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Exploration on Dental Tourism Development as a Medical Tourism in Bali

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Abstract
Medical tourism has become a positive trend across the world. People travel aboard can access the health services at once. Not to mention, the dental tourism. The development of dental tourism is important to support people in health care access, besides, also provide business opportunity for the nations. Bali has become the most visited tourism in Indonesia, and has a potential in dental tourism. However, few explorations on dental tourism are investigated. This paper aims to explore how the development of dental tourism can be a profitable business opportunity in Bali, as well as analyze strategies that can be applied to maximize this potential, with a focus on the integration of sustainable health and tourism services. This study is a descriptive qualitative study with Focus Group Discussion conducted with related parties such as dentists, clinic management team and representatives from Bali Medical Tourism Association. Besides, interviews and observation were also performed to describe the exploration. The results of the study reveal that Bali has promising business opportunity through dental tourism. The potentials are the competitive cost and high quality of service, tourism attraction, and easy accessibility. The business opportunity is also supported by the clinics that serve international tourists, integration of tour package and digital promotion and patient testimony. The branding of "dental care and vacation combination" becomes the attractive way to manifest dental tourism in Bali. In conclusion, Bali has the potential of becoming the promising dental tourism with some supporting facilities and infrastructure and qualified dental care providers.

Keywords: Bali, Dental Care, Dental Tourism, Medical Tourism

1. Introduction

Social-economic factors have become the reason numerous patients want to get dental health care at a lower rate (Trohel et al. 2016). The factors comprise first is the dental care cost which is quite expensive for some patients. The second factor is access to dental care clinics considering mobility to get treatment right away. Third, is the factor of some people feel satisfied with the care given in other places. Fourth, the cost of dental care compared to economic flight is way more expensive. Fifth, the internet plays a role in increasing traveling for dental care and last is the reason of fees, regulations, medical choices, time, and quality for people to prefer dental tourism (Husain Akbar et al. 2020).

Dental tourism creates dental health care that can be conducted in recreational activities such as attending cultural shows. Increasing comfort for people to access dental care is a considered factor in achieving a healthy life for every citizen. It is stated that about 57% of foreign tourists come to Malaysia to get medical treatment, of which 332.437 are Indonesians. Some of the most sought medical cares are preventive medical services and dental care (Saub et al. 2019). This phenomenon can be an evaluation for Indonesia to develop medical treatment, such as dental treatment. Medical tourism should be the evaluation of healthcare quality in Indonesia so that Indonesians and more people trust to come to Indonesia to get treatment (Asa et al. 2024; Md Zain et al. 2022; Damayanti et al. 2021).

Tourism is one of the mainstay sectors supporting the Balinese economy (Artini et al. 2020). In addition to offering natural beauty, cultural richness, and the friendliness of its people, Bali continues to innovate to respond to the growing global trends in the tourism industry, one of which is dental tourism (Astuti et al. 2024). Dental tourism, or dental health tourism, refers to tourists traveling abroad to get dental health care while enjoying a vacation experience. This trend is increasingly in demand by tourists from developed countries such as Australia, the United States, and Europe, where dental health care costs are relatively expensive compared to developing countries such as Indonesia.

Bali has great potential to become a major destination for dental tourism. This advantage is supported by several factors, including more affordable treatment costs, continuously improving service quality by adopting international standards, and unmatched tourism appeal. Several dental clinics in Bali, especially in the Denpasar, Kuta, and Seminyak areas, have integrated dental health services with tourist needs, such as foreign language consultations, transportation arrangements, and service packages connected to recreational activities (Agung Putri Dwiastuti, Dewi Kumala Ratih, and Kristianto 2023).

This great potential is also driven by the role of the Bali Medical Tourism Association (BMTA), which has facilitated collaboration between the health and tourism sectors to create a more organized health tourism ecosystem. However, despite the great opportunities available, the development of dental tourism in Bali still faces various challenges, such as the lack of uniform regulations, the need for investment in health infrastructure, and less-than-optimal promotion in the international market.

This study aims to explore how the development of dental tourism can be a profitable business opportunity in Bali, as well as analyze strategies that can be applied to maximize this potential, with a focus on the integration of sustainable health and tourism services.

This research was conducted in Bali, focusing on areas that are centers of dental tourism activities, such as Denpasar, center for dental clinics with international standards, Badung, an area that is frequently visited by foreign tourists and has clinics that serve the medical needs of tourists, and Ubud, an area with world-class tourism infrastructure that has the potential to support health tourism.

2. Method

This research used a descriptive qualitative approach with primary and secondary data collection. The primary data was obtained through the Focus Group Discussion (FGD) method. This was conducted with related parties such as dentists and clinic management serving international tourists and representatives from the Bali Medical Tourism Association (BMTA). Meanwhile, the secondary data was obtained from Bali tourism reports and statistics, including data on foreign tourist visits, scientific articles, journals, and reports related to medical tourism and dental tourism in Indonesia and globally, publications from associations, such as BMTA, as well as market reports from international bodies related to health tourism.

The collected data was analyzed using descriptive qualitative analysis techniques that simplify relevant data from interviews, observations, and documents to focus on the main research issues.

The validity and reliability of the data were performed with the triangulation method, namely Source Triangulation which comparing data from interviews, observations, and secondary documents to ensure consistency of information and Triangulation, using different methods (interviews, observations, document analysis) to gain a comprehensive understanding.

This study produces an analysis of supporting factors for the development of dental tourism in Bali, potential business opportunities that can be utilized by local business actors, strategies to overcome the challenges, such as promotion, regulation, and service standardization.

This methodology is designed to provide a holistic picture of dental tourism development in Bali, while providing practical recommendations for business actors and policy makers to optimize opportunities in this sector.

3. Results

This study reveals several important findings related to the development opportunities of dental tourism in Bali as a promising business sector. First, Bali's great potential as a dental tourism destination. Bali has a unique combination of medical service excellence and tourist attractions, making it a potential destination for dental tourism. Some of the main potentials found in this study include first, competitive cost and high quality of service. The cost of dental treatment in Bali is much cheaper compared to countries such as Australia, the United States, and Europe. Besides, dental clinics in Bali, especially in Denpasar, Badung and Ubud, have adopted modern technology and international service standards. Beside the competitive cost, it is supporting tourism attractions. Bali is known as an international tourist destination with its natural beauty, rich culture, and friendly people. Tourists who come for dental treatment can also enjoy a memorable holiday experience, such as visiting beaches, spas, and cultural attractions. Besides that, an easy accessibility in which Bali has Ngurah Rai International Airport with good global connectivity, making it easy for tourists from various countries to access dental tourism services. Second main result is business opportunities in the dental tourism sector. This study identifies major opportunities for local and international business actors who want to develop businesses in the dental tourism sector, namely development of international standard clinics. Clinics that serve international tourists can develop premium services with tourist-friendly facilities, such as foreign-speaking consultants, comfortable waiting rooms, and advanced technology. Besides, is the integration of services with tour packages which comprises great opportunity to create health tourism packages that include dental care, accommodation, and tourist activities and collaboration between dental clinics and hotels, restaurants, and travel agents can increase the appeal of this service.

According to Zoltan and Maggie, (2010) from the model "Get there, stay there, Live there" what has been happening in Bali is shown in Figure 1.

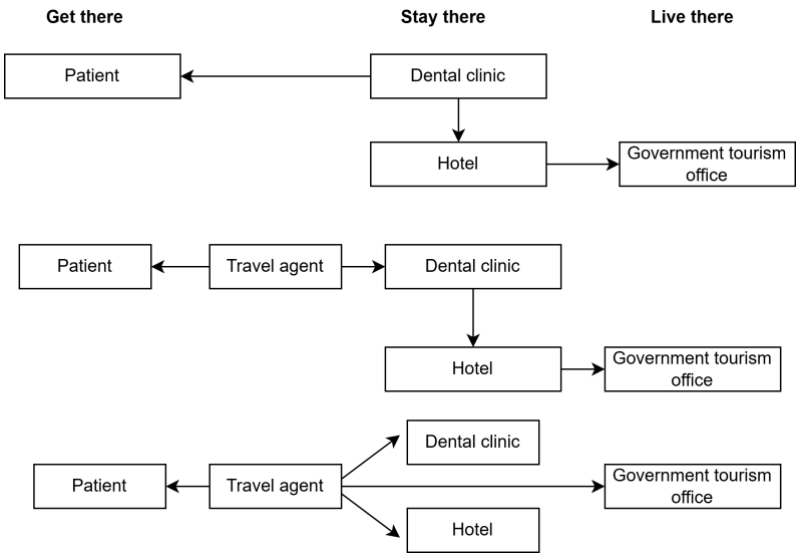

Figure 1: Bali Tourism Model

Figure 1 shows the first model, that the main point is the clinic, so that the tourist experience in the destination is only an accessory, organized by the hotel or at the request of the patient, as there is no integration with the destination, through the tourism business. It is also possible that the second model has an intermediary between the clinic and the patient by the travel agent, making the organization of the experience more efficient and consequently expanding the market. However, these two models do not include the tourist experience in the destination in the dental tourism market. Only the third model in which the travel agency plays a major role with direct access to the destination, namely packaging, organizing, offering the entire experience will provide space for the development of real dental tourism. The three models differ in terms of the intermediaries involved, the level of product integration, and the main point of the experience. This has been the concern of BMTA and is being designed in collaboration with the Bali Medical Tourism Board (BMTB) so that it can promote medical tourism in Bali more intensively and organized. It is expected that the tourist visit time will be longer, the destinations will be more numerous, so the country's foreign exchange will increase.

Another business opportunity in dental tourism is digital promotion and patient testimony. Global market can be reached through a strong digital promotion strategy, including social media, reviews on international health platforms, and testimonials from successful patients. Using the branding of "dental care and vacation combination", it can attract developed countries markets such as Australia, Europe, and the United States.

4. Discussion

Medical tourism is a method of getting medical treatment while travelling aboard. Another definition of medical tourism is a travel intended to receive health services. Travelling aboard to get medical services is driven by some factors including cost-effectiveness, access to services and health service unavailability. Medical tourism has become the positive trend and developed in to global industry. It is known that tourism as an industry has become one of largest sectors that demonstrate the growth of world globalization which connects between individuals and nations (Vovk, Beztelesna, and Pliashko 2021; Lovelock, Lovelock, and Lyons 2018; Zhong et al. 2021; Tahir, Hasan, and Dinar 2023).

Bali has great potential to develop dental tourism as a promising business opportunity. The combination of competitive treatment costs, increasing service quality, and international tourist attractions provide advantages that many other destinations do not have. However, the success of developing this sector depends on collaboration between the government, business actors, and local communities in overcoming existing obstacles. Because the success of medical tourism relies on the stakeholder involvement and collaboration at divergent level (Supriadi et al. 2024). In efforts to develop dental tourism in Bali in 2024, the role of dentists, the health office and the tourism office already exist. With the right strategy, dental tourism can become one of the main pillars in diversifying Bali's economy and strengthening its position as a global tourism destination.

According to the research findings, the following are recommendations to optimize the potential of dental tourism in Bali, such as strengthening regulations and service standards by local governments together with associations such as BMTA need to set quality standards for clinics serving medical tourists, and certification of clinics that are oriented towards international tourists can increase patient confidence. Besides, is integrated promotion by integrating dental tourism into Bali's overall tourism promotion strategy, for example through branding "Bali as a health tourism destination", digital campaigns with a focus on markets in countries with expensive dental care costs, such as Australia and the United States. Another recommendation is by multisector collaboration. This can be performed by encouraging collaboration between tourism actors and health service providers to create integrated tourism packages that combine medical services with recreational activities, and last recommendation is infrastructure development, such as investment in health facilities and training of medical personnel to improve service quality and improving connectivity between health services and major tourist centers in Bali.

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S.A.P.D. ; Writing – Original Draft Preparation, S.A.P.D. ; Writing – Review & Editing, S.A.P.D. ; Visualization, IADKR; Supervision, S.A.P.D. ; Project Administration, S.A.P.D. ; Funding Acquisition, S.A.P.D.

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Systematic Review on Impacts of Vitamin C, Thiamin, and Hydrocortisone in Sepsis

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Abstract
Sepsis is one of the most common conditions causing prolonged hospitalizations. Sepsis is a systemic infectious process that can be caused by multiple sources and types of infection in the human body. In developing and developed countries, sepsis is a condition that can put a financial burden on the health system due to longer stays in the hospital and the need for mechanical ventilators and vasopressors. Also, sepsis has a higher rate of mortality and morbidity for patients in lower-income countries due to lower levels of symptom awareness, health inequity, delay in care, and under-resourced healthcare facilities. Healthcare professionals are interested in finding evidence-based approaches to decrease mortality and morbidity and reduce the financial burden on an already stressed health system. This systematic article review aims to appraise articles using a hierarchy of evidence to address the clinical question regarding the efficacy of vitamin C, steroids, and thiamine in sepsis and septic patients when added to the standard treatment. After reviewing the randomized control trial, we found that study results on the regular use of vitamin C, steroids, and thiamine in sepsis and septic shock are conflicting. More research is needed to assess the efficacy of vitamin C, steroids, and thiamine in sepsis and septic shock to improve patient outcomes and reduce the length of hospitalizations.

Keywords: Vitamin C, Steroids, Thiamine, Sepsis, and Septic shock

1. Introduction

Sepsis is one of the most common causes of prolonged hospitalization for patients seen in healthcare facilities. According to Rudd et al. (2020), sepsis caused around 11 million deaths in 2017 worldwide, which accounted for around 19.7% of global deaths. This number might underestimate the burden of sepsis globally because data collection on the incidence is poorly collected in lower- and middle-income countries. In many countries, access to healthcare services is limited and health records are only partially complete (Dugani et al., 2017). Globally, around 30 million sepsis cases occur yearly, leading to more than 8 million deaths, where 40-50% occur in lower-income countries (Cohen et al., 2015; Fleischmann et al., 2016).

The data on the burden of sepsis in lower-income countries is limited due to incomplete medical charts and the lack of incorporation of the International Classification Diseases Code system (Dugani et al., 2017). However, in

the United States, about 55% of patients diagnosed with sepsis need care management at the intensive care unit level, with a death rate of 20% to 30% (Rhee et al., 2017). According to Rhee et al. (2017), in the United States, sepsis ranks as the third leading cause of healthcare facility death. The patient population who survives sepsis is often at risk of experiencing poor physical and mental or cognitive outcomes and a suboptimal quality of life (Yende et al., 2016). It is difficult to estimate the financial burden of sepsis globally. Van den Berg et al. (2017) in a systematic review assessed the hospital-related financial burden of sepsis around the world and found that the relative amount of healthcare budget spent on sepsis was 2.65% which is 0.33% of the gross national product. In the United States, sepsis costs $38 billion annually (Hollenbeck et al., 2023).

Sepsis is an infectious condition that can lead to high mortality and morbidity rates (Rudd et al., 2020), but does not have a current universal definition. From 1991 to 2016, multiple definitions have been suggested. In 2016, sepsis was generally defined as a life-threatening condition with organ dysfunction as the body's response to infectious processes (Singer et al., 2016).

Sepsis has higher mortality and morbidity rates than other conditions requiring prolonged hospitalization, with a substantial financial burden on the health system in lower and higher-income countries. In lower-income countries health inequity, limited financial resources, health disparity, corruption, suboptimal healthcare services, and resilient public health are the main contributors to the sepsis burden (Rudd et al., 2018).

The definition of sepsis was developed in 1991 at a consensus conference that linked infection with the systemic inflammatory response (Bone et al., 1992); (See **Table 1** illustrating sepsis criteria). According to Chakraborty & Burns (2023), systemic inflammatory response syndrome (SIRS) is the human body's response to internal and external toxic or stressor stimuli such as infection, trauma, surgery, burn, or malignancy. SIRS in the adult population is objectively defined by the presence of two criteria (body temperature more than 38 or less than 36 degrees Celsius, heart rate more than 90/minute, respiratory rate more than 20/minute, and white blood count more than 12000 or less than 4000/microliters or the presence of bandemia at greater than 10% band cells). Kaukonen et al. (2015) added to the theory that almost all septic patients meet SIRS criteria. However, all patients with SIRS criteria are not septic.

It is essential to highlight the subgroups of patients who might not meet SIRS criteria when they present to the healthcare facility, specifically the old patient population. The older patient population can develop multi-organ failure and severe forms of infections and death (Kaukonen et al., 2015). It can be difficult for the local provider to diagnose older patients from either SIRS or classical forms of sepsis.

This debate between a clear definition of SIRS and a more detailed definition of sepsis led the European Society of Intensive Critical Medicine (SCCM) to create a new task force that developed Sepsis-3, a new definition of sepsis (Fernando et al., 2018). According to Fernando et al. (2018), the new definition entailed any life-threatening organ dysfunction due to the body's dysregulated response to infection. The new definition for the diagnosis of sepsis does not entail SIRS criteria to establish a delineation between symptoms to define the diagnosis further.
Currently, the Sequential Organ Failure Assessment (SOFA) scores are used as a vital criterion in the diagnosis of a patient with sepsis (Singer et al., 2016). According to Vincent et al. (1996), SOFA scores are based on assessing six systems: respiratory, cardiovascular, liver function, coagulation profile, kidney function, and nervous system. Each system is scored 0 to 4 (Vincent et al. 1996). (See **Table 2** illustrating SOFA criteria). According to Chakraborty & Burns (2023), besides SOFA, several scoring systems are used to assess organ dysfunction, such as the Acute Physiology and Chronic Health Evaluation (APACH) score II and III, Multiple Organ Dysfunction (MOD) score, and Logistic Organ Dysfunction (LOD) score.

To date, the medical measures that have enhanced outcomes for sepsis patients are early initiation of antibiotics, fluid resuscitation, and other appropriate interventions to control or address the source of infection (Rhodes et al., 2017). Different measures are suggested to help manage sepsis, including administering intravenous Vitamin C, hydrocortisone, and thiamin in observational studies based on biological plausibility (Merik et al., 2017; Wilson, 2013). The need exists for a universal definition of sepsis to support the review of potential interventions to address this health condition. The purpose of this systematic is to assess the effects of vitamin C, thiamine, and

hydrocortisone in sepsis patients to determine if they have any significant impact on patients' early discharge from the hospital, ventilator free time, vasopressor-free time, mortality, in randomized controlled trials.

Table 1: Definitions of Sepsis

Bone et al. (1992)	**Levy et al. (2003)**	**Singer et al. (2016)**
Sepsis: Infection with two or SIRS criteria Severe Sepsis: Sepsis with organ dysfunction Septic shock: Hypotension with sepsis despite adequate fluid resuscitation along with indicators of abnormal perfusion: lactic acidosis, oliguria, altered mental status	Suspected or confirmed sources of infection with follow some of the following parameters **General Indicators:** Fever (core temperature > 38.3°C); hypothermia (core temperature < 36°C); heart rate > 90 beats per min or > 2 SD above the normal value for age; tachypnea: respiratory rate > 30 breaths per min; altered mental status; significant edema or positive fluid balance (>20 mL kg over 24 h) Hyperglycemia (plasma glucose > 110 mg dL) in the absence of diabetes **Inflammatory Indicators:** Leukocytosis (white blood cell count > 12,000/μL); leukopenia (white blood cell count < 4000/μL); normal white blood cell count with > 10% immature forms; plasma C-reactive protein > 2 SD above the normal value; and plasma procalcitonin > 2 SD above the normal value **Hemodynamic Indicator:** Hypotension (systolic blood pressure < 90 mmHg, MAP < 70 mmHg, or a systolic blood pressure decrease > 40 mmHg in adults or < 2 SD below normal for age, mixed venous oxygen saturation > 70%, cardiac index > 3.5 L min^{-1} m^{-2}) Organ dysfunction parameters: Arterial hypoxemia (PaO_2/FIO_2 < 300); acute oliguria (urine output < 0.5 mL/kg/ h); creatinine increase ⩾ 0.5 mg/ dL; coagulation abnormalities (international normalized ratio > 1.5 or activated partial thromboplastin time > 60 s); ileus; thrombocytopenia (platelet count < 100,000 μL) Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL) **Tissue perfusion Indicator:** Hyperlactatemia (>3 mmol L^{-1}); decreased capillary refill or mottling	Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection. **Sepsis criteria** Suspected or documented infection and presence of ⩾2 SOFA points Septic shock is defined presence of sepsis with persisting hypotension, Requiring vasopressor therapy to elevate MAP ⩾ 65 mmHg Lactate > 2 mmol L (18 mg/dL) despite adequate fluid resuscitation

Source: Gyawali, B., Ramakrishna, K., & Dhamoon, A. S. (2019). Sepsis: The evolution in definition, pathophysiology, and management. SAGE open medicine, 7, 2050312119835043. https://doi.org/10.1177/2050312119835043.

Table 2: SOFA Criteria

Respiratory system		
PaO2/FiO2 (mmHg)	SOFA score	
> 400		0
< 400		1
< 300		2
< 200 with respiratory support		3
< 100 with respiratory support		4
Nervous system		
Glasgow Coma Scale	SOFA score	
15		0
13–14		1
10–12		2
6–9		3
< 6		4
Cardiovascular system		
Mean arterial pressure (MAP) OR administration of vasopressors required	SOFA score	
MAP > 70 mmHg		0
MAP < 70 mm/Hg		1
Dopamine ≤ 5 µg/kg/min or dobutamine (any dose)		2
Dopamine > 5 µg/kg/min OR epinephrine ≤ 0.1 µg/kg/min OR norepinephrine ≤ 0.1 µg/kg/min		3
Dopamine > 15 µh/kg/min OR epinephrine > 0.1 µg/kg/min OR norepinephrine > 0.1 µg/kg/min		4
Liver		
Bilirubin (mg/dl) [µmol/L]	SOFA score	
< 1.2 (< 20)		0
1.2–1.9 [20–32]		1
2.0–5.9 [33–101]		2
6.0–11.9 [102–204]		3
> 12.0 [> 204]		4
Coagulation		
Platelets ×103/ml	SOFA score	
> 150		0
< 150		1
< 100		2
< 50		3
< 20		4
Kidneys		
Creatinine (mg/dl) [µmol/L]; urine output	SOFA score	
< 1.2 [< 110]		0
1.2–1.9 [110–170]		1
2.0–3.4 [171–299]		2
3.5–4.9 [300–440] (or urine output < 500 ml/day)		3
> 5.0 [> 440]; urine output < 200 ml/day		4

Source: Vincent, J. L., Moreno, R., Takala, J., Willatts, S., De Mendonça, A., Bruining, H., Reinhart, C. K., Suter, P. M., & Thijs, L. G. (1996). The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive care medicine, 22(7), 707–710. https://doi.org/10.1007/BF01709751.

1.1. Etiology of Sepsis

According to Mahapatra & Heffner (2023), the 2009 European Prevalence of Infection in Intensive Care (EPIC II study) indicated that one of the most common etiology of sepsis is gram-negative bacterial infections. Gram-

negative bacterial infections account for 62% of the cases, followed by gram-positive infection, which accounts for 47% (Vincent et al., 2009). Study results determined causative bacterial organisms in septic patients as *Staphylococcus aureus* (20%), *Pseudomonas* (20%), and *Escherichia coli* (16%) (Vincent et al., 2009). Site-specific infections are commonly respiratory (42%), bloodstream (21%), and genitourinary (10%) (Mayr et al., 2010). Mahapatra & Heffner (2023) highlighted that diabetes, trauma, chronic liver disease, chronic kidney disease, immunocompromised state, burns, hemodialysis, indwelling catheters, major surgery, older age, and chronic use of steroids are considered the risk factors that can predispose to sepsis.

1.2. Sepsis Epidemiology

Cases of sepsis have increased in the last decades. In the United States, around 600,000 to 1,000,000 patients were hospitalized for sepsis per year from 2000 through 2008 (Elixhause et al., 2011). Mortality from sepsis can vary from country to country due to specific demographics such as age, sex, race, the existence of comorbid conditions, and organ failure (Mahapatra & Heffner, 2023). Elfeky et al. (2017) indicated that mortality associated with sepsis depends on the number and degree of organ failure, with crucial predictors being respiratory, hepatic, cardiovascular, and neurologic failure.

2. Search Strategy

We used PubMed.gov and Cochrane Library databases for articles on the effects of vitamin C, steroids, and thiamine in sepsis and septic shock patients. We included randomized control trials published within the last five years and excluded studies published prior to 2018 and those not written in English. Also, we excluded studies that investigated the vitamin C, steroids, and thiamine individually. We reviewed the abstracts of articles based on inclusion/exclusion criteria. In the first stage, we identified potentially 141 relevant articles. During the screening stage, we noticed that eight articles were duplicates. Moreover, during the screening process, we applied the inclusion criteria: (1) articles on the role of intravenous vitamin C, steroids, and thiamine in sepsis and septic shock patients, (2) participants of the study 18 years old or older, (3) articles that were published within the last five years in English, and (4) randomized controlled trials. In the eligibility phase, we excluded articles that were randomized clinical trials in which vitamin C, thiamine, and hydrocortisone were investigated individually. We found that 8 articles were eligible and included in our review. The literature selection process is described in the PRISMA diagram (Moher et al., 2015); (See **Figure 1** illustrating selection flow diagram**)**.

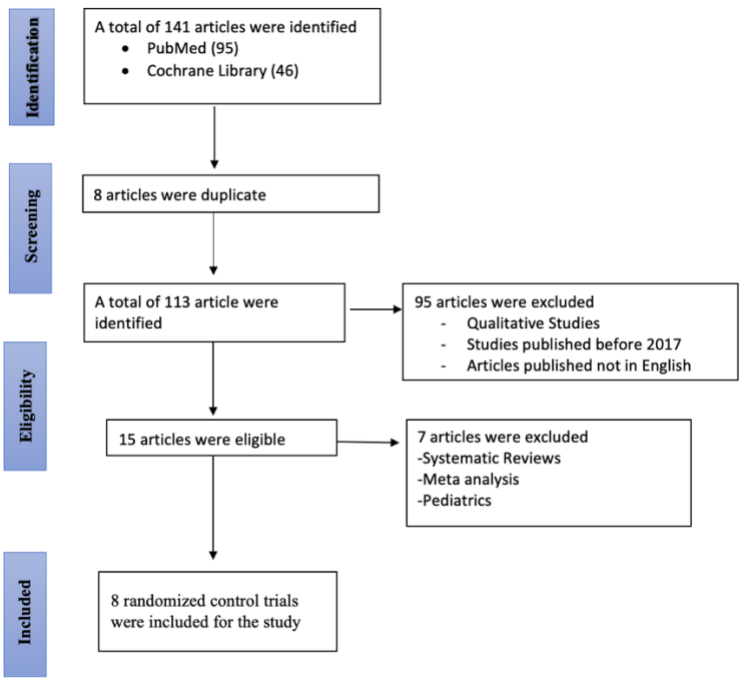

Figure 1: Selection Flow Diagram

2.1. Articles Quality Grading

We used the Oxford Center for Evidence-Based Medicine (Burn et al., 2011) scale to grade the quality of articles and included Level-1 evidence randomized control trials in our review; (see **Table 3** illustrating level of evidence and type of evidence) **.**

Table 3: Level and Type of Evidence

Type of evidence	**Level of evidence**	**Number of Articles**
All articles	L1, L2, L3, and L4	113
Randomized control trial	L1	8
Systematic Review, Meta analysis, and Pediatrics	L1	7
Other studies	L2, L3, and L4	95

Source: Burns, P. B., Rohrich, R. J., & Chung, K. C. (2011). The levels of evidence and their role in evidence-based medicine. Plastic and reconstructive surgery, 128(1), 305–310. https://doi.org/10.1097/PRS.0b013e318219c171.

3. Role of the Ascorbic Acid, Hydrocortisone, and Thiamine in Sepsis Patients on Ventilator and Vasopressor

3.1. Study Design

Sevransky et al. (2021) designed a randomized, double-masked study with an adaptive sample in adult patients with respiratory and circulatory failure needing vasopressors due to sepsis. Participants from 43 healthcare facilities were enrolled in the study in the United States. Participants were randomly assigned 1:1 to intervention and placebo groups.

3.2. Trial Participants

Participants aged 18 and older with respiratory and cardiovascular failure secondary to sepsis were enrolled in the study. Criteria for respiratory failure were arterial partial pressure ratio to the fraction of inspired oxygen ≥300 or blood oxygen saturation ratio to fraction inspired oxygen (FiO2) ≥315 and on the ventilator, and patients on noninvasive positive pressure ventilation, or oxygen with high-flow nasal cannula with rate of 40 L/min or higher with FiO2 40%. Criteria for shock included mean arterial blood pressure >65 on pressors for more than 60 minutes (Sevransky et al., 2021).

3.3. Intervention

Participants were given intravenous study agents ascorbic acid (1.5 gram), thiamine (100 mg), and hydrocortisone (50 mg) or a placebo within 4 hours of randomization and then four times a day until the participants were discharged from the intensive care unit or died. The clinical team was not blinded to the use of corticosteroids, and they could give the participants up to 200 mg of hydrocortisone (Sevransky et al., 2021).

3.4. Variables

According to Sevransky et al. (2021), the study's primary outcome was to measure ventilator and vasopressor-free days after administration of study agents in the first month. The second main objective of the study was to estimate mortality in the first month. Moreover, reduction in the intensive care unit length of stay, delirium, mortality, and improvement in kidney functions were other outcomes explored to support the efficacy of the treatment. Hypersensitivity, nephrolithiasis, injection site complication, and hemolysis were included in the Safety endpoints (Sevransky et al., 2021).

3.5. Analysis

In the statistical analysis, categorical data was reported in percentages and frequencies and continuous data (variables) as means with standard deviation and medians with interquartile ranges. In the primary analysis, Sevransky et al. (2021) calculated ventilator and vasopressor free time using medians and interquartile, and 95% confidence interval and *P* value (*P*=0.022) were used to report bivariable differences between intervention and placebo groups, and mortality was reported as a percentage.

3.6. Results

A total of 3243 participants in 43 hospitals were screened, and 501 participants were included in the study (median age 62, 54% male, 46% females, 41% on ventilator and vasopressor, 21% on ventilator alone, and 38% on vasopressor alone). After the screening to determine eligibility, 252 participants were randomly assigned to the intervention group and 249 to the placebo group. Participants had similar characteristics in both groups: disease severity, source of infection, and other comorbid conditions. The median time to start the study intervention (agents) and the onset of shock and respiratory failure was 14.7 hours.

Sevransky et al. (2021) noticed no significant difference in measuring the primary outcome (ventilator and vasopressor-free days) between the intervention group and placebo group, with a confidence interval of 95%, p = 0.85, the median difference in ventilator and vasopressor-free days was -1 day.

The percentage of all-cause mortality was 22% in the intervention group and 24% in the placebo group. Long-term effects were assessed at 180 days, and they noticed that the percentage of mortality was 40.5% in the intervention group and 37.8% in the placebo group (difference, 2.7%; 95% CI, −11.3% to 5.8%). Also, there was no significant difference in the intervention and placebo groups when measuring exploratory outcomes reducing the length of intensive unit stay (*p=0.79),* delirium (*p*=0.45), and improving kidney functions (*p*=0.58).

3.7. Adverse Events

No serious adverse effects were reported in either group. One participant developed hemorrhagic shock, and in one participant, kidney function got worse in the intervention group; Both events were deemed as potential adverse events related to the intervention.

3.8. Biases

One limitation of the study was that it was terminated early due to funding issues, and it was not completed, which could have underpowered the study results. Also, participants' blood concentrations of ascorbic acid were not tested to adjust the dose based on the needs of individuals.

4. Early Administration of Ascorbic Acid, Hydrocortisone, and Thiamin in Septic shock

4.1. Study Design

Lyu et al. (2022) performed a double-masked randomized trial in an intensive unit of a hospital in China. Participants were randomly assigned 1:1 to intervention and placebo groups. Participants who met septic shock criteria were treated with intravenous antibiotics and intravenous fluid for three hours to maintain a mean arterial blood pressure of 65 mmHg. Participants who were not responsive to intravenous fluids were started on norepinephrine within the first hour of diagnosis of septic shock.

Participants in the intervention group received intravenous ascorbic acid (2 gram), hydrocortisone (200mg), and thiamine (200mg) for five days or until they were discharged from the intensive care unit. Clinicians were not blinded to prescribing 200 mg steroids to patients who needed it, for example, patients with chronic pulmonary obstructive disease exacerbation.

4.2. Objectives

The main objective of the study was to measure all-cause mortality at three months. The secondary outcome measured mortality in 28 days, after discharge from the healthcare facility or intensive care unit. Moreover, septic shock resolving rate, time, early discharge from the intensive care unit, reduced length of hospital or intensive care unit stay, and ventilator and vasopressor free time (Lyu et al., 2022).

4.3. Statistical Analysis

Lyu et al. (2022) included 406 participants in the study to project a 90% power for the trial to capture an absolute difference of 15 percent points after a power analysis was performed (Marik et al., 2017).

Luy et al. (2022) noted that data did not have normal distribution using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Thus, the median was reflected for numerical data and percentage for categorical data. Survival time among participants was measured via Cox Proportional Hazard Regression Analysis, and the results were shown as a hazard ratio with a 95% confidence interval.

4.4. Results

According to Luy et al. (2022), 408 participants were included in the study; 203 participants were assigned to the intervention group and 205 to a placebo group. At baseline, the participants had similar characteristics, and they found no significant difference between the intervention group and the placebo group in comorbid conditions, age, sex, site of infection, sequential organ failure score, and acute physiology and chronic health evaluation score (p >0.05).

There was no significant difference in all-cause mortality between groups at three months. The mortality percentage in the intervention group was 40.4% and 39.0% in the placebo group (p=0.77). Also, there was no significant difference between groups for the secondary outcomes including 28 days mortality (p = 0.80), shock reversal time (p = 0.30),
length of stay in the hospital bed (p = 0.35), intensive unit stay (p = 0.85), (Luy et al., 2022).

4.5. Adverse Events and Biases

Common side effects included elevated levels of sodium in the blood, blood glucose dysregulation, and volume overload in both groups. The study was a single-center trial, which impacted its external validity and generalizability. Also, ascorbic acid and thiamin blood levels were not measured, and it was unknown if the amount of given medication met the required blood levels.

5. Effect of Ascorbic Acid, Corticosteroids, and Thiamine on Organ Injury in Septic Shock

Moskowitz et al. (2020) tested the hypothesis that ascorbic acid, corticosteroids, and thiamine can improve Sequential Organ Failure Assessment (SOFA) scores within 72 intensive care unit admissions in patients with septic shock.

5.1. Study Design

A multicenter, randomized, masked, superiority trial was conducted in 14 centers in the United States to compare the combination of ascorbic acid, hydrocortisone, and thiamin with placebo in patients with septic shock (Moskowitz et al., 2020).

5.2. Population

Eligibility for participation included patients aged ≥18 years who were on vasopressor for septic shock and had confirmed or suspected sources of infection. Patients with renal stones, hemochromatosis, glucose-6-phosphate

dehydrogenase deficiency, allergic to investigating drugs, and patients who used the study intervention for other indications were excluded (Moskowitz et al., 2020).

Participants were randomized to intervention and placebo groups with a 1:1 group size. Participants in the intervention groups were intravenous ascorbic acid, hydrocortisone, and thiamine, and the placebo group received a matching amount of normal saline along with standard sepsis management protocols (Moskowitz et al., 2020).

5.3. Outcome

The trial's primary outcome was to improve SOFA score ranges (0 = best and 24 = worst outcome) within 72 hours of enrollment in the study. Secondary outcomes of the study were ventilator and vasopressor free time, reduced all-cause mortality, reduced hospital length of stay, and more rapid intensive unit discharge time.

5.4. Results

A total of 205 participants were randomly assigned with half of them assigned to the intervention group (103) and half to the placebo group (102). Participants in both groups had similar demographic and diagnostic characteristics. Nine participants (9.1%) in the placebo group and 10 participants (9.9%) in the intervention group died before reaching the 72-hour time point. For the primary outcome, Moskowitz et al. (2020) found no statically significant difference between the groups for improvement in the SOFA score (95% CI, -1.7 to 0.2; $p = 0.12$) over 72-hour point time. Furthermore, 64 participants expired within 30 days of enrollment, and for the 30-day mortality, with no statistically significant differences between the intervention and placebo groups (95% CI, 0.8 to -2.2; $p = 0.26$) (Moskowitz et al., 2020). Moskowitz et al. (2020) highlighted that the median number of ventilator-free days within seven days of enrollment for secondary outcomes was not statistically significant between the groups (95% CI, -1.9 to 1.9 days ; $p > 0.99$). They found that the septic shock-free days (number of days in which the patient was alive and needed < 6 hours of any vasopressors) were significantly improved in the intervention group compared to the placebo group (95% CI, 0.2 to1.8 days; $p < 0.01$), and during the first 72 hours, cardiovascular SOFA score in the intervention group (95% CI, -0.9 to-0.1days; $p = 0.3$).

Moskowitz et al. (2020) noticed statically no significant difference between the intervention group and the placebo group for any other SOFA score based on: liver panel (95% CI, −0.3 to 0.1; $p = 0.22$), neurologic elements (95% CI, −0.6 to 0.1; $p = 0.14$), the kidney panel (95% CI, −0.2 to 0.4; $p = 0.52$), the respiratory system (95% CI, −0.3 to 0.3; $p = 0.84$), or the coagulation element (95% CI, −0.2 to 0.2; $p = 0.92$).

5.5. Adverse Events

No serious adverse events were noticed related to drugs under investigation. The most common adverse events were hyperglycemia, hypernatremia, and hospital-acquired infection.

5.6. Limitation of Study

The number of participants in the study by Moskowitz et al. (2020) study is smaller (205), which potentially limits the results' generalizability. Also, the drugs under investigation were administered to the participants 13.5 hours after the administration of vasopressors; the same limitation was noticed in other studies (Annane et al., 2018; Fujii et al., 2020; Venkatesh et al., 2018). Moskowitz et al. (2020) assumed a shorter duration between the initiation of vasopressor and study agent might have resulted in better outcomes.

6. A Prospective, Randomized Clinical Study Comparing Ascorbic Acid, Thiamine, and Hydrocortisone to Hydrocortisone Alone to Determine Decreasing Mortality in Septic Patients

6.1. Objective

Hussein et al. (2021) conducted a prospective randomized clinical trial to assess the difference between triple therapy ascorbic acid, thiamin, and hydrocortisone (ATH) and hydrocortisone (H) alone in decreasing mortality and mitigating organ failure in septic shock patients.

6.2. Study Design

Hussein et al. (2021) conducted a prospective, comparative, randomized study in the Air Force Specialized Hospital in Cairo, Egypt. The study participants were patients who had septic shock on admission or developed septic shock during their stay in the hospital. Criteria for diagnosis of septic shock were the need for a vasopressor to keep mean arterial blood pressure ≥ 65, lactate ≥ 2 mmol/L, and SOFA score ≥ 2 (Bone et al., 1992; Jansen et al., 2010). Participants were randomly assigned 1:1 to the ATH group and H group. Participants in the H group received hydrocortisone, and participants in the intervention (ATH) group received ascorbic acid (1.5 gram), thiamine (200 mg), and hydrocortisone (50 mg) in addition to the standard local protocol for the treatment of septic shock (Hussein et al., 2021).

6.3. Outcome

The study's primary outcome was to assess 28-day mortality in the hospital and intensive care unit. The study's secondary outcome included assessing vasopressor and ventilator-free time, improving liver and renal function, and septic markers such as lactate and procalcitonin (Hussein et al., 2021).

6.4. Results

Participants in both groups had similar socio-demographic, clinical, and biochemical or diagnostic characteristics at baseline. Hussein et al. (2021) found no statically significant differences between the ATH and H group for 28-day intensive care unit and hospital mortality rates ((95% CI = 0.506-1.85, p value = .623). Moreover, no significant differences between groups were noticed regarding mechanical free time between the ATH group and the H group. Alternatively, vasopressor-free time was significantly improved in the intervention group ($p = 0.1$).

6.5. Limitation

The study was a single-center study with a small sample size, which limited the generalizability of the study results.

7. A Pilot Study on how Ascorbic Acid, Thiamin, and Hydrocortisone versus Hydrocortisone Alone Effects Microcirculation in Septic Shock Patients

7.1. Objective

Wang et al. (2023) investigated the effects of ascorbic acid, thiamine, and hydrocortisone (ATH), versus hydrocortisone (H) to assess sublingual microcirculation in patients with septic shock.

7.2. Study Design

For this pilot study, a prospective, double-masked, randomized trial method was used to assess the effects of hydrocortisone (H) alone versus ascorbic acid plus thiamin, and hydrocortisone, (ATH) on the perfused small blood vessel density in the sublingual area via side stream dark-field imaging in septic shock patients. Participants were randomly assigned in a 1:1 ratio to the ATH group and the H group. Participants in the treatment (ATH) group received ascorbic acid (1.5 gram), hydrocortisone (200 mg), and thiamine (200mg) in addition to the standard treatment of septic shock. Participants in the H group were treated with hydrocortisone alone in addition to standard treatment for the septic shock Wang et al. (2023).

7.3. Outcome

Wang et al. (2023) defined the perfusion to small vessels as blood vessels 0-20μm in diameter. The study's primary outcome was to assess the small vessel perfusion, which was described as 0 to 20μm in diameter 24 hours after treatment. Wang et al. (2023) used imaging to monitor the perfusion of small blood vessels at baseline, 4 hours, and 24 hours after the initiation of hydrocortisone alone versus ascorbic acid, hydrocortisone, and thiamin. The secondary outcome included an assessment of other blood flow parameters, small vessel density, flow index, and perfusion 24 hours after the initiation of treatment.

7.4. Results

Wang et al. (2023) screened 108 participants and included 27 after applying the exclusion criteria. Participants were randomly assigned: 15 to the ATH group and 12 to the H group. The perfused blood vessel was significantly more in the ATH group than in the H group after 4 hours of treatment (95% CI, 2.227-11.857; $p = 0.009$) and 24 hours (5% CI, 2.390-11.759; $p = 0.008$) (Wang et al., 2023).

7.5. Limitation

The study had a small number of participants (27) and was a single-center study design, which could limit its generalizability.

8. Comparing Ascorbic Acid, Thiamin, and Hydrocortisone to Hydrocortisone Alone in Septic Patients

8.1. Objective

Fujii et al. (2020) investigated the effects of ascorbic acid, hydrocortisone, and thiamin (AHT) compared to hydrocortisone (H) alone to assess septic shock resolving time (mean arterial blood pressure > 65 mmHg without any types vasopressors support for four hours).

8.2. Study Design

Fujii et al. (2020) conducted a multicenter, open-label, parallel-group randomized trial to assess the effects of ascorbic acid (1.5 gram every 6 hours), thiamine (200 mg twice), and hydrocortisone (50 mg every 6 hours) in patients with septic shock in 10 intensive care units in three countries: New Zealand, Australia, and Brazil.

8.3. Study Population

Participants aged≥ 18 years old who were admitted with a diagnosis of septic shock were screened for eligibility. Septic shock was diagnosed based on the Third International Consensus Definitions for Sepsis and Septic Shock which included (a) patient with confirmed and suspected source of infection, (b) 2 points on SOFA score, (c) lactate > 2 mmol/L, and (d) need for a vasopressor to maintain mean arterial blood pressure ≥ 65 for at least two hours at the time of enrollment (Singer et al., 2016; Vincent et al., 1996). Participants were randomly assigned 1:1 to the AHT group and H group. Besides the treatment protocol for septic shock, participants in the AHT group received ascorbic acid, hydrocortisone, and thiamine, and the H group was given hydrocortisone alone (Fujii et al., 2020).

8.4. Outcomes

The study's primary outcome was vasopressor-free time and reduced mortality rate at day seven after participants were randomized. Secondary outcomes included mortality rates measured at 28-day, 90-day, during intensive care unit, and hospital stay. Other variables for secondary outcomes were 28-day cumulative vasopressor-free days, ventilator-free days, and renal replacement therapy-free days, improvement of SOFA score at day 3, and reduced intensive care unit and hospital length of stay.

8.5. Results

A total of 211 participants were randomized into the intervention (AHT) group (100) and H group (104) from 10 intensive units in Australia, Brazil, and New Zealand (Fujii et al., 2020). Fujii et al. (2020) indicated no significant difference between the intervention (AHT) group and the H group in vasopressor free time and reducing mortality rate day 7 after randomization (p =0.83).

For secondary outcomes, there was no significant difference between the ATH group and the H group in all-cause mortality at 28 days (p = 0.69) and 90 days (p = 0.51). Also, Fujii et al. (2020) found no significant difference in 28-day cumulative vasopressor time (p = 0.66), mechanical ventilator time (p = 0.73), and renal replacement therapy time (p = 0.73) between the ATH group and the H group.

8.6. Adverse Events

No serious adverse events were noticed with the intervention under investigation. One participant developed gastrointestinal bleeding in the H group, and two participants in the ATH group were reported to have volume overload and hyperglycemia.

8.7. Limitations

According to Fujii et al. (2020), one of the significant limitations of the study was that it was open-label and did not entail masked outcome assessment. The level of thiamine was not measured in the blood of participants in the intervention group. The sample size was small (211).

9. Evaluating the Effects of Hydrocortisone, Ascorbic Acid, and Thiamine in Septic Shock Patients

9.1. Objective

Mohamed et al. (2023) aimed to assess the effects of hydrocortisone, ascorbic acid, and thiamine on the mortality of septic shock patients.

9.2. Study Design

The study compared the effects of ascorbic acid (1.5 gram), hydrocortisone (50 mg), and thiamine (200 mg) combined with standard treatment versus standard treatment with hydrocortisone alone in a multicenter, randomized, open-label, two-arm parallel-group, pragmatic trial.

9.3. Population

Participants of the study were patients older than 18 with a diagnosis of septic shock that required vasopressor to maintain the mean arterial blood pressure >65 and had lactate level of more than 2mmol/L with adequate volume resuscitation **(**Mohamed et al., 2023).

9.4. Outcome

The primary outcome was to assess mortality at 60 days or the time of hospital discharge, whichever came first. The secondary outcomes included SOFA score, time to death, vasopressor free time, and length of stay in the hospital and intensive unit.

9.5. Results

One hundred six participants were randomly assigned 1:1 to the hydrocortisone group (H) and ascorbic acid, hydrocortisone, and thiamine intervention (AHT) group (53). Participants in both groups had similar diagnostic

characteristics at baseline. The primary sources of infections were pulmonary 35.8%, intra-abdominal 27.4%, and urinary 17.9%.

9.6. Primary outcome

There was no statistical difference between the hydrocortisone-only group (H) and the intervention (AHT) group for hospital mortality at the time of discharge or at 60 days (p = 0.41). Moreover, no statistically significant difference was determined in vasopressor free time (p = 0.44), mechanical ventilator duration (p = 0.36), SOFA score at 72 hours (p = 0.16), and intensive unit stay (p = 0.83) (Mohamed et al., 2023).

9.7. Limitation

The study had multiple limitations: it was open-label, small sample size, and was terminated early due to funding issues.

10. Effects of ascorbic acid, thiamine, and glucocorticoids in Sepsis Patients

10.1. Objective

Iglesias et al. (2020) aimed to assess the effects of hydrocortisone, ascorbic acid, and thiamine on the clinical outcomes of septic shock and sepsis patients.

10.2. Study Design

Iglesias et al. (2020) conducted a randomized, double-blinded trial to determine the effects of ascorbic , hydrocortisone, and thiamine in addition to standard septic shock and sepsis treatment. Participants of the study were adults (18 years of age) who were diagnosed with septic shock and sepsis according to the 2016 Surviving Sepsis Campaign criteria (Rhodes et al., 2017).

10.3. Outcomes

The study's primary outcome was improvement in the SOFA score and septic shock resolution.

10.4. Results

Iglesias et al. (2020) randomly assigned 69 participants to the intervention group and 68 to the comparator group. Participants in both groups at baseline had similar socio-demographic and diagnostic characteristics, SOFA scores, laboratory values, and comorbid conditions. The primary sources of infections were pulmonary 43%, urinary system 31%, bacteremia 14%, and abdominal and other 12%. Also, at the time of enrollment, 50% of the total enrolled participants were on mechanical ventilators and 75% on vasopressors.

Iglesias et al. (2020) found a significant difference between the intervention group and the comparator group for the resolution of septic shock ($p < 0.001$). However, they found no significant change in the SOFA score (p = 0.18). Moreover, Iglesias et al. (2020) indicated that there was no significant difference in the secondary outcomes of intensive unit mortality (p = 0.37) and hospital mortality (p= 0.65).

10.5. Adverse Events

No serious adverse events related to study intervention were reported. One participant with chronic pulmonary obstructive disease hypoxia worsened, and the adverse events committee indicated that it was secondary to the pulmonary condition and was not related to the study intervention.

10.6. Limitation

The number of participants in the study was small and primarily white/Caucasian, which is considered a relative weakness of the study.

11. Discussion

11.1. Ventilator and Vasopressor

Multiple studies investigated the effects of ascorbic acid (vitamin C), thiamine, and hydrocortisone (ATH) with standard sepsis treatment. Sevransky et al. (2021) found no significant effects of ATH on ventilator and vasopressor-free days ($p = 0.85$). Also, Luy et al. (2022) indicated no significant difference in shock reversal time ($p = 0.30$) with the addition of ATH to the standard septic shock treatment. However, Moskowitz et al. (2020) indicated that septic shock-free days (number of days in which the patient was alive and needed < 6 hours of any vasopressors) were significantly improved by adding ATH to the standard septic shock treatment ($p <0.0$). Iglesias et al. (2020) found a resolution of septic shock with the addition of ATH to septic shock standard treatment ($p < 0.001$).

11.2. ATH and SOFA Score

Moskowitz et al. (2020) found no statically significant improvement in the SOFA score (95% CI, -1.7 to 0.2; $p = 0.12$) over 72 hours after adding ATH to septic shock treatment. Mohamed et al. (2023) ($p = 0.16$) and Iglesias et al. (2020) ($p = 0.18$) noted no improvement in the SOFA score at 72 hours after adding ATH to standard septic shock treatment.

11.3. ATH Effects on Inpatient Length of Stay and Mortality

Several studies indicated that the addition of ATH to the standard treatment of sepsis and septic shock did not significantly decrease the intensive care unit and hospital length of stay (Lyu et al., 2022; Moskowitz et al., 2020; Sevransky et al., 2021). Furthermore, there was no significant reduction in the 28-day mortality, 90-day mortality, and 60-day mortality rates ((Fujii et al., 2020; Hussein et al., 2021; Lyu et al., 2022; Mohamed et al., 2023).

12. Recommendations

Based on the conflicting findings in the reviewed trials, it is hard to determine and recommend regular use of ATH in combination with the standard treatment of sepsis and septic shock with the intention that it will improve patient outcomes. More studies in this field might explain if ATH can reduce mortality and morbidity in sepsis and septic shock patients. We recommend that future studies measure the vitamin C level in participants' blood and adjust the dosage of vitamin C to note any improvements or resolution in symptoms and changes in patient outcomes. Furthermore, sepsis and septic shock can be caused by different infectious sources in the human body. It might be more helpful to study if ATH has positive effects on patient outcomes in relation to specific sources of infections. Using this systematic review as a foundation, further application to treatments for sepsis and septic shock needs be investigated.

13. Conclusion

Sepsis and septic shock are common pathways to higher rates of mortality and morbidity. According to the recently reported data, Approximately 20% of deaths are caused by sepsis globally, with a higher financial burden on already stressed healthcare systems. A systematic review of 8 studies was conducted on studies involving the use of vitamin C/ascorbic acid, thiamine, and hydrocortisone in sepsis and septic shock patients. The authors of the clinical trials found no strong evidence for the regular use of vitamin ascorbic acid, thiamine, and hydrocortisone in sepsis and septic patients. So far, study results have conflicting findings, and more studies in the field might provide more information on the effects of ascorbic acid, thiamine, and hydrocortisone in sepsis and septic patients.

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Practice Related to Ergonomics: A Cross-Sectional Study Among Dentists Practicing in the Private Sector

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Abstract
Context: Musculoskeletal disorders affect 100% of dentists practicing in the city of Agadir, Morocco and the association between the development of these disorders and the inappropriate working posture adopted by the dental professional is confirmed in the literature. Aims: The aim of the present study is to assess the knowledge and practices toward ergonomics among dentists working in the private sector in the city of Agadir. Methods and Material: A cross-sectional study was conducted among dentists in the city of Agadir, by using an anonymous questionnaire after informed consent. Statistical analysis used: For the Data entry and statistical analysis, we used SPSS software at the Community Health, Epidemiology and Biostatistics Laboratory of the faculty of dentistry of Casablanca. Results: The respect for the eight rules of working posture is incorrect. It does not exceed 50% for back posture, 21.4% for hands and forearms posture and 31.1% for leg posture. Correct arm posture is the least respected (18.9%). For the participants, the main factors preventing compliance with ergonomic posture are the difficulty of the surgical procedures (73%), time (53.9%) and unsuitable equipment (28.6%). Conclusions: To prevent the observed shortcomings, we propose the integration of work ergonomics into continuing education cycles providing frequent reminders for dentist and dental students. Comparative studies using the same protocol in other cities in our country can be conducted and additional observational studies assessing posture using RULA/REBA, or motion recording sensors should be carried out.

Keywords: Dentist, Ergonomics, Working posture, Musculoskeletal Disorders

1. Introduction

The dental profession is widely affected by musculoskeletal disorders (MSDs), which cause pain in different parts of the body (Bonanni, 2022; Brown, 2010; Chenna, 2022). In a study conducted by Altaş and al, 54% to 93% of the dentists suffered from MSDs due to their practice (Altaş, 2022). In 2023, we carried out a study among dentists working in the private sector in Agadir, Morocco. The results showed that 100% of dentists reported at least one musculoskeletal complaint. 57.5% of our study population reported a change in work frequency as the main consequence of their MSDs (Brown, 2010).

Several factors may lead or contribute to the appearance of MSDs, such as psychological stress, lack of physical activity, pathological changes in the musculoskeletal system (Pope-Ford, 2020; Valachi, 1939). Numerous studies have highlighted the correlation between poor working postures adopted by dentists and MSDs (Pope-Ford, 2020; Custódio, 2012; Benkiran, 2018; Sakzewski, 2014). Various parameters can influence working posture, including

workplace equipment, choice of instruments, practices, patient positioning, lighting conditions (Pîrvu, 2014; Dable, 2014).

Due to these constraints related to the nature of the dental work, ergonomics has received particular attention. The principles of ergonomics play an important role in the organization of all medical fields including dentistry. Ergonomics was introduced to improve working conditions in the dental practice (Dable, 2014). It is focused on various concept, such as the working posture of dentists, the position of their patients, the arrangement and the way of using instruments, the organization of the working environment and the impact of all of these factors on the dentist's health. It therefore acts by reorganizing interventions and procedures for maximum comfort and safety in in the workplace, limiting and simplifying movements, and rationally using the available surface area (Valachi, 2003). In ergonomics, working posture is the way in which different parts of the body are positioned, establishing relationships between them that enable the execution of a specific task. In dentistry, the working posture is represented by the spatial arrangement of the dentist's body around the patient (De Sio, 2018). There is currently a growing demand for ergonomic studies assessing dentists' knowledge of ergonomic work posture and comparing this with the reality of their daily practice in order to better understand their suffering (Pîrvu, 2014; Dable, 2014; Valachi, 2003; De Sio, 2018). Our aim in this study is to evaluate the knowledge and practices in terms of ergonomics among dentists practicing in the private sector in the city of Agadir.

2. Subjects and Methods

To meet our objective, we conducted a descriptive cross-sectional study between May 2022 and January 2023 in the city of Agadir, Morroco. permission to participate in the study was obtained from each dentist prior to data collection.

The list of dentists practicing in the private sector in the city of Agadir was obtained by contacting the National Dental Council by email. The list included the names, addresses and telephone numbers of the 234 dentists in the city. The same eligibility criteria applied in the first part of the work were used in this study to select participants (Benfaida, 2024). As in the previous study, participants registered with the National Dental Association and accepting to participate in the survey were selected. A total of 234 dentists were selected, of which 57.3% were female and 42.7% were male. All age groups were represented. The average age of dentists was 38.96 years (+/- 10.5). Practitioners under 35 represented 43.2% of our population.

Data were collected using a questionnaire comprised 19 closed questions relating to dentists' knowledge and practices in terms of dental ergonomics. The questionnaire was developed using data from the literature. The anonymous questionnaire took around 10 minutes to complete.

The questionnaires were distributed and collected by visiting dental offices. Practitioners were given one to two weeks to complete the questionnaire. The names of practitioners who returned questionnaires were progressively deducted from a pre-established list of all the city's practitioners, in order to ensure proper follow-up of responses. Results were compiled and statistically analyzed using SPSS software at the Epidemiology and Research Laboratory of the Faculty of Dentistry, Casablanca.

3. Results

Of the 234 participants, 206 responded. The results of the study concerning ergonomics and its application in dental practices were obtained. The results show that dentists do not correctly respect working posture. The most affected regions by musculoskeletal disorders in our previous work are the same areas whose posture is not respected by the participants. Only the posture of the feet was respected by 74.8% of participants, while the posture of the remaining limbs doesn't exceed 50% for the back, 18.9% for the arms, 21.4% for the hands and forearms, 27.2% for the knees and 31.1% for the legs. 84.5% of dentists report having enough space in the treatment room to work ergonomically. 48.5% of dentists sometimes adjust the position of the stool and 44.2% have invested in an ergonomic stool. 79.6% of participants "Always" adjust the position of the patient chair before the treatment. (Table 1).

Other ergonomic errors related to the instrument tray organization, the use of indirect vision, operating lights, optical aids or magnification accessories and operating aids were noticed (Tables 2,3,4,5 and 6):

Table 1: Ergonomics of the treatment room

	Percentage(%)
The surface area of the room allows you to work ergonomically	
- Yes	84.5
- No	15.5
Adjusting the dental stool before working	
- Always	39.3
- Sometimes	48.5
- Never	12.2
Possession of an ergonomic stool	
- Yes	44.2
- No	55.8
Adjustment of the chair position according to the procedure to be performed	
- Always	79.6
- Sometimes	20.4
- Never	0

Table 2: Results for the organization of the worktray

	Percentage(%)
Checking the tray before starting treatment	
- Always	73.3
- Sometimes	18.9
- Never	7.8
Instruments placed within easy reach	
- Always	64.1
- Sometimes	34
- Never	1.9
Instruments organized during care sessions	
- Always	51.9
- Sometimes	41.8
- Never	6.3
Moving to get instruments during care sessions	
- Always	7.2
- Sometimes	68
- Never	24.8

Table 3: Results for indirect vision, luminosity and optical aids

	Percent (%)
Working with indirect vision	
- Always	24.3
- Sometimes	68.9
- Never	6.8
Reasons preventing working with indirect vision	
- Concern for doing well	66.2
- Difficulty	36.6
- Lack of know-how	11.5
- Fogging on the mirror	2.9
Adjustment of brightness intensity according to dental sectors	
- Always	57.8
- Sometimes	29.1
- Never	13.1
Possession of optical aids or magnification accessories	
- Yes	64.6
- No	35.4

Table 4: Results for operating aids

	Percent (%)
Working with a dental assistant	
- Absolutely necessary	82.5
- Moderately necessary.	17
- Not at all necessary	0.5
- Always necessary	84
- Sometimes	15.5
- Never	0.5

Table 5: Results for pauses between patients and stretching exercises

	Percent (%)
Taking breaks between patients (N=206)	
- Always	18.4
- Sometimes	67.5
- Never	14.1
Length of breaks (N=177)	
- 2 minutes	11.9
- 3 minutes	9
- 5 minutes	56
- 10 minutes	20.9
- 15 minutes	2.2
Performance of stretching exercises between patients (N=206)	
- Always	3.9

- Sometimes	43.2
- Never	52.9

Table 6: Results for factors preventing compliance with ergonomic rules

Variables	Percent (%)
Difficulty of surgical procedures	73
Time	53.9
Unsuitable equipment	28.6
Lack of patient cooperation	11.7
Lack of assistant competence	2.5

4. Discussion

We conducted a cross sectional study in Agadir city in order to assess the ergonomics practices. During data collection, we were confronted with a number of difficulties, such as the absence of certain dentists, the refusal to participate in the study, and the reluctance to share certain personal information. We must also take into account when interpreting the results of dentists' subjective assessment of work posture, since the ergonomic data were reported by dentists using closed-ended questions. Despite these difficulties and limitations, our work presents certain strengths, namely, an exhaustive survey of the city of Agadir with 88.04% as participation rate. The questionnaire we used in this survey represents a synthesis of the various proposals in the literature. The questions used were validated in the literature, and we added other sections to ensure the most complete version possible of the questionnaire.

In a previous study on the same population, we found that 100% of dentists in Agadir reported at least one musculoskeletal complaint (Benfaida, 2024). In the same study, we showed that the presence of musculoskeletal pain in our population could be explained by several factors, including obesity, physical inactivity, type of professional activity and number of years of dental practice. In this work, our objective was to assess practical ergonomic knowledge in the same population. The results of our survey highlighted a number of shortcomings that explain the prevalence of MSDs found:

For the surface area of the treatment room, the rules of ergonomic posture according to Custódio are rarely respected in small treatment rooms (Custódio, 2012). Benkirane et al have shown that the surface area of a treatment room without a desk should be a minimum of 9 square meters, with the ideal being 12 square meters. If the room includes an office, the minimum surface area is 12 square meters, and the optimum 15 square meters (Benkiran, 2018). 84.5% of dentists in our study replied that they had enough space to work ergonomically, we weren't able to investigate all the treatment rooms in the dental offices to be sure of the surface area.

For the dental stool adjustment, only 39.3% always adjust the position of the stool, and only 44.2% have invested in an ergonomic stool. The correct use of an ergonomic stool makes a major contribution to the adoption of a balanced posture (Sakzewski, 2014). The height adjustment of the stool is necessary for the correct orientation of the lower limbs. If the stool is too high, the dentist's weight is poorly distributed, tilting towards the edge of the seat. As a result, dentist's back loses contact with the back of the stool, and there is a risk of loss of balance and slipping. On the other hand, too low stool adjustment reduces the natural lumbar curvature of the spine due to posterior rotation of the pelvic region (Pîrvu, 2014). A stool with a horizontal seat can cause posterior rotation of the pelvic region and a reduction in lumbar curvature. In addition, the horizontal base is wide with hard edges, which can lead to compression of the thighs and disruption of blood circulation. A saddle seat, or a seat inclined within a range of 5° to 15° to prevent slippage, avoids these phenomena by positioning the trunk and thighs at an angle greater than 90°. They also allow closer proximity to the patient and therefore better visibility (Pîrvu, 2014). A study carried out in India on 90 dental students showed that students suffering from musculoskeletal pain reported an improvement in their symptoms after 3 months' use of horse-saddle stools (Dable, 2014). Back support is considered to be essential to avoid muscle fatigue and reduce lumbar curvature during long procedures (Valachi, 2003). Another study demonstrated that back support does not influence the postural behavior of dentists

(Dable,2014). For long clinical procedures, the manual support of the stool can prevent back pain and increased tension in the shoulders and neck. However, stools with this type of support are often avoided by practitioners, as they take up more space and restrict the doctor's movements (Pîrvu, 2014).

Several authors highlight the importance of the adjusting of the dental patient chair (De Sio, 2018; Hill, 1986; Kroemer,1986). Kroemer and Hill have shown that when the back and head are straight, the preferred downward angle of vision is 29° to the horizontal. Postural muscle fatigue occurs when this angle reaches 45° or more. The higher the patient's height, while respecting the minimum eye-to-object distance, the more the practitioner will raise the head, thus avoiding flexion of the spine (Hill, 1986; Kroemer, 1986).

Instruments should be positioned correctly. Ideally, if the dentists want to search an instrument, he should only move his arm horizontally or vertically, without compromising the balanced posture. The further apart the instruments are, the more extreme the movements required to grip them. The most frequently used instruments should therefore be positioned close to the practitioner (Pîrvu, 2014; HAMEL, 2013). Araùjo et al. conducted a study of dental students in Maranhão, Brazil and found that 77.3% of students kept instruments close to their hands during work (Custódio, 2012).
For the compliance with ergonomic posture rules, the dentists' self-assessment of their own posture revealed several postural errors:

- Back posture: The back should be straight with respect for body symmetry to avoid C-rounding of the spine. Only 50% of participants keep their backs straight. In Poland, the spinal alignment of 40 female dentists was examined using a SonoSens ultrasonic measurement system. The results found that all subjects exceeded the norms in various segments of the spine. A correlation was observed between the severity of the dentists' back pain and the values of parameters assessed in the frontal plane of the lumbar section and the transverse plane of the thoracic and lumbar sections (Nowotny-Czupryna, 2018). A similar study in the Netherlands assessing the posture of 1,250 dentists showed that 89% adopted a forward-flexing posture exceeding the accepted postural limits of 20°-25° (Santana Sampaio, 2021). Araùjo et al. showed that only 52.3% of dental students in Maranhaõ, Brazil, maintain a straight back during treatment (Araújo, 2021). A similar study carried out among students and interns at the Faculty of Dentistry in Bhopal, India, showed that 70.5% put themselves in a cervical flexion position to gain better visibility (Munaga, 2013).
- Arm posture: The arms should be positioned 10 cm from the body. Only 18.9% respected this postural rule. A study of 5th year dental students in Casablanca showed that 25% respected this ergonomic rule (Benkiran, 2016).
- Hand and forearm posture: forearms should be perpendicular to the arms, and hands should be in line with the arms. Only 21.4% comply with these two postural rules. Dentists are most affected by disorders of the hand and wrist, the pain engendered can result from numerous musculoskeletal disorders, principally carpal tunnel syndrome (Gupta, 2013). The polyarticular muscles of the forearm respond to the tenodesis effect. This effect creates an extension of the fingers when the wrist is flexed, and vice versa. This tenodesis effect is a risk factor for rheumatological pathologies of the forearm, wrist and hand. When the hand is not in line with the forearm, and the wrist is flexed, this creates difficulty in holding instruments correctly, and requires much greater effort from the finger flexor muscles (HAMEL, 2012).
- The distance between the practitioner's eyes and the patient: The eyes must be located 50 cm from the oral cavity. The minimum distance between the patient's mouth and the practitioner's eyes is 25cm for a normal eye. Below this distance, the precision of vision decreases (HAMEL, 2012). In our study, 28.2% of dentists complied with this rule. In Maranhão, Brazil, a similar study showed that 61.4% of students positioned their eyes at approximately 25cm from the oral cavity and 38.6% at approximately 40cm (Munaga, 2013). In the literature, the main errors confirmed are extreme forward tilting of the head and over-stretched neck, tilting and rotation of the trunk to one side, raising one or both shoulders and adopting an increased curvature of the thoracic spine (De Sio, 2018).

For the indirect vision only 24.3% of dentists "always" use indirect vision. A study among dental students and interns in Bhopal, India, showed that 76.6% prefer working with direct vision (Munaga, 2013). Nachemson has shown that when the dentist leans forward by flexing the trunk, this causes increased intradiscal pressure on the discs. The 3rd or 4th lumbar disc has to bear a weight of 180 to 230 kg in this position. It is therefore essential to avoid leaning forward to work, for example, with direct vision of the maxillary teeth. For the operating lights, 57.8% of dentists adjust it according to the dental sector concerned. The intensity ratio between operating room lighting and general treatment room lighting should be between 3 and 1.6 (Partido, 2020). The scialytic should be oriented in such a way that the light beam is parallel to the direction of observation, thus maintaining shadow-free illumination with a good distance between the light and the patient's mouth (Munaga, 2013). The use of corrective glasses and magnification accessories such as magnifying glasses or microscopes helps prevent excessive torsion and tilting of the dentist's head (Pîrvu, 2014). 64.6% of dentists in Agadir have invested in it. Microscopes have the advantage of reducing working distance, and above all, their angulation reduces flexion of the spine, enabling the dentist to maintain a comfortable eye position (HAMEL, 2012).

For operating assistants, 84% were "always" helped by an assistant during treatment. In Poland, a study conducted by Kierklo et al. showed that only 63.6% of dentists work without a dental assistant (Kierklo,2011). The dental assistant plays an important role in reducing the practitioner's repetitive movements and improving posture (De Sio,2018). Dentists need to get used to working with a dental assistant from their clinical training years onwards.

Dentists must take breaks between dental treatments. In our population, only 67.5% of the dentists took "Sometimes" breaks between patients and 54.2% estimated 5 min as a maximal duration of breaks. Kierklo et al. found that among 220 Polish dentists, only 8% took a break after each patient. 36.4% were satisfied with just one break during the working day (Kierklo, 2011).

Performing stretching exercises after each treatment session and at the end of the working day has been described as the most effective measure for preventing musculoskeletal disorders. 52.9% of the dentists in our study "never" did stretching exercises during their breaks. It is well known that the prolonged static posture adopted by dentists during treatment requires the contraction of 50% of the body's muscles. To reduce this muscular tension, slow, gentle, pain-free stretching exercises for a minimum of 15 to 30 seconds, were recommend 2 to 3 times a day (De Sio, 2018).

Concerned the factors preventing the participants from complying with ergonomic rules, we found that the main obstacles were: difficulty of operating procedures (73%), time (53.9%) and unsuitable equipment (28.6%). A similar study among the 5th-year dental students at the Casablanca Faculty of Dentistry showed that the main factors preventing students from complying with ergonomic rules were time (69.4%), unsuitable equipment (67.6%) and the difficulty of surgical procedures (42.6%) (Benkiran,2016). The continuing dental education programs treating dental ergonomics are mandatory to motivate dentists to follow ergonomic rules. Mohan Kumar P et al. conducted a comparative study among dental students in three different dental schools and found that the knowledge and practice scores of dental students were increased after applying ergonomic-related instructions than before in all the three different colleges of all the year students (Munaga, 2013).

The results of our study confirmed that there is a strong correlation between the musculoskeletal disorders observed in our population and the deficiencies observed namely:

- Failures in the organization of the work-space (the adjust of the stool, the operating lights, dental instruments tray…)
- Failure to respect back posture, position of arms, hands and forearms and lower limbs, distance between practitioner's eyes and patient
- The non-use of indirect vision
- Lack of investment in ergonomic equipment such as stools and optical aids...
- Continuous work without taking breaks between dental treatments

5. Conclusion and future perspectives

Our study has shown that compliance with the various ergonomic posture rules among dentists in the private sector in the city of Agadir is deficient. This result explains the alarming rate of practitioners reporting at least one musculoskeletal complaint. To prevent the observed shortcomings, we propose:

- To integrate of work ergonomics into continuing education cycles to raise dentists' awareness of the impact of ergonomics on career longevity and dental office productivity.
- To provide frequent reminders on work ergonomics and in particular work posture for dental students during their clinical training years by planning seminars and round tables discussions.
- To conduct observational studies in order to assess the posture's errors of dentists more accurately using RULA/REBA charts filled in by researchers, or by taking photos/videos or using motion recording sensors to identify errors more accurately.
- To conduct studies to better understand the role of professional activity and the layout of the dental practice in the development of MSDs.
- To conduct comparative studies using the same protocol in other cities in our country, as well as in the student population of the Faculty of Dentistry.

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Reduced Costs of Managing Adverse Reactions with DT3aP-HBV-IPV/Hib Versus DT2aP-HBV-IPV-Hib in Vietnam: Results of a Cross-Sectional Survey and Mathematical Projections of Vaccination of Infants

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Abstract
In Vietnam, hexavalent vaccines are routinely given during early childhood. Hexavalent vaccines DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib differ in composition and therefore, reactogenicity, with DT3aP-HBV-IPV/Hib shown to cause fewer adverse reactions (ARs) than DT2aP-HBV-IPV-Hib. Online surveys for physicians and parents/caregivers who manage post-vaccination ARs in children were used to explore AR management in the Vietnamese private healthcare setting. Survey data were used to estimate healthcare resource utilization (HCRU) and its associated costs, and indirect costs to parents/caregivers. A mathematical projection tool used survey results to approximate the difference in costs associated with post-vaccination childhood AR management following primary doses of DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib. Parent/caregiver attitudes towards childhood vaccination in relation to management of ARs in their children were also explored. Around a third of parents/caregivers in Vietnam reported that their child experienced post-vaccination AR(s), the management of which led to significant HCRU and indirect costs to parents/caregivers. A primary dose of DT3aP-HBV-IPV/Hib compared with DT2aP-HBV-IPV-Hib led to 420 985 fewer ARs in Vietnam. Subsequently, HCRU burden and associated direct costs were reduced by ~11% and indirect costs to parents/caregivers were reduced by 14%. Parents/caregivers reported indirect costs of ~3 million VND per parent/caregiver per AR to manage ARs in their children. Additionally, parents/caregivers reported notable emotional concerns over ARs of rashes, diarrhea, and fever. However, despite costs and emotional burdens, most parents/caregivers did not express hesitancy toward future vaccinations. The substantial financial benefits of a vaccine with fewer ARs should be considered from a cost effectiveness perspective by decision-makers when evaluating vaccine alternatives.

Keywords: Acellular Pertussis, Adverse Reactions, Childhood Vaccination, Healthcare Resource Utilization, Hexavalent Vaccine, Vaccine Costs, Vaccine Hesitancy

1. Introduction

In Vietnam, childhood immunization has proven to be cost-effective and highly successful in the prevention of infectious diseases, compared with late-stage interventions (Jit et al., 2015). The World Health Organization's (WHO) Expanded Programme on Immunization (EPI), initiated in 1981, substantially reduced the occurrence of vaccine preventable diseases and their rates of mortality (Nguyen et al., 2015). In 2009, Vietnamese national coverage of vaccines included in the EPI reached an average of 95% in infants under one year of age. However, a Vietnamese cluster survey identified that this coverage varied significantly between vaccines included in the program (diphtheria, tetanus toxoid, hepatitis B, polio, measles, and tuberculosis vaccines), with birth dose hepatitis B coverage as low as 20.6% in 2009 (Nguyen et al., 2015).

Multivalent vaccines may increase vaccination uptake by simplifying vaccination schedules (Özen et al., 2024). Childhood vaccinations against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and Hemophilus influenzae type B are often administered together as a hexavalent vaccine worldwide. Currently, there are two hexavalent vaccines containing acellular pertussis licensed for childhood vaccination in the Vietnamese private healthcare setting; DT3aP-HBV-IPV/Hib was licensed in 2006, and DT2aP-HBV-IPV-Hib was licensed in 2018 ("European Medicines Agency 2021a. Hexaxim," ; "European Medicines Agency 2021b. Infanrix Hexa,"). For hexavalent vaccines containing acellular pertussis, the WHO recommends three doses starting at 6 or 8 weeks with 4-week intervals, and a booster dose 6 months after the final dose (*WHO Recommendations for Routine Immunization*, 2024). DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib differ in formulation and antigen constitution, and therefore have different reactogenicity profiles (Knuf et al., 2021).

An open-label study in 2019 evaluating the safety of three early childhood doses of a DT2aP-HBV-IPV-Hib vaccine, found that the hexavalent vaccine was well-tolerated in Vietnamese infants with no safety signals (Vu et al., 2019). The safety profile of a primary early childhood dose of DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib was later compared via a systematic review and meta-analysis of head-to-head randomized controlled trials (RCT) (Mukherjee et al., 2021). The odds ratios of experiencing an adverse reaction (AR) were lower with DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib, varying from 0.67 to 0.96 across the local and systemic ARs analyzed (Mukherjee et al., 2021). In a follow-on analysis, a mathematical projection tool was developed to simulate vaccination of infants with these two hexavalent vaccines in six European countries (George et al., 2023). The absolute risk reduction (ARR) of local or systemic childhood ARs with DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib ranged from 3.0 (95% confidence interval [CI]: 2.8%–3.2%) to 10.0% (95% CI: 9.5%–10.5%) across the ARs analyzed. The study estimated that in 2020, vaccination with DT3aP-HBV-IPV/Hib led to fewer childhood ARs compared with DT2aP-HBV-IPV-Hib, ranging from ~31 000 to >269 000 fewer cases per country (George et al., 2023). Similar results were found when the tool was applied to four countries in Southeast Asia. In 2023, between 80 000 and ~280 000 fewer ARs were estimated with use of one dose of DT3aP-HBV-IPV/Hib over DT2aP-HBV-IPV-Hib across assessed countries (Mohy et al., 2024). These studies highlight the country-level impact of utilizing vaccines with fewer ARs, and the importance of reactogenicity as well as efficacy, when evaluating vaccines.

The management of post-vaccination childhood ARs incurs substantial healthcare resource utilization (HCRU) and associated direct medical costs (Liu et al., 2024). In addition to the burden of post-vaccination ARs on healthcare systems, further hidden costs are also incurred by parents/caregivers when managing post-vaccination ARs experienced by their child. Indeed, a US cross-sectional survey of parents/caregivers of children who received co-administered vaccines, reported an average total of 42 United States Dollars (USD) for medical and treatment costs, and 192 USD for work absenteeism per AR case (Lieu et al., 2000). Despite these costs, childhood vaccines remain a cost-effective intervention. An evaluation of the economic impact of routine childhood immunization over one year (2009) estimated a reduction of ~55.3 billion USD to societal costs, which included administration, parent travel, and absenteeism, compared with no vaccination interventions in the US (Zhou et al., 2014).

Parent/caregiver vaccine hesitancy may be expected to increase if their child experiences a post-vaccination AR (Brown et al., 2010), especially with hexavalent vaccines administered during infancy as these vaccines contain multiple antigens. A recent cross-sectional survey predicted that 8.9% of parents in Vietnam were hesitant towards

childhood vaccination, with hesitancy related to unemployment and exposure to news reporting ARs following vaccinations (Truong et al., 2024). Furthermore, only a third of Vietnamese parents reported vaccinating their child on schedule (Truong et al., 2024). Utilizing vaccines with proven safety profiles is important to improve infant vaccination compliance in Vietnam.

In this study, a survey was completed by physicians who manage post-vaccination ARs in early childhood to assess typical AR management and HCRU in the real-world private healthcare setting in Vietnam. A second survey targeted at parents/caregivers of children who had received an early childhood vaccination was used to estimate the indirect costs incurred by parents/caregivers when managing any ARs their child experienced post-vaccination. With these data, a mathematical projection tool estimated and compared the incidence and associated costs to manage ARs following an early childhood dose of DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib in Vietnam in 2023.

An additional objective was to report the emotional impact of ARs following early childhood vaccination, and the impact of these ARs on parent/caregiver attitudes towards future childhood vaccinations in Vietnam.

2. Methods

2.1. Overall Survey Design

Physicians that manage ARs associated with an early childhood, single-dose vaccination, and parents/caregivers of children who have received a dose of an early childhood vaccination were recruited from existing panels in Vietnam by third-party agencies: Medefield for physicians, and Dynata for parents/caregivers. Eligible participants received the survey link via email. Surveys were completed between 27th July – 31st August 2023, and 5th – 14th July 2023 by physicians and parents/caregivers, respectively.

Physicians based their responses on their caseload of early childhood vaccinations (received at aged 0–14 months) over the past 3 months (recall only). The physician survey aimed to capture physician demographics and the typical management of ARs associated with early childhood vaccination. Responses were used to estimate the HCRU of healthcare professionals (HCPs) visits, treatments prescribed, tests/assessments conducted, and hospitalizations.

Parents/caregivers based their responses on the most recent vaccine administered to their child (aged 0–14 months) within the past 4 months, excluding any received within the 2 weeks prior to survey completion. The parent/caregiver survey aimed to capture child and parent/caregiver demographics, and to estimate the indirect costs incurred in HCP visits, out-of-pocket prescribed treatments, absenteeism and lost earnings, travel and parking expenses, and childcare to manage ARs in their child. Parents/caregivers also completed questions to assess the emotional impact of managing post-vaccination ARs, and their attitudes towards future vaccinations. A seven-point Likert scale was administered for each AR of interest (1: No concern at all – 7: High level of concern), where scores ≥5 were considered concerning.

This survey examined 11 specific ARs: injection site pain, injection site redness, injection site swelling, fever, drowsiness, irritability, persistent crying, loss of appetite, vomiting, diarrhea, and rash.

Vaccines in scope of the survey had to be injectable, recommended up to 12 months of age, and administered in Vietnam in the private healthcare setting or as part of the national funded program: hepatitis A, B or AB combined, Bacillus Calmette-Guérin, inactivated polio, combined pentavalent/hexavalent (diphtheria, tetanus, polio, pertussis, Hemophilus influenza type B, and hepatitis B), pneumococcal conjugate, meningitis B or C, varicella, measles, the combined measles, mumps and rubella, meningococcal ACWY conjugate, influenza, and the Japanese encephalitis inactivated vaccine.

2.2. Study Population

To be eligible, the physicians were required to consent; to be fully qualified general practitioners (GPs), primary care physicians (PCPs), or preventative medicine specialists who manage ARs following primary childhood vaccination; to have practiced for at least 3 years, and to manage at least ten cases a month (on average in the past 12 months) of children experiencing post-vaccination ARs.

The parents/caregivers were required to consent, be aged at least 18 years at the time of the child's vaccination and to have been responsible for the wellbeing of the child at the time of vaccination and during the 2 weeks that followed. Parents/caregivers of children who were considered immunocompromised, and therefore may follow different vaccination recommendations and/or whose condition may interfere with the level of reactogenicity, were excluded from the study.

2.3. Estimation of Direct Medical Costs to Manage ARs Associated with Vaccination

Physician data were used to estimate the HCRU for HCP visits, treatments prescribed, tests/assessments conducted, and hospitalizations associated with typical management of each post-vaccination AR. Frequency of each HCRU item was multiplied by published Vietnamese unit cost data for the private healthcare sector to estimate the total cost of each HCRU item. Recent published unitary cost data were collected from literature and official databases by a specialized third-party agency, Weber, and adjusted to account for 2023 inflation levels (**Appendix A1**). Where different published costs were found, the lowest cost was used by default. Costs were calculated in 2023 Vietnamese Dong (VND) and reported as mean cost per case of AR.

2.4. Estimation of Indirect Medical Costs to Manage ARs Associated with Vaccination

Parent/caregiver data were used to estimate the indirect costs incurred from the management of ARs associated with early childhood vaccination. Parents/caregivers were asked to estimate lost employment time, and subsequent losses from household monthly earnings due to absenteeism. Parents/caregivers also estimated the costs of out-of-pocket treatments, childcare, travel, and parking, as well as any other costs for each AR. Costs were calculated in 2023 VND and reported as mean cost per case.

2.5. Costs Comparisons of the Management of ARs with DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib

To compare the cost to manage ARs for each vaccine, the number of individuals vaccinated with at least one dose of DT3aP-HBV-IPV/Hib or DT2aP-HBV-IPV-Hib in the private healthcare setting in Vietnam was estimated, using the 2023 birth cohort and 2022 vaccination coverage (GSK, 2023), (*World Population Prospects 2022: Summary of Results*, 2022).

For each AR, the number of AR cases following a primary dose of DT3aP-HBV-IPV/Hib or DT2aP-HBV-IPV-Hib was calculated by multiplying the total vaccinated population by the proportion of AR cases attributed to one dose of each vaccine (Mukherjee et al., 2021). Subsequent multiplication of the number of AR cases by the proportion of the population that sought medical advice, as reported by the parent/caregiver survey, estimated the number of cases where medical advice was sought for the given AR per vaccine. The number of these cases was then multiplied by the mean HCRU reported for the given AR (HCP visits, treatments prescribed, test/assessments, and hospitalization), as from the physician survey, to estimate the HCRU per vaccine for the given AR. The direct medical costs were then calculated using the published unit cost data from Weber. An example calculation for the direct medical costs of hospitalization to manage fever following a single dose of DT3P-HBV-IPV/Hib is shown in **Equation 1**. The total direct medical costs to manage each post-vaccination AR were calculated by combining the HCP visit, treatments prescribed, tests/assessments conducted, and hospitalization costs. Costs were calculated in 2023 VND and reported as mean cost per case.

1 418 890 (2023 Vietnamese birth cohort) x 69% (vaccination coverage in Vietnam) =
979 034 individuals vaccinated with one dose of DT3P-HBV-IPV/Hib
979 034 x 48% (proportion of DT3P-HBV-IPV/Hib cases leading to fever [Mukherjee et al., 2010]) = 469 936 cases of fever after vaccination with one dose of DT3P-HBV-IPV/Hib
469 936 x 90% (proportion of fever cases with sought medical attention [parent/caregiver survey]) =
422 943 cases of sought medical attention for fever
422 943 x 1.3% (hospitalization rate for fever [physician survey]) =
5 498 cases of hospitalization for fever
5 498 x 3 850 000 VND (unit cost for hospitalization [Weber]) =
21 168 283 697 VND calculated in hospitalization costs to manage fever for the Vietnam 2023 birth cohort following a single dose of DT3P-HBV-IPV/Hib (1)

The same process was used to calculate the indirect costs to parents/caregivers when managing each AR following a childhood dose of DT3aP-HBV-IPV/Hib or DT2aP-HBV-IPV-Hib in Vietnam. Potential reductions in direct and indirect medical costs following one dose of DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib vaccination were calculated by comparing cost estimates for the entire birth cohort from 2023 and per AR. As diarrhea and rash were not analyzed in the RCT review of AR incidence, odds ratios were therefore not calculated (Mukherjee et al., 2021). These two ARs were consequently excluded from the DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib mathematical projection tool. Vomiting was also not included in cost calculations as there were no significant differences in the reported proportions of ARs.

2.6. Statistical Analysis

A descriptive analysis was conducted using the Institute for Business Value (International Business Machines, IBM) Survey Reporter (version 7.5) and Stata (version 17.0). Descriptive statistics were used to summarize the HCRU variables. Specifically for categorical variables: number and frequency, and for numeric/count variables: number, standard deviation, and frequency.

Univariate sensitivity analyses (SA) were performed to assess the costs avoided for all AR types. The AR proportions of DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib were varied based on the 95% CI data from the RCT systematic review and meta-analysis, comparing each vaccine versus the mean of the other vaccine (Mukherjee et al., 2021). A second SA was applied based on an arbitrary variation of 20% applied to the ARRs, as previously described in the mathematical projections of ARs following DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib in six European countries (George et al., 2023).

3. Results

3.1. Demographics

A total of 100 physicians from Vietnam completed the survey and were included in the analysis. Of these, 40 were GPs/PCPs, 59 were pediatric specialists, and one was a preventative medicine specialist. The physicians reported an average caseload of 219 patients per month experiencing ARs associated with early childhood vaccination (primary or booster dose).

A total of 150 parents/caregivers from Vietnam completed the survey and were included in the analysis. On average, the child of the parent/caregiver received their most recent vaccination 3.6 weeks prior to completion of the survey. Most children (43%) were between the ages of 6–9 months at the time of vaccination, 31% were 2–6 months old, 16% of children were <2 months old, and 10% were >9 months old.

3.2. Management of ARs in the Vietnamese Real-World Setting

The majority of parents/caregivers (71%) reported that their child was vaccinated but did not experience an AR. Of those who did experience an AR, 91% of cases caused parents/caregivers to seek medical advice. Fever was

the AR for which medical advice was most often sought, at 90% (n=20 parents/caregivers), followed by the local ARs of injection site pain at 40% (n=20), injection site redness at 33% (n=18), and injection site swelling at 40% (n=15) (**Table 1**).

In terms of HCP visits, pediatricians in Vietnam were most frequently consulted across all ARs examined (50%–71%), except for drowsiness, where 67% of parents/caregivers reported with their child to the emergency room or accident and emergency (A&E) department. For each of the 11 ARs of interest, patient examination was the most common assessment conducted, ranging from 33%–100% of cases, followed by blood tests, and urinalysis (both 0%–33%).

In vaccination cases where parents/caregivers sought medical advice, the physician survey reported that loss of appetite was the AR that most frequently caused hospitalization, with a rate of 1.9% (n=20 physicians). This was followed by a 1.4% (n=14) hospitalization rate for vomiting and 1.3% (n=96) for fever. Injection site pain was the only local AR which resulted in hospitalization, though the rate was low at 0.4% (n=93) (**Table 1**).

Table 1: Type of AR for which Parents/Caregivers Sought Healthcare Advice and Rates of Hospitalization in Vietnam

AR of interest	**Percentage of cases where parents/caregivers sought medical advice, % (n)[a]**	**Percentage of cases where medical advice was sought and which led to hospitalisation, % (n)[b]**
Injection site pain	40 (20)	0.4 (93)
Injection site redness	33 (18)	0.0 (71)
Injection site swelling	40 (15)	0.0 (75)
Fever	90 (20)	1.3 (96)
Drowsiness	0 (6)	0.7 (3)
Irritability	14 (7)	0.0 (32)
Persistent crying	14 (14)	0.1 (20)
Loss of appetite	43 (7)	1.9 (20)
Vomiting	0 (0)	1.4 (14)
Diarrhea	0 (1)	0.1 (38)
Rash	100 (1)	0.5 (42)

Data were based on one dose of a single antigen or combination vaccine. **[a]** Cases reported by parents/caregivers where the child of the parent/caregiver experienced any AR. Data were based on the parent/caregiver survey. **[b]** Calculations based on the cases where the child of the parent/caregiver experienced any AR and medical advice was sought. Data were based on the parent/caregiver and physician survey. **AR**: adverse reaction.

3.3. Physician-Reported Direct Medical Costs to Manage ARs Associated with Childhood Vaccinations

Although few hospitalizations were reported, these cases were the largest contributor to total direct medical costs, of up to 8 900 000 VND per AR across the ARs examined (**Table 2**). Across ARs, HCP visits also significantly contributed to overall costs, and ranged between 621 250 and 1 800 000 VND per AR. Compared to hospitalization and HCP visits, overall treatments and test/assessment costs were minimal, and ranged between 774 and 28 789 and between 2 457 and 81 500 VND, respectively.

When looking at specific AR-related costs, injection site pain incurred high direct medical costs owing to an estimated 8 900 000 VND contribution from hospitalization expenses (n=1 physician). Rash, fever, and persistent crying incurred moderate direct medical costs also due to substantial contributions from hospitalization expenses, which were estimated at 3 550 000 VND (n=1), 3 850 000 ± 1 739 253 VND (n=6), and 3 550 000 VND (n=1)

per case, respectively. ARs of diarrhea, irritability, and injection site swelling cost the least to manage, partially owing to the lack of reported hospitalization by physicians.

Table 2: Direct Medical Costs Associated with the Management of Post-Vaccination ARs in Vietnam per AR – Breakdown Cost per Case

	HCP visits[a]			Treatment[b]			Tests/assessments[c]			Hospitalization[d]		
	VND	SD	n	VND	SD	n	VND	SD	n	VND	SD	n
Injection site pain	671 905	331 841	42	15 429	52 562	42	7 810	35 349	42	8 900 000	-	1
Injection site redness	689 688	469 217	32	7 838	10 838	32	2 457	14 407	32	1 800 000	-	1
Injection site swelling	710 625	539 324	32	7 375	8 899	32	0	0	32	-	-	-
Fever	621 250	113 051	40	10 109	6 393	40	49 288	106 723	40	3 850 000	1 739 253	6
Drowsiness	1 800 000	-	1	1 719	-	1	81 500	-	1	1 800 000	-	1
Irritability	733 571	319 918	14	774	2 749	14	35 071	76 756	14	-	-	-
Persistent crying	957 778	996 729	9	3 344	5 329	8	64 111	129 021	9	3 550 000	-	1
Loss of appetite	948 333	671 851	6	9 093	18 185	4	27 333	66 953	6	1 800 000	-	1
Vomiting	947 143	455 584	7	2 630	1 862	6	0	0	7	1 800 000	0	2
Diarrhea	737 059	346 460	17	5 024	8 072	17	24 088	56 220	17	-	-	-
Rash	706 667	460 818	18	28 789	50 105	18	27 333	62 891	18	3 550 000	-	1

[a] Calculated based on the following equation: number of visits to HCP x unitary cost per visit. Costs for each HCP were combined. Response options included PCP/GP, A&E department, pediatrician/pediatric specialist, other hospital specialist, pharmacist*, nurse, and other*. **[b]** Calculated based on the following equation: number of treatments required per day x number of days medication was taken x unitary cost per treatment. Costs of each treatment were combined. Response options included cold compress or bath*, heating pad*, analgesic medication, antipruritic medication (except antihistamines), antipyretic medication, anti-diarrhea medication, antihistamines, IV fluid, anaphylaxis medication, anti-emetic medication, oral rehydration salts, dietary changes*, other*, and no treatment*. **[c]** Calculated based on the following equation: number of tests/assessments x unitary cost. Costs for each test/assessment were combined. Response options included patient examination*, blood test, urine analysis, other laboratory tests*, X-ray, CT scan, MRI, lumbar puncture, and other*. **[d]** Calculated based on the following equation: number of night stays x unitary cost per night. * No unitary cost data were available or applicable. **A&E**: Accident & Emergency; **AR**: adverse reaction; **CT**: computed tomography; **GP**: general practitioner; **HCP**: healthcare professional; **IV**: intravenous; **MRI**: magnetic resonance imaging; **PCP**: primary care physician; **SD**: standard deviation; **VND**: Vietnamese Dong.

3.4. Parent/Caregiver-Reported Indirect Costs to Manage ARs Associated with Early Childhood Vaccination

According to parents/caregivers, the management of fever, the local ARs (injection site pain, redness, and swelling), and irritability incurred indirect costs, with an average total varying from 941 000 to 3 962 455 VND per AR case. No indirect costs were reported for the other six ARs of interest (**Figure 1**).

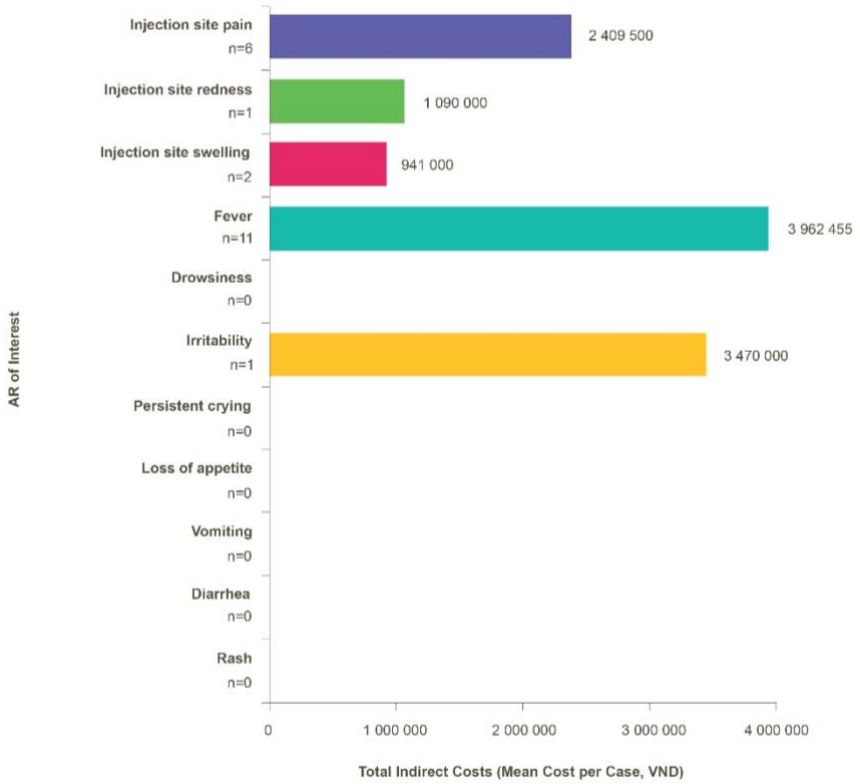

Figure 1: Total Indirect Costs to Manage Specific ARs in Vietnam, Mean Cost per Case

AR(s): adverse reaction(s); **VND**: Vietnamese Dong.

The average total absenteeism costs were 1 137 368 VND (n=38), with an average of 22.7 hours of lost work time per AR case (reported by n=38 parents/caregivers) in the two weeks following their child's vaccination. Total average out-of-pocket treatment costs were 284 359 VND (n=39), and childcare, travel, parking, tests, and other costs totaled an average of 2 001 432 VND (n=44) (**Appendix A2**).

3.5. Costs of the Management of ARs with DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib

Single doses of the two hexavalent vaccines containing acellular pertussis approved for childhood vaccination in Vietnam, DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib, were compared using a newly developed mathematical projection tool. The model assumed a 2023 Vietnamese birth cohort of 1 418 890 individuals, and 69% vaccination coverage for both vaccines (GSK, 2023), (*World Population Prospects 2022: Summary of Results*, 2022).

A primary dose of DT3aP-HBV-IPV/Hib resulted in 420 985 fewer ARs compared with DT2aP-HBV-IPV-Hib (**Table 3**), representing an 8% reduction in overall ARs. When estimating HCRU, there were 175 149 (−11%), 175 149 (−11%), 175 149 (−11%), and 1 566 (−13%) fewer HCP visits, prescribed treatments, tests/assessments, and hospitalizations, respectively, predicted with DT3aP-HBV-IPV/Hib compared with DT2aP-HBV-IPV-Hib.

The reduction in occurrence of ARs with a primary dose of DT3aP-HBV-IPV/Hib lead to a reduction of ~134 billion VND in direct medical costs to manage ARs, compared with DT2aP-HBV-IPV-Hib, marking an overall cost reduction of −11% (**Table 3**). The projection tool estimated that DT3aP-HBV-IPV/Hib reduced HCP visit costs by ~121 billion VND, treatment costs by ~1.70 billion VND, test/assessment costs by ~5.67 billion VND, and hospitalization costs by ~5.85 billion VND, compared with DT2aP-HBV-IPV-Hib.

When looking at the indirect costs to parents/caregivers, significant reductions were also predicted with a primary dose of DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib. The projection tool estimated reductions of ~182 billion VND in absenteeism expenses, ~44 billion VND in out of pocket treatments, and ~219 billion VND in additional costs (which included childcare, travel, parking, tests, and other costs) with DT3aP-HBV-IPV/Hib over DT2aP-HBV-IPV-Hib, marking an overall ~441 billion VND (−14%) reduction in indirect costs.

Table 3: Reduction in HCRU and Indirect Costs from Vaccination with DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib

Management of AR outcomes	DT3aP-HBV-IPV/Hib	DT2aP-HBV-IPV-Hib	DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib	
			Absolute difference	Percent difference, %
Overall number of ARs	4 591 670	5 012 655	-420 985	-8
HCRU				
HCPs visits	1 422 243	1 597 392	-175 149	-11
Hospitalizations	10 373	11 939	-1 566	-13
Treatments	1 422 243	1 597 392	-175 149	-11
Tests/assessments	1 422 243	1 597 392	-175 149	-11
Total direct costs, VND	**1 121 121 378 507**	**1 255 368 940 794**	**-134 235 569 119[e]**	**-11**
HCPs visits[a]	1 030 403 783 290	1 151 433 225 678	-121 029 442 389	-11
Hospitalizations[b]	38 458 525 210	44 305 307 065	-5 846 781 855	-13
Treatments[c]	13 284 130 480	14 981 605 933	-1 697 475 453	-11
Tests/assessments[d]	38 974 939 528	44 648 802 119	-5 673 862 591	-13
Total indirect costs, VND	**2 758 084 293 535**	**3 202 878 972 838**	**-441 465 963 364[e]**	**-14**
Absenteeism	1 111 728 802 565	1 293 732 127 781	-182 003 325 216	-14
Out-of-pocket treatments	308 422 438 585	352 128 656 082	-43 706 217 497	-12
Others	1 337 933 052 384	1 557 018 188 975	-219 085 136 591	-14

[a] Calculated based on the following equation: number of visits to HCP x unitary cost per visit. Costs for each HCP were combined. Response options included PCP/GP, A&E department, pediatrician/pediatric specialist, other hospital specialist, pharmacist*, nurse, and other*. **[b]** Calculated based on the following equation: number of night stays x unitary cost per night. **[c]** Calculated based on the following equation: number of treatments required per day x number of days medication was taken x unitary cost per treatment. Costs of each treatment were combined. Response options included cold compress or bath*, heating pad*, analgesic medication, antipruritic medication (except antihistamines), antipyretic medication, anti-diarrhea medication, antihistamines, IV fluid, anaphylaxis medication, anti-emetic medication, oral rehydration salts, dietary changes*, other*, and no treatment*. **[d]** Calculated based on the following equation: number of tests/assessments x unitary cost. Costs for each test/assessment were combined. Response options included patient examination*, blood test, urine analysis, other laboratory tests*, X-ray, CT scan, MRI, lumbar puncture, and other*. **[e]** Given iterations of rounding across calculations, the sum of each cost item does not perfectly match the total cost of the respective cost category (direct and indirect), with a minor variation of <1%. * No unitary cost data were available or applicable. **A&E**: Accident & Emergency; **AR**: adverse reaction; **CT**: computed tomography; **GP**: general practitioner; **HCP**: healthcare provider; **HCRU**: healthcare resource utilization; **IV**: intravenous; **MRI**: magnetic resonance imaging; **PCP**: primary care physician; **VND**: Vietnamese Dong.

3.6. Emotional Impact on Parents/Caregivers of Managing Early Childhood ARs

Rash (100%, n=1 parent/caregiver), diarrhea (100%, n=1), fever/high temperature (85%, n=20), and loss of appetite (71%, n=7) were the ARs parents/caregivers reported as causing the greatest emotional concern following vaccination (**Figure 2**). Injection site redness (39%, n=18) and injection site swelling (33%, n=15) were the least emotionally concerning ARs for parents/caregivers.

When looking at vaccine compliance, 95% of parents/caregivers would continue with a vaccination schedule as normal, and only 5% stated that they were hesitant to continue all vaccinations, despite their child experiencing

an AR. No parents/caregivers stated that they would refuse to continue with any vaccinations due to ARs experienced by their child. Additionally, 80% of parents/caregivers would not change the timing of future childhood vaccinations. Of the 5% of parents/caregivers that expressed uncertainty, 57% expressed hesitancy towards co-vaccinations of different vaccines during the same appointment, whereas no parents/caregivers reported hesitation towards multivalent vaccines alone; 43% of parents/caregivers expressed the hesitancy towards both co-vaccination and multi-valent vaccinations.

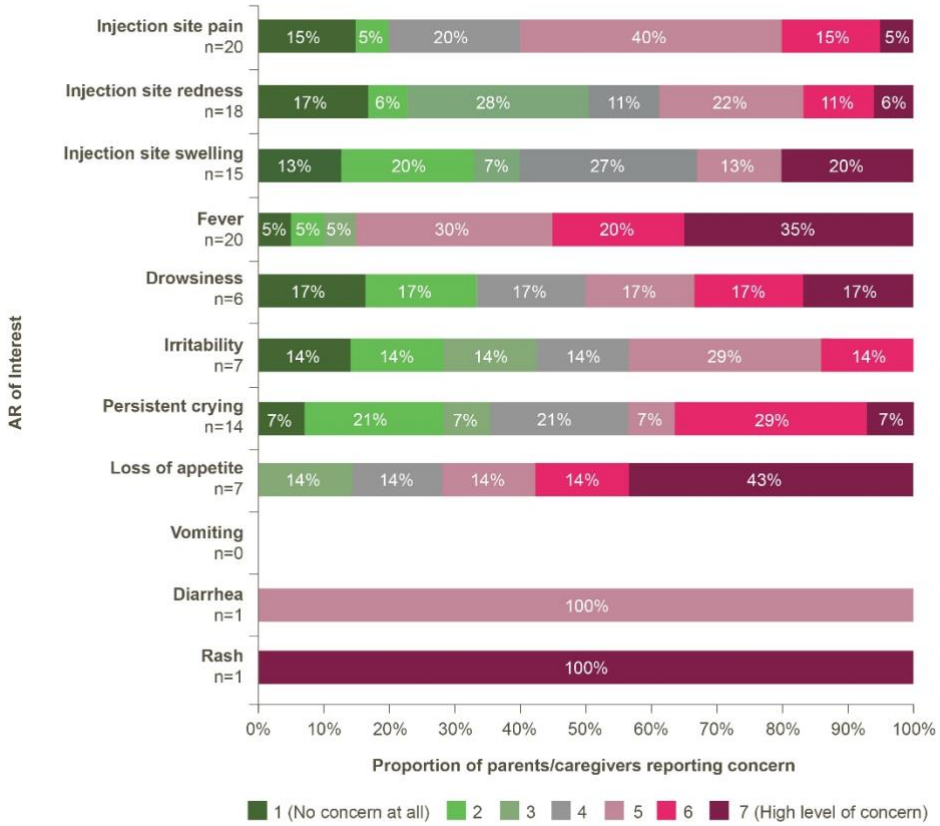

Figure 2: Parent/Caregiver Reported Levels of Emotional Concern Following AR(s)

Scores ≥5 are described as concerning. n represents the number of parents/caregivers who experienced in AR in question. Numbers are rounded up.**AR**: adverse reaction; **ARR**: absolute risk reduction.

3.7. Sensitivity Analysis

SAs were performed on AR-specific data, i.e., the proportion of each AR for DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib, as well as the ARRs. These results are presented in terms of variations in the direct medical costs saved (**Appendix A3**). As expected, the model is significantly more sensitive to the variation of the ARs' incidences compared with the ARR. This finding confirms the robustness of the analysis.

4. Discussion

To our knowledge, this is the first study which explored the management of ARs associated with early childhood vaccinations in Vietnam. This is also the first study to estimate the reduction in direct medical costs as well as indirect costs to parents/caregivers, which may arise due to the management of fewer ARs when vaccinating with a primary dose of DT3aP-HBV-IPV/Hib over DT2aP-HBV-IPV-Hib in Vietnam.

According to this survey administered to parents/caregivers of children receiving a dose of an early childhood vaccine, fever and the local ARs (injection site pain, redness, and swelling) were the most frequent cause for parents/caregivers to seek medical advice. The results of this study corroborate findings from a 2015 review of ARs associated with early childhood vaccinations (infants aged <2 years) in the US. The review examined a

comparable scope of vaccines, and similarly identified that fever and injection site pain and swelling were the most commonly reported ARs by parents/caregivers (Saleh et al., 2017).

A survey was also administered to physicians who manage ARs associated with early childhood vaccinations. Based on the physician survey and unit cost data, hospitalizations were estimated to be the largest contributor to the total direct medical costs required to manage post-vaccination childhood ARs, despite low hospitalization rates. This study found that vaccination with a primary dose of DT3aP-HBV-IPV/Hib over DT2aP-HBV-IPV-Hib in Vietnam was estimated to reduce post-vaccination related hospitalizations by 11%, and consequently the associated costs. A vaccine which leads to fewer AR-related hospitalizations would in turn reduce the HCRU burden needed to manage the ARs. These projections were based on a single dose of DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib, however, multiple doses of both vaccines are required to complete the vaccination course, suggesting that cost reductions with DT3aP-HBV-IPV/Hib compared with DT2aP-HBV-IPV-Hib could be even greater when considering the full vaccination course (*WHO Recommendations for Routine Immunization*, 2024).

In accordance with the markedly lower odds ratios of developing local and systemic ARs with DT3aP-HBV-IPV/Hib compared with DT2aP-HBV-IPV-Hib found previously (Mukherjee et al., 2021), the mathematic projection tool utilized here estimated significant reductions in the occurrence of local and systematic ARs with DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib in Vietnam. Similar reductions in AR occurrence were predicted when corresponding mathematical projection tools were applied to Europe and Southeast Asia (George et al., 2023; Mohy et al., 2024). Subsequently, the estimated HCRU to manage post-vaccination ARs in Vietnam was lower for DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib, and associated direct medical costs were reduced per primary dose. When looking at indirect costs incurred by parents/caregivers when managing AR(s) experienced by their child, parents/caregivers reported money lost from absenteeism, expenditure on out-of-pocket treatments, and additional costs including childcare, travel, parking and more, totaling an average of ~3 million VND per parent/caregiver per AR. However, reductions of these costs proved possible with DT3aP-HBV-IPV/Hib, such that indirect costs were reduced by 14% compared with DT2aP-HBV-IPV-Hib.

Vaccine hesitancy was identified as one of the top ten threats to global health by the WHO in 2019, highlighting the importance of managing this uncertainty (*World Health Organisation: Ten threats to global health in 2019*, 2019). Negative past experiences with vaccines have been indicated to increase parental vaccine hesitancy at a global level (Obohwemu et al., 2022), and a 2019 survey of Chinese parents identified that perceptions of vaccination safety, and risks of severe side effects, strongly influenced vaccination decisions (Li et al., 2022). In this study, although rashes, diarrhea, and fever caused significant emotional concern among parents/caregivers in Vietnam, the majority would continue with vaccination schedules as normal and would not delay future vaccinations. Having physicians inform parents/caregivers of the expected post-vaccination ARs may reduce safety and emotional concerns (Ventola, 2016). Parents/caregivers in Vietnam showed higher vaccine hesitancy towards co-vaccination compared with multivalent vaccination. This is reflected in the literature, with higher compliance rates reported for multivalent vaccinations compared with single antigen vaccines only, due to lower overall perceived risks and logistical convenience (Kurosky et al., 2017; Marshall et al., 2007). Furthermore, the use of co-vaccinations or multivalent vaccinations with low risks of ARs following vaccination can improve vaccine uptake (Happe et al., 2007). These results emphasize the importance of developing multivalent vaccines with low risks of ARs, to improve compliance and perceptions of vaccine safety.

This study was associated with some limitations. Regarding the surveys, it was not possible to determine the HCRU impact and the associated costs of patients experiencing a combination of simultaneous ARs. As with all online surveys, the presentation and framing of questions may influence respondents. Additionally, once the predefined sample quotas were met the survey closed, which may have introduced bias between respondents, as fast respondents may differ from those who delayed their response. This study may have benefitted from subgroup analyses exploring the impact of parent/caregiver experience in managing post-vaccination ARs, North versus South Vietnam physicians, parent/caregiver demographics, and infant age as these characteristics may alter preferences and therefore, management of post-vaccination ARs. The mathematical projection tool was limited to ARs analyzed in the Mukherjee et al. (2021) review, and therefore diarrhea and rash were excluded from the calculation. According to the physician survey, rashes incurred moderate hospitalization HCRU and contributed

substantially to the overall direct medical costs. Therefore, it would have been of interest to include rashes in the mathematical projection tool. HCRU was estimated from the physician survey and was consequently subject to recall bias as no databases nor patient records were accessed. Furthermore, in several cases HCRU was estimated based on a small sample of answers, which may reduce confidence in the reported values. As the sample size varied across ARs analyzed, the statistical power also varied. As aforementioned, multiple doses of DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib are recommended. However, this study did not calculate the total number of ARs experienced over the full vaccination course, and instead only considered the number of children receiving at least one dose, potentially skewing the estimated burden and costs of AR management. If a child experiences an AR with the first dose, it is reasonable to expect similar reactions with subsequent doses, suggesting that the total burden and costs might be underestimated. Conversely, if no AR occurs with the initial dose, it can be assumed that no reactions would occur with subsequent doses, leading to potential overestimation of burden and costs. However, since these over- and underestimations could counterbalance, the assumption of considering at least one dose may still be an acceptable input for analysis.

5. Conclusions

Vaccines are important to reduce the burden of disease. Multi-antigenic vaccines are a proven approach to reduce this burden across multiple diseases simultaneously. To our knowledge, this study is the first to highlight the significant reduction in HCRU and costs related to the management of ARs following a primary early childhood dose of DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib in Vietnam, and also represents the first estimation of the cost of post-vaccination AR management in Vietnam. Decision bodies may consider the financial and societal benefits of selecting vaccines with fewer ARs in their holistic evaluation and decision-making process for vaccines, and how these benefits may improve vaccine adherence.

Author contributions: Substantial contributions to study conception and design: AMo, GN, MD, MN, AMa, and DVO; substantial contributions to analysis and interpretation of the data: AMo, GN, MD, VG, GC, EH, MN, ED, AMa, and DVO; drafting the article or revising it critically for important intellectual content: AMo, GN, MD, VG, GC, EH, MN, ED, AMa, and DVO; final approval of the version of the article to be published: AMo, GN, MD, VG, GC, EH, MN, ED, AMa, and DVO.

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Conflicts of interest: AMo, MD, ED, AMa, and DVO: employees of and hold financial equities in GSK; GN: employee of, holds financial equities in, and has received grants/contracts from GSK; VG: receives consultant fees from Amaris Consulting, working as a contingent worker for GSK; GC and EH: the authors declare no conflict of interest; MN: employee of GSK. The funding sponsor had a role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results. Conflicts of interest are as reported during analysis and development of the manuscript.

Ethics approval: This study complied with all applicable laws regarding participant privacy and all participants provided informed consent prior to inclusion in the study. Study results are in tabular form and presented as aggregate analyses that omit subject identification; therefore, ethics committee or IRB approval was not required. Study documents were nevertheless submitted to a single central IRB (WCG IRB). The IRB reviewed the protocol, consent forms, data collection materials as well as a study specific form, which included a summary of the study, documents submitted and relevant certificates (CV and ethical training certification). Approval was granted from the WCG IRB on 16th June 2023 (decision ID: 20232715).

Data availability statement: All data generated or analyzed during this study are included in this published article/as supplementary information files.

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Appendix A

A1. Published Unit Cost Data

Item[a]	Cost in Vietnamese private healthcare (VND)
HCP Visits	
General practitioner visit	440 000
Pediatric specialist visit	690 000
Other hospital specialist visit	690 000
Pharmacist visit	NA
Nurse (hospital) visit	240 000
Emergency room visit	1 800 000
Tests/Assessments	
Blood test	164 000
Urinalysis	81 500
X-ray	250 000
CT scan	2 150 000
MRI	2 750 000
Lumbar puncture	1 680 000
Treatments[b]	
Analgesic and Antipyretic	(Paracetamol) 1 718.64
Antipruritic	(Hydrocortisone) 34 652.00
Anti-diarrhea medication	(Racecadotril sachet) 402.24
Antihistamine	(Desloratadine) 2 691.67
IV fluid	(Sodium chloride) 36 265.78
Anaphylaxis medication	(Epinephrine IM) 125.54
Sedative	(Midazolam IV) 81.70
Anti-emetic medication	(Metoclopramide) 538.01
Oral rehydration salts	(Hydration sachets) 82.00
Hospitalization	
Room per day	3 550 000 (double room)

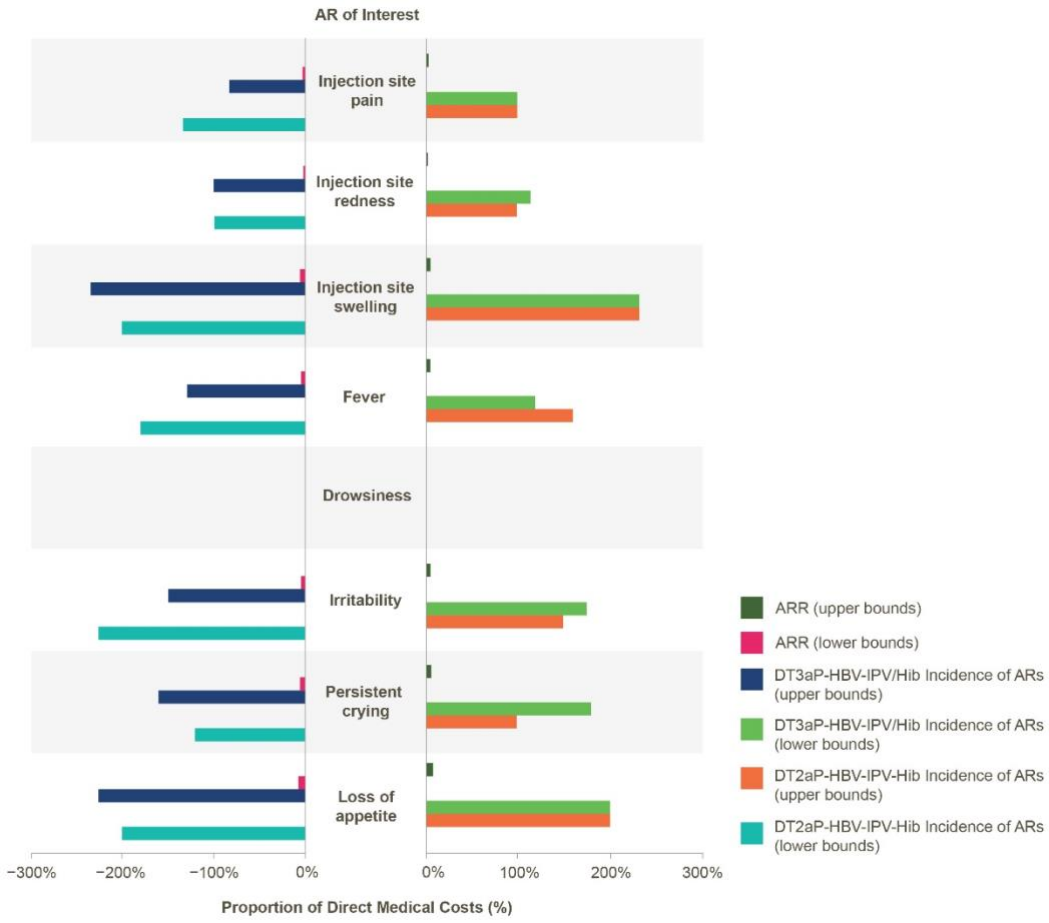
[a] Published unit cost data provided by a third-party agency, Weber, a consultancy firm specialized in HCRU data. Weber used published scientific literature and official databases to identify published unit costs for HCP visits, prescribed treatments, tests/assessments, and hospitalization. Weber used the most recent published data available and provided all references for unit cost data. **[b]** Treatment costs per administration. **CT**: computed tomography; **HCP**: healthcare professional; **IV**: intravenous; **MRI**: magnetic resonance imaging; **NA**: not applicable; **VND**: Vietnamese Dong.

A2. Indirect costs to parents/caregivers in Vietnam per case – Mean cost per case

Expense to Parent/Caregiver	VND	SD	n
Absenteeism	1 137 368	1 808 279	38
Tests	408 455	1 198 880	44
Parking	51 955	183 656	44
Travel	352 955	806 424	44
Childcare	715 682	2 298 885	44
Other	472 386	1 662 303	44

SD: standard deviation; **VND**: Vietnamese Dong

A3. Sensitivity Analyses of the Eight Adverse Reactions Analyzed in Vietnam



AR: adverse reaction; **ARR**: absolute risk reduction.

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A Review of How Artificial Intelligence Could Influence the Emergency Department Workflow

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Abstract
Emergency departments play a critical role in healthcare systems, serving the initial point that patients and hospitals contact. Emergency physicians deal with emergent and life-threatening conditions in an unpredictable environment. With the growing prominence of artificial intelligence in the medical environment, understanding its potential impact on the quality of care delivered by physicians and staff is crucial to improving patient care and increasing patient satisfaction. While existing literature has explored artificial intelligence's influence on emergency department workflow from a specific point of view, this study briefly examines how artificial intelligence could transform care delivery in emergency departments from triage to patient disposition.

Keywords: Artificial Intelligence (AI), Emergency Department (ED), Emergency Room, Triage, Image Analysis, ECG Interpretation, Risk Prediction, Metrics

1. Introduction

Artificial intelligence (AI) refers to a technology that enables computers to play human cognitive functions (Kachman et al., 2024). AI uses previous data and knowledge to enhance the efficacy and accuracy of human ability and performs tasks that require human intelligence or intervention (Nagahisarchoghaei et al., 2023). AI could empower services used every day and has the potential to transform healthcare and the medical field (Jiang et al., 2017). In the healthcare setting, AI can speed up data analysis, helping practitioners identify conditions that would otherwise be overlooked and enhancing medical decision-making (Jiang et al., 2017). By leveraging AI in hospital settings, the system would become faster, smarter, and more efficient in providing patient care and could be future-transforming (Alowais et al., 2023). Embracing innovative AI approaches in emergency medicine could transform the care delivered to patients, improve patient outcomes and satisfaction, and reduce costs (Tareen et al., 2023). In the setting of ED, the utilization of generative AI has been studied in different aspects: patient triage, interpretation of medical images, managing patient flow, risk prediction, and metrics to optimize resource utilization (Kachman et al., 2024, Jiang et al. 2017, Tareen et al., 2023). Many variables could influence the efficacy of services provided in the ED. Lack of staff is one important issue. Another major element every ED deals with is overcrowding, which increases the risk of errors and gives rise to insufficient treatment, delayed diagnosis, and longer patient wait times. The lack of resources is also an essential factor influencing the quality of delivered care (Tareen et al., 2023). These variables may also affect medical team members' capacity to perform critical and life-saving procedures, so it seems to be crucial that every ED applies innovative technologies to

improve patient care and augment the care providers' effectiveness. AI-powered technology has the potential to provide feasible, quicker, and more precise care (Tareen et al., 2023, Kirubarajan et al., 2020). In this review, we first introduce types of AI mainly used in the healthcare field and medicine based on their applied technology. Then, demonstrate how AI could be useful and assist the healthcare provider in the emergency field and explore the capacity of AI to empower ED care. While most previous works have assessed the utilization of AI in a specific domain, in this study, authors, aim to take a more detailed but brief look at the capability of AI to reform emergency care delivery.

2. Types of AI

AI is a collection of technologies. Some of them have higher significance to the healthcare field that will be explained here:
The most popular and primary AI technologies used in the healthcare area were rule-based expert systems (composed of sets of 'if-then' rules). Sets of rules in each field were produced by human experts and knowledge engineers. The initial aim of these technologies was to tackle complex challenges and provide a specific solution (Alowais et al., 2023). Though they are simple to comprehend, they might become unstable if there are many rules, and in the sphere of healthcare, machine learning algorithms are gradually replacing them (Shaw et al., 2019).

Machine learning (ML) is a statistical method for fitting models to data. It is characterized as supervised learning because it needs a training dataset for which the final variable, such as disease onset, is known (Nagahisarchoghaei et al., 2023). The most popular use of classic ML in the healthcare industry is the precision medicine field, which aims to determine which therapeutic regimen is likely to be effective for a specific condition based on a variety of patient characteristics and treatments (Shaw et al., 2019). Additionally, neural networks (a more sophisticated type of ML) approach problems in terms of input and connect the input to output and are commonly employed in classification tasks such as predicting a person's tendency to obtain a specific disease.

Another more advanced AI technology is called deep learning (DL), which employs multi-layer neural networks with multiple layers of variables. It is helpful and effective in predicting outcomes. Otherwise, Image analysis, illness diagnosis, and acute disease detection are common uses of DL in the healthcare scope (Alowais et al., 2023).

Natural language processing (NLP) technology can recognize speech, analyze texts, translate, and perform other language-related objectives. NLP has several uses in the medical sector, such as question answering, summarizing texts, classifying structured data, and mapping it to organized fields. Thus, it could enhance the integrity of clinical data (Jiang et al., 2017).

Other important technologies used in the healthcare area are physical robots which are trained by a predetermined task, and in recent times, they have become more cooperative with humans. Surgical robots have the potential to enhance a surgeon's visual perception, facilitate precise and minimally invasive incisions, and perform other tasks (Alowais et al., 2023).

Computer vision, a newly advanced technology, uses ML and neural networks to derive information from images, videos, and every visual input. It is applicable in healthcare systems for the purpose of medical image analysis and surveillance (Nagahisarchoghaei et al., 2023). Figure 1 summarizes the different types of AI used in the healthcare system.

Recently, the application of AI in medicine has become increasingly popular. EDs can significantly benefit from AI, as it is potentially practical across various aspects of care delivery in the ED (Kachman et al., 2024).

In Figure 2, we summarized the points that AI could influence emergency design.

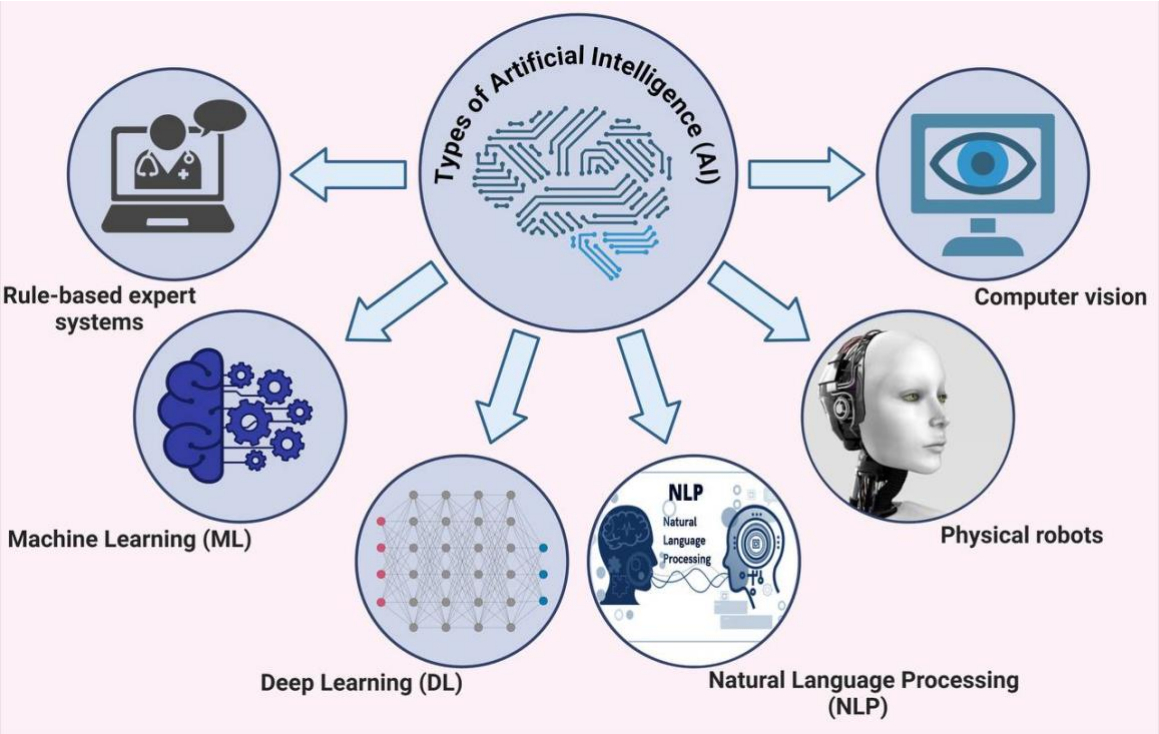

Figure 1: Different types of artificial intelligence used in healthcare system

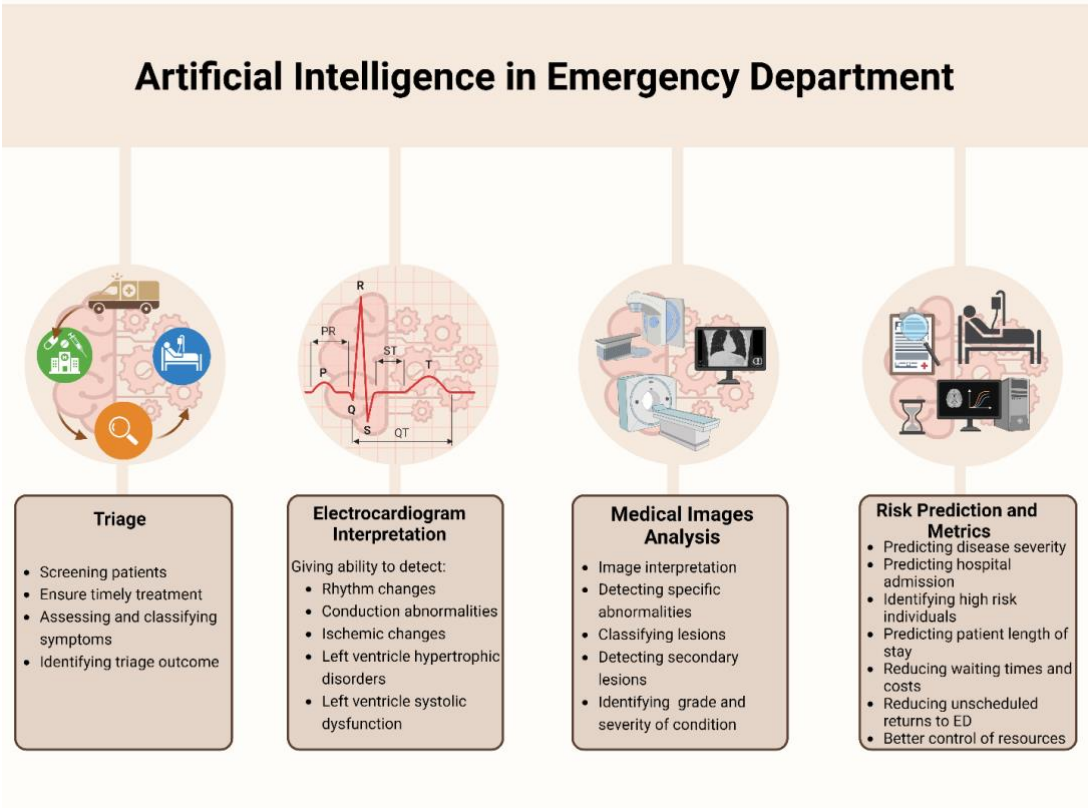

Figure 1: Spots where artificial intelligence can influence emergency departments. ED: emergency department

3. Triage

Upon arrival at the ED, patients are categorized based on their vital signs and the severity of their conditions. Various systems are in place for this categorization named triage. However, all triage systems share a common goal: to streamline time utilization while giving priority to resources. Under-triage can lead to delayed treatment and escalate morbidity and mortality, while over-triage could exacerbate overcrowding in the ED and increase resource consumption (Cameron et al., 2015). AI-based applications have shown their ability in retrospective studies to help physicians and nurses in the triage bay and provide precise support for medical triage decisions (Niederdockl et al., 2021). In most AI-based tools, the ED triage outcome is classified into two disposition classes: hospital admission or not and critical condition or not (Delshad et al., 2021). It seems that applying NLP techniques, such as recurrent and convolutional neural networks, could be probed in the future for better triage performance (Pasli et al., 2024). However, research has shown that ML improves triage capacity by screening patients efficiently and reducing errors. Advanced AI models that are based on big data would find critically ill patients for timely and best available care (Gao et al., 2022). AI-based triage tools that use ML and NLP technologies accurately assess symptoms and classify patients to identify those needing urgent treatment, thus helping care providers prioritize high-risk individuals (Zhang et al., 2021). A recent meta-analysis showed that AI technologies for patient triage demonstrate acceptable levels of accuracy and facilitate prompt and precise decision-making (Kaboudi et al., 2024).

4. Electrocardiogram (ECG) interpretation

AI has given clinicians a special diagnostic ability to interpret ECGs to detect arrhythmia, QT prolongation, ST segment and T-wave changes, and other abnormalities; the potential to translate the ECG into a unique modality that is integrated into practice workflow (Attia et al., 2021. Martinez et al., 2023). Studies have demonstrated that some algorithms can accurately identify heart rhythms and provide thorough ECG analyses; these models perform very well for various rhythm disturbances, conduction abnormalities, ischemic changes, and waveform morphology; providing a promising capability of the algorithm to predict beyond rhythm abnormalities (Kashou et al., 2020). Choi et al. (2022) demonstrated superior performance in detecting ST-elevation myocardial infarction compared to clinicians. Additionally, Attia et al. (2021) demonstrated that applying AI to the standard ECG could potentially enhance its ability to identify medical conditions that were previously undetectable using a standard ECG or to do so with exceptional accuracy. Such improvements include precise identification of heart rhythm, detection of atrial fibrillation during normal heart rhythm, identification of valvular heart disease, channelopathies, and diagnosis of hypertrophic cardiomyopathy. Therefore, a simple, non-invasive method would empower physicians with challenging differential diagnoses. Adedinsewo et al. (2020) explored that AI could enable ECG to detect patients presenting with dyspnea who have left ventricular systolic dysfunction (LVSD). Utilizing a convolutional neural network has given ECG algorithms to identify LVSD with ejection fraction< 35%, making the ECG an inexpensive, painless, rapid, and effective choice in detecting LVSD when analysed with AI. This has the potential to enhance the confidence of healthcare practitioners when evaluating differential diagnoses in the ED. Some deep neural network (DNN) algorithms for 12-lead ECG interpretation showed a high accuracy rate in the ED (Smith et al., 2019).

5. Medical Images Analysis

Imaging is widely used in EDs and plays a crucial role in diagnosing abnormalities and therapeutic plan decisions. Regarding image analyses, DL algorithms have achieved high accuracy in detecting abnormalities, classifying conditions, and providing predictions (Li et al., 2023). Multiple algorithms have been created with high-performance levels and acceptable sensitivity and specificity, making AI a promising option for future use in medical diagnosis (Yoon et al., 2021). AI tools in radiology practice have become increasingly prevalent and provide valuable assistance in the ED radiology practice (Dundamadappa et al., 2021). The most used imaging modalities in the EDs will be discussed next.

Bone X-ray: Specific fractures could be complicated for junior physicians to diagnose; the misdiagnosed fractures affect patient management and may cause serious complications. Several research studies have used DL models

to analyze and classify fractures, and DL has become a cutting-edge technique for improving medical image analysis. Combined with convolutional neural networks, it can significantly reduce classification errors (Rayan et al., 2019. Reichert et al., 2021). Additionally, some fractures are subtle or challenging to diagnose; such as subtle spinal compression fractures (Oppenheimer et al., 2021), distal radius fractures (Oka et al., 2021), scaphoid fractures (Kraus et al., 2023), and ankle fractures (Kim et al., 2021); and AI models could be reasonable assistance in the diagnosis. The results of the Dupuis et al. (2022) algorithm had an accuracy of 90–93% in children's fractures, especially those above four. Additionally, Rosa et al. (2023), demonstrated that AI had a high negative predictive value in detecting pelvic fractures. Assistance of AI in trauma radiology has led to a significant decrease in false-negative findings and an increase in sensitivity by around 20%. Additionally, there has been a 0.6% increase in specificity. The time taken to interpret fractures per study has also decreased by 10–16 seconds on average, based on the Reichert et al. (2021) study.

Chest Radiographs (CXR): Interpreting CXR is difficult and demands both experience and expertise, and emergency physicians may not perform as well as experienced radiologists (Al Aseri et al., 2009). In a specific establishment, Hwang et al. (2023) evaluated the effectiveness of DL algorithms in interpreting CXR in EDs. Their results indicated that the algorithms were highly capable of classifying CXR with significant abnormalities. Although some models did not enhance the accuracy of diagnosing acute thoracic conditions in patients who arrived at the ED with acute respiratory symptoms compared to diagnosis by a radiology trainee, overall, it makes the CXR more valuable in detecting specific conditions (Nana et al., 2019). The coronavirus disease 2019 (COVID-19) pandemic led to the development of AI algorithms for detecting pneumonia in CXR, achieving accuracies of 83.5% to 98% (Laino et al., 2021). Liong-Rung et al. (2021) released an AI-based model that performed well in identifying pulmonary edema in elderly patients who presented with dyspnea. It provided critical information that could assist physicians in narrowing the differential diagnoses of the patients manifesting with dyspnea in the ED. In addition, Su et al. (2021) DL model could detect subphrenic air on CXR in cases suspected of hollow organ perforation and pneumoperitoneum.

Abdominal X-Ray: Abdominal X-ray is still used as an adjunct or optional test in the EDs. Small bowel obstruction is a serious surgical situation that can lead to tissue death and perforation. AI-based models accurately detected small bowel obstruction in abdominal radiographs (Cheng et al., 2018. Km et al., 2021). Their model had a sensitivity of 83% and a specificity of 68% in detecting bowel obstruction. Park et al. (2023) developed a DL model that detected pneumoperitoneum in both supine and upright positions, which can help evaluate patients for whom taking an upright X-ray is impossible. In a study on ileocolic intussusception in young children, Kim et al. (2019) found that the AI algorithm demonstrated higher sensitivity than the radiologists, while there was no difference in specificity.

Chest Computed Tomography (CT): CT of the chest is a cross-sectional examination of the lungs, heart, airways, mediastinum, bones, and soft tissue. Work on CT scans includes numerous models that commonly evaluate one class of abnormalities at a time, such as pneumothorax, emphysema, interstitial lung disease, and pneumonia (Kim et al., 2019. Laino et al., 2021. Liong-Sung et al., 2021. Su et al., 2021). Draelos et al. (2020) created a DL model to classify multiple abnormalities; they trained the model to recognize nine labels: nodule, opacity, atelectasis, pleural effusion, consolidation, mass, pericardial effusion, cardiomegaly, and pneumothorax with excellent performance. Laino et al. 's research (2021) demonstrated the benefits of AI in different domains in the case of COVID-19 infection, including identification, screening, and risk stratification of cases. Additionally, the Rueckel et al. model (2021) streamed data for multiple trauma patients, which reduced missed secondary thoracic findings. Computed tomography pulmonary angiogram (CTPA) is the preferred diagnostic method for detecting pulmonary embolism (PE). AI algorithms have been created to identify PE on CTPA images. Ma et al. two-step DL system (2022) effectively recognized severe and life-threatening PE cases, particularly those that were central and acute. It also helped in ruling out PE and had the potential to demonstrate different subtypes of existing PE. Kligerman et al. (2018) and Soffer et al. (2021) review demonstrated that AI-based technology has 88% sensitivity and 86% specificity for diagnosing PE on CTPA images.

Abdominopelvic CT: Singh et al. (2020) created a DL algorithm with reconstruction capabilities that demonstrated better performance in terms of image quality and detection of clinically important abnormalities in

chest and abdominopelvic CT scans compared to iterative reconstruction methods. Katzman et al. algorithms (2023) offered similar image quality and diagnostic confidence when assessing abdominal and pelvic CT scans for female pelvic conditions. Prod'homme et al. (2024) demonstrated that DL models effectively detected urolithiasis, providing better image quality than iterative reconstruction and requiring less radiation. The Vanderbecq et al. model (2024) showed great potential in detecting obstruction, which evaluated bowel obstruction by CT.

Brain CT Scan: Prevedello et al. model (2017) utilized AI to detect important findings on head CT scans automatically, and scans were initially interpreted and categorized as either having potential positive (e.g., hemorrhage, stroke, hydrocephalus) or negative findings. Recently, Li et al. (2024) developed a deep learning model that effectively diagnoses intracerebral hemorrhage (ICH) in brain CT scans. Their results demonstrated both effectiveness and robustness in ICH detection. However, according to Kundisch's research (2021), AI often fails to detect some cases of ICH located in the subarachnoid space and under the calvaria. Buchlak et al. (2024) showed the ability of a comprehensive AI-based model to assist radiologists in detecting a variety of abnormalities on non-contrast CT images.

Ultrasound Imaging: Research specifically addressing the combined application of point-of-care ultrasound (POCUS) and AI is limited. However, AI has demonstrated its effectiveness in evaluating the inferior vena cava during POCUS assessments (Blaivas et al., 2020). Motazedian et al. (2023) found that AI-assisted POCUS has more than 92% sensitivity and specificity in detecting abnormal left ventricle ejection fraction. The accuracy of lung ultrasound was investigated by Lehmann et al. (2022) and was acceptable, and Abdel-basset et al. (2022) demonstrated the efficacy of lung US for diagnosing COVID-19 pneumonia. According to Nhat et al. (2023), applying AI assistance to lung ultrasound significantly enhanced the performance of beginners. Kim et al. (2024) reviewed the accuracy of AI in POCUS and demonstrated that the use of AI is practical and feasible overall.

6. Risk Prediction and Metrics

Arrivals to the ED show some variations and usually peak at predictable times; there are usually some mismatches with workflows in other parts of the hospital. Otherwise, crowded EDs are a global issue that could lead to delays in providing medical care and worsen patient outcomes. It is essential to assess and prioritize patients promptly. Hu et al. (2023) developed a model to predict ED volume that could be used to enhance patient care. Patel and colleagues' model (2022) used triage notes and electronic health records (EHR) to foresee hospital admissions from the ED. Establishing this predictive model, they incorporated ED-specific data like patient demographics, vital signs, ESI triage level, triage notes, and laboratory information. Their work demonstrated the effectiveness of ML in anticipating hospital admissions originating from the ED. Raita et al. (2019) employed ML models to forecast patient outcomes and contrasted their accuracy with the Emergency Severity Index (ESI) system. The model displayed better accuracy in predicting critical care and hospitalization results and additionally exhibited a greater sensitivity for critical care outcomes, leading to higher specificity for hospitalization results. Lee et al. (2022) developed an AI model to determine the need for urgent hospitalization for patients, that utilized a small set of factors to predict which patients would require hospitalization, enabling timely care or quick discharge. However, the model's predictive ability varied across different patient groups, such as nontraumatic adults, pediatrics, trauma, and environmental emergencies. In addition, hospital admission prediction in the Cusido et al. model (2022), which used an extensive database of emergency registered patients, demonstrated excellent predictive performance. During COVID-19, the Arnaud et al. model (2022) effectively categorized the patients who had presented in the ED with COVID-19 infection. It showed the capability of AI models for better resources management during pandemics by predicting whether patients are likely to be discharged or admitted. ML-driven models have demonstrated great potential in predicting the severity of diseases. Sepsis is the leading cause of death in hospitals globally, and early prediction of the mortality rate can assist physicians in providing timely care. Park et al. (2024) developed a model for predicting mortality in sepsis patients, demonstrating excellent predictive performance. ML-based prediction models have also shown their potential in trauma patients. Tu et al. (2022) ML-based algorithm predicted the outcome and mortality of TBI patients. The model provided early and quick mortality prediction, which could guide physicians in better patient management.

While waiting times influence patient satisfaction in EDs, Pak et al. (2021) streamed a model that could predict waiting times in patients with minor medical concerns. Such information and taking actions to reduce waiting times impact the experience and anxiety levels of patients and may also lead to fewer patients leaving without

receiving medical attention. Bin et al. study (2022), during the COVID-19 pandemic, used AI technology to reduce the time required for medical care registration, health screening, and waiting for care. It improved the waiting time by about 12 minutes.

Regarding trauma patients' length of stay in the ED, Stonko et al. (2023) developed a model that could predict the length of stay with great specificity. It used only the data that were available at the patient admission. Another aspect of the quality of care is unexpected ED returns, and ML models could assist in identifying high-risk patients to minimize errors and save time and costs (Lee et al. 2024). Providing a comprehensive overview of patient volume, symptom severity, and patient outcomes and reducing wasted time is a significant step forward in successful ED management, and AI can be very helpful in this regard.

6. Challenges and Limitations

Despite AI's promising role in improving care delivered in the EDs, some ethical concerns should be addressed. First, AI may exhibit bias in the decision-making process, sometimes providing inaccurate results, which could lead to incorrect patient management (Li et al., 2023). In addition, there is a lack of transparency regarding how AI arrives at conclusions, which makes it difficult to trust (Li et al., 2023. Chenais et al., 2023). Data privacy during the analysis process is a concern that should be addressed (Li et al., 2023). Most studies of AI Applications in the medical field and ED are retrospective data set analyses that need validation in clinical trials (Kirubarajan et al., 2020). Regarding diagnostic image interpretation, there are concerns as model performance may vary when it comes to specific subtypes (Seyam et al., 2022). For predictive purposes, the range of algorithms used is limited and needs to be addressed in future works (Kinoshita et al., 2022). Issues regarding the accuracy and practicality of some predictive models should be marked to use these models with greater confidence (Lee et al., 2024). Finally, it's crucial to consider how AI will integrate and be adopted into existing systems, as well as the potential challenges healthcare providers may face when using AI-based tools (Challen et al., 2019).

7. Conclusion

AI is expected to be used in more medical applications, such as ED care. It would support doctors and staff as they provide care in the ED. AI can predict ED arrivals so managers can modulate their resources according to demands. AI tools can assist in triage and guide patients to the appropriate setting using AI-driven symptom-checking systems. AI aids in interpreting medical images and reduces time spent on medical image interpretation. Some subtle and second findings could be discovered by AI, reducing the risk of missed diagnosis and missed management. AI algorithms can be helpful in resource-limited EDs and in settings that do not have around-the-clock radiology coverage. Healthcare professionals can benefit from the integration of AI in various aspects of clinical decision-making. AI can assist in predicting patient outcomes, identifying clinical deterioration, assessing the likelihood of hospital admissions, estimating the duration of a patient's length of stay in the ED, and predicting ED return. The information from resource allocation allows managers to convert hospital wards into dedicated units based on the predicted bed demand. Overall, AI assistance has the potential to improve the quality of care and enhance patient safety and satisfaction significantly.

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Compounds and Histopathological Effect of *Terminalia Catappa L.* Leaves Extract for Anti-Bleeding Agent Tooth Extraction in Mice (*Mus Musculus*)

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Abstract
Complications in tooth extraction are such as bleeding, fracture, dry socket, swelling, shock, and several other complications. Ketapang (Terminalia catappa L.) is known to contain flavonoids which play a role in wound healing. The flavonoid content of *T. Catappa L.* can accelerate wound healing in the angiogenesis process by stimulating vascular endothelial growth factors. This study aims to examine the chemical sub-element of *T. Catappa L.* leaves extract and its toxicity by Lethal Dose (LD50) test in mice. This research was experiment in a laboratory of making ethanol extract from *T. Catappa L.* leaves. The LD50 test of ethyl acetate fractionated *T. Catappa L.* leaves extract was carried out on 20 mice divided into 5 treatment groups, namely 1, 2, 4, 8, and 16 g/kg body weight (BW). Graphical analysis of the results of the Liquid chromatography-mass spectrometry (LCMS) test was carried out to determine the detected chemical compounds and histopathology images were obtained. *T. Catappa L.* has tannin and flavonoid compounds. The results of the LD50 test show that no mice were poisoned and died. Histopathological tests on mice that were given a dose of 16gr/kg BW show that the liver has diffuse hydrophilic degeneration, while the normal kidneys have no abnormalities. Ethyl acetate fractionated ethanol extract of *T. Catappa L.* leaves is categorized as non-toxic. Based on the content of tannin and flavonoid compounds, it is suggested to use *T. Catappa L.* leaves as an anti-bleeding agent after tooth extraction.

Keywords: Herbal Plant, Histopathology, Ketapang Leaves, Terminalia Catappa L., Tooth Extraction

1. Introduction

Dental problems are a major challenge as they affect people around the world around 3.5 billion with dental caries dominating (Chandran & Usha, 2024). Dental caries is a pivotal reason for tooth extraction, which has now become the major treatment in dentistry (Rahmadhini & Wahyuni, 2023; Sharif et al., 2020). Tooth extraction often causes bleeding in the gingiva due to the creation of a tooth socket. The bleeding occurrence extends the damage to the tissue and can continue for 1 – 2 days, which causes uncomfortable moments for patients (Soltani et al., 2014). This situation is unavoidable as a consequence of unstable blood clots. Bleeding can cause

complications such as sluggishness, lethargy, and anemia (Ariestiana et al., 2023). Hence, the prevention of bleeding after tooth extraction is indispensable.

Tannins and flavonoids are compounds that contribute to blood clotting (Marcińczyk et al., 2022). Tannin and flavonoids are naturally occurring compounds that can be found in plants (Pouyfung & Sukati, 2021). One of the herbal medicines used by people in Indonesia to treat bleeding is Ketapang leaves. Ketapang leaves also known as Indian almond is a member of the Combretaceae family. It is native to Southeast Asia with the genus of Terminalia and species of T. catappa L . (Habibullah et al., 2023). Ketapang leaves are used by the community as a traditional herb for the treatment of several diseases because they have antimicrobial (Allyn et al., 2018; Dewi & Mardhiyani, 2021), antiparasitic (Nugroho et al., 2016), antibacterial (Terças et al., 2017), anti-inflammatory (Ngemenya et al., 2021), antidiabetic (Iheagwam et al., 2023), antioxidant (Vyn et al., 2020), hepatoprotective (Bhasker Shenoy, 2020), and anticancer activities (Dewi & Mardhiyani, 2021). Although herbal medicine is utilized for pain, it still has potential for harm due to self-medication and low awareness. Therefore, the toxicity of herbal medicine needs to be examined (Yuan et al., 2016).

A study of *T. Catappa L.* by Purwaningsih, et al. (2020) was used to examine the elucidation of the resistor efficacy against the growth of S. Aureus as the bacteria causing gingivitis. The results show that the higher the concentration of the extract (5%), the wider the zone of the resistor area. The extract of *T. Catappa L.* contains tannin, saponin, terpenoid, and flavonoid (Purwaningsih et al., 2020). Leaves of *T. Catappa L.* extract show a good function on wound healing activity than using povidone-iodine and vaseline in mice (Mus musculus) conducted by Nugroho, et al. (2019). Mice were grouped into control, Vaseline, provided iodine group and treatment groups consisting of ethanolic extract either green (GLE) or brown leaves (BLE), and water extract green (GLW) and brown (BLW) leaves of Terminalia catappa L as an ointment. The mice were previously prepared with excision. The mice treated with GLE and GLW were better on day 12. Another research by Nguy, et al (2023) who used *T. Catappa L.* seed oil (TCO) for examining the physiological effects in mice proves that by using a high oral dose of 21780 mg/kg of mice, all instinctive behavior of mice is normal and the survival rate is 100%. Prolonging the intake of TCO makes the mouse coat is thick, soft, and smooth compare to just in short time use (72-h) (Nguy et al., 2023). However, little research was conducted in the integrated evaluation of chemical compounds, toxicity and histopathological effect of *T. Catappa L.* leaves.

The investigation consists of a test on the acute lethal dose (LD50) ethanol extract of *T. Catappa L.* As *T. Catappa L.* is accessible in Indonesia, this plant has the potential for the preparation of bleeding after tooth extraction. Given the benefit of *T. Catappa L.* as a medicine for bleeding, this study aims to investigate the chemical compounds, toxicity, and histopathological effects of its plant in mice (Mus musculus).

2. Method

This research has received approval of ethical clearance No. LB.02.03/EA/KEPK/0254/2022 from KEPK (Ethical Committee) of Poltekkes Kemenkes Denpasar, Bali.

This research method is an experiment in the laboratory with three variables: the existence of chemical compounds, toxicity defined by mice's (Mus musculus) behavior for 2x24 hours after being given *T. Catappa L.* extract, and histopathological abnormality defined by the changes that occurred in the liver and kidneys of mice after 2x24 hours of being given *T. Catappa L.*

2.1 Population and Sample

The Ketapang leaves used in the study were numbered 3 – 6 from the base, at a tree height of 6 meters. Ketapang leaves were picked at about 1 kilogram.

2.2. Steps of Research

The processes that are carried out as shown in Figure 1.

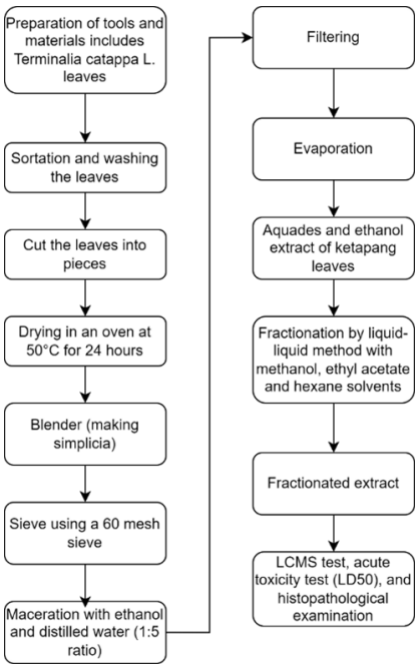


Figure 1: Research flowchart

1) Preparation of Ketapang leaves extract (*T. Catappa L.*)

Before conducting the acute lethal dose (LD50) toxicity test, the researchers prepared the leaf extract to be tested. The weight of Ketapang leaves to be extracted was 1 kilogram and the powder obtained was 500 gr. The active compounds of *T. Catappa L.* In general, will be maximally produced if a polar solvent is used, namely the ethanol extract of Ketapang leaves which is fractionated with ethyl acetate. The mature leaves are used because the older the leaves, the more the effect on the secondary metabolite content. Older leaves are indicated by a dark green color. The leaves were subsequently washed under running water (Sirat & Senjaya, 2021).

2) Making simplicia

The dark green Ketapang leaves were used. Older leaves affect the content of secondary metabolites. The leaves were washed under running water. Next, the Ketapang leaves were cut into smaller pieces. Then it was dried at 50°C for 24 hours. After the leaves dried, the simplicial was made by blending the dried Ketapang leaves. The blended Ketapang leaves were sieved with a 60-mesh sieve.

3) Ethanol and aquadest extract making

Ketapang leaf powder was then macerated with ethanol and distilled water (ratio of 1:5) for 3 days at room temperature. The filtrate was obtained by filtering with Whatman No.1 filter paper. The dregs obtained were then macerated again with 1000 mL of ethanol 2 times (Purwaningsih et al., 2020). The filtrates obtained were combined and then evaporated using a vacuum foam evaporator (Iwaki, Japan) at 400°C. Evaporation results obtained Ketapang leaves ethanol crude extract (*T. Catappa L.*) and Ketapang leaves aquades crude extract (*T. Catappa L.*). Crude extract is obtained in the form of a paste which is assumed at a concentration of 100% (Purwaningsih et al., 2020).The macerate obtained was filtered and evaporated using a rotary evaporator. The rotary evaporator helped the extract not damaged by high temperatures (Dhora, 2017).

4) Fractionation

The ethanol-condensed extract or distilled water condensed extract (coarse extract) of Ketapang leaves was then partitioned using ethyl acetate with a composition of 4 mg of crude extract and 200 ml of ethyl acetate (Purwaningsih et al., 2020). The mixture was shaken in a separatory funnel. Then, it was left for a while until the

ethanol and the hexane phases were seen. The two phases were separated, and the solvent for each phase was evaporated in a vacuum rotary evaporator to obtain ethanol of the ethyl acetate fraction. The ethanol extract of the ethyl acetate fraction of Ketapang leaves obtained was then used as an acute lethal dose (LD50) toxicity test material against mice (Mus musculus).

5) Procedure for acute lethal dose toxicity test (LD50)

The acute lethal dose (LD50) toxicity test procedure was carried out according to applicable regulations of the statute of Indonesia Food and Drugs Agency Supervisor Number 7, 2014 about Guidelines for In Vivo Nonclinical Toxicity Testing (Pedoman Uji Toksisitas Nonklinik Secara In Vivo (Guidelines for In Vivo Nonclinical Toxicity Testing), 2014). This procedure is adopted by researchers with toxicity test studies.(Dhora, 2017; Herli & Wardaniati, 2019; Munira et al., 2018; Pambudi et al., 2015; Purwaningsih et al., 2020). This procedure is as follows (Pambudi et al., 2015).

a. Preparation of extract solution.

Ethyl acetate fractionated ethanol extract was dissolved using 0.3% Na-CMC. Preparation of 0.3% Na-CMC solvent, namely, as much as 300 mg of Na-CMA dissolved with distilled water to a volume of 100 ml. Stir gently until homogeneous.

b. Preparation of extract solution

The dosages used were 1, 2, 4, 8, and 16 g/kg BW Mice (5 treatments). The average weight of mice is 22 grams.

c. Preparation of experimental animals

A total of 20 experimental animals were involved in this research with the following criteria: Balp/c strain mice, male, aged 2 to 2.5 months, weighing 21 to 24 grams were prepared as many as 20. The mice were divided into 5 treatment groups, randomly. Each group consisted of 4 mice. Then labeled/marked in each treatment group to differentiate between groups. The mice were fasted overnight for about 12 – 18 hours before the induction of anesthesia.

d. Treatment preparation

The 5 treatment groups in this research are according to the dose used, i.e. 1) the dose group is 1 g / kg BW, 2) the dose group is 2 g / kg BW, 3) the dose group is 4 g / kg BW, 4) the dose group 8 g / kg BW, 5) The dose group is 16 g / kg BW. As many as experimental animals, each was given 1 cc of extract solution orally (gastric sonde). Then observed for 2 x 24 hours.

6) Procedure for histopathological examination

Experimental animals were euthanized using cervical dislocation techniques. After the experimental animal has died, then disinfect the external abdominal area with 70% alcohol, then perform surgery on the abdominal area. Once the internal organs are exposed, the kidney and liver tissue are taken. Liver and kidney tissues were washed with 0.9% NaCl, then fixed with 10% buffered formalin. (in a 50-cc plastic pot). The tissue was then cut (trimming), with a thickness of 5mm. The tissue that had been cut earlier (specimen) was placed on the embedding cassette, then inserted into the tissue processor with the time setting of fixation NBF 10% 2 hours (Chandran & Usha, 2024; Rahmadhini & Wahyuni, 2023), fixation NBF 10% 2 hours, and dehydration (Sharif et al., 2020): 70% alcohol 2 hours, 95% alcohol 2 hours, 100% alcohol 2 hours, 100% alcohol 3 hours. The next process was clearing using toluol for 3 hours 2 times. Impregnation was performed afterward with paraffin for 2 hours 2 times. The preparations were put into the incubator and left overnight. The preparations were then stained with Harris-Haematoxyllin-eosin dye. After the staining process was complete, an examination was carried out under a microscope with 10x and 40x magnification, to see tissue histopathological changes.

3. Results

UPLC-MS was used for the analysis of the metabolite profile of the ethanol extract of the aquades fraction. UPLC can lower the consumption of mobile phase in the amount of 80%, which is a shorter time than using HPLC. Metabolite profile analysis was commenced by sample injection and it will be entered. The analysis of the metabolite profile of the ethanol extract from the aquades fraction of Ketapang leaves starts with injecting the sample, which is then introduced into the column. C18 column or octadecyl silica was used as the stationary phase. The benefit of using octadecyl silica as the stationary phase is its ability to separate compounds with varying polarities, from low to medium to high (Herli & Wardaniati, 2019).

Masslynx 4.1 application was used to process chromatograms to predict the molecular formula and the content of compounds. The results of the metabolite profile are shown in Figure 2.

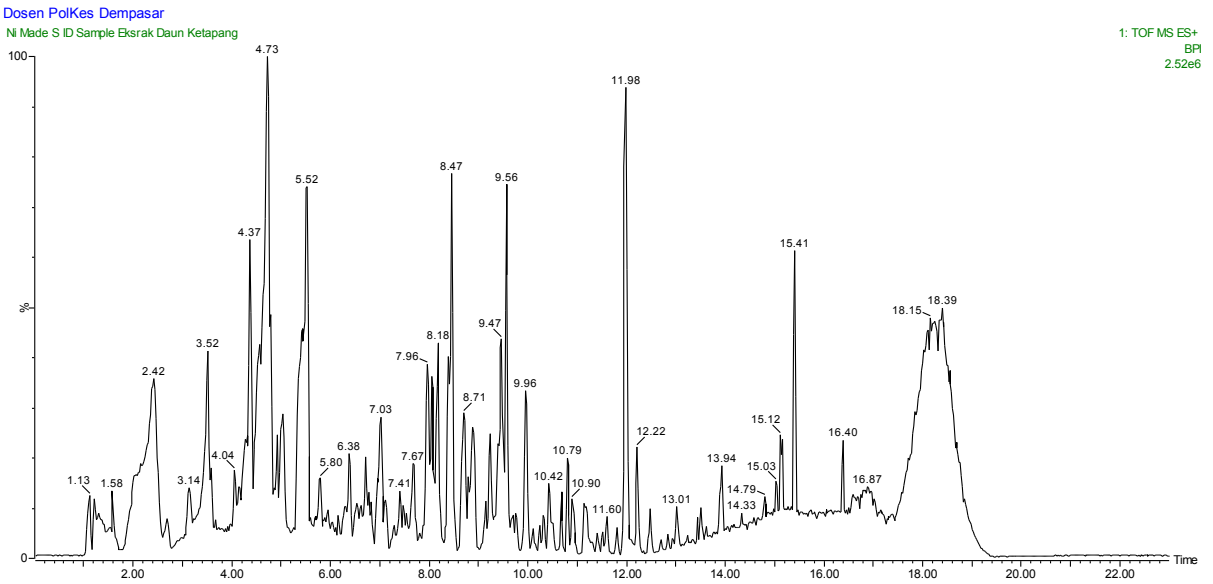


Figure 2: UPLC-MS chromatogram of the ethanol extract of the aquadest fraction of *Terminalia catappa L.*

Each peak in the chromatogram represents a distinct compound. The mass values obtained from the measurements, along with the calculated mass values in the spectra, allow for the prediction of the molecular formula. The measured and calculated mass values must be adjusted by subtracting the mass of one hydrogen atom (1.0078) because the addition of hydrogen atoms occurs during the separation process in the column, as a result of the ESI (+) ionization. The molecular formula is then determined based on the difference between the measured and calculated mass, which is within a ± 0.0005 range. The molecular formula is further confirmed using the www.chemspider.com website.

The results found that there are 19 compounds in the ethanol extract of the aquadest fraction (Table 1).

Table 1: Toxic category

Retention Time	Measured Mass	Calculated Mass	Formula	Compound
1.13	151.0352	151.0395	C_8H7O_3	Mandelate
1.58	130.0873	130.0868	$C_6H_{12}NO_2$	6-Aminohexanoate
2.42	120.0814	120.0813	$C_8H_{10}N$	1-Allylpyridinium
3.14	1102.1033	1102.1029	$C_{40}H_{16}N_{25}O_{14}S$	Unknwon
3.52	188.0720	188.0745	$C_8H_{14}NO_2S$	2-methoxy-1-(2-methyl-4H-thiazol-5-yl)propan-1-ol
4.37	449.1087	449.1084	$C_{21}H_{21}O_{11}$	Cyanidin-3-glucoside
4.73	433.1144	433.1135	$C_{21}H_{21}O_{10}$	**Pelargonidin 3-O-glucoside**
5.52	585.1256	585.1244	$C_{28}H_{25}O_{14}$	Unkown
5.80	197.1178	197.1178	$C_{11}H_{17}O_3$	3-Hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptane-1-carboxylate
6.38	261.1128	261.1127	$C_{15}H_{17}O_4$	7-Hydroxy-4-(methoxycarbonyl)-2-(2-methyl-2-propanyl)chromenium
7.03	309.0872	309.0875	$C_{17}H_{13}N_2O_4$	3-Carbamoyl-1-[2-oxo-2-(2-oxo-2H-chromen-3-yl)ethyl]pyridinium

7.41	570.2218	570.2187	$C_{26}H_{36}NO_{13}$	1-[(4-methoxyphenyl)methyl]-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinolin-2-ium;(2R,3R)-2,3,4-trihydroxy-4-oxo-butanoate
7.67	648.4308	648.4345	$C_{35}H_{62}N_5O_2S_2$	Unknown
7.96	275.2017	275.2011	$C_{18}H_{27}O_2$	(9E,11E,13E,15E)-9,11,13,15-Octadecatetraenoate
8.18	645.2926	645.2924	$C_{35}H_{41}N_4O_8$	Unknown
8.47	345.0617	345.0610	$C_{17}H_{13}O_8$	5,7-Dihydroxy-2-(4-hydroxy-3,5-dimethoxyphenyl)-4-oxo-4H-chromen-3-olate
8.71	181.1230	181.1229	$C_{11}H_{17}O_2$	2-(5-Hexen-1-yl)-5-hydroxy-3,4-dihydropyranium
9.47	343.0454	343.0454	$C_{17}H_{11}O_8$	Unknown
9.56	343.1188	343.1188	$C_{19}H_{19}O_6$	(3R)-3-(2,3-Dihydro-1,4-benzodioxin-6-yl)-3-(3,4-dimethoxyphenyl)propanoate
9.96	345.1337	345.1338	$C_{19}H_{21}O_6$	(1R,2R,5S,8S,9S,10R,11S,12S)-5,12-Dihydroxy-11-methyl-6-methylene-16-oxo-15-oxapentacyclo[9.3.2.$1^{5,8}$.$0^{1,10}$.$0^{2,8}$]heptadec-13-ene-9-carboxylate
10.42	214.2535	214.2535	$C_{14}H_{32}N$	tetradecylammonium
10.79	627.2828	627.2819	$C_{35}H_{39}N_4O_7$	3-{(3S,4S)-5-{2-[(3-Ethyl-5-formyl-4-methyl-1H-pyrrol-2-yl)methyl]-5-(methoxycarbonyl)-3-methyl-4-oxo-1,4-dihydrocyclopenta[b]pyrrol-6-yl}-3-methyl-2-[(3-methyl-5-oxo-4-vinyl-2,5-dihydro-1H-pyrrol-2-y l)methyl]-3,4-dihydro-2H-pyrrol-4-yl}propanoate
10.90	271.1692	271.1692	$C_{18}H_{23}O_2$	(17β)-17-Hydroxyestra-1(10),2,4-trien-3-olate
11.60	277.2166	277.2166	$C_{18}H_{29}O_2$	linolenate
11.98	601.5199	601.5148	$C_{22}H_{65}N_{16}OS$	unknown
12.22	425.3632	425.3632	$C_{27}H_{45}N_4$	unknown
13.01	425.3607	425.3644	$C_{27}H_{45}N_4$	unknown
13.94	423.3973	423.3991	$C_{31}H_{51}$	unknown
14.33	423.3975	423.3991	$C_{31}H_{51}$	unknown
14.79	423.3984	423.3991	$C_{31}H_{51}$	unknown
15.03	419.3139	419.3140	$C_{27}H_{39}N_4$	5-Ethyl-2-methyl-1-[3-({4-[(E)-phenyldiazenyl]-5,6,7,8-tetrahydro-1-naphthalenyl}amino)propyl]piperidinium (Alkaloid piperidin)
15.12	423.3979	423.3991	$C_{31}H_{51}$	unknown
15.41	423.3986	423.3957	$C_{19}H_{51}N_8S$	unknown
16.40	423.3958	423.3991	$C_{31}H_{51}$	unknown
16.87	423.3968	423.3991	$C_{31}H_{51}$	unknown

The major compound in the ethanol extract of the aquadest fraction is Pelargonidin 3-O-glucoside with an iFit percentage of 97.56%. Pelargonidin 3-O-glucoside is a type of anthocyanin including the flavonoid compound (Firdaus Kamal et al., 2014). Spectra and chemical structure of the compound can be seen in Figure 3.

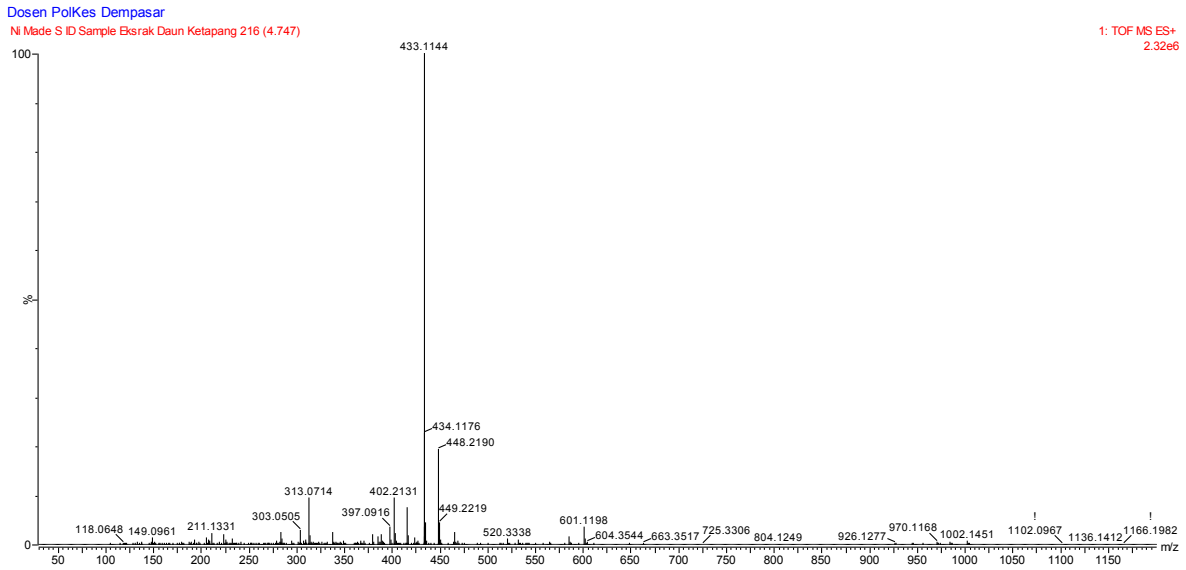
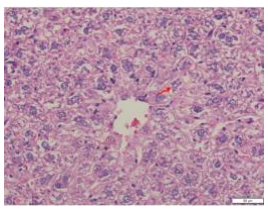


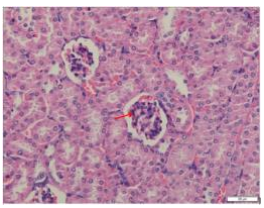
Figure 3: Spectra and chemical structures of major compounds

The ethanol extract of the aquadest fraction of Ketapang leaves contains several secondary metabolites such as alkaloids, i.e. 1-Allylpyridinium and 5-Ethyl-2-methyl-1-[3-({4-[(E)- phenyldiazenyl]-5,6,7,8-tetrahydro-1-naphthalenyl} amino) propyl] piperidinium and the flavonoid group, namely Cyanidin-3-glucoside and Pelargonidin 3-O-glucoside. Hence, the ethanol extract of the aquadest fraction can be utilized as a medicine to control bleeding after tooth extraction.

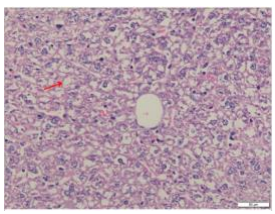
The results of the acute toxicity test (LD50), it was found that during the 2x24 hour observation period, all (100%) mice in the five treatment groups did not show signs of poisoning, mice moved agilely, and mice also kissed/smelled each other. In all treatment groups (100%), after 2 x 24 hours of administration of ethyl acetate fractionated Ketapang leaf ethanol extract, no deaths were found. The histopathology images of the mice's liver and kidney after LD50 test were carried out as shown in Figure 4.



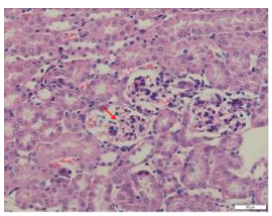
(a) Liver of mice treated with 1g/kg BW. Severe damage occurs in the form of hydrophic degeneration in the liver in all places (diffuse).



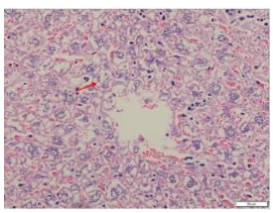
(b) Mice kidneys treated with 1g/kg BW. The kidneys look normal, there is no glomerular reduction.

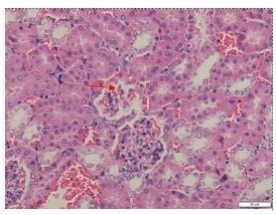


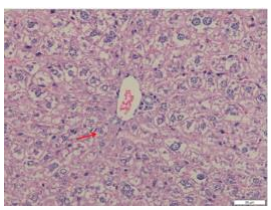
(c) Liver of mice treated with 2g/kg BW. Severe damage occurs in the form of hydrophic degeneration in the liver in all places (diffuse).

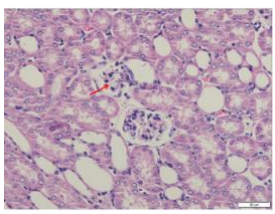


(d) Mice kidneys treated with 2g/kg BW. Damage occurs in the form of moderate glomerular reduction in the kidneys in one place (focal).







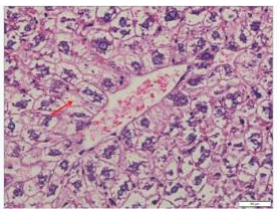


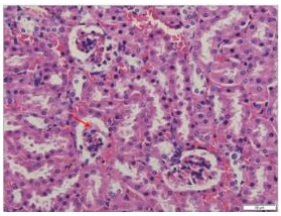
(e) Liver of mice treated with 4g/kg BW. Severe damage occurs in the form of hydrophic degeneration in the liver in all places (diffuse).

(f) Mice kidneys treated with 4g/kg BW. Damage occurs in the form of moderate glomerular reduction in the kidneys in one place (focal).

(g) Liver of mice treated with 8g/kg BW. Severe damage occurs in the form of hydrophic degeneration in the liver in all places (diffuse).

(h) Mice kidneys treated with 8g/kg BW. Damage occurs in the form of moderate glomerular shrinkage in the kidneys in several places (multifocal).





(i) Liver of mice treated with 16g/kg BW. Severe damage occurs in the form of hydrophic degeneration in the liver in all places (diffuse).

(j) Mice kidneys treated with 16g/kg BW. Damage occurs in the form of moderate glomerular shrinkage in the kidneys in several places (multifocal).

Figure 4: Histopathology images of the liver and kidney of the mice after LD_{50} test of ethanol extract of *T. Catappa L.*

The liver in the doses either 1g/kg BW, 2 g/kg BW, 4 g/kg BW, 8 g/kg BW, and 16 g/kg BW shows severe damage in the liver. The kidney with 1 g/kg BW shows normal condition. Meanwhile, in 2 g/kg BW, 4 g/kg BW shows focal light damage, and 8 g/kg BW as well as 16 g/kg BW shows multifocal moderate damage in the kidney. The results of the histopathology condition in the liver and kidney and the statistical calculation of the damage show that in all treatment groups, mice were found whose hepatocyte cells experienced a severe degree of hydropic degeneration shown in Table 2.

Table 2: Histopathology results in mice liver

No. of mice	Dose Group					p-value
	1 g/kg BW	2 g/kg BW	4 g/kg BW	8 g/kg BW	16 g/kg BW	
Liver						
1	3	3	0	3	3	0.331
2	0	3	3	3	3	
3	3	3	3	3	3	
4	3	3	3	3	3	
Kidney						
1	0	0	0	2	2	0.002
2	0	1	2	2	2	
3	0	1	1	2	2	
4	1	1	1	2	2	

Score 0 shows the normal condition without damage, score 1 shows the focal (moderate) damage in one place, score 2 shows multifocal (moderate) damage in several places, and score 3 shows diffuse (severe damage) in all places. The damage is hydropic degeneration in the liver and glomerulus reduction in the kidney. The result of the p-value in Table 2 of histopathology in the liver shows 0.331, meaning that there is no significant difference in liver damage of the mice in treatment groups. Meanwhile, the kidney damage of the Kruskal Wallis test resulted in a p-value of 0.002 shown in Table 2, meaning that there is a significant difference in kidney damage in the mice.

4. Discussion

Based on the results of examination and analysis of LCMS results, 20 compounds can be identified and 15 compounds whose compound names are unknown. Compounds that can be identified include the types of flavonoids, and tannin compounds also belong to the flavonoid group. The presence of tannins can precipitate

blood proteins and constrict the narrow blood vessel network. Tannins can act as an astringent that causes the closing of skin pores hardens the skin, and stops exudate and light bleeding. Meanwhile, flavonoids can act as an anti-inflammatory which can reduce inflammation and pain.

The results of the acute lethal dose (LD50) toxicity test of the ethanol extract of *T. Catappa L.* in mice showed that the ethanol extract of ketapang leaves is safe, and not toxic. In general, the smaller the LD50 value, the more toxic the compound is (Raj et al., 2013). The results obtained (in mg/kg BW) can be divided into several classes according to the potential for acute toxicity of the test compounds, i.e super toxic is with LD50 5 mg/kg BW or less, extremely toxic with 5 – 50 mg/kg BW, very toxic with 50 – 500 mg/kg BW, medium toxic with 0.5 – 5 g/kg BW, fairly toxic with 5- 15 g/kg BW, non-toxic>15 g/kg BW.

Ethanol extract of Ketapang leaves and aquadest is concluded in the practically non-toxic category. Histopathological examination of the liver and kidney organs of mice with the highest dose (16gr/kg BW), showed diffuse hydropic degeneration (spreading) in the liver. These results were slightly different from the studies of Astawan, et al. (2005) which histomorphological showed degeneration of cells in the liver and kidneys, especially in the 4, 8, and 16 g/kg BW treatment groups (Astawan et al., 2005). While in this study mice were fed 16g/kg BW of *T. Catappa L.* extract, there was no liver degeneration. The results are in line with Nugroho, et al. (2020) in which the mice were extracted with *T. Catappa L.* of green and brown leaves doses of 125 mg/kg, 250 mg/kg, 500 mg/kg, 750 mg/kg and 1000 mg/kg shows the toxic effect on the liver of mice in terms of necrosis and degeneration damage (Rudy et al., 2020). The dose at 1000 mg/kg BW shows the most significant liver degeneration among all the doses in the aforementioned study. This is in line with the present study that shows at 16 gr/kg BW shows the degeneration of cells in the liver and kidney. The studies show also that the color of the leaves either green or brown can cause toxic effects on the liver of mice at certain doses, specifically at more than 1000 mg/kg BW.

The highest dose used of ethyl acetate fraction of the peel Kandis acid (Garnicia cowa Roxb) shows dangerous active damage. Besides, the use of ethyl acetate is observed to have the significant effect on the activity of Serum Glutamic Pyruvic Transaminase (SGPT) in white mice (Wahyuni et al., 2017). The present study performed the testing on the mice with *T. Catappa L.* extract once for 2x24 hours and extracting ethyl acetate in the fractionation process. The extract which is given repeatedly and for a long time, can cause an accumulation of dangerous active ingredients toxic to the tested animal it is proven that repeated intake of Hibiscus rosa-sinensis L. extract in high doses of 800 mg/kg for 14 days can cause liver and kidney toxicity in mice (Nath & Yadav, 2015). However, in fact, the factor which affects the tested animal was proven by Wahyuni, et al. (2017) is the dose ($p < 0,05$) and the duration of administration of the extract does not significantly affect ($p>0,05$) (Ridzwan et al., 2014; Wahyuni et al., 2017). This is in line with research by Deshpande, et al. (2015) which shows that the exposure of 90-day repeated dose oral administration of Urban leaves (Centella asiatica) produced no significant toxic effect in rats with LD50 > 2000 mg/kg (Deshpande et al., 2015). However, the study suggests that a low dose of Hibiscus rosa-sinensis L. extract i.e. 400 mg/kg can be considered safe for traditional medicine (Nath & Yadav, 2015). This is in line with the present study in which the dose of 1 g/kg, 2 g/kg, 3 g/kg, and 4 g/kg is proven safe, even in 8 g/kg. Although 16 g/kg dose is toxic somehow, particularly for liver cell degeneration.

The liver is crucial for nutrient metabolism, glucose and lipid synthesis, and the detoxification of drugs and foreign substances. It is commonly the primary organ affected by chemical damage. Various compounds can harm liver cells, with oxidative stress being a major contributor, as an excess of pro-oxidants can damage cells, often leading to cell death. The main function of the kidneys is to eliminate waste products, during the reabsorption process, potentially toxic chemicals can predispose the kidneys to injury.

The kidney's vulnerability to toxic damage is linked to the complexity of its structure and function. Nephrotoxicity can arise as a serious complication from drug treatments or chemical exposure. This study demonstrates that, after the LD50 test, the liver experiences more severe damage than the kidneys in mice. This is understandable considering the function of the liver as the main organ of detoxification. Considering that the cause of hydropic degeneration is diet or toxicity, and based on the results of the LD50 test, this study shows that the ethanol extract

of *T. Catappa L.* is not toxic or safe. The cause of hydropic degeneration may be diffuse in the liver of mice, namely the diet from the ethanol extract of *T. Catappa L.* given as treatment.

Many plant families harbor potentially toxic alkaloids (Griffiths et al., 2021). Secondary metabolites in plants, such as alkaloids, flavonoids, saponins, tannins, steroids, and triterpenoids, can be toxic to both plants and animals (Paiva et al., 2023). In some plants, these compounds serve as a defense mechanism against threats, but at specific doses, they may also have medicinal properties. The potential liver and kidney damage observed in mice after the LD50 test could be attributed to the secondary metabolites present in the ethanol extract of *T. Catappa L.* leaves.

This study presents the histopathological experiment of T. catappa L which is exposed to mice with the limitation of dose to 1 g/kg, 2 g/kg, 3 g/kg, 4 g/kg and 8 g/kg and 16 g/kg BW. The results show there is diffuse hydropic degeneration in the liver with dose of 16 g/kg BW. Meanwhile, in the kidney, there is no degeneration occurred. T. catappa L. is categorized as a non-toxic substance. Regarding the importance of safe pain curing using plants, an extension for the near future is the use of the T. catappa L. to be tested in real as an anti-bleeding agent after tooth extraction.

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Depression and Anxiety in Patients with Stroke and their Caregivers: A Literature Review

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Abstract
Stroke poses various forms of burden on those who suffer from it. It can lead to not only physical and cognitive disabilities but also psychological conditions, including stress, depression, and anxiety. These psychological and physical burdens resulting from stroke may also predict its recurrence, therefore, caregivers play an important role in taking care of patients and preventing exposure to risk factors. Literature has focused on the effects of stroke on patients, and there has been limited research on its effects on caregivers. Thus, this literature review aims to explore the link between patients' physical and psychological health post-stroke and its influence on caregivers' psychological health. It also outlines the effects of caregivers' psychological health on patients' health outcomes and recovery. Research shows the interdependent link between these factors, such that caregivers with poor psychological health may pose psychological stress on their patients and vice versa. Current intervention methods to improve patient-caregiver psychological health were discussed, and findings on their treatment outcomes were mixed.

Keywords: Depression, Anxiety, Stroke, Stroke Patients, Caregivers, Well-Being, Prevalence, Cognitive Behavioral Therapy, Mindfulness-Based Stress Reduction, Mindfulness-Based Cognitive Therapy

1. Introduction

Neurological diseases, including dementia, Alzheimer's, and strokes, are prevalent in a large portion of the world's population. The growth and aging of our population contribute to the increasing cases of stroke, and of the 15 million annual cases of stroke, 5 million are faced with permanent disability (World Health Organization, n.d.). Stroke risk is associated with various preventable behavioral and environmental factors (Feigin et al., 2024). For instance, high BMI, diets with high-sugar beverages and red meat, and low physical activity were factors associated with a global increase in the rate of life-year loss due to stroke-related disability from 1990 to 2021 (Feigin et al., 2024).

Family caregivers play an important role in their patients' recovery. Patients' psychological health poses implications on the risk of stroke recurrence, thus, caregivers' supervision plays a crucial role in maintaining patients' physical health and well-being after discharge, which could reduce rates of recurrence. However, caregivers may suffer from sudden life changes as a result of the stroke incident, such as adjusting to new responsibilities and having their routine and social life interrupted. This disruption, ranging from sleep disturbances to reduced social life, may lead to worsened quality of life and mental health conditions such as

anxiety and depression. Therefore, caregivers' mental and physical health needs should be looked after to mitigate their and their loved ones' health outcomes. This literature review aims to outline the implications between caregivers' psychological well-being and stroke patients' physical and mental health and current interventions.

2. Prevalence and Onset of Post-Stroke Depression and Anxiety

2.1. In Patients

There is a difference between the geographical distribution of stroke burdens worldwide (Feigin et al., 2024). In this analysis, stroke burden refers to the prevalence, deaths, age-standardized incidence, and DALY rates, which indicates the total life-year loss due to premature death and disability (World Health Organization, n.d.). Countries in the middle, high-middle, and low-middle SDI regions were observed to have the most stroke burden, including East and Central Asia and Sub-Saharan (Feigin et al., 2024). High-income countries such as North America, Australasia, and Latin America reported a lower stroke burden. There was a decrease in PAF-population attributable fraction, which refers to the proportion of stroke-related life-year loss as a result of exposure to risk factors (World Health Organization, n.d.), such as diets low in vegetables/fiber, environmental pollution, and smoking overall. Despite this, observed increases in stroke-DALY rates of LICs reflect their ineffective prevention strategies, whereas decreases in DALY rates of HICs reflect their successful prevention strategies (Feigin et al., 2024).

Among around 5 million acute ischemic stroke patients in the U.S. from 2003 to 2017, around 163,226 experienced depression, and 258,782 experienced generalized anxiety disorder (Patel et al., 2023). Compared to anxiety, depression was more prevalent among these patients. An analysis of data of 4,079 stroke patients in Glasgow, United Kingdom, found 24% of patients with possible to definite abnormal depression and 29% with possible to definite abnormal anxiety, and these proportions are similar for the 1,247 patients with transient ischemic attack or minor stroke (Broomfield et al., 2014). Within 36 countries in West/South Asia and Africa, the prevalence ranges from 30.43% to 50.24% for post-stroke depression and around 10% and 44.19% for post-stroke anxiety as measured by semi-structured interviews and questionnaires, respectively (Mahadevan et al., 2021).

The presence of depression and anxiety in stroke patients might pose worsened health outcomes for them. Compared to those with anxiety and with either symptom, depressed patients were 40% more likely to have functional loss, to go to a care facility post-discharge, and 36% more likely to stay in the hospital for longer than 10 days (Patel et al., 2023). While anxiety did not have a higher prevalence or predict disability or length of hospital stay in these patients, it increased the likelihood of them going to a care facility post-discharge. Patients with comorbidities such as hyperlipidemia and alcohol and drug abuse had a higher prevalence of depression, and those who smoke showed a higher prevalence of anxiety (Patel et al., 2023).

Unlike other medical comorbidities, such as diabetes and a history of stroke, depression and anxiety at 1 month post-stroke did not predict patients' functional outcomes and quality of life after 1 year, regardless of stroke severity and pre-morbid conditions (Donnellan et al., 2010). Regardless, depression was associated with poorer outcomes at both 1-month and 1-year individually (Donnellan et al., 2010). In contrast, Lee et al. (2019) found that anxiety at the acute phase of stroke, despite not being associated with patients' neurological severity or physical disability, was predictive of these outcomes a year after stroke. For instance, those who had anxiety 2 weeks post-stroke, compared to those without it, showed worsened functional outcomes 1 year later. As such, it is suggested that anxiety's presence at the acute phase of a stroke may reflect the initial shock of the event rather than the patient's mental health status as a result of their functional loss, but in the long run, it may develop as the loss becomes more apparent to patients and interfere with their recovery (Lee et al., 2019). Therefore, to reduce the effects of anxiety on patients' functional recovery, it is recommended that anxiety be screened early, as those with severe strokes who take longer to recover may be more prone to developing anxiety, which might slow down their recovery (Lee et al., 2019).

Results for the prevalence of depression and anxiety concerning time points after stroke are mixed. For instance, depression prevalence was found to be 35% at 1-month post-stroke (Donnellan et al., 2010) but 30% at four months

and 24% at six months (De Wit et al., 2008). Notably, these studies included samples from hospitals and rehabilitation wards. Therefore, the decreasing rates of prevalence from 35-25% from 1-month to 6-months across studies may be due to patients' recovery from either rehabilitation or, as suggested earlier, from the initial shock of the stroke event. Anxiety prevalence ranges from 22 to 34% at 6 months and one year post-stroke, respectively (Donnellan et al., 2010; De Wit et al., 2008). Overall, both studies reported prevalence rates for depression ranging from 24-35% from 1-6 months, while anxiety ranges from 25-34% from 6-months to 1 year post-stroke. Regardless, the prevalence of both symptoms was comparable at 1-month and 1-year post-stroke (Donnellan et al., 2010) and was also found to be relatively similar across 2, 4, and 6-months post-stroke (De Wit et al., 2008). Patients who have not initially reported symptoms of depression and anxiety may experience symptoms later on. After 1 year, 22% remained depressed among the 35% who reported depression at 1 month, and depression and anxiety were reported in an additional 14% and 11% of those who did not initially report symptoms, respectively (Donnellan et al., 2010). Consistently, De Wit et al. (2008) found an increase in depressive and anxious symptoms after 4 and 6 months among patients who did not initially experience mood changes 2 months after a stroke. Unlike the observed decreases in anxiety severity over time, depression severity seemed to remain unchanged (De Wit et al., 2008). However, the severity of symptoms among patients who were constantly depressed or anxious during 2-6 months post-stroke was significantly worse than that of those who only became anxious or depressed at certain time points (De Wit et al., 2008). Since their sample consisted of patients in rehabilitation wards, the unchanging severity of symptoms and the additional number of patients experiencing these symptoms over time may reflect limitations in the current rehabilitation procedure in helping with recovery, suggesting the need for both early and long-term screening for the potential development of mood disorders (De Wit et al., 2008).

A meta-analysis of studies in 22 countries, comparing 3000 stroke patients and 3000 individuals without a history of stroke, showed that depression and home or workplace psychosocial stress were ones of the 10 most significant risk factors of stroke, besides other medical and behavioral risks such as a history of hypertension, smoking habits, diets low in fruits and fish and high in red meat or fried foods (O'Donnell et al., 2010). While a history of hypertension, smoking, and depression was associated more with one subtype of stroke than another, diet, psychological stress, and physical activity were associated with an increased risk in all types of stroke (ischaemic vs. intracerebral hemorrhagic).

2.2. In Caregivers

Factors associated with the first stroke event might also predict the recurrence of stroke. For instance, a study showed that 30.7% of 358 ischaemic stroke patients had one or more recurrent strokes over the 2-year post-stroke period (Zhuo et al., 2020). Compared to first stroke patients, those who experienced recurrence were older, smokers, diabetic, had moderate to severe depression, higher stroke severity, and certain medical conditions including hypertension. A meta-analysis of 4648 stroke patients reported 537 recurrences (Wu et al., 2019). They showed a prevalence rate of post-stroke depression (PSD) ranging between 15.9% and 40.5% and that those with PSD had a 48% higher risk of recurrence than those without PSD. The study also reported the association to be stronger within the 2-year follow-up period, which suggests that the risk of developing recurrence in depressed patients is higher after the acute phase of the initial stroke (Wu et al., 2019). Thus, caregivers play important roles in supporting patients with comorbidities, whether they appear before or after the stroke event, which may reduce recurrence rates.

However, patterns of results in cases of depression and anxiety among caregivers indicate a lack of attention to caregivers' mental health needs. A meta-analysis including 1756 caregivers of stroke patients reported a prevalence of 40.2% for depression, which is 2 times higher than the general population, and 21.4% for anxiety (Loh et al., 2017). Among a sample of 45 carers of stroke patients recently discharged from rehabilitation or hospital, 51% were anxious at 1-month post-discharge, and 78.3% of them remained anxious after 3 months (Greenwood & Mackenzie, 2010). Notably, they reported that while carer depression scores reduced significantly from one to three months, their anxiety scores did not show a significant difference, indicating its prevalence in the acute phase and endurance. This pattern differed from that reported in a previous study (De Wit et al., 2008), where anxiety decreased over time. Similarly, about 78% and 64% of caregivers who were initially anxious and

depressed remained so after 3 months (De Wit et al., 2008); these symptoms may not reduce over time and remain high up to 6 months after the stroke event in caregivers of stroke patients (Chow et al., 2007).

3. Factors contributing to caregiver's well-being

3.1. Care-duration

Caregivers play an important role in supporting patients who have survived stroke, especially those who faced physical and cognitive impairments and hence have higher dependency on caregivers. Caregiving tasks may demand several hours of the caregiver's day, ranging anywhere from 5.87 hours (Grant et al., 2013) to >8 hours per day (Zhao et al., 2021). Most caregivers in the reviewed studies are female and spouses of the patients (Zhao et al., 2021; Yuliana et al., 2023; Greenwood & Mackenzie, 2010; Atteih et al., 2015). Along with other factors, the duration of care per day is a factor contributing to higher caregiver depression, anxiety, and burden (Zhao et al., 2021; He et al., 2023; Woodford et al., 2018; Villa-García et al., 2024; Hu et al., 2018). Caregiver burden is defined as the extent to which caregiving negatively impacts caregivers' physical and mental health, social life, and financial status (Zarit et al., 1986). Zarit et al. (1980) have developed a scale for measuring caregiver burden that is used in a variety of studies examining the level of discomfort caregivers experience while enduring the aforementioned impacts of caregiving (He et al., 2023; Hu et al., 2018). He et al. (2023) assessed aspects of patients' post-stroke health and its association with caregiver burden, using the Zarit Burden Interview (ZBI). Among the 966 ischemic stroke patient-caregiver dyads, longer hours of care, higher stroke severity, and depressive symptoms in patients are significantly associated with more caregiver burden. In line with He et al. (2023)'s findings, Hu et al. (2018) found that higher symptoms of depression and anxiety in caregivers were associated with higher caregiver burden. About 43.9% and 53.9% of their sample of 117 caregivers reported symptoms of anxiety and depression, respectively, and around 68.4% reported caregiver burden.

A qualitative study showed that for caregivers having mild symptoms of depression and anxiety, having less time to spare was reported as exhausting, causing unhappiness and a sense of confinement (Woodford et al., 2018), even among those having taken up the caregiving role for up to 22 years. Caregiving intensity correlates with higher levels of patients' dependency; for instance, Villa-García et al. (2024) showed that mild to moderate levels of dependency were linked to 21 to 40 hours of care/week, respectively. The dependent variables were 1) caregiver burden (assessed using the "Care-related Quality of Life" scale, measuring 7 dimensions of caregivers' mental, physical, financial, social, and life-activity outcomes, fulfillment, and social support) and 2) caregiver well-being (using the CarerQoL-VAS). The independent variables were caregivers' characteristics (e.g., age, gender, socioeconomic, employment status); care-receivers' characteristics (including dependency, severity of stroke, and quality of life); and aspects of caregiving intensity. Results suggest that while 75-80% of caregivers were fulfilled with caregiving tasks at 6 months after stroke regardless of levels of dependency, caregiving-related mental, physical, financial, daily-activities, and relational problems increased with a higher level of dependency. Additionally, being a female and having to provide constant supervision (their sample averaged 30.7 care hours/week) were also associated with higher caregiver burden, regardless of levels of dependency. Importantly, they found a correlation between patients' anxiety and depression (i.e: 1 of the 5 dimensions of patient's quality of life measured by the EuroQoL-5D-5L scale) and caregivers' low levels of happiness, and they suggested the need for interventions supporting women who spend more time caring for patients with poor mental health. Depression in caregivers was linked to caregiver burden. Higher caregiver burden and more depressive/anxious symptoms in patients were related to lower scores on caregiver happiness (Villa-García et al., 2024).

A 1-year longitudinal study suggests that the type of factors contributing to caregiver burden might change over time (Rigby et al., 2009). They have used two different scales to assess the caregiver burden (i.e, the Relatives Stress Scale (RSS) and the Bakas Caregiving Outcomes Scale (BCOS)). Results showed that during the acute period post-stroke (7 days), patient demographics such as older age and male gender might predict increased burden; however, over time, other factors regarding patients' functional disability and poor mental health may be more important in predicting increased burden. Notably, their results also showed that patients' cognitive function and dependency (measured with the Barthel Index) significantly improved over the 12-months period. While a higher burden on the RSS is associated with a patient's functional impairments, the higher burden on the BCOS is

associated with older age and male gender. The difference between the correlations observed on the RSS and the BCOS reflects the differing contributing factors on caregiver burden when assessed on different scales.

3.2. Social support

The lack of certainty as a result of the deficiency in social and health support was also one of the main themes of difficulty that led to distress, anger, and sadness among caregivers of stroke patients (Woodford et al., 2018). In this qualitative study, two participants who received written informational leaflets reported the information provided to be often generalized, making it hard to identify which applies to them. Social support has been found to contribute to fewer symptoms of depression in stroke patients, which is associated with fewer mental and physical health deficits in their respective caregivers (He et al., 2023; Sit et al., 2004). Social support may come in various forms, including emotional, tangible, and informational support (Sit et al., 2004). 83% of their sample of 102 Cantonese/Mandarin-speaking caregivers of stroke patients have experienced deficits in physical health during the first three months after taking up the caregiving role. They found that those who received more tangible (e.g., help with chores and provision of necessary materials) and social companionship and perceived their patients as less dependent showed better psychological health. This finding, to an extent, corresponds to Wade et al. (1986)'s finding, suggesting that support with physical caregiving tasks alone may not be sufficient to reduce caregivers' psychological stress. Similarly, Villa-García et al. (2024) reported that most caregivers were fulfilled with the caregiving tasks regardless of the patient's dependency, but the problems with psychological stress increased with more dependency. Therefore, their results suggest the role of social companionship and support in mitigating caregivers' stress.

The types of support most lacking were tangible and informational support, despite them having attended educational workshops. They suggested that since information is often provided by health professionals, it is less suitable for the caregiving job, which occurs daily and may require more in-depth details of what to do in a specific situation, rather than general knowledge (Sit et al., 2004). They also found that lower education is linked to less informational support and attributed this to the potential miscomprehension of the information that is often provided in written form. This may further highlight the need for adequate availability of resources to support caregivers, particularly within home settings. Caregivers' perspective of their support sources is much higher than the actual sources available to them; and as for professional health-related service, this deficiency is reflected in their need for resources that would support caregiving at home, and if these are already available, they should be more personalized and intend to target both patients and caregivers (He et al., 2023; Woodford et al., 2018; Sit et al., 2004).

3.3. Demographics- gender, age, education, and financial status

Effects of demographic discrepancies on the extent of caregiver burden were also found. Female caregivers tend to experience more burden than male caregivers (Villa-García et al., 2024). Depression and anxiety were more likely found in females and Caucasians than in males and Asians (Patel et al., 2023). Consistently, there was an increased prevalence of depression in female and Caucasian caregivers who care for female stroke patients (Loh et al., 2017). Data for anxiety was not generated due to a lack of studies on these moderators, suggesting the need for research in this area. The heightened prevalence of anxiety in stroke patients has been linked to socioeconomic and demographic characteristics such as younger age, female gender, and living in less supported areas (Broomfield et al., 2015). On the other hand, although Hu et al. (2018) found significantly higher symptoms of depression and anxiety in female than male caregivers, this gender factor contributed to the variations in depression and anxiety to a lesser extent when considered with other factors such as care duration, educational level, and medical payment methods. Along with being caregivers of patients with stroke in comparison to patients with other neurological diseases, less education is also predictive of depression and anxiety at 6 months post-stroke (Chow et al., 2007)

4. Implications of caregivers' mental health on their patients' psychological health and recovery

Regarding the relationship between caregiver and patient health outcomes, a study reported that patients' and caregivers' depression and anxiety were interdependently predictive of aspects of both their own and their partner's quality of life (QoL) (Yuliana et al., 2023). Their study used the DASS-42 Questionnaire to measure depression, anxiety, and stress symptoms, and the "WHODAS 2.0 Indonesian Version" to measure patients' stroke-related disability. They hypothesized that these variables may pose direct and independent decreases in patients' and their caregivers' mental, physical, and overall QoL. Anxiety symptoms in caregivers and their patients are found to correlate with lower scores in all three aspects of their own and their partner's QoL. In other words, lower overall mental and physical QoL in caregivers may be linked to their own and their patients' high anxiety symptoms. Interestingly, depression symptoms in caregivers do not predict their own poor mental QoL, however, it predicts both their partner's poor physical and mental QoL. Similarly, Atteih et al.'s (2015)'s study has shown the interdependence relationship between caregiver and patient's depression and anxiety symptoms. This further emphasizes the influence of caregivers' well-being on their patients' physical and psychological health. The severity of the patient's disability was also negatively correlated with both the physical and mental aspects of their own QoL, but only negatively impacted the caregiver's mental QoL (Yuliana et al., 2023). Additionally, the stress levels of caregivers are only negatively associated with their patients' mental QoL and not with the patients' overall or physical QoL.

Similarly, a 2-year longitudinal study assessed how depressed moods (not clinical mood disorders) in caregivers were impacted by patient factors, including the patient's disability, level of social activities, and depression, and the caregivers' perception of recovery (Wade et al., 1986). They used the "Wakefield Self-assessment Depression Inventory" to measure depression and the Barthel Index, Frenchay activities index, and the Hodkinson mental scale to measure aspects of patients' mental state. Depressed caregivers were more likely to perceive less recovery. Increased anxiety and irritability were the most commonly reported mood changes at 6 months post-stroke. Despite findings on elevated caregiver depression and anxiety with higher stroke severity and level of dependence (Zhao et al., 2021; Villa-García et al., 2024), Wade et al. (1986) found that the links between caregivers' depression and different aspects of the patient's health state disappeared after 2 years, despite being present in the first year post-stroke. Thus, they suggested that the initial mood changes at the earlier stage post-stroke (from 6 months) and the association of depression with patient health outcomes at 1 year post-stroke may be attributed to the shock that accompanies a major life event rather than the nature of the long-term caregiving role (Wade et al., 1986). They further suggested that since depression was present in caregivers of independent patients, increased physical help with the caregiving tasks may not reduce caregivers' stress as stress might mitigate with time. Thus, other forms of support they have received from support groups could have helped. Similarly, Hu et al. (2018) suggests that the association between anxiety and depression and caregiver burden was higher in the personal rather than the responsibility domain, suggesting that the lack of knowledge could have led to longer care time and limited support, which may result in personal and social problems rather than problems with the responsibilities associated with caring. Thus, Wade et al. (1986) suggested that patient-related physical disability factors only partially accounted for the likelihood of depression in caregivers, and other factors should be further investigated. On the contrary, another longitudinal study found that at 1-year post-stroke, the main predictors of caregiver's psychological health were their own well-being and physical health (Franzén-Dahlin et al., 2007), not that of the patient.

To an extent, the above findings similarly suggest the importance of caregiver well-being at the acute phase after the stroke, in which caregivers might experience unexpected shock that poses detrimental psychological stress, regardless of patient factors. This could be addressed in future research aiming at caregivers' coping mechanisms in the face of major stressful events such as strokes, which could mitigate their stress. For instance, Grant et al. (2013) found that depression in patients and caregivers is higher among patients with more impairments, and this relationship is influenced by the caregivers' emotional reactions to the situation. After having ruled out the direct effect of impairments on patients' depression, higher caregivers' depression is still associated with higher patients' depression That is, they found more patient disability to correlate with more depressive symptoms, but the strength of this relationship is influenced by the caregivers' reaction, in which negative reactions were associated with higher depressive symptoms in patients, regardless of impairments (Grant et al., 2013). Caregivers' life satisfaction and depressive symptoms account for about 40.50% of the relationship between the number of post-stroke impairments and patients' depression. Similarly, the negative effects of patient disability on caregivers' mental

QoL are significantly mediated by caregivers' depressive symptoms (Yuliana et al., 2023). They further showed that the effects of stroke-related disability on patients' QoL may also be indirectly mediated by their own depression, anxiety, and stress symptoms. These psychological problems of patients can interdependently mediate the negative effects of their disability on both their own and their caregivers' mental and physical QoL (Yuliana et al., 2023). Though neither study design allows for causal effects, the results may be interpreted in the same manner, suggesting the potential mediation effects of caregivers' well-being on their patients' health outcomes.

Higher symptoms of anxiety and depression in caregivers are also associated with a higher risk of patient mortality 6 months post-stroke; there was a higher percentage of patient deaths in the group with more anxious and depressed caregivers than s non-anxious and non-depressed groups (Zhao et al., 2021). This study also assessed a few factors associated with higher anxiety and depression symptoms in caregivers; these include older caregiver age, more patient dependency, longer care duration, and self-finance vs. medical insurance. During the rehabilitation phase, depressed patients showed fewer improvements in their motor and cognition activities, as measured by the Functional Independence Measure, compared to non-depressed patients. Depressed patients also stayed in rehabilitation for longer. Despite this, the non-significant differences between function gains among the two groups at discharge indicate that depression might reduce the efficiency of recovery, but depressed patients might still be able to recover with longer rehabilitation time. In other words, although depressed patients showed smaller improvements during rehabilitation compared to non-depressed patients, the longer rehabilitation duration resulted in almost equivalent improvements at discharge. Another study showed that 12.8% of their sample of 179 caregivers experienced high strain 6 weeks after stroke (Oosterveer et al., 2014). Lower patient's life satisfaction and more anxiety symptoms were associated with higher caregivers' strain, and this association is stronger among caregivers of patients receiving inpatient rehabilitation compared to no or outpatient rehabilitation. This was suggested to be due to the high level of functional dependency experienced by patients who needed inpatient rehabilitation.

On the contrary, a study of 75 caregiver-patient dyads reported that 24% and 18% of caregivers showed symptoms of anxiety and depression, while 36% of patients showed symptoms of anxiety, and 44% displayed "clinically significant" depression (Balhara et al., 2012). However, the study observed no association between caregivers and patients' anxiety and depression symptoms, and the only predictor of caregiver anxiety was their gender. Notably, they excluded patients who had stroke-related language and cognitive limitations, as measured by the Mini-Mental Status Examination (MMSE). This was done to ensure full participation in the experiment. However, the variable measuring a patient's level of functional dependency or impairments may be important in the association between patients and caregivers' psychological health. As mentioned in other studies, multiple other factors might contribute to this relationship. Moreover, the study was conducted one week after hospitalization, and the duration of caregiving has been shorter compared to other studies that have found effects, therefore, caregivers might not have yet experienced physical and mental challenges. However, this study implies the importance of early screening of anxiety and depression among caregivers.

5. Current Intervention

Considering the potential interdependent links between caregivers' and patients' mental health and their health outcomes, interventions and support should aim at improving aspects of both of their mental health. Since caregivers' sources of support vary depending on their needs, it is suggested that care interventions target different sources of support within the caregivers' social network to effectively address all their needs (Sit et al., 2004). For instance, any need for health-related information should be addressed by health professionals, and daily caregiving tasks like helping patients move should be addressed by family or friends.

5.1. Social support

In comparison to non-depressed patients, those with more depressive symptoms received less social support (He et al., 2023). This heightened depressive symptoms in patients, along with higher stroke severity, longer duration of care, and lower caregiver's perceived social support, were significantly associated with higher caregiver burden (He et al., 2023). Social support was found to alleviate caregiver burden despite the negative impacts of patients'

physical deficits and depressive symptoms (He et al., 2023). With the current findings that anxiety, unlike depression, might not reduce over time in some caregivers, it was suggested that interventions used to treat depression should not be assumed to be effective for anxiety, too (Greenwood & Mackenzie, 2010). At 6 months post-stroke, caregivers' dissatisfaction with the quality of care received is associated with heightened depression and anxiety symptoms, and the prevalence of these symptoms was equivalent in caregivers and patients (Atteih et al., 2015). Since this link was found to be significant in various studies, interventions should aim at providing more support, in various kinds, for caregivers.

Information regarding patients' health status might be useful in reducing caregivers' uncertainty regarding patients' health condition, which might result in higher stress. Patients and caregivers who have received a single 2-hour information and training session showed significantly more satisfaction compared to those receiving the standard rehabilitation program, with the information provided on knowledge of stroke, resources to support adaptation post-discharge, contact with health professionals to resolve questions, and caregiver training (Aguirrezabal et al., 2013). Interestingly, their levels of satisfaction only became distinct concerning the level of support patients received after discharge from the rehabilitation unit, as they were equally less satisfied with the therapy(speech and physiotherapy) received during rehabilitation. This finding emphasized the importance of not only providing patients and caregivers with knowledge of health conditions but also making sure they understand the information provided (Aguirrezabal et al., 2013).

Health literacy in patients has been linked to more recovery, less depressive symptoms, and social participation in mildly disabled stroke patients up to a year post-stroke (Flink et al., 2023). Health literacy may refer to the availability, understanding, and use of information and resources that promote better health (World Health Organization, 2024). This benefit with health literacy was significant regardless of participants' level of education (Flink et al., 2023). Therefore, health literacy may be beneficial in promoting positive health outcomes in a variety of individuals, for instance, those of lower educational backgrounds (Flink et al., 2023). Notably, this study was conducted in a sample of patients from Sweden, within which 62% had sufficient health literacy, and 48% attended university, thus, the result may not be generalizable to countries with lower health literacy.

A systematic review of social factors preventing patients' adherence to medication found that low health literacy was a barrier to treatment adherence in ischemic stroke patients (Ruksakulpiwat et al., 2023). Stroke patients who self-administered stroke prevention medication might be reluctant to continue taking medication because of the lack of information on its effectiveness due to lack of consultation time and the ability to understand the information provided by doctors during the acute phase after stroke (Viprey et al., 2020). Patients may consider stroke a one-time incident, hence, medication is regarded as a cure of present symptoms rather than a prevention of future recurrence (Viprey et al., 2020). Hence, they might be more reluctant to take medication as the side effects outweigh the preventative benefits (Viprey et al., 2020). The lack of confidence in knowledge could also result in a reluctance to inform doctors of problems with adherence and, eventually, a discontinuation of treatment (Viprey et al., 2020). Therefore, improving patients' health literacy might also act as a form of empowerment, allowing patients to be more confident in their communication with professionals about their problems with treatment (Viprey et al., 2020). An understanding of patients' perceptions by health professionals would also address their inaccurate perception of the disease and treatment (Viprey et al., 2020).

In contrast, a meta-analysis on the use of eHealth interventions to improve health literacy and stroke recurrence found no sufficient evidence to support its effectiveness, although significant improvements in health-related QoL and healthy behaviors were found (Vu et al., 2025). They suggested that patients might have already obtained basic knowledge about stroke within healthcare programs; thus, additional information provided by these applications is not necessary, while remote and frequent reminders to take medications or contact health professionals were efficient in promoting medication adherence (Vu et al., 2025).

5.2. Cognitive Behavioral Therapy for treating post-stroke depression:

As for the use of clinical treatments such as cognitive behavioral therapy for treating depression in stroke patients, results have been mixed. Among the Korean population of stroke patients, CBT was found to be effective in

reducing symptoms of depression and anxiety and in improving self-efficacy and rehabilitation motivation (Choi & Kim, 2024). Although the intervention consisted of 20 sessions, about 30 minutes of each 1-hour session was dedicated to general occupational therapy (OT). Findings suggest the integration of occupational therapy with CBT to be effective in reducing depression and anxiety in stroke patients (Choi & Kim, 2024; Kootker et al., 2012). As the focus of this type of "augmented" CBT was to help patients achieve goal-oriented and fulfilling activities, this integrated and individualized intervention aimed to facilitate their ability to both mentally and physically obtain their goals (Kootker et al., 2012). A meta-analysis of 20 studies and 17 934 patients (hospital, rehabilitation, and population-based) assessing predictors of post-stroke depression (PSD) at various time points after stroke (ranging from discharge to 5 year) showed that loss of physical ability and decreased cognitive function were factors most commonly associated with PSD (Hackett & Anderson, 2005). Thus, it could be argued that although depression onset might vary at different time points after stroke, the aforementioned predictors might be consistent in predicting the prevalence of depression, thus, interventions aiming at both these psychological and physical functional recovery might be beneficial to improve patients' health after stroke.

CBT sessions introduced techniques for the relaxation and reconstruction of patients' negative and distorted beliefs and educated them on knowledge about stroke and CBT, received feedback from therapists about and reflected on their progress (Choi & Kim, 2024). Their integrated qualitative assessment of patients' therapy experience revealed an increased sense of psychological stability through successful identification and reframing of thoughts during stressful scenarios and recognition of strengths (Choi & Kim, 2024). The learning of communication and problem-solving skills and replacement of negative thoughts about their current post-stroke incapabilities and life changes allowed for more positive thinking, beliefs in current capabilities, rehabilitation motivation, and better communication and stress management (Choi & Kim, 2024).

On the contrary, Lincoln & Flannaghan (2003) found no observed improvement in mood among mildly and moderately depressed patients as a result of the interventions received 1, 3, or 6-months after stroke. These were explained by the potential short duration of the intervention and the study's selection of patients based on the severity of depressive symptoms rather than the appropriate treatment, which might have excluded severely depressed patients who might have been unable to complete the depression questionnaires (Lincoln & Flannaghan, 2003). Although Kootker et al. (2012)'s study of 61 stroke patients found improvements, they found no group differences between augmented CBT and computerized cognitive training tasks in improving depression, anxiety symptoms, quality of life, and satisfaction with social participation after at least 3 months post-stroke. Both groups equally improved over time, hence, it is suggested that both treatments might be beneficial.

Interestingly, although interventions were targeted at patients, caregivers of those who received CBT showed more improvements in mental health problems and worrying compared to those receiving cognitive tasks in the control group (Kootker et al., 2019). These contradicting outcomes might have been a "Hawthorne" effect due to the home-based aspects of CBT, where caregivers benefitted from having patients committed to completing homework to achieve oriented goals (Kootker et al., 2019). Despite this, caregivers' practical burden remained unaffected by the intervention, which might be attributed to the functional limitations that patients continue to experience post-stroke (Kootker et al., 2019).

5.3. Other interventions

The effects of other interventions, such as mindfulness-based interventions and patient-caregiver dyads interventions on health outcomes were investigated in a meta-analysis (Tao et al., 2022). Two kinds of mindfulness-based interventions were mentioned: mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT). MBCT is a group training program aiming to allow people to recognize and detach from depressive thoughts, which in turn reduce negative patterns of thinking and relapse (Teasdale et al., 2000). The program encourages awareness of the present moment and avoidance of automatic negative patterns of thinking, which are early signs of relapse of depressing thought patterns, by involving family members or reminders to look out for habitual negative thinking patterns that do not necessarily reflect reality (Teasdale et al., 2000). MBCT, in addition to usual treatment, was found to reduce the risk of depression relapse among patients who recently recovered from depression 60 weeks after initial treatment (Teasdale et al., 2000). Those who

previously experienced 3 or more depressive episodes showed half a reduction in relapse rate, whereas those who had 2 episodes did not, which was attributed to the program's ability to interrupt the more frequent patterns of negative thoughts among those with more depressive episodes and hence prevent relapse (Teasdale et al., 2000). Both interventions significantly improved depression (Teasdale et al., 2000), while Kraines et al. (2022) suggested mixed results in terms of their effectiveness in treating depression. Their meta-analysis provided contrasting outcomes for studies using 2 different study designs to assess the effectiveness of MBCT and MBSR on depressed people: while all single-arm trials showed at least 1 positive effect in cognitive functions, only two out of five randomized-controlled trials showed effect.

6. Conclusion

There is a link between the stroke-related physical and psychological health outcomes of patients and the psychological health of their caregivers. Although some of these studies included only a small sample of caregiver-patient dyads, they consistently reported the presence of depression and anxiety in caregivers and the effects of these psychological challenges on their patients. Results also suggest a prevalence of depression and anxiety among stroke patients, and their well-being interdependently affects their caregivers.

Functional disability and cognitive deficiencies were associated with post-stroke-depression among patients. Further, the current literature review also found that caregivers' reaction towards patients' stroke-related disabilities also influence their mental health, such that more negative attitudes lead to more symptoms of depression in patients.

The majority of studies included in this review suggested effective outcomes for uses of interventions such as CBT, promotion of health literacy, and MBCT/MBSR to treat post-stroke depression among stroke patients. Only one study suggested insufficient evidence to support the effectiveness of eHealth application to promote health literacy. One study was included to suggest improvements among caregivers of patients receiving augmented CBT. This study should be interpreted in light of limitations, as only a limited amount of studies were included, the literature review does not cover all research that has been done on the topic. Further research should be done to outline the effectiveness of current intervention methods.

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