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Original Article

Modified Surgical Treatment for Achilles Tendon Rupture Secondary to Insertional Achilles Tendinopathy Using Midline Dorsal Approach

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Abstract

Objective: To assess the pain relief and functional outcomes of patients who undergo surgical management of Achilles tendon rupture secondary to insertional Achilles tendinopathy and associated conditions using a midline dorsal approach.

Methods: This prospective observational study included 30 patients diagnosed with Achilles tendon rupture secondary to insertional Achilles tendinopathy. This study recorded risk factors, predisposing factors, and co-morbidities for all cases. Pain relief and functional improvement were assessed by comparing Visual Analogue Scale (VAS) scores and American Orthopedic Foot and Ankle Score (AOFAS) at the time of presentation and at the final follow-up. This study conducted statistical analysis using SPSS 21.0 software, with a significance level of $p<0.05$.

Results: Of the participants, 17 (56.67%) were male and 13 (43.13%) were female, resulting in a male-to-female ratio of 1:0.76. The mean age of male and female patients was comparable ($p=0.7515$). The majority of patients (60%) were overweight, while 9 (30%) were obese, and 3 (10%) had a normal body mass index. This study observed a significant reduction in pain and functional improvement in the studied cases, as evidenced by a statistically significant reduction in VAS scores and improvements in AOFAS. Eight (26.66%) patients experienced minor complications that could be managed conservatively, but no major complications were observed.

Conclusion: Modified surgical treatment of Achilles tendon rupture secondary to insertional Achilles tendinopathy using a midline dorsal approach leads to significant improvements in pain and functional outcomes, with an acceptable complication rate.

Keywords: Achilles tendon rupture, functional outcome, midline dorsal approach, surgical management

Introduction

Insertional Achilles tendinopathy is a clinical condition that includes several acute and chronic pathologies involving the area around the Achilles tendon insertion and surrounding tissues. It is most commonly observed in young individuals, with a reported annual incidence of 7-9% in runners.[1]

The etiology of insertional Achilles tendinopathy is mainly overuse, particularly in professional and amateur athletes who engage in physical activity without taking appropriate precautions. Contributing factors include pes cavus, obesity, prolonged steroid use, hyperpronation, and the use of estrogen and fluoroquinolones. Predisposing factors also include connective tissue diseases (such as Ehlers-Danlos syndrome and Marfan's syndrome), systemic inflammatory diseases (psoriatic arthropathy, spondyloarthritis, rheumatoid arthritis, and Reiter's disease), and systemic illnesses like diabetes mellitus.[2,3]

Symptoms of Achilles tendinopathy can range from mild discomfort while walking to severe and debilitating pain that

significantly impairs function.[4] This pain may be exacerbated by external irritants such as wearing ill-fitting shoes or increasing activity levels. [5] In many cases of insertional Achilles tendinopathy, there is a prominent lateral posterosuperior calcaneal tuberosity, also known as Haglund's prominence. On imaging, apparent calcification may be visible at the tendon insertion. Clinical findings suggestive of Achilles tendinopathy, along with X-ray evidence of calcification within the tendon insertion and Haglund's lesion, are usually sufficient for diagnosis, although MRI may be necessary in selected cases.[6]

Patients with Achilles tendinopathy are at risk of tendon rupture, characterized by a sudden onset of sharp pain in the heel accompanied by a snapping sound as the tendon breaks. Tendon rupture is more common in people in their 30s to 50s, and approximately 2-6% of tendon ruptures in individuals over the age of 60 can be attributed to the use of fluoroquinolones.[7] Diagnosis is based on symptoms, history of events, and clinical examination, including the Simmond's test.[8]

Achilles tendon rupture can be treated with both surgical and nonsurgical approaches. Nonsurgical management is typically chosen for minor degrees of rupture, individuals with lower activity levels, and those with comorbid severe systemic illnesses that prevent surgery. Surgical outcomes are generally favorable, leading to improved pain and function.[9] The need for a modified surgical approach in management of Achilles tendon rupture arises out of limitations observed when standard operative techniques are used particularly in patients with underlying insertional Achilles tendinopathy. conventional methods often fail to address the altered biomechanical properties due to chronic inflammation and degenerative changes. The proposed midline dorsal approach differs significantly from conventional techniques by providing direct access to the affected insertion point, allowing for precise debridement and repair while minimizing disruption to the surrounding healthy tissue. This method also aims to reduce surgical trauma and associated postoperative complications, potentially leading to shorter recovery time and improved functional outcomes.[10]

This prospective observational study was conducted to analyze the outcomes of patients who were treated with a modified surgical approach for tendo Achilles rupture secondary to Insertional Achilles tendinopathy and associated conditions. The study utilized a midline dorsal approach.

Methods

This is a prospective observational study conducted on adult patients undergoing surgery for tendo Achilles rupture caused by insertional Achilles tendinopathy and associated conditions, using a midline dorsal approach. The study took place in the Department of Orthopedics at Prakash Institute of Medical Sciences and Research Centre in Islampur, Sangli, India, from October 2023 to September 2024. Informed and written consent was obtained from all patients. Since this was an observational study without ethical concerns, no ethical committee clearance was required. The study included adults aged 18 and above with a diagnosis of Achilles tendon rupture confirmed through clinical examination and imaging, specifically with underlying insertional Achilles tendinopathy. Patients with non-insertional Achilles tendinopathy, previous Achilles tendon surgeries, systemic inflammatory diseases not controlled by medication, active infections at the surgical site, and those unwilling to provide informed consent were excluded. The sample size was calculated using the formula:

$$n= (Z_\alpha^2) \ X \ SD^2/ \ Precision^2$$

with OpenEpi, Version 3.01, 2013 USA, based on a pilot study on the surgical management of Achilles tendon rupture. With 90% power and a 95% confidence interval, a sample size of 30 patients was determined.

Demographic details, such as age, gender, and occupation, were recorded for all cases. The medical history of significant illnesses, including systemic diseases like diabetes mellitus, hypertension, autoimmune disorders, or arthropathies, was noted. All cases underwent comprehensive blood tests, including a complete blood count (CBC), C-Reactive Protein (CRP), erythrocyte sedimentation rate, and rheumatoid factor. Foot X-rays (lateral view with plantarflexed foot) were performed to check for calcification in and around the Achilles tendon and to rule out fractures or arthropathies. Upon presentation, a visual analogue score was used to assess the severity of pain in all cases, and patients were informed about the management options and the type of surgery, including its potential outcome. Ultrasound examination
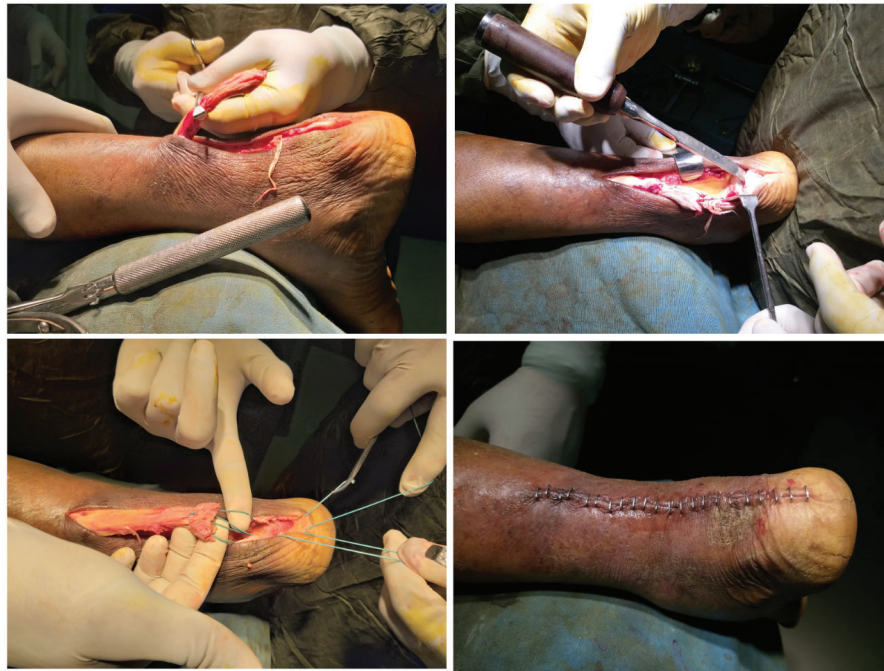
Fig. 1 (Clockwise from left upper) Posterior Longitudinal Midline Incision, Exposing the Posterosuperior Calcaneal Tuberosity, Suturing and Final Completion of Procedure

of the affected foot was performed in all cases, and magnetic resonance imaging was advised for selected cases where peroneal and posterior tibial tendon involvement was suspected. After confirming the diagnosis, patients were evaluated for pain severity using the Visual Analogue Score[11] and functional assessment using the American Orthopaedic Foot and Ankle Score (AOFAS).[12]

Surgeries were performed by a team of five surgeons, three of whom were senior surgeons. The surgeries were done under spinal anesthesia, with intravenous antibiotics administered before the procedure. To ensure proper tourniquet placement and avoid lumbar strain, the involved extremity was exsanguinated using an elastic bandage and an inflated tourniquet (280 mm Hg) before placing the patient in a prone position on the operating table. The patient's ankle was positioned at the end of the table, and a roll of foam was placed under the affected leg to slightly flex the knee. The skin was scrubbed with povidone iodine, and the affected limb was draped up to the level of the popliteal fossa.

A midline posterior longitudinal incision was made over the calcaneus and distal Achilles tendon using a size 22 blade. A sleeve of tendon material attached to the insertion site was identified for extraction of the diseased portion. The remnant insertion of the Achilles tendon and Sharpey's fibers were sharply elevated and secured with a size 15 blade. Double prong skin hooks were used for soft tissue retraction, limited to deeper tissues. Superficial tissue planes were sparingly dissected, except for careful mobilization of the paratenon for layered closure. The sural nerve was protected by the lateral limb of the Achilles tendon. The paratenon was debrided, and a longitudinal incision in the anterior wall facilitated closure over the sutured tendoachilles.

The retracted tendon's terminal inches were squeezed with Allis forceps to achieve the desired length. Tendon inspection revealed tendinosis and calcification, with the diseased portions excised. Inflammatory tissue in the retrocalcaneal bursa was also debrided. A direct posterior approach exposed the posterosuperior calcaneal tuberosity and diseased insertion site, where a calcaneal exostectomy was performed with an osteotomy. Small Hohmann retractors were used for exposure without skin tension. An intra-tendinous spur was excised with an osteotome, and Haglund's prominence was removed.

The posterior calcaneus was decompressed

for tendon reattachment. The elevated Achilles tendon insertion was reattached to the calcaneus with a size 5 coated braided nonabsorbable polyester suture through drill holes. Three drill holes were made, and a Kessler-type suture facilitated balanced reattachment. After excision of the affected tendon and bone, the wound was irrigated to remove resected fragments. The tendon split was repaired with 2-0 vicryl suture, and the paratenon was sutured with a running 2-0 vicryl suture (Fig 1).

Patients were instructed to remain non-weightbearing, and their ankle was immobilized in the posterior sugar tong splint position. This positioning was done in order to avoid placing excessive tension on the tendon for a period of six weeks, allowing for satisfactory wound healing. After this, a weight-bearing cast was applied for an additional four (4) weeks to help the patient regain mobility while still protecting the repair. Typically, patients can begin using athletic shoes around two to three months after surgery. Postoperatively, physiotherapy was initiated, which included gentle ankle motion exercises and a graduated program to strengthen the gastrocnemius and soleus muscles. Once the repair was deemed adequately healed, an eccentric stretching protocol could be beneficial. Full recovery typically took between six to twelve months. It was strongly recommended that patients be educated about the extended recovery period prior to surgery.

Patients were followed up monthly for the first few months, and then every three months until one year. The Visual Analog Scale (VAS) was used to assess pain. The VAS score ranged from 0 (indicating no pain) to 10 (indicating the worst pain imaginable). Patients marked a point on the line that corresponded to their current pain intensity. The AOFAS scores were used to evaluate functional outcomes. The outcomes were categorized as follows: excellent (90–100), good (80–89), fair (60–79), and poor (less than 60). Statistical analysis was performed using SPSS version 21.0. Quantitative data was presented as mean and standard deviation, while qualitative data was presented using incidence and percentage tables. The unpaired t-test was used for analyzing quantitative data, with a p-value less than 0.05 considered statistically significant.

Results

Out of the 30 patients included in this study, 17 (56.67%) were males and 13 (43.13%) were females, resulting in a male-to-female ratio of 1:0.76. The analysis of age group distribution revealed that the most common age group among males was 51–60 years (23.33%), followed by 41–50 years (20%). Similarly, among females, the most common age group was 51-60 years (16.67%), followed by 41-50 years (13.33%). The mean age of male patients was 53.24 +/- 12.56 years, while for female patients it was 51.68 +/- 14.10 years, showing no significant difference (p=0.7515).

Regarding patients' occupations that might predispose them to Achilles tendonitis, 40% of patients were daily wage workers involved in strenuous labor, 26.67% were housewives, 6.66% had sedentary office jobs, and 13.33% were engaged in various sports activities. The remaining 6.66% consisted of two policemen and two conductors.

The analysis of patients based on the presence of co-morbidities revealed that the most common co-morbidity among the studied cases was diabetes mellitus, which was present in 11 (33%) patients. Other co-morbidities included hypertension (20%), seronegative spondyloarthropathy (6.66%),

Table 1 Presence of Co-Morbidities in Studied Cases

Co-morbidity	Number of cases	Percentage
No Co-Morbidity	10	33.33
Diabetes Mellitus	11	36.67
Hypertension	6	20.00
Ankylosing spondylitis	2	6.67
Seronegative spondyloarthropathy	2	6.67
Psoriatic arthritis	1	3.33
Rheumatoid arthritis	1	3.33

* 3 patients had diabetes as well as hypertension

Table 2 Duration of Pain, Precipitating Factor, Physical Findings and Previous Interventions

Duration of Pain and History		Number of Patients	Percentage
Duration of pain	1–6 months	4	13.33
	6–12 months	6	20.00
	1–2 years	10	33.33
	2–3 years	5	16.67
	3–5 years	3	10.00
	More than 5 years	2	6.67
	Total	30	100.00
	Mean duration of pain = 28.54 +/- 14.48 Months		
Precipitating factor for rupture	History of trivial trauma	20	66.66
	Spontaneous rupture	10	33.33
Physical findings	Tenderness at insertion zone	30	100
	Bony prominence at lateral aspect of calcaneus (haglund deformity)	27	90
History of previous interventions	Physiotherapy	7	23.33
	Steroid injection	10	33.33

ankylosing spondylitis (6.66%), psoriatic arthritis (3.33%), and rheumatoid arthritis (3.33%) (Table 1).

Out of 30 cases, the majority of individuals (60%) were overweight, while 9 (30%) patients were obese and 3 (10%) patients had a normal body mass index. In most cases, the history of pain had been present for over a year. In 10 (33.33%) cases, the pain had been present for 1–2 years, followed by 6-12 months in 6 cases (20%) and 2-3 years in 5 cases (16.67%). The mean duration of pain was 28.54 +/- 14.48 months. In 20 (66.66%) cases, there was a history of trivial trauma such as slipping a step, loss of balance, or a small jump, while in the remaining 10% of patients, there was no precipitating factor present. On physical examination, tenderness at the insertion of the tendo-Achilles was present in all cases (100%), and 27 (90%) had a bony prominence at the lateral aspect of the calcaneus (Haglund deformity). In 10 (33.33%) patients, there was a history of steroid injection, and 7 (23.3%) patients were undergoing physiotherapy sessions for heel pain (Table 2).

All patients underwent surgical treatment using a midline dorsal approach. Pain severity was assessed using the VAS score, and functional assessment was done using the American Orthopaedic Foot and Ankle Score (AOFAS) score. The mean VAS score at the initial presentation was 8.12 +/- 2.34. After surgery, the VAS score gradually decreased, with mean scores of 5.10 +/- 1.92, 3.98 +/- 1.46, and 2.90 +/- 1.12 at 1 month, 2 months, and 3 months follow-up, respectively. At the final follow-up, the mean VAS score was 0.86 +/- 0.52. Pain reduction was observed in almost

Table 3 Severity of Pain (VAS Score) at Presentation and During Follow Up

VAS Score	Mean	Std Deviation
At Presentation	8.12	2.34
1 month	5.10	1.92
2 months	3.98	1.46
3 months	2.90	1.12
6 months	1.24	0.92
9 months	0.90	0.62
1 year	0.86	0.52

95% CI- -6.6979 to -5.7821; $p < 0.0001$* (Highly significant)

AOFAS Scores

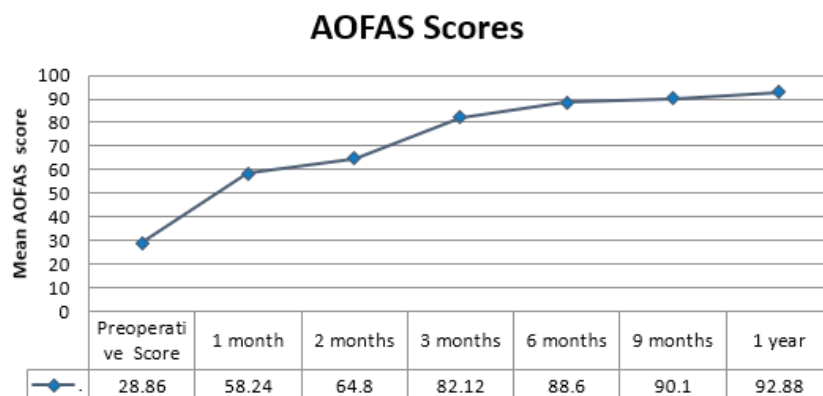|	Preoperative Score	1 month	2 months	3 months	6 months	9 months	1 year
◆	28.86	58.24	64.8	82.12	88.6	90.1	92.88

Fig. 2 Comparison of AOFAS Score at Presentation and During Follow Up

all patients. The mean VAS score at the 1-year follow-up was significantly lower compared to the initial presentation (p<0.0001) (Table 3).

The patients were assessed functionally based on the AOFAS score. All patients had significant functional impairment at the time of presentation. The mean AOFAS score at presentation was 28.86 +/- 11.02. After surgery, the AOFAS score gradually increased. At the 1-month, 3-months, and 6-months follow-up visits, the mean AOFAS scores were found to be 58.24 +/- 18.36, 82.12 +/- 20.36, and 88.60 +/- 22.34, respectively. At the final follow-up, the mean AOFAS score was 92.88 +/- 10.24. There was a considerable functional improvement in patients at the time of the final follow-up compared to the time of presentation (p<0.0001) (Fig. 2).

The analysis of complications in patients who underwent surgical treatment showed that out of 30 cases, 22 (73.33%) patients experienced no side effects. Transient pain was reported in 3 (10%) patients, while 2 (6.66%) patients experienced limping. Skin discoloration, allergic reaction, and tissue swelling were each observed in 1 (3.33%) patient (Fig 3).

Discussion

In this study, a higher number of males were found to have Achilles tendon rupture, with a male-to-female ratio of 1:0.76. The average age of male patients was 53.24 +/- 12.56 years, while the average age of female patients was 51.68 +/- 14.10 years, showing comparability.
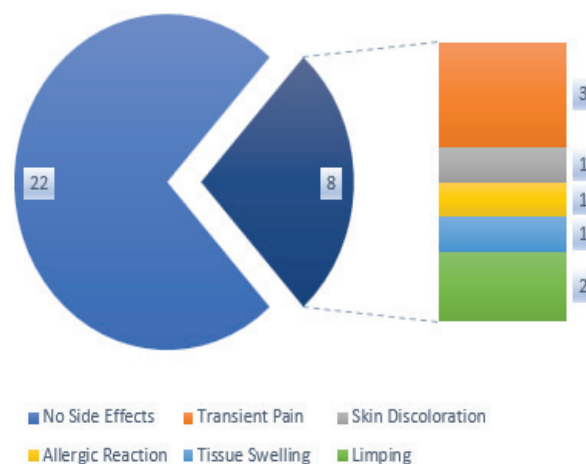

Fig. 3 Complications in the Studied Cases

Houshian *et al.* conducted a study over a period of more than a decade to examine the epidemiology of Achilles tendon ruptures.[13] The mean age of the patients in the study was 42.1 years, ranging from 3 to 82 years old, with the majority (62%) falling within the 30–49 age group. Of the ruptures, 74.2% were sport-related, with 89% occurring during ball and racket games. The annual occurrence rate of Achilles tendon ruptures increased from 18.2 per 100,000 individuals in 1984 to 37.3 per 100,000 in 1996. The highest frequency of sport-related ruptures was observed among individuals aged 30–49 years, while non-sport-related ruptures were more common in older patients, particularly those aged 50–59 years. The average age of the patients in our study closely mirrored that of the aforementioned research. Similar demographic characteristics of patients with Achilles tendon rupture were also reported by Ganestam *et al.*[14] and Weinfeld.[15]

In this study, the majority of patients were overweight (BMI>25) and had occupations that required prolonged standing or long hours. Being overweight is considered a significant factor because a higher BMI can increase the load and stress on the Achilles tendon, potentially contributing to tendinopathy. Occupations that involve prolonged standing, repetitive motion, or high physical activity may also predispose individuals to this condition due to the consistent strain placed on the tendon.

The definitive treatment for significant Achilles tendinopathy with rupture is surgery, which involves removing the affected and calcified tendon, as well as excising the retrocalcaneal bursa. This is followed by resection of the posterior calcaneal prominence and tendon repair. In general, postoperative time to full recovery tends to be proportional to the extent of the disease. A recent comparison of outcomes for surgical management of Achilles tendinopathy and isolated retrocalcaneal bursitis suggests that patients with insertional Achilles tendinopathy take longer to achieve maximum relief of symptoms and have a lower proportion of "satisfying outcomes."[16]

Several surgical procedures have been used to treat insertional Achilles tendinopathy, including resection of retrocalcaneal bursa and the prominent posterior calcaneal process. Various types of incisions can be used for this, including vertical and J-shaped incisions on both the medial and lateral sides of the tendon, peritendinous incisions, transverse incisions,

and a single central incision.[17] The central longitudinal Achilles tendon splitting incision is preferred because it allows for optimal visualization of all pathologies associated with insertional Achilles tendinosis, such as intra-substance tendinosis, calcification, retrocalcaneal bursitis, and Haglund's prominence. This type of repair also enables pullout sutures and suturing to the remaining tendon.

Hammit *et al*. conducted a study to assess wound healing in 33 consecutive patients with Achilles tendon rupture who underwent surgery using the modified midline posterior approach. The patients had an average age of 48 years, ranging from 16 to 83 years. The average follow-up period was 24 months, with a range of 12 to 73 months. The surgical interventions included procedures such as ankle and pantalar arthrodesis (both primary and revision), talectomies with tibio-calcaneal arthrodesis, nonunion fracture repairs, reconstruction of chronic Achilles rupture, and hardware removal, as well as multiple debridements for chronic osteomyelitis. The study found no cases of skin flap necrosis. One patient with diabetic neuropathic arthropathy developed a minor superficial wound eschar, which healed with only dressing changes. Four patients experienced deep infections, two of whom had a history of deep infection, while the other two had significant comorbidities. Based on these results, the authors concluded that the modified midline posterior approach to the distal tibia, ankle, and hindfoot has a low rate of primary wound complications while providing sufficient exposure.[18] This approach is suitable for any procedure requiring posterior access to the distal tibia, ankle joint, or subtalar joint. In our study, diabetic patients were under strict glycemic control so significantly to minimize wound infection. Similar results with the posterior approach were also reported by Pellegrini *et al*.[19]

In this study, there was a significant decrease in pain at the final follow-up visit compared to the time of presentation, as demonstrated by a significant reduction in the VAS score. Furthermore, there was a notable improvement in function, as indicated by a significant improvement in the American Orthopaedic Foot and Ankle Score (AOFAS). The authors, such as Tejwani *et al.,*[20] also reported pain reduction and functional improvement in their studies. No significant complications were observed in any of the surgically treated cases in our study. However, eight cases (26.66%) did experience

minor adverse effects that were successfully managed conservatively. Postoperative pain was the main cause of limping, but it subsided with the use of analgesics.

One limitation of the study was the relatively short follow-up period of only one year, which prevented an assessment of long-term complications. Thus, future research with a longer follow-up period is needed to evaluate potential long-term complications.

The central tendon-splitting approach proved to be an effective surgical technique for managing insertional Achilles tendinopathy with tendo Achilles rupture. This approach provided optimal exposure and allowed for good closure of the peritendinous sheath, resulting in a high success rate with improvements in pain and functional outcomes and an acceptable complication rate.

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Original Article

Serum Magnesium Levels in Patients Admitted with Septic Shock and Its Correlation with Outcome

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Abstract

Objective: To evaluate the initial serum magnesium levels of critically ill septic shock patients upon admission to the intensive care unit (ICU) and correlate these levels with the patients' requirements and outcomes, including ventilator support, length of stay in the ICU, occurrence of cardiac arrhythmias, and mortality rates.

Methods: This was an observational study involving 60 patients who were admitted to the medical Intensive Care Unit (ICU) for septic shock. Serum magnesium levels were measured upon admission to the ICU. A comparison was made between patients with normal and abnormal magnesium levels at the time of admission to evaluate the need for vasopressor support, the average duration of assisted ventilation and dialysis, the incidence of arrhythmia, the average length of ICU stay, and mortality rates.

Results: Out of the 60 cases studied, there were 42 males (70.00%) and 18 females (30.00%), resulting in a M:F ratio of 1:0.42. The mean age of both male and female patients was found to be comparable. The need for assisted ventilation and renal replacement therapy was found to be comparable in patients with normal and abnormal serum magnesium levels. The number of days for which assisted ventilation was required, the incidence of arrhythmia, the mean duration of ICU and hospital stay, and mortality were significantly higher in patients with abnormal magnesium levels at the time of ICU admission (P<0.05).

Conclusion: Abnormal serum magnesium levels are associated with increased morbidity and mortality in critically ill septic shock patients admitted to the ICU.

Keywords: Arrhythmias, hypomagnesemia, mortality, septic shock

Introduction

Critical illnesses, such as septic shock, often manifest as complex physiological derangements that go beyond the primary insult. In critically ill patients, various factors contribute to the delicate balance of homeostasis and electrolyte imbalances, which significantly influence the final outcome. Disruptions in electrolyte levels are common during times of severe physiological stress and can have profound consequences.[1] Critical illnesses usually provoke a cascade of physiological responses that impact multiple organ systems. Electrolyte imbalances frequently occur as the body tries to cope with the stress of the disease. Maintaining appropriate levels of sodium, potassium, calcium, and magnesium is important for vital physiological functions, such as cellular membrane stability, nerve conduction, and muscle contraction. The dysregulation of these electrolytes can worsen the severity of critical illness and have a negative impact on the final outcome.[2]

In critical care medicine, patients often have a range of electrolyte imbalances. Hyponatremia and hypernatremia are common disturbances

that can occur due to changes in fluid balance and hormone secretion. Potassium imbalances, particularly hypokalemia, can be caused by factors such as renal dysfunction or medications. Calcium dysregulation, which is frequently observed in sepsis, can result in cardiovascular instability. Amongst these imbalances, magnesium disturbances are increasingly being recognized as significant factors contributing to the clinical condition of patients.[3]

Magnesium, an intracellular cation, plays a crucial role in enzymatic reactions, neuromuscular transmission, and cardiovascular stability. In critically ill patients, serum magnesium levels can change dynamically due to various factors. Sepsis is associated with an increase in pro-inflammatory cytokines and oxidative stress, resulting in a higher demand for magnesium.[4] Concurrent Additionally, factors such as gastrointestinal losses, renal dysfunction, and therapeutic interventions can further disrupt magnesium homeostasis. Therefore, Understanding the etiopathogenesis of magnesium imbalances in critical illness is imperative for devising targeted interventions.[5]

The crucial importance of serum magnesium as a prognostic marker has garnered interest among researchers. Magnesium plays a vital role in cellular function, myocardial stability, and vascular tone, and has been found to affect the outcomes of patients admitted to the ICU.[6] However, limited research has focused on the intricate interplay between magnesium status at admission and the subsequent clinical trajectory in septic shock patients. Therefore, understanding how magnesium levels influence outcomes in this specific subset of critically ill patients having septic shock is crucial for refining treatment strategies and optimizing patient care.[8]

This prospective observational study aims to analyze the impact of serum magnesium abnormalities, specifically hypomagnesemia and hypermagnesemia, on the outcomes of patients diagnosed with septic shock and admitted to the medical ICU.

Methods

This is a prospective observational study conducted in the department of general medicine at the Regional Institute of Medical Sciences in Imphal, India. Since the study was purely observational and no ethical issues were involved, no ethical clearance was required. The study duration was one year, from January 2023 to December 2023.

The inclusion criteria for the study were patients above 18 years of age admitted to the medical ICU with a diagnosis of septic shock, as defined by Sepsis III. This includes the clinical diagnosis of sepsis with significant hypotension requiring vasopressors to maintain a mean arterial pressure above 65 mm Hg and a serum lactate level greater than 2 mmol/L (18 mg/dL) after adequate volume resuscitation. Informed and written consent was obtained from the patients' relatives.

The following patients were excluded from the study: those under 18 years of age, patients or relatives who refused consent, patients who received any form of magnesium therapy within 3 days of admission to the NICU, patients on drugs known to affect magnesium levels such as diuretics, gentamicin, cisplatin, and cyclosporine, and patients with end-stage renal disease.

The sample size was calculated using the formula

$$n = Z^2 P (1-P)/d^2$$

using OPENEPI software, based on pilot studies conducted on the topic of electrolyte imbalance in septic shock. With 90% power and a 95% confidence interval assumed, a determination of 50 patients was made, resulting in the inclusion of 60 patients in this study.

The demographic details of patients, including age, gender, and occupation, were noted. A thorough history was taken regarding the duration of illness, signs and symptoms, and the presence of any localizing signs. A comprehensive clinical examination, including a systemic examination, was performed. Hemodynamic parameters, such as pulse rate, respiratory rate, mean arterial pressure, and SpO2, were recorded for all cases. Routine blood investigations, including a complete blood count, renal function test (blood urea, serum creatinine), hepatic function test, and electrolytes (serum sodium, potassium, magnesium, and calcium), were conducted at the time of admission to the ICU. The patients were comprehensively evaluated using the SOFA (Sequential Organ Failure Assessment) score,[9] which consists of three key components: altered mental status, hypotension, and an increased respiratory rate, as well as the APACHE II (Acute Physiology and Chronic Health Evaluation) score[10], a scoring system that considers various physiological parameters, including vital signs, laboratory values, and age. Patients were divided into

three groups based on their serum magnesium level at the time of admission to the ICU: normal (1.6 to 2.5 mg/dL), increased (serum magnesium >2.5 mg/dL), or decreased (serum magnesium <1.6 mg/dL). Patients were compared in terms of outcome, including vasopressor-free days, ventilator-free days, incidence of QTc prolongation, incidence of arrhythmia, length of ICU stay, length of hospitalization, and mortality rates, between the three groups. Statistical analysis was performed using SPSS version 21.0 software. Quantitative data was presented as mean and standard deviation. Unpaired t-tests were used for quantitative data, and Chi-square tests were used for qualitative data. A p-value <0.05 was considered statistically significant.

Results

Out of 60 patients diagnosed with septic shock according to sepsis III criteria, there were 42 (70.00%) males and 18 (30.00%) females, resulting in a male-to-female ratio of 1:0.42. The most common age group was between 41-50 years (46.67%), followed by above 50 years (30.00%) and 31-40 years (16.67%). Only 4 patients (6.67%) were under 30 years old. The mean age of male patients (48.24 +/- 11.28 years) was comparable to that of female patients (46.92 +/- 12.84 years) (P=0.6917) (Table 1).

The analysis of risk factors showed that out of 60 patients, 18 (30.00%) had type II diabetes mellitus, 9 (15.00%) had some form of immunosuppression such as HIV, were on immunosuppressive therapy, or were on long-term steroid therapy. Additionally, 4 (6.67%) patients had burns, and 2 (6.67%) patients had a history of undergoing abdominal surgeries (Fig. 1).

Out of 60 cases, 38 (63.33%) had a normal magnesium level (1.6 to 2.5 mg/dL), while

14 (23.33%) patients had hypomagnesemia (<1.6 mg/dL), and the remaining 8 (13.33%) patients were found to have hypermagnesemia (>2.5 mg/dL). The analysis of patients with normal and abnormal magnesium levels at the time of admission was based on APACHE II and SOFA scores. The mean APACHE II score in patients with normal magnesium levels was 13.12±4.12, while in patients with abnormal magnesium levels, it was 15.82 +/- 5.34. The mean SOFA score in patients with normal magnesium levels was 6.14 ± 2.98, and in patients with abnormal magnesium levels, it was 8.40 +/- 3.12. Both the APACHE II and SOFA scores were higher in patients with abnormal magnesium levels, and the difference was statistically significant (P<0.05) (Table 2).

Out of the patients who had normal magnesium levels at the time of admission to the ICU, 7 (18.42%) required some form of assisted ventilation, while 31 (81.58%) patients did not require assisted ventilation. Among the 22 patients with abnormal magnesium levels, 5 (22.73%) required assisted ventilation.

Moreover, out of the patients who had normal magnesium levels at the time of admission to the ICU, 6 (15.79%) required dialysis, whereas 32 (84.21%) patients did not require any renal replacement therapy. Among the 22 patients with abnormal magnesium levels, 4 (18.18%) required dialysis. It was observed that the need for assisted ventilation, as well as renal replacement therapy, was comparable in patients with both normal and abnormal serum magnesium levels (Table 3).

The analysis of patients regarding the number of days for which vasopressors were required showed that patients with normal magnesium levels required vasopressor support for an average of 5.12 +/- 2.98 days, while patients with abnormal magnesium levels required support for an average of 6.36

Table 1 Age Distribution of the Cases with Sepsis

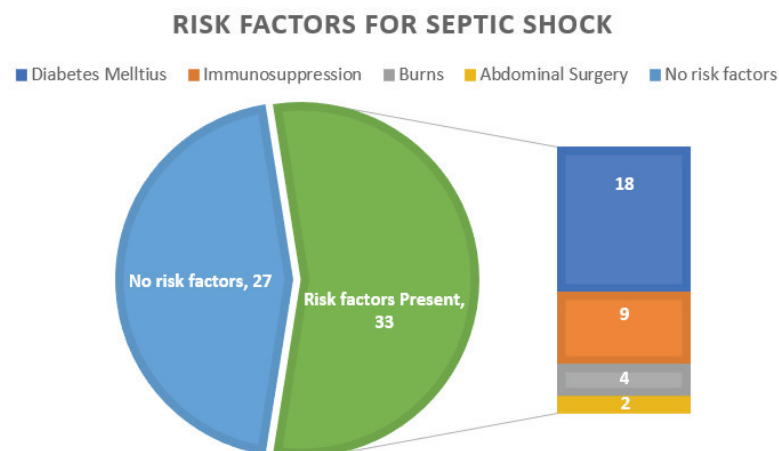|	Male		Female	
	No of patients	**Percentage**	**No of patients**	**Percentage**
<30 years	3	5.00%	1	1.67%
31–40 years	9	15.00%	1	1.67%
41–50 years	19	31.67%	9	15.00%
Above 50 years	11	18.33%	7	11.67%
Total	42	70.00%	18	30.00%
Mean Age	48.24 +/- 11.28 years		46.92 +/- 12.84 years	

p=0.6917 (Not Significant)

Fig. 1 Analysis of Risk Factors for Septic Shock in Studied Cases

Table 2 Mean APACHE II and SOFA Score in Studied Cases

APACHE II and SOFA Scores	Patients with Normal Magnesium Levels (1.6 to 2.5 mg/dL) (n=38)	Patients with Hypomagnesemia or Hypermagnesemia (< 1.6 or >2.5 mg/dl) (n=22)	Significance
Mean APACHE II score	13.12±4.12	15.82 +/- 5.34	0.032 significant
Mean SOFA score	6.14 ± 2.98	8.40 +/- 3.12	0.007 significant

+/- 3.12 days. The number of days for which assisted ventilation was required in patients with normal and abnormal magnesium levels were 2.12 +/- 1.48 and 3.12 +/- 1.62, respectively. Renal replacement therapy was required for 1.12 +/- 0.98 days in patients with normal magnesium levels and 1.46 +/- 1.10 days in patients with abnormal magnesium levels. In the normal magnesium level group, 4 (10.53%) patients had some form of arrhythmia during their ICU stay, while in the abnormal magnesium level group, 8 (36.36%) patients experienced some or the other form of arrhythmia. Mean ICU stay as well as mean hospital stay were longer in patients with abnormal magnesium levels at the time of

Table 3 Serum Magnesium Level and Need of Assisted Ventilation and Dialysis

Assisted Ventilation and Dialysis	Assisted Ventilation		Renal replacement therapy/Dialysis	
	Required	Not Required	Required	Not Required
Patients with normal magnesium levels (1.6 to 2.5 mg/dL) (n=38)	7 (18.42%)	31 (81.58%)	6 (22.73%)	32 (84.21%%)
Patients with abnormal magnesium levels (< 1.6 or >2.5 mg/dL) (n=22)	5 (22.73%)	17 (77.27%)	4 (18.18%)	17 (81.82%)
p-value	p=0.744 (not significant)		p=0.5109 (not significant)	

Table 4 Comparison of Patients on Various Parameters During ICU Stay

Assisted Ventilation, Renal Replacement Therapy and Comparison of Hospital Stay in Patients		Normal Magnesium Level (1.6 to 2.5 mg/dL) (n=38)	Hypomagnesemia or Hypermagnesemia (< 1.6 or >2.5 mg/dL) (n=22)	p-value
Number of days for which vasopressor was required		5.12 +/- 2.98	6.36 +/- 3.12	p=0.1322 not significant
Number of days for which assisted ventilation was required		2.12 +/- 1.48	3.12 +/- 1.62	p=0.017 significant
Number of days for which renal replacement therapy was required		1.12 +/- 0.98	1.46 +/- 1.10	p=0.220 not significant
QTc prolongation/Arrythmia	Yes	34	14	p=0.0221 significant
	No	4	8	
Mean duration of ICU stay		7.12 +/- 2.34	9.64 +/- 3.62	0.001 significant
Mean duration of hospital stay		11.32 +/- 4.40	14.40 +/- 5.12	0.01 significant

admission to the ICU, and this difference was found to be statistically significant (p<0.05) (Table 4).

Finally, the analysis of mortality in the studied cases showed that out of the 38 patients with normal magnesium levels, 5 (13.16%) patients expired. On the other hand, out of the 22 patients with abnormal magnesium levels, 9 (40.91%) patients succumbed to complications of septic shock (Table 5).

Discussion

Electrolyte imbalance is common in critically ill patients due to a complex interplay of a number of factors inherent to critical illnesses. The physiological stress caused by severe illness, combined with systemic inflammatory responses, often disrupts the equilibrium of electrolytes. Other factors that contribute to these imbalances include altered renal function, fluid resuscitation, and medications administered during intensive care management. Additionally, the nature of critical illness requires close monitoring and aggressive interventions, which can unintentionally impact electrolyte homeostasis. Understanding relationship between the severity of illness and electrolyte derangements is important for planning therapeutic strategies effectively, thereby optimizing patient outcomes.[11]

In this study, it was found that 38 (63.33%) participants had a normal magnesium level (1.6 to 2.5 mg/dL), while 14 (23.33%) patients had hypomagnesemia (<1.6 mg/dL), and the remaining 8 (13.33%) patients had hypermagnesemia (>2.5 mg/dL) upon admission to the ICU. Overall, abnormal magnesium levels were observed in 22 (36.67%) patients. Charles BS *et al* conducted a study to assess the levels of magnesium in critically ill patients upon their admission to the ICU. The purpose of the study was to

Table 5 Mortality in Patients With Normal and Abnormal Serum Magnesium Levels

Mortality in studied cases	Normal Magnesium Level (1.6 to 2.5 mg/dL) (n=38)		Hypomagnesemia or Hypermagnesemia (< 1.6 or >2.5 mg/dL) (n=22)	
Recovered	33	86.84%	13	59.09%
Expired	5	13.16%	9	40.91%
Total	38	100.00%	22	100.00 %

p=0.0249: significant

determine if systematically correcting low magnesium levels had an impact on patient outcomes.[12] The study found that the incidence of hypomagnesemia was 23.96%. Correcting serum magnesium levels resulted in a decrease in the mean duration of ICU stay (p=0.78), the percentage of patients requiring mechanical ventilation (52.08% vs. 65.625%), and the duration of mechanical ventilation (p=0.04). Mortality was higher in the comparison group (p=0.01). Based on these findings, the authors concluded that screening for and correcting magnesium levels in critically ill patients leads to reduced morbidity and mortality. Similar incidences of abnormalities in magnesium levels were also reported by Hansen *et al.*[13] and Pannem *et al.*[14]

In this study, patients with abnormal magnesium levels required vasopressor support for a longer period compared to patients with normal magnesium levels. However, the difference was not statistically significant. Similarly, patients with abnormal magnesium levels experienced a prolonged need for assisted ventilation (which was significantly higher in the abnormal magnesium level group) and renal replacement therapy (with no statistically significant difference) compared to their counterparts with normal magnesium levels. The incidence of arrhythmias during ICU stay was significantly higher in the abnormal magnesium level group. Importantly, patients with abnormal magnesium levels at ICU admission exhibited a significant increase in both the mean duration of ICU stay and hospital stay.

Solanki *et al.*[15] conducted a study to analyze serum magnesium levels in critically ill patients. In this study, 246 critically ill patients admitted to the ICU were examined, and their serum total magnesium levels were measured upon ICU admission. The primary outcome assessed was ICU mortality, while secondary outcomes included the necessity and duration of ventilator support, length of ICU stay, and the occurrence of cardiac arrhythmias. The findings indicated that patients with hypomagnesemia experienced significantly higher rates of ICU mortality compared to those with normal magnesium levels. Additionally, hypomagnesemia was linked to a greater requirement for ventilator support, extended ICU stays, elevated APACHE II scores, QTc prolongation, and a higher frequency of cardiac arrhythmias compared to patients with normal magnesium levels. Hypomagnesemia was identified as an independent and statistically significant

predictor of ICU mortality. The study concluded that low magnesium levels were correlated with an increased mortality rate, prolonged ventilator support and ICU stay, and higher APACHE II scores among critically ill patients. Similar outcomes were also reported by other authors, such as Gonuguntla *et al.*[16] and Velissaris *et al.*[17]

Finally, the analysis comparing mortality outcomes showed that out of 38 patients with normal magnesium levels, 5 (13.16%) patients expired. In contrast, out of 22 patients, 9 (40.91%) patients succumbed to complications of septic shock. Patients with abnormal serum magnesium levels were found to have a significantly higher risk of mortality compared to patients with normal serum magnesium levels. Zafar *et al* conducted a study to investigate the mortality pattern in critically ill patients and their serum magnesium levels.[18] The study included 70 patients admitted to the ICU. Among these critically ill patients, 50 patients (71.43%) had normal magnesium levels, 17 patients (24.29%) had hypomagnesemia, and 3 patients had hypermagnesemia. The differences in ICU stay duration, Acute Physiology and Chronic Health Evaluation-II (APACHE-II) scores, and the presence of co-morbidities between the groups were not statistically significant (p>0.05 for ICU stay, p=0.34 for APACHE-II scores, and p=0.360 for co-morbidity). Hypomagnesemia patients often had co-existing electrolyte imbalances.

The most common electrolyte imbalances observed in patients included hypokalemia (58.82%), hyponatremia (47.05%), hypocalcemia (70.58%), and hypophosphatemia (29.41%). A significant portion of the hypomagnesemia patients (76.47%) were taking medications known to lower magnesium levels, compared to 46% of those with normal magnesium levels (p= 0.030). The mortality rate was significantly higher in the hypomagnesemia group (74.47%) compared to the normomagnesemia group (36%), with a P-value of 0.004.

Similar high mortality rates have been reported in critically ill patients with abnormal magnesium levels by Upala *et al.*[19] Abnormal magnesium levels at the time of admission to the ICU are associated with an increased need for assisted ventilation, a higher incidence of arrhythmia, a longer mean duration of ICU and hospital stay, as well as increased mortality rates. This study highlights the importance of monitoring magnesium levels in critically ill patients admitted to the ICU.

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Interpretation of Platelet Histograms and Its Correlation with Peripheral Smear in Data Showing Thrombocytopenia

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Abstract

Objective: To analyze the significance of platelet histograms and peripheral smears in understanding thrombocytopenia and compare them for the incidence of pseudothrombocytopenia.

Methods: This prospective study was conducted in the Department of Pathology at a tertiary care medical institute. The study included 200 cases of thrombocytopenia. Platelet parameters (PCT, PDW, MPV) were obtained using an autoanalyzer, and peripheral smears were examined manually. Thrombocytopenia cases were classified into hyper-destructive, hypo-productive, and abnormal pooling categories based on etiology and platelet histogram patterns. The incidence of pseudothrombocytopenia was also compared. A p-value of less than 0.05 was considered statistically significant.

Results: The gender distribution showed a male preponderance (56% male, 44% female). The mean age of the patients was 26.8 years. The study found hyper-destructive thrombocytopenia to be the most common type, with viral fever, sepsis, and malaria being the common etiologies for this type of thrombocytopenia. Histogram analysis revealed distinct patterns for different types of thrombocytopenia. The study also noted a higher incidence of pseudothrombocytopenia in automated analysis compared to manual methods, with a statistically significant difference.

Conclusion: Platelet histograms combined with peripheral smear analysis provide crucial information about the etiology and nature of thrombocytopenia. This integrated approach enhances diagnostic accuracy and aid in effective patient management.

Keywords: Peripheral smear, platelet histogram, pseudo-thrombocytopenia, thrombocytopenia

Introduction

Thrombocytopenia is a common condition characterized by a reduced platelet count below 150,000/cumm in the circulating blood. It is linked to various diseases, and understanding its etiology is crucial for patient management.[1] The condition can be caused by hypoproduction, hyper destruction, or abnormal platelet pooling. Recent advancements in automated hematology analyzers have revolutionized laboratory practices by providing not only platelet counts but also valuable platelet indices such as Mean Platelet Volume (MPV), Plateletcrit (PCT), and Platelet Distribution Width (PDW). These indices, especially when analyzed through platelet histograms, offer a deeper insight into the nature and underlying causes of thrombocytopenia.[2]

The study of platelet histograms, specifically the maximum or peak of the volume distribution curve, has become an important parameter in assessing thrombocytopenia. By combining this approach with peripheral smear analysis, a deeper understanding of this condition can be achieved. Peripheral smears, a traditional method in hematology, involve

examining blood smears under a microscope to identify and quantify different blood cells. When used in conjunction with automated indices, it offers a comprehensive view of the patient's hematological profile.[3]

Recent research has emphasized the significance of these indices in different clinical scenarios. Infections like dengue fever, malaria, and rickettsial diseases often exhibit thrombocytopenia with notable changes in platelet indices such as MPV and PDW. These platelet indices could not only serve as potential indicators for these diseases but also indicate the worsening condition of the affected patient as thrombocytopenia becomes more severe.[4]

Platelet indices can also be used to determine the etiology of thrombocytopenia to some extent. In order to better understand the pathophysiological mechanisms of thrombocytopenia in specific diseases, it can be categorized into three main groups: reduced production, increased destruction, and abnormal pooling..[5] Since different etiologies have distinct pathophysiological mechanisms in the development of thrombocytopenia, a fairly accurate diagnosis can be made by using these indices in conjunction with relevant investigations such as serological tests and bone marrow examinations in selected cases.[6]

Furthermore, platelet indices also play a crucial role in diagnosing hyper-destructive thrombocytopenia, such as Immune Thrombocytopenic Purpura (ITP), hemolytic anemia, drug toxicities, and infections.[7] Indices like MPV and PDW are generally higher in ITP patients compared to those with hypo-productive thrombocytopenia. Understanding these differences in various platelet indices and the basic mechanisms of thrombocytopenia development in a specific case is essential for effectively managing patients with thrombocytopenia.[8]

In the context of diseases such as viral fever, malaria, and autoimmune conditions causing thrombocytopenia, Pseudothrombocytopenia poses a diagnostic challenge. Pseudothrombocytopenia is a laboratory artifact that is often misinterpreted as true thrombocytopenia.[9] Automated analyzers are efficient in high output settings, but they may occasionally misclassify pseudothrombocytopenia caused by platelet clumping or size variability. On the other hand, manual analysis offers the advantage of direct visualization, which allows for more accurate identification of platelet aggregates and other anomalies. However, it is a labor-intensive process and is subject to human error.[10]

Taking into consideration all of these factors, a study was undertaken to analyze the correlation between the platelet histogram and peripheral smear in cases of thrombocytopenia.

Methods

This was a prospective study conducted in the Department of Pathology from April 2023 to December 2023. The Institutional Ethical Committee approved the study (Ref BV (DU) MC &H/Sangli/IEC/510/23, dated 08/03/2023). The sample size was calculated using the formula

$$N = (Z_\alpha{}^2) \: X \: SD^2 / \: d^2$$

OPENEPI software version 3 was used for this study, based on pilot studies conducted on the topic of surgical management of perianal fistula. Using a power of 90% and a confidence interval of 95%, a sample size of 200 was determined. As a result, 200 cases with thrombocytopenia were included in the study. All samples received in the hematology lab displaying thrombocytopenia were included, and there were no specific exclusion criteria.

Demographic details of all patients, including age and gender, were noted. The clinical details of the patients were reviewed from their medical records. Special attention was given to their fever history, intake of any drugs that could cause thrombocytopenia, and history of any autoimmune disorders. If any relevant history was missing, the treating physician was contacted to obtain the necessary information. Serological tests that could help determine the cause of thrombocytopenia, such as Dengue IgG, IgM, or NS1, as well as serological tests for typhoid or rickettsial fever, were also examined and reviewed.

In the study, all the samples_received in hematology lab with thrombocytopenia were studied. EDTA anti-coagulated venous samples were processed within four hours of sample collection in the autoanalyzer.[11] Platelet parameters obtained includes– PCT, PDW and MPV. A peripheral smear stained with Leishman stain was reviewed with a specific purpose to rule out pseudo-thrombocytopenia cases. The analyzer was regularly calibrated for accuracy as well as precision using standardized quality control material.

The reports were divided into patients

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Table 1 Age Distribution of the Studied Cases

Age Category	Number of Cases n=200	Percentage
0–20	82	41.00
20–40	78	39.00
>40	40	20.00

Mean Age: 26.8 +/- 14.2 years

with hyper-destructive thrombocytopenia, hypo-productive thrombocytopenia, and thrombocytopenia due to abnormal pooling.[12] The histograms of all cases with thrombocytopenia were analyzed using an automated hematology analyzer. The histograms were categorized into Normal curve, Curve not touching baseline, Bimodal, short peak, Saw tooth, and broad based on the shape of the histogram. A correlation between platelet histograms and peripheral smear was conducted in all cases.[13] Additionally, pseudothrombocytopenia, an artifact resulting from platelet aggregation primarily due to the anticoagulant EDTA in automated analyzers, was identified. Cases of suspected pseudothrombocytopenia were confirmed by manually examining the peripheral blood smear for evidence of clumping and comparing these observations with the automated counts.

The statistical analysis was done by SPSS version 21.0 software. Mean and standard deviation were used to present quantitative data, such as the age of patients and platelet count. On the other hand, qualitative data was presented as tables showing incidence and percentages for the causes of thrombocytopenia. A p-value less than 0.05 was considered as statistically significant.

Results

The analysis of patient gender distribution revealed that out of 200 cases of thrombocytopenia, there were 112 (56%) males and 88 (44%) females. There was a higher prevalence of males, with a male-to-female ratio of 1:0.78. The most commonly affected age group was below 20 years, with 82 (41%) patients. Additionally, 78 (39%) patients were between 20-40 years old, while 40 (20%) patients were above 40 years of age. The mean age of the cases was 26.8 +/- 14.2 years (Table 1).

The analysis of the type of thrombocytopenia showed that hyper-destruction, constituted the largest group with 152 cases, accounting for

Table 2 Type of Thrombocytopenia and Etiological Causes

Etiology	Causes	Number of cases n=200	Percentage
Group A (Hyper-destruction)	Viral fevers	75	37.50
	Sepsis	24	12.00
	Malaria	15	7.50
	Liver disease	11	5.50
	Renal disease	9	4.50
	Cardiac disease	5	2.50
	ITP	13	6.50
Group B (Hypo-production)	Anemia	15	7.50
	MDS	6	3.00
	Leukemia	16	8.00
	Pancytopenia	3	1.50
Group C (Abnormal pooling)	Splenomegaly	8	4.00

Table 3 Distribution of Various Histogram Curves in Various Groups

Etiology	Type of Curves on Histogram	Number of cases n=200	Percentage
Group A (Hyper-destruction)	Normal curve	5	3.29
	Normal curve not touching the baseline	83	54.61
	Broad base	14	9.21
	Bimodal	11	7.24
	Short peak	36	23.68
	Saw tooth	3	1.97
Group B (Hypo-production)	Normal curve	10	25.00
	Normal curve not touching the baseline	6	15.00
	Broad base	4	10.00
	Bimodal	5	12.50
	Short peak	12	30.00
	Saw tooth	3	7.50
Group C (Abnormal pooling)	Normal curve	1	12.50
	Normal curve not touching the baseline	2	25.00
	Broad base	1	12.50
	Bimodal	1	12.50
	Short peak	1	12.50
	Saw tooth	2	25.00

76% of the total. Within this group, the major causes included Viral fevers (37.50%), Sepsis (12%) and Malaria (7.5%). Hypo-production group included 26 cases, making up 13% of the total. The causes in this group were Anemia (7.5%), leukemia (8%) Myelodysplastic Syndromes (MDS) (3%), and Pancytopenia (1.5%). Lastly thrombocytopenia due to
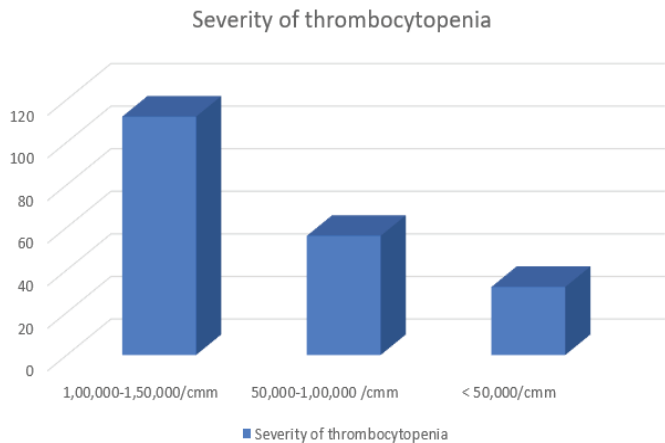

Fig. 1 Severity of Thrombocytopenia in Studied Cases

Table 4 Pseudothrombocytopenia in Manual Method Versus Automated Analysis

	Thrombocytopenia	Pseudothrombocytopenia	Total
Manual	197	3	200
Automated	189	11	200

p=0.03 (Significant)

abnormal pooling was seen in 8 (4 %) cases, predominantly caused by Splenomegaly (Table 2).

The analysis of the severity of thrombocytopenia showed that the majority of the patients had a platelet count between 100,000-150,000/cmm (56%), followed by 50,000-100,000/cmm (28%), and <50,000/cmm (16%) (Fig. 1).

The analysis of histograms revealed that in group A (Hyper destruction), out of 152 patients, the most common pattern was a normal curve that did not touch the baseline, which was seen in 83 (54.61%). The other common patterns were a short peak (23.68%) and a broad-based (9.21%) histogram. Among the 40 patients in group B, the most common histogram patterns were a short peak (30.00%) and a normal curve (25.00%). Finally, among the 8 patients in group C, the most common histogram patterns were a normal curve that did not touch the baseline (25.00%) and a sawtooth (25.00%) pattern (Table 3).

All samples were analyzed for the presence of pseudothrombocytopenia using both manual and automated methods. Out of the 11 (5.5%) samples analyzed using automated analysis, pseudothrombocytopenia was detected, while only 3 samples showed pseudothrombocytopenia when analyzed manually. The incidence of pseudothrombocytopenia was found to be higher in the automated analysis compared to the manual method, and this difference was statistically significant (p<0.03) (Table 4).

Discussion

It is crucial to analyze the relationship between automated hematology analyses and traditional microscopic examination. Studies have shown that automated cell counters may not always capture the complete hematological profile particularly in cases of anemia and thrombocytopenia.[14] The interpretation of platelet histograms offers a detailed view of platelet size distribution which is helpful in understanding the underlying pathology of thrombocytopenia.[15] The correlation between platelet histograms and peripheral smear findings is significant. For instance, a study by Sandhya *et al*.[16] demonstrated a strong correlation between RBC histograms and peripheral smear in anemia typing suggesting a similar potential in thrombocytopenia cases. This correlation is also significant in diagnosing and categorizing thrombocytopenia whether it is hyper destructive, hypo productive or due to abnormal pooling.

In this study, the most common etiology of thrombocytopenia was viral fever (37.50%), sepsis (12%), leukemia (8%), and malaria (7.5%). Abnormal pooling of platelets was found to be the cause of thrombocytopenia in 8 (4%) cases. Patel *et al.* conducted a study to analyze the etiology of thrombocytopenia. In this study, the most common causes of thrombocytopenia were malaria, viral fever, and dengue. Non-infectious causes included cirrhosis, neonatal septicemia, gestational thrombocytopenia, iron deficiency anemia, preterm neonate, megaloblastic anemia, pneumonia, ITP, DIC, acute myeloid leukemia, and chronic lymphoid leukemia. The study found malaria to be the leading cause of thrombocytopenia, followed by viral fever (other than dengue) and dengue fever, with cirrhosis and neonatal septicemia also being significant contributors.[17] Viral fever and malaria were also common etiologies in this study. Similar etiological causes were also reported by Gauer *et al*[18] and Fountain *et al*.[19]

The histograms of all samples were analyzed. In group A (Hyper-destruction), the most common pattern was a normal curve that did not touch the baseline, which was observed in 83 cases (54.61%). Among the 40 patients in group B, the common histogram patterns were a short peak (30.00%) and a normal curve (25.00%). Lastly, among the 8 patients in group C, the common histogram patterns were a normal curve that did not touch the baseline (25.00%) and a saw tooth pattern (25.00%). Shetty A *et al*. analyzed the variations of histograms in various mechanisms of thrombocytopenia. In this study, adults with thrombocytopenia

were divided into four groups based on the mechanism of thrombocytopenia, and variations in platelet histograms were studied in all groups. The following variations in histograms were observed in this study: a normal curve (8.03%), a curve not touching/reaching the baseline (43.75%), a broad-based curve (10.71%), a bimodal curve (7.14%), a curve with a short peak (25.9%), and a saw-tooth appearance of the curve (4.47%).[20] Similar histogram findings were also reported by Walle *et al.*[21] and Bhola *et al.*[22]

In this study, the comparison of manual and automated analysis for pseudothrombocytopenia showed that the incidence of pseudothrombocytopenia was higher in automated analysis compared to the manual method. The difference was significant (P<0.03). A similar study conducted by Lardinois *et al.*[23] also found an increased

risk of pseudothrombocytopenia (PTCP) in automatic blood analyzers. The authors recommended that PTCP be considered in the assessment of low platelet count particularly when automated blood analyzers were used.

Combining platelet histograms with peripheral smear analysis is an effective strategy for diagnosing thrombocytopenia and increasing diagnostic accuracy. This integrated approach not only improves accuracy, but also aids in effective patient management. The study also emphasizes the significance of manual analysis in detecting pseudothrombocytopenia, which is often overlooked in automated analysis. In conclusion, it is important to understand platelet morphology changes to differentiate the causes of thrombocytopenia and identify cases of pseudothrombocytopenia.

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Original Article

Study of Clinical and Demographic Profile of Scrub Typhus Patients Admitted to a Tertiary Care Hospital in Central India

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Abstract

Objectives: To study epidemiological characteristics, clinical features, laboratory findings, and clinical outcomes in cases of scrub typhus. Additionally, the study aims to identify the predictors of disease severity.

Methods: This cross-sectional study was conducted in the Department of General Medicine at Dr PDM Medical College in Amaravati, India. The study duration was 6 months, from July 2023 to December 2023. All clinically confirmed patients with scrub typhus were evaluated through history, clinical examination, and appropriate laboratory investigations. The clinical and laboratory profiles, hospital course, and outcomes were analyzed. Organ dysfunction upon admission was assessed using the sequential organ failure assessment (SOFA) score.

Results: A total of 200 cases were included in the study. The majority of the cases were in the age range of 31–40 years, and most of them were males. The highest number of scrub typhus cases occurred in September. The most common presenting symptoms were fever (81%), followed by nausea (37.5%), generalized weakness (34%), abdominal pain, eschar (21.5%), breathlessness, and cough (21% each), headache (19%), vomiting (15%), and altered sensorium (4.5%). The majority of patients (72.5%) did not experience any complications, while 55 patients (27.5%) developed multi-organ dysfunction syndrome (MODS) as a complication. The mortality rate was 1%.

Conclusion: Scrub typhus is a significant cause of acute febrile illness in the Vidarbha region of Maharashtra. It can present with various clinical manifestations, with or without an eschar. Early diagnosis and appropriate treatment of these cases can lead to minimal complications.

Keywords: Clinical profile, Eschar, multi-organ dysfunction syndrome, scrub typhus

Introduction

Scrub typhus is a rickettsial infection that continues to be a significant public health challenge in the Asia-Pacific region. It is a vector-borne disease caused by Orientia tsutsugamushi.[1] The disease is transmitted through the bite of infected chiggers, specifically the Leptotrombidium mite.[2] Scrub typhus can present with a wide range of clinical manifestations, from mild febrile illness to severe multi-organ dysfunction.[3]

The geographical distribution of scrub typhus extends from the far eastern parts of Russia in the north to Australia in the south, and from Japan in the east to Afghanistan in the west, forming a vast "tsutsugamushi triangle".[4] Over a billion people are susceptible to infection by Orientia tsutsugamushi. Despite its widespread prevalence in India and the potential severity of the disease, scrub typhus is often under-recognized and underreported

due to its varied clinical presentations.[5]

The clinical presentation of scrub typhus can be diverse, ranging from non-specific symptoms such as fever, headache, myalgia, and cough, to more severe manifestations such as pneumonitis, acute renal failure, meningitis, and disseminated intravascular coagulation.[6] The hallmark of scrub typhus is the presence of an eschar at the site of the chigger bite. While this characteristic skin lesion is a critical diagnostic clue, it may not be present in many cases.[7] Therefore, it is important to be aware of the variability in clinical presentation and maintain a high index of suspicion for scrub typhus in endemic areas, particularly during the peak transmission seasons.[8]

The diagnosis of scrub typhus relies on a combination of clinical suspicion and confirmatory laboratory tests. The Weil-Felix test, which was once popular, is neither sensitive nor specific. Modern diagnostic techniques, such as the indirect immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA), and polymerase chain reaction (PCR), offer higher accuracy but may not be universally available in resource-limited settings where scrub typhus is endemic.[9]

Prompt administration of antibiotics is generally effective in the treatment of scrub typhus. Doxycycline is the first-line drug used for treatment in men and non-pregnant women. It is highly effective in patients with scrub typhus. However, there are challenges in the management of this disease, including delays in diagnosis. Another problem is the development of antibiotic resistance, as well as the need for alternative treatment in pregnant women (since doxycycline is contraindicated) and patients with severe allergies to first-line antibiotics. The potential for severe complications and mortality associated with untreated or improperly treated scrub typhus emphasizes the importance of early detection and appropriate antimicrobial therapy.[10]

In light of these considerations, the present study aims to investigate the epidemiological features, clinical profile, laboratory features, and clinical outcomes in scrub typhus cases. Furthermore, it aims to identify predictors of disease severity and examine their correlation with disease mortality.

Methods

This study was a cross-sectional study conducted during a scrub typhus outbreak in central India from July 2023 to December 2023. The protocol was approved by the Ethical Committee of Dr. PDM Medical College, and consent was obtained from all study participants. The study included clinically confirmed scrub typhus adult patients who provided written consent and were admitted to Dr. PDMMC and a tertiary-care hospital. Patients under 18 years of age, those who refused consent, those with immunocompromised status or uncontrolled systemic diseases, and those later found to have fever from other causes were excluded. The study duration was 6 months (July 2023 to December 2023).

A total of 200 cases were collected for the study. The sample size was calculated using the formula

$$N = (Z_\alpha^2) \times SD^2/d^2$$

and the OPENEPI software version 3, assuming 90% power and a 95% confidence interval. Demographic details such as age, gender, and area of residence were recorded for all cases. Detailed medical history, previous treatments, and existing health conditions were documented. A comprehensive history of the duration of symptoms and specific signs and symptoms was also noted. Thorough clinical examinations, including general and systemic examinations, were conducted. Patients were also examined for the presence of characteristic eschar. Vital signs were recorded, and necessary laboratory tests, including blood, urine, and sputum cultures, as well as a smear test for acid-fast bacilli using the Ziehl–Neelsen method, were performed.

The diagnosis was confirmed using IgM enzyme-linked immunosorbent assay (ELISA) test (InBios International Inc., USA), which identifies IgM antibodies against a specific 56 kDa antigen. Further investigations in the study cases included the Mantoux test, chest X-ray, and abdominal ultrasound. In selected cases, contrast-enhanced CT scans of the thorax and abdomen, CT brain, and cerebrospinal fluid analysis were also performed. Biochemical tests, such as fasting blood sugar, renal function tests, and liver function tests, were conducted for all cases. Once the diagnosis was confirmed, patients were treated with Doxycycline, starting at 200 mg daily with adjustments based on the severity of the disease. Antibiotic treatment was modified according to the severity of illness. Clinical features, laboratory investigations, hospital course, and patient outcomes were carefully recorded.

Patients with serious complications, such

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Table 1 Baseline Characteristics of the Cases

Baseline Characteristic		Number of Cases n=200	Percentage
Age (years)	≤10	16	8.00
	11–20	24	12.00
	21–30	37	18.50
	31–40	43	21.50
	41–50	29	14.50
	51–60	26	13.00
	61–70	16	8.00
	71–80	9	4.50
Gender	Male	113	56.50
	Female	87	43.50
Residence	Rural	159	79.50
	Urban	41	20.50
Occupation	Farmer	84	42.00
	Laborer	83	41.50
	School going	33	16.50

as septic shock, acute respiratory distress syndrome (ARDS), or signs of hepatic or renal failure, received appropriate intensive care. The Sequential Organ Failure Assessment (SOFA) score was used to assess the extent and severity of organ dysfunction.[11] The collected data was organized in Microsoft Excel and analyzed using SPSS software. The analysis involved comparing averages with the Student t-test and assessing qualitative variables using the Chi-square and Fisher's exact tests. A p-value below 0.05 was considered statistically significant.

Results

A total of 200 cases of scrub typhus were examined, resulting in a response rate of 100%. The majority of patients, 43 (21.5%), belonged to the 31–40 years age group, followed by 37 (18.5%) in the 21–30 years age group, and 29 (14.5%) in the 41–50 years age

Fig.1 Monthly Incidence of Scrub Typhus in Studied Cases

Table 2 Laboratory Profile of the Studied Cases

	Value	Number of cases n=200	Percentage
Hemoglobin	Normal (12 gm/dL or above)	198	99.00
	Reduced (<12 gm/dL)	2	1.00
Total Leucocyte count (TLC)	Normal (4000–11000/mm^3)	159	79.50
	Raised (> 11000/mm^3)	31	15.50
	Reduced (< 4000/ mm^3)	10	5.00
Platelet	Normal (> 1.5 lac mcL)	153	76.50
	Reduced (<1.5 lac mcL))	47	23.50
Serum bilirubin	Normal (0.1-1.2 mg/dL)	166	83.00
	Raised (> 1.2 mg/dL)	34	17.00
Transaminases	Normal (30-50 IU/L)	188	94.00
	Raised (> 50 IU/L)	12	6.00
Urea	Normal (5-20 mg/dL)	162	81.00
	Raised (> 20mg/dL)	38	19.00
Serum Creatinine	Normal (0.6-1.2 mg/dL)	162	81.00
	Raised (> 1.2 mg/dL)	38	19.00

group, and so on. The majority of patients were male (56.5%). Of all the patients, 159 (79.5%) were living in rural areas. According to their occupational history, the highest number of cases, 84 (42%), were farmers, followed by 83 (41.5%) who were laborers, and 33 (16.5%) who were students. (Table 1)

The highest number of scrub typhus cases occurred in September (65 cases), followed by August (53 cases), July (28 cases), and October (26 cases) (Fig. 1).

The most common presenting complaint among scrub typhus patients was fever (81%), followed by nausea (37.5%), generalized weakness (34%), abdominal pain and eschar (21.5%), breathlessness and cough (in 21% each), headache (19%), vomiting (15%), and altered sensorium (4.5%) (Fig. 2).

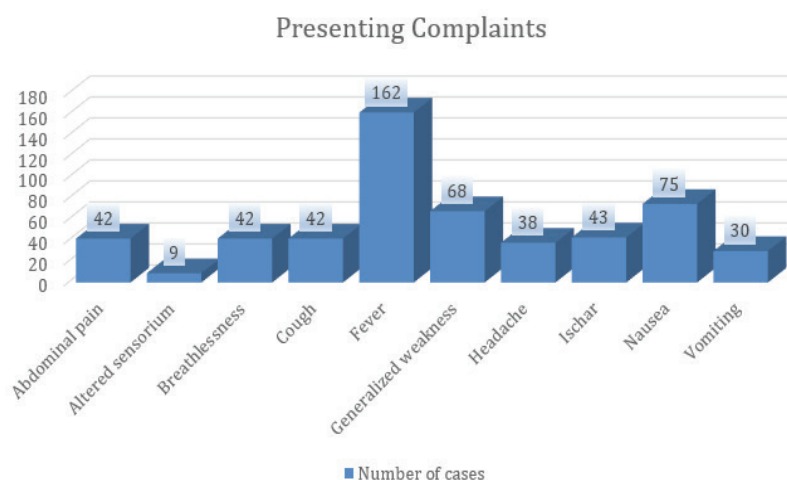Laboratory profile of scrub typhus patients has shown that Hb was normal among 99%

Fig. 2 Presenting Complaints in Cases with Scrub Typhus

Table 3 Complications Seen in Patients With Scrub Typhus

Complications	Number of cases	Percentage
AKI	5	2.50
Scrub encephalitis with septicemia with AKI	7	3.50
Septicemia	4	2.00
Scrub encephalitis with ARDS with AKI with septicemia with septic shock	2	1.00
Septicemia with thrombocytopenia	17	8.50
Septicemia with thrombocytopenia with AKI	6	3.00
Thrombocytopenia	6	3.00
Thrombocytopenia with AKI	6	3.00
Death	2	1.00
No complications	145	2.50

of patients, total leucocyte count was raised in 15.5% of patients, platelets were reduced among 23.5% of patients, serum bilirubin was raised in 17% of patients, transaminase levels were raised among 6% of patients, urea, and serum creatinine were raised among 19% of patients each. (Table 2)

In the present study, the majority of patients, specifically 145 (72.5%), did not experience any complications. However, 55 (27.5%) patients developed multiorgan dysfunction syndrome (MODS) as a complication. Among the cases of scrub typhus, the most common complication was septicemia with thrombocytopenia, affecting 9.5% of the patients. This was followed by scrub encephalitis with septicemia with acute kidney injury (AKI) at 3.5%. Other complications included septicemia with thrombocytopenia with AKI, thrombocytopenia, and thrombocytopenia with AKI, each occurring in 3% of the patients. Additionally, acute kidney injury occurred in 2.5% of the patients, septicemia in 2%, scrub encephalitis with acute respiratory distress syndrome (ARDS) with AKI with septicemia and septic shock, and death, each affecting 1% of the patients (Table 3).

Discussion

In this cross-sectional study, all 200 cases of scrub typhus were analyzed, resulting in a response rate of 100%. The majority of the patients (21.5%) belonged to the age group of 31–40 years, followed by 18.5% from 21–30 years, 14.5% from 41–50 years, and so on. There was a higher proportion of males (56.5%). Most of the patients (79.5%) were residents of rural areas. Individuals between the ages of 21–40 years, who are more likely to work and sleep in farms, are at a higher risk of getting bitten by infected chiggers. Occupational history revealed that the majority of cases (42%) were farmers, followed by 41.5% who were laborers and 16.5% who were students. The highest number of cases occurred in September, followed by August. A similar study conducted by Narlawar *et al.*[12] also found that the majority of cases (77.5%) were from rural areas, with a peak occurrence in September.

The most common presenting complaint among scrub typhus patients was fever (81%), followed by nausea (37.5%), generalized weakness (34%), abdominal pain, eschar (21.5%), breathlessness, and cough (21% each), headache (19%), vomiting (15%), and altered sensorium (4.5%). Similar findings were reported by Takhar *et al.*[13] who found that fever was the most common symptom (100%), followed by breathlessness (66.7%), hemoptysis (63.6%), oliguria (51.5%), altered mental status (39.4%), eschar (12%), and lymphadenopathy (18%). Varghese *et al.* also noted that fever was the most common presenting symptom, followed by other symptoms such as nausea, vomiting, breathlessness, cough, altered sensorium, and eschar. Similar presenting complaints in cases of scrub typhus were also reported by authors such as Narvencar *et al.*[14] and Kumar *et al.*[15]

In terms of laboratory profile, Hb levels were normal among 99% of patients suffering from scrub typhus, total leukocyte count was

raised in 15.5%, platelets were reduced in 23.5%, serum bilirubin levels were raised in 17%, transaminase levels were raised in 6%, and urea and serum creatinine levels were raised in 19% each. This is in line with Varghese,[16] who reported that elevated transaminase levels (87%), thrombocytopenia (79%), and leukocytosis (46%) were common laboratory findings. Kamath et al.[17] noted that common laboratory abnormalities included leukocytosis (34.3%), thrombocytopenia (68.8%), and transaminitis (87.5%).

Fortunately, the majority of patients (72.5%) in our study did not experience any complications, while 27.5% developed MODS as a complication. The most common complication among scrub typhus cases was septicemia with thrombocytopenia (9.5%), followed by scrub encephalitis with septicemia with acute kidney injury (AKI) (3.5%), septicemia with thrombocytopenia with AKI, thrombocytopenia, and thrombocytopenia with AKI in 3% each, acute kidney injury in 2.5%, septicemia in 2%, scrub encephalitis with ARDS with AKI with septicemia, and septic

shock and death in 1% each. Bhattacharya et al.[18] conducted a study to explore the clinical profile and determinants of scrub typhus and found that out of 78 patients with scrub typhus, 38 (48.71%) presented with sepsis. It was observed that the mean age in the sepsis group was significantly lower than in the non-sepsis group. The mortality rate was markedly higher in the sepsis group at 71.05%, compared to none in the non-sepsis group. Regression analysis showed that eschar, Acute Respiratory Distress Syndrome (ARDS), and a Glasgow Coma Scale (GCS) <10 was predictive of increased mortality in patients with scrub typhus and sepsis. Similar complications of scrub typhus were also reported by authors such as Li et al[19] and Jamil et al.[20]

Scrub typhus is one of the important causes of febrile illness in the Vidarbha region of Maharashtra. It can present with diverse clinical manifestations, with or without an eschar. Early diagnosis and appropriate intervention would help in reducing the complications and case fatality associated with the disease.

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Original Article

Characteristics of the Mothers on Stunting Toddlers 12–36 Months West Bandung Regency, Indonesia

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Abstract

Objective: To determine the characteristics of respondents with stunted toddlers aged 12–36 months in the Batujajar and Cihampelas districts of West Bandung District.

Methods: A case-control study with a pretest-posttest design was conducted from May to August 2022 in West Bandung Regency, Indonesia. The study included 124 mothers with stunted toddlers, who were divided into two groups-control and treatment-with 62 toddlers each, using simple random sampling.

Result: The majority of children under the age of five in this study were female. In the case group, the majority of mothers were in the 20–29 age range (40.3%), while in the control group, the majority were in the 30–39 age range (38.7%). Most mothers in both the control and case groups had a high school education (41.8%). The majority of participating mothers were housewives (85.5%). Childcare was primarily provided by mothers, and most of the resource persons were also mothers.

Conclusion: Based on the characteristics observed in this study, the majority of children under the age of five were female in both the case and treatment groups. Most mothers in both groups had a high school education, and the majority of participating mothers were housewives. Childcare was primarily handled by mothers, and most of the resource persons were also mothers.

Keyword: District area, parents characteristic, stunting

Introduction

The issue of stunting remains a persistent global health concern that has yet to be effectively addressed. Stunting refers to impaired linear growth resulting from inadequate food intake and malnutrition, as indicated by a height-for-age z-score (height/age) that falls below -2 standard deviations according to WHO guidelines. According to the WHO in 2019, the prevalence of stunting was estimated at 21.3%, with 144.2 million children worldwide experiencing stunting. The World Health Assembly is determined to reduce the global prevalence of stunting in children by 40% by 2025, aiming to decrease the number of stunted children from 171 million in 2018 to approximately 100 million in 2025.[1]

Stunting is a significant health concern due to its correlation with increased susceptibility to morbidity, mortality, and developmental abnormalities. In Indonesia, the problem of stunting and child development has decreased in numbers, but it has not yet met the government's achievement targets. Efforts are needed to improve nutrition and address developmental deviations in stunted children, particularly during the critical period of early childhood (under 5 years old).[5] The

government has implemented integrated interventions, including specific nutritional interventions and socialization, counseling, training, and education related to stunted growth problems.

However, these efforts have not succeeded in reducing the incidence of stunting and nutritional problems in Indonesia. The government has overlooked the importance of increasing knowledge of good nutrition and promoting changes in parental behavior to improve healthy lifestyles in addressing stunting issues. In the West Bandung District of Indonesia, the coverage deviation for stunted children was 28.8% in 2020, which is still above the standard set by West Java Province (13-14%). In this area, the growth of children is the lowest compared to other districts/cities, with only 16.8% (6,726 children) receiving examinations. This suggests that the assessment of children's growth in this region is suboptimal, particularly for those experiencing stunting.

A study conducted at the Kalasan Public Health Centre in Yogyakarta found a notable correlation between stunting status and various aspects of child growth. The study revealed an odds ratio of 3.9, indicating that children with stunting are more likely to experience growth delays in these areas.[3] Based on interviews with 10 mothers of children in the Batujajar and Cihampelas areas, 90% of them stated that they still lacked clear knowledge about monitoring child growth, especially in terms of early detection of child development and how to carry it out. Mothers of toddlers only perceive abnormal growth based on their age and rely solely on routine monitoring conducted at the posyandu, which includes weighing and measuring height to assess the child's growth, but not their development. As a result, mothers of toddlers have limited knowledge in this area.[4]

Furthermore, the lack of health resources and difficult access to demographics make it challenging to conduct comprehensive examinations. The local posyandu, assisted by cadres, can only measure weight and height according to the age recorded in maternal and child health books, with developmental checks rarely being carried out. This can negatively impact the health and development of stunted children due to inadequate nutritional intake.[5]

Methods

This study utilized a quasi-experimental design with a two-group pretest-posttest design. The research was conducted from May to August 2022 in Batujajar and Cihampelas Subdistricts, West Bandung Regency, Indonesia. The research was approved by the Center for the Study of Health Systems and Education Innovation for Health Workers, Faculty of Medicine, Padjadjaran University, Indonesia, under ethical test number 276/UN6.KEP/EC/2022. The study included 124 mothers with stunted toddlers, divided into two groups: the control group and the case group, with 62 toddlers in each group. The sample selection was carried out using simple random sampling. The inclusion criteria for mothers with stunted toddlers were as follows: mothers with toddlers aged 12–36 months, biological parents of the child, residing in Batujajar and Cihampelas Districts, and responsible for parenting at home or by the closest family members, such as grandparents or babysitters.

The exclusion criteria included physically disabled toddlers and those with significant pathological abnormalities based on physical examination. Research instruments included questionnaires to gather information about the characteristics of the respondents. The data used in this study consisted of primary and secondary data. Secondary data was obtained from the register of toddlers in Batujajar district who experienced stunting between the ages of 12–36 months, while primary data was collected through questionnaires. The objective of the univariate analysis was to provide a comprehensive description of various attributes related to the research subjects, including the gender of the toddler, age of the mother, educational background of the mother, and occupation of the mother. Data analysis was conducted using SPSS software Version 25.0.

Results

Based on the data presented in Table 1, this study found that the majority of children under five in both the control and treatment groups were female (54.8%). Additionally, the majority of mothers fell into the age categories of 20–29 years (40.2%) and 30–39 years (38.7%). Furthermore, most of the mothers had a high school education (41.9%) in both groups. The study also revealed that the majority of mothers who participated were housewives (85.5%). Finally, it was observed that the majority of respondents regarding children's parenting and sources of information were the mothers themselves

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Table 1 Distribution of Respondent Characteristics Mothers and Toddlers

Characteristics	Group		Total
	Control	Cases	
Gender			
Man	30 (48.4%)	28 (45.2%)	58 (46.8%)
Woman	32 (51.6%)	34 (54.8%)	66 (53.2%)
Mother's Age (years)			
<20	6 (9.7%)	3 (4.8%)	9 (7.3%)
20–29	23 (37.1%)	25 (40.3%)	48 (38.7%)
30–39	24 (38.7%)	24 (38.7%)	48 (38.7%)
40–49	9 (14.5%)	10 (16.1%)	19 (15.3%)
Education			
Primary school	13 (21.0%)	13 (21.0%)	26 (21.0%)
Junior high school	23 (37.1%)	22 (35.5%)	45 (36.3%)
Senior high school	26 (41.9%)	26 (41.9%)	52 (36.3%)
University	0 (0.0%)	1 (1.6%)	1 (1.6%)
Employment			
Employed	14 (22.6%)	9 (14.5%)	23 (18.5%)
Unemployed	48 (77.4%)	53 (85.5%)	101 (81.5%)
Type of work			
Housewife	48 (77.4%)	53 (85.5%)	101 (81.5%)
Teacher	0 (0.0%)	1 (1.6%)	1 (0.8%)
Employee	14 (22.6%)	5 (8.1%)	19 (15.3%)
Farmer	0 (0.0%)	3 (4.8%)	3 (2.4%)
Child Care			
Mother	47 (75.8%)	54 (87.1%)	101 (81.5%)
Grandmother	5 (8.1%)	5 (8.1%)	10 (8.1%)
Aunt	6 (9.7%)	1 (1.6%)	7 (5.6%)
Household assistant	3 (4.8%)	1 (1.6%)	4 (3.2%)
Daycare	1 (1.6%)	1 (1.6%)	2 (1.6%)
Source person			
Mother	42 (67.7%)	45 (72.6%)	87 (70.2%)
Father	11 (17.7%)	11 (17.7%)	22 (17.7%)
Grandmother	4 (6.5%)	2 (3.2%)	6 (4.8%)
Grandfather	2 (3.2%)	3 (4.8%)	5 (4.0%)
Aunt	2 (3.2%)	1 (1.6%)	3 (2.4%)
Daycare	1 (1.6%)	0 (0.0%)	1 (0.8%)

(87.1% and 72.6%, respectively).

Discussion

Consistent with the findings of a study conducted by Gosdin in 2018, the results indicate a correlation between gender and the prevalence of stunting.[6] The sex of the child is related to their growth and development achievements, considering the differences in growth spurts between girls and boys.[7] In a 2019 study conducted in China, it was

discovered that females in China have a higher susceptibility to stunting compared to boys. This disparity can be attributed to variations in poor nutritional intake resulting from societal norms favoring boys, particularly in rural areas. This discrepancy in weight status between genders may be partially explained by these factors.[8] Over time, many boys are overweight, while rural girls are at risk of stunting.[9]

Age plays a role in increased physical and psychological maturity, as well as the ability to think and work. The age of the respondents in this study was evenly distributed within the reproductive age range. However, there were also respondents who were too young or too old. The age of the mothers in this study ranged from <20 years to 50 years. Age is associated with richer experience, more information, and better emotional maturity for decision making. The two groups of respondents in this study are similar in terms of emotional maturity, experience, and information, as the age of the respondents in the two groups was not significantly different.

The findings of this study are consistent with previous research conducted in 2019, which examined the impact of family factors on the prevalence of stunting.[10] Specifically, the study found that a proportion of mothers had completed high school education, while the majority of mothers were engaged in homemaking activities. The prevalence of stunting in children born to mothers without formal education is twice as high as those born to mothers with bachelor's degrees.[11] The level of maternal education significantly impacts parenting behaviors, particularly in terms of nutrition regulation during feeding practices and the maintenance of child health.[12] Parental employment is an indirect factor in the occurrence of stunting.

Mothers who work outside often have less time for housework compared to mothers who don't work, so parenting styles influence the child's growth and development, which can ultimately be disrupted.[13] The characteristics of the mother also need to be considered, as stunting is a chronic condition that occurs due to long-standing conditions such as poverty, poor parenting due to busy parents, busy work schedules, poor maternal nutrition knowledge due to low levels of education, and frequent relapses due to unhealthy living and eating.[9]

Parenting is a practice carried out by caregivers such as mothers, fathers, grandmothers, or others to maintain health, provide food, provide emotional support to children, and provide the stimulation children need during growth and development. Negative parenting patterns are associated with an increased likelihood of stunting in children. However, it is essential to note that while access to information may be easier for the millennial generation, it does not necessarily translate to increased access to health-related information. This discrepancy may be one of the contributing factors to the lack of correlation between information access and the incidence of stunting.[14]

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Risk Factors for Treatment Drop Out Among Pulmonary Tuberculosis Patients at the UPT Public Health Center in Medan Sunggal

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Abstract

Objective: To determine the factors contributing to treatment dropout in tuberculosis (TB) patients.

Methods: This study utilized a case-control design with a sample size of 81 participants. Univariate, bivariate, and multivariate analyses were conducted, and an accidental sampling technique was employed. The study was conducted at the Public Health Center/*Puskesmas* Medan Sunggal, in the Medan Sunggal District, City of Medan, and North Sumatra Province. The research took place from February to April 2023.

Results: The research analysis revealed a significant relationship between knowledge and family support ($p<0.05$). However, there was no significant relationship found between drug side effects and treatment dropout ($p>0.05$). This lack of significance may be attributed to the consistent occurrence of side effects throughout the different stages of treatment.

Conclusion: In conclusion, this research demonstrates a significant correlation between patients' knowledge, family support, and treatment dropout ($p<0.05$). Conversely, no significant correlation was found between drug side effects and treatment dropout ($p>0.05$).

Keywords: Drug side effect**,** pulmonary TB, TB treatment drop out

Introduction

Tuberculosis is a disease that has spread widely in various countries. The TB bacteria commonly affect the lungs but can also occur outside the lungs. Nearly a quarter of the world's population is infected with Mycobacterium tuberculosis, with about 89% of TB cases occurring in adults and 11% in children. Until this moment (during the COVID-19 pandemic), TB remains the leading cause of death after HIV/AIDS and is one of the top 20 causes of death worldwide. Indonesia ranks third in the world with the highest number of TB cases, following India and China. Globally, it is estimated that 9.9 million people had TB in the year 2020.[1]

Drug-resistant tuberculosis (DR-TB) remains a threat to TB control and is one of the major public health problems in many countries around the world. Globally, in 2019, an estimated 3.3% of new TB cases and 17.7% of previously treated TB cases were classified as drug-resistant TB patients. In the same year, it was estimated that there were 9.96 million incidents of TB worldwide, with 465,000 of them being TB cases with either multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB). Out of the estimated 465,000 DR-TB patients, only 206,030 were successfully detected and 177,099 (86%) were treated, with a global treatment success rate of 57%. In Indonesia, DR-TB accounted for about 2.4% of all new TB cases and 13% of previously treated TB cases, with an estimated total of 24,000 incidents or 8.8 per 100,000 population. In 2019, approximately 11,500 RR-TB patients were detected and reported, with nearly 48% of patients starting second-line TB treatment, and the treatment success rate being 45%.[2]

Based on data from the Health Department of Medan City, it was found that there are still many TB patients who drop out of treatment. In the year 2022, there were a total of 377 TB patients who decided to discontinue their treatment. This can undoubtedly lead to higher levels of drug resistance and increase the risk of transmission to other individuals. According to data at the Public Health Center/*Puskesmas* level, *Puskesmas* Medan Sunggal has the second-highest dropout rate, accounting for 13.6% of the 25 Puskesmas located in Medan City.

Based on the researchers' observations, in Medan Sunggal, there are still many TB patients who stop their treatment, while some continue with the treatment. The researchers aim to investigate the factors that trigger patients to discontinue their treatment. In accordance with the views from the research study conducted by Nugroho,[3] it is stated that the factors leading to treatment dropout are lack of knowledge, lack of family support, and distance to healthcare services, with a significance value of p<0.05. This is consistent with the research by Sholihah[4] and Kurnia,[5] which state that the factors contributing to dropout include individuals' lack of knowledge about the treatment duration, absence of a treatment supervisor, and drug side effects leading someone to decide to discontinue treatment, with a significance value of p<0.05.

Methods

This research employs quantitative research methods with a descriptive analysis approach in a case-control study. The study was conducted at the *Puskesmas* Medan Sunggal, in the Medan Sunggal District, City of Medan, and North Sumatra Province. The research took place from February to April 2023.

The total population of TB patients between 2021 and 2022 was 183. The research sample consisted of 27 cases and 54 controls, following a 1:2 ratio for comparison. Data were collected using a Likert scale questionnaire. The questionnaire presented statements in negative form with four response options: a score of 4 for "never," a score of 3 for "sometimes," a score of 2 for "often," and a score of 1 for "very often."

The validity of the questionnaire was tested using the Product Moment Correlation, and reliability was assessed using the Cronbach's Alpha coefficient. Initially, the questionnaire consisted of 32 items, and after the validity test, all questions were found to be valid.

The reliability test was conducted on the same 32 items, and all statements were considered reliable based on the results, with the calculated r value greater than the tabled r value, ranging around 0.668. Ethical clearance Number: 01.25/37/KEPK/POLTEKKES KEMENKES MEDAN 2023. The grouping was done by calculating the total scores for each assessment component based on predetermined categories. Subsequently, the data were analyzed using frequency distribution, Chi-Square, and Logistic Regression with the step-wise method.

Results

Based on Table 1 above, it is known that more than 50% of respondents who are TB sufferers stated that they lacked knowledge about the impact of dropping out of treatment, the impact of taking OAT, the causes of TB, and the nature of TB disease.

Based on the information provided in Table 2, it is evident that TB sufferers are given 10 questions to assess the severity of drug side effects. On average, more than 50% of respondents experience mild symptoms, including reddish urine, nausea, and loss of appetite. Additionally, the most severe symptoms reported by TB sufferers are itchy skin redness, which affects 60.5% (39) of respondents.

Based on Table 3 above, it is evident that the respondents' most common responses regarding family support are as follows: family consistently reminds TB patients to take their medication, family frequently provides support for TB patients' recovery, and family occasionally demonstrates a positive attitude towards the disease experienced by TB patients.

Based on the information provided in Table 4, it is evident that both dropouts and non-dropouts among TB patients have a limited understanding of TB disease. The chi-square analysis resulted in a p-value of 0.017, indicating a significant relationship between treatment dropouts and knowledge (p-value<0.05). Further analysis revealed odds ratios (OR) of 2.08 and 1.875. These values indicate that TB patients with poor knowledge are 2.081 times more likely to discontinue treatment compared to patients with good knowledge, while those with reasonably good knowledge are 1.875 times more likely to become treatment dropouts.

Based on the data presented in Table 5, it can be concluded that both individuals who

Table 1 Frequency Distribution Based on Knowledge

Questions	Category				Total	
	Don't Know		Know			
	n	%	n	%	n	%
What is TB disease?	42	51.9	39	48.1	81	100
What causes TB?	49	60.5	32	39.5	81	100
Do you know the symptoms of TB?	30	37	51	63	81	100
Do you know how long TB treatment lasts?	10	12.3	71	87.7	81	100
Do you understand the instructions for taking anti-TB drugs?	5	6.2	76	93.8	81	100
Do you know the consequences of interrupting treatment?	63	77.8	18	22.2	81	100
Do you know the effect of taking TB drugs?	50	61.7	31	38.3	81	100

dropped out of TB treatment and those who completed it experienced severe drug side effects. The chi-square analysis resulted in a p-value of 0.453, indicating that the observed p-value is greater than 0.05. Therefore, there is no significant relationship between treatment dropouts and drug side effects. Additionally, the odds ratio (OR) value is 1.862, signifying

Table 2 Frequency Distribution Based on Drug Side Effects

Questions	Category				Total	
	No		Yes			
	n	%	n	%	n	%
Do you feel nauseous after taking the drug?	27	33,3	54	66,7	81	100
Do you experience a loss of appetite after taking the drug?	28	34.6	53	65.4	81	100
Do you feel stomach pain after taking the drug?	45	55.6	36	44.4	81	100
Do you feel feverish after taking the medicine?	57	70.4	24	29.6	81	100
Does your urine turn reddish after taking the medicine?	2	2.5	79	97.5	81	100
Do you feel a burning sensation in your legs after taking the medicine?	56	69.1	25	30.9	81	100
Do you experience skin itchy redness on your skin after taking the drug?	32	39.5	39	60.5	81	100
Do you experience hearing loss after taking the drug?	47	58	34	42	81	100
Do you experience balance disorders after taking medication?	58	71.6	23	28.4	81	100
Visual impairment	62	76.5	19	23.5	81	100

Table 3 Frequency Distribution Based on Family Support

Questions	Category								Total	
	Never		Sometimes		Often		Always			
	n	%	n	%	n	%	n	%	n	%
Does your family remind you to take your medication?	8	9.8	19	23.5	20	24.7	34	42	81	100
Does your family consistently provide support for your recovery?	7	8.6	19	23.5	32	39.5	23	28.4	81	100
Does your family exhibit attitude that make you feel happy and peaceful?	2	2.5	22	27.2	29	35.8	24	29.6	81	100
Do you feel cared for by your family?	6	7.4	22	27.2	29	35.8	24	29.6	81	100
Do you feel valued within your family?	3	3.7	21	25.9	29	35.8	28	34.6	81	100
Is your family positive about the disease you are suffering from?	6	7.4	23	28.4	31	38.3	21	25.9	81	100
Does your family play a role in helping you cope with anxiety?	9	11.1	19	23.5	28	34.6	25	30.9	81	100
Does your family instill confidence in you that you can manage this illness well?	10	12.3	14	17.3	30	37	27	33.3	81	100

that patients who encounter severe drug side effects are 1.862 times more likely to discontinue treatment compared to patients experiencing mild drug side effects.

Based on the information presented in Table 6, it is evident that TB patients receive considerable support from their families throughout the lengthy treatment process, which can span across several months. The chi-square analysis reveals a p-value of 0.003, indicating a statistically significant relationship between treatment dropouts and the level of family support as p-value <0.05. Furthermore, the OR value of 4.643

Table 4 Relationship between Knowledge and the Incidence of Pulmonary TB Treatment Dropouts

Knowledge	Drop Out				Total		p-value	OR (95% CI)
	DO		Not DO					
	n	%	n	%	n	%		
Not good	21	88	24	60	45	70	0.017	2.081 (1.046–4.138)
Good	3	12	16	40	19	30		
Total	24	100	40	100	64	100		
Quite good	3	50	14	47	17	47	0.017	1.875 (0.151–5.054
Good	3	50	16	53	19	53		
Total	6	100	30	100	36	100		

p-value 0.710>0.05, there have significant between drug side effect and incidence of pulmonary TB treatment

Table 5 Relationship between Drug Side Effects and Incidence of Pulmonary TB Treatment Dropouts

Drug Side Effects	Drop Out (DO)				Total		p-value	OR (95%CI)
	DO		Not DO					
	n	%	n	%	n	%		
Severe	25	93	47	87	72	89		
Mild	2	7	7	13	9	11	0.710	1.862 (0.35–9.642)
Total	27	100	54	100	81	100		

p-value 0.710>0.05, there have significant between drug side effect and incidence of pulmonary TB treatment

Table 6 Relationship between Family Support and Incidence of Pulmonary TB Treatment Dropouts

Family Support	Drop Out (DO)				Total		p-value	OR (95%CI)
	DO		Not DO					
	n	%	n	%	n	%		
Not Good	13	48	9	17	22	27		
Good	14	52	45	83	59	73	0,010	4.643 (1.641–13.139)
Total	27	100	54	100	81	100		

p-value 0.010<0.05, there have significant between family support and incidence of pulmonary TB treatment

suggests that individuals with insufficient family support are 4.643 times more likely to discontinue treatment compared to patients who have strong family support.

Discussion

In this study, a statistically significant relationship was found between treatment dropouts and knowledge, with a p-value of <0.05. It was observed that TB patients have insufficient knowledge about TB disease. This finding is consistent with the research conducted by Rumoalat,[6] which also highlighted a significant relationship between TB treatment dropouts and knowledge. Similar results were obtained by Sulistyoningtyas and Khusnul[7], who reported a significant relationship between treatment dropouts and knowledge.

The researcher's investigation revealed that the services provided by the Puskesmas (Community Health Centre) are generally satisfactory, as healthcare personnel always educate TB patients when they are initially diagnosed with the disease, explaining its impact on them. However, the education provided by the healthcare personnel is often not retained by the patients after the initial diagnosis.

According to Nugroho's research, newly diagnosed TB patients often experience shock as they never expected to have TB. With healthcare personnel providing education only at the time of diagnosis, it is recommended that alternative methods of conveying education and information to TB patients be used to improve their understanding.

Furthermore, Marselia's research indicates that successful treatment outcomes can be achieved by providing patients with good knowledge about TB.[8] Patients with limited knowledge have a 1.3 times higher risk of not undergoing treatment compared to those who are well-informed about TB. These findings can serve as a reference for medical professionals to enhance education for TB patients, with the aim of achieving optimal and complete treatment. The study did not find a significant relationship between treatment dropouts and drug side effects, which aligns with the research by Tika and Cahyati[9] and Fitriani[10]. However, their studies stated that severe drug side effects can contribute to treatment discontinuation. On the other hand, Merzistya[11] indicated a relationship between

treatment dropouts and drug side effects. Their study revealed that drug side effects are more common in the early weeks of treatment (the first and second week), leading patients to lose hope as the symptoms worsen instead of improving. To alleviate drug side effects, measures such as administering pain relievers (ibuprofen) and vitamin B6 can be taken, particularly to prevent peripheral neuropathy caused by isoniazid, an anti-TB medication. Flu-like symptoms caused by anti-TB drugs, such as weakness, fever, and headaches, can be managed by providing paracetamol to alleviate the experienced side effects. Effective communication, information, and education to healthcare professionals and the public are necessary to minimize the risks associated with drug side effects. However, the observations made by the researcher indicate that healthcare professionals have not provided comprehensive information about the impact of TB drug side effects. They only inform TB patients of common side effects, such as reddish urine, loss of appetite, and itching. It is crucial for healthcare professionals to provide a brochure detailing the potential side effects that patients may experience and inform them about solutions to manage these side effects, so that patients do not discontinue treatment.

In this study, a significant relationship was found between treatment dropouts and family support. TB patients generally receive good family support. This is consistent with the research conducted by Merzistya[12] and Nugiawati[13], which also highlighted a significant relationship between treatment dropouts and family support. Family support is a crucial factor in ensuring an individual's adherence to TB treatment until completion. Syafruddin[14] found that a balanced combination of family support and the patient's desire to recover can have a positive impact and increase treatment completion rates.

Through direct observations made by the researcher, it was revealed that family support in Puskesmas Sunggal is generally good, as families consistently support patients in completing their treatment. However, there are still some families who neglect their sick relatives, resulting in TB patients being cared for by their cousins or grandchildren. Despite these challenges, some TB patients show considerable strength and determination to recover.

In conclusion, this research emphasizes the importance of addressing knowledge gaps, providing comprehensive patient education, effectively managing drug side effects, and fostering strong family support systems to enhance TB treatment adherence and completion rates. These insights can inform healthcare strategies aimed at optimizing TB patient care and improving treatment outcomes.

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Original Article

Analysis of the Relationship Between Age and Immunization Completeness with Measles Incidence in Medan City

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Abstract

Objective: To analyze the relationship between age and immunization completeness and the occurrence of measles in Medan City in 2022.

Methods: This study is quantitative research with a case-control study design. The respondents in this study are the entire population of Medan City. The sample size for this research is 96 respondents, with 48 in the case group and 48 in the control group, all recorded in the measles case report at the Health Department of Medan City in 2022. The study was conducted from January to July 2023.

Results: Forty respondents in this study belonged to the toddler group, and most of whom had an incomplete immunization history. Based on chi-square analysis, a significant relationship was found between age and the occurrence of measles (p-value <0.05), as well as between immunization completeness and the occurrence of measles (p-value <0.05) with an odds ratio (OR) of 11.0. This means that respondents who are not immunized are 11 times more likely to experience measles compared to those who are immunized. Respondents with incomplete immunization are also 11 times more likely to experience measles compared to those with complete immunization.

Conclusion: There is a significant relationship between age and immunization completeness and the occurrence of measles. Respondents with an incomplete immunization history are at 11 times higher risk of experiencing measles compared to those with a complete immunization history. For future research, it is recommended to increase the number of study respondents and further explore and expand on risk factors such as the history of contact with measles cases in the city of Medan.

Keywords: Age, immunization, measles

Introduction

Measles is a contagious disease that affects the respiratory and immune systems. The symptoms of measles consist of three stages. Firstly, during the prodromal stage, patients experience symptoms such as fever, fatigue, loss of appetite, throat inflammation, and eye inflammation occurring within a period of 3 to 5 days. Subsequently, during the eruption stage, a rash appears on the face and behind the ears. Lastly, during the convalescent stage, the rash changes color and becomes darker.

According to data from the WHO in 2019, it was found that approximately 40 million children have been infected with measles over the past ten years, with about 74% of whom eventually dying. The majority of these measles cases occurred in preschool and elementary school-age children. In Indonesia, the death toll from measles reaches around 30,000 children, with many experiencing complications such as diarrhea, blindness, pneumonia, encephalitis (inflammation of the brain), and hearing impairment.[1]

There were 2,931 suspected measles cases

in Indonesia, with 75 confirmed positive cases, resulting in an Incidence Rate (IR) of 0.48 per 100,000 population.[2] According to the Ministry of Health of the Republic of Indonesia, measles cases increased by approximately 32 times in 2022 compared to 2021. In 2022, the Ministry of Health received reports of measles cases exceeding 3,341, spread across 223 districts/cities in 31 provinces in Indonesia.[3] This increase in measles cases occurred during the Covid-19 pandemic, which has sparked the interest of researchers in analyzing the distribution of ages among measles-affected respondents in Medan City, as well as understanding the immunization history of those affected and unaffected by measles.

The diversity of complications caused by measles, which often lead to deaths, is primarily due to the lack of public awareness regarding various risk factors associated with measles. Education and awareness about the importance of immunization and healthcare can help reduce the number of measles cases and their complications. John Gordon stated that the occurrence of diseases is determined by three components: the host, agent, and environment. These factors also apply to measles, with host factors including gender, age, exclusive breastfeeding, immunization status, individual nutritional status, and vitamin A supplementation.

Agent factors consist of the measles virus, while environmental factors include biological, social, and physical aspects.[4] To protect children from the measles virus, it is crucial to ensure immunization completeness. Vaccination is highly important in building immunity against the disease and preventing its spread. By ensuring that children receive the recommended immunizations on time, we can protect them and boost community immunity, thereby lowering the overall risk of measles outbreaks. The purpose of this research is to analyze the relationship between risk factors for measles occurrence, specifically age and immunization completeness, among the population in the city of Medan, and the reported measles cases in 2022.

Methods

This quantitative study employed a case-control design and utilized secondary data. The research instrument used was an observation sheet obtained from the Health Department of Medan City, specifically regarding measles cases in 2022. The population for this research consisted of all suspected measles cases,

totaling 282 cases recorded in the data reports of the Medan Health Department in 2022. The sample size for this study was determined based on calculations using the analytical categorical sampling formula, resulting in a sample size of 96 individuals. This sample size included 48 respondents in the case group and 48 respondents in the control group. The inclusion criteria for the case group were respondents with positive laboratory results directly observed from the laboratory report records at the Health Department of the City of Medan. The control group included respondents with negative lab results directly observed from the laboratory report records at the Health Department of the City of Medan. The exclusion criteria for both the case and control groups were respondents with pending lab results. The sampling technique utilized in this research was simple random sampling. The sampling procedure involved a lottery method, where the researcher wrote sequential numbers on small pieces of paper, rolled them up, and placed them inside a plastic cup with a small hole covered. The researcher then shook the cup until one rolled-up paper emerged. Each number drawn was recorded and used as a sample for the research. The variables in this study were age and completeness of immunization.

The completeness of respondents' immunization is determined based on the data from the measles vaccine report. It is considered complete if the respondent has received the measles vaccine three times, as indicated in the report data. Conversely, it is deemed incomplete if the respondent has received less than three doses of the measles vaccine. Data collection for this study involves analyzing the compilation of measles case reports and distinguishing between groups with positive and negative results from measles lab tests. The Health Department of Medan City acquires these reports through routine reports from 41 primary health centers in Medan. The data analysis conducted for this study includes univariate and bivariate analyses, employing the chi-square test. The research was carried out in Medan City from January 2023 to July 2023. Ethical approval for this study has been obtained from the Health Research Ethics Committee at *Politeknik Kesehatan* Kemenkes Medan, under reference number 01. 25 149 / KEPK/POLTEKKES KEMENKES MEDAN 2023.

Results

Based on the research results, the majority of

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Table 1 Characteristics of Respondents

Variable	Sample (n=96)	
	Frequency (n)	Percentage (%)
Age		
Toddlers	40	41.7
Children	33	34.4
Adolescents	21	21.9
Adults	2	2.1
Immunization Completeness		
Complete	28	29.2
Incomplete	68	70.8

the 96 respondents are toddlers. When their immunization completeness is observed, it is clear that many respondents still have incomplete immunizations. This characteristic can be seen in Table 1.

Based on the bivariate analysis using the chi-square test at a 5% significance level, the results show a significant relationship between age and measles occurrences (p-value<0.05). The toddler group has the highest proportion of individuals experiencing measles. Additionally, the statistical test yielded an Odds Ratio (OR) value of 0.215, with lower and upper limits below 1 (0.110–0.418). These findings indicate that age acts as a significant protective factor against measles occurrences. The results of this analysis can be seen in Table 2.

Based on the analysis of the immunization completeness variable using the chi-square test at a significance level of 5%, the results show a significant relationship between immunization completeness and measles occurrences (p-value<0.05). Moreover, we obtained an odds ratio (OR) of 11.000, indicating that respondents with an incomplete measles immunization history are 11 times more likely to experience measles compared to those with a complete measles immunization history. The results of this analysis can be seen in Table 3.

Discussion

Measles can affect not only infants or toddlers, but also adults. The results indicate that the majority of respondents in the case group fall into the toddler age category. This is consistent with Khotimah's study in Lebak, which found that toddlers aged 2 to 5 years are more susceptible to measles.[5] Additionally, the study by Ahadi *et al.* in Afghanistan indicated that the majority of individuals affected by measles were aged 2 to 5 years old.[6] Based on bivariate statistical analysis, it is known that age has

Table 2 Analysis Chi Square of the Relationship between Age and Measles Incidence

Age	Measles Incidence				p-value	OR (95% CI)
	(+) Measles		(-) Measles			
	n=48	%	n=48	%		
Toddlers	28	29.2	12	12.5		
Children	20	20.8	13	13.5	0.000	0.215 (0.110 – 0.418)
Adolescents	0	0	21	21.9		
Adults	0	0	2	2.1		

Table 3 Analysis Chi Square of the Relationship between Immunization Completeness with Measles Incidence

Immunization Completeness	Measles Incidence				p-value	OR (95% CI)
	(+) Measles		(-) Measles			
	n	%	n	%		
Incomplete	44	91.7	24	50	0.000	11.000 (3.416–5.425)
Complete	4	8.3	24	50		
Total	48	100	48	100		

a significant relationship with the incidence of measles (p<0.05). This is consistent with Andriani's study at the Wonoayu Health Center in Sidoarjo Regency, which indicated that there is a significant relationship between age and the number of measles cases.[7]

There is also a significant correlation between age and measles cases in the study conducted by Yanti & Sulistyaningsih in Bantul District.[8] Furthermore, the study conducted by Azis and Rahmadhani in South Tangerang City demonstrates a significant relationship between age and measles incidence.[9]

The measles virus is transmitted through droplets from the nose, mouth, and throat of infected individuals when they cough, sneeze, or talk. Maternal antibodies in a child's body decrease as they grow older, making them more vulnerable to the measles virus.[10] Indeed, during the first year of a child's life, they still possess antibodies passed on by the mother to combat measles virus infections. However, as the child reaches 6–12 months of age, the level of these maternal antibodies declines, thereby increasing the child's vulnerability to measles.[11]

Children often play and interact with their peers, increasing their chances of contracting the measles virus from infected individuals. This is supported by a study conducted by Mujiati *et al*., which showed that children are more likely to contract measles from schoolmates or contacts with measles patients residing in the same household.[12] Incomplete immunization is closely related to measles incidence. In this study, cases with incomplete immunization accounted for a higher percentage (91.7%) compared to cases with complete immunization (8.3%). The chi-square test analysis revealed a significant relationship between immunization completeness and measles occurrences (p<0.05). This finding is consistent with a previous study by Harisnal & Ediana in Bukittinggi City, which also found a significant relationship between immunization completeness and measles occurrences.[13] Similarly, the research conducted by Falawati *et al*. in Muna Regency also demonstrated a significant relationship between immunization status and measles

occurrences.[14] Immunization has two significant effects: it forms humoral immunity and cellular immunity.[15] Initially, a measles infection in the surroundings will induce IgG from immunization. Then, there is an increase in IgG, and IgG produced from vaccination will be induced again by the surrounding measles infection.[16] According to the information obtained from surveillance officers, the respondents' incomplete immunization in Medan City was due to the pandemic, as routine immunization activities were interrupted and healthcare personnel were redirected to handle the COVID-19 pandemic.

This aligns with the findings of Mukhibin *et al*.,[17] where healthcare workers reported that immunization officers at their workplace were redirected to COVID-19 services. Respondents also reported that immunization services in their residential areas were temporarily suspended during the PSBB (Large-Scale Social Restrictions) period. The limitations of this study include the lack of age matching, which may have caused bias in the research. The study also did not further analyze the respondents' antibody titers (immune status) and contact history. Therefore, these aspects should be investigated further in future research. Overall, this study provides insights into several risk factors for measles.

This study discovered a significant relationship between age and measles incidence in Medan City in 2022 (P value: 0.000; OR: 0.215; 95% CI 0.110–0.418). Furthermore, there is a significant association between immunization completeness and measles incidence in Medan City in 2022 (P value: 0.000; OR: 11.000; 95% CI 3.416–35.425).

Age and immunization completeness are both significantly related to the occurrence of measles in the city of Medan (p-value<0.05). Respondents with incomplete immunization history are 11 times more likely to experience measles compared to those with a complete immunization history. For future research, it is recommended to increase the number of study respondents and further investigate and expand on risk factors such as the history of contact with measles cases in Medan City.

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Detection of Leptospira sp. Bacteria and Factors Related to The Incidence of Leptospirosis in Semarang City

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Abstract

Objective: The Case Fatality Rate (CFR) of Leptospirosis in Semarang City has shown a tendency to increase from 2019 to 2022. In 2022, there were 30 cases reported, with 8 deaths (CFR 27%). The purpose of this study was to detect *Leptospira* sp. bacteria in rats and analyze the risk factors for leptospirosis in Semarang City.

Methods: This study employed an observational approach with a Case-Control Study design. The research was conducted in Semarang City from November to December 2023. Non-random sampling techniques were used, specifically the total sampling method, resulting in a sample size of 45 case groups and 45 control groups. Bivariate analysis was performed using the Chi-square test, with a significance level set at <0.05.

Results: Based on the Chi-Square test results, the following variables were found to be associated with the incidence of leptospirosis in Semarang City: the presence of rats (p<0.0001), the presence of *Leptospira* sp. bacteria (p<0.0001), house conditions (p=0.260), sewer condition (p<0.0001), presence of pets (p=0.001), condition of landfills (p=0.001), presence of vegetation (p=0.005), temperature (p=0.299), humidity (p=0.495), lighting (p=0.023), history of wounds (p=0.001), and knowledge level (p=0.025).

Conclusion: The risk factors for leptospirosis in Semarang City include the presence of rats, the presence of *Leptospira* sp. bacteria, sewer conditions, the presence of pets, conditions of landfills, the presence of vegetation, lighting, history of injury, and level of knowledge.

Keywords: Detection, leptospirosis, microscopy, rats, risk factors

Introduction

Currently, zoonoses remain a global threat to public health, with zoonoses accounting for 60.3% of all emerging infectious diseases (EIDs).[1] Leptospirosis, caused by the bacteria *Leptospira* sp., is a zoonotic disease transmitted by animals carrying infective *Leptospira* bacteria.[1] Animals such as rats, dogs, and farm animals like cattle and pigs can act as reservoirs for the disease. The bacteria reside in the kidneys of the host and are excreted in urine.[2] Transmission of leptospirosis can occur through direct contact with environments contaminated with the urine of animals carrying *Leptospira* sp. bacteria, or through indirect contact with environments at risk of contamination. The bacteria can enter the human body through wounds, skin abrasions, or ingestion, such as consuming water contaminated with the bacteria. *Leptospira* bacteria can survive in water and soil for weeks to months. Transmission primarily occurs from animals to humans, with human-to-human transmission being very rare.[3]

Leptospirosis is a significant health issue in

Indonesia, particularly in flood-prone areas.[4] According to the 2021 Indonesian Health Profile, leptospirosis cases in Indonesia have been increasing in the past five years, with 734 cases and a Case Fatality Rate (CFR) of 11.4% reported in 2021.[2] Central Java Province has been declared an endemic area for leptospirosis, with 113 cases and a CFR of 22.12% recorded in 2021.[1] Data from the Semarang City Health Office indicates that the CFR of leptospirosis has been on the rise from 2019 to 2022. In 2022, there were 30 cases reported, resulting in 8 deaths (CFR 27%).[5]

Based on previous research conducted in Demak in 2020 and in Banten in 2021, the risk factors for the incidence of leptospirosis include: presence of stagnant water, sewer conditions, use of personal protective equipment, behavioral habits of washing feet and washing hands with soap, presence of pets, history of injury, environmental conditions, conditions of landfills, and the presence of vegetation.[3,6,7] The purpose of this study was to detect *Leptospira* sp. bacteria in rats and analyze the risk factors for leptospirosis in Semarang City.

Methods

This study is an observational study conducted in Semarang City from November to December 2023, using a Case-Control Study approach. The study population consisted of all leptospirosis patients (cases) recorded in the Semarang City Health Office working area from January 2022 to July 2023, as well as non-leptospirosis patients (controls) who were the closest neighbors of the cases. The sampling technique used in this study was non-random sampling, specifically the total sampling method, taking into account the exclusion and inclusion criteria. The inclusion criteria included recovered leptospirosis patients or families of leptospirosis patients who had recovered or died, as well as neighbors of leptospirosis patients. Exclusion criteria consisted of individuals who were unwilling to participate as respondents or had moved from their recorded address. Therefore, the case sample for this study consisted of 45 people, as did the control sample.

Prior to conducting the study, the researchers explained the purpose and objectives to the respondents, who were then asked to sign an Informed Consent Form if they agreed to participate. The tools and materials used in the field included rat traps, sacks, bait, masks, and gloves for catching rats, as well as pens, questionnaire sheets, thermohydrometers, cameras for environmental observation, interviews, and documentation. Rat catching took place over two days and two nights, with traps being checked every morning. Any captured rats were immediately taken to the Integrated Laboratory of the Faculty of Public Health, Diponegoro University, where they underwent the process of identifying rats and examining *leptospira* sp. bacteria found in their feces, urine, and blood using microscopic methods. The tools and materials used in the laboratory included ketamine, syringes, cloth sacks, surgical scissors, tweezers, stationery, scales, rulers, calipers, masks, and Chinese ink for examining the *leptospira* bacteria under a microscope.

The steps taken are the preparation of the object glass and negative painting. a. Clean the object glass using a cotton swab that has been soaked in 70% alcohol. b. Give the code to the bacterial culture on the left side of the object glass. c. Use an ode to take a small number of bacterial colonies. d. Add 1–2 drops of Chinese ink, then add 1-2 drops of Chinese ink again. Add 1–2 drops of Chinese ink, then mix thoroughly. e. Swap the mixture using another object glass or deck glass with a 45° tilt, so that a thin smear is formed. f. Let the smear dry for 15 minutes. g. After it has dried, observe using a microscope. The microscopic magnification used is 100x.[7]

The variables that were examined in this study include: the presence of rats, the presence of *Leptospira* sp. bacteria, house conditions, sewer conditions, the presence of pets, wound history, condition of landfills, the presence of vegetation, temperature, humidity, lighting, and knowledge level.

The data analysis involved using univariate analysis to determine the frequency distribution of each variable. Bivariate analysis was then performed to assess the relationship between the independent and dependent variables. The Chi-square test was used to calculate the p-value at a confidence level of <0.05 and a 95% Confidence Interval. Microsoft Excel software and SPSS v.24 were used for data analysis.

This study has been approved by the Health Research Ethics Commission under the reference number: 589/EA/KEPK-FKM/2023.

Results

The results of rat trapping in 90 houses over the course of 2 consecutive days are as follows: a total of 180 traps were set, and 43 houses

tested positive for rats. A total of 54 rats were caught, resulting in a relative density of 15%. Microscopic examination of these 54 rats revealed that 88% of them tested positive for *leptospira* bacteria.

Table 1 shows a comparison of different variables between the case and control groups. Out of the 45 case houses, 32 of which (71.1%) tested positive for caught rats, while 31 rats (68.9%) were positive for *Leptospira* sp. bacteria. Additionally, 22 houses (48.9%) had poor conditions, 36 house gutters (80%) were in poor condition, 33 houses (73.3%) had pets, 38 houses (84.4%) had inadequate garbage disposal conditions, 30 houses (66.7%) had vegetation, 26 houses (57.8%) had lighting levels below 60 lux, 31 cases (68.9%) had a history of injury, and 24 people (53.3%) had a lack of knowledge. In comparison, the 45 control houses had 12 houses (26.7%) that tested positive for caught rats, with 8 rats (17.8%) testing positive for *Leptospira* sp. bacteria. Furthermore, 19 houses (42.2%) had poor conditions, 16 house sewers (35.6%) were in poor condition, 18 houses (40%) had pets, 25 houses (55.6%) had inadequate landfill conditions, 23 houses (51.1%) had vegetation, 18 houses (40%) had lighting levels below 60 lux, 17 people (37.8%) had a history of injury, and 18 people (40%) had a lack of knowledge.

Based on the results of data analysis in Table 1 using the Chi-Square test (p-Value <0.05), it can be concluded that several independent

Table 1 Frequency Distribution and Chi-Square Test Data Analysis of Risk Factors for Leptospirosis in Semarang City

Variable		Incidence of Leptospirosis		p Value
		Case	Control	
		(n=45) (%)	(n=45)(%)	
Presence of rats	Yes	32 (71.1)	12 (26.7)	<0.0001
	No	13 (28.9)	33 (73.3)	
Presence of *Leptospira* sp.	Positive	31 (68.9)	8 (17.8)	<0.0001
	Negative	14 (31.1)	37 (82.2)	
House conditions	Bad	22 (48.9)	19 (42.2)	0.260
	Good	23 (51.1)	26 (57.8)	
Sewer condition	Bad	36 (80.0)	16 (35.6)	<0.0001
	Good	9 (20.0)	29 (34.4)	
Presence of pets	Yes	33 (73.3)	18 (40.0)	0.001
	No	12 (26.7)	27 (60.0)	
Condition of landfills	Bad	38 (84.4)	25 (55.6)	0.001
	Good	7 (15.6)	20 (44.4)	
Presence of vegetation	No	15 (33.3)	22 (48.9)	0.005
	Yes	30 (66.7)	23 (51.1)	
Temperature	Optimum	13 (28.9)	14 (31.1)	0.299
	Not optimum	32 (71.1)	31 (68.9)	
Humidity	>60%	15 (33.3)	16 (35.6)	0.495
	<60%	30 (66.7)	29 (64.4)	
Light	<60 lux	26 (57.8)	18 (40.0)	0.023
	>60 lux	19 (42.2)	27 (60.0)	
Injury history	Yes	31 (68.9)	17 (37.8)	0.001
	No	14 (31.1)	28 (62.2)	
Knowledge	Bad	24 (53.3)	18 (40.0)	0.025
	Good	21 (46.7)	27 (60.0)	

variables have a relationship with the incidence of leptospirosis in Semarang City. These variables include the presence of rats, the presence of *Leptospira* sp. bacteria, sewer conditions, the presence of pets, the condition of landfills, the presence of vegetation, lighting, history of injury, and level of knowledge.

Discussion

In this study, rats are identified as one of the animals that serve as reservoirs for the transmission of leptospirosis. The success of rat capture can be influenced by several factors: the quality of the trap, the accuracy of bait selection, and the placement of the trap. The quality of the trap plays a significant role in catching rats, as it acts as a barrier when rats enter the trap. If the trap is of poor quality, rats that have been caught may escape and damage the trap.[8] During the research in Semarang City, it was observed that many traps were closed, the bait was missing, but the rats were not caught and the traps were damaged. This could be due to the shape of the trap not matching the size of the rat, allowing rats that have entered to break out and potentially causing damage to the trap.

In addition to trap selection, the accuracy of bait selection also greatly influences the success of rat capture. The bait used in this study was a mixture of milkfish, tofu, meatballs, and roasted coconut. It was found that grilled coconut and milkfish mixed with tofu were the most preferred baits for rats in Semarang City. The placement of traps also plays a role in the success of catching rats. Traps are strategically placed in areas that are expected to be rat paths and frequently visited. Rats exhibit thigmotaxis, meaning they follow the same trajectory every time they search for food, return to the nest, and engage in other rat activities.[9]

There are three types of rodents that have been successfully found in the Semarang City area: Rattus norvegicus, Rattus tanezumi, and Mus munculus. The results showed that Rattus norvegicus was the most common rat found in Semarang City, with 27 rats. Meanwhile, there were 24 Rattus tanezumi and 3 Mus munculus. The presence of Rattus norvegicus in Semarang City may be due to the poor condition of the home environment, gutters, and garbage disposal. Rattus norvegicus is commonly found in waterways or sewers in urban settlements, which is why it is also known as the sewer rat. Rattus norvegicus is known as a reservoir of leptospirosis, a disease that can be transmitted to humans. These rats carry harmful serovars such as ballum and autumnal.[10] These results are consistent with the research conducted by Alfira *et al*, where Rattus norvegicus was found to be the most commonly caught rat in Tandang Village, Semarang City.[8]

Other species found in Semarang City in this study were Rattus tanezumi and Mus musculus. The native habitat of Rattus tanezumi and Mus musculus is inside the house, as these rats are domestic rats that forage, shelter, nest, and breed inside houses. Rats will migrate if they lack food.[10]

Leptospira sp. bacteria thrive in hot and humid soil, such as in tropical conditions. These bacteria can survive up to 43 days in suitable soil. *Leptospira* bacteria are very small and can only be seen under a microscope. Dark field microscopy is used to examine *Leptospira* sp. bacteria. The samples taken for examination include rat kidneys, rat blood, rat urine, and feces.

Unqualified house components and arrangements can increase the incidence of leptospirosis. Houses that are not rat-proof can increase the risk of rats entering the house. House components that do not meet health requirements can become a nesting place for various vectors and reservoirs that can cause diseases such as rats.[11] A rat-proof house or building is one whose foundation is made of strong materials such as concrete, the floor is made of concrete and is at least 10 cm thick, the walls are made of bricks or concrete, there are no cracks or gaps that rats can pass through, the gap between the door and the floor is ≤6mm, and any ventilation larger than 6mm is closed with a strong wire mesh. This study is consistent with research conducted in Banyumas in 2019, which showed no significant relationship between the condition of the home environment and the incidence of leptospirosis, with a p-value of 0.195.[12]

The sewer is the place that is most often used as a living space or a route in and out of the house for rats. Based on the research of Sukismanto *et al.*[13] in Sleman Yogyakarta in 2018, the success of catching rats in the house is higher in open sewage conditions than in houses with closed sewage channels. This is supported by Rahmawati's research in Boyolali in 2014, which found that 87% of respondents' houses with poor sewers had more rats caught.[14] The most important environmental factor for rat infestation was indicated by the presence of access from the sewage system. The peridomestic habits of rats cause them to be more strongly associated

with unused buildings and access sources, especially sewage systems.[14]

The pets found around the houses studied were cats and dogs. Based on the results of research by Sutikno *et al.*,[15] the animals that are most commonly kept at home are cats, accounting for 48.38% of households. This situation is thought to contribute to a relatively small presence of rat pests in residential houses in Pekanbaru City, around 23.64%.Based on the results of spatial analysis in Fajriyah *et al* research in Semarang in 2017, it is known that the presence of pets that have the potential to become reservoirs of *Leptospira* sp. is a risk factor of 13.6%.[16]

The condition of open rubbish dumps is a potential place favored by rats due to the presence of piles of garbage, such as food waste, fish, bread, etc. According to Lestari's research, the mapping results from the condition of open trash cans showed that there were more rats inside and outside the house.[17] The presence of garbage around the house can increase the rat population. Rats can also be attracted by improper waste management within the house. Nugroho's research showed that the presence of waste, especially food waste left in open bins, is associated with the spread of leptospirosis.[18]

The results of observations when catching rats in residential areas reveal that there are numerous shrubs, trees, and plants both inside and outside people's homes. Rats can easily enter houses that have branches or twigs creeping into them, and the presence of trees can also provide shelter for rats.[19] This finding is supported by Nordmeier's research on the Otago Peninsula in 2020, which indicates a significant relationship between the probability of rat presence and the amount of vegetation (p=0.009).[20]

Temperature is measured using a thermometer at the location where the trap is placed. Temperature is one of the abiotic factors affecting the existence of mice. Rats are mammals with a limited temperature range, with higher temperatures being more deadly for them compared to lower temperatures. The average temperature in respondents' homes is 27ºC – 31ºC, which is considered an environmental factor that can influence the high rat population. According to research by Supranelfy *et al*, rats that were caught and identified as *Leptospira* sp. were found at an optimal temperature range of 24.0°C–26.9°C.[21]

Humidity is measured using a multimeter around the mousetrap placement. High air humidity (>60%) is considered ideal for mouse activity. Poor lay out of buildings can exacerbate the humidity levels inside the house, turning it into a place for mice to live, hide, or pass through.[15] This aligns with the findings of Kusumajaya *et al.* research in the settlements of Ajibarang District, which showed a relatively high mouse density with an average air humidity in residential areas of 71%, surpassing the optimal humidity limit for mice.[22]

Lighting measurements were carried out at the location where the mouse trap was placed. Insufficient lighting increases the likelihood of presence of mice. Rats are primarily active at night and tend to search for food just before or at sunset. Yulianto *et al.*[23] research in Sukajadi Village, Pekanbaru, supports this, stating that there is a correlation between lighting and rat vectors in houses. Good lighting refers to artificial or natural illumination that thoroughly lights up a room with a minimum intensity of 60 lux.

Leptospira bacteria can enter the human body through wounds on the skin,[24] as well as through mucous membranes (nose, mouth, eyes) and from stagnant water. The transmission of leptospirosis is significantly influenced by a history of wounds, as *Leptospira* bacteria can enter the body through wounds. If a person with a wound comes into direct contact with an environment contaminated with *Leptospira* bacteria, they can contract leptospirosis. The most common type of wound is on the feet and hands, typically related to the person's work. Even the smallest wound or skin abrasion can become the gate for *Leptospira* bacteria to enter the human body.[25]

A person's health is greatly impacted by their knowledge. With sufficient knowledge, individuals will strive to live a clean and healthy lifestyle and undergo regular health checks. In Indonesia, despite leptospirosis causing significant health problems, it receives little attention. This lack of information contributes to the respondents' limited knowledge about leptospirosis.[8] There is still a lack of public awareness regarding the factors that contribute to the presence of rats, the transmission of leptospirosis from animals to humans, and how to prevent and control the disease. One limitation of this research is the suboptimal quality of mouse traps used in the field when catching mice.

In conclusion, this research identifies several variables related to the incidence of leptospirosis in Semarang City, including the presence of rats, the presence of *Leptospira*

sp. bacteria, the condition of sewers, the presence of pets, the condition of rubbish dumps, the presence of vegetation, lighting, history of injuries, and level of knowledge. It is recommended that health officers in the City of Semarang play an active role in increasing public knowledge about leptospirosis. Furthermore, the public should be encouraged to maintain a clean home environment and broaden their knowledge about preventing and controlling leptospirosis.

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Original Article

Subclinical Left Ventricular Dysfunction Prevention in Breast Cancer Patients after FAC Chemotherapy: A Carvedilol Trial

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Abstract

Objective: To assess the cardioprotective effects of Carvedilol in preventing subclinical left ventricular dysfunction (SLVD) in breast cancer patients after completing FAC chemotherapy.

Methods: This prospective study employed a quasi-experimental clinical trial conducted from September 2018 to May 2019. Breast cancer patients receiving FAC chemotherapy were divided into two groups: intervention (IG) and control (CG). The IG received Carvedilol 6.25 mg b.i.d., which was increased every three weeks until reaching a tolerated dose. The study evaluated changes in left ventricular global longitudinal strain (GLS) and the incidence of SLVD (GLS reduction ≥15% and GLS >-18%) 24 weeks after initiating the FAC regimen.

Result: Of the 81 women enrolled in the study, 31 were in the IG. No significant changes in GLS were observed during or after completing FAC chemotherapy in the IG, whereas the CG showed contradictory results. At the end of the follow-up period, the delta GLS reduction was lower in the IG (0.7; 95% CI -0.60, 3.60) compared to the CG (3.00; 95% CI -2.16, 4.19), with a p-value of 0.035. Similarly, the percentage reduction in GLS was 3.6% in the IG and 14.29% in the CG, resulting in a p-value of 0.05. The incidence rate of SLVD (GLS reduction ≥15% and GLS >-18%) was lower in the IG (41.9% and 25.8%) than in the CG (58% and 48%).

Conclusion: Carvedilol may have a cardioprotective effect in preventing the incidence of SLVD, as evaluated by GLS reduction and changes, in women with breast cancer after completing a full cycle of the FAC regimen.

Keywords: Breast cancer, carvedilol, chemotherapy, fluorouracil–adriamycin–cyclophosphamide, global longitudinal strain

Introduction

Breast cancer is the most prevalent form of cancer in women in Indonesia and worldwide.[1-3] According to GLOBOCAN statistics in 2018, breast cancer ranks as the fifth leading cause of death globally. It is estimated that approximately 2 million women have been diagnosed with breast cancer, resulting in 626,679 deaths.[4] In West Java alone, with a population of nearly 48 million residents, around 49.3% are women, and approximately 0.5% of these women have been diagnosed with breast cancer.[3] The systemic therapy for breast cancer includes chemotherapy and endocrine therapy. Anthracyclines-containing regimens, such as doxorubicin and epirubicin, are commonly used as adjuvant and neoadjuvant chemotherapy for breast cancer patients.[5-6] It is important to note that type 1 (irreversible) cardiotoxicity is primarily associated with anthracycline-containing chemotherapy regimens, particularly those with a dose-related effect, such as FAC.[5-7]

Cardiotoxicity due to anthracyclines can occur at a cumulative dose as low as 250 mg/m^2, and a decrease in left ventricular function can be observed at doses of 60-98 mg/m^2.[8-9]

The examination of myocardial deformation using echocardiography is an imaging technique that assesses subclinical dysfunction of the left ventricle, preferably evaluated using the Speckle Tracking Echocardiography (STE) technique. Global Longitudinal Strain (GLS) is a standard examination for SLVD, with predictive value for mortality and morbidity.[10,11] Carvedilol is chosen as a cardioprotective agent due to its antioxidant properties, which are the primary mechanism of cardiotoxicity caused by anthracyclines.[12] Despite supporting studies, Carvedilol has not been routinely used as a protective agent for anthracycline-induced cardiotoxicity in breast cancer patients. This study aims to evaluate the cardioprotective effect of Carvedilol in preventing the occurrence of SLVD in women with breast cancer undergoing FAC regimen chemotherapy.

Methods

This prospective study was a Quasi-Experimental clinical trial conducted at Dr. Hospital Hasan Sadikin Bandung from September 2018 to May 2019. The study included breast cancer patients who were scheduled to undergo six cycles of the FAC chemotherapy regimen, which was administered by oncologists. Prior to participation, all patients provided signed informed consent. The ethical committee board of Hasan Sadikin General Hospital granted approval for the cardio-oncology registry and this study, which were registered as no. LB.02.01/X.6.5/346/2018 and LB.04.01/A05/EC/222/VII/2018 respectively. Furthermore, data confidentiality was ensured throughout the research process.

The inclusion and exclusion criteria before and after a complete cycle of chemotherapy were as stated in a previous study conducted by Martha *et al*.[12] The control group consisted of patients selected from the cardio-oncology registry at Hasan Sadikin General Hospital. After obtaining the control group data, patients who met the inclusion criteria were consecutively enrolled in the study as the intervention group. Both groups received six cycles of an intravenous FAC regimen over a period of 18 weeks. This regimen included 5-fluorouracil at a dose of 600 mg/m2, Adriamycin at a dose of 60 mg/m2, and cyclophosphamide at a dose of 600 mg/m2. One week before the administration of the FAC regimen, the intervention group was given Carvedilol at an initial dose of 6.25 mg b.i.d. The dose was gradually increased every three weeks until reaching the target dose of 25 mg b.i.d., or until the patient reached a tolerated dose. The criteria for achieving the tolerated dose were as follows: systolic blood pressure above 90 mmHg, pulse rate around 60 bpm, and serum creatinine level below 2.5 mg/dl. In case of symptomatic hypotension or bradycardia, the dose was reduced to the previous dose or the tolerated dose.

The clinical symptoms and 2D trans-thoracic echocardiography (TTE), including GLS, were compared at various time points (baseline, 3, 12, and 24 weeks after the first cycle) during chemotherapy in both groups. The incidence of SLVD was evaluated using GLS, with a criteria of delta GLS reduction ≥15% and GLS >-18%. The changes in GLS were also assessed and compared between the intervention and control groups at the end of chemotherapy. GLS measurements were obtained using TTE with the speckle tracking echocardiography (STE) method (%), and were analyzed by highly trained cardiologists using the General Electric (GE) Vivid 7, S-6, and T-8 echocardiography machine. The frame rate for image acquisition was set at 50–80 frames per second.

Standard echocardiographic parameters and 2D grayscale images were acquired over five cardiac cycles and evaluated at the end of the systolic phase, just before the aortic valve closed. Data evaluation was conducted offline using ECHOPAC software version 113. The statistical analysis of the study involved descriptive statistics and normality tests for the variables, employing either the Shapiro-Wilks or Wilcoxon test. Normally distributed data will be presented as means and standard deviations, while non-normally distributed data will be presented as medians and interquartile ranges. Unpaired T-tests, Chi-Square tests, or exact Fisher analysis were used to compare the intervention and control groups. Changes in GLS over time during chemotherapy were analyzed using Friedman's analysis. Alternatively, the unpaired t-test or Mann-Whitney test was employed to compare delta GLS, GLS reduction percentage, and the frequency of SLVD after a complete cycle of FAC chemotherapy between the control and intervention groups. A p-value ≤0.05 indicates a statistically significant difference between the two groups. Power analysis was

performed using G*Power version 3.1.9.6, and the calculations yielded approximately 90.7% (>80%). This level of statistical test ability allows for the detection of actual differences, with the Mann-Whitney U test exhibiting good strength in detecting differences between two groups with a d-effect size of 0.7. A significance level of 0.05 was employed.

The power analysis results indicate a strong likelihood of rejecting the null hypothesis in the presence of significant differences. The primary outcomes consisted of the incidence rate of new left ventricular systolic dysfunction, defined as a 15% reduction in LV GLS and LV GLS >-18%, as well as changes in LV GLS during chemotherapy. The secondary outcomes included changes in LVEF during chemotherapy and the incidence of cardiotoxicity at 24 weeks.

Results

Eighty-one patients were included in the study and were divided into intervention and control groups consisting of 31 and 50 patients, respectively. Figure 1 shows the patient enrollment process. Baseline age and GLS values in the two groups were found to be not significantly different, as shown in Table 1. The mean age of the study subjects in the intervention group was 49.35±9.891 years, while in the control group it was 47.20±7.907 years (p=0.283). Prior to chemotherapy, the median GLS in the intervention group was 19.4%, whereas in the control group it was 20.40% (p=0.600).

The number of subjects with cardiovascular risk factors in the two groups was similar. The prevalence of obesity was 25.8% in the intervention group, whereas it was 34.0% in the control group (p=0.641). The hypertension rate in the intervention group was 45.2%, compared to 28.0% in the control group (p=0.114). Only 3.2% of patients in the intervention group had diabetes mellitus, whereas the prevalence was 12.0% in the
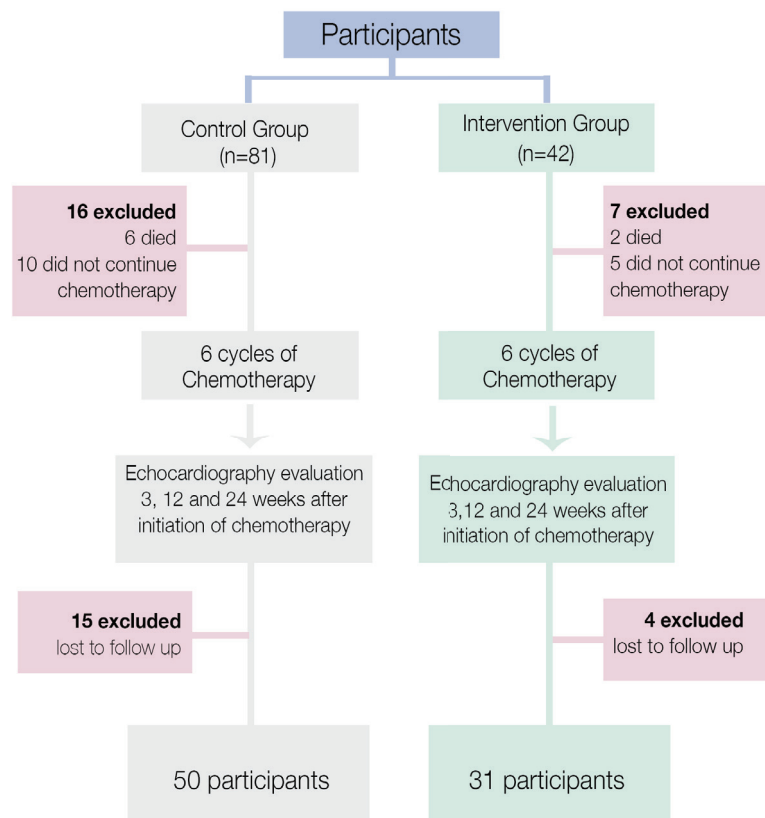

Fig. 1 Patient's Enrolment. The CG were Patients from Cardio-oncology Registry at Dr. Hasan Sadikin General Hospital. Following the CG enrollment, Consecutive Patients were Assigned as IG

Subclinical Left Ventricular Dysfunction Prevention in Breast Cancer Patients after FAC Chemotherapy: A Carvedilol Trial

Table 1 Study Characteristics

Baseline Characteristics	Participant n=81	Group Intervention n=31	Group Control n=50	P-value
[a]Age (Year), mean ± SD	48.02±8.7	49.35±9.9	47.20±7.9	0.283[a]
[a]Body Mass Index, n (%)				
18.5–22.9 kg/m²	19 (23.4%)	8 (25.8%)	11 (22,0%)	0.435[a]
23.0–24.9 kg/m²	21 (25.9%)	7 (22.6%)	14(28.0%)	
25.0–29.9 kg/m²	25 (30.9%)	8 (25.8%)	17(34%)	
>29.9 kg/m²	16 (19.8%)	8 (25.8%)	8(16%)	
Risk Factors, n (%)				
Obesity	41 (50.7%)	16 (51,6%)	25 (50%)	0.888[b]
Hypertension	28(34.6%)	14 (45,2%)	14 (28,0%)	0.114[b]
Hypertensive Heart Disease	0(0.0%)	0(0.0%)	0(0.0%)	1.000[b]
Smoking	0(0.0%)	0 (0,0%)	0 (0,0%)	1.000[b]
Diabetes Mellitus	7 (8.6%)	1 (3,2%)	6 (12,0%)	0.242[c]
Dyslipidemia	6(7.4%)	3(9.7%)	3(6.0%)	0.670[c]
Family CHD History	4(4.9%)	2 (6.5%)	2 (4.0%)	0.635[c]
GLS (%)				
Median	-20.0	-19.4	-20.4	0.600[d]
Range (min-max)	-28.50–(-10.30)	-24,80–(-16.20)	-28,50–(-10.30)	
LVEF (%)				
Median	69.0	69.0	69.5	0.925[d]
Range (min-max)	48.0–81.0	55.0–80.0	48.0–81.0	

Analyzed by [a]T-test, [b]Chi-Square, [c]exact Fisher, [d] Mann Whitney

Table 2 Time-to-time GLS and LVEF Score Changes During Chemotherapy in the Intervention And Control Group

Variable	GLS Score (%) Pre	3 weeks	12 weeks	24 weeks	P-value	LVEF (%) Pre	3 weeks	12 weeks	24 weeks	p-value
Intervention group (n=31)					0.161[a]					0.018*
Median	-19.4	-19.0	-18.8	-19.2		69.0	68.0	66.0	64.0	
Range (min-max)	-24.8-(-16.2)	-24.9-(-15.4)	-22.5-(-14.9)	-24.9-(-4.2)		55.0-80.0	53.0-83.0	58.0-75.0	28.0-78.0	
Control group (n=50)					0.0001[a]*					0.0001*
Median	-20.40	-19.63	-18.80	-17.40		69.5	67.5	65.5	62.5	
Range (min-max)	-28.5-(-10.3)	-26.9-(-11.2)	-23.0-(-9.6)	-24.10-(-5.3)		48.0-81.0	49.0-79.0	50.0-82.0	25.0-76.0	

[a]Analyzed using Friedman test. * Statistically significant (p<0.05)

2A

SLVD INCIDENCE RATE
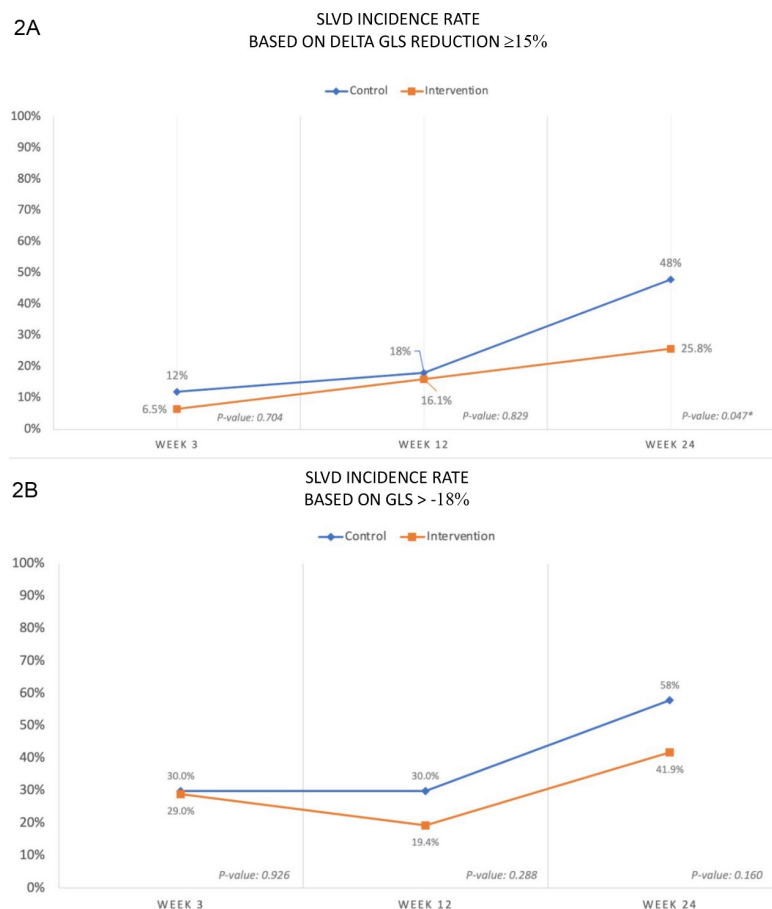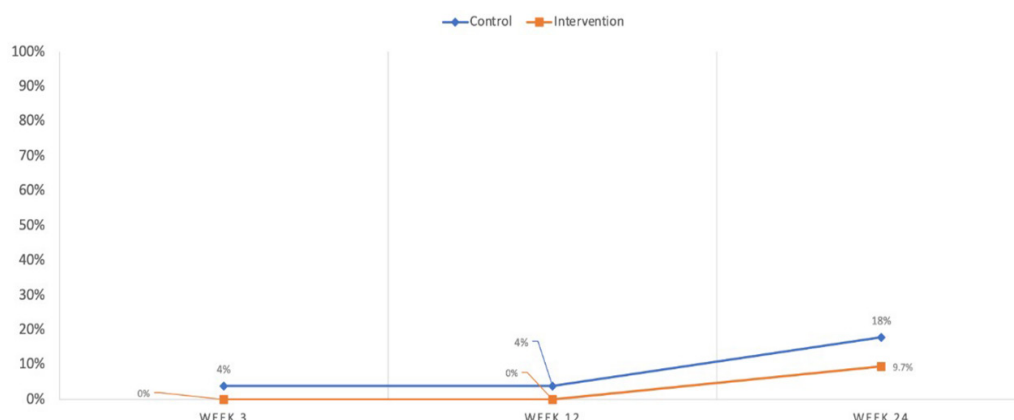BASED ON DELTA GLS REDUCTION ≥15%

2B

SLVD INCIDENCE RATE
BASED ON GLS > -18%

Fig. 2 Significant Different of Subclinical LV Dysfunction Incidence Rate; (2A) Based on GLS reduction of ≥15%, there were significantly a smaller number of SLVD in IG and based on GLS >-18% (2B) more patients with SLVD were detected in CG compared to IG

control group (p=0.242). The percentage of patients with a family history of CAD was 6.5% in the intervention group and 4.0% in the control group (p=0.635). Neither group had any subjects with smoking as a risk factor.

Both groups were ethnically Indonesian, with the majority being Sundanese, followed by some Javanese and Melayu patients.

A comparison of changes in GLS scores during chemotherapy is presented in Table

Table 3 GLS Changes Before and After Chemotherapy in Intervention and Control Groups

Variable	Group		P-Value
	Intervention	Control	
Delta GLS score (%) Median Range (min-max)	0.70 -3.60-17.20	3.00 -4.30-12.60	0.035[a]
GLS reduction percentage (%) Median Range (min-max)	3.6 (2.9-17.5)	14.29 (10.7-20.8)	0.05[a]

Note: [a]Analysis using Mann Whitney

Fig. 3 Incidence of Cardiotoxicity. The IG Had Lower Incidence of Cardiotoxicity at Week 24 Compared to CG

2. There was no significant reduction in GLS observed during chemotherapy in the intervention group (IG). However, in the control group (CG), there was a significant decrease in GLS during chemotherapy. The values gradually declined from a median of -20.4% (-28.5-(-10.3) %) at baseline to -19.6%, -18.8%, and -17.4% (-24.1-(-5.3) %) at 3, 12, and the completion of chemotherapy, respectively. Both the IG and CG experienced a reduction in LVEF during chemotherapy, but the values remained within normal limits, and there was no significant difference between the two groups (Table 2). At the end of chemotherapy (Table 3), the median delta GLS showed a less significant reduction in the IG at 0.70% (95% CI–0.60, 3.60) compared to the CG at 3.00% (95% CI–2.16, 4.19) (p=0.035). Additionally, the percentage of GLS score reduction was lower in the IG (3.62%) compared to the CG (14.29%) (p=0.05), as shown in Table 3.

The incidence of patients with a reduction in GLS of ≥15% was significantly lower in the intervention group (IG) than in the control group (CG) (Figure 2a). At three and twelve weeks after initial chemotherapy, there was no significant difference in the percentage of patients with a delta GLS of ≥15% between the intervention and control groups. However, a significant difference was observed between baseline and 24 weeks' GLS; 25.8% of the IG and 48% of the CG experienced a reduction in GLS of ≥15%. Additionally, a smaller number of patients in the IG developed subclinical LV dysfunction 24 weeks after chemotherapy initiation. Figure 2b showed a significant

increase in patients with subclinical LV dysfunction evaluated by GLS >-18%. A total of 41.9% of patients in the IG and more than half in the control group (58%) experienced SLVD at the end of chemotherapy. During chemotherapy, only 5 (12%) patients achieved the maximum dose of Carvedilol, 26 (62%) were on 12.5 mg bid, and 11 (26%) were on 6.25 mg bid.

Most did not achieve the maximum dose because their heart rate was around 60 bpm. At the end of chemotherapy, cardiotoxicity occurred in 3 patients of the IG (9.7%) and 9 patients of the CG (18.0%). There were no severe adverse effects, and no patient was excluded due to adverse effects. Several patients experienced cardiotoxicity at weeks 3, 12, and 24, as seen in Figure 3. The incidence of cardiotoxicity increased over time to a rate of 9.7% at 24 weeks.

Discussion

This study revealed that patients in the intervention group had a significantly lower incidence of subclinical left ventricular dysfunction. This was demonstrated by a reduced occurrence of GLS reduction ≥15%, a notable increase in the percentage of patients with GLS >-18%, and less delta GLS changes at 24 weeks after chemotherapy. These results indicate the potential efficacy of carvedilol 6.25 mg twice daily in preventing subclinical left ventricular dysfunction in breast cancer patients undergoing anthracycline chemotherapy. The control group had a higher rate of subclinical LV dysfunction and

cardiotoxicity compared to the intervention group. Additionally, the number of patients with delta GLS ≥15% and GLS > -18% increased during chemotherapy and reached a significant level 24 weeks after initiating the first cycle of chemotherapy in the control group. Previous studies have suggested cut-offs ranging from >10-15% for delta GLS score reduction to predict the occurrence of cardiotoxicity.[7-10]

This result is in line with the expert consensus and position paper, which suggests that a GLS ≥15% could be a predictive value for cardiotoxicity.[13]. These findings are consistent with previous studies indicating that Carvedilol can prevent a decline in left ventricular systolic function in breast cancer patients undergoing chemotherapy with anthracycline-containing regimens [11,14]. The FAC regimen is currently one of the first-line options for managing breast cancer and carries a five-fold higher risk of cardiotoxicity compared to other regimens.[5,6] Carvedilol is a non-selective, third-generation beta-blocker that inhibits both beta one and two receptors. It also exhibits alpha-one insulating properties, resulting in peripheral vasodilation.[15,16] Moreover, Carvedilol has antioxidant effects, including inhibition of electron transport enzymes such as 5,5-dimethylprolin-1-oxidase and 2-methyl-nitrosopropane, as well as lipid peroxidase and neutrophil O_2 release inhibitors. These effects help preserve the body's natural antioxidants, such as glutathione and vitamin E, and other antioxidant protective systems.[15] Consequently, Carvedilol is the preferred agent for releasing neutrophil O_2, preserving the body's natural antioxidants (glutathione or vitamin E) and other antioxidant protective systems.[15]

It may have potential cardioprotective effects due to increased free radicals resulting from anthracycline, which is considered the primary mechanism of anthracycline-induced cardiotoxicity.[11] Most of the patients in this study were administered Carvedilol 12.5 mg b.i.d, which already demonstrated a significant reduction in GLS and LVEF compared to the control group. This suggests that the achieved tolerated dose may have a cardioprotective effect by preventing SLVD in the intervention group. Previous trials of carvedilol in heart failure patients typically reached 75% of the maximum dose with varying levels of tolerability. A study by Farahani MM *et al*. revealed that the maximum tolerated dose of carvedilol in the intervention group was 12.5

mg twice a day in non-metastatic HER2 breast cancer patients undergoing trastuzumab treatment. This dose was effective in preventing GLS decline and may also reduce systolic and diastolic function impairment based on echocardiographic findings. The study showed significant changes in the GLS variable in the control group (p<0.0001) but not in the carvedilol group (p=0.080).[17] GLS evaluation is advantageous over LVEF assessment as it detects changes at an earlier stage. Therefore, GLS evaluation could be beneficial for preventing chemotherapy-induced cardiotoxicity.[9]

This study found that the intervention group's GLS did not decrease during chemotherapy over time, whereas the control group did experience a decrease. The mean delta GLS reduction was significantly greater in the control group (3%) compared to the intervention group (0.7%), p=0.035. In this study, the mean cumulative dose of anthracycline was 565.85±65 mg/m². A previous study conducted by Elitok *et al*.[18] in 2014 demonstrated that administering Carvedilol to breast cancer patients could prevent the reduction of strain imaging evaluated by Tissue Doppler Imaging (TDI) in the intervention group, particularly with small cumulative doses (≤240 mg/m²). In 2016, Beheshti *et al*.[19] conducted a similar study comparing changes in systolic function in 70 breast cancer patients undergoing chemotherapy with an anthracycline.The baseline LVEF did not differ from LVEF after chemotherapy in both the Carvedilol and control groups. The TDI examination in the control group (placebo) revealed a decrease in strain and strain rate in the septal, lateral basal, inferior basal, and anterior basal segments (all p-value <0.001) compared to baseline. No strain changes were observed in the Carvedilol group.

In this study, GLS was calculated using the 2-D STE technique, which detects subclinical myocardial damage and is unaffected by the patient's position. A study by Avila *et al*.[20] and Beheshti *et al*. showed no significant changes in LVEF between the carvedilol group and the control group following chemotherapy with an anthracycline-containing regimen.[19] However, the use of carvedilol resulted in a significant reduction in troponin levels and diastolic dysfunction.[20] This study showed a 5% decrease in LVEF in the intervention group and a 7% decrease in the control group. Both groups experienced a decrease in LVEF, although it remained within the normal

limit, and there was no substantial difference in chemotherapy completion compared to baseline. In this study, the adriamycin cumulative dose exposure was 556.65±89 in the intervention group and 573±51 in the control group (p>0.4). Previous studies have shown that the benefits of carvedilol in preventing cardiotoxicity are more significant in studies with higher cumulative doses or more accompanying risk factors. [11, 14]

In the study by Jhorawat *et al.*,[21] the prophylactic use of carvedilol protected the systolic functions of the left ventricle in patients receiving anthracycline. Similarly, in a study by Huang *et al.*,[22] the prophylactic use of carvedilol had no impact on the early asymptomatic decrease in LVEF but appeared to reduce the frequency of clinically overt cardiotoxicity and prevent ventricular remodeling.

In this study, nearly half of the population had hypertension, with 45% in the intervention group and 28% in the control group. The percentage of breast cancer patients with diabetes mellitus risk factors was 3.2% in the intervention group and 12% in the control group. Subjects with a family history of coronary heart disease accounted for 4% in the intervention group and 6.5% in the control group. Carvedilol was administered as a cardioprotective agent in this study, regardless of cardiovascular disease risk. There were no significant differences in CVD risk factors between the intervention group and the control group.

After the administration of carvedilol, there was a lower incidence of SLVD with a similar CVD risk profile between the groups. This suggests that a cardio-protective agent may be necessary for every patient who undergoes chemotherapy with an anthracycline regimen, regardless of their risk score. This result differs from the recently published SUCCOUR trial that was just published.[23] The trial revealed that there was no difference between GLS-guided and LVEF-guided evaluation at 1 and 3 years after cardioprotective administration in breast cancer patients given an anthracycline regimen. However, the GLS cut-off used in the study (<12% reduction) for cardio-protection was lower than the SLVD cut-off used in most societies, including this study. Additionally, the cardiac function may have recovered to baseline after more than a year of follow-up in the SUCCOUR trial, compared to the 24 weeks in this study.

This study had several limitations, including a small sample size, the absence of randomization, and being conducted at a single center. Furthermore, several patients were excluded due to discontinuation of chemotherapy or being lost to follow-up. Additionally, the patient demographic data was not explained in detail, which could have provided more specificity to the research findings, particularly regarding the variability in the study's outcome. The intervention group did not receive a uniform dose of carvedilol due to individual variability in medication tolerance, and data on the number of doses administered were not available. Although a protective effect of carvedilol administration against subclinical LV dysfunction during chemotherapy was observed, the long-term impact remains unpredictable due to the follow-up period. Advanced research could be conducted to assess the effect of the dosage given to individuals.

In conclusion, this study demonstrates that carvedilol administration during chemotherapy may have a cardioprotective effect in preventing the incidence of subclinical LV dysfunction and GLS changes. The intervention group exhibited a significantly lower reduction in delta GLS and fewer new cardiotoxicity events compared to the control group, 24 weeks after initiating FAC regimens. Thus, carvedilol administration with GLS evaluation during chemotherapy may be necessary in preventing subclinical LV dysfunction.

Acknowledgment

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Case Series of Imaging Features of Trilateral and Quadrilateral Retinoblastoma: What Radiologists Need to Know

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Abstract

Objective: To identify the differences between trilateral and quadrilateral retinoblastoma based on radiologic imaging.

Case: This researcher found three cases of retinoblastoma at Sanglah General Hospital. The retinoblastoma patients we found were boys under the age of 5. The first patient presented with swelling, pain, and impaired vision in the right eye. The second and third patients presented with eye protrusion and leukocoria. Computed tomography (CT) imaging revealed a calcified mass in the intraorbital region that extended to the cerebral hemispheres. It may be accompanied by hair-on-end periosteal reaction. In the first patient, the mass extended to the pineal gland. In the second and third patients, the mass extended to the suprasellar and pineal regions. Trilateral retinoblastoma consists of a primordial midline neuroectodermal tumor that originates in the pineal or suprasellar region. It is an uncommon combination of unilateral or bilateral retinoblastomas. Quadrilateral retinoblastoma, on the other hand, presents with bilateral retinoblastoma and tumors in both the suprasellar and pineal regions. The histopathology of trilateral and quadrilateral retinoblastoma shows a different pattern from retinoblastoma.

Conclusion: Retinoblastoma poses one of the most challenging problems due to its distinct patterns of growth, extension, and recurrence. Intracranial metastasis of trilateral and quadrilateral retinoblastoma exhibits a different pattern. The prognosis and diagnosis of retinoblastoma are significantly influenced by clinical examination, radiologic imaging, and histopathology.

Keywords: Pineal gland, quadrilateral, retinoblastoma, suprasellar, trilateral

Introduction

Annually, between 8,000 and 10,000 children under the age of five are diagnosed with retinoblastoma, which is the most common intraocular malignancy in this age group. There are no discernible predispositions based on geography, race, or gender.[1,2] Orbital retinoblastoma is a major cause of death and is associated with a poor prognosis for survival.[3] Inherited retinoblastomas can either occur sporadically or as a result of a germline mutation in the retinoblastoma protein tumor suppressor gene (RB). Bilateral tumors, which account for 30–40% of cases, almost always have a germline mutation, while unilateral tumors account for 60-70% of germline mutations. Trilateral retinoblastoma (unilateral or bilateral retinoblastomas and pineoblastoma), quadrilateral retinoblastoma (trilateral retinoblastoma and suprasellar CNS embryonal tumor), and osteosarcoma are additional conditions that may develop in children with germline mutations. These conditions typically present in early stages, with a median age of diagnosis at 12 months.[4]

The most common initial manifestations of retinoblastoma are white pupillary reflex known as leukocoria, strabismus, and impaired vision. Patients in the advanced

stages of the disease may also experience iris color changes, corneal and globe enlargement, inflammation of the orbits, and exophthalmos. Retinoblastoma is a malignancy that originates from the retina and can exhibit diffuse, infiltrative growth along the retina, endophytic growth into the vitreous chamber, or exophytic growth into the subretinal space.[1] In some cases, retinoblastoma can metastasize to the leptomeninges through direct orbital dissemination, transmission via the optic nerve to the brain, or invasion of the subarachnoid space. It can also metastasize hematogenously, with a preference for the liver, bone marrow, and bone.[4] This case series on retinoblastoma aims to help radiologists distinguish between trilateral and quadrilateral retinoblastoma based on radiologic imaging.

Cases

Case 1

A two-year-old child came to the public health center with swelling in the right eye. The child had a history of itching in the right eye for four months, followed by an enlargement of the eye, impaired vision, redness, and increasing pain. There were no signs of atypical white reflection from the eye. The child had previously undergone multiple examinations at a regional facility but was finally diagnosed with retinoblastoma through a clinical examination.

The right eye continued to enlarge until it was the size of a ping-pong ball. The child received one cycle of radiotherapy around two months before, according to allo-anamnesis; however, no medical record exists regarding
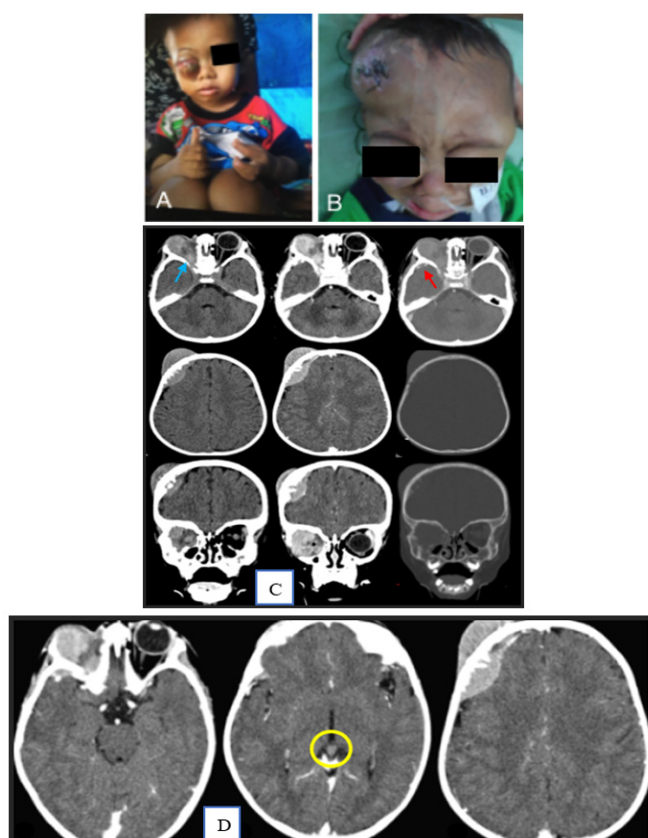

Fig. 1 **(A) Swelling of the right eye for the past 4 months, followed by (B) the extension of a mass to the right frontoparietal region. (C) Computed tomography (CT) of the head with axial and coronal contrast revealed a mass in the right frontoparietal region, which also extended to the right optic nerve (blue arrow) and the lateral wall of the orbit (red arrow).** Additionally, there was erosion and a hair-on-end periosteal reaction in the adjacent bone, as well as involvement of the meninges and soft tissues. (D) Enlargement of the pineal gland with contrast enhancement (yellow circle)
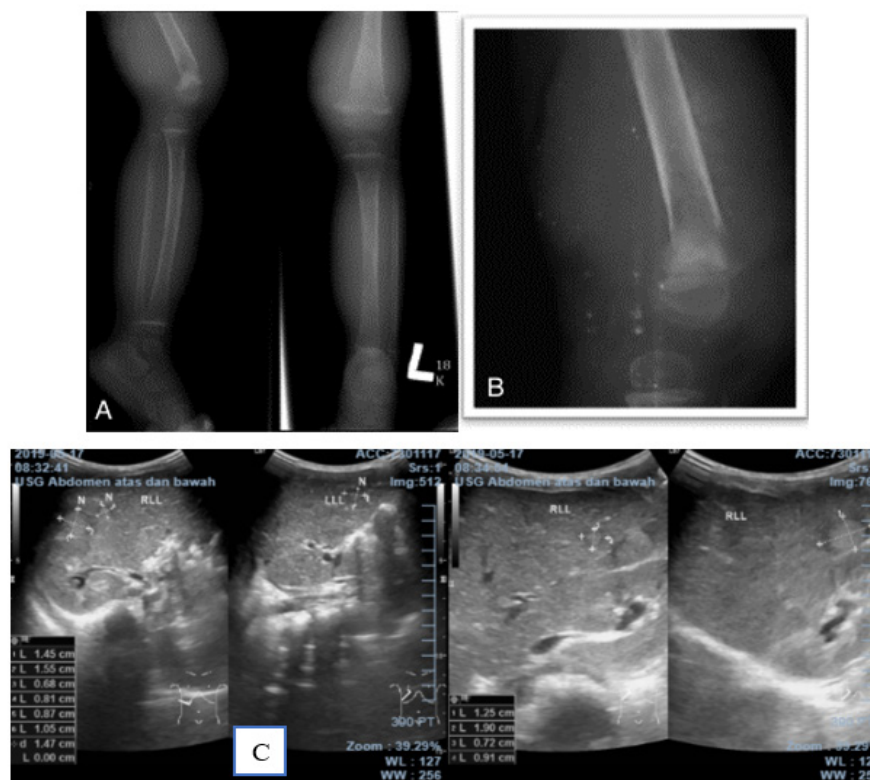
Fig. 2 (A) Cortical destruction was observed on the distal femoral and proximal tibial bones of the left leg. In addition, an interrupted periosteal reaction and diminished trabeculation were seen on the AP and lateral projections of the radiograph. (B) The distal femoral bone showed an interrupted periosteal reaction. (C) A liver ultrasound image revealed numerous hyperechoic nodules on both lobes of the liver.

the radiotherapy. After the eyeball ruptured and started bleeding, emergency enucleation was performed. The histopathology laboratory confirmed that the child had a malignant round-cell tumor based on an analysis of the ocular tissue section. About a month before, the child also began experiencing symptoms of a mass in the right frontal region that extended to the right parietal region. Consequently, the child was referred to our facility for further evaluation and treatment. The initial CT examination did not reveal any symptoms in the left eye.

Additionally, there was progressive weight loss. A broad-based mass was identified in the right lateral orbital wall on the contrast head CT imaging. This mass extended into the right optic nerve and measured approximately 1.9 x 2.0 x 1.8 cm. Another mass was observed in the right frontoparietal region, which was exerting pressure on the right frontal lobe. The surrounding bone exhibited attrition and a hair-on-end periosteal reaction, indicating the

involvement of the meninges and soft tissues. The size of the pineal gland was approximately 7.30 x 7.08 x 5.81 mm, which was slightly larger than the normal range of 6.1 mm ± 1.2 x 3.7 mm ± 0.8 x 4.8 mm ± 1.1. The cranial index of the pineal gland was relatively average. Additionally, there was contrast enhancement observed in the pineal gland, suggesting the possibility of a remaining pineal mass.

The destruction of the cortex in the proximal tibia and left distal femoral bone was assessed through lower limb radiography. In addition, there was disruption in the periosteal reaction, leading to a "hair on end" appearance and a reduction in bone trabeculation. Furthermore, we observed multiple hyperechoic lesions of varying sizes in both lobes of the liver. Therefore, it is unlikely that there are retroperitoneal and mediastinal masses present.

During the patient's hospitalization, the mass in the right frontoparietal region grew larger and spread to other areas, including
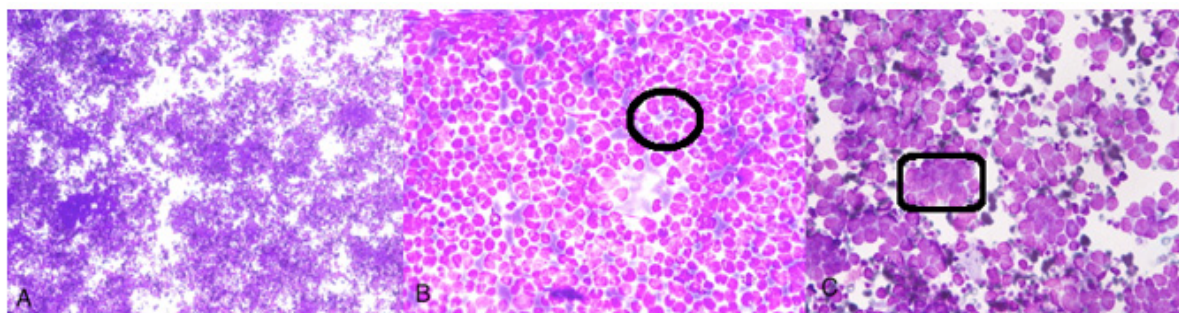
Fig. 3 Malignant round cell tumor was identified by histopathology. (A) Dispersed neoplastic cells amidst tissue hypercellularity (MGG, x100). (B) Rossete structure (MGG, x400) with (C) round-ovoid notched cells arranged in moldings accompanied by an increased nuclear-cytoplasmic ratio, anisocorics. The cells have an irregular core membrane, hyperchromatic and inconspicuous nucleolus. The arrow points to apoptotic cells (MGG, x1000).

the left frontal region, forearm, and foot. The histopathology findings of the right frontal mass indicated a small blue round cell as the second result, while the malignant round cell tumor with a Rosette's component was identified as the third result for the left frontal region, forearm, and foot.

Case 2

A 17-month-old boy presented with a complaint of swelling and discharge from the left eyeball for 2 days before hospitalization. The eyeball was more prominent than it was 6 months before, appeared more swollen, and had a reddish bulge 5 days before hospitalization. The patient also had a red eyelid and white discharge. The patient sleeps with the left eye not closing completely. The patient was born normal, cried immediately, was full-term, assisted by a midwife, and had a birth weight of 3 kg. The patient is the only child. At the age of three months, the patient presented with a white eye and was evaluated by a pediatrician who diagnosed the condition as a cataract of the left eye. At the age of six months, the patient was evaluated by an ophthalmologist in Sumba who diagnosed the infant with glaucoma and recommended a referral to a hospital in the city.

The patient was admitted to the intensive care unit for 21 days after experiencing recurrent seizures at the age of 13 months, during which time their consciousness did not recover. Following this, they were referred to Sanglah General Hospital. One month later, the patient had another seizure more than 3 times. The patient underwent craniotomy surgery and tumor removal with frozen section and was diagnosed with primary malignant brain tumor ec pilocytic astrocytoma, with a differential diagnosis of brainstem glioma and ependymoma; left orbital proptosis retrobulbar tumor ec neuroblastoma post craniotomy and tumor removal. The histopathology result revealed a small round-cell tumor. One month after being admitted, the patient's condition deteriorated and he passed away.

Case 3

At 7 months of age, a 2-year-old child presented to the hospital with symptoms including lumps in both eyes and head. Initially, a white spot appeared in the right eye and the patient experienced decreased vision. The right eye and the right side of the head became more prominent. The patient was then taken to an ophthalmologist who diagnosed cancer and suggested surgery, but the patient's parents refused at that time. The patient was the third of three children, born normal and full-term, with the assistance of a doctor, weighing 3 kg at birth.

There was no family history of similar complaints. Subsequently, a contrast head CT examination was performed, revealing a heterogeneous solid mass with partially indistinct boundaries measuring approximately 9 x 9.8 x 13.8 cm in the right orbital region. This mass extended to the left-right sphenoidal sinus, left-right ethmoidal sinus, right suprasellar area, and right fronto-parieto-temporal lobe, causing a midline shift of approximately 0.34 cm to the left.
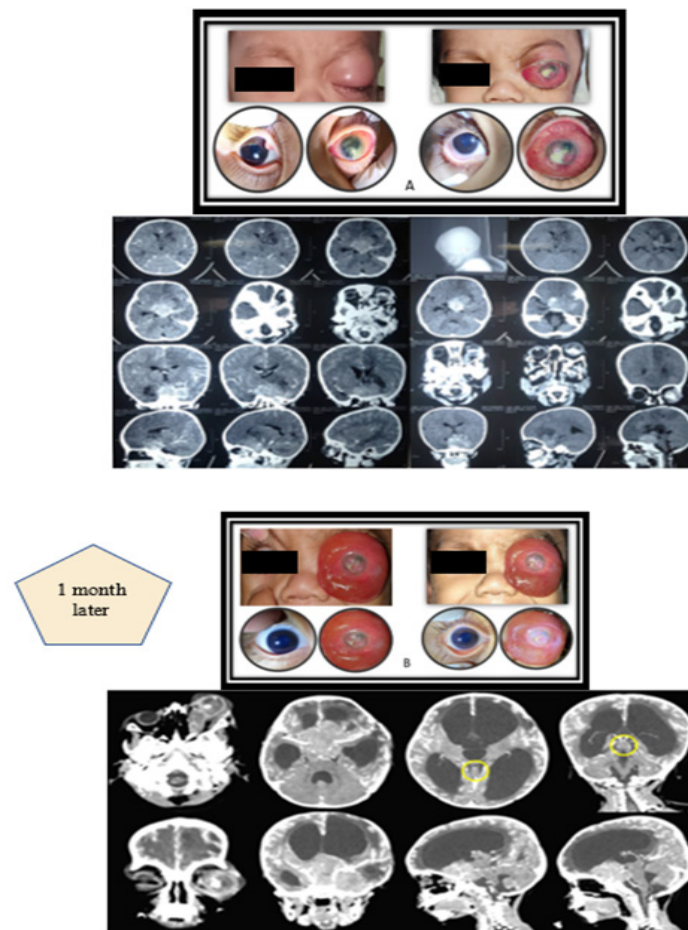
Fig. 4 (A) At 2 months of age, there was swelling in the left eyeball and a reddish bulge. Contrast head CT imaging showed an endophytic mass with a calcified component on the right orbital, extending to the suprasellar gland and causing pineal gland enlargement. **(B)** One month after craniotomy surgery, the left eye became more prominent and swollen, with a reddish bulge that persisted for the last 5 days. Contrast head CT imaging showed an enlarged suprasellar mass (axial diameter ± 6.23 cm) that had extended to the pineal gland, resulting in pineal gland enlargement (±10.6 x 16.4 x 15.5 mm) with contrast enhancement (indicated by the yellow circle) and communicating hydrocephalus.

Additionally, it exerted pressure on the anterior horn of the right lateral ventricle and encouraged leftward movement of the right-side midbrain. The mass also extended to the sinus cavernous, left retrobulbar to infiltrate the left orbital causing left proptosis oculi accompanied by left intraorbital calcification, extended to the right maxillary sinus to the right mandible and eroding the left right fronto-parieto-temporal osseus, clivus, greater wing and right sphenoid osseus, ethmoidalis osseus, lamina papiracea, right mastoid osseus, right zygomaticus osseus, right maxillary osseus, right mandibular osseus, with surrounding hair-on-end periosteral reaction and pineal gland enlargement measured ± 7. 4 x 8.1 x 7.8 cm with slight contrast enhancement. The patient had undergone chemotherapy for several months but in the 9th month, the patient's condition worsened and later died.

Discussion

11% of all cancers diagnosed in infants within the first year of life are retinoblastomas, which are the most common malignant intraocular
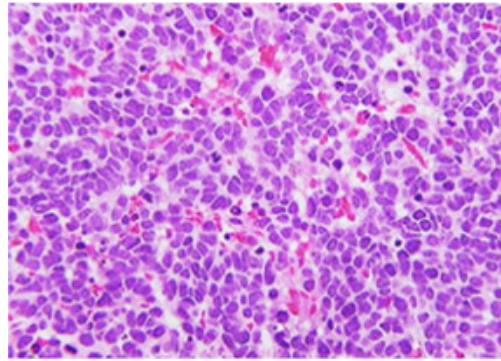
Fig. 5 As determined by histopathology, a small round cell tumor was identified. The tumor mass consists of neoplastic cell proliferation arranged in a solid nest pattern, which is partially molded and partially resembles pseudo rosette formation. The cellular features include a narrow eosinophilic cytoplasm, an elevated N/C ratio, an irregular nuclear membrane, an ovoid-round nucleus, and hyperchromaticity. There were 3 mitoses observed in 10 large fields of view.

tumor in this age group. Approximately one-third of cases are bilateral. Retinoblastomas are most commonly observed in early infancy, with 95% of cases manifesting before the age of five. The average age of diagnosis is 13 months. The effects of retinoblastoma are equally experienced by boys and girls, with no racial bias.[5] In this case series, all patients were boys aged 1–2 years.
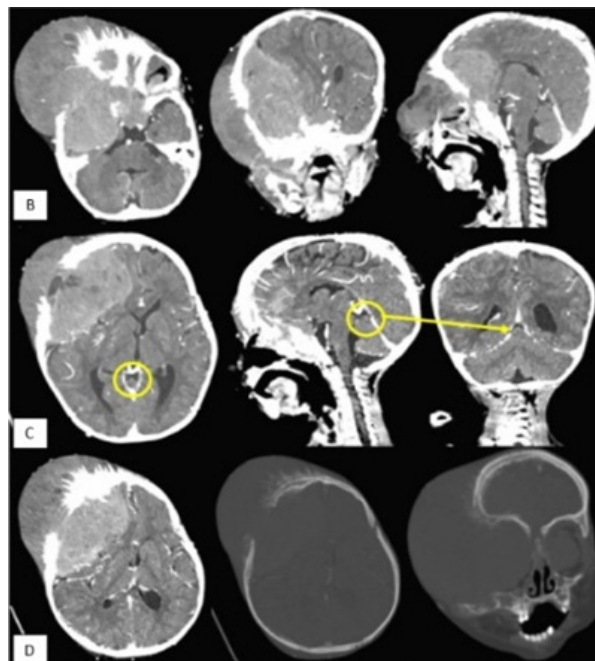
Retinoblastoma can occur unilaterally,

Fig. 6 **(A) The patient has had lumps in both eyes and the right side of the head since she was 7 months old. Contrast head CT imaging revealed a calcified mass extending from the right orbital into the paranasal sinus and left orbital. (B) It also showed compression of the right cerebral hemisphere in the right fronto-parieto-temporal and suprasellar regions. (D) This was characterized by periosteal reaction, resulting in a hair-on-end appearance in the adjacent bone. (C) Additionally, there is an extension to the pineal gland, measuring approximately 7.4 x 8.1 x 7.8 cm, with slight contrast enhancement.**

bilaterally, trilaterally, or quadrilaterally.[6] It has been estimated that 0.5-6% of patients with bilateral retinoblastoma will develop trilateral retinoblastoma.[2] The incidence of quadrilateral retinoblastoma is even lower than that of trilateral retinoblastoma. Trilateral retinoblastoma was first described by Jacobiec *et al*. It refers to the formation of a primary intracranial primitive neuroectodermal tumor in a patient who already has intraocular retinoblastoma. Trilateral retinoblastomas are typically located in the pineal gland, suprasellar region, or parasellar region, although there have been a few exceptional cases.

Quadrilateral retinoblastomas involve a tumor and bilateral ocular retinoblastomas in both the suprasellar and pineal regions. Rather than being a metastasis, the presence of an associated midline intracranial tumor indicates multifocal disease. The cause of intracranial lesions in patients with retinoblastoma is still unknown. There are two possible sources of intracranial tumors: pineal photoreceptors, which resemble retinal photoreceptors in both function and appearance, and ectopic foci of retinal cells on the floor of the third ventricle. One possible explanation for this coexistence of diseases is the shared photoreceptor origin shared by the retina and pineal gland. In the first case, there was right unilateral retinoblastoma with intracranial extension and involvement of the pineal gland, as confirmed by histopathological examination showing small round blue cells. This establishes the diagnosis of trilateral retinoblastoma. In the second case, there was right unilateral retinoblastoma with involvement of the suprasellar and pineal glands.

Histopathological examination revealed a small round cell tumor, leading to the diagnosis of quadrilateral retinoblastoma. In the third case, the retinoblastoma was bilateral and extended to the paranasal sinuses, with involvement of the suprasellar region and pineal gland. Based on CT imaging, it was suspected to be quadrilateral retinoblastoma. Typically, patients with retinoblastoma exhibit a white pupillary reflex. Retinoblastoma is responsible for up to 50% of cases of pediatric leukocoria. In addition to symptoms such as strabismus, ocular irritation, vision loss, and redness of the eyes, retinoblastoma can also cause orbital inflammation that resembles cellulitis. The presence of leukocoria is often assessed using CT imaging. In our case series, all patients exhibited leukocoria, as well as lumps and orbital pain. Retinoblastoma is a malignant tumor known for its invasive properties, often leading to metastasis in distant organs via the circulatory system. Metastasis and invasiveness can occur early in the development of retinoblastoma.[2]

Retinoblastoma can extend into the suprasellar region through the optic nerve.[7] The incidence of metastatic retinoblastoma ranges from 4.8% to 11%. Typical sites for extraocular retinoblastoma include the orbit, preauricular nodes, skeleton, central nervous system (CNS), and liver. Trilateral retinoblastoma is associated with an elevated risk of second primary malignancies in skeletal and soft tissues, such as osteosarcoma, leiomyosarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, angiosarcoma, Ewing sarcoma, PNET, and spindle cell sarcoma. The involvement of multiple bones and tissues indicates the presence of metastases rather than multifocal second primary malignancies. Bone metastases, which most commonly occur in the cranium and long bones, can cause symptoms such as atypically low blood counts, pain, and fever in patients with trilateral retinoblastoma.[3] In our case series, two cases of trilateral retinoblastoma with bone metastases in the head were observed, as well as one case with metastases in the long bones and liver. The diagnosis of retinoblastoma typically involves specialized ophthalmologists using funduscopy (conducted under general anesthesia) and ultrasound.

The primary distinguishing feature of retinoblastoma, intratumoral calcifications, can be detected using ultrasound (US). However, while ultrasound is specifically designed to detect superficial ocular masses, it is less sensitive than CT and MR imaging in detecting deeper tumor extensions such as optic nerve invasion and intracranial disease. CT is highly specific and sensitive in detecting calcifications.[8] It is the preferred method for detecting intraocular calcifications. MR imaging is used to detect leptomeningeal enhancement and parenchymal metastases, as well as assess primary midline intracranial lesions. Unilateral retinoblastoma is typically treated with surgical enucleation, while bilateral cases often require superior eye preservation. Enucleation alone is not sufficient for treating more advanced cases; additional treatments such as radiation (EBRT=external beam radiation therapy, plaque radiation), consolidation therapies (cryotherapy and transpupillary

thermotherapy), and chemotherapy (IVC=intravenous chemotherapy, IAC=intra-arterial chemotherapy, IvitC=intravitreal chemotherapy, intracameral chemotherapy) are necessary. Untreated retinoblastoma is usually fatal in the majority of the cases.[1,9]

The combination of high-dose chemotherapy and stem cell rescue is an alternative therapeutic strategy for the management of metastatic and advanced retinoblastoma.[9] Metastasis indicates a poor prognosis. Trilateral retinoblastoma, which occurs when the tumor has spread to the subarachnoid space, is associated with an unfavorable prognosis. Those who receive treatment for a detected pineal or sellar mass have an average survival time of 9.7 months, compared to 1.3 months for those who do not receive treatment.[5] An analysis using histopathology can identify neuroepithelial-derived small round cell tumors. Under a microscope, Homer-Wright pseudorosets (also present in other PNETs) and Flexner-Wintersteiner rosettes (which are relatively specific to retinoblastoma) are visible.[4] A subset of round cell tumors with an increased nuclear-cytoplasmic ratio are highly aggressive malignancies characterized by their monotonous, undifferentiated, and relatively small size.

Peripheral neuroectodermal tumor, rhabdomyosarcoma, non-Hodgkin's lymphoma, neuroblastoma, hepatoblastoma, Wilms' tumor, desmoplastic small round cell tumor, and synovial sarcoma are all neoplastic tumors that fall into this category. Malignant small round cell tumors are tumors composed of malignant round cells that are marginally larger than or double the size of red blood cells in air-dried smears. These neoplasms are defined by small, spherical, relatively undifferentiated cells.[10] In the first case, a histopathological examination revealed a malignant round cell tumor in the right frontal region, as well as Rosette components in the forearm, leg, and left frontal region. The second case showed the presence of a small round-cell tumor with partial formation of a pseudorosette during histopathological examination.

A comprehensive understanding of retinoblastoma requires a multidisciplinary team of specialists for proper treatment, long-term monitoring, and optimal survival while preserving vision, as well as a meticulous examination for precise diagnosis. Radiology plays a crucial role in distinguishing between trilateral and quadrilateral retinoblastoma cases.

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