, *et al.* (2024)	RCT	India	328	Episiometer	• Higher episiotomy angle and fewer OASIS events than conventional technique; no significant difference in perineal pain.

eyeball mediolateral episiotomy. Table 1 summarizes the study characteristics and key findings.

Across four randomized controlled trials (RCTs) from Iran, India, and Thailand (total n=543) (Table 1), the use of dedicated episiotomy angle-guiding devices was consistently associated with improved episiotomy angle compared with conventional scissors, with several studies also suggesting a reduction in obstetric anal sphincter injuries (OASIS).

Episiotomy incision length was examined in studies such as Hajhashemi *et al*. (2023), the Episcissor device achieved significantly higher episiotomy angles than standard technique, indicating better adherence to a more lateral mediolateral episiotomy trajectory; notably, no OASIS cases were observed in the Episcissors arm and only 2 cases of grade 3 sphincter rupture occurred in the Mayo group. Sawant *et al*. (2015) similarly reported that Episcissors produced episiotomy incisions approximately 12° more lateral than controls, reflecting a clinically meaningful shift toward the recommended angle range; this trial recorded zero OASIS events in the intervention group versus one event in the control group using Braun-Stadler scissor. In Thailand, Thanapongpibul *et al*. (2022) evaluated the Episioguide and found that it yielded significantly higher episiotomy angles relative to conventional scissors, reinforcing the device's role in standardizing incision direction and reducing operator variability. The largest included RCT, Sriram *et al*. (2024), assessed the Episiometer and demonstrated significantly higher episiotomy angles in the device group alongside a significantly lower incidence of OASIS compared with routine practice and found no significant difference in the perineal pain.

Taken together, findings across diverse settings and device types indicate angle-guiding tools reliably increase episiotomy angle toward more optimal lateral orientation and may translate into clinically important reducing in severe perineal trauma, particularly OASIS, when compared with conventional episiotomy approaches.

Risk of bias assessment is shown in Figure 2. Most studies had low risk for missing outcomes data and outcome measurement because angle and OASIS outcomes were objectively assessed and outcome data were largely complete. Concerns were mainly related to randomization procedures, limited blinding, operator dependence, and incomplete information on whether all outcomes were prespecified. Sawant and Kumar (2015) was judged as high overall risk because of concerns in the randomization process and limited reporting of allocation concealment. Sriram *et al*. (2024) was judged as low overall risk, while the remaining studies had some concerns.

Figure 3 present the meta-analysis of OASIS incidence rate using guided and non-guided tools. Four Studies involving a total of 543 participants (63 in the Episcissor group, 44 in the Episioguide group, 164 in the Episiometer group, and 272 in the control group) were included. The pooled analysis showed that angle-guiding episiotomy tools significantly consistently facilitate episiotomy in higher degree angles (SMD 0.88, 95% CI 0,69-1.06; Z = 9.33 (P<0.00001). However, heterogeneity was substantial (Chi^2=87.08, df=3; P<0.00001; I^2=97%), indicating that the magnitude of effect differed across

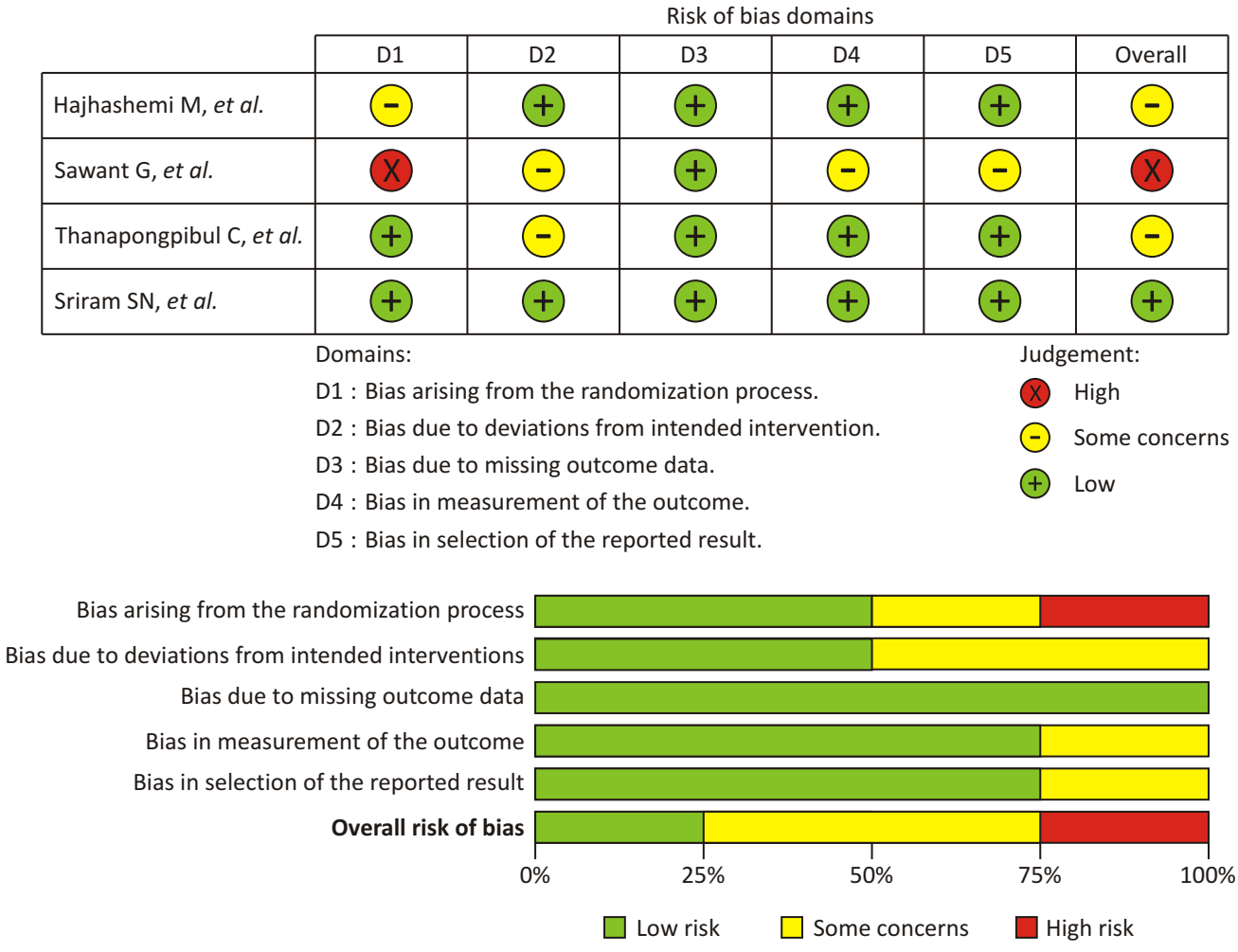

Figure 2. Risk of Bias Assessment generated by the robvis tool

trials. The result should be interpreted as an average direction of benefit rather than a uniform effect that can be generalized to every device and clinical setting.

Across the four trials, OASIS occurred in 3 of 271 participants in the guided group and in 14 of 272 participants in the eyeball group. Based on the pooled contingency table, the odds of OASIS were higher in the eyeball group than in the guided group (OR 4.85, 95% CI 1.38017.07; Chi^2=7.31; *P*=0.0069). Because OASIS was a rare outcome and several studies reported zero event in one or both arms, this estimate should be interpreted cautiously. It supports a clinically plausible reduction in OASIS with guided technique, but it does not prove superiority of one guided device over another.

DISCUSSION

This systematic review found that dedicated angle-guiding devices for mediolateral episiotomy were associated with higher post-suture episiotomy angles than conventional eyeball technique. This finding was consistent across the four included randomized controlled trials and clinically relevant because post-suture angle is closely related to the final direction of the incision relative to the anal sphincter complex.

The biological and technical rationale for these findings is plausible. During crowning, the perineum is stretched and the apparent cutting angle may narrow after delivery and suturing. A clinician attempting to estimate the angle visually may there cut too close to the midline, particularly in urgent deliveries or when operator experience is limited. Devices such as Episcissors-60, Episioguide, and Episiometer are designed to externalize the angle reference at the bedside, helping the operator maintain a more lateral trajectory despite perineal distension.[14,16,20,21]

The pooled contingency table suggested lower OASIS incidence in the guided group. This consistent with previous research, when correctly angled can reduce the risk of anal sphincter extension compared with poorly

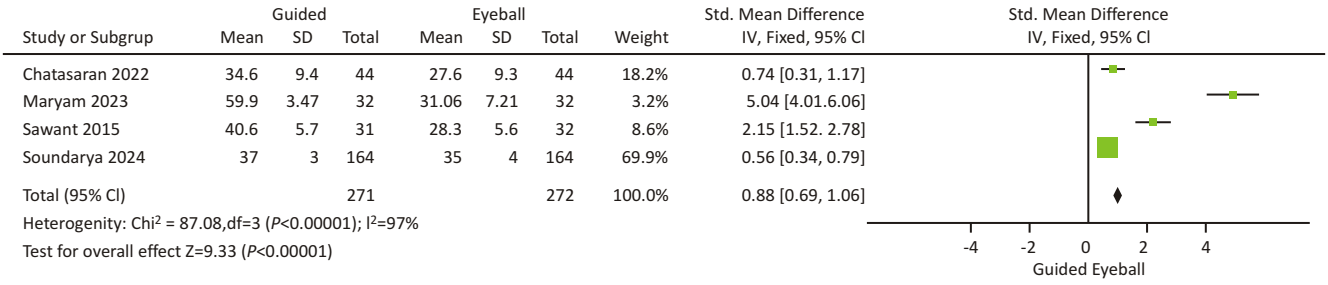

Figure 3. Forest Plot generated by Revman tool

TABLE 2
Pooled OASIS incidence included studies

Variables	Oasis	No Oasis	
Guided	3	268	271
Eyeball	14	258	272
	17	526	543

X	7,305944285
df	1
P	0,006872687
OR	4.85

angled incisions.[12,22–24] Nevertheless, OASIS is a rare outcome, and the total number of events in the included trials was small. The confidence interval around the OASIS estimate was wide, meaning that the true magnitude of benefit may be smaller or larger than the point estimate.[25,26,7]

The high Heterogeneity for the angle outcome is an important limitation. The included trials differed in device type, sample size, population, delivery setting, operator training, episiotomy indication, and outcome measurement. The largest trial evaluated the Episiometer, while smaller trials evaluated Episcissors-60 and Episioguide. Therefore, the pooled estimate should not be interpreted as direct evidence that one device is superior to another. The present review supports the concept of angle guidance as a technique-standardization strategy, but device ranking would require head-to-head randomized trials or a sufficiently powered network meta-analysis.

From an implementation perspective, the devices may have different advantages. Episcissors-60 may be easier for clinicians already familiar with conventional scissors because the angle guide is integrated into the instrument.[17] Episiometer may be more affordable and easier to disseminate in low-resource setting, although it requires preparation and correct placement.[16] Episioguide may standardize the cutting direction but its acceptability, discomfort during placement, and effect on workflow require better prospective measurement. These practical considerations are important for maternity units, primary health facilities, and midwifery-led services where variability in episiotomy technique bay be high.[27]

Several limitations should be acknowledged. First, only four trials were included, limiting statistical power and preventing reliable subgroup analysis or meta-regression. Second, no trial directly compared one guided device with another, therefore, all device comparisons are indirect. Third, OASIS was rare, producing sparse event data and wide confidence intervals. Fourth, heterogeneity for the angle outcome was substantial, suggesting that pooled result may be influenced by differences in device design, operator experience, population characteristics, and measurement methods. Another limitation is that the review protocol was not prospectively registered before the conduct of the review. Although the methods were structured according to PRISMA 2020, the absence of prospective registration may reduce transparency and should be considered when interpreting the findings.

CONCLUSION

Angle-guiding devices for mediolateral episiotomy may improve post-suture angle accuracy compared with conventional eyeball technique and may reduce OASIS incidence. However, the current evidence is based on only four randomized controlled trials, sparse OASIS event, indirect comparison between devices, and substantial heterogeneity for angle outcome. These devices should therefore be viewed as promising technical aids rather than definitive replacement for training, clinical judgment, and comprehensive perineal protection strategies. Future multicentre randomized trials should prespecify primary and secondary outcomes, use standardized angle and OASIS definitions, report patient discomfort and cost-effectiveness, and directly compare available devices in different clinical

REGISTRATION AND PROTOCOL

This systematic review was registered in PROSPERO under registration number CRD420261402158.

CONFLICT OF INTEREST

The authors declared no conflicts of interest. No funding was received for this study.

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Original Article

Comparative Effectiveness of Etoricoxib and Diclofenac Sodium in Improving Quality of Life Among Osteoarthritis Patients

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Abstract

Background : The effectiveness of etoricoxib versus diclofenac in outpatiens with pain due to osteoarthritis is unclear. There is still debate regarding the relative effectiveness and safety between both in improving the quality of life of OA patients
Aims : To assess the effectiveness of etoricoxib compared to diclofenac by assessing the quality of life outcomes of Osteoarthritis patients using instruments such as the EQ-5D-5L.
Methods : Study design using a cross-sectional study design by looking at the results of the quality of life of patients using NSAIDs in the form of diclofenac sodium and etoricoxib.
Results : The results showed that moderate positive correlation between etoricoxib or diclofenac sodium therapy in OA patients decreasing utility value (0.294; 95% CI = 0.098 – 0.467; p = 0.003). A strong positive correlation was shown between etoricoxib or sodium therapy in OA patients and VAS (0.558; 95% CI = 0.402 – 0.682; p = <0.000). These results indicate that each therapeutic use of etoricoxib or diclofenac sodium can improve the utility value or VAS, or conversely.
Conclusion : The quality of life value of etoricoxib is better than diclofenac sodium, which is 0.924 and there is a positive correlation between the use of etoricoxib and diclofenac sodium in improving quality of life and VAS values in osteoarthritis patients.

Keywords : Diclofenac Sodium, Etoricoxib, Osteoarthritis, QALYs, Utility

INTRODUCTION

Osteoarthritis (OA) is the most common joint disease worldwide, affecting approximately 10% of men and 18% of women over the age of 60 years.[1] The pain and loss of function can be debilitating; in developing countries, the resulting socio-economic burden is substantial, costing between 1–0% and 2–5% of gross domestic product.[2] Traditionally, treatment of osteoarthritis consisted of pain management with joint replacement for end-stage disease.[3–5]

Management of OA has focused on symptom relief, given the limited understanding of etiopathogenesis that hinders the development of appropriate disease-modifying drugs. According to regulations set by the American College of Rheumatology (ACR) and Osteoarthritis Research Society International (OARSI), a basic management of OA includes patient education and self-management, exercises such as strengthening, cardio, balance, neuromuscular, or mind-body exercises, as well as weight management for overweight or obese individuals. Additionally, for knee OA, the guidelines suggest alternative management such as aquatic exercise, walkers, topical and oral nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular steroid injections, and tibiofemoral bracing.[6, 7] NSAID drugs that are often used as osteoarthritis therapy are non-selective NSAIDs in the form of diclofenac sodium and for selective NSAIDs, etoricoxib.[8,9]

Although these two drugs have been widely used, there is still debate regarding the relative effectiveness and safety between etoricoxib and diclofenac sodium in improving the quality of life of OA patients. Some studies have shown that etoricoxib has a better safety profile regarding the risk of cardiovascular events compared to diclofenac sodium, but its effectiveness in improving overall quality of life still needs to be studied further. This study aims to determine the factors associated with the use of etoricoxib and diclofenac sodium, specifically while comparing the effectiveness of etoricoxib and diclofenac sodium in improving the quality of life of OA patients using the EQ 5D 5L questionnaire.[10,11]

METHODS

This study is an observational study with a cross-sectional study design. Data collection was conducted retrospectively with taking from patients medical record for the previous period and prospectively conducting quality of life data by follow up on the same subjects after the research has begun. This research have ethical approval number 481/UN6.KEP/EC/2024. Secondary data collection was carried out using medical records, while primary data collection to measure quality of life was measured using the EQ-5D-5L questionnaire in the period January 2023 to March 2024. The population in this study were all patients with a diagnosis of osteoarthritis who were undergoing outpatient care at Dr. Rivai Abdullah Hospital during the study period. The sampling technique used purposive sampling on all outpatients with OA at Dr. Rivai Abdullah Hospital in the period January 2023 to December 2023 who met the inclusion and exclusion criteria. The population of OA patients with diclofenac sodium therapy was 207 patients and etoricoxib therapy was 377 patients. Determination of sample size was calculated using the Lemeshow formula because the population size was known. The calculation of the study sample is as follows:

$$\text{Sample quantity of etoricoxib} = \frac{377.1{,}962^2 0{,}2.0{,}8}{0{,}1^2(377-1)+.1{,}96^2 0{,}2.0{,}8} = 53 \text{ patients}$$

$$\text{Sample quantity of diclofenac sodium} = \frac{207.1{,}962^2 0{,}2.0{,}8}{0{,}1^2(207-1)+.1{,}96^2 0{,}2.0{,}8} = 48 \text{ patients}$$

This research analyses data through several stages. First, univariate analysis was used to describe the characteristics of respondents in the form of frequencies and percentages. Second, bivariate analysis was run using the chi-square test to determine the factors associated with the use of sodium and etoricoxib drugs. Third, multivariate analysis with logistic regression test was performed to determine the most influential factors on the use of diclofenac sodium and etoricoxib drugs in OA patients. Fourth, to determine the correlation between the use of diclofenac sodium and etoricoxib drugs on improving the quality of life of OA patients, the Spearman test was conducted.

RESULTS

This study involved 101 outpatient OA patients consisting of 53 patients with etoricoxib therapy and 48 patients with diclofenac sodium therapy. The majority of patients were >60 years old (50.5%), female (73.3%), unemployed (58.4%), and primary school education level (62.4%). All patients were domiciled in Palembang and Banyuasin (100%). Table 1 presents the characteristics of the respondents.

Table 2 shows the results of bivariate analysis using chi-square. The results showed that employment status (p=0.014) was associated with the use of diclofenac sodium and etoricoxib therapy in OA outpatients.

Table 3 shows the results of multivariate analysis using logistic regression test conducted to determine the variables or factors that have the most influence on the use of diclofenac sodium and etoricoxib therapy in outpatient osteoarthritis patients.

TABLE 1
Characteristics of Osteoarthritis Patient Respondents Receiving Etoricoxib or Diclofenac Sodium Therapy

Characteristics	N	%
Age (years olds):		
18–39	0	0
40–59	50	49.5
> 60	51	50.5
Gender		
Male	27	26.7
Female	74	73.3
Employment status		
Work	42	41.6
Not Employed	59	58.4
Education level		
Basic Education	63	62.4
Secondary Education	38	37.6
Domicile		
Palembang or Banyuasin	101	101
Outside of Palembang or Banyuasin	0	0

TABLE 2
Factors Influencing NSAID Use in OA Patients' and 'Correlation Between NSAID Use and Quality of Life Scores

Respondent characteristics	*P* value	OR	95% CI
Ages	0.622	0.821	0.376 – 1.796
Gender	0.599	0.789	0.327 – 1.908
Employment status	0.014	0.896	0.314 – 0.830
Education Level	0.673	0.812	0.039 – 0.353
Number of diagnoses	0.248	0.876	0.127 – 0.273

TABLE 3
The Most Significant Factors Influencing the Administration of Etoricoxib or Diclofenac Sodium Therapy in Osteoarthritis Patients

Respondent characteristics	*P* value	OR	95% CI
Employment status (job)	0.128	1.271	0.934 – 1.731
Number of diagnoses	0.087	0.516	0.242 – 1.100

TABLE 4
Utility, QALY(s) and VAS Values of Osteoarthritis Patients Using Etoricoxib and Diclofenac Sodium Therapy

Therapy	Average utilities	Average QALY(s)	Average VAS
Etoricoxib	0.924	0.924	91.51
Diclofenac sodium	0.792	0.792	83

TABLE 5
Relationship Between Etoricoxib and Diclofenac Sodium Therapy Use and Utility and VAS Values

Factors	*P* value	Direction of Correlation	95% CI
Value of Utility	0.003	0.294	0.098 – 0.467
VAS	< 0.000	0.558	0.402 – 0.682

Utility and VAS values

Table 4 shows the mean values of utility, QALY, and VAS in Osteoarthritis patients using diclofenac sodium and etoricoxib. Respondents showed that the average utility in OA patients with etoricoxib therapy (0.924) was higher than patients with diclofenac sodium therapy (0.792).

Table 5 shows the results of the Spearman test analysis. There was a moderate positive correlation between etoricoxib or diclofenac sodium therapy in OA patients decreasing utility value (0.294; 95% CI = 0.098 – 0.467; $p = 0.003$). A strong positive correlation was shown between etoricoxib or sodium therapy in OA patients and VAS (0.558; 95% CI = 0.402 – 0.682; $p = <0.000$). These results indicate that each therapeutic use of etoricoxib or diclofenac sodium can improve the utility value or VAS, or conversely.

DISCUSSION

Outpatient with osteoarthritis (OA) at Dr. Rivai Abdullah Banyuasin Hospital in this study were mostly older than 60 years (50.5%), female (73.3%), Studies conducted in Turkey, USA, and Canada also showed similar results, with an average age of respondents of 60 years (Lee *et al*., 2017; Nur *et al*., 2018; Pagé *et al*., 2016). Aging has been widely attributed as the main etiologic cause of OA, due to articular cartilage losing water content, experiencing modifications in ECM composition, and chondrocyte depletion.[12,13] Osteoarthritis is most commonly experienced by women compared to men. This is supported by the findings of a meta-analysis, and women also have a higher risk of developing knee and hand OA, especially in the postmenopausal period, which is consistent with the results of our study.[14,15]

The results of the quality of life analysis showed that patients treated with etoricoxib had a utility of 0.924, indicating a near-perfect quality of life equal to 1, when compared to patients treated with diclofenac sodium with a utility of 0.792. While the spearman test analysis showed a significant positive correlation between the use of etoricoxib or diclofenac sodium therapy in reducing utility and VAS values in OA patients. The side effects of each drug type may be attributed to these results, previous studies have shown that etoricoxib has a lower risk of causing gastrointestinal side effects than diclofenac, but a higher risk of cardiovascular side effects is equally demonstrated by both drugs.[16–18] Nonetheless, a meta-analysis study still showed that treatment with diclofenac and etoricoxib were similar as the most effective NSAIDs for OA pain.[19]

A previous study conducted in four hospitals in the north of the West Bank of Palestine showed that older age, lower education level, and employment.[20] These findings are consistent with our study, where the majority of respondents were older than 60 years, had primary school education, and were not employed. Older age is associated with the effects of OA on physical activity, along with social withdrawal which will negatively affect their quality of life.[21] Lower education levels and unemployed patients have a significant influence on patients' quality of life.[20] This is a negative effect associated with less physical activity in patients, resulting in higher levels of stress and depression.[22–24] Cumulative exposure to physically strenuous work, heavy manual lifting, kneeling or squatting, and standing or walking, as well as past cumulative workload may be associated with hospitalization for knee OA.[25]

This study grouped occupations broadly without distinguishing specific physical characteristics (e.g., work duration, repetitive movements, or lifting load). As a cross-sectional design, it cannot establish temporality,

and the broad categorization may lead to non-differential misclassification, potentially underestimating the association between occupation and OA prevalence. Unmeasured confounding from specific occupational factors may also remain. Thus, findings should be interpreted cautiously, and future studies with more detailed exposure assessment are needed.

CONCLUSION

Etoricoxib was associated with higher utility and VAS scores compared to diclofenac sodium, indicating better quality of life outcomes in osteoarthritis patients, which is 0.924 and there is a positive correlation between the use of etoricoxib and diclofenac sodium in improving quality of life and VAS values in osteoarthritis patients

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Original Article

Association of C-Reactive Protein and Modified Rodnan Skin Score with Carotid Intima-Media Thickness in Systemic Sclerosis

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Abstract

Background : Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by vasculopathy and progressive fibrosis with an increased risk of cardiovascular disease. The common carotid artery intima-media thickness is an indicator of subclinical atherosclerosis and may reflect inflammatory activity in SSc. Quantitative C-reactive protein (CRP) and the modified Rodnan Skin Score (mRSS) are associated with SSc disease activity, although their relationship with common carotid intima-media thickness remains unclear.
Aims : To evaluate the relationship between quantitative CRP levels and mRSS values with common carotid intima-media thickness in adult patients with SSc.
Methods : A cross-sectional study was conducted on 26 SSc patients at Dr. Kariadi General Hospital, Semarang. Common carotid intima-media thickness was measured using ultrasonography on both sides. Subjects were categorized based on the presence of intima-media thickening according to the ≥75th percentile for age and sex. Quantitative CRP levels were analyzed using the Mann-Whitney test, while differences in mRSS were analyzed using an independent T-test.
Results : Increased common CIMT was observed in 9 patients (34.6%). There was no significant difference in quantitative CRP levels between subjects without and with intima-media thickening (0.40 [0.07–1.10] vs. 0.40 [0.20–0.83] mg/L; P = 0.787). mRSS values also did not differ significantly between the two groups (18.29 ± 9.38 vs. 18.78 ± 12.48; P = 0.912).
Conclusion : There was no significant relationship between quantitative CRP levels or mRSS values and common carotid intima-media thickness in patients with SSc. These findings may be influenced by immunosuppressive therapy and study design.

Keywords : Systemic sclerosis, Skin fibrosis, Common carotid intima-media thickness, C-reactive protein, Modified Rodnan skin score

INTRODUCTION

Systemic sclerosis (SSc), also known as scleroderma, is a chronic autoimmune rheumatic disease characterized by fibrosis of the skin and visceral organs. The autoimmune reaction targets connective tissue throughout the body, involving the skin, vasculature, gastrointestinal system, heart, lungs, and kidneys. This systemic involvement leads to a broad spectrum of clinical presentation, from mild cutaneous manifestations to life-threatening visceral organ dysfunction. The heterogeneity of organ involvement contributes to significant variability in disease course, prognosis, and response to treatment among patients.[1] SSc is a relatively rare condition which prevalence is estimated at 17.6 cases per 100,000 population with an incidence of 1.4 cases per 100,000 per year. Despite the lack of epidemiological data for Indonesia, SSc prevalence in Asia is lower at approximately 6.8 per 100,000 population. Geographic variation in SSc prevalence may imply the influence of genetic background and environmental exposure in SSC pathogenesis.[2] Similar to other autoimmune diseases, SSc occurs more frequently in women up to 3–7 times higher than men.[3,4]

The exact etiology of SSc remains unclear. Genetic susceptibility and environmental exposures contribute to SSc development. Proposed environmental triggers include cytomegalovirus and Epstein Barr virus infections, as well as exposure to silica dust and organic solvents. Occupational exposure and chronic oxidative stress have also been suggested to be involved in the disease initiation.[5,6] The pathogenesis of SSc involves vascular injury, immune dysregulation, and progressive fibrosis. Endothelial activation promotes vasoconstriction, coagulation, and smooth muscle proliferation, leading to chronic inflammation and microvascular damage. Impaired vascular repair results in persistent hypoxia.[7] Abnormal immune activation also plays a significant role as cytokine imbalance promotes profibrotic pathways while activated B cells produce disease specific autoantibodies.[8]

SSc presents with heterogeneous clinical manifestations depending on disease subset and organ involvement. The three major subsets are limited cutaneous SSc (lcSSc), diffuse cutaneous SSc (dcSSc), and SSc sine scleroderma (ssSSc). Cutaneous involvements include skin thickening, Raynaud phenomenon, and digital ulcers. Internal organ involvement contributes to significant morbidity, including interstitial lung disease, arthritis, and scleroderma renal crisis.[7,8]

Cardiovascular complications are increasingly recognized in SSc.[9] Microvascular dysfunction appears early in the disease course and contributes to macrovascular abnormalities, such as increased large artery stiffness, atherosclerotic plaque formation, and increased carotid intima media thickness (CIMT). Patients with autoimmune diseases show a higher prevalence of carotid arterial thickening than healthy individuals.[10,11] Chronic inflammation accelerates vascular smooth muscle proliferation and extracellular matrix deposition, resulting in arterial wall thickening. These vascular changes may occur in the absence of traditional cardiovascular risk factors, suggesting the role of immune-mediated injury in vasculopathy and atherosclerosis development in SSc.[12–15]

C-reactive protein (CRP) is an acute phase reactant produced in response to systemic inflammation and is widely available. Although traditionally viewed as a passive inflammatory marker, CRP may also contribute to disease progression through complement modulation and immune complex clearance.[16] Reports on CRP levels in SSc vary widely due to heterogeneity in disease phenotype and activity.[17] The modified Rodnan skin score (mRSS) is a semiquantitative clinical tool that assesses skin thickening in SSc. It correlates well with histopathological findings of SSc and is widely used to monitor disease severity and treatment response. Both CRP and mRSS have been proposed as markers to reflect systemic inflammatory state and fibrosis burden. However, their ability to reflect vascular involvement remains uncertain, especially in the context of subclinical atherosclerosis.[18]

Several studies have explored associations between CRP or mRSS and CIMT in SSc with inconsistent findings.[19–23] Evidence remains limited in the Indonesian population, whereas understanding these relationships may improve cardiovascular risk stratification in SSc. Identifying clinical and laboratory markers associated with subclinical vasculopathy and atherosclerosis may facilitate early identification of patients at higher cardiovascular risk, allowing closer monitoring to reduce long-term complications. Therefore, this study aims to analyze the association between quantitative CRP levels and mRSS with CIMT in patients with SSc.

METHODS

This cross-sectional study was conducted at the Rheumatology Outpatient Clinic, Central General Hospital Dr. Kariadi, Semarang, Indonesia in May to August 2025. We recruited adult patients (≥18 years of age) diagnosed with SSc based on the ACR/EULAR 2013 criteria (Table 1). Consecutive sampling was applied to minimize selection bias and represent a real-world outpatient setting. Patients that presented with other autoimmune disease, acute infection, tuberculosis, malignancy, or pregnancy were excluded. Ethical approval was received from the Health Research Ethics Committee of the Faculty of Medicine, Diponegoro University/Central General Hospital Dr. Kariadi Semarang (No. 16416/EC/KEPK-RSDK/2025). The study was conducted in accordance with the Declaration

TABLE 1
ACR/EULAR criteria for the diagnosis of systemic sclerosis

Criteria	Sub-criteria	Score
Skin thickening of the fingers of both hands from proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers (*count the highest score)*	Puffy fingers	2
	Sclerodactyly (distal to MCP but proximal to the PIPs)	4
Finger tip lesions	Digital tip ulcers	2
	Finger tip pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Lung involvement	Pulmonary arterial hypertension or interstitial lung disease	2
Raynaud's phenomenon		3
Scleroderma-related antibodies	At least one of anticentromere antibody, anti-topoisomerase I antibody, or anti-RNA polymerase III antibody	3

ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; MCP: metacarpophalangeal; PIP: proximal interphalangeal joint; RNA: ribonucleic acid.

of Helsinki and all participants provided written informed consent prior to enrollment.

Data were collected during outpatient visit through interview, physical examination, laboratory examination, and carotid ultrasonography (Figure 1). Baseline characteristics data included age at initial presentation, sex, and cardiovascular comorbidities, such as hypertension, type 2 diabetes mellitus (DM), and hyperlipidemia. Hypertension was diagnosed if systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and/or the patient was currently taking antihypertensive medications.[24] Type 2 DM was diagnosed if fasting plasma glucose ≥126 mg/dL, plasma glucose ≥200 mg/dL two hours after a 75 gram–oral glucose tolerance test, random plasma glucose ≥200 mg/dL in the presence of classic symptoms or hyperglycemic crisis, HbA1c ≥6.5%, or current use of antidiabetic medications.[25] Dyslipidemia was diagnosed if plasma lipid panel had total cholesterol ≥200 mg/dL, LDL cholesterol ≥130 mg/dL, HDL cholesterol <40 mg/dL or >60 mg/dL, and/or triglyceride >150 mg/dL.[26] History of immunosuppressants consumption in the context of SSc treatment was retrieved from the electronic medical record.

Assessment of mRSS was performed on 17 skin areas reported by Clements *et al*.: fingers, dorsum of the hands, forearms, upper arms, face, chest, abdomen, thighs, lower legs, and dorsum of the feet (Table 2). Each area was given a score of 0 to 3 according to the most severe thickening in the corresponding area. A score of 0 indicated normal skin with no signs of thickening, 1 indicated mild thickening, 2 indicated moderate thickening, and 3 indicated severe thickening with inability to pinch the skin. The total mRSS score ranged from 0 to 51 with higher scores indicating more extensive skin involvement. To reduce interobserver variability, all examinations were conducted by an experienced rheumatologist who had undergone standardized training in mRSS assessment.[18,27]

Quantitative CRP was measured from the venous blood using the Quantikine® human CRP enzyme-linked immunoassay (ELISA) kit (R&D Systems, Minneapolis, USA) at an independent out-of-hospital laboratory. CIMT was measured by a cardiovascular specialist using a B-mode ultrasound system (LOGIQ™ S7, GE HealthCare, Wisconsin, USA) and a 12 MHz transducer (GE HealthCare, Wisconsin, USA) during the outpatient visit. Measurements were taken from the lumen intima border to the media adventitia border. The evaluation was conducted on the far wall of the common carotid artery, located 1 cm proximal to the carotid bifurcation. Both the right and left carotid arteries were assessed.[29] Increased CIMT was defined when at least one measurement was equal to or above the 75th percentile

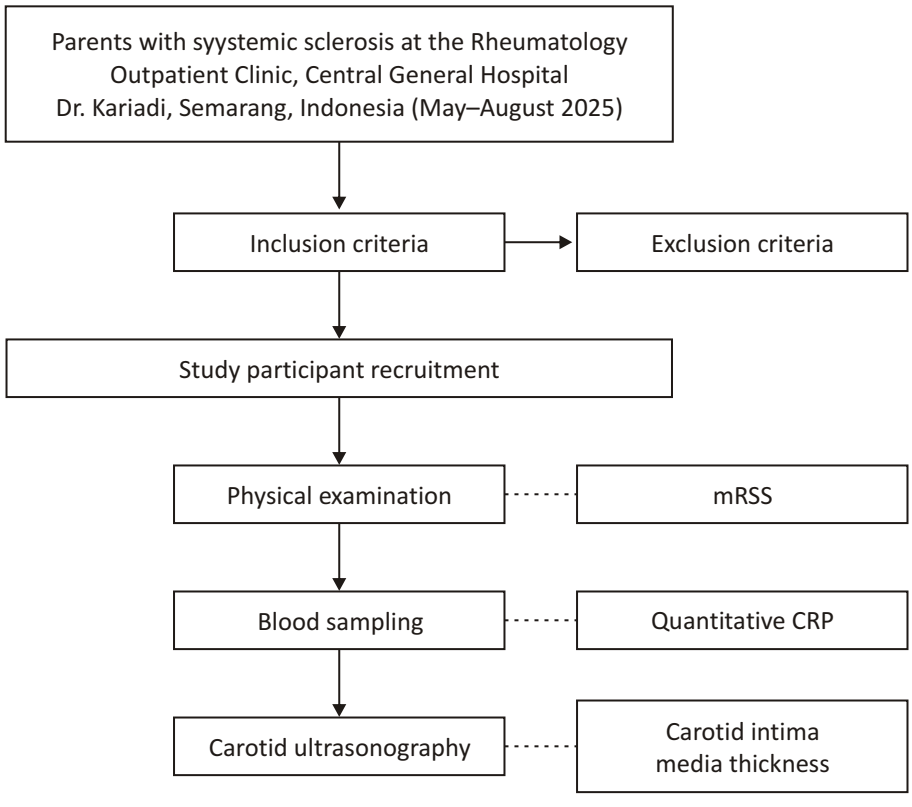

Figure 1. Flow of study participants recruitment.
mRSS: modified Rodnan skin score; CRP: C-reactive protein.

TABLE 2
Modified Rodnan skin score assessment technique based on the skin area.[28]

Skin area	Technique
Fingers	The backs of the fingers between the proximal interphalangeal and metacarpophalangeal joints are evaluated.
Forearms and upper arms	The extensor side is prefered to the flexor side.
Face	The cheeks (below the zygomatic arch and over the mandible) are prefered to the forehead.
Chest	The patient is seated and skin thickening is evaluated from the uppermost to the lowermost margin of the sternum, including the breasts.
Abdomen	The patient is in the supine position and skin thickening is evaluated from the lowermost margin of the sternum to the uppermost margin of the pelvis.
Thighs, lower legs, and dorsum of the feet	The patient is in the supine position with bent knees.

for age and sex based on Asian population reference values (Table 3).[30]

Continuous data were reported as mean ± standard deviation (SD) or median (quatile 1–quartile 3), as appropriate. Data normality was tested using the Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages. Comparisons of pre-test and post-test data were performed using the paired T-test or Wilcoxon test according to the data distribution normality. Independent T-test or Mann-Whitney test were used to compare the control groups to the treatment groups. For normally distributed numerical data, one-

TABLE 3
Normal range of carotid intima media thickness based on sex, age, and location in Asian population.[30]

Sex	Age (years)	Left carotid (mm)			Right carotid (mm)		
		P25	P50	P75	P25	P50	P75
Male	<30	0.42	0.44	0.49	0.39	0.43	0.48
	31–40	0.44	0.47	0.57	0.42	0.46	0.50
	41–50	0.50	0.55	0.61	0.46	0.50	0.57
	>50	0.53	0.61	0.70	0.46	0.52	0.62
Female	<30	0.30	0.44	0.46	0.39	0.40	0.43
	31–40	0.44	0.47	0.51	0.42	0.45	0.49
	41–50	0.46	0.51	0.57	0.44	0.48	0.53
	>50	0.52	0.59	0.64	0.50	0.54	0.59

way analysis of variance (ANOVA) were conducted and followed by the post-hoc analysis; otherwise, the Kruskal-Wallis test and Mann-Whitney test were used, consecutively. Statistical significance was defined as *P* value of ≤0.05. A two-tailed analysis approach was used for all statistical analysis. SPSS™ Statistics Version 26 (IBM®, Illinois, USA) software was used to perform all statistical analysis.

RESULTS

During the data collection period, 26 patients met the eligibility criteria and were included in the analysis. A total of 25 participants were women, and more than half were aged 40 years or older with an age range of 20 to 72 years. All participants were in the dcSSC spectrum and receiving at least one type of immunosuppressive agent with mycophenolate mofetil (MMF) being the most frequently prescribed. Eighteen participants (69.2%) had a history of receiving or were currently receiving two or more immunosuppressive drugs, most commonly a combination of MMF and either methylprednisolone or prednisone. The least frequently used agents were hydroxychloroquine and methotrexate. The baseline characteristics of the study subjects are presented in Table 2.

Participants were categorized into two groups based on the presence of intima media thickening. Among nine participants with increased CIMT, only one demonstrated bilateral thickening. The group with CIMT thickening had a higher mean age compared to the group without intima media thickening, although the difference was not statistically significant (P = 0.083). Three participants had a diagnosis of hypertension, and all of them exhibited increased CIMT. The baseline characteristics of participants according to CIMT status are presented in Table 3.

There was no significant difference in quantitative CRP levels and mRSS scores between the groups with and without intima media thickening. The comparison of quantitative CRP levels and mRSS scores based on CIMT status is presented in Table 4.

DISCUSSION

Our study found no significant association between quantitative CRP levels and mRSS with CIMT in patients with SSc. Most participants in this study were women, which is consistent with the higher susceptibility of female sex to autoimmune diseases in general. Women may have up to a five-fold increased risk of developing SSc,[31] possibly due to hormonal factors, abnormal X-chromosome inactivation, and stronger B-cell–mediated immunity.[32] Estrogen has been shown to modulate immune responses by enhancing humoral immunity and promoting autoantibody production, while X-linked gene expression may further amplify this immune dysregulation cascade.[33] These mechanisms may contribute to the sex disparity in SSc prevalence. All participants had dcSSc which is more frequently observed in Asian patients.[34] Genetic differences, particularly affecting HLA alleles, may contribute to this pattern by manipulating antigen presentation and the development of disease specific autoantibodies. In addition, regional differences in environmental exposures and healthcare access may influence the clinical phenotype and timing of diagnosis, thus affecting the observed distribution of disease subsets.[35]

A third of participants of this study showed increased common carotid intima media thickness which was mostly unilateral. The left carotid artery was more frequently affected; this is expected due to its direct origin

TABLE 4
Baseline characteristics of the study population

Characteristics	Total (n = 26)
Age (years)	41.62 ± 13.43
<40	12 (46.2)
≥40	14 (53.8)
Female sex	25 (96.2)
Hypertension	3 (11.5)
Type 2 diabetes mellitus	2 (7.7)
Hyperlipidemia	1 (3.8)
SSc subsets	
lcSSc	0 (0.0)
dcSSc	26 (100.0)
ssSSc	0.46
Immunosuppressants use	
Mycophenolate mofetil	23 (88.5)
Cyclophosphamide	8 (30.8)
Cyclosporine	2 (7.7)
Hydroxychloroquine	1 (3.8)
Methotrexate	1 (3.8)
Methyprednisolone/Prednisone	11 (42.3)
Carotid intima-media thickness (mm)*	
Average	0.46 (0.42–0.54)
Right	0.45 (0.41–0.52)
Left	0.44 (0.41–0.52)

*Median (Q1–Q3)
SSc: systemic sclerosis; lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; ssSSc: sine scleroderma SSc.

from the aorta. Participants with increased CIMT tended to be older, consistent with increasing age as a risk factor of thickened CIMT.[36] This trend is also observed in Indonesian population.[37] Age-related vascular remodeling involves progressive endothelial dysfunction, increased arterial stiffness, and accumulation of extracellular matrix, all of which contribute to CIMT progression.[38] Sex and age had no significant influence on the CIMT status because this study controlled those confounding factors using sex and age specific reference values.[39] All hypertensive participants demonstrated increased CIMT thickening. This finding was likely related to chronic shear stress on the vascular wall, regardless the presence of any vasculopathy or atherosclerosis.[40]

The finding of unilateral carotid thickening predominance, particularly in the left carotid artery, may also be explained by hemodynamic factors. The left common carotid artery arises directly from the aortic arch that exposes it to higher pulsatile pressure and turbulent flow compared to the right side, which originates from the brachiocephalic trunk. This anatomical difference may predispose the left carotid artery to earlier vascular remodelling, including increased CIMT. Certain vascular geometry and flow may also influence regional susceptibility to endothelial dysfunction.[36]

In this study, quantitative CRP levels and mRSS values did not differ significantly between groups with and without increased CIMT. CRP is an acute phase protein which level fluctuates depending on the

TABLE 5
Baseline characteristics of the study population according to the carotid intima media thickness status

Characteristics	Increased CIMT (n=17)	Normal CIMT (n=9)	*P*
Age (years)	38.29 ± 11.04	47.89 ± 15.88	0.083
<40	10 (58.8)	2 (22.2)	0.110
≥40	7 (41.2)	7 (77.8)	
Sex			1.000
Male*	1 (5.9)	0 (0.0)	
Female*	16 (94.1)	9 (100.0)	
Hypertension*	0 (0.0)	3 (33.3)	**0.032**
Type 2 diabetes mellitus*	0 (0.0)	2 (22.2)	0.111
Hyperlipidemia*	0 (0.0)	1 (11.1)	0.346
SSc subsets			–
lcSSc	0 (0.0)	0 (0.0)	
dcSSc	17 (100.0)	9 (100.0)	
ssSSc	0 (0.0)	0 (0.0)	
Immunosuppressants use*			
Mycophenolic acid	14 (82.4)	9 (100.0)	0.529
Cyclophosphamide	5 (29.4)	3 (33.3)	1.000
Cyclosporine	2 (11.8)	0 (0.0)	0.529
Hydroxychloroquine	1 (5.9)	0 (0.0)	1.000
Methotrexate	1 (5.9)	0 (0.0)	1.000
Methyprednisolone/Prednisone	9 (52.9)	2 (22.2)	0.217

*Fisher's exact test
**Mann-Whitney test
CIMT: carotid intima media thickness; SSc: systemic sclerosis; lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; ssSSc: sine scleroderma SSc.

TABLE 6
C-reactive protein level and modified Rodnan skin score based on the carotid intima media thickness status

Characteristics	Total (n=26)	Increased CIMT (n=17)	Normal CIMT (n=9)	*P*
CRP (mg/L)	0.40 (0.16–0.99)	0.40 (0.07–1.10)	0.40 (0.20–0.83)	0.787
mRSS	18.46 ± 10.30	18.29 ± 9.38	18.78 ± 12.48	0.912

*Mann-Whitney test
**Independent-T test
CIMT: carotid intima media thickness; CRP: C-reactive protein; mRSS: modified Rodnan skin score

inflammatory activity. Because this study used a cross-sectional design, the measurements did not necessarily reflect peak inflammatory levels throughout the disease course. SSc has heterogeneous disease progression. Early disease is characterized by active inflammation which may increase CRP levels, while later stages are dominated by fibrosis and stabilization of inflammatory markers. Skin fibrosis usually appears after one to three

years in dcSSc.[41] Therefore, a single time-point measurement adapted in the cross-sectional approach may underestimate the cumulative inflammatory condition experienced by the patient over time. Longitudinal assessment of CRP levels may provide a more accurate representation of chronic inflammation and its relationship with vascular changes.

Inflammatory biomarkers such as ESR, CRP, and leukocyte counts do not always increase in untreated systemic rheumatic diseases. In SSc, inflammation tends to be less pronounced than in other autoimmune diseases, such as rheumatoid arthritis or systemic lupus erythematosus.[42] This relatively low-grade inflammatory profile may explain the weak association between CRP and structural vascular changes, such as CIMT. Although CRP may reflect inflammatory vascular injury, CIMT measurement by ultrasound cannot differentiate whether increased CIMT is due to vasculopathy or atherosclerosis. This limitation is quite significant in SSc where both immune-mediated vasculopathy and classic atherosclerosis plaque development may coexist and contribute to arterial wall thickening. Similarly, mRSS reflects the extent of skin fibrosis rather than direct vascular involvement. Although fibrosis and vasculopathy share common pathogenesis, including cytokine activation and endothelial dysfunction, the temporal progression of these processes may be different. As a result, mRSS may not accurately represent the degree of vascular remodeling occurring alongside with skin thickening.[1,5,43]

No significant elevation in CRP levels and mRSS may also be secondary to the use of immunosuppressive therapy. All participants were already receiving immunosuppressants at the time of blood sampling. Immunosuppressive agents used in SSc commonly reduce inflammatory cell activity or inhibit IL-6 mediated pathways.[44] Methotrexate inhibits AICAR transformylase that increases extracellular adenosine levels and suppresses T cell activation to reduce IL-6 production.[44] Mycophenolic acid inhibits inosine monophosphate dehydrogenase that inhibits lymphocyte proliferation.[45] Cyclophosphamide is an alkylating agent that induces apoptosis in rapidly dividing immune cells. Rituximab targets CD20 that affects the depletion of B lymphocytes.[46] Short-term glucocorticoids also provide potent anti-inflammatory effects by suppressing transcription factors, such as nuclear factor-kappa B (NF-κB) dan activator protein-1, thereby reducing proinflammatory cytokine production. Slightly different from other immunosuppressant agents, tocilizumab exerts its anti-inflammatory effects by blocking IL-6 receptors directly and thus inhibits CRP synthesis in hepatocytes.[47] As a result, CRP levels in patients receiving tocilizumab may not accurately reflect the true inflammatory state, leading to underestimation of its association with vascular changes. When inflammation subsides or improve due to treatment, Skin fibrosis may therefore regress spontaneously in advanced disease stages. This regression involves suppression of fibroblast activity which is driven by proinflammatory signaling. Prolonged immunosuppressive therapy may also alter the natural course of vascular remodeling by reducing endothelial activation and limiting progression of subclinical atherosclerosis.[48] Another possible explanation for the lack of association is the relatively small sample size which limits the statistical power to detect slight correlations between variables. Individual variability in disease duration, treatment response, and comorbid conditions may confound the results of this study. Moreover, the cross-sectional approach used in this study did not allow the identification of causal relationships between inflammation, fibrosis, and vascular changes.

Our study had several limitations. First, the measured quantitative CRP levels and mRSS scores did not necessarily reflect the peak inflammation state throughout the course of the disease due to the cross-sectional approach. Second, clinical data were obtained in patients already taking immunosuppresants, potentially reducing the systemic inflammation by the time of examination. Third, our study did not document the onset of the disease, autoantibodies present in each patient, medication history and its duration of administration. Difference on disease onset and duration of drug administration might cause variability on the inflammatory state. Lastly, carotid ultrasound cannot accurately distinguish whether increased CIMT is mainly contributed from vasculopathy or atherosclerosis. Overall, the widespread use of immunosuppressive therapy in this study population might have already suppressed the skin fibrosis by reducing systemic inflammation, cytokine production, and fibroblast activity. These mechanisms may explain the lack of significant association between CRP, mRSS, and CIMT in this study. Despite these findings, the presence of increased CIMT in a significant proportion of patients presents the importance of cardiovascular risk assessment in SSc, even in the absence of increased inflammatory markers. Further longitudinal prospective study is needed, preferably in patients naive to immunosuppressants, to reflect the true inflammatory state of each individuals. Disease onset, autoantibodies, and the duration of immunosuppressants also need to be documented to observe any difference in the inflammatory markers and CIMT.

CONCLUSION

There was no association between quantitative CRP levels and mRSS scores with CIMT in SSc patients. These findings may be influenced by the use of immunosuppressant agents in the cohort which may not

reflect the peak inflammatory state in SSc patients. The cross-sectional design may limit the ability to identify temporal changes in systemic inflammatory state and vascular remodeling.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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Original Article

Prolonged P-wave Dispersion Increases Risk of Perioperative Atrial Fibrillation After CABG Surgery

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Abstract

Background : Postoperative Atrial Fibrillation (POAF) is a secondary Atrial Fibrillation caused by cardiac surgical intervention, especially Coronary Artery Bypass Graft (CABG) Surgery. P-wave dispersion (Pdis) represents the difference between the maximum and minimum P-wave durations obtained from a standard 12-lead ECG. P-wave dispersion is considered a non-invasive ECG marker of atrial remodeling and may predict the occurrence of atrial fibrillation.
Aims : This study analyzes the association between P-wave dispersion and Perioperative Atrial Fibrillation after Coronary Artery Bypass Graft Surgery.
Methods : This was an observational, analytic study with a retrospective design. The total number of subjects was 48 patients, divided into the POAF group (n=24) and no POAF group (n=24). Demographic data and preoperative ECG records were obtained from the patient's medical records. The significance of P-wave dispersion was analyzed using independent t-test and logistic regression. The Receiver Operating Characteristic (ROC) test was used to define cut-off values, sensitivity, and specificity of P-wave dispersion.
Results : The total number of subjects in this study was 48 patients, consisting of 43 men and five women. The mean age of the patients was 57.85 ± 5.83 years. The mean P-wave dispersion was higher in patients who experienced POAF (64.97 ± 13.21 vs. 50.55 ± 7.14; p<0.001). P-wave Dispersion was significantly associated with the incidence of POAF (p<0.001; cut-off 55.65 ms; OR 9.00; 95% CI 2.437–33.244).
Conclusion : P-wave Dispersion is significantly associated with Postoperative Atrial Fibrillation. P-wave dispersion value greater than 55.65 ms increases the risk of POAF after CABG by 9-fold.

Keywords : Coronary Artery Bypass Graft, P-wave Dispersion, Postoperative Atrial Fibrillation

INTRODUCTION

Coronary artery disease remains the second leading cause of mortality in Indonesia, contributing to 95.68 deaths per 100,000 Indonesian population or around 14.4% of total deaths in Indonesia.[1] CABG (Coronary Artery Bypass Graft) is typically indicated in the presence of severe obstruction in one or more major coronary arteries, and/or percutaneous coronary intervention (PCI) has failed to adequately relieve the blockage.[2] According to hospital claim data reported by Indonesia's Social Security Agency for health, known as Badan Penyelenggara Jaminan Sosial (BPJS) Kesehatan, a total of 5.967 patients have survived CABG surgery from 2017 to 2022.[1]

Postoperative atrial fibrillation (POAF) was reported in patients undergoing either cardiac or non-cardiac surgery.[2,3] The incidence of POAF in cardiac surgeries is 20–40% compared to 3% in non-cardiac surgeries.[4] Approximately 30% of patients undergoing CABG develop POAF.5 In the vast majority of cases, approximately 90%, POAF manifests during the initial six-day window following a surgical procedure.[6,7] A definitive concept of POAF has not been established, as the criteria used to define POAF differ among authors and within the literature.[4] Generalized definitions of POAF amongst various publications include any POAF that requires treatment, AF lasting greater than 30 seconds in a postoperative patient, new onset of AF post-operation regardless of the duration, or any AF post-operation lasting more than ten minutes.[8] The pathophysiological mechanism underlying POAF is not fully understood, but various etiological factors are recognized as contributing to its development.[4] Preoperative, intraoperative and postoperative factors may contribute to the development of POAF.[4]

P-wave dispersion (Pdis) represents the difference between the maximum and minimum P-wave durations obtained from a standard 12-lead ECG.[9] P-wave duration reflects the time required for complete electrical depolarization of both atria.[23] The local theory suggests that diverse P-wave lengths observed in 12-lead ECG are a result of non-uniform conduction speeds across different regions of the atria.[9] Thus, Pdis is considered to be a non-invasive ECG marker for atrial remodeling and could be used as a predictor of AF.[9,10]

We identified several conflicting findings in the literature regarding mean P-wave dispersion differences between the POAF and the non-POAF group. Research by Jazi MH *et al*. and Achmad C *et al*. demonstrated that the mean P-wave dispersion was significantly higher in the POAF group compared to the no POAF group.[11,24] Conversely, a similar study conducted by Chandy J *et al*. reported no significant differences in Pdis between the two cohorts.[12] In addition, prior studies reported a wide range of mean P-wave dispersion values, indicating significant heterogeneity among study findings. Consequently, the predictive role of P-wave dispersion in stratifying POAF risk after CABG remains uncertain. To the best of our knowledge, this is the first study to establish a specific P-wave dispersion (Pdis) cut-off value for the risk stratification of POAF. Therefore, this study aimed to further investigate differences in Pdis values between the two groups and their association with POAF following CABG surgery.[11–13,24]

METHODS

This research was conducted from November 2023 to September 2024 at RSUP Dr. Kariadi, in Semarang, Central Java, Indonesia. Our study was an analytical observational study with a case-control design without matching. Subject selection used a total sampling method. Every medical record of patients who underwent CABG from October 2022 to October 2023 was screened. POAF was evaluated by Cardiology Arrhythmia Consultant using Holter ECG 96 hours after surgery. The exclusion criteria were patients diagnosed with atrial fibrillation before CABG surgery, arrhythmia in baseline ECG, primary valvular heart disease, congenital heart disease, and incomplete data (missing preoperative ECG or medical record).

The preoperative 12-lead ECG paper was scanned using a *Brother Portable Compact Mobile Scanner DS-640*. P-wave dispersion measurements were performed digitally using ImageJ software by a trained investigator blinded to subject's AF status. The Pdis value was measured by subtracting the longest and shortest P-wave durations from 12-leads ECG with a standard calibration of 25 mm/s. The onset of the P-wave is the first deflection of the isoelectric line defined by the T-P segment, while the offset is defined as the intersection of the tip of the P-wave and its return to the baseline.

Demographic data, including age and sex, were evaluated in two groups; those with AF and those with normal sinus rhythm. Patient's comorbidities evaluated in this study include the presence of diabetes mellitus (DM), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), previous episode of myocardial infarction (MI), and pericardial effusion. Surgical factors, including aortic cross clamp time (XCT) and cardiopulmonary bypass time (CPB), were also taken into account.

Data analysis was carried out using SPSS version 23.0. The *Shapiro-Wilk* test was used to assess the normality of the data. Either an independent t-test or a *Mann-Whitney* test was used to analyze the numeric variable, whereas the Chi-square test was used to analyze the categorical variable. The intraclass correlation coefficient (ICC) with its 95% confidence interval was used to assses the intrarater reliabiltiy analyses for agreement on absolute agreement with a two-way mixed

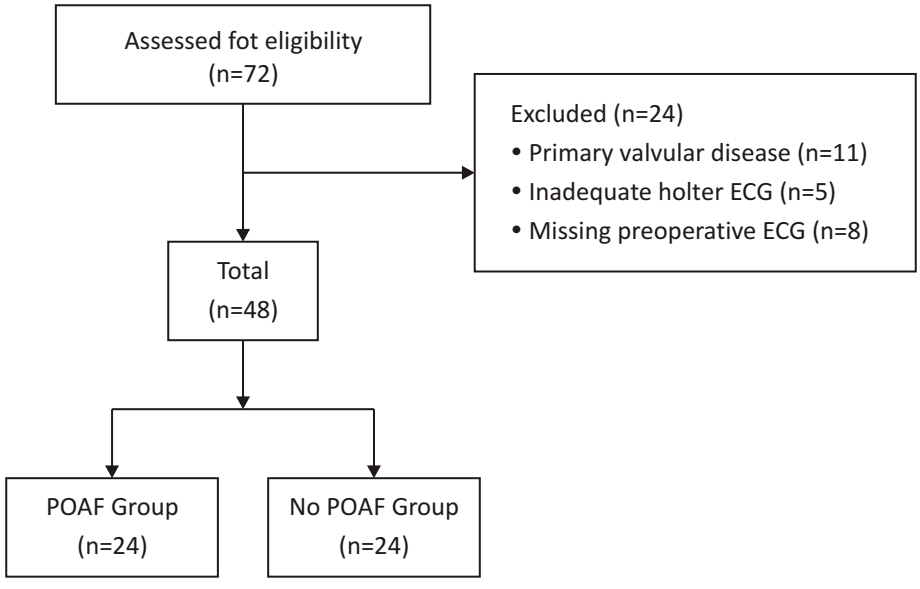

Figure 1. Flowchart of Patient Selection and Grouping

effects model. ICC estimates were calculated on a basis of a total two measurement on 10 participants (the second measurement was performed two weeks after the first measurement). The *Receiver Operating Characteristic* (ROC) test was used to define cut-off values, sensitivity, and specificity of Pdis. Multivariable logistic regression analysis with backward elimination was undertaken to assess the predictors of POAF. Variables with a *p*-value <0.25 in the bivariate analysis were included in the multivariate analysis.

Ethical clearance was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Diponegoro, Semarang, with number 169/KEPK/FK-UNDIP/IV/2024.

RESULTS

The total number of subjects was 48, divided equally between the POAF and non-POAF groups. The majority of subjects were men (89.6%). The mean age of the research subjects was 57.85 ± 5.83, and the mean BMI was 25.51 ± 3.76. Patient's comorbid data were DM (39.6%), congestive heart failure (37.5%), COPD (4.3%), CKD (10.4%), and history of MI (43.8%). The mean duration of CPB was 67.94 ± 10.89 minutes, and XCT was 54.90 ± 10.09 minutes. A total of 16 patients (33.3%) developed pericardial effusion after CABG surgery. The baseline characteristics of the subjects was shown in Table 1.

Patients with POAF were one year older than those who remained in sinus rhythm. However, there was no significant difference between the two groups (58.42 ± 5.08 vs 57.29 ± 6.56; *p*=0.51). Regarding gender, there was no significant difference among subjects who developed POAF. As shown in Table 2, subjects who developed AF had a similar body surface area to those with sinus rhythm (26.01 ± 4.27 vs 25.0 ± 3.19; *p*=0.46). Other comorbidities, including DM, CHF, COPD, CKD, history of MI, and pericardial effusion, were similar between the two groups.

No statistically significant differences were observed in surgical variables between the POAF and the non-POAF group. The mean CPB duration was 67.46 ± 10.83 minutes in the POAF group compared to 68.42 ± 11.16 minutes in the no POAF group (*p*=0.764). Likewise, the mean XCT duration was 54.42 ± 10.14 minutes in POAF and 55.38 ± 10.24 minutes in non-POAF (*p*=0.836).

Bivariate analysis with an independent t-test showed that Pdis was significantly higher in patients with POAF (64.97 ± 13.21 vs. 50.55 ± 7,14 ms, *p*<0.001). There were no significant differences in confounding variables between the POAF and the non-POAF groups. A detailed bivariate analysis of confounding variables is presented in Table 2.

Reliability analyses between two measurements indicated good intrarater correlations across P-wave dispersion, as illustrated in Table 3.

Based on ROC analysis, the area under the curve (AUC) was 0.845 (*p*<0.001), indicating very good accuracy. In addition, the cut-off value for P-wave dispersion was 55.65 ms with a sensitivity and specificity of 75%.

Multivariate analysis used logistic regression with P-wave dispersion and left atrial diameter as predictors. In this study, P-wave dispersion was the only variable that influenced the incidence of POAF (OR 9.00, *p*<0.001). These results indicate that patients who have a

TABLE 1
Baseline Characteristics Comparison

Variable	Freq.	%	Mean ± SD	Median (min – max)
Group				
POAF	24	50.0		
No POAF	24	50.0		
Age (years)			57.85 ± 5.83	57 (46 – 71)
Sex				
Men	43	89.6		
Women	5	10.4		
BMI (kg/m^2)			25.51 ± 3.76	24.85 (16.77 – 35.16)
Systolic BP (mmHg)			125.77 ± 20,33	125.5 (86 – 168)
Diastolic BP (mmHg)			72.96 ± 11.88	74.5 (26 – 90)
Diabetes Mellitus				
Yes	19	39.6		
No	29	60.4		
Congestive heart failure				
Yes	18	37.5		
No	30	62.5		
COPD				
Yes	2	4.3		
No	46	95.7		
Chronic kidney disease				
Yes	5	10.4		
No	43	89.6		
History of MI				
Yes	21	43.8		
No	27	56.2		
Pericardial effusion				
Yes	16	33.3		
No	32	66.7		
CPB duration (minutes)			67.94 ± 10.89	65.5 (40–90)
XCT duration (minutes)			54.90 ± 10.09	55 (27–78)
Left atrium diameter				
≤ 40 mm	37	77.1		
> 40 mm	11	22.9		
P-wave dispersion			57.76 ± 12.78	55.65 (34.04–93.09)

BMI: Body Mass Index; BP: Blood Pressure ; COPD: Chronic Obstructive Pulmonary Disease ; MI: Myocardial Infarction ;
CPB: Cardiopulmonary Bypass ; XCT: Aortic Cross-clamp.

TABLE 2
Bivariate Analysis of P-wave Dispersion and Confounding Factor

Variable	Group		*p* value
	POAF	No POAF	
Age (years)	58.42 ± 5.08	57.29 ± 6.56	0.510
Sex			
Men	21 (87.5)	22 (91.7)	0.500
Woman	3 (12.5)	2 (8.3)	
BMI (kg/m^2)	26.01 ± 4.27	25.0 ± 3.19	0.360
Sistolic BP (mmHg)	120.79 ± 19.75	130.75 ± 20.07	0.090
Diastolic BP (mmHg)	70.58 ± 14.20	75.33 ± 8.66	0.239
Diabetes Mellitus			
Yes	5 (20.8)	14 (58.3)	0.376
No	19 (79.2)	10 (41.7)	
Congestive heart failure			
Yes	11 (45.8)	7 (29.2)	0.371
No	13 (54.2)	17 (70.8)	
COPD			
Yes	1 (4.2)	1 (4.2)	1.000
No	23 (95.8)	23 (95.8)	
Chronic kidney disease			
Yes	2 (8.3)	3 (12.5)	0.637
No	22 (91.7)	21 (87.5)	
History of MI			
Yes	10 (41.7)	11 (45.8)	0.771
No	14 (58.3)	13 (54.2)	
Pericardial effusion			
Yes	8 (33.3)	8 (33.3)	1.000
No	16 (66.7)	16 (66.7)	
CPB duration (minutes)	67.46 ± 10.83	68.42 ± 11.16	0.764
XCT duration (minutes)	54.42 ± 10.14	55.38 ± 10.24	0.836
Left atrium diameter			
≤ 40 mm	16 (66.7)	21 (87.5)	0.086
> 40 mm	8 (33.3)	3 (12.5)	
P-wave dispersion (ms)	64.97 ± 13.21	50.55 ± 7.14	<0.001*

*Considered significant (*p* value <0.05). BMI: Body Mass Index; BP: Blood Pressure ; COPD: Chronic Obstructive Pulmonary Disease ; MI: Myocardial Infarction ; CPB: Cardiopulmonary Bypass ; XCT: Aortic Cross-clamp

TABLE 3
Intra-Rater Reliability

	Reliability
P-wave dispersion	0.819 (0.293–0.955)

TABLE 4
P-wave Dispersion Cut-off's Value

	Cut-off	AUC	*p* value	Sensitivity	Specificity
P-wave dispersion	55.65 ms	0.845	<0.001*	75%	75%

*Considered significant (*p* value <0.05)

TABLE 5
Multivariate Analysis Regression Logistic

	Odds Ratio	*p* value	95% CI
P-wave dispersion	9.00	<0.001*	2.437–33.244
Left atrium diameter	3.69	0.085	0.836–16.373

*Considered significant (*p* value <0.05)

preoperative P-wave dispersion higher than 55.65 ms have 9x higher risk of experiencing POAF.

DISCUSSION

The underlying mechanism of POAF has not been completely elucidated.[4] Current evidence suggests that POAF develops through the interaction of a broad spectrum of risk factors, including patient- and surgery-related factors as well as reversible factors. Generally, risk factors of POAF can be classified into three groups based on the perioperative period: preoperative, intraoperative, and postoperative.[14] Among the variables we evaluated, only P-wave dispersion exhibited a significant difference between patients with POAF and those who remained in sinus rhythm (64.97 ± 13.21 vs. 50.55 ± 7.14; p<0.001). These results indicate that the POAF group experienced significantly slower electrical conduction than the non-POAF group. Electrical conduction abnormalities, characterized by prolonged P-wave duration, may be caused by chronic atrial electrical and structural remodeling.[7] While fibrosis protects the myocardial wall, collagen-rich scar tissue can disrupt cardiomyocyte continuity, forcing electrical impulses to traverse longer and slower conduction pathways.[7] Compared with previous studies, we found relatively different Pdis values. Achmad C *et al*. found 53.0 ± 3.8 ms vs. 44.0 ± 2.0 ms, while Khosropanah Sh *et al*. found 79.44 ± 25.0 ms vs. 70.12 ± 22.4 ms.[13,24] We believe this difference may be due to several factors, such as the measurement method used and interobserver variability. We attempted to measure Pdis as accurately as possible to reduce intraobserver variability through digital measurements. Despite these differences, our findings align with previous studies showing that preoperative Pdis values were higher in the POAF group.

In our study, Pdis demonstrated a strong diagnostic performance with an Area Under the Curve (AUC) of 0.845. Using a cut-off value of 55.65 ms, the parameter yielded balanced sensitivity and specificity levels of 75%. These results indicate that Pdis is a reliable predictor for POAF, showing high statistical significance (p<0.001). The same findings were reported by Sahin YB *et al*., who found that AF patients demonstrated significantly elevated Pdis and LAVI.[15] Nevertheless, Sahin YB *et al*. noted that upon multivariate regression, Pdis was the sole parameter to remain independently predictive of AF.[15] In line with our results, Erciyes D *et al*., found that renal transplant recipients with POAF had higher P-wave dispersion than those who maintained a normal sinus rhythm (54.46 ± 1.31 ms vs. 36.28 ± 8.04 ms, p<0.001).[16] Our proposed cut-off value may assist in identifying patients at greater risk of developing POAF, as individuals with a P-wave dispersion greater than

55.65 ms were found to have a ninefold increased risk of POAF. These findings may help clinicians recognize high-risk patients earlier, thereby enabling more intensive monitoring and consideration of preventive strategies.

Confounding preoperative and intraoperative factors that potentially led to the formation of the fibrotic substrate were analyzed in our study. These included aging, Diabetes Mellitus, COPD, CHF, history of MI, LA diameter, CPB and XCT duration.[17,18] However, our study found no differences in confounding factors between the POAF and the non-POAF groups. We initially hypothesized that the POAF group had a higher myocardial fibrosis substrate. As the atria enlarge, fibrosis increases and disrupts normal heart function.[19,23] Thus, a longer P-wave on an ECG is considered an indicator of a larger left atrium. We evaluated left atrial (LA) enlargement using LA diameter to assess pathological changes that could be structurally visualized.[25] However, in this study, LA diameter did not differ significantly between the two groups (p=0.086). Despite the POAF group exhibiting a higher LA diameter compared to the non-POAF group, the disparity was statistically insignificant (p=0.086). Thus, the study failed to support our hypothesis regarding atrial anatomical changes in CABG patients. We concluded that this heterogeneity in conduction was caused by pre-existing conditions, namely microfibrosis, which was not yet apparent in LA diameter parameters.

Eventually, patients experiencing POAF exhibit a more pronounced process of atrial structural remodeling. This progression leads to a disruption in atrial depolarization, primarily driven by conduction blockages within the fibrotic tissue.[19] Based on the higher P-wave dispersion value in this research, patients who developed POAF have a greater substrate component, which elevates the risk of POAF after CABG. However, substrate-related components are not the sole determinants of POAF.[20] Various intraoperative and postoperative factors may also contribute to its development.[21] In this context, a fibrotic atrial substrate may represent a pre-existing condition that predisposes patients to POAF, whereas perioperative factors likely act as triggering mechanisms for the occurrence of POAF in this study population.[22] We believe this study has important clinical relevance and practical applicability, as a 12-lead ECG is routinely obtained during preoperative evaluation and the digital method for P-wave dispersion measurement is relatively simple to perform.

LIMITATIONS

We had several limitations in this study. Firstly, this study was a small, retrospective, and single-center study. Secondly, the P-wave dispersion was measured at a paper speed of 25 mm/s, whereas it is ideally measured at a 50 mm/s for greater precision. Our study focused on the preoperative period, the findings may be limited by unaccounted preoperative and postoperative variables that could have influenced the study's outcome. Nevertheless, several improvements may be considered in future clinical applications and research. These include measuring Pdis at 50 mm/s and analyzing other perioperative variables such as inflammatory markers, medication use, and electrolyte levels.

CONCLUSION

Higher P-wave dispersion significantly associated with the incidence of POAF after CABG. P-wave dispersion value greater than 55,65 ms increases the risk of POAF after CABG by 9 times. Utilizing preoperative P-wave dispersion for risk stratification facilitates the preoperative identification of high-risk candidates slated for CABG.

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CONFLICT OF INTEREST

The authors have no conflicts of interest that could affect the results or interpretation in this report.

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Original Article

Relationship between Serum Interleukin-6 Level and Severity of Acne Vulgaris in Women

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Abstract

Background : Acne vulgaris is more common in women than men and is observed more frequently in older adolescents than younger adolescents (pre-teens). This is due to higher sebum production, which supports the growth of *Propionibacterium acnes*. *Propionibacterium acnes* contributes to initiating and maintaining inflammatory processes induced by immunological reactions. It activates the Toll-like receptor (TLR) 2 and 4 immune systems by releasing interleukin-6 (IL-6) as a core mediator of inflammation.
Aims : This study aims to determine the relationship between serum IL-6 levels and the severity of acne vulgaris in women.
Methods : This research employs an analytical observational study design with a cross-sectional approach, involving 15 female subjects diagnosed with acne vulgaris, divided into three groups. The study will occur in Semarang city from July 2024 to September 2024.
Results : This study involved 15 female students from Diponegoro University, categorized based on the severity of acne vulgaris (mild, moderate, severe). Blood samples were taken to measure serum IL-6 levels using the ELISA method. The average IL-6 levels found were: mild 1.00 ± 0.55 pg/ml, moderate 1.47 ± 0.27 pg/ml, and severe 1.99 ± 0.42 pg/ml. Analysis revealed a significant relationship between serum IL-6 levels and the severity of acne vulgaris (p = 0.011), supporting the hypothesis of a correlation between the two.
Conclusion : There is a significant relationship between serum IL-6 levels and the severity of AV in women. There is a meaningful difference in serum IL-6 levels between the mild and severe AV groups.

Keywords : Acne Vulgaris, IL-6 Levels, Severity of Acne Vulgaris.

INTRODUCTION

Acne vulgaris (AV) is a common chronic skin disorder that affects 80–100% of the population. It is caused by keratin blockage in the sebaceous gland ducts.[1] AV is characterized by both non-inflammatory lesions, such as comedones (blackheads and whiteheads), and inflammatory lesions (papules, pustules, nodules, and cysts). These lesions primarily occur in areas with a high density of sebaceous glands, such as the face, chest, and upper back.[2]

Other external factors, such as stress, diet, and the use of cosmetics, can also significantly influence the severity of acne vulgaris (AV). Psychological stress has been shown to exacerbate acne by increasing the production of sebum and triggering inflammatory responses in the skin. This stress-induced exacerbation is believed to be mediated by the activation of the hypothalamic-pituitary-adrenal (HPA) axis, which in turn stimulates the secretion of cortisol and other hormones that increase sebum production.[23] Additionally, certain dietary factors, particularly high glycemic index foods, dairy products, and foods rich in saturated fats, have been implicated in the worsening of acne. These foods may trigger an insulin-like growth factor (IGF-1) pathway that promotes sebum production and inflammation. The role of cosmetics is also a significant external factor, as many products contain comedogenic ingredients that can clog pores and contribute to the formation of acne lesions.[24] Understanding the interplay between internal (e.g., hormonal imbalances) and external factors provides a more comprehensive view of the pathogenesis of acne vulgaris.

The highest prevalence of AV is found in adolescents and young adults, with 85% of cases occurring between the ages of 12 and 25. Women tend to have a slightly higher prevalence than men. AV typically appears between the ages of 14 and 17 in women, while in men, it is most common between 16 and 19 years.[3] While acne often resolves after puberty, it can persist into the 30s, especially in women.

Women may experience a greater psychological burden from AV due to several factors. Hormonal imbalances, such as fluctuations in androgens and estrogens, can increase sebum production, particularly during menstruation, pregnancy, or perimenopause.[4] Psychosocial factors also play a role, as AV can lead to depression and diminished self-esteem due to concerns about appearance. Additionally, cosmetics can exacerbate the condition by clogging pores and worsening acne.[5]

The prevalence of common acne (acne vulgaris) is very high across various countries and age groups, with significant variation. Epidemiological studies indicate that at least 80–90% of adolescents and young adults experience acne vulgaris to some degree, making it one of the most common skin conditions worldwide.[16] In Indonesia specifically, acne vulgaris is prevalent among adolescents and young adults, with women tending to report more persistent conditions compared to men, primarily due to hormonal fluctuations, cosmetic use, and differing skin responses during the menstrual cycle.[17] Detailed epidemiological data from various countries also indicate that the prevalence of AV in women can reach over 85% from adolescence through young adulthood, and often persists into their 30s or beyond.

The impact of AV is not only physical but also psychosocial. A visible skin condition can lead to social stigma, reduce self-confidence, and trigger emotional disturbances such as anxiety and depression, particularly in women, who often face greater social pressure regarding their appearance.[18] Women with AV are reported to be more prone to feelings of shame, a reduced quality of life, and interpersonal relationship difficulties compared to women without AV, highlighting the need for a holistic approach to AV management, including psychological aspects.[19]

In Indonesia, the Lehmann classification, established at the 2nd Round Table Meeting in Vietnam (2003), is commonly used to classify the severity of AV into three levels based on the number of lesions: mild, moderate, and severe.[3]

Acne vulgaris is caused by multiple factors, with four key contributors:[6]

- Androgen stimulation, which increases sebum production.
- Hyperkeratosis and follicular obstruction.
- Proliferation of *P. acnes*.
- Inflammation.

P. acnes triggers the immune system through TLR2 and TLR4 on keratinocytes and monocytes, releasing pro-inflammatory cytokines such as IL-1α, IL-1β, IL-6, IL-8, IL-12, and TNF-α. These cytokines contribute to prolonged inflammation. IL-6, in particular, plays a critical role in acute and chronic inflammation in acne vulgaris. It stimulates antibody production, activates Th17 cells in the adaptive immune response, and promotes hyperkeratosis in the pilosebaceous ducts. [7,8]

A study by Nauli, Putra, and Jusuf (2023) involving 45 AV patients and 45 healthy controls found higher serum levels of IL-6 and hs-CRP in the AV group.[8] Similarly, Stańkowska *et al*. (2020) reported elevated IL-6 levels in AV patients, especially men, compared to controls. However, limited research exists on the relationship between serum IL-6 levels and AV severity in women, underscoring the need for further studies to explore this connection.[9]

Previous studies have demonstrated that Interleukin-6 (IL-6) functions as a pivotal pro-inflammatory cytokine not only in acne vulgaris but also in a wide range of other chronic inflammatory and

immune–mediated conditions. IL–6, originally identified as a B–cell stimulatory factor, plays a significant role in initiating and sustaining inflammatory responses through pathways involving NF–κB and STAT3, and its dysregulation has been implicated in chronic inflammatory diseases, autoimmune disorders, and even cancer. IL–6's involvement in systemic inflammation is well documented, highlighting its central role in mediating local and systemic immune reactions across various tissues.[20]

In dermatology, IL–6 contributes to the pathogenesis of several inflammatory skin conditions beyond acne. For example, IL–6 and its receptor dynamics have been associated with inflammatory responses in psoriasis and atopic dermatitis, where chronic activation of keratinocytes and immune cells contributes to persistent inflammation and skin barrier dysfunction. Moreover, IL–6/IL–6R signaling has been shown to mediate inflammatory factor upregulation in skin exposed to UVB radiation, underscoring its role in chronic skin inflammation and pigmentation disorders. These findings suggest that IL–6 is not only a marker of acne severity but also a broader mediator of cutaneous inflammatory processes.[21]

The broader significance of IL–6 in inflammation is further supported by research showing its elevated levels in autoimmune conditions such as rheumatoid arthritis, where IL–6 activity correlates with disease progression and severity, and in chronic inflammatory states characterized by persistent cytokine production. This evidence highlights the multifaceted roles of IL–6 in both systemic and skin–specific inflammatory pathways, providing a theoretical foundation for investigating its association with acne vulgaris and its potential as a therapeutic target.[22]

In conclusion, acne vulgaris is a multifactorial condition, influenced by both internal factors, such as hormonal imbalances, and external factors like stress, diet, and cosmetic use. IL-6 plays a significant role in the development and severity of acne, as it is involved in the inflammatory processes that characterize the condition. Given its broader impact on other inflammatory skin conditions and autoimmune diseases, IL-6 serves as a crucial mediator in both local and systemic inflammation. Therefore, understanding the relationship between IL-6 and acne vulgaris is essential for improving diagnosis and treatment strategies. This highlights the need for further research to better understand how IL-6 serum levels correlate with the severity of acne vulgaris, especially in women, to enhance therapeutic options for this common skin disorder.

METHODS

This study employed an analytical observational design with a cross-sectional approach, where data were collected at a single point in time to examine the relationship between serum Interleukin-6 (IL-6) levels and the severity of acne vulgaris (AV) in women. The study was conducted at Diponegoro University, Semarang, and included young adult female patients diagnosed with AV, selected according to specific inclusion and exclusion criteria.

The sampling process involved consecutive sampling, which is a non-probability sampling technique where participants are selected based on their availability and willingness to participate. The inclusion criteria for this study were as follows:

1. Female participants aged between 18 to 23 years.
2. Diagnosed with acne vulgaris by a certified dermatologist.
3. Willingness to provide informed consent and participate in the study, including the provision of a blood sample.

The exclusion criteria were:

1. Individuals with other skin conditions (e.g., rosacea, folliculitis) that could interfere with the diagnosis of acne vulgaris.
2. Participants with any systemic diseases such as hypertension, liver disease, or autoimmune disorders that might affect IL-6 levels.
3. Individuals who had been treated with systemic or topical antibiotics, steroids, or retinoids within one month prior to the study.
4. Pregnancy or lactating women, as hormonal fluctuations during these conditions may significantly alter serum IL-6 levels.

Data collection began with a thorough anamnesis of participants to gather relevant medical and demographic information. Informed consent was obtained from all participants after providing them with a detailed explanation of the study's purpose, procedures, and potential risks. Facial photographs were taken for later assessment of acne severity, which were reviewed by a dermatologist to classify the acne as mild, moderate, or severe using the Lehmann classification (as described in your previous work).

A 5 mL blood sample was drawn from the median cubital vein using sterile techniques, in accordance with ethical standards for human sample collection. The blood samples were then processed in the GAKI Laboratory at Diponegoro University by centrifugation to separate the serum from the cellular components. The serum was stored at -20°C until further analysis.

Serum IL-6 levels were measured using an enzyme-linked immunosorbent assay (ELISA) high-sensitivity kit, which allows for precise and sensitive detection of IL-6 concentrations in serum samples. The assay was performed according to the manufacturer's instructions, and IL-6 levels were recorded in pg/mL. This method has been validated for clinical use and is widely accepted for cytokine measurement in

inflammatory conditions.

The data were analyzed using IBM SPSS Statistics software (version 26). Descriptive statistics were used to summarize the demographic characteristics of the participants, including age, BMI, and acne severity. The Shapiro-Wilk test was first applied to assess the normality of the data. Given the small sample size, non-parametric tests were employed where necessary.

For hypothesis testing, the study used:

1. Spearman's correlation test to analyze the relationship between IL-6 serum levels and acne severity.
2. One-way ANOVA was used to compare the mean serum IL-6 levels between the three groups (mild, moderate, and severe acne). In cases of non-normal distribution, appropriate data transformation was applied, and Kruskal-Wallis test was used for comparison.
3. A post-hoc Tukey test was performed to identify specific group differences after the ANOVA test.

Ethical approval for this study was granted by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Diponegoro University, under the approval number 198/EC/KEPK/FKUNDIP/V/2024. All participants were informed of the study's procedures and provided their consent to participate.

RESULTS

Table 1 shows the characteristics of the 15 female subjects in this study, categorized by age, BMI, and severity level of acne vulgaris.

Table 2 shows the analysis of the relationship between serum IL-6 levels and the severity of acne vulgaris (AV) using the Spearman correlation test. The *p*-value obtained was 0.005, which is less than 0.05, indicating a significant relationship between serum IL-6 levels and the severity of AV. The correlation coefficient (r = 0.680) suggests a strong positive correlation, meaning that as the severity of AV increases, the serum IL-6 levels also increase. The correlation coefficient indicates a strong positive correlation since it is above 0,5.

Table 3 presents the results of the one-way ANOVA test to compare IL-6 serum levels across the different severity levels of AV. The data passed the normality test (Shapiro-Wilk, $p = 0.534$), indicating that the distribution of IL-6 serum levels is normal. The ANOVA test showed a significant difference in serum IL-6 levels among the three severity groups ($p = 0.011$), suggesting that IL-6 levels vary based on the severity of acne vulgari.

Table 4 shows the post hoc test results, indicating a significant difference between the mild and severe AV groups (p=0.008, p<0.05). However, no significant

TABLE 1
Characteristics of Study Subjects

Characteristics	Frequency (n)	Percentage (%)
Age		
19 years	1	6.7
20 years	4	26.7
21 years	7	46.7
22 years	3	20.0
Gender		
Female	15	100
Male	0	0
BMI		
Underweight	5	33.3
Normoweight	8	53.3
Overweight	2	13.3
Severity Level		
Mild	5	33.3
Moderate	5	33.3
Severe	5	33.3

TABLE 2
Relationship Between Serum IL-6 Levels and Severity of Acne Vulgaris

Variable	*p*	r	Description
Severity Level IL–6	0.005	0.680	Significant, Positive, Strong

Note: Spearman test, significant ($p<0.05$)

TABLE 3
Serum IL-6 Levels Based on the Severity of Acne Vulgaris

Variable	Severity of Acne Vulgaris			*p* value
	Mild	Moderate	Severe	
IL–6 (pg/ml)	1.00 ± 0.55	1.47 ± 0.27	1.99 ± 0.42	0.011*

Note: *One-way ANOVA test, significant ($p<0.05$)

difference was observed between the mild and moderate groups, or between the moderate and severe groups, with *p*-values of 0.227 and 0.177, respectively ($p > 0.05$).

Several previous studies have examined the relationship between IL–6 levels and acne severity, supporting the inflammatory role of IL–6 in acne pathogenesis. For example, research has shown that serum IL–6 levels are significantly elevated in individuals with acne vulgaris compared to controls, and higher IL–6 concentrations are associated with more severe lesions, indicating a strong positive correlation between IL–6 and disease severity. This aligns with our findings that serum IL–6 levels increase as acne severity worsens.[26]

Not all studies report consistent results; some research has found that differences in IL–6 levels between acne patients and controls are not always statistically significant, especially when other interleukins such as IL–8 and IL–17 are considered primary drivers of inflammatory responses in acne.

Genetic studies investigating IL–6 gene promoter polymorphisms suggest that while IL–6 may play a role in susceptibility to acne vulgaris, its direct association with severity is not always evident across different populations (Ragab *et al*., 2021). These variations highlight the complexity of cytokine involvement in acne and underscore the need for further research to clarify how IL–6 interacts with other inflammatory mediators in determining disease progression and clinical outcomes.[28]

In this study, the distribution of serum IL–6 levels varied across the mild, moderate, and severe acne vulgaris groups, reflecting the inflammatory burden associated with increasing severity. The mean IL–6 levels rose progressively from 1.00 ± 0.55 pg/ml in the mild group to 1.99 ± 0.42 pg/ml in the severe group (Table 4), which suggests a gradation of inflammatory response corresponding to clinical severity. This pattern aligns with current understanding that IL–6, as a pro–inflammatory cytokine, is upregulated in proportion to the level of tissue inflammation seen in more severe acne lesions, as has been demonstrated in other studies of chronic inflammatory skin diseases where higher cytokine levels correlate with increased disease activity.[29]

It is important to note that cytokine data can be inherently variable due to the biology of these molecules. Cytokines like IL–6 are produced in low concentrations, have short half–lives, and can be influenced by systemic factors beyond local skin inflammation, which may affect their distribution patterns in serum. Accurate measurement using ELISA, while reliable, may still be affected by analytical variability and biological noise, such as transient elevations due to minor infections, stress responses, or inter–individual differences in immune activation.[30]

In addition, potential confounding factors could influence the observed distribution of IL–6 levels. For example, genetic variation in immune response pathways has been shown to contribute to individual differences in acne severity and cytokine expression, independent of clinical lesion counts. A systematic review on genetic variants associated with acne severity supports the notion that host genetic factors may modulate cytokine production and inflammatory responses, potentially affecting IL–6 serum levels in a way that is not solely dependent on lesion severity.[26]

Other confounders that could bias the serum IL–6 distribution include demographic characteristics (e.g., age, BMI), lifestyle factors (diet, stress, smoking), and subclinical infections that were not controlled for in this

TABLE 4
Post Hoc Test for Serum IL-6 Levels Based on the Severity of Acne Vulgaris

Severity of Acne Vulgaris	Severity of Acne Vulgaris	*p*
Mild	Moderate	0.227
	Severe	**0.008***
Moderate	Mild	0.227
	Severe	0,177
Severe	Mild	**0.008***
	Moderate	0.117

Note: * post hoc Tukey HSD test, significant (p <0.05)

cross–sectional design. These variables can independently alter systemic inflammatory markers and may lead to overlapping IL–6 values between severity groups. Moreover, the relatively small sample size in this study also limits the statistical power to fully account for such variabilities, which could explain why some comparisons do not reach significance despite apparent trends in average IL–6 levels across groups. Future studies with larger cohorts and multivariate adjustment for potential confounders are needed to clarify these influences.

DISCUSSION

The study found that all participants were women. According to Ruba *et al*. (2020), the incidence of acne vulgaris is higher in women (70.9%) than in men (29.1%). 10 Women tend to experience more severe acne earlier, likely due to higher sensitivity of androgen receptors and an earlier onset of puberty. Acne is also more persistent in women, who are often more concerned about their appearance and may use cosmetics. About 89.1% of women develop acne as a result of improper use of cosmetics.[11,12]

This study observed the highest prevalence of acne vulgaris in 21-year-olds (46.7%). Acne typically affects individuals between 12 and 25, peaking in adolescence. Ruba *et al*. (2020) reported that 26.7% of participants were aged 15–20, and 34.7% were aged 21–25.[10] Heng *et al*. (2022) also reported a high prevalence in the 2024 age range.[1] In Pakistan, Luqman *et al*. (2020) observed that 72% of acne vulgaris patients were women, highlighting the gender difference in prevalence.[13]

Most participants in this study had a normal body mass index (BMI), with 53.3% falling within the normal weight range. Lajevardi *et al*. (2014) found that while severe acne was less common in underweight individuals (BMI < 18.5), there was no significant correlation between BMI and acne severity among participants in their study.[14]

This research involved 15 women students from Diponegoro University, categorized by the severity of acne vulgaris (AV) into three groups: mild, moderate, and severe. Blood samples were collected to measure serum IL-6 levels using a high-sensitivity (HS) kit with the ELISA method. The results indicated that the mean IL–6 levels were 1.00 ± 0.55 pg/ml for mild acne, 1.47 ± 0.27 pg/ml for moderate acne, and 1.99 ± 0.42 pg/ml for severe acne. Bivariate analysis revealed a significant positive relationship between serum IL-6 levels and AV severity (p=0.011, p<0.05), supporting the hypothesis that increasing AV severity is associated with elevated serum IL-6 levels.

These findings are consistent with those of Stankowska *et al*. (2020), who reported higher IL-6 levels in 47 patients with acne vulgaris compared to 41 controls (p=0.0319). The IL-6 levels in the acne patients ranged from 1.39 to 67.41 pg/ml, while in the control group, levels ranged from 1.00 to 14.24 pg/ml.[9] Similarly, Nauli *et al*. (2023) observed increased IL-6 and hs-CRP levels in acne vulgaris patients, with a mean IL-6 of 63.3 ng/L compared to 56.9 ng/L in controls (p = 0.014).[8] Elhanboli *et al*. (2021), in a meta-analysis, also found elevated IL-6 levels in acne vulgaris patients and a significant correlation between IL-6 levels and lesion severity.[15]

IL-6 plays a pivotal role in the pathogenesis of acne vulgaris. Lipopolysaccharides from bacteria induce it and activate Th17 cells, which produce inflammatory cytokines like IL-8, contributing to inflammation in acne lesions. Moreover, IL-6 can induce hyperkeratosis in the pilosebaceous ducts, inhibit serum flow, and facilitate the colonization of *P. acnes*, exacerbating acne severity.[7]

One of the key mechanisms by which IL–6 contributes to the pathogenesis of acne vulgaris is through its regulation of both innate and adaptive immune responses. IL–6 is a pleiotropic cytokine that is secreted by various cell types, including keratinocytes, macrophages, and sebocytes, in response to stimuli such as Cutibacterium acnes colonization and Toll–like receptor activation. Once released, IL–6 can activate the

NF–κB signaling pathway, which amplifies the expression of other pro–inflammatory cytokines and chemokines, thereby sustaining inflammation in the pilosebaceous unit. This cascade promotes recruitment of neutrophils and other immune cells, contributing to lesion formation and progression from mild to more severe inflammatory acne.[32]

Beyond these effects on innate immunity, IL–6 also influences the adaptive immune response by facilitating the differentiation of naïve CD4+ T cells into Th17 cells a subset of pro–inflammatory T helper cells. The Th17 pathway has been shown to be significantly activated in inflamed acne lesions, with IL–6 serving as a critical driver of Th17 polarization and IL–17 production. This IL–6–mediated Th17 response further amplifies inflammation by inducing additional cytokines (e.g., IL–17 and IL–8) that increase neutrophil recruitment and sustain chronic inflammation in acne–affected skin.[33]

As acne severity increases, this complex interplay between IL–6, Th17 cells, and other inflammatory mediators becomes more pronounced. In mild acne, IL–6 levels may be elevated primarily due to early innate immune activation, while in moderate to severe acne, adaptive immune mechanisms particularly Th17–driven inflammation play a larger role in lesion persistence and severity. The differential activation of these pathways helps explain why serum IL–6 levels correlate with acne severity in many studies and highlights the central position of IL–6 as both an initiator and amplifier of inflammatory signaling in acne vulgaris.[29]

The role of IL–6 in chronic skin inflammation extends beyond acne vulgaris and has been documented in other dermatological conditions with similar immunopathogenic pathways. For instance, elevated serum IL–6 levels have been observed in patients with psoriasis, a chronic immune–mediated inflammatory skin disease, where IL–6 contributes to keratinocyte proliferation and amplifies immune responses through the JAK–STAT signaling pathway, thereby driving persistent inflammation and lesion severity. Elevated IL–6 in psoriasis has also been associated with the severity of disease and neurogenic inflammatory processes, suggesting that IL–6 acts as a central mediator of skin inflammation across different conditions. Similarly, in rosacea another chronic inflammatory disorder of the face higher serum IL–6 levels have been reported compared to healthy controls, indicating its involvement in disease pathogenesis and severity. These parallels support the notion that IL–6 functions as a common pro–inflammatory mediator in various skin diseases, reinforcing the significance of our finding that IL–6 increases with acne severity.[34]

IL–6 signaling has broader relevance beyond local skin inflammation. Hirano (2021) described IL–6 as a pleiotropic cytokine involved not only in acute inflammation but also in autoimmunity and tumorigenesis, acting through both classic membrane-bound receptor signaling and trans-signaling via soluble IL–6 receptor (IL–6R).[20] This dual signaling capacity may explain why even modest elevations in serum IL–6, such as those observed in mild acne in the present study, can still translate into measurable inflammatory activity at the tissue level. In addition, Inoue *et al*. (2025) demonstrated that IL–6R expression in keratinocytes is upregulated by external stressors such as UVB exposure and increases with age, sensitizing skin cells to IL–6-mediated inflammatory signaling.[21] This suggests that environmental and hormonal factors relevant to young women, including sun exposure and skin maturation, may modulate individual susceptibility to IL–6-driven acne severity, independent of absolute serum IL–6 concentration. Supporting a genetic contribution, Ragab *et al*. (2021) reported that polymorphisms in the IL–6 gene promoter are associated with both the presence and severity of acne vulgaris, indicating that variability in IL–6 production between individuals may be partly determined by genetic background rather than disease activity alone.[27] These findings align with a more recent clinical study by Triatmakusuma *et al*. (2024), who similarly found a positive correlation between serum IL–6 levels and acne vulgaris severity, reinforcing the consistency of this relationship across different populations.[28] Given the central role of IL–6 in this inflammatory cascade, IL–6 receptor blockade has been explored therapeutically in other chronic inflammatory conditions; Aletaha *et al*. (2021) summarized consensus recommendations on IL–6 and IL–6 receptor inhibition in inflammatory disease, raising the possibility that similar targeted anti-inflammatory strategies could eventually be adapted for severe, treatment-resistant acne vulgaris.[22]

Several limitations should be considered when interpreting these findings. The sample size of 15 participants, while sufficient to detect a statistically significant association, limits the generalizability of the results and reduces statistical power to detect smaller effect sizes between severity subgroups. As a cross-sectional study, this design captures serum IL–6 levels at a single time point and cannot establish causality or describe how IL–6 levels change over the course of acne development and resolution. Furthermore, Knight and Sepiashvili (2025) highlighted that cytokine measurements, including IL–6, are highly sensitive to pre-analytical factors such as sample handling, storage time, and assay platform, which can introduce variability between studies and complicate direct comparison of absolute IL–6 values across different research settings.[30] Future studies with larger, more diverse cohorts, longitudinal follow-up, and standardized cytokine assay protocols are needed to confirm the role of serum IL–6 as a reliable biomarker of acne vulgaris severity. Additionally, standardizing acne severity grading criteria across future studies, alongside serum IL–6

measurement, would further strengthen the reproducibility and clinical applicability of these findings in dermatological practice.

CONCLUSION

This study demonstrates a significant relationship between serum IL-6 levels and the severity of acne vulgaris (AV) in women. The findings reveal that IL-6 levels progressively increase with the severity of acne, with a notable difference between the mild and severe AV groups. These results support the hypothesis that elevated IL-6 is associated with greater acne severity, reinforcing the central role of IL-6 in driving inflammation in acne lesions. Furthermore, the study highlights the importance of understanding the inflammatory processes underlying AV, which can contribute to the development of targeted therapeutic approaches. Future research with larger sample sizes and broader demographic groups will be crucial to validate these findings and explore the potential of IL-6 as a biomarker for monitoring acne progression.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest related to this study.

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Original Article

Relationship Between Location and Number of Lesions Based on Head CT Scan with Behavioral Psychological Symptoms of Dementia

A Study on Post-Ischemic Stroke Patients with Vascular Cognitive Impairment at Kariadi Hospital Semarang

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Abstract

Background : Behavioral and Psychological Symptoms of Dementia (BPSD) frequently occur in patients with Vascular Cognitive Impairment (VCI) after stroke and significantly affect functional outcomes. However, data regarding the association between lesion characteristics and BPSD remain limited.
Objectives : To determine the relationship between the location and number of lesions on head CT scan and BPSD in post-ischemic stroke patients with VCI.
Methods : Cross-sectional study involving post-ischemic stroke patients at the Neurology Outpatient Clinic of Kariadi Hospital Semarang. An evaluation was conducted on the location and number of stroke lesions in relation to the occurrence of Behavioral Psychological Symptoms of Dementia, based on Abe's Behavioral Psychological Symptoms of Dementia Score. The confounding variables of the study were age, occupation, education level, nutritional status, and caregiver. Analysis was conducted using the Independent T test, Mann Whitney U and Kruskal-wallis. Significant results $p<0.05$.
Results : The mean ABE BPSD score was 7.17 with a median of 4. The most common symptoms were depression/low mood, irritability, and sleep disturbance (33.3% each), followed by excitement and agitation (28.6%). Of the total subjects, 31% had stroke in the non-dominant hemisphere, 26.2% in the dominant hemisphere, and 42.9% in both hemisphere. A total of 64.3% had frontal lesions, while 35.7% had non-frontal lesions. Based on the number of lesions, 54.8% had single lesions and 45.2% had multiple lesions. The location of the lesions in the frontal region ($p<0.001$), the number of multiple lesions ($p<0.001$) and younger age ($p=0.042$) were significantly associated with a more severe ABE BPSD score.
Conclusion : Frontal lesion location, multiple lesions, and younger age are significantly associated with increased severity of BPSD in post-ischemic stroke patients with VCI.

Keywords : BPSD, number of lesions, location of lesions, ischemic stroke, VCI.

INTRODUCTION

The sign and symptoms of disruptions in perception, thinking content, mood, or behavior are known as Behavioral and Psychological Symptoms of Dementia (BPSD). An essential component of dementia's natural progression is BPSD. Aggression, psychosis, agitation, despair, apathy, wandering, sleep difficulties, and a variety of socially unacceptable behaviors are all signs of BPSD. These symptoms are one of the most complex aspects of care and result in significant adverse health outcomes for patients, including morbidity, mortality, and hospital admissions.[1]

BPSD has been linked to greater rates of pharmaceutical use, poor prognosis, and high caregiver load, all of which raise the social effect and financial needs of dementia patients.[2] *Caregivers of dementia patients report BPSD, particularly symptoms such as aggression and shouting, as the most challenging issues to manage*.[3] From mild cognitive impairment to dementia, BPSD is a diverse collection of non-cognitive symptoms and behaviors that are frequently seen across the board. If left untreated, BPSD can lead to accelerated disease progression, worsening of daily functioning, impaired quality of life, increased healthcare needs, increased stress on caregivers, reduced quality of life for dementia patients and their families, and higher economic burdens on caregivers.[4–6]

BPSD can accompany vascular cognitive impairment (VCI), thereby significantly impacting the functional and cognitive status of post-stroke patients.[6] VCI is a heterogeneous group of disorders with various types of cerebrovascular lesions contributing to cognitive dysfunction up to dementia.[9,10,25] More than 55 million people worldwide are living with dementia, and over 90% of people with dementia experience behavioral and psychological symptoms.[7] Based on a study involving 30 studies worldwide, the prevalence of BPSD varies from 4% (mania) to 32% (apathy).[8] A study in Singapore found that the prevalence of BPSD ranges from 67.9%, with 30% of the population experiencing three or more BPSD episodes in the past month.[7] In a study of 76 post-stroke patients with vascular cognitive impairment at Adam Malik Hospital in Medan, 30 patients (39.47%) experienced at least one BPSD symptom. The most common symptoms were apathy and indifference (19.7%), followed by depression and a gloomy mood (17.1%). The least common symptom was aggression, observed in only 2 patients (2.6%).[8]

Research shows that certain stroke characteristics explain the increased risk of dementia in stroke patients. Lacunar stroke and hemorrhagic stroke are predictors of post-stroke dementia, according to studies examining stroke subtypes. The presence of multiple lesions, infarct volume, and stroke location (e.g., left hemisphere) have also been identified as risk factors for post-stroke dementia. According to neuroimaging research, leukoaraiosis and medial temporal lobe atrophy, two common white matter abnormalities linked to subcortical stroke injury, can raise the risk of memory loss and cortical gray matter thinning, which in turn raises the risk of cognitive impairment.[9] The emergence of conditions such as decreased interest and apathy may be caused by medial frontal lobe atrophy, while reduced neurotransmitter function in monoaminergic circuits and decreased frontal and temporal lobe volume are associated with depressive mood.[10] Additionally, it is hypothesized that stroke may trigger neurodegenerative processes by disrupting amyloid clearance or by activating an autoimmune response to brain antigens produced post-stroke. Therefore, the likelihood of dementia following a stroke is most likely to be influenced by persistent cerebrovascular injury brought on by vascular risk factors, immunological processes, and pathogenic mechanisms.[11–13]

The meta-analysis found that vascular impairment is significantly associated with an increased prevalence and severity of behavioral and psychological symptoms of dementia (BPSD).[5]

Epidemiological data on BPSD and research on the relationship between the location and number of stroke lesions and BPSD remain limited. The location and number of stroke lesions are significantly suspected to influence the occurrence of BPSD as one form of Vascular Cognitive Impairment in post-stroke patients. The aim of this study is to demonstrate the relationship between the location and number of lesions based on CT scan of the head and BPSD. The potential role of location and total number of lesion in identifying patients may benefit from closer BPSD screening and caregiver/rehabilitation planning.

METHODS

Design and Location

This study is an observational analytical study with a cross-sectional approach, conducted at Dr. Kariadi General Hospital in Semarang over a six-month period from July 2024 to December 2024. Ethical clearance was obtained from the Health Research Ethics Committee (KEPK) of Dr. Kariadi General Hospital in Semarang with No. 468/EC/KEPK/FK-UNDIP/IX/2024.

Population and Criteria

The study subjects were post-ischemic stroke patients at the Neurology Outpatient Clinic of Dr. Kariadi General Hospital in Semarang. The study sample was obtained using consecutive sampling, yielding a total of 42 respondents. Inclusion criteria were first-ever ischemic stroke confirmed by CT scan, onset 3 months–1 year, MoCA-INA score <26, age ≤75 years, and ability to communicate. Exclusion criteria included severe aphasia,

sensory impairment, delirium, severe disability, prior psychiatric or dementia history and anemia.

Research Procedures

The procedure began with the selection of subjects who had experienced their first ischemic stroke with onset 3 months–1 year prior, met the inclusion criteria, and did not meet the exclusion criteria. After obtaining informed consent, a medical history is taken, a questionnaire-based examination is conducted, and CT scan data is retrieved from medical records. Cognitive function is assessed using the MoCA-INA, and if the score is < 26, the Abe's BPSD Score was administered based on information obtained from the primary caregiver. Nutritional status is assessed using the MNA-SF.

Data Analysis

Data analysis included univariate analysis to describe variable characteristics, bivariate analysis to assess the relationship between CT scan lesions and BPSD symptoms using statistical tests appropriate for the data distribution, and multivariate analysis with linear regression for significant variables (p<0.25) to determine the most influential factors, with results considered significant if p<0.05.

RESULTS

Evaluation of 42 subjects with ischemic stroke accompanied by cognitive impairment based on the MoCA-INA score conducted at Kariadi Hospital, Semarang produced the following findings.

A total of 42 subjects were included, with a mean age of 53.79 ± 8.75 years. Most patients were female (52.4%). Lesions were predominantly located in both hemispheres (42.9%) and in the frontal region (64.3%). Single lesions were slightly more common (54.8%) than multiple lesions. The most common BPSD symptoms were depression, irritability, and sleep disturbances (33.3%), followed by agitation (28.6%). Bivariate analysis showed that frontal lesion location and multiple lesions were significantly associated with higher BPSD scores (p<0.001). In contrast, hemisphere location was not significantly associated (p=0.960). Age was also significantly associated with BPSD severity (p=0.042), with younger patients showing higher scores.

TABLE 1
Characteristics of Research Subjects

Variable	n (%)	Mean ± SD	Median (min–max)
Age		53.79 ± 8.75	55.5 (32–68)
<36 years old	1 (2.4)		
36–45 years old	8 (19)		
46–55 years old	12 (28.6)		
56–65 years old	17 (40.5)		
>65 years old	4 (9.5)		
Sex		–	–
Male	20 (47.6)		
Female	22 (52.4)		
Hemispheric location		–	–
Hemisphere non-dominant	13 (31)		
Hemisphere dominant	11 (26.2)		
Both hemisphere	18 (42.9)		
Location of lesions by region		–	–
Frontal	27 (64.3)		
Non-Frontal	15 (35.7)		
Number of lesions		–	–
Single	23 (54.8)		
Multiple	19 (45.2)		

TABLE 2
Characteristics of Behavioral Psychological Symptoms of Dementia based on ABE BPSD

Variable	n (%)	Mean ± SD	Median (min–max)
ABE BPSD	–	7.17 ± 7.46	4 (0–26)
Pacing inside/outside the house			
Yes	8 (19)		
No	34 (81)		
Eating and toilet problems		–	–
Yes	8 (19)		
No	34 (81)		
Delusion and hallucination		–	–
Yes	5 (11.9)		
No	37 (88.1)		
Speaking rudely / offensively		–	–
Yes	11 (26.2)		
No	31 (73.8)		
Day and night upside down		–	–
Yes	14 (33.3)		
No	28 (66.7)		
Excitation and agitation		–	–
Yes	12 (28.6)		
No	30 (71.4)		
Apathetic and indifferent		–	–
Yes	10 (23.8)		
No	32 (76.2)		
Depression and gloom		–	–
Yes	14 (33.3)		
No	28 (66.7)		
Acts of violence		–	–
Yes	2 (4.8)		
No	40 (95.2)		
Easily offended		–	–
Yes	14 (33.3)		
No	28 (66.7)		

Multivariate analysis revealed that lesion location, number of lesions, and age were independent predictors of BPSD severity.

Based on the Table 2, the mean total score of ABE BPSD (Assessment of Behavioral and Psychological Symptoms of Dementia) was 7.17 ± 7.46 with a median value of 4 (range 0–26), indicating a fairly large variation in symptoms between individuals. The symptoms most commonly experienced by patients included changes in sleep patterns such as being inverted between day and

TABLE 3
Relationship between location, number of lesions and age with BPSD

Variable	ABE BPSD	*p*
Hemisphere location		0.960¶
Hemisphere non-dominant	7.46 ± 8.82; 4 (0–26)	
Hemisphere dominant	6.82 ± 6.63; 7 (0–19)	
Both hemisphere	7.17 ± 7.30; 4.5 (0–26)	
Location of lesions by region		<0.001‡
Frontal	9.70 ± 7.77; 7 (0–26)	
Non-Frontal	2.60 ± 4.03; 1 (0–15)	
Total number of lesions		<0.001†
Single lesion	3.13 ± 2.43; 3 (0–8)	
Multiple lesions	12.05 ± 8.58; 12 (0–26)	
Age		0.042¶
<36 years old	32 ± 0; 32 (32–32)	
36–45 years old	13.38 ± 9.02; 14 (0–6)	
46–55 years old	8.42 ± 8.40; 4.5 (1–26)	
56–65 years old	3.29 ± 3.25; 3 (0–11)	
>65 years old	4.5 ± 2.38; 4.5 (2–7)	

†Independent t-test; ‡Mann Whitney U; ¶Kruskal-Wallis; significant $p<0.05$

TABLE 4
Factors associated with BPSD

Variable		Unstandardized Coefficient		Standardized Coeff B	t	Sig.	CI 95%	
		B	Std. Error				Lower	Upper
BPSD	Age	-.382	.085	-.449	-4.481	<.001	-.555	-.210
	Total number of lesions	5.537	1.508	.374	3.673	<.001	2.485	8.589
	Location of lesions by region	-6.030	1.465	-.392	-.392	<.001	-8.996	-3.064

Linear regression; significant $p<0.05$

night (33.3%), irritability (33.3%), and depression and gloom (33.3%). Excitation and agitation were found in 28.6% of patients, while harsh/offensive speech appeared in 26.2%. In contrast, the least frequently reported symptoms were acts of violence (4.8%) and delusions/hallucinations (11.9%).

ABE BPSD scores were significantly higher in patients with lesions in the frontal region compared to non-frontal ($p<0.001$), and in patients with multiple lesions compared to single lesions ($p<0.001$). These findings suggest that involvement of the frontal region and a higher number of lesions significantly contribute to the severity of behavioral and psychological symptoms of dementia. In contrast, no significant differences were found based on cerebral hemisphere location ($p = 0.960$), indicating that hemisphere laterality does not significantly affect the manifestation of BPSD in patients in this study.

The results of the analysis showed that there was a significant difference in ABE BPSD scores based on age group ($p = 0.042$). The highest score was found in the age group <36 years (mean 32), followed by 36–45 years (13.38 ± 9.02), while older age groups, especially 56–65 years and >65 years, showed significantly lower

scores.

A joint evaluation of the factors influencing the ABE BPSD score showed that the strongest influencing factors were the location of the lesions based on the region (p<0.001), the number of lesions (p<0.001) and age (p<0.001). Frontal lesions location (B= -6.03; CI95% -8.99–(-3.06)), a greater number of lesions (B= 5.53; CI95% 2.48–8.58) and younger age (B= -0.38; CI95% -0.55–(-0.21)) were associated with higher ABE BPSD scores.

DISCUSSION

Based on the results of the study, the average age falls into the elderly category (53.79 years). Aging is the strongest unmodifiable risk factor for stroke, which doubles every 10 years after the age of 55. Approximately three-quarters of all strokes occur in people aged ≥65 years. As the number of people aged ≥65 years is projected to increase, the number of stroke events in older adults is expected to rise. With advancing age, both cerebral microcirculation and microcirculation undergo structural and functional changes. Neurovascular coupling, compromised cerebral autoregulation, and endothelial dysfunction are the mechanisms behind age-related microcirculatory alterations. defective cerebral autoregulation can result in microvascular damage, endothelial dysfunction encourages neuroinflammation, and defective neurovascular coupling will encourage cortical dysfunction. Human intracranial and extracranial cerebral arteries undergo numerous notable alterations with aging in healthy persons, which can be used to predict the risk of stroke in the future.[12]

Gender-specific stroke risks include those associated with oral contraceptive pill (OCP) use, pregnancy, menopause, and hormone replacement therapy (HRT), in addition to age. Although stroke incidence is lower in reproductive-age women, OCP use significantly increases stroke risk, with the highest risk associated with high-oestrogen OCPs. Oestrogen has many positive cardiovascular effects, but it also increases coagulation and may increase the risk of coagulation in women taking OCPs containing estrogen.[13] Although men generally have a higher incidence of ischemic stroke during early and middle adulthood, stroke risk increases among women with advancing age and after menopause. Declining ovarian sex hormones, particularly estrogen, may contribute to changes in vascular risk during the menopausal transition. Recent evidence indicates that early menopause is associated with an increased risk of ischemic stroke, with menopause before approximately 43 years of age associated with a higher risk of ischemic stroke.[14]

The frontal lobe is the dominant location in stroke events, which is attributed to the emergence of decreased interest and apathy caused by medial frontal lobe atrophy, while decreased neurotransmitter function in the monoaminergic circuit and decreased frontal and temporal lobe volume are associated with depressive mood.[10] Furthermore, it is hypothesized that stroke could initiate neurodegenerative processes by interfering with the removal of amyloid or by triggering an immunological reaction to brain antigens generated after a stroke. Thus, it is very likely that the risk of dementia after stroke may be influenced by persistent cerebrovascular injury brought on by vascular risk factors, immune system functions, and pathogenic mechanisms.[11]

The symptoms generally do not present as severe, but the proportion of symptoms such as depression and sleep pattern disturbances is quite prominent and requires clinical attention in further management. Apathy, depression, irritability, agitation, and anxiety are the most prevalent individual symptoms of BPSD in dementia patients, whereas euphoria, hallucinations, and disinhibition are the least prevalent. The three symptoms that are most clinically significant are anxiety, apathy, and depression. Approximately 50% of patients have at least four neuropsychiatric symptoms simultaneously.[15] Apathy, depression, anxiety, and agitation are the most common forms of BPSD.[16] However, BPSD can also be diagnosed in non-dementia cognitive disorders, such as mild cognitive impairment (MCI), although the prevalence of patients is generally lower in MCI compared to dementia.[17] Research found the frequency of BPSD in patients with dementia to be 63.2%, significantly higher than in MCI (30.8%).[18] Due to its size, the frontal lobe is frequently implicated in strokes. Ischemic or hemorrhagic involvement of the middle cerebral artery causes the majority of strokes, and damage to the motor cortex's precentral gyrus (pre-Rolandic area) is the main cause of their clinical manifestations.[19]

The anatomical distribution of brain lesions may influence the manifestation of BPSD. Neuroimaging studies have demonstrated associations between neuropsychiatric symptoms and structural alterations within frontal and fronto-limbic circuits. Apathy has been associated with abnormalities involving the medial and inferior frontal cortex, orbitofrontal cortex, anterior cingulate cortex, and temporal regions, whereas agitation has been associated with structural changes in frontal regions and the temporal pole. Depressive symptoms have also been linked to atrophy involving the inferior frontal, insular, limbic, and temporal regions.[20] Agitation has been associated with various macrostructural cortical changes, such as global atrophy and reduced volume in the right posterior cingulate, left hippocampus, and front limbic regions. The rate of progression of regional atrophy, particularly in the lateral frontal or parietal lobes, correlates with the severity of BPSD.[18,21]

Multiple cerebral infarcts can arise from several mechanisms, including large-artery atherosclerosis and

cardioembolism, although the underlying etiologies are heterogeneous. Large-artery atherosclerosis can cause arterial stenosis or occlusion and subsequent cerebral ischemia, whereas cardioembolic sources such as atrial fibrillation can generate emboli that occlude cerebral arteries and produce infarcts in multiple vascular territories. In addition, vascular comorbidities such as hypertension, diabetes mellitus, and dyslipidemia contribute to vascular injury, atherosclerosis, and thromboembolic risk, thereby increasing the likelihood of ischemic stroke and multiple cerebral infarctions. [22]

The analysis results showed a significant association between age and ABE BPSD scores ($p = 0.042$), with younger age groups tending to exhibit more severe behavioral and psychological symptoms. The highest scores were recorded in the <36 years age group (32), followed by the 36–45 years age group (13.38 ± 9.02). Conversely, older age groups such as 56–65 years and >65 years had lower scores. This is related to age in relation to several BPSD components, namely depression, anxiety, agitation, and sleep or eating disorders. In their study noted that younger age is associated with a diagnosis of personality disorder. The pattern of average cumulative MOAS scores shows that younger individuals (18–29 years) are significantly more aggressive than older individuals (>50) ($p < 0.001$).[23] Adolescents and young adults, particularly women, are particularly susceptible to eating disorders, anxiety disorders, and depression. Higher disease load, worse prognosis, and more severe symptoms are linked to eating disorders that co-occur with anxiety or depression. High anxiety/depression is associated with more severe eating disorder symptoms. Older age and greater impairment in mood dysregulation, self-esteem, and perfectionism are associated with more severe eating disorder symptoms. Younger age is thought to strengthen the association between anxiety/depression and eating disorder symptoms.[24] Our findings suggest that routine assessment of location and total number of lesion on head CT may provide clinically useful information for identifying post-stroke VCI patients who may benefit from closer behavioral and psychological assessment. In particular, the presence of frontal or multiple ischemic lesions may prompt earlier behavioral assessment and closer follow-up. Recognition of BPSD may also facilitate caregiver education and individualized non-pharmacological interventions.[25–27]

CONCLUSION

Behavioral and psychological symptoms (BPSD) in post-ischemic stroke patients with vascular cognitive impairment (VCI) are significantly associated with several key clinical factors. The location of lesions in the frontal region and the presence of multiple lesions based on head CT scan results have been shown to play an important role in increasing the severity of BPSD. Additionally, younger age is associated with higher BPSD scores, indicating differences in neuropsychiatric responses across age groups. On the other hand, confounding factors such as occupation, educational level, nutritional status, and the presence of a caregiver do not show a significant association with BPSD in the studied population. Further research is recommended to consider caregiver training as well as controlling for therapeutic variables and the onset of ischemic stroke to minimize bias and enhance the validity of BPSD-related outcomes in post-stroke patients.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this study.

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Evidence Based Case Report

Treatment with Platelet-Rich Plasma: an Evidence Based Case Report of Leprosy Ulcers

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Abstract

Background : Leprosy foot ulcers occur in patients with leprosy-related neurological disorders and are classified as grade 2 disabilities. These chronic, non-healing ulcers represent a significant clinical challenge. Platelet rich plasma (PRP) application has emerged as a breakthrough treatment.
Case report : Two females (aged 48 and 58) with multibacillary leprosy presented with chronic midfoot ulcers persisting for 16 and 24 weeks. At baseline, ulcer areas were measured and biopsies were performed to assess TGF-β1, PDGF, and collagen density. Follow-up measurements for biomarkers occurred on day 13, and ulcer area was reassessed on day 41.
Discussion : Both patients received standard therapy plus PRP, resulting in reduced ulcer area, increased TGF-β1, and higher collagen density. PDGF levels increased in one patient but decreased in the other. PRP promotes epithelial and endothelial cell proliferation during neovascularization and stimulates extracellular matrix synthesis. Furthermore, it modulates the inflammatory response, facilitating tissue regeneration by balancing the immune system.
Conclusion : Combining standard therapy with PRP shows strong potential for healing chronic leprosy ulcers. Results demonstrated reduced ulcer area, increased TGF-β1, and improved collagen density, though PDGF levels remained inconsistent.

Keywords : platelet rich plasma (PRP), leprosy ulcer, TGF-β1, PDGF, collagen density.

INTRODUCTION

A leprosy ulcer, traditionally termed a trophic, neuropathic, or perforating plantar ulcer, is clinically defined as a chronic, recurrent ulceration of the anaesthetic foot.[1] Thirty percent of leprosy patients experience peripheral nerve damage and 10–20% of them experience neuropathic ulcers due to peripheral nerve damage.[2] In clinical cohorts monitored at specialized centers, approximately 36.4% of patients are found to already have established nerve injury at the time of their initial leprosy diagnosis.[3] Recent studies have found a prevalence of 60% in regional cohorts (such as Northeast Ethiopia), which closely aligns with other observed rates globally, including 55% in Toronto, 63% in India, and 67% in the United States. Depending on localized endemicity and healthcare infrastructure, rates can range from as low as 13% to 13.8% (as seen in prospective cohorts in Bangladesh and retrospective electronic health records in Colombia) to as high as 97.4% in highly endemic settings like Ecuador.[4] Chronic wound is defined as the normal wound healing process fails within 46 weeks.[5] Wound healing may be impaired due to a lack of growth factors and cytokines.[6] Pathophysiological progression of leprosy ulcers include: the initiating event; neuro-invasion and neural damage (sensory, autonomic, motor neuropathy) occur, followed by mechanical shearing and micro-necrosis, and Charot neuropathy also occurs, followed by chronic inflammation, poor healing and secondary infection.[7]

The management of leprosy ulcers remains controversial, particularly regarding antibiotic use and wound care. Some studies suggest more aggressive antibiotic use, while others recommend a more conservative approach.[8] Management of leprosy ulcers may consist of topical, physical, offloading, and preventive modalities.[9]

The purpose of this case series report is to present PRP therapy, which has only recently been used in leprosy ulcers with good results.[10–12] Application of PRP accelerates the healing process by providing a concentrated supply of growth factors and cytokines, resulting in significant improvements in wound size reduction, increased growth factor concentration, and enhanced collagen density.[13] The specific biological factors that undergo massive local increases, and their direct contributions to accelerating leprosy wound healing include: platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-beta1 and TGF-beta2), epidermal growth factor (EGF), fibrinogen and adhesive proteins (fibronectin, vitronectin), anti-inflammatory cytokines and anti-infective mediators.[14] To measure the therapeutic superiority or non-inferiority of PRP, clinical studies compare these interventions across several key parameters: wound healing time, ulcer area and volume,[15,16] growth factor and cytokine increase, collagen and fibroblast density.[14] Clinical research on PRP therapy has established several key findings: acceleration of wound healing,[10] delivery of concentrated biomolecules, safe and painless profile.[14] Despite highly encouraging case series and pilot studies, critical scientific and clinical gaps prevent PRP from becoming a globally standardized treatment for leprosy ulcers: inconclusive large-scale clinical evidence, lack of standardized preparation protocols, undetermined dosing and delivery regimens, infrastructure barriers in resource-limited settings.[15]

CASE PRESENTATIONS

Case 1

A 48-year-old female patient with a history of multibacillary leprosy complained of chronic ulcer on the midfoot of the left sole for 16 weeks. Baseline ulcer area was 3.36 cm^2 (Figure 1A), a biopsy of the ulcer site revealed transforming growth factor-ß1 (TGF-ß1), platelet derived growth factor (PDGF) levels, and collagen density on baseline were 18.55%, 0%, and 87.1% respectively (Figures 1B, 1C, 1D). On the 41st day after therapy, ulcer area was 2.72 cm^2 (Figure 1E), TGF-ß1, PDGF levels, and collagen density on day 13 were 41.71%, 7.3%, and 88.16% respectively (Figures 1F, 1G, 1H).

Case 2

A 58-year-old female with a history of multibacillary leprosy complained of chronic ulcer on the midfoot of the left sole for 24 weeks. Baseline ulcer area was 1.37 cm^2 (Figure 2A), a biopsy of the ulcer site revealed TGF-ß1, PDGF levels, and collagen density on day 0 were 36.90%, 19.38%, and 67.82% respectively (Figures 2B, 2C, and 2D). On the 41st day after therapy ulcer area was 0,76 cm^2, (Figure 2E), TGF-ß1, PDGF levels, and collagen density on day 13 were 44.34%, 16.62%, and 74.48% respectively (Figures 2F, 2G, and 2H).

Both patients have been given a combination of daily standard therapy; irrigation with natrium chloride (NaCl) solution, ulcer debridement, and use of sterile dressings, topical/systemic antibiotic treatment if needed, and applying PRP; through blood collection and processing by centrifugation, and ready-to-use PRP was administered using aseptic technique, PRP was applied on the ulcer by spreading it and a closed bandage was applied with sterile gauze and pads.[10] The adjuvant therapy was given once a week for 6 weeks (Figure 3).

The result of the therapy revealed in case 1 reduction of ulcer area from baseline was 3.36 cm^2 (Figure 1A) to 2.72 cm^2 (Figure 1E) on day 41. Increased TGF-ß, PDGF levels, and collagen as well from baseline were 18.55%, 0%, and 87.1% (Figures 1B, 1C, 1D) respectively to 41.71%, 7.3%, and 88.16% (Figures 1F, 1G, 1H)

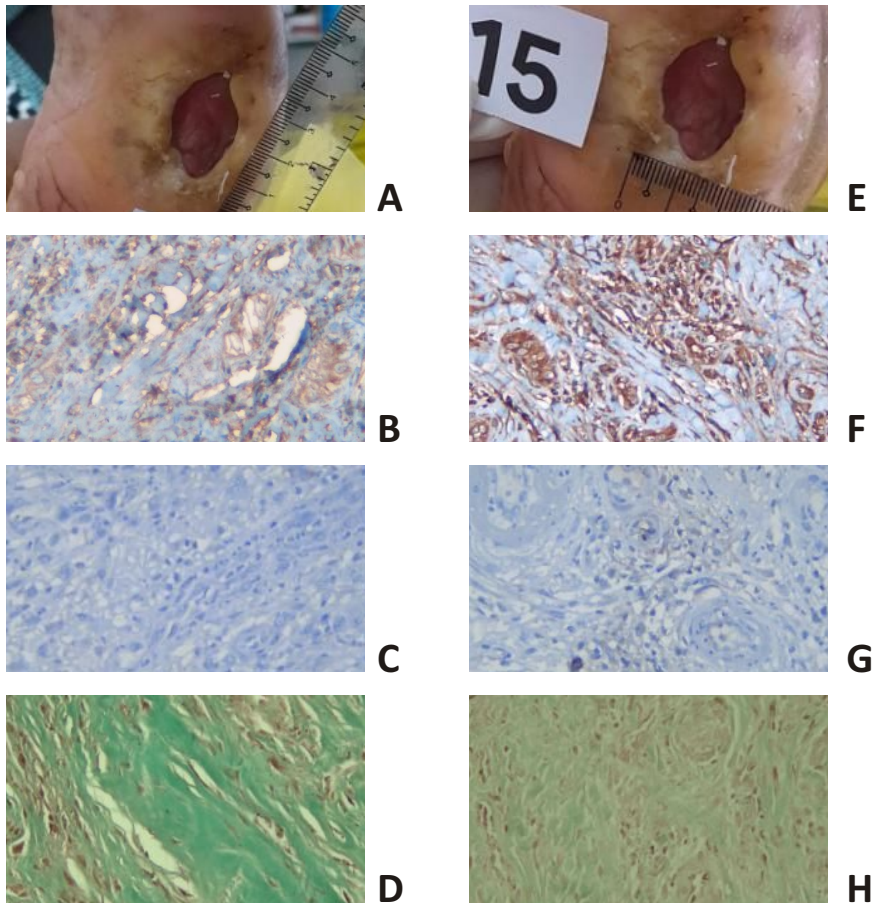

Figure 1.

A. Ulcer area on baseline (3.36 cm^2)
B. TGF-ß1 on baseline (18.55%)
C. PDGF level on baseline (0%)
D. Collagen density on baseline (87.1%)
E. Ulcer area on day 41 (2.72 cm^2)
F. TGF-ß1 on day 13 (41.71%)
G. PDGF level day 41 (7.3%)
H. Collagen density day 13 (88.16%)

respectively. The similar result also found in case 2 reduction of ulcer area from baseline was 1.37 (Figure 2A) cm^2 to 0.76 cm^2 (Figure 2E) on day 41. There was only an increasing TGF-ß1levels, while PDGF levels decreased and collagen increased from the baseline of 36.90%, 19.38%, and 67.82% (Figures 2B, 2C, and 2D) respectively to 44.34%, 16.62%, and 74.48% (Figures 2F, 2G, 2H) respectively.

The problem faced is a leprosy patient with grade 2 disability, namely chronic plantar ulcers. Will PRP administration accelerate ulcer healing? Can PRP administration reduce wound area, increase TGF-beta and PDGF levels, and collagen density?

The search for evidence is traced through scholarly articles (including systematic reviews, clinical trials, randomized controlled trials, and case reports published in English). Data were searched through PubMed, ResearchGate, Scopus, Proquest, and Google Scholar specifically keywords used Platelet-Rich Plasma (PRP), autologous blood products (L-PRF), and treatment of leprosy ulcers (trophic ulcers) or related are relatively scarce. There are 9 manuscripts provided (Table 1).

If Platelet-Rich Plasma (PRP), autologous blood products (L-PRF), and treatment of leprosy ulcers (trophic ulcers) used as keywords, there were eight manuscripts, consisting of four cohort studies,[10,11,17,19] one randomized control trial,[12] two case reports,[14,20] and one case series[18] (Table 1).

DISCUSSION

World Health Organization (WHO) data, in 2023 at least 182,815 which corresponds to a new case detection rate of 22.7 per million population, 5% higher than new cases in 2022 reported globally, the largest number of new cases 131,425 (71.9%) in the South East Asia region, and grade 2 leprosy lesions of 1.2 per million population, with 9,729 patients reported from 184 countries. In Indonesia,

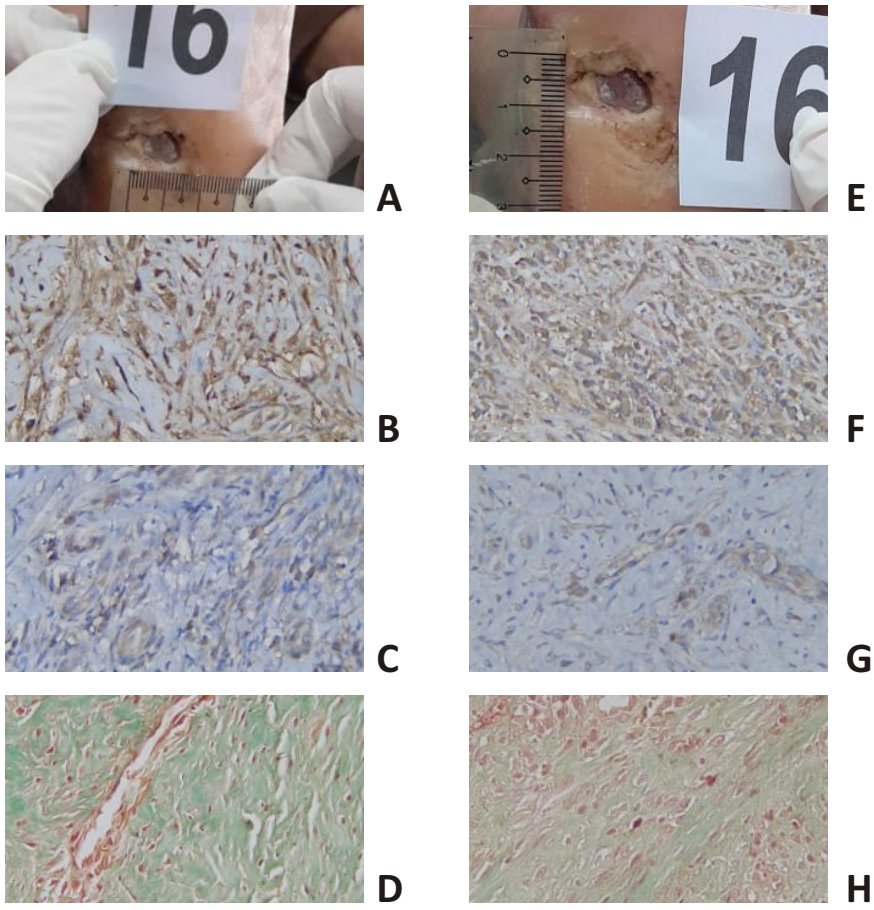

Figure 2.

A. Ulcer area baseline (1.37 cm^2)
B. TGF-ß1 on baseline (36.90%)
C. PDGF level on baseline (19.38%)
D. Collagen density baseline (67.82%)
E. Ulcer area on day 41 (0.76 cm^2)
F. TGF-ß1 day 13 (44.34%)
G. PDGF level day 13 (16.62%)
H. Collagen density day 13 (74.48%)

Treatment procedure						
Week 1st	**Week 2nd**	**Week 3rd**	**Week 4th**	**Week 5th**	**Week 6th**	
Natrium chloride dressing was change everyday						
Day 1	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 36**	**Day 42**
Irrigation with NaCl, administration of PRP	Irrigation with NaCl, administration of PRP	Irrigation with NaCl, administration of PRP	Irrigation with NaCl, administration of PRP	Irrigation with NaCl, administration of PRP	Irrigation with NaCl, administration of PRP	Irrigation with NaCl, administration of PRP
ulcer size						ulcer size
TGF-ß, PDGF levels		TGF-ß, PDGF levels				

Figure 3. Treatment Procedure

TABLE 1
Manuscript provided

No.	Keywords: Platelet-Rich Plasma (PRP), autologous blood products (L-PRF), and treatment of leprosy ulcers (trophic ulcers) or related	Keywords: Platelet-Rich Plasma (PRP), autologous blood products (L-PRF), and treatment of leprosy ulcers (trophic ulcers)	Note
1	Anandan V *et al.* did a study, focus on a study of 50 leprosy patients showing 92% complete healing with autologous PRP over a mean time of 4.38 weeks.[10]	Anandan V *et al.* did a study, focus on a study of 50 leprosy patients showing 92% complete healing with autologous PRP over a mean time of 4.38 weeks.[10]	Cohort study
2	Rather PA, *et al*. **did a study**, focus on investigated the efficacy and safety of PRP in a tertiary care setting.[17]	Rather PA, *et al*. **did a study**, focus on investigated the efficacy and safety of PRP in a tertiary care setting.[17]	Cohort study
3	Saha S *et al.* did a study focus on RCT showing PRP + total contact casting (TCC) is more effective than TCC alone (91% reduction in area vs 79%).[12]	Saha S *et al*. did a study, focus on RCT showing PRP + total contact casting (TCC) is more effective than TCC alone (91% reduction in area vs 79%).[12]	Observer-blind randomized controlled study
4	Vendan *et al*. **wrote** a case series, focus on prospective study of 11 patients (18 ulcers) showing success with L-PRF, with healing achieved in 4 weeks.[18]	Vendan *et al*. did a case series, focus on prospective study of 11 patients (18 ulcers) showing success with L-PRF, with healing achieved in 4 weeks.[18]	Case series
5	Conde-Montero E, *et al.* wrote a case report, focus on a case report highlighting success with intralesional PRP.[14]	Conde-Montero E, *et al.* wrote a case report, focus on a case report highlighting success with intralesional PRP.[14]	Case report
6	Napit *et al.* did a study, focus on trial evaluating L-PRF/PRP on leprosy neuropathic foot ulcers, noting that while L-PRF is used in ILC-2022, evidence is still developing.[19]	Napit *et al.* did a study, focus on trial evaluating L-PRF/PRP on leprosy neuropathic foot ulcers, noting that while L-PRF is used in ILC-2022, evidence is still developing.[19]	Cohort study
7	Suryawati *et al*. wrote a case report. PRP showed to be promising in the management of non-healing trophic ulcers in leprosy patients.[20]	Suryawati *et al*. wrote a case report. PRP showed to be promising in the management of non-healing trophic ulcers in leprosy patients.[20]	Case report
8	Sari *et al.* did a study, focus on the effects of platelet rich plasma topical gel on chronic plantar ulcer nealing in leprosy patients.[11]	Sari *et al.* did a study, focus on the effects of platelet rich plasma topical gel on chronic plantar ulcer nealing in leprosy patients.[11]	Cohort study
9	Napit et al. **wrote a systematic review** focus on systematic review confirming that, although evidence is limited, L-PRF and PRP show potential in treating chronic ulcer.[15]	–	Sytematic review

14,376 new cases of leprosy were reported in 2023, ranking 3rd in the world. Approximately 30% of new leprosy patients already have some degree of nerve function impairment when they are first diagnosed. If the disease goes untreated, up to 70% of people with leprosy can develop nerve function impairment, which is a hallmark of the disease. The vast majority of ulcers in patients with leprosy are a direct consequence of the peripheral nerve damage.[21] Predisposition to the front of the foot is 79%, the middle of the foot is 7% and the back of

the foot is 14% of plantar ulcers.[22] Both patients had leprosy ulcers in the middle of the foot.

The use of PRP for leprosy ulcers (specifically chronic plantar ulcers) is an emerging therapy aimed at overcoming the stagnant healing process caused by neuropathy and poor vascularity. Recommendation of the use of PRP for leprosy ulcer is level B and evidence level is level 2 (2a – 2b). Only eight articles were found regarding PRP and leprosy ulcers, consisting of four cohort studies,[10,11,17,19] one randomized control trial,[12] two case report,[14,20] and one case series.[18] The therapy is recommended as an adjunctive treatment (additional to standard care when conventional off-loading and wound dressing fail after 46 weeks.[22]

This case series describes the potential of PRP in improving the healing of chronic leprosy ulcers. The observed reduction in ulcer area and elevated level of TGF-ß1 in both patients, but PDGF level increased in 1 patient meanwhile in other patient decreased generally in line with the known mechanism of action of PRP that contains growth factors, namely encouraging the proliferation of epithelial cells, endothelium in the process of neovascularization, and the synthesis of extracellular matrix components, as well as modulating the inflammatory response which tissue repair and regeneration occurs when there is balance and control of the immune system needed to clean debris and pathogens from wounds.[23,24]

PRP is safe and increases the healing time of chronic wounds.[10–12,20,24–29] Making PRP requires separating red blood cells and leukocytes. There are no standard guidelines for the making of PRP, single or double centrifugation can be carried out and the length of time and speed of centrifugation can vary.[29] There are two variations of PRP that exist, namely: PRP with minimal leukocytes and rich in leukocytes. The centrifugation process allows the extraction of some isolate cells and higher concentrations of growth factors.[30] According to the procedure for making PRP it is possible to make various types of PRP such as leukocyte-platelet rich fibrin (L-PRF),[10] platelet-rich fibrin matrix (PRFM).[31]

Both cases obtained reduction of ulcer area similar with almost all other studies or case reports,[20,26,29] in both cases the location were on midfoot, differente with Anandan *et al*.[10] study in which leprosy ulcer patients were more prone on forefoot. PRP administration can stimulate granulation, accelerate wound healing, and reduce hospital stay and morbidity.[10] Sari *et al*.[11] gave PRP gel to leprosy ulcers, giving good results in improving wound size, increasing macrophages, neovascularization and granulation tissue.

Transforming growth factor-ß1 (TGF-ß1) regulates cellular processes, differentiation, extracellular matrix formation and immunosuppression.[29] TGF-ß has 3 isoforms, namely TGF-ß1, TGF-ß2, and TGF-ß3. TGF-ß1 secreted as inactive precursors and activation is required before binding to the TGF-ß1 receptor. The process of recruiting fibroblasts and immune cells from the circulation and wound edges to the wound area is stimulated by several growth factors such as TGF-ß1, TGF-ß2 and TGF-ß3. Granulation tissue, angiogenesis and collagen synthesis and production will then be formed. Barriers to the formation of matrix metalloproteinases (MMPs) will stimulate the buildup of collagen fibers, the main ones being type I fibroblasts by TGF-ß1. Reduction of TGF-β1 can explain the failure of healing in chronic wounds and in general can represent a chronic condition.[32] Both patients revealed increasing TGF-ß1 level, but based on the available studies, it is more accurate to state that the scientific literature does not show an increase in TGF-β1 after effective leprosy ulcer treatment.[33] Only one study showed an increase TGF-β1 in ozone therapy in diabetic foot ulcers,[34] more studies needed to determine whether application of PRP can increased TGF-ß1 level.

Cell growth and division are regulated by growth factors, one of which is PDGF. PDGF is a mitogenic agent, it is also a chemoattractant for fibroblasts and smooth muscle cells.[35] The presence of neutrophils and monocytes is influenced by PDGF.[36] Several cells produce PDGF including smooth muscle cells, activated macrophages, and endothelial cells.[37]

Platelet-rich plasma (PRP), which is rich in growth factors including PDGF, helps in chronic ulcers. This study has shown that the direct application of PRP leads to accelerated wound healing, increased granulation tissue formation, and faster wound closure in patients with chronic wounds, including those from leprosy and diabetes. This demonstrates that increasing the concentration of PDGF at the wound site is an effective therapeutic strategy.[38] Both patients showed different PDGF levels. One patient showed an increase, the other showed a decrease PDGF levels. The scientific literature does not show an increase in PDGF after effective leprosy ulcer treatment, only one study showed an increase PDGF in ozone therapy in diabetic foot ulcers.[34]

Evaluation of ulcer healing correlates with collagen deposits which can be measured from collagen density, in accordance with the study by Yumun *et al*.[39] which showed that combination therapy of hyperbaric oxygen and PRP or separate therapy had an effect on angiogenesis and proliferation of new collagen fibers, also with Duran's study[40] which found increasing collagen in wound healing proses in rat treated with PRP.

CONCLUSION

The combination of standard and PRP therapies has shown potential in promoting the healing of chronic leprosy ulcer, as revealed reduction in ulcer area can increase TGF-β1 level, and improved collagen density PDGF level inconsistency result. The findings in both

patients warrant larger randomized clinical trials and longer treatment durations.

CONFLICT OF INTEREST

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the materials discussed in this manuscript.

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Evidence Based Case Report

Organic Catatonia Secondary to Central Nervous Infection: An Evidence Based Case Report

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Abstract

Background : Organic catatonia has been associated with various infectious etiologies, particularly central nervous system infections. While benzodiazepines and electroconvulsive therapy (ECT) are the most extensively studied treatments, accurate identification and targeted management of the underlying cause remain essential for effective treatment
Aims : evaluating evidence-based therapeutic strategies for the management of organic catatonia in patients with infections.
Methods : Electronic Data Based was conducted using PubMed, ScienceDirect, Google Scholar, Cochrane, and Proquest. Eligible studies published between 2015 and 2025 included randomized controlled trials, systematic reviews, and case reports or case series focusing on the treatment of organic catatonia associated with central nervous system infections. Literature reviews, abstracts, non-English publications, and studies not aligned with the predefined PICO were excluded. Selected articles were critically appraised using the Joanna Briggs Institute (JBI) Critical Appraisal tools.
Results : 458 articles was identified, two studies (case series and case report) met the inclusion criteria. Abhijita et al. emphasized evidence-based management of organic catatonia secondary to meningitis (treated with ceftriaxone, doxycycline, lorazepam, and olanzapine, in addition to electroconvulsive therapy), while Doval et al. highlighted key diagnostic and therapeutic considerations in organic catatonia following encephalitis (treated with haloperidol, promethazine, lorazepam, amantadine, and escitalopram). Overall, these case reports offer valuable clinical insights.
Conclusion : Alongside infection-directed therapy, early recognition and timely pharmacological management of organic catatonia are essential for achieving optimal clinical outcomes.

Keywords : organic catatonia, meningitis, encephalitis, infection, treatment.

INTRODUCTION

Catatonia is a complex neuropsychiatric syndrome that remains frequently underrecognized, particularly when it arises as a manifestation of underlying medical or neurological disorders. In organic catatonia, catatonic symptoms result from general medical conditions, such as neurological diseases, infections, metabolic disturbances, or autoimmune processes, rather than from primary psychiatric illness alone. This condition can occur across all age groups and presents with a broad range of clinical features, including motor, behavioral, and autonomic abnormalities. Without timely recognition and appropriate treatment, catatonia may rapidly progress to life-threatening states such as malignant catatonia, characterized by hyperthermia, autonomic instability, severe rigidity, and impaired consciousness. Therefore, a thorough understanding of the pathophysiological mechanisms underlying organic catatonia is essential to improve diagnostic accuracy and clinical outcomes.[1–3]

Organic catatonia has been reported in association with a wide spectrum of infectious diseases, including viral, bacterial, and parasitic etiologies, with the strongest evidence pointing toward infections involving the central nervous system. A systematic review found that approximately one-fifth of catatonia cases are attributable to underlying medical conditions, among which inflammatory disorders of the CNS–encompassing both infectious (encephalitis, meningitis, etc) and immune-mediated processes–constitute nearly one-third. In certain reports, resolution of catatonia followed successful antimicrobial treatment, whereas other cases necessitated targeted neuropsychiatric interventions such as benzodiazepines or electroconvulsive therapy. The pathophysiological mechanisms linking infection to catatonia remain incompletely understood. Proposed explanations include direct toxic effects on neural tissue, secondary psychological stress responses, or systemic inflammatory pathways associated with the acute-phase reaction. Numerous pathogens have also been implicated as potential triggers of catatonic states. Notably, the majority of reported viral-associated cases involved neurotropic viruses, supporting the hypothesis of direct central nervous system involvement. Similarly, several bacterial pathogens with the capacity to invade the CNS have also been associated with the development of organic catatonia.[4,5]

Benzodiazepines and electroconvulsive therapy (ECT) remain the most extensively investigated therapeutic options for organic catatonia. Nevertheless, a standardized treatment approach has not yet been established, and widely accepted clinical guidelines for the management of catatonia are still lacking. However, benzodiazepines are still considered as first line treatment. Accurate identification and appropriate treatment of the underlying condition are fundamental components of effective organic catatonia management.[6]

This evidence-based case report describes a 22-years-old woman diagnosed with organic catatonia in the context of a suspected central nervous system infection (toxoplasmosis or meningitis or encephalitis), with overlapping clinical and laboratory findings suggestive of both toxoplasmosis and bacterial infection. The patient presented with prominent catatonic features, necessitating urgent intervention, while the underlying etiology remained uncertain despite cerebrospinal fluid analysis revealing inflammatory changes, including the presence of diplococci. Given that delayed or inadequate management of organic catatonia may lead to rapid clinical deterioration and life-threatening complications, this EBCR focuses on evaluating evidence-based therapeutic strategies for the management of organic catatonia in patients with infections.

CASE ILLUSTRATIONS

A 22-year-old woman, was brought to a hospital, with chief complaints of prolonged immobility and restlessness. Approximately three months prior to admission (August 2025), the patient developed fever and cough. During this period, she frequently accompanied and cared for her mother, who had end-stage renal disease requiring hemodialysis three times weekly for the past two years and a history of stroke seven years earlier. Following one of these hospital visits, the patient experienced fever that was managed at home with paracetamol without temperature measurement. She subsequently complained of headache and insomnia. The family initially attributed these symptoms to fatigue, as similar complaints had previously resolved spontaneously. After two days of fever, the patient began exhibiting abnormal behavior, including frequent daydreaming, bizarre actions, incoherent and tangential speech, and inappropriate urges to leave the house late at night. She expressed fear of being followed and reported hearing whispering voices. Over time, she became increasingly withdrawn, frequently remaining silent and failing to respond when spoken to by family members. Due to lack of improvement, she was evaluated by a general practitioner and diagnosed with fever and vertigo; her disorganized speech was attributed to sleep deprivation.

The patient's condition continued to deteriorate. She became unable to care for her mother or perform household tasks and ceased interacting with her family and surroundings. Most of her time was spent sitting silently. Activities of daily living such as eating, drinking, and bathing required step-by-step instructions and assistance from her sister. She was subsequently hospitalized for approximately one week under the care

TABLE 1
Case Illustration

Category	Details
Patient	22-year-old woman
Chief Complaint	Progressive mutism, immobility, withdrawal, and behavioral changes for 3 months
History of Present Illness	Symptoms began with fever, cough, headache, and insomnia, followed by psychotic symptoms (paranoia, auditory hallucinations, disorganized behavior and speech). The patient gradually became withdrawn, mute, unable to perform daily activities, and dependent on family for self-care.
Mental Status Examination	Confused consciousness, poor eye contact, hypoactive psychomotor activity, mutism, dysphoric mood, constricted affect, loose associations, and psychomotor retardation.
Neurological Findings	Neck stiffness and positive Babinski sign.
Investigations	CT scan suggestive of meningitis; MRI normal. CSF showed elevated protein, mild pleocytosis, positive Pandy test, and Gram-positive diplococci. Serology revealed elevated *Toxoplasma gondii* IgM/IgG and positive HSV-1 IgG. HIV test was negative.
Diagnosis	Organic catatonic disorder secondary to suspected central nervous system infection (encephalitis/meningitis).
Treatment	Risperidone 1 mg twice daily, lorazepam 1 mg nightly, diazepam as needed, intravenous dexamethasone, ceftriaxone, metronidazole, fluid therapy, and electrolyte correction.
Hospital Course	Hospitalized for 12 days. Catatonic symptoms persisted with mutism, withdrawal, and psychomotor slowing, resulting in significant impairment in self-care and social functioning.

of a neurologist and was reportedly diagnosed with encephalitis (brain inflammation). However, after discharge, the patient did not attend follow-up visits. Two weeks prior to the current admission, her symptoms worsened significantly. She became increasingly withdrawn, spoke only one to two words at a time, and often remained motionless without purposeful activity. She occasionally screamed or spoke incoherently, rarely slept at night, appeared frightened, and was no longer capable of caring for her mother. The family sought psychiatric consultation at Hospital due to persistent symptoms.. The patient was prescribed risperidone 1 mg twice daily; however, there was no clinical improvement. She became increasingly distressed, cried frequently, and was unable to sleep for three consecutive days, prompting the family to bring her to the Emergency Department of the hospital, where she was admitted. Initial asesment it was found the patient was largely mute, failed to respond verbally to questions, and only stared at the examiner. She frequently looked at her sister and tugged at her clothing without speaking. She was hospitalized for 12 days in the psychiatric ward. Throughout hospitalization, the patient remained mostly silent, responded slowly with brief answers, and repeatedly attempted to leave the ward when not accompanied by her sister, expressing a desire to go home. She was diagnosed with organic catatonic disorder and treated with risperidone 1 mg twice daily and lorazepam 1 mg nightly. There was no prior history of psychiatric illness. According to the family, the patient had never experienced similar symptoms, episodes of elevated mood, excessive energy, or prolonged depressive symptoms. She denied substance use. A history of headache was noted.

On examination, the patient opened her eyes spontaneously, demonstrated poor eye contact, was able to follow simple commands, but had significant difficulty communicating. She was predominantly mute and intermittently tearful. Vital signs were within normal limits. Neurological examination revealed neck stiffness and a positive Babinski sign. Mental status examination showed confused consciousness, poorly sustained and inappropriate psychic contact, hypoactive psychomotor behavior, and uncooperative attitude. Her mood was dysphoric with constricted and incongruent affect. Speech quantity and quality were markedly reduced. Thought processes were non-realistic with loose associations and psychomotor retardation. Thought content and perceptual disturbances could not be adequately assessed. Overall, these symptoms had persisted for approximately three months, resulting in significant functional impairment in role functioning, use

of leisure time, and self-care.

A contrast-enhanced head CT scan performed previously (September 1, 2025) showed features consistent with meningitis. Current laboratory investigations included TORCH and HSV panels, which revealed elevated Toxoplasma gondii IgM (1.03) and markedly elevated IgG (67.6), indicating prior infection with possible recent activity, and positive HSV 1 IgG. HIV screening was non-reactive. Chest radiography was unremarkable. Lumbar puncture demonstrated slightly turbid cerebrospinal fluid with positive Pandy test (6%), elevated protein (85 mg/dL), normal glucose ratio, mild pleocytosis (MN 8 cells/mm^3, PMN 6 cells/mm^3), and Gram-positive diplococci on Gram staining. Brain MRI was within normal limits. Although serological findings suggested toxoplasmosis, cerebrospinal fluid analysis, PCR studies, and neuroimaging did not demonstrate active infection, raising the possibility of partial resolution or an alternative infectious etiology, such as meningitis or encephalitis.

From a psychiatric division, supportive care was initiated with intravenous Ringer's lactate infusion at a rate of 20 drops per minute to maintain hydration. For acute agitation, diazepam 10 mg was administered intravenously as a slow bolus when required. Pharmacological management of catatonic symptoms included risperidone 1 mg orally every 12 hours and lorazepam 1 mg orally once daily at night. Neurological and medical management focused on treating the suspected central nervous system infection and associated inflammation. The patient was administered intravenous dexamethasone 10 mg every 8 hours to reduce cerebral inflammation. Empirical broad-spectrum antimicrobial therapy consisted of ceftriaxone 2 g intravenously every 12 hours and metronidazole 500 mg intravenously every 8 hours. Gastric protection was provided with ranitidine 50 mg intravenously every 8 hours. Electrolyte imbalance was corrected with intravenous potassium chloride supplementation. The patient received 25 mEq of potassium chloride administered at a controlled infusion rate of 2 mEq per hour.

METHODS

The clinical question was developed based on the population, intervention, comparison, and outcome (PICO) of this topic. The population (P) was determined to be organic catatonia patients with CNS system infection; the intervention (I) was any antibiotic, antiviral or standard treatment for organic catatonia with CNS infection (meningitis, encephalitis); the comparison (C) was -; and the outcome (O) was recovery or clinical improvement.

Literature search was done using online databases from PubMed, Science direct, Cochrane, Proquest and Google Scholar using keywords such as 'organic catatonia', 'meningitis', 'encephalitis', 'postencephalitic', and 'treatment'. The articles were then screened using inclusion criteria. The article selection was limited to randomized controlled trials (RCTs), systematic review, and case reports or case series studying treatment in organic catatonia with CNS infection (meningitis, encephalitis), published in the last 10 years (2015 – 2025). The exclusion criteria used in this study were literature review articles, abstracts, journals that were not in English, and studies that were not relevant to the PICO mentioned above. Filtered articles were then critically reviewed for their validity, importance and applicability using The Joanna Briggs Institute (JBI) Critical Appraisal tools.

RESULTS

A total of 598 articles were obtained from searches on PubMed, Science Direct, Google scholar, Cochrane and Proquest. The selection process is shown in Figure 1. At the end of the selection process, 2 articles were included in this study. The summary of these 2 studies is shown in Table 2. The two studies were then reviewed with The JBI Critical Appraisal tools. The critical appraisal results are shown in Table 3.

Based on the JBI critical appraisal checklist for case reports, both studies demonstrate overall good methodological quality.[7,8] In both reports, patient demographic characteristics, including age and sex, were clearly described at the beginning of the case presentation. The patients' clinical histories were presented in a chronological timeline, detailing symptom onset, disease progression, prior diagnostic evaluations, and therapeutic interventions. In one study, the patient's clinical condition at presentation was clearly described, beginning with hospitalization in the internal medicine ward for suspected meningitis, followed by organic catatonia treatment.[7] Similarly, the other study clearly reported the patient's initial presentation with altered sensorium and seizures due to meningoencephalitis, followed by partial neurological recovery and subsequent development of catatonic features, including mutism, negativism, and generalized rigidity.[8] In both reports, diagnostic investigations and assessment methods were adequately described, and the results were appropriately reported. Interventions were clearly detailed in both studies. One report described the use of antimicrobial therapy, benzodiazepines, antipsychotics, and electroconvulsive therapy,[7] whereas the other reported treatment with antipsychotics, benzodiazepines, antidepressants, and dopaminergic agents.[8] Post-intervention clinical outcomes were clearly described, with both cases demonstrating clinical improvement following treatment. However, neither report explicitly described adverse or unanticipated

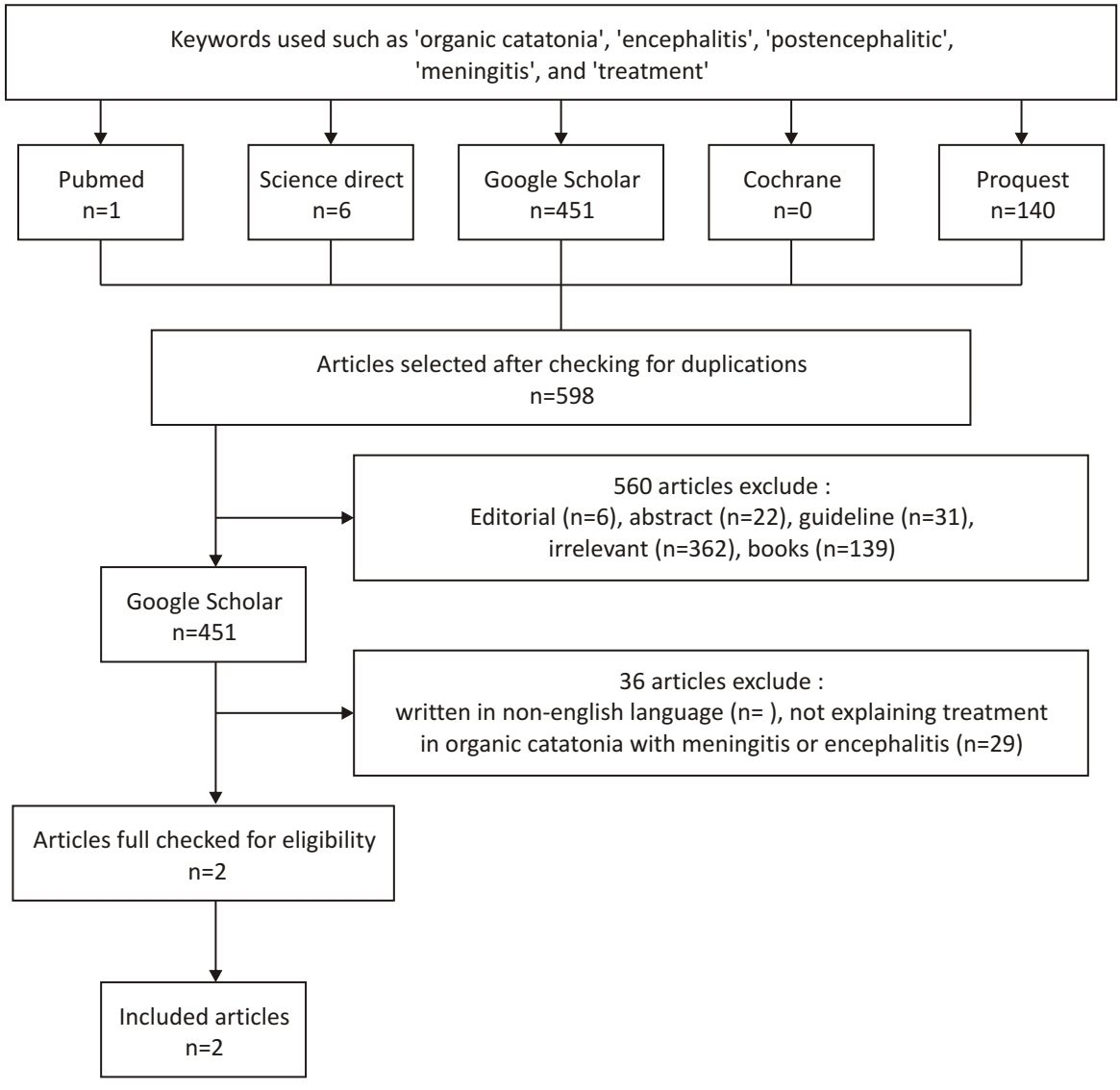

Figure 1. Articles selection process

events, which represents a limitation according to JBI appraisal criteria. Despite this limitation, both case reports provide meaningful clinical takeaways. One Study emhasized the importance of evidence-based management of organic catatonia secondary to meningitis,[7] whereas the other highlighted key considerations in the diagnosis and treatment of organic catatonia following encephalitis.[8] Overall, these case reports offer valuable clinical insights, although their inherent descriptive design limits generalizability.

DISCUSSION

Catatonia is a neuropsychiatric syndrome that has traditionally been associated with severe mental illnesses but is also increasingly recognized in the context of various general medical conditions. It is defined by a constellation of symptoms involving marked disturbances in motor activity and communication, often presenting as immobility, mutism, or reduced responsiveness, and may be accompanied by agitation, confusion, or restlessness. Historically, catatonia was regarded as a subtype of schizophrenia; however, revisions in the DSM-5 have redefined it as a distinct clinical syndrome that may occur in association with multiple psychiatric disorders. Furthermore, catatonia may also be diagnosed independently of any primary psychiatric or medical disorder.[9–11]

The conceptualization of catatonia has evolved significantly since it was first described as a separate entity by Karl Kahlbaum in 1874. Clinically, catatonia presents with a diverse array of motor, behavioral, and

TABLE 2
Summary of the studies

Author	Study design	Subjects	Summary of results	Level of Evidence
Abhijita *et al,* 2025[7]	Case series	1 case out of 4 cases (27 year old male with organic catatonia and meningitis)	The patient was initially hospitalized in the internal medicine ward with a working diagnosis of meningitis and was empirically treated with ceftriaxone and doxycycline. Two weeks after symptom onset, due to the persistence of symptoms, he was referred for psychiatric evaluation. A lorazepam challenge test resulted in a notable but incomplete improvement; despite dose escalation up to 24 mg, the patient continued to exhibit poor oral intake and impaired self-care. Consequently, electroconvulsive therapy was initiated, leading to complete remission of catatonic symptoms after six sessions, as reflected by a BFCRS score of zero. Given the presence of catatonia associated with another mental disorder, olanzapine was introduced and titrated to 15 mg daily. The patient subsequently received maintenance ECT totaling 12 sessions, while lorazepam was gradually tapered to 10 mg daily without relapse of symptoms.	4
Doval *et al*, 2015[8]	Case report	32-year-old female with Japanese encephalitis and organic catatonia	After childbirth, the patient developed altered sensorium and seizures and was treated for meningoencephalitis, with partial neurological recovery. Persistent behavioral symptoms progressed to aggression and hyperactivity; initial oral antipsychotics were ineffective, and parenteral haloperidol 10 mg plus promethazine 50 mg twice daily for 5 days controlled agitation but were followed by reduced oral intake, mutism, negativism, and generalized rigidity. She was hospitalized with a provisional diagnosis of organic catatonia as a postencephalitic sequel. Intravenous lorazepam 4 mg led to initial improvement in speech and feeding; subsequently, lorazepam was increased to 6 mg/day in three divided doses for 2 days, but the response diminished. MRI showed bilateral basal ganglia, thalamic, and temporal involvement consistent with encephalitis, and CSF was positive for Japanese encephalitis IgM. The patient was transferred to neurology care and started on amantadine 200 mg/day in divided doses; lorazepam was gradually tapered, and escitalopram 10 mg/day was added. Over the next 2 weeks, oral intake, verbal output, rigidity, and emotional dysregulation improved, with full independence in activities of daily living achieved by 3 months.	4

speech abnormalities, with a diagnosis requiring the presence of at least three characteristic signs. While it is commonly observed in patients with schizophrenia or mood disorders, catatonia may also develop in individuals with underlying medical conditions. Various general medical illnesses can either mimic catatonia or predispose patients to its development, leading to potential diagnostic delays. Case reports have

TABLE 3
Critical Appraisal of the Studies

Checklist	Abhijita *et al*, 2025[7]	Doval *et al*, 2015[8]
Were patient's demographic characteristics clearly described?	Yes. The patient's demographic characteristics, including age, sex, and socioeconomic status were clearly stated at the beginning of the case description.	Yes. The patient's demographic characteristics, including age, and sex, were clearly stated at the beginning of the case description.
Was the patient's history clearly described and presented as a timeline?	Yes. The patient's history was clearly described in chronological order, outlining symptom onset, progression, prior evaluations, and treatments over time.	Yes. The patient's history was clearly described in chronological order, outlining symptom onset, progression, prior evaluations, and treatments over time.
Was the current clinical condition of the patient on presentation clearly described?	Yes. the patient's clinical condition at presentation was clearly described, the patient was initially hospitalized in the internal medicine ward with a working diagnosis of meningitis. Two weeks after symptom onset the patient continued to exhibit poor oral intake and impaired self-care.	Yes. the patient's clinical condition at presentation was clearly described, the patient developed altered sensorium and seizures and was treated for meningoencephalitis, with partial neurological recovery, but were followed by reduced oral intake, mutism, negativism, and generalized rigidity.
Were diagnostic tests or assessment methods and the results clearly described?	Yes. The diagnostic tests, assessment methods, and their results were clearly described and appropriately reported.	Yes. The diagnostic tests, assessment methods, and their results were clearly described and appropriately reported.
Was the intervention(s) or treatment procedure(s) clearly described?	Yes. The patient received pharmacological treatment including ceftriaxone, doxycycline, lorazepam, and olanzapine, in addition to electroconvulsive therapy.	Yes. The patient was treated with haloperidol, promethazine, lorazepam, amantadine, and escitalopram.
Was the post-intervention clinical condition clearly described?	Yes. Clinical improvement achieved post treatment.	Yes. Clinical improvement achieved post treatment.
Were adverse events (harms) or unanticipated events identified and described?	Not reported	Not reported
Does the case report provide takeaway lessons?	Yes. The case report highlights important clinical lessons regarding evidence-based management of organic catatonia secondary to meningitis causes.	Yes. The case report highlights important clinical lessons regarding evidence-based management of organic catatonia secondary to encephalitis causes.

documented catatonia in association with conditions such as encephalitis, meningitis, etc. The diagnostic criteria for catatonia in the DSM-5 require the presence of three or more features, including stupor, waxy flexibility, catalepsy, mutism, posturing, negativism, stereotypy, mannerisms, grimacing, agitation, echopraxia, or echolalia. These criteria apply to both adult and pediatric populations, although in children, catatonia more frequently arises secondary to somatic illness or substance use.[9,12]

Management of catatonia typically involves benzodiazepines, particularly lorazepam, which may be used alone or in combination with antipsychotic medications to alleviate symptoms. Electroconvulsive therapy represents a highly effective definitive treatment, especially when initiated early or in cases refractory to pharmacotherapy. Given the heterogeneity of its presentation and etiologies, catatonia remains a

diagnostic challenge and is frequently underrecognized in both psychiatric and medical settings. Despite advancements in diagnostic classification with the DSM-5, clinicians must maintain a high index of suspicion and consider catatonia in the differential diagnosis of patients presenting with compatible clinical features to ensure timely and appropriate treatment.[9]

Catatonia due to a medical condition is less likely to respond to benzodiazepine therapy if the primary causes were not treated; therefore identification and treatment of the underlying cause is crucial in the treatment of organic catatonia.[6,13,14] For example, in patients with bacterial meningitis and organic catatonia, immediate hospitalization with broad-spectrum antibiotics (like Ceftriaxone, metronidazole) and possibly corticosteroids for swelling was given, while encephalitis (often viral) needs antivirals (like acyclovir for herpes), seizure control (anticonvulsants), and inflammation reduction (corticosteroids) with supportive care like IV fluids, often requiring inpatient care.[15,16] The recommended empiric ceftriaxone dosing regimen for acute bacterial meningitis in adults is 2 g every 12 h. After penicillin-susceptible *Streptococcus pneumoniae* is isolated as a causative microorganism, the ceftriaxone dose may be continued or reduced to a single dose of 2 g every 24 h, per institutional preference.[17] In patients with a suspected *Toxoplasma gondii* infection, treatment is typically initiated empirically based on clinical suspicion without waiting for confirmatory test results. The recommended first-line regimen consists of pyrimethamine, administered as a 200 mg loading dose followed by 50 mg daily in patients weighing less than 60 kg or 75 mg daily in those weighing more than 60 kg, in combination with sulfadiazine at a dose of 1000 mg four times daily for patients under 60 kg and 1500 mg four times daily for patients over 60 kg. Trimethoprim–sulfamethoxazole may be used as an alternative therapy. The induction phase of treatment should be continued for six weeks, followed by long-term maintenance therapy. Folic acid supplementation is routinely included to prevent folate deficiency, as sulfadiazine interferes with folic acid synthesis.[18]

One case report described a patient who initially presented with neuropsychiatric symptoms in the context of meningitis, was treated with empirical antimicrobial therapy (ceftriaxone and doxycycline). Despite their meningitis condition, catatonic features exist, prompting psychiatric referral. Although the patient showed partial improvement following a lorazepam challenge, high-dose benzodiazepine therapy alone was insufficient to restore basic functioning. The subsequent initiation of electroconvulsive therapy resulted in complete remission of catatonic symptoms, highlighting the effectiveness of ECT in benzodiazepine-refractory catatonia. Maintenance ECT combined with antipsychotic therapy allowed successful tapering of benzodiazepines without symptom recurrence, underscoring the role of multimodal treatment in sustaining remission.[7]

Another case report described a case of catatonia emerging as a postencephalitic sequel following meningoencephalitis in the postpartum period. Initial treatment with antipsychotics controlled aggressive behavior but was followed by worsening catatonic features, including mutism, negativism, and rigidity, illustrating the potential limitations and risks of antipsychotic monotherapy in catatonia. Benzodiazepine therapy led to initial symptomatic improvement; however, the response was not sustained. Neuroimaging and cerebrospinal fluid findings confirmed an underlying encephalitic process, and the introduction of amantadine as a glutamatergic modulator resulted in gradual and sustained clinical improvement. This case highlights the importance of addressing both residual neurological dysfunction and catatonic symptoms through targeted pharmacological strategies beyond benzodiazepines alone.[8]

Early initiation of treatment in organic catatonia is essential to reduce the risk of serious complications.[19] Prolonged immobility significantly increases the risk of deep venous thrombosis and pulmonary embolism, while reduced mobility and refusal of oral intake may lead to malnutrition, infections, and musculoskeletal complications. Despite these risks, most patients experience symptom resolution with timely and appropriate management. The presence of autonomic instability should prompt urgent evaluation for an underlying life-threatening medical condition, as treating the primary cause is crucial for clinical recovery. Benzodiazepines are still considered first-line therapy for catatonia or organic catatonia, except in cases of malignant catatonia. They act by enhancing GABA-A receptor activity and correcting inhibitory neurotransmission deficits. Lorazepam is most commonly used, although other benzodiazepines may be considered depending on clinical context. A lorazepam challenge test, administered intravenously or intramuscularly, can aid diagnosis and predict treatment response. Initial dosing typically ranges from 2–6 mg/day and may be titrated up to 12–16 mg/day, with clinical improvement usually observed within several days. Treatment duration remains variable, as premature tapering may lead to symptom recurrence.[9]

Benzodiazepines and ECT are the first treatments for which there is clinical evidence of catatonia. However, identifying and treating the underlying disorder is essential in the treatment of organic catatonia. Moreover, the role of antipsychotics is not yet entirely clear. However, there does not seem to be evidence for the use of antipsychotics as therapy for catatonic patients without any underlying psychotic disorder. Typical antipsychotics can worsen the clinical picture.[6,20]

Effective management of organic catatonia depends on accurate identification and treatment of the underlying etiology, alongside supportive care and appropriate pharmacological intervention. Therapeutic options primarily include agents that enhance γ-aminobutyric acid (GABA) activity, such as benzodiazepines, medications that augment dopaminergic transmission, including amantadine, and agents that modulate glutamatergic activity, such as memantine. In addition to reducing catatonic symptoms, benzodiazepines facilitate more thorough assessment of underlying psychopathology, thereby guiding targeted treatment of the primary condition.[21–23]

Since the 1980s, benzodiazepines have replaced short-acting barbiturates as the preferred agents for diagnostic challenge testing in catatonia. Lorazepam, administered at doses of 1–2 mg via oral, intramuscular, or intravenous routes, is the most commonly used agent. A positive response is characterized by rapid and often marked improvement in catatonic features following a single dose, enabling improved communication and clinical evaluation. Although initially considered a short-term or diagnostic intervention, benzodiazepines are now regarded as first-line therapy, with approximately 70% of patients demonstrating a rapid clinical response. Lorazepam, at daily doses ranging from 2 to 16 mg administered orally or parenterally, or diazepam, is most frequently prescribed, although other benzodiazepines such as oxazepam, clonazepam, and midazolam have also shown efficacy. The therapeutic effects of benzodiazepines are mediated through GABAergic mechanisms and may indirectly enhance dopaminergic function within the basal ganglia. In cases of malignant catatonia, higher doses of lorazepam, up to 8–24 mg per day, have been recommended. Despite their effectiveness in alleviating catatonic symptoms, benzodiazepines do not address the underlying cause, which typically requires specific treatment. While antipsychotic medications may exacerbate catatonia, they can be beneficial in managing concurrent psychotic disorders when present; however, their routine use in catatonia is generally not recommended. Catatonic symptoms are relatively common and should be actively assessed in patients presenting with psychomotor retardation or agitation. When identified early, treatment response is often favorable, with benzodiazepines serving as the treatment of choice during ongoing clinical assessment and diagnostic evaluation.[21,24,25]

CONCLUSION

This case underscores the importance of maintaining a high index of clinical suspicion for organic catatonia secondary to infectious etiologies, particularly central nervous system infections such as meningitis or encephalitis. Early identification of the underlying infection and prompt initiation of appropriate antimicrobial therapy are essential to prevent catatonic symptoms, systemic complications, and prolonged morbidity. Failure to address the primary infectious process may result in delayed recovery and results in other comorbidity such as organic catatonia. Therefore, in addition to infection-directed treatment, early recognition and appropriate pharmacological management of organic catatonia, particularly with benzodiazepines, are crucial to achieving clinical improvement. A multidisciplinary approach involving psychiatry, neurology, and internal medicine is fundamental to ensure optimal management of both the infectious process and its neuropsychiatric manifestations, thereby improving overall clinical outcomes in patients with organic catatonia.

CONFLICT OF INTEREST

The authors declare that they have no competing interests or conflicts of interest related to the publication of this article.

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ORIGINAL ARTICLE

Research manuscript should adhere guidelines as follow:

Title :
1. Is neither too long nor too short, approximately 12–14 words
2. Describes research design
3. Contains no abbreviation unless standard

Abstract :
1. Is well structured (background, aim, method, result, conclusion)
2. Consists of maximum 250 words
3. Consists of 3-8 keywords
4. Is presented in English

Introduction :
1. Consists of 2 paragraphs/parts. The first paragraph consists of research background (research justification): what have been known and what need to be added. The second paragraph consists of hypothesis or research aim.
2. Is supported by relevant and strong references

Methods :
1. Explains research design, settings and time
2. Explains population and sample, sampling technique, sample size (equation doesn't need to be enclosed), inclusion and exclusion criteria.
3. For clinical trial, explains randomization and conceal allocation, and Kappa test if conducted and detailed investment
4. Thoroughly explains method, instrument, measurement technique and data collection
5. Explains data analysis with proper tests according to data, significance and confidence interval
6. Explains computer program (software) used
7. Explains ethical clearance and informed consent

Results :
1. Is presented in a logical sequence
2. Presents subject characteristics (in a table). For clinical trial, subject characteristic of each group before trial are presented
3. Explains subjects who drop out and the reasons. If possible, provides consort diagram
4. Maximum 3-4 tables
5. Provides hypothesis without commentary

Discussion :
1. Discusses all relevant findings and its association with practice. There is no redundant repetition of findings already presented in the results section.
2. Is compared with previous study findings.
3. Mentions research strengths/weaknesses and its impact on findings.

Conclusion :
1. Should answer research question
2. Should be based on research findings, not quotation
3. Can provide suggestion for future research

References :
1. Uses Vancouver style (see *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*) www.icjme.org

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July 2026

Authors and institutions :

1. Present complete name of authors without academic title along with office/institution/work place address under the title
2. Provide correspondences
   The main author provides a statement explaining that article has never been published nor sent for publication to other journals and has already been approved by all co-authors evidenced by a statement sheet. All sent articles are reviewed by profession groups (peer reviewers) and editors. All articles should provide ethical clearance issued by Ethical Review Board and 2 sheets of inform consent form already signed in "pdf" format.

CASE REPORT

Title :
1. Is neither too long nor too short, approximately 12-14 words
2. Contains no abbreviation unless standard

Abstract :
1. Is well structured (background, aim, case report, discussion, conclusion)
2. Consists of maximum 250 words
3. Consists of 3-8 keywords
4. Is presented in English

Introduction :
1. Consists of 2 paragraphs/parts. The first paragraph consists of research background (justification of the case report). The second paragraph consists of aim of case report emphasizing diagnose/pathogenesis/therapy.
2. Is supported by relevant and strong references

Case report :
1. Presents short case involving medical history, physical examinations, and investigations.
2. Stresses new or rare cases or new therapies or procedures
3. Provides patient's picture (if necessary), investigations such as radiology or laboratory or others as needed. Pictures/photos size minimum 300 dpi.
4. Obtains patients' or families' informed consent for publication for patients with easily identified features. Editors may conceal physical features considered unnecessary.
5. Contains maximum four photos/pictures for each article.

Discussion :
1. Provides epidemiology data showing that rare cases occur or new procedures are conducted.
2. Provides relevant discussion according to aim of the case report emphasizing diagnose/pathogenesis/therapy comparing/relating to other cases and providing LoE (Level of Evidence).

Conclusion and suggestion :
1. Are in line with the aim of case report.
2. Suggestion consists of improvement for case management.

Reference :
1. Uses Vancouver style (see *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*). www.icjme.org

Author and institution :
1. Complete name of authors and office/institution/workplace address are presented under the title.

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SERTIFIKAT

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Kementerian Pendidikan, Kebudayaan, Riset dan Teknologi Republik Indonesia

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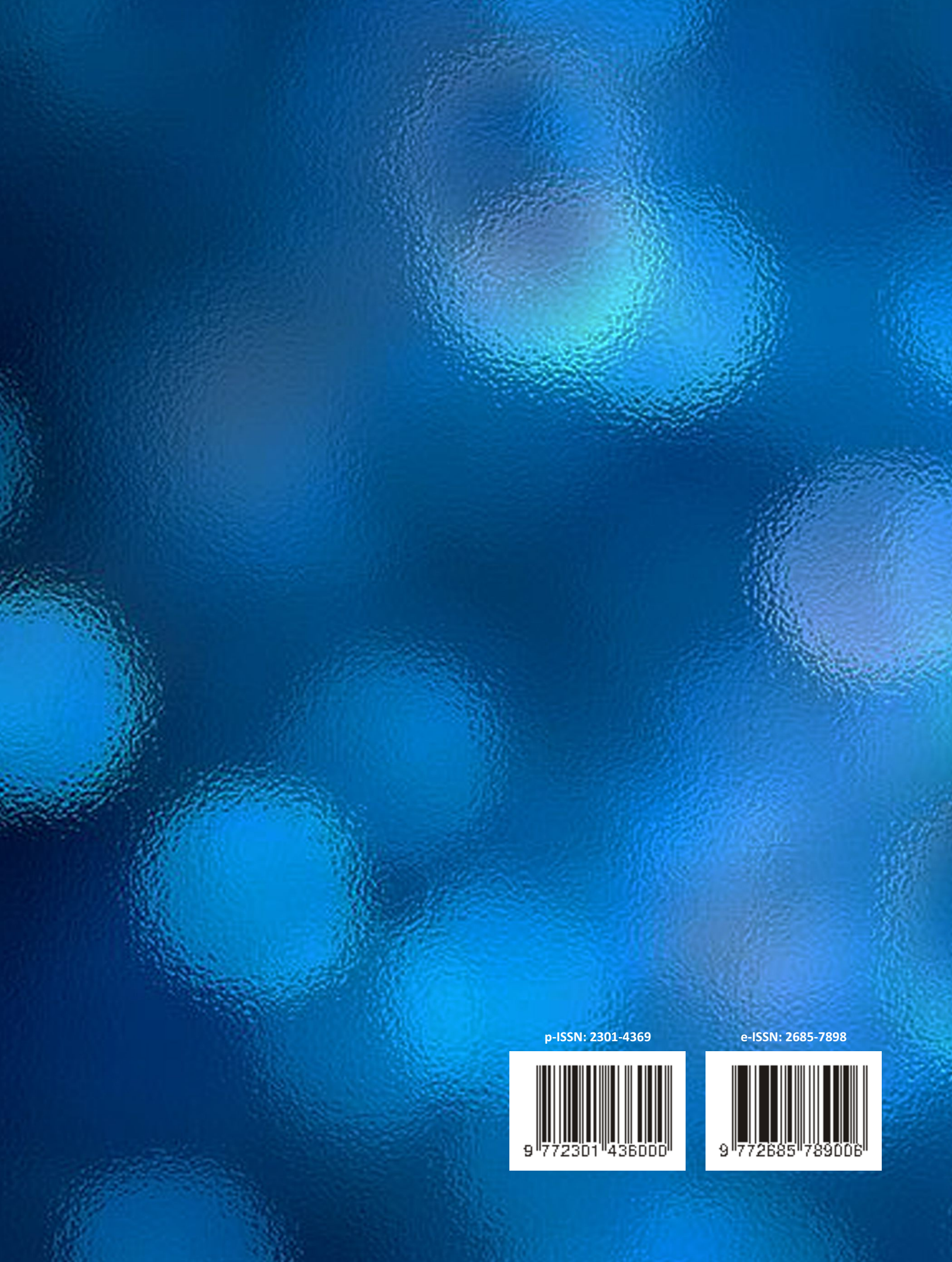

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