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Review Article

A Comprehensive Review of Fluid Resuscitation Techniques in Sepsis in Patients with Heart Failure

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ABSTRACT

Introduction: Fluid management in sepsis patients with pre-existing heart failure presents a complex clinical challenge, as these patients require adequate resuscitation while avoiding fluid overload that could worsen cardiac function. This article aims to explore optimal fluid resuscitation strategies for patients with pre-existing heart failure who develop sepsis, a group at high risk for fluid management complications.

Methods: We conducted a narrative review of studies published between 2010 and 2024, utilizing PubMed, ScienceDirect, and Google Scholar. We employed Boolean formulas and search terms that evolved from broad to specific, refining the focus on fluid resuscitation in septic heart failure patients. Human studies focusing on fluid resuscitation, sepsis management, and outcomes in heart failure were included. Exclusion criteria included animal studies, non-English articles, and case reports.

Results: Guideline-recommended fluid resuscitation (30 mL/kg within 3 hours) shows a neutral or positive effect on mortality in sepsis patients with pre-existing heart failure when monitored appropriately. Patients with reduced ejection fraction (HFrEF) and those with preserved ejection fraction (HFpEF) exhibit different tolerances to fluids. Advanced hemodynamic monitoring — including bedside echocardiography, lactate clearance, central venous pressure, and BNP levels — is essential for personalizing fluid therapy.

Conclusion: Early guideline-compliant fluid resuscitation followed by a conservative, individualized fluid strategy guided by hemodynamic monitoring optimizes outcomes in sepsis patients with heart failure. Future prospective studies are needed to develop standardized protocols.

1. Introduction

Sepsis and septic shock are the significant causes of death globally, with a 25-30% mortality rate, particularly in hospitals [1]. This is especially true in the post-COVID era, underscoring the importance of timely intervention in critical care and highlighting the need for comprehensive research to refine therapeutic approaches and enhance patient outcomes.

If sepsis progresses to septic shock, a type of distributive shock, it will lead to vasodilation, resulting in circulatory, cellular, and metabolic abnormalities, which may lead to multiple organ failure, requiring vasopressor treatment to maintain adequate perfusion [1]. The population at risk for sepsis includes the elderly, intensive care unit patients, immunocompromised individuals, and neonates. When sepsis coincides with heart failure, fluid resuscitation plays a crucial role in preventing fluid overload and acute decompensated heart failure [2]. However, there is a paucity of literature specifically addressing this issue in patients with sepsis and heart failure. This narrative review aims to determine the safety, timing, rates, volumes, and types of fluids needed in patients with heart failure and sepsis, shedding light on an overlooked aspect of critical care and committed to improving outcomes for post-sepsis survivors. Though there are not any standardized definitions for fluid overload, it is majorly a clinical decision based on signs like respiratory distress with coarse crackles, peripheral edema, ascites, hepatomegaly, congestive heart failure, jugular venous distention or quantitative criteria like weight gain of >10%, a positive fluid balance of >5 L, or radiologic evidence of pulmonary edema.

2. Methods

We conducted a narrative review of studies published between 2010 and 2024 using PubMed, ScienceDirect, and Google Scholar, employing Boolean formulas and search terms that evolved from

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Table 1: Sepsis definition [1, 2]

Parameter	qSOFA Score	NEWS Score
Purpose	Rapid assessment for sepsis outside ICU	Early warning score for acute illness
Score Range	0 to 3 2 to 3 high risk 0 to 1 not high risk	0 to 7 0–4 low risk 5–6 medium risk 7 high risk
Respiratory Rate	22 breaths/min (1 point)	0: 12–20 breaths/min 1: 9–11 or 21–24 breaths/min 2: 8 or 25 breaths/min
Altered Mental Status	GCS < 15 (1 point)	New confusion
Systolic Blood Pressure	100 mmHg (1 point)	0: 111 mmHg 1: 101–110 mmHg 2: 91–100 mmHg 3: 90 mmHg
Heart Rate	–	0: 51–90 bpm 1: 41–50 or 91–110 bpm 2: 111–130 bpm 3: 40 or 131 bpm
Oxygen Saturation	–	0: 96% 1: 94–95% 2: 92–93% 3: 91%
Temperature	–	0: 36.1–38.0°C 1: 35.1–36.0 or 38.1–39.0°C 2: 35.0 or 39.1°C
Use of Supplemental O_2	–	2: Yes
Use in Clinical Setting	Non-ICU setting Screening tool	Hospital and emergency departments Prediction tool

ICU, Intensive Care Unit; qSOFA, Quick Sequential Organ Failure Assessment score; NEWS, National Early Warning Score

broad to specific to refine the focus on fluid resuscitation in septic heart failure patients. Human studies focusing on fluid resuscitation, sepsis management, and outcomes in heart failure were included. Exclusion criteria included animal studies, non-English articles, and case reports. Articles were analyzed with a focus on the research question: the safety of fluid administration in sepsis with heart failure. Relevant data were extracted and cited using Vancouver style via Zotero.

2.1. Background

The diagnosis of sepsis has evolved over time, the most recent one being the Sepsis-3 definition as measured by the Sequential Organ Failure Assessment score (SOFA) score and National Early Warning Score (NEWS), is presented in Table 1- which emphasizes the presence of organ dysfunction, particularly cardiovascular dysfunction, like decreased peripheral resistance and increased vascular permeability, leading to tissue hypoperfusion, oliguria, elevated lactate and creatinine levels, coagulopathies, and subsequent organ failure. While effective fluid resuscitation is a mainstay of sepsis management, aiming to restore hemodynamic stability and improve tissue perfusion, this also raises concern in heart failure patients [3].

Cardiovascular insufficiency in heart failure can arise from structural or functional heart disorders that impair the heart's ability to fill with or eject blood. The pathophysiology of HF is complex, involving hemodynamic, neurohormonal, and cellular mechanisms. Hemodynamic changes include a reduced cardiac output and elevated ventricular filling pressures due to volume overload and impaired relaxation. Neurohormonal activation significantly impacts HF, with the renin-angiotensin-aldosterone system (RAAS) causing vasoconstriction, sodium retention, and fluid overload [4]. The sympathetic nervous system (SNS) increases catecholamine levels, thereby raising heart rate and contractility, but also contributes to myocardial damage over time [5]. On a cellular level, myocytes undergo hypertrophy to handle the increased workload, fibrosis stiffens the myocardium due to excess collagen, and apoptosis, or the programmed cell death of myocytes, further impairs cardiac function [6].

Sepsis is a life-threatening condition resulting from a dysregulated immune response to infection, leading to widespread inflammation, tissue damage, and organ dysfunction. The immune response in sepsis involves both pro-inflammatory and anti-inflammatory processes. Pro-inflammatory responses include the release of cytokines such as TNF-, IL-1, and IL-6 [7]. Anti-inflammatory responses involve the production of IL-10 and other mediators to counteract inflammation [7]. Endothelial dysfunction is a key feature of sepsis, with increased permeability leading to fluid leakage, edema, and hypotension [7], and microvascular thrombosis occurring due to coagulation activation and impaired fibrinolysis [7]. Metabolic changes in sepsis include mitochondrial dysfunction, which reduces ATP production and contributes to cellular energy failure [7], and hyperglycemia resulting from stress-induced insulin resistance and increased gluconeogenesis [7]. These processes contribute to multiple organ dysfunction syndrome (MODS), characterized by impaired perfusion and oxygen delivery to tissues [7].

Table 2: Mechanisms of Cardiac Dysfunction alongside Sepsis [5, 6, 7]

Mechanism	Description	Impact
Myocardial Depression	Cytokines (TNF-, IL-1, IL-6) and nitric oxide reduce myocardial contractility.	Decreased cardiac output, hypotension.
Autonomic Dysfunction	Altered autonomic regulation leads to impaired heart rate variability and reduced baroreflex sensitivity.	Tachycardia, arrhythmias.
Microvascular Dysfunction	Endothelial damage and microthrombi reduce coronary perfusion.	Ischemia, myocardial infarction.
Mitochondrial Dysfunction	Impaired oxidative phosphorylation leads to reduced ATP production.	Energy deficit, impaired contractility
Increased Afterload	Systemic vasodilation and hypotension initially, followed by increased vascular resistance.	Increased workload on the heart, heart failure
Electrolyte Imbalance	Sepsis-induced AKI and other factors cause electrolyte disturbances	Arrhythmias, impaired contractility

TNF, Tumor Necrosis Factor; IL, Interleukin; ATP, Adenosine Triphosphate; AKI, Acute Kidney Injury

2.2. Impact of Sepsis on Cardiac Function

Sepsis exerts profound effects on cardiac function, leading to septic cardiomyopathy, a reversible dysfunction of the heart. Hemodynamically, the combined effects of heart failure and sepsis lead to decreased preload and mean arterial pressure (MAP), increased heart rate, neutral effect on systemic vascular resistance, and varying effect on contractility [4]. The mechanisms of cardiac dysfunction in sepsis are summarized in Table 2: The pathophysiological processes in a patient with heart failure complicated by sepsis are multifaceted and interlinked. The systemic inflammatory response of sepsis exacerbates cardiac dysfunction, precipitates coagulopathy, and leads to multi-organ failure. Understanding these mechanisms is crucial for managing such critically ill patients and highlights the need for integrated therapeutic approaches to mitigate the impact of these concurrent conditions. The challenge lies in finding the delicate balance between providing sufficient fluid to support circulation without exacerbating heart failure; careful monitoring is essential, as fluid overload in the above condition has been associated with exacerbation of heart failure with vasodilation, pulmonary edema, peripheral edema, elevated jugular venous pressure, increased intra-abdominal pressure leading to liver and kidney injury-hyponatremia in critically ill patients, and increased mortality [8]. Heart failure can manifest as either a reduced ejection fraction or a preserved ejection fraction. Both types are further complicated by sepsis, because the inflammatory response can worsen cardiac function and lead to fluid overload.

However, evidence suggests that guideline-based fluid resuscitation (30 mL/kg within 3 hours) is associated with lower in-hospital mortality compared to restrictive approaches in sepsis patients with HF [9, 10]. The use of careful management of chronic HF medications and consideration of -blockers after hemodynamic stabilization with balanced crystalloids and albumin may be beneficial [10]. Additional research is needed to determine optimal fluid resuscitation strategies in this population, as clinicians must balance the need for volume expansion against the risk of fluid overload and worsening of cardiac dysfunction.

2.3. Safety profile and other outcomes

The Surviving Sepsis campaign recommends giving at least 30ml/kg fluid bolus, preferably with IV Crystalloids, in septic shock patients within 3 hours as a best practice measure to correct hypotension, but this recommendation is criticized as based on poor quality evidence, as it doesn't take other patient comorbidities into consideration [11]. Additionally, the Centers for Medicare and Medicaid Services also mandated this recommendation as part of its SEP-1 sepsis management bundle. Despite these guidelines, many physicians are often hesitant to administer fluid resuscitation to sepsis patients with heart failure due to concerns about potential fluid overload [12]. In line with this, several retrospective cohort studies have indicated that patients with heart failure often experience delays in fluid administration [13] those who are more likely to fail to comply with guidelines for fluid resuscitation [14, 15, 16] and generally receive less aggressive resuscitation compared to sepsis patients without heart failure [17, 18].

In a study of 552 patients, Wardi et al. in a retrospective cohort study found that individuals with sepsis and heart failure with reduced ejection fraction (HFrEF) received an average of 9.8 mL/kg less fluid compared to those without HFrEF (31.7 mL/kg versus 41.5 mL/kg, respectively; $p = 0.03$). Moreover, among the heart failure patients, those who did not survive received 21 mL/kg of fluid, whereas survivors with HFrEF received 35 mL/kg ($p = 0.16$). These findings suggest that administering a fluid bolus of at least 30 mL/kg could be beneficial for this subgroup of patients. However, the study's findings may be constrained by the relatively small number of heart failure patients included [19].

Among a retrospective cohort of 505 patients, Singh et al. found that sepsis patients with HFrEF who received more than 3 liters of fluid had a higher in-hospital mortality and longer hospital stays. While Singh et al.'s findings suggest an association between higher fluid volumes and increased mortality in septic patients with HFrEF, the retrospective design and limited adjustment for clinical variables, such as sepsis severity or vasopressor use, introduce potential confounding elements. The absence of a detailed methodology and a small sample size further limits the generalizability of these results. Therefore, these observations should be viewed as hypothesis-generating. Future prospective studies with proper control of confounders are needed to clarify the causal relationship between fluid resuscitation strategies and outcomes in this high-risk population [20].

Additionally, current guidelines may allow for the administration of more than 3 liters of fluid in patients with a body weight of 100 kg, which means that many individuals may not reach the threshold for excessive fluid according to these guidelines. But most importantly, the study did not report the period over which the fluid was administered, making it challenging to apply these findings in clinical practice [20]. Additionally, in a more comprehensive retrospective study, Tam et al. found that patients with sepsis who had a known history of heart failure (HF) received less fluid than those without HF at 6, 12, 24, and 48 hours post-injury. Despite this reduced fluid volume, patients with HF still received over 40 mL/kg of fluids within the first 6 hours of sepsis onset. Nevertheless, there were no significant differences between the HF and non-HF groups in terms of net fluid balance at 6 and 48 hours, hospital length of stay (LOS), ICU LOS, rates of persistent hypotension at 48 hours, intubation, CPAP/BIPAP use, cardiovascular complications, acute kidney injury (AKI), or mortality [21]. In this context, administering at least the recommended 30 mL/kg of fluid resuscitation within the first six hours of sepsis might be safe for patients with septic shock or severe sepsis and a known history of HF. A recent case-control study of 671 patients revealed that compliance with 30ml/kg fluid resuscitation was lower in sepsis patients, with even lower compliance among heart failure patients with sepsis. However, the study also found that the use of a fluid bolus (30 mL/kg) in heart failure patients presenting with severe sepsis or septic shock appeared to reduce the risk of in-hospital mortality (OR 0.95, 95% CI 0.90–0.99, $p<0.05$). Additionally, there was no increased risk of mechanical ventilation associated with the fluid bolus (OR 1.01, 95% CI 0.96–1.06, $p = 0.70$) [10].

In a retrospective chart review, Boccio et al. found that the only significant difference between sepsis fluid bolus-compliant and non-compliant patients with congestive heart failure (CHF) was a shorter stay in the intensive care unit (ICU) for the compliant group. Additionally, there were no statistically significant differences in mortality rates, the probability of intubation within 72 hours or during hospitalization, or inpatient length of stay among CHF patients who were compliant versus those who were noncompliant. However, the sample size may have been insufficient to detect a meaningful difference in mortality.[14]. In their retrospective chart review, Akhter et al. categorized sepsis patients with a history of CHF and/or ESRD into two groups based on their fluid intake: those who received at least 30 ml/kg and those who received a fluid-restrictive regimen of < 30 ml/kg. They found that the compliance group did not have a higher likelihood of intubation compared to the other group. There was also no significant difference in hospital length of stay or mortality. However, the study has limitations, including potential baseline differences- unadjusted confounders between the two patient groups, like sepsis severity or vasopressor use, and insufficient sample size(for calculating mortality), which may have influenced the results [22]. However, in a separate study with a larger sample size and similar patient grouping in a prospective observational design, Akhter et al. utilized a multivariate logistic regression model to account for confounding factors and showed that sepsis fluid bolus administration does not elevate the risk of mortality or intubation [23]. Similarly, in a retrospective cohort study, Duttuluri et al demonstrated that in heart failure patients with severe sepsis or septic shock presenting with hypotension, an adequate fluid bolus (30 mL/kg) decreased the risk of in-hospital mortality and intubation [24]. In a smaller prospective observational study by Ehrman et al., patients with reduced left ventricular ejection fraction (rLVEF) and those without rLVEF received similar volume fluid boluses. Interestingly, despite this similarity in fluid administration, both groups had comparable hospital days, ICU days, and ventilator days [25].

Khan et al., in a retrospective study, found that administering more than 30 mL/kg of fluid resuscitation was not independently linked to intubation (aOR 0.75, 95% CI 0.41-1.36, $p = 0.34$) after adjusting for confounders using multivariable generalized estimating equations. The number of ICU-free days at 28 days was similar between the restricted and standard fluid groups (17 ± 10 days vs. 17 ± 11 days, p=0.64). Additionally, there was no significant difference in the number of days on mechanical ventilation between the groups (11 ± 16 days vs. 10 ± 12 days, p=0.96), and hospital mortality rates were comparable (45 [21%] vs. 19 [18%], p=0.21), but an insufficient sample size may limit the study [26]. Ouellette and Shah, in their case-control study, used total intravenous fluid volume administered during the first 24 hours of patient admission as exposure and found no correlation between intravenous fluid volume and the PO2/FiO2 (oxygenation) at 24 hours in either cohort ($r2 = 0.019$ for cases, $r2 = 0.001$ for controls). In-hospital mortality rates ($P = 0.117$) and intubation rates at 24 hours ($P = 0.687$) were not significantly different between cases and controls either. However, the study may have been underpowered to detect differences in mortality [27].

In a retrospective cohort study Kuttab et al. found that, after accounting for various confounders, patients who did not receive the 30-by-3 fluid resuscitation protocol had higher odds of in-hospital mortality (OR=1.52, 95% CI 1.03–2.24), delayed onset hypotension (OR=1.42, 95% CI 1.02–1.99), and a longer ICU stay among those admitted to the ICU (mean increase of about 2 days, =2.0, 95% CI 0.5–3.6). The study also showed that patients with severe sepsis and septic shock who were elderly, male, obese, with documented volume "overload" from bedside examination, and had a history of heart failure or end-stage renal disease were less likely to receive the 30-by-3 protocol [12]. An older retrospective study by Shah and Ouellette found that adherence to early goal-directed therapy improved in-hospital mortality in patients with a reduced LVEF and sepsis [28]. In a retrospective study using claims data from elderly patients with a history of congestive heart failure (<35% EF) who presented with severe sepsis or septic shock, adherence to the initial fluid resuscitation guidelines outlined in the 3-hour sepsis bundle was associated with better in-hospital and [29] one-year mortality outcomes [29]. These results are also validated by a massive multisite observational study of nearly 15,000 severe sepsis/septic shock patients across three independent, prospective cohorts. Strict adherence to a 3-hour sepsis bundle, emphasizing rapid intervention that is not reliant on physiological endpoints, demonstrated lower in-hospital mortality, even after adjusting for confounding factors. This compliance also yielded significant cost savings in cohorts 2 and 3, which included over 7,500 patients. Furthermore, these results were validated within the CHF subpopulation of the study [30].

Liu et al. assessed the effects of implementing a treatment bundle for sepsis patients with intermediate lactate levels across multiple centers. This retrospective study found that the bundle implementation significantly improved compliance and brought down hospital mortality rates. Crucially, this drop in mortality did not result in longer hospital stays or more ICU transfers. When patients were stratified based on pre-existing heart failure or kidney disease, those with these conditions experienced significant reductions in both hospital and 30-day mortality post-implementation. Compliance with antibiotic timing and lactate reassessment was similar in these patient groups before and after implementation, highlighting that the improved outcomes were largely due to increased fluid

administration for patients with heart failure and/or chronic kidney disease [31].

A recent large retrospective cohort study revealed that patients with septic shock and HFrEF were less likely to receive guideline-recommended intravenous fluids compared to those with septic shock but without HFrEF. Even after adjusting for confounding factors, HFrEF was linked to a reduced likelihood of receiving 30 mL/kg of intravenous fluid within the first 6 hours of sepsis onset (aOR-0.63; 95% confidence interval [CI], 0.47-0.85; P = 0.002). However, the adjusted risk of mortality did not significantly differ between patients with HFrEF (aOR-0.92; 95% CI, 0.69-1.24; P = 0.59) and those without it, and there was no interaction with the volume of intravenous fluid administered (aOR-1.00; 95% CI, 0.98-1.03; P = 0.72) [15].

In a retrospective study by Herndon et al., involving a cohort primarily consisting of patients with various types of heart failure and sepsis-induced hypoperfusion, no difference in mortality was found between those who received the recommended 30 mL/kg fluid bolus and those who did not. The study observed shorter hospital and ICU lengths of stay, as well as a higher incidence of new invasive or noninvasive mechanical ventilation. But multivariate analysis indicated that these outcomes were influenced by factors unrelated to the initial fluid bolus. This suggests that administering a 30 mL/kg fluid bolus did not significantly impact outcomes in patients with mixed types of heart failure and sepsis-induced hypoperfusion [32].

In contrast to the above studies, Wiczorek et al., in a retrospective study of sepsis patients with CHF/CKD, found a significant correlation between receiving more than 30 mL/kg of intravenous fluids at 3 and 6 hours from emergency department arrival and the need for BiPAP (p-value 0.006, p 0.02, respectively). Surprisingly, there was no statistically significant difference in in-hospital mortality between the sepsis patients with CHF/CKD and those without CHF/CKD, with regard to receiving more than 30 mL/kg of IVF at either 3 or 6 hours from ED (p-value 0.614, p-value 0.115, respectively) [33].

Multiple studies have found that higher fluid balance is associated with negative outcomes. A recent retrospective cohort study by Dong et al. sought to investigate the link between fluid management and in-hospital mortality in sepsis patients with heart failure. The study aimed to identify a superior indicator for fluid management among fluid balance (FB), fluid intake (FI), and the fluid intake ratio (FB/FI), termed the fluid accumulation index (FAI). The findings revealed that a high FAI (FB/FI ratio) correlated with an increase in in-hospital mortality in these patients [34]. To understand the link between fluid balance (FB) and in-hospital mortality, a retrospective study by Zhang et al. categorized sepsis patients with heart failure into two groups based on FB levels: high (55.85 ml/kg) and low (< 55.85 ml/kg). Their research uncovered that a high FB was an independent predictor of both in-hospital and 30-day mortality and was also linked to extended ICU and hospital stays. These conclusions remained solid and consistent even after adjusting for potential confounders, making them a dependable measure for evaluating the impact of FB on patient outcomes in clinical practice [35]. In a study of 633 patients, Dhondup et al. revealed that each 1-liter increase in daily negative fluid balance during the de-escalation phase significantly lowered mortality rates across several time points: ICU, hospital, 90-day, and 1-year [36].

Overall, research on the safety, complications, and outcomes of fluid resuscitation in heart failure patients with sepsis is still limited. Septic shock treatment is structured into four phases: Resuscitation, Optimization, Stabilization, and Evacuation. Based on existing literature, following SCC fluid resuscitation guidelines is advisable, as they are likely to produce favorable or neutral outcomes with minimal adverse effects. Nonetheless, the risk of volume overload persists, as highlighted by recent studies [36, 34, 35]. Thus, fluid management should be optimized in heart failure patients with septic shock, and it is advisable to adopt a conservative approach during the other phases of septic shock treatment. New prospective studies are essential to conclusively determine the safety and effectiveness of fluid management in this subgroup.

3. Discussion

Managing fluid resuscitation in patients with sepsis and underlying heart failure remains one of the more delicate challenges in acute care. Although the Surviving Sepsis Campaign recommends administering 30 mL/kg of intravenous fluids within the first three hours—a protocol now widely adopted into quality metrics—this directive often raises concern among clinicians, especially when heart failure complicates the clinical picture. Clinicians are often caught balancing the urgency of reversing hypoperfusion against the risk of fluid overload and its potential consequences. Our review draws on a growing body of evidence indicating that a standardized initial fluid bolus, even in patients with known heart failure, may not only be safe but also potentially beneficial when administered with careful oversight. Several studies suggest that failure to comply with early fluid resuscitation guidelines in this population is common and often driven by fear of worsening cardiac function. Yet, data increasingly indicate that withholding or delaying fluids may be more detrimental, and that compliance with the recommended 30 mL/kg bolus does not uniformly increase adverse outcomes like intubation or mortality. What this review brings to the table is a cohesive, evidence-informed perspective that acknowledges the complexity without defaulting to blanket caution. We argue that early adherence to fluid resuscitation guidelines—guided by dynamic monitoring and clinical judgment—should remain a priority in the initial phase of sepsis management for patients with heart failure. Importantly, we advocate for a shift from one-size-fits-all protocols to phase-specific strategies: aggressive resuscitation when perfusion is threatened, followed by deliberate, conservative fluid strategies during stabilization and recovery. Balanced crystalloids may reduce acid-base disturbances compared to saline, though data in HF patients are limited.

Monitoring of fluid overload is needed for assessing fluid overload during the administration of fluids, and it requires a multimodal approach of clinical examination along with hemodynamic and imaging tools. Central venous pressure (CVP), while historically used, offers limited predictive value when used alone and must be interpreted using other clinical data. We recommend using point-of-care ultrasound, with lung ultrasound identifying B-lines consistent with pulmonary edema and inferior vena cava (IVC) assessment suggesting volume status based on diameter and collapsibility. Focused cardiac ultrasound for the evaluation of ventricular function and preload. Ultimately, combining these with laboratory markers, such as elevated BNP, and bedside clinical findings provides a more comprehensive and accurate evaluation of fluid overload.

By weaving together fragmented data from diverse clinical settings, we provide a clearer roadmap for frontline providers —one that

respects the nuances of heart failure but doesn't paralyze action. We also highlight gaps in the literature, including inconsistent definitions of fluid overload, limited reporting of fluid timing and monitoring, and a general lack of prospective trials tailored to this vulnerable subgroup. This is what future research must focus on. In short, our review reinforces that timely, well-monitored fluid resuscitation is not only possible in patients with sepsis and heart failure—it may be key to improving outcomes when approached with the nuance and precision these patients deserve.

This review is limited by heterogeneity in study designs, patient populations, and the lack of standardized definitions for fluid overload. Some studies had insufficient statistical power, which limited the conclusions drawn from non-significant outcomes. Additionally, the variability of heart failure phenotypes and the impact of different fluid types were not addressed due to limited data.

4. Conclusions

Fluid resuscitation in sepsis patients with pre-existing heart failure remains a complex clinical challenge, marked by a tension between the urgency of restoring perfusion and the risk of fluid overload. While traditional caution has often led to under-resuscitation in this population, emerging evidence reviewed in this manuscript suggests that early administration of 30 mL/kg of intravenous fluids, when coupled with careful monitoring, may be both safe and beneficial. Our review consolidates the available literature to emphasize that guideline-directed fluid resuscitation does not uniformly result in adverse outcomes among heart failure patients, and in some cases, may even improve mortality and reduce the duration of ICU stays.

By framing fluid management through a phase-specific lens, we advocate for a more dynamic, patient-tailored approach: one that prioritizes timely intervention during the resuscitation phase, followed by thoughtful de-escalation as the clinical picture evolves. This perspective challenges the conventional hesitancy surrounding fluid therapy in heart failure and calls for a shift toward evidence-guided flexibility rather than rigid restraint. Ultimately, our review not only synthesizes key findings across existing studies but also highlights critical areas for future research, particularly the need for prospective trials that can refine volume thresholds, optimal timing, and monitoring strategies, as well as differentiate between different types of heart failure in this high-risk subgroup. With a more nuanced and structured approach to fluid resuscitation, we can move toward safer and more effective sepsis care for patients with underlying heart failure.

Conflicts of Interest

The authors declare no conflicts of interest related to this manuscript.

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Large Language Model

We have employed an advanced large language model to enhance and refine English language writing. This process focused solely on improving the text's clarity and style, without generating or adding any new information to the content.

Authors Contribution

MSO and ST contributed to the conceptualization of the work. Literature search, review of articles, and analysis of fluid resuscitation outcomes were carried out by MSO, ST, AVM, NM, N, and STi. MSO and ST were responsible for the write-up and synthesis of inferences and recommendations, as well as editing the manuscript for journal submission. AVM contributed to the introduction and background writing and provided key inputs during editing. NM was involved in writing the abstract and pathophysiology section and editing. N contributed to conclusion writing and inference synthesis. STi assisted in literature search and proofreading for reference consistency. Project supervision, guidance, and final review were completed by MSO and ST.

Data Availability

This review article does not contain any new primary data. All information discussed is derived from previously published sources and publicly available databases, as cited in the manuscript.

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ASIDE Internal Medicine

Original Article

Epidemiological Assessment of Risk Factors for Inguinal Hernia Among Male Patients in Iraq: A Case-Control Study

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ABSTRACT

Introduction: Inguinal hernia is one of the most common surgical conditions, particularly among males. Despite its prevalence, limited regional data exist on the associated risk factors in Iraq. This study aimed to identify socio-demographic, lifestyle, and clinical risk factors contributing to inguinal hernia among male patients.
Methods: A case-control study was conducted on 250 male patients diagnosed with inguinal hernia at multiple public hospitals and surgical clinics across three major cities in Iraq: Wasit, Baghdad, and Basra. Compared with a 250-member control group. Data were collected using structured questionnaires covering socio-demographic details, occupational exposure, lifestyle habits, medical history, and family history. Univariate and logistic regression analyses were performed to identify significant risk factors.
Results: Most patients (57.5%) were between 41 and 60 years old. Heavy lifting (63.6%), smoking (62.0%), chronic cough (38.6%), and constipation (32.4%) were frequently reported. A positive family history was noted in 22.4% of cases. Univariate analysis revealed significant associations between inguinal hernia and heavy lifting ($p < 0.001$), smoking ($p < 0.001$), chronic cough ($p = 0.002$), constipation ($p = 0.020$), and a family history of inguinal hernia ($p = 0.001$). Logistic regression confirmed heavy lifting (OR=2.78), family history (OR=2.46), smoking (OR=1.69), and chronic cough (OR=1.54) as independent risk factors.
Conclusion: Heavy lifting, smoking, chronic cough, and family history were significantly associated with increased risk of inguinal hernia among Iraqi males. Public health strategies that focus on prevention, early identification, and lifestyle modification are essential for reducing the incidence and recurrence of this condition.

1. Introduction

Inguinal hernia, characterized by the protrusion of abdominal contents through the inguinal canal, represents a prevalent surgical concern worldwide [1, 2]. This condition exhibits a higher incidence in males, particularly in regions with specific demographic and occupational characteristics [3]. Patients with inguinal hernia often present with a visible or palpable bulge in the groin area, which may be accompanied by discomfort or pain, especially during activities that increase intra-abdominal pressure, such as lifting or straining [3]. Diagnosis is primarily clinical, especially in men, but supported by imaging studies, especially ultrasound and Magnetic Resonance Imaging (MRI) for better quality in occult hernia, as ultrasound may miss it, or in women, as imaging is necessary to assess the hernia's characteristics and plan appropriate management [4, 5, 6].

In Iraq, particularly in areas like Al-Basra, there is a notable prevalence of inguinal hernia among male patients, potentially linked to the region's industrial and manual labor activities. A prospective study at Al-Basra Teaching Hospital reported that 88.4% of the 250 patients with inguinal hernia were male, with ages ranging from 16 to 82 years [7].

Several risk factors have been identified as contributing to the development of inguinal hernias in males. A Chinese case-control study among males presenting to the surgical clinic of the University of Hong Kong Medical Centre, with 709 cases compared to 709 controls, indicated that males with a family history are eight times more likely to develop primary inguinal hernias [8]. Strenuous physical activities, especially those involving heavy lifting over prolonged periods, have been associated with a higher incidence of inguinal hernias [9]. Smoking has been associated with an increased risk of inguinal hernia recurrence [10]. A study at Al-Basra Teaching Hospital found that half of the patients were smokers, and all cases of recurrent hernias occurred among smokers [7]. Advancing age is a significant risk factor, with studies showing that the incidence of inguinal hernia increases with age [11]. In the Rotterdam Study, the risk of inguinal hernia increased with each

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year of age. The relationship between BMI and inguinal hernia risk is complex. For instance, the Rotterdam study observed a decreased risk of inguinal hernia in males with a BMI over 25 kg/m² [11]. Conversely, obesity is generally considered a risk factor for various types of hernias due to increased intra-abdominal pressure [12]. Respiratory conditions that lead to persistent coughing can also increase intra-abdominal pressure, thereby elevating the risk of hernia development. Studies have identified chronic obstructive airway disease as a contributing factor [13]. Understanding the risk factors associated with inguinal hernia is crucial for developing targeted prevention and intervention strategies. Identifying modifiable risk factors (e.g., smoking, heavy lifting, constipation) offers a basis for preventive programs such as workplace safety regulations, smoking cessation campaigns, and early screening initiatives. There is limited data from Iraq and the broader Middle East regarding risk factors for inguinal hernia. This study aimed to assess risk factors associated with inguinal hernia in Wasit Province, Iraq. It adds context-specific evidence that can inform national health strategies and future regional studies. In addition, the results can be used to educate patients about avoidable behaviors and health conditions that contribute to hernia development, thereby helping to reduce recurrence and postoperative complications.

2. Methods

2.1. Study Design and Setting

This case-control study was conducted at multiple public hospitals and surgical clinics across three major cities in Iraq: Wasit, Baghdad, and Basra. The study was conducted from January 2023 to December 2024.

2.2. Study Population

A total of 250 male patients diagnosed with inguinal hernia were enrolled in the study. These patients were either admitted for elective hernia repair surgery or presented to outpatient surgical clinics for evaluation and treatment. The control group comprised 250 healthy male individuals, matched for age and gender, with no clinical or ultrasound evidence of inguinal hernia.

2.3. Inclusion Criteria

Male patients aged 18 years and above were included in this study. They have to be diagnosed with a primary inguinal hernia by a consultant general surgeon, based on clinical examination and/or ultrasound confirmation, and those willing to participate and provide informed consent.

2.4. Exclusion Criteria

Those patients with recurrent or bilateral inguinal hernias and those with previous abdominal surgeries unrelated to hernia repair were excluded. Patients with significant comorbidities such as advanced cancer, end-stage liver or renal disease, were also excluded, in addition to incomplete or missing clinical data.

2.5. Data Collection

Data were collected using a structured questionnaire developed from a Nigerian case-control study at the general surgical clinic of Ikorodu General Hospital, with a few modifications tailored to the study's needs [14]. An expert performed the translation into the Arabic language to ensure both linguistic accuracy and cultural appropriateness. The questionnaire was validated by experts in both surgery and community medicine to ensure content relevance and appropriateness for the study objectives. These experts reviewed the items for clarity, accuracy, and comprehensiveness, confirming that the questionnaire adequately covered all necessary domains related to inguinal hernia and associated factors. Following expert validation, the questionnaire was pretested on 10 participants drawn from the target population. The pretest aimed to assess the clarity, relevance, and comprehensibility of the questions, as well as the overall flow and length of the instrument. Participants were encouraged to provide feedback on any items that were ambiguous or difficult. Based on this feedback, necessary modifications were made to improve question wording and structure, ensuring that the final questionnaire was user-friendly and capable of eliciting accurate and reliable responses. This process helped enhance the validity and reliability of the questionnaire before its use in the main study. The questionnaire was administered through self-reporting forms conducted with the help of medical staff. The information collected included Demographic data, such as age, occupation, residence (urban or rural), and socioeconomic status. Lifestyle factors, which consisted of smoking history, physical activity, and history of heavy lifting (occupational or recreational). Clinical history regarding the presence of chronic cough, constipation, BMI (measured at the time of visit), and family history of hernia.

2.6. Definition of Risk Factors

Heavy lifting was defined as lifting objects weighing more than 20 kg regularly (more than 3 times per week). Smoking included both current and former smokers who had smoked at least 100 cigarettes in their lifetime. Chronic cough was defined as a cough lasting longer than three months. Obesity was classified as a BMI of 30 kg/m² or higher, and overweight as a BMI between 25 and 29.9 kg/m². Constipation was defined as fewer than three bowel movements per week or persistent straining during defecation. A positive family history was considered if a first-degree male relative had a documented inguinal hernia.

2.7. Statistical Analysis

All data were entered and analyzed using IBM SPSS version 26. Descriptive statistics were used to summarize the demographic and clinical characteristics of the patients. Frequencies and percentages were calculated for categorical variables, while means and standard deviations were reported for continuous variables. Chi-square tests were used for initial bivariate analysis to examine the relationship between potential risk factors and the occurrence of inguinal hernia. Multivariate logistic regression analysis was then performed to identify independent risk factors, adjusting for potential confounders. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). A p-value of less than 0.05 was considered statistically significant.

2.8. Ethical approval

Ethical approval was obtained from Wasit University/College of Medicine. Institutional Review Board on December 1, 2022. Verbal consent was obtained from each participant prior to the start of the interview.

3. Results

A total of 250 male patients diagnosed with inguinal hernia were included in this study. Another 250 male controls without an inguinal hernia. The mean age of participants in both groups was 46.2 ± 15.3 years. The distribution of socio-demographic and clinical characteristics is summarized in (**Table 1**). Most patients (57.5%) fall within the 41–60 age group. Most patients (72.8%) were from urban areas, and 65.2% were classified as having a moderate socioeconomic status. The majority of patients were

Table 1: Socio-demographic characteristics of male patients with inguinal hernia (cases) and controls

Characteristic	Cases (n = 250)		Controls (n = 250)		p-value
	Frequency	%	Frequency	%	
Age group					0.999
18–40 years	62	25.0	62	25.0	
41–60 years	144	57.5	144	57.5	
61+ years	44	17.5	44	17.5	
Residence					0.582
Urban	182	72.8	175	70.0	
Rural	68	27.2	75	30.0	
Socioeconomic status					0.598
Low	43	17.2	37	15.0	
Moderate	163	65.2	170	68.0	
High	44	17.6	43	17.0	
Occupation					<0.001
Manual laborer	135	54.0	63	25.0	
Office worker	56	22.4	75	30.0	
Unemployed	34	13.6	38	15.0	
Other	25	10.0	75	30.0	

manual laborers (54.0%), followed by office workers (22.4%) and unemployed individuals (13.6%).

A significant proportion (63.6%) of patients reported a history of frequent heavy lifting due to occupational or lifestyle factors. More than a third (38.8%) of the patients had a chronic cough (lasting more than 3 months), commonly attributed to smoking or untreated respiratory infections. Around two-thirds (62.0%) of the sample were current or former smokers. Based on BMI calculations, 21.2% were classified as obese and 37.6% as overweight. Chronic constipation was reported in 28.4% of patients. Only 19.2% had a first-degree relative with a history of inguinal hernia. **(Table 2)** presents the clinical and lifestyle risk factors among cases and controls. Chi-square tests were performed to compare the prevalence of risk factors between cases and controls. Heavy lifting, smoking, chronic cough, constipation, and family history were significantly more prevalent among cases than controls ($p < 0.05$). Obesity did not show a statistically significant difference between the two groups ($p = 0.421$).

Heavy lifting, smoking, chronic cough, constipation, and family history were significant risk factors ($p < 0.05$). Obesity did not show a statistically significant association in the univariate model; however, it was considered for inclusion in the multivariate analysis due to its clinical relevance. **(Table 3)** presents the results of the multivariate logistic regression analysis, including odds ratios (ORs) and 95% confidence intervals (CIs) for the independent risk factors. In the multivariate model, heavy lifting (OR = 2.78, 95% CI: 1.80 - 4.30), smoking (OR = 1.69, 95% CI: 1.10 - 2.59), chronic cough (OR = 1.54, 95% CI: 1.01 - 2.36), and family history (OR = 2.46, 95% CI: 1.28 - 4.73) remained significant independent risk factors for inguinal hernia. Constipation (OR = 1.41, 95% CI: 0.91 - 2.18) and obesity (OR = 0.95, 95% CI: 0.54 - 1.67) did not show significant independent associations.

4. Discussion

This study highlights the importance of early identification and management of key risk factors to reduce the burden and prevalence of inguinal hernias in Iraqi males. With proper public health interventions, occupational reforms, and patient education, the incidence and complications of inguinal hernia can be significantly reduced. The mean age of the study participants was 46.2 years, with a range from 18 to 80 years. This is in line with studies indicating that the incidence of inguinal hernia increases with age [3, 15]. Age-related weakening of abdominal wall muscles contributes to this increased risk, as collagen plays a major role in this process of weakness [16]. Analyzing the results from this study, which involved 250 male patients with inguinal hernias, reveals several significant associations with known risk factors such as heavy lifting, smoking, and chronic cough. These findings align with the study conducted in the USA [15].

The results of this study identified heavy lifting as a significant risk factor, with 159 out of 250 patients (63.6%) reporting this activity. This finding corroborates previous research; a study in northern India found that 55% of patients engaged in heavy weight lifting, highlighting its role in hernia development [17]. In Iraq, the physical demands of jobs involving heavy lifting and strenuous labor in industrial sectors may increase the risk of developing inguinal hernias. Studies from Al-Basra Teaching Hospital show a predominance of inguinal hernia cases in men, many of whom are engaged in physically demanding work, supporting this occupational link [7].

Smoking was reported by 155 patients (62.1%) in our cohort. This is consistent with findings from a large U.S. study, which noted that tobacco use was associated with a higher incidence of inguinal hernia repair among women, though not significantly among men [18]. The discrepancy may be due to differences in study populations and methodologies.

Chronic cough was identified in 97 patients (38.6%) in this study. This aligns with earlier research that associates chronic obstructive airway disease with an increased risk of inguinal hernia [8]. Persistent coughing can lead to increased intra-abdominal pressure, which in turn contributes to the formation of a hernia.

Table 2: Clinical and lifestyle risk factors among cases and controls

Risk Factor	Cases (n = 250)		Controls (n = 250)		p-value
	Frequency	%	Frequency	%	
Heavy lifting	159	63.6	75	30.0	<0.001
Smoking	155	62.0	88	35.0	<0.001
Chronic cough	97	38.8	38	15.0	<0.001
Chronic constipation	71	28.4	25	10.0	<0.001
Family history	48	19.2	20	8.0	0.002
Obesity (BMI ≥ 30)	53	21.2	45	18.0	0.421

BMI, Body Mass Index

Table 3: Multivariate logistic regression analysis of independent risk factors

Risk Factor	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Heavy lifting	2.78	1.80 – 4.30	<0.001
Smoking	1.69	1.10 – 2.59	0.016
Chronic cough	1.54	1.01 – 2.36	0.045
Constipation	1.41	0.91 – 2.18	0.121
Family history	2.46	1.28 – 4.73	0.007
Obesity (BMI ≥ 30)	0.95	0.54 – 1.67	0.856

OR, odds ratio; CI, confidence interval; BMI, body mass index; %, percentage; p-value, probability value

The current study observed that 53 patients (21.2%) had a BMI of 30 or higher. This contrasts with findings from the Rotterdam Study, which reported that overweight or obese individuals had a lower risk of inguinal hernia [11]. Another population-based incidence study, which took place in Olmsted County, reviewed all inguinal hernia repair surgeries performed on adult residents and found that obesity may be considered a protective factor [19]. The inverse relationship observed in some studies may be attributed to several explanations: 1) Excess pre-peritoneal fat or intra-abdominal fat could provide a barrier effect by acting as a "plug" to prevent herniation of abdominal contents. 2) Obese patients could have poor overall health due to obesity related comorbidities, making them unsuitable candidates for an elective operation. 3) Obese patients are less able to perform strenuous physical exercise, and 4) When mentioning the self-awareness of an inguinal hernia, it would be more difficult in obese individuals due to body habitus.

Constipation was noted in 81 patients (32.4%) in this cohort. This finding is supported by previous studies linking altered bowel habits to an increased risk of inguinal hernia, such as a case control study among 100 cases who visited the General Surgery Outpatient Unit, Harran University, Sanliurfa, Turkey, and 100 healthy controls [20] and another prospective observational study was conducted for 2 years at the Bakirköy Dr. Sadi Konuk Training and Research Hospital General Surgery Clinic, which found that constipation is one of the independent risks for incarceration [21]. Straining during bowel movements elevates intra-abdominal pressure, a known risk factor for hernia development.

A positive family history of inguinal hernia was reported by 56 patients (22.4%). This finding is consistent with earlier research between January 2002 and January 2004, among male patients who presented with primary inguinal hernia at the general surgical in the University of Hong Kong Medical Centre, which indicated that individuals with a family history are at a higher risk, with one study noting an odds ratio of 8.73. Genetic factors likely play a role in predisposing individuals to hernia development [8].

This study recommends initiating public health campaigns that focus on the dangers of heavy lifting without proper technique, particularly for individuals engaged in manual labor. Educate the public on modifiable risk factors such as smoking cessation, healthy weight management, and treatment of chronic cough and constipation. Implement targeted screening programs for high-risk populations, particularly men over 40, individuals with a positive family history, and those in occupations involving manual labor. Include hernia risk assessments in routine primary care check-ups for these groups.

Conduct larger and longitudinal studies across different regions of Iraq to validate and expand upon these findings. Include female patients and establish control groups in future research for comparative analysis.

This study is strengthened by its focused design on a high-risk population (male patients), adequate sample size, and use of a structured questionnaire to assess multiple lifestyle, clinical, and demographic variables. The application of both univariate and multivariate analyses enhances the reliability of the findings by controlling for potential confounders. Additionally, this research fills a regional knowledge gap by providing localized data from Iraq, a setting often underrepresented in hernia-related research.

Limitations: Variables such as smoking history, heavy lifting, constipation, and family history were collected via self-reported questionnaires. This introduces recall bias and social desirability bias, which may result in underreporting or overreporting of behaviors and symptoms. This limitation means the results should be interpreted with caution. Still, the findings offer valuable insight and form a strong foundation for future larger or longitudinal studies.

5. Conclusions

This study provides valuable insight into the socio-demographic, lifestyle, and clinical risk factors associated with inguinal hernia among male patients in Iraq. Heavy lifting, smoking, chronic cough, and family history were significantly associated with increased risk of inguinal hernia among Iraqi males. Among these, heavy lifting and smoking emerged as the most prevalent and statistically significant risk factors. While obesity did not show a significant independent association in multivariate analysis, its role

cannot be overlooked, especially in the context of intra-abdominal pressure and other comorbidities.

Conflicts of Interest

The authors declare no conflicts of interest related to this manuscript.

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Large Language Model

We have employed an advanced Large Language Model (LLM) to enhance and refine the English-language writing. This process focused solely on improving the text's clarity and style, without generating or adding any new information to the content.

Authors Contribution

All authors contributed equally in conceptualization, methodology, software, writing the draft, and approving the final manuscript.

Data Availability

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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ASIDE Internal Medicine

Original Article

Concurrent Diabetic Ketoacidosis and Acute Coronary Syndrome: A Systematic Review of Case Reports

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ABSTRACT

Background: Diabetic ketoacidosis (DKA) and acute coronary syndrome (ACS) represent serious medical emergencies with a complex bidirectional relationship. The clinical presentations and outcomes of these conditions when they co-occur remain incompletely characterized in the literature. We aim to investigate this correlation.
Methods: We systematically searched the PubMed, Scopus, and Web of Science databases, using terms related to acute coronary syndrome (including myocardial infarction, unstable angina, STEMI, and NSTEMI) combined with diabetic ketoacidosis terms, from inception to April 2025, for case reports. The CARE checklist was applied to assess the risk of bias in the included reports.
Results: Twenty-one case reports met inclusion criteria, describing 11 males and 9 females (one unspecified) with a mean age of 51 years. Patients had both type 1 (42.8%) and type 2 (57.1%) diabetes mellitus. Chest pain was the most common presenting symptom (52.3%), but was absent in nearly half of the cases. Six patients (28.5%) on sodium-glucose cotransporter-2 (SGLT2) inhibitors presented with euglycemic DKA. ST-segment elevation was observed in 61.9% of patients, while five patients had normal coronary arteries despite elevated troponin levels. All patients survived after receiving standard DKA management and appropriate cardiac interventions.
Conclusion: This systematic review highlights the importance of maintaining high clinical suspicion for concurrent DKA and ACS, even when typical symptoms such as chest pain or hyperglycemia are absent. We recommend routine cardiac evaluation, including ECG, troponin assessment, and echocardiography, for all DKA patients to ensure early recognition and appropriate management of these potentially life-threatening conditions.

1. Introduction

Diabetic ketoacidosis (DKA) is one of the most serious complications of diabetes mellitus (DM), with approximately 220,000 patients with a primary diagnosis of DKA in the United States, representing nearly 60 cases per 100,000 hospital admissions [1]. This high prevalence contributes significantly to the financial burden of DKA, with hospitalization costs for DKA reaching nearly 6.76 billion dollars, with an average length of stay of only three days [2]. DKA results from insulin depletion that often happens in cases of undiagnosed DM, with a triad of hyperglycemia, ketosis, and high anion gap [3, 4]. On the other hand, nearly 805,000 acute myocardial infarctions (AMI) occur each year, with approximately 600,00 of them being first-time myocardial infarction (MI) events [5]. Acute coronary syndrome (ACS) refers to conditions caused by a sudden reduction or blockage of blood supply to the heart. It includes unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI) [6].

DKA and ACS are medical emergencies requiring immediate intervention to prevent potentially fatal outcomes. However, the relationship between the two conditions appears bidirectional and clinically significant, as DM is one of the modifiable risk factors for ACS. At the same time, ACS can precipitate DKA by inducing physiological stress responses [7]. Additionally, there is a strong association between DM and cardiovascular diseases, with approximately one-third of diabetes patients reporting serious cardiovascular events [8]. The precise pathophysiological mechanisms connecting DKA and ACS remain incompletely understood, despite the clear epidemiological association between the two

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conditions, as MI and heart failure account for 28% mortality in DKA cases [9]. The diagnostic challenge is further complicated by euglycemic diabetic ketoacidosis (DKA), particularly in patients using sodium-glucose cotransporter-2 (SGLT2) inhibitors, where normal or mildly elevated glucose levels may delay recognition of ketoacidosis in those presenting with cardiac symptoms. To better understand this relationship, we aim to systematically investigate reported cases of DKA and ACS, describe the clinical presentation and laboratory patterns when both conditions co-occur, and evaluate the effect of this comorbidity on patient outcomes and hospitalization course.

2. Methods

In this systematic review of case reports, we followed the updated version of the Preferred Reporting Items for Systematic Reviews (PRISMA) [10].

2.1. Data Source and Search Terms

We searched PubMed, Scopus, and Web of Science from inception until April 2025 to find relevant case reports on ACS and DKA, with notifications enabled on PubMed, using these search terms ((acute coronary syndrome) OR "ACS" OR (myocardial infarction) OR "MI" OR (unstable angina) OR "UA" OR (non-ST-segment elevation) OR "NSTEMI" OR (ST-segment elevation) OR "STEMI") AND ((diabetic ketoacidosis) OR "DKA" OR (diabetic acidosis)). For detailed search strategy and filters applied in each database, as shown in Supplementary **(Table 1)**.

2.2. Eligibility Criteria and Study Selection

We included case reports published in English that reported DKA complicated by ACS or vice versa. Other study designs, animal studies, and studies published in languages other than English were excluded. After searching the mentioned databases, we imported the search results into EndNote (Clarivate Analytics, PA, USA) to eliminate duplicates. The remaining unique references were then exported to Rayyan [11]. Four researchers independently screened the titles and abstracts of all identified studies. They then sorted out full-text articles of potentially eligible studies and assessed them for inclusion. Conflicts were resolved by discussion. Finally, a manual review of backwards and forward citations was done for all references cited in the included studies.

2.3. Data Extraction

Four independent authors extracted data from each of the final included studies' papers into Microsoft Excel spreadsheets to ensure the accuracy of our data. Any conflicts were resolved by discussion or by another reviewer. Extracted data included patients' age, sex, diabetes type, presentation, troponin, BNP, ECG, coronary angiography findings, home medication, blood sugar levels, pH, serum potassium (K), serum bicarbonate HCO_3, HbA1c level, and the outcome of the presented case.

2.4. Risk of Bias and Quality Assessment

The CARE checklist was used to assess the risk of bias between included studies. Eight key domains were evaluated: 1. Demographics Clearly Described 2. History Presented as Timeline 3. Current Clinical Condition Described 4. Diagnostic Tests Described 5. Treatment Procedure Described 6. Post-Intervention Condition Described 7. Adverse Events Described 8. Takeaway Lessons Provided. Each domain was assessed as yes, no, unclear, or not applicable for each study. Two independent researchers evaluated each study, and any disagreements were resolved by consensus.

2.5. Statistical Analysis

Due to the heterogeneity in case report methodology and the descriptive nature of the data, meta-analysis was not feasible. Data synthesis was performed using descriptive statistics in Microsoft Excel 365. Categorical variables are expressed as frequencies and percentages, with denominators specified for each variable based on available data. Missing data were handled by calculating percentages from the total number of cases with available information for each specific parameter.

3. Results

In our systematic review, 1,743 records were initially identified from the searched databases, of which only 1,278 were retrieved after removing 465 duplicate articles. A total of 1212 records were excluded following title and abstract screening, resulting in 66 records for full-text screening. Of these, 45 records did not meet our eligibility criteria. Finally, we included 21 case reports [12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32], as shown in Figure 1.

3.1. Patients' Characteristics

Out of review included 21 patients, with a male predominance of 11 males (52.3%) and 9 females (42.8%). The patients' ages ranged from 18 to 77, with a mean age of 51. The majority of patients were between 50 and 60 years old. Out of these 21 patients, 12 (57.1%) were diagnosed with type 2 diabetes mellitus (T2DM) and 9 (42.8%) with type 1 diabetes mellitus (T1DM). Additionally,

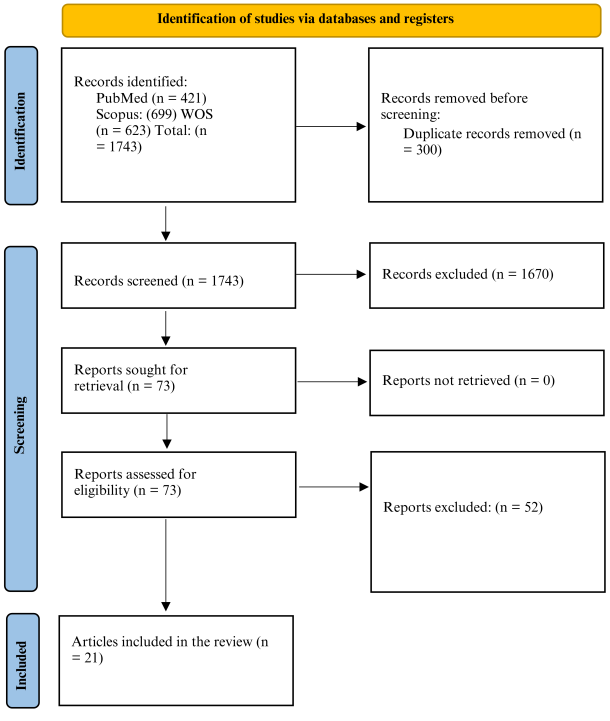

Figure 1: Flowchart of Study Selection Process for Systematic Review.

Table 1: Summary of Patient Demographics and ACS Presentation

Author	Age, years	Sex	Diabetes type	Presentation	Troponin, ng/ml	Type of ACS
Baral 2021 [12]	77	M	T2DM	SOB, cough, fever for 3 days, oxygen saturation 80% on 10 liters nasal cannula (improved to 95% on a non-rebreather mask with 15L/min).	Initial: 0.923, Peaked at 23.684	STEMI
Baytu0̆11fan 2023 [13]	61	M	T2DM	CP, generalized weakness, polyuria, nausea & vomiting for several days.	161.7	STEMI
Bouzhir 2024 [14]	76	F	T2DM	Severe CP at rest, palpitations post-cataract surgery, persistent symptoms after 30 hours, & a dry cough for 10 days.	3,859	STEMI
Briggs 2022 [15]	56	F	T2DM	48 hours of nausea, vomiting, generalized abdominal pain, and diarrhea. No CP, SOB, or fever.	212	STEMI
Çakır 2012 [16]	18	F	T1DM	Fatigue, weakness, nausea, vomiting for two days, and abdominal pain. No CP.	WNL	Non-STEMI
Doherty 2022 [17]	24	M	T2DM	CP radiating to the left arm, sweating, tachycardia, 24-h history of vomiting & diarrhoea after alcohol consumption.	1212	STEMI
Dorcely 2021 [18]	61	M	T2DM	Nausea and CP	Negative	Inferior Q waves, unchanged from prior ECG.
Eliades 2014 [19]	71	F	T2DM	Abdominal pain, vomiting, confusion, & altered mental status.	5.67	STEMI
Fronczyk 2016 [20]	20	M	T1DM (diagnosed 10 years prior)	Weakness, low-grade fever, epigastric and abdominal pain, nausea, vomiting, burning retrosternal pain, and high blood glucose for 2 days.	WNL	STEMI
Gerede 2016 [21]	58	F	T1DM (diagnosed 33 years prior)	Confusion, nausea, vomiting, cough, sore throat, fever, dehydration, and an inclination to sleep.	5.43	Non-STEMI
Goto 2021 [22]	52	F	T2DM	Tachypnea, vomiting, decreased blood pressure, metabolic acidosis (euglycemic DKA), and myocardial ischemia.	324.5	Non-STEMI
Kaefer 2019 [23]	49	M	T1DM	DKA, nausea, and vomiting after inappropriate insulin therapy, troponin elevated to 142ng/l after 14 h post-admission and peaked at 142 ng/l at 38 h post-admission, no CP but ST elevation less than 2mm.	33, 14 h post-admission, peaked at 142, 38 h post-admission	STEMI
Landa 2021 [24]	48	M	T1DM	Diffuse pain and fatigue. He began feeling tired three days prior to the presentation with associated nausea and vomiting, but denied any fever, chills, or CP.	0.04	STEMI
Lee 2014 [25]	60	M	T2DM (New diagnosis)	Intermittent central CP radiated to left shoulder & neck, not affected by posture or exertion, with polydipsia, polyuria, weight loss, fever, sore throat.	0.77 µg/L	STEMI
Mhanna 2020 [26]	50	F	T1DM	Lethargy and low Blood pressure.	On admission: 0.21; second day: 20	STEMI
Odubanjo 2017 [27]	Middle age	NA	T1DM	Nausea & vomiting for 1 day.	On admission: 0.012, day 2: 7.3	STEMI
Oriot 2023 [28]	77	F	T2DM	CP, later respiratory distress & atrial fibrillation.	143	STEMI
Petersen 2023 [29]	28	M	T2DM	CP, diagnosed as NSTEMI after PCI.	NA	Non-STEMI
Umadat 2022 [30]	61	M	T1DM	Epigastric abdominal pain, nausea, & vomiting.	336	Nonspecific T-wave abnormalities
Wray 2020 [31]	19	M	T1DM	One day of nausea, vomiting, diffuse back & abdominal pain. Tender abdomen & back without trauma.	Undetectable	STEMI
Zughaib 2023 [32]	54	F	T2DM	Several days of typical CP, intractable nausea & vomiting. Repeated ED visits.	0.13	STEMI

ACS, Acute coronary syndrome; AFib, Atrial fibrillation; CP, Chest pain; DKA, Diabetic ketoacidosis; ED, Emergency department; F, Female; M, Male; NA, Not available; NSTEMI, Non-ST-elevation myocardial infarction; PCI, Percutaneous coronary intervention; SOB, Shortness of breath; STEMI, ST-elevation myocardial infarction; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; WNL, Within normal limits; ng/mL, Nanograms per milliliter; µg/L, micrograms per liter.

Table 2: Summary of Patient Echocardiographic, Angiographic, Laboratory, and Outcome Data

Author	EF%	Coronary Angiography	Home Medication	RBS (mg/dL)	pH	K (mmol/L)	HCO_3 (mEq/L)	HbA1c	Outcome
Baral 2021 [12]	15–20%	95% occlusion RCA at ostium, hazy filling defect in stent, patent LAD stent	Aspirin, clopidogrel, atorvastatin, metoprolol	541	7.36	5.8	16	NA	DES in RCA. Discharged after 32 days with EF 25–30%.
Baytu01fan 2023 [13]	50%	Total occlusion of proximal LAD	Amlodipine/perindopril metformin, dapagliflozin	171	7.03	5.03	5.6	9.60%	Successful PCI, insulin and bicarbonate, discharged day 6.
Bouzhir 2024 [14]	43%	No significant stenosis	NA	NA	NA	NA	NA	NA	Full LV recovery, EF 62% post-event.
Briggs 2022 [15]	40–45%	100% occlusion mid-circumflex, LAD 50%, RCA 60%	Rivaroxaban	392	7.2	NA	NA	NA	Successful PCI with stent, discharged post-op day 2.
Çakır 2012 [16]	NA	Not performed	None	476	7.07	2.1	NA	11.07%	Resolved with insulin, saline. Discharged stable.
Doherty 2022 [17]	49%	Occlusion of distal PLV branch, RCA thrombus	Olanzapine, fluoxetine	20.4 mmol/L	metabolic acidosis	3.2	15	64 mmol/mol	PCI and insulin therapy. Discharged day 4.
Dorcely 2021 [18]	Stress-induced abnormalities	Total occlusion mid-RCA, non-obstructive elsewhere	Empagliflozin, metformin, liraglutide, rosuvastatin, ezetimibe, omeprazole	84	metabolic acidosis	NA	17	8.30%	CP and DKA resolved. SGLT2 discontinued.
Eliades 2014 [19]	30%	Normal coronaries	Insulin, metformin	NA	NA	NA	NA	NA	EF improved to 45–50% in 10 days.
Fronczyk 2016 [20]	No contractility abnormalities	Normal coronaries	Insulin pump	33.1 mmol/L	7.18	Normal	5.6	10.37%	Pain and ECG normalized. Discharged day 11.
Gerede 2016 [21]	No wall motion abnormality	Non-obstructive lesions	Insulin, ramipril	522	7.159	6.3–6.4	5.8	NA	ECG/biochem normalized. Discharged day 8.
Goto 2021 [22]	NA	Coronary stenting	Empagliflozin, sitagliptin, ezetimibe, rosuvastatin, clopidogrel	178	6.84	-	2.1	NA	ICU, VA-ECMO, CRRT. Discharged ICU day 15.
Kaefer 2019 [23]	Apical dyskinesia	No occlusion	-	38.9 mmol/L	6.93	-	2.7	10.4	Angioplasty, stenting.
Landa 2021 [24]	Fair LV function	NA	Insulin only	952	6.94	7.6	<5	10.4	ICU insulin drip.

Table 2 (continued): Summary of Patient Echocardiographic, Angiographic, Laboratory, and Outcome Data

Author	EF%	Coronary Angiography	Home Medication	RBS (mg/dL)	pH	K (mmol/L)	HCO_3 (mEq/L)	HbA1c	Outcome
Lee 2014 [25]	Normal	50% LCX obstruction	NA	35.6 mmol/L	7.25	NA	13	17%	ICU admission, abscess drainage, 10-week stay.
Mhanna 2020 [26]	60–65% to 25%	Normal coronaries	NA	1637	6.8	7.6	2.7	NA	Extubated, Life Vest, outpatient insulin.
Odubanjo 2017 [27]	Normal	Non-obstructive	NA	565	6.99	5.8	<5	NA	DKA resolved. Treated myocarditis. Discharged day 4.
Oriot 2023 [28]	41%	Triple-vessel disease, LAD stented	Metformin, nebivolol, statin, aspirin, spironolactone, citalopram	247	7.2	NA	6.1	7.80%	Discharged day 22, basal insulin.
Petersen 2023 [29]	NA	LAD NSTEMI	Full diabetes and cardiac regimen	154	7.048	5.8	<7	11.1	ICU stay, DKA resolved in 5 days, outpatient follow-up.
Umadat 2022 [30]	NA	99% LAD, 90% diagonal	Aspirin, statin, insulin pump	326	7.39	5	14	8%	Post-DKA PCI with stenting. Discharged on pump.
Wray 2020[31]	NA	Normal coronaries	NA	700	7.09	5.7	9.07	NA	PCI showed normal coronaries. Discharged day 3.
Zughaib 2023 [32]	NA	Ulcerated RCA plaque, mild LAD/LCX disease	Metformin, Empagliflozin	135	NA	3.2	NA	NA	PCI and stent. Resolved CP and DKA. Discharged.

DES, drug-eluting stent; EF, ejection fraction; RBS, random blood sugar; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; PLV, posterior left ventricular branch; NSTEMI, non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; DKA, diabetic ketoacidosis; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; SGLT2, sodium–glucose cotransporter-2 inhibitor; T1DM, type 1 diabetes mellitus; HbA1c, hemoglobin A1c; NA, not available; mg/dL, milligrams per deciliter; mmol/L, millimoles per liter; mEq/L, milliequivalents per liter; pH, potential of hydrogen; HCO_3, bicarbonate; SC, subcutaneous; BID, twice daily; TIMI, Thrombolysis In Myocardial Infarction flow grade; GRACE, Global Registry of Acute Coronary Events; CP, chest pain; AFib, atrial fibrillation; ICU, intensive care unit.

six patients (28.5%) were reported to be on SGLT2 inhibitors, as shown in **(Table 1)**.

3.2. Clinical Presentation

The most common presenting symptoms included chest pain (n = 11, 52.3%), nausea and vomiting (n = 5, 23.8%), and fatigue or weakness (n = 4, 19.0%). Other reported symptoms included abdominal pain, shortness of breath, and altered mental status, with a duration of symptoms before presentation ranging from several hours to several days, as shown in **(Table 1)**.

3.3. Vital Signs

Initial vital signs showed variable presentations. Blood pressure measurements ranged from hypotensive (lowest recorded 74/64 mmHg) to hypertensive (highest recorded 193/83 mmHg). Heart rate was frequently elevated, ranging from 69 to 155 beats per minute. Respiratory rates were notably high in several patients, ranging from 15 to 40 breaths per minute, with many patients presenting with Kussmaul breathing, a characteristic of metabolic acidosis. The body temperature was generally within the normal range; however, some patients presented with fever.

3.4. Laboratory Findings

Blood glucose levels varied widely, ranging from 84 to 1637 mg/dL, with a notable finding that five patients presented with euglycemic DKA (glucose <250 mg/dL) while on SGLT2 inhibitors. Arterial pH was significantly reduced in most cases, ranging from 6.80 to 7.39, indicating severe acidosis in many patients. Serum bicarbonate levels were markedly decreased, with values as low as <5 mEq/L, confirming metabolic acidosis. Additionally, serum potassium levels varied from hypokalemic (2.1 mmol/L) to hyperkalemic (7.6 mmol/L), as shown in **(Table 2)**.

3.5. Cardiac Markers

Troponin levels were elevated in most patients, ranging from slightly elevated to markedly increased (maximum recorded 23.684 ng/mL). Several patients showed progressive elevation of troponin levels during hospitalization, peaking hours after admission, as shown in **(Table 1)**.

3.6. Glycemic Control

Glycated hemoglobin (HbA1c) values were reported in 11 patients, ranging from 7.8% to 17%, indicating poor long-term glycemic control in most cases, with a mean HbA1c of 10.4% **(Table 2)**.

3.7. Electrocardiographic Findings

ECG abnormalities were observed in almost all patients. ST-segment elevation was the most common finding (n=13, 61.9%), predominantly in the inferior (leads II, III, aVF) or anterolateral leads (V1-V6). ST-segment depression was noted in 9 patients (42.8%). Other ECG findings included T-wave inversions, bundle branch blocks, and atrial fibrillation, as shown in **(Table 1)**.

3.8. DKA management

All patients received standard DKA management, including intravenous insulin infusion and fluid resuscitation. Electrolyte replacement, particularly potassium, was administered as needed. In one case of severe acidosis, sodium bicarbonate was used, as shown in **(Table 2)**.

3.9. Coronary Interventions

Coronary angiography was performed in 18 patients (85.7%), and percutaneous coronary intervention (PCI) with stenting was performed in 4 patients (19%). Notably, five patients had normal coronary arteries on angiography despite presenting with clinical and ECG findings suggestive of ACS, as shown in **(Table 2)**.

3.10. Risk of Bias and Quality Assessment

Quality assessment using the CARE checklist revealed that studies demonstrated high compliance for most reporting domains: demographics (21/21, 100%), current clinical condition (21/21, 100%), diagnostic tests (21/21, 100%), and treatment procedures (21/21, 100%) were adequately described in all studies, while post-intervention conditions (20/21, 95%) and timeline presentation of history (17/21, 81%) were well-documented in the majority of cases. However, adverse event reporting was suboptimal, with only 8 out of 21 studies (38%) providing adequate documentation, and takeaway lessons were present in 12 out of 21 studies (57%).

4. Discussion

The relationship between DKA and ACS is bidirectional, with each condition capable of precipitating and influencing the pathogenesis of the other. ACS can precipitate DKA through a stress response, that occurs due to the release of significant amount of counter-regulatory hormones, such as epinephrine, glucagon and cortisol [23]. This hormonal surge raises blood glucose level, antagonizes the action of insulin, promotes fat breakdown, facilitates the production of ketones and eventually triggers the development of DKA [33]. On the other hand, DKA can lead to the occurrence of myocardial ischemic damage by a multitude of mechanisms, including free fatty acids accumulation, metabolic acidosis and counter-regulatory hormones [34].

When acidosis of the blood occurs, it leads to the acceleration of intracellular ionic movement of calcium Ca^{2+}, resulting in the accumulation of Ca^{2+} inside the myocardial cells. This excess intracellular Ca^{2+} facilitates the process of protein breakdown, known as proteolysis [35]. This process is accompanied by a reduced ability of calcium to bind to the contractile proteins in the heart muscle—an effect caused by acidosis—which ultimately leads to impaired pump function, a phenomenon known as myocardial stunning. Ultimately, the combined effect of proteolysis and myocardial stunning results in myocardial injury leading to an increase in the serum cardiac troponin level [36]. Moreover, acute decompensation of diabetes is associated with a sudden increase in the levels of counter-regulating hormones, such as epinephrine, cortisol, and glucagon, to try to increase the blood glucose level and provide energy during exacerbation [37, 36]. However, these hormones can significantly increase the workload and metabolic demand of the cardiac muscle. In patients who already have coronary artery disease (CAD), this increase in the myocardial oxygen demand can induce the occurrence of ACS [37]. Additionally, acute diabetic decompensation such as DKA is associated with a significant increase in the level of circulating free fatty acids (FFA). The excess FFA can be incorporated into the myocytes of the heart muscle, forming micelle-like formations that weaken and destabilize the cell membrane [38]. Additionally, the severe lack of insulin, associated with increased ketone bodies and FFA, results in dysfunctional glucose uptake by the cardiac muscles and promotes the alternative uptake of FFA as the main energy source [38, 37].

Generally, the interpretation of cardiac biomarkers, such as troponin, in DKA patients can be challenging, as ACS may either initiate the onset of DKA or arise as a consequence of it [31]. Additionally, the increase in troponin associated with DKA patients could be due to either the presence of underlying CAD disease, which is exacerbated by metabolic stress and acidosis, or to the infiltration of myocytes by the excess FFA associated with the

severe insulin deficiency [39, 40]. This could explain the absence of coronary abnormalities on some patients despite a rise in troponin. Moreover, our analysis revealed that both type 1 and type 2 diabetes mellitus (T1DM and T2DM) were present almost equally (42.8% vs. 57.1%), underscoring that neither diabetes phenotype is exempt from the risk of ACS during DKA. This demographic pattern aligns with established epidemiological data for acute coronary syndrome, where middle-aged males represent the highest-risk population, suggesting that traditional ACS risk factors may contribute to the concurrent presentation. T1DM patients are at risk of acquiring DKA due to their absolute insulin deficiency. In contrast, T2DM patients suffer from relative insulin deficiency, which is exacerbated by the rise in counter-regulatory hormones in cases of severe events, such as infection or stress [41, 42].

Clinical presentation of patients included a wide variety of symptoms and signs, such as chest pain, abdominal pain, nausea, vomiting, fatigue, altered mental status, hypertension, hypotension and tachypnea. The most common symptom presented was chest pain, however it should be noted that it was absent in nearly half of the patients. Our analysis demonstrated that some patients-mainly old patients- did not report chest pain, despite having high troponin and coronary artery abnormalities. This could be attributed to the sensory neuropathy associated with DM, which can decrease the pain perception of these patients, preventing the sensation of chest pain during the anginal attack [43]. The absence of chest pain in these patients poses a critical diagnostic challenge, potentially leading to delayed recognition of ACS. This atypical presentation, combined with the metabolic focus required for DKA management, creates a scenario where cardiac evaluation may be deprioritized. Healthcare providers managing DKA patients should maintain heightened awareness for silent myocardial ischemia, particularly in patients with cardiovascular risk factors, unexplained hemodynamic instability, or ECG changes that cannot be attributed solely to electrolyte abnormalities [44].

This fact complicates the process of ischemic heart disease diagnosis in DM patients, as in these patients the diagnosis is mainly based on the presence of non-specific angina-equivalent symptoms such as dyspnea and dizziness along with abnormal glucose level [45].

In the majority of cases, DKA was associated with an increased blood glucose level; however, in six cases of individuals receiving SGLT2i drugs at home, euglycemic DKA with a blood glucose level below 250 mg/dL was a prominent feature. Notably, euglycemic DKA occurred in 6 patients (28.6%), which contrasts sharply with the general DKA population, where euglycemic presentations account for only 2.6-3.2% of cases [48). This atypical presentation of DKA can delay the diagnosis and obscure the coexisting myocardial damage [46]. SGLT2i drugs can cause euglycemic DKA by enhancing urinary glucose excretion, thereby lowering blood glucose levels, which in turn can lead to a reduction in insulin secretion or dosing. Additionally, SGLT2i can also stimulate glucagon release, which, when accompanied by a diminished insulin level, promotes a shift in metabolism towards lipolysis, leading to increased ketone production [47]. Thus, the reliance on high blood glucose level alone to diagnose DKA is not a proper clinical practice, especially in patients who are receiving oral anti-diabetic drugs [48]. Additionally, this also underscores the importance of heightened monitoring of DKA patients who are on SGLT2i drugs and the need for immediate discontinuation of the drug in cases of DKA suspicion [49]. The association between SGLT2 inhibitors and euglycemic DKA in our cohort raises important ethical considerations regarding informed consent and risk-benefit communication. Clinicians prescribing SGLT2 inhibitors must ensure that patients understand the risk of DKA, particularly those with additional risk factors, such as insulin deficiency, acute illness, or planned procedures. The cardiovascular benefits of SGLT2 inhibitors are well-established, but the potential for life-threatening ketoacidosis, especially with atypical presentations, necessitates careful patient selection, education, and monitoring protocols [50].

Regarding the analysis of the treatments provided, all of the included cases received the standard DKA therapy, which included aggressive fluid resuscitation, electrolyte correction and IV insulin infusion [51]. Only one patient who was associated with severe metabolic acidosis (PH>7, HCO3=5.6) was indicated to receive intravenous bicarbonate administration. This aligns with current recommendations which deter from routine use of bicarbonate in the treatment of DKA, due to the risk of cerebral edema [52]. Hence, the use of bicarbonate should be solely exclusive in cases with refractory metabolic acidosis that failed to be corrected with standard DKA therapy [53]. Furthermore, 18 cases underwent PCI for the treatment of ACS, of which five patients had normal coronaries suggesting either demand ischemia or coronary vasospasm.

In our review, despite the severity of the presentation of some cases, the majority of the patients survived the acute phase and no mortality was reported. However, some cases, particularly patients with severe metabolic acidosis and elevated cardiac biomarkers, required prolonged hospitalization after undergoing the PCI procedure or after admission to the ICU. Patients with euglycemic DKA on SGLT2i drugs suffered from delayed diagnosis which might have influenced their clinical course and prolonged their hospital stay. Furthermore, whereas no mortality was reported in the selected cohort, the lack of long-term follow up for potential complications limit our understanding of the true long-term prognosis of those patients.

Another important observation is the significantly high HbA1c level in the reported cases, indicating in the process significantly poorly controlled diabetic status. In literature, patients with HbA1c levels above 9% are significantly more likely to develop DKA compared to those with lower levels with one study reporting that this risk could be five times more likely compared to patients with HbA1c levels between 7% and 8% [54]. Moreover, the level of HbA1c could correlate to the severity level of DKA as well as the severity level of the associated metabolic acidosis [55]. Furthermore, elevated HbA1c level alone is an independent risk factor for ACS and is associated with significantly worse outcomes and prognosis [56]. This highlights the importance of good monitoring of diabetic patients, especially patients who are at high risk for CAD [57]. Proper control of blood glucose level over the long-term can be beneficial in preventing the exacerbating events of DKA and ACS [58]. Our findings advance clinical understanding in several key areas: First, the prevalence of euglycemic DKA in concurrent presentations is substantially higher than in general DKA populations, suggesting unique pathophysiological or pharmacological mechanisms. Second, the high frequency of atypical presentations without chest pain necessitates revised diagnostic protocols that include routine cardiac evaluation in DKA patients with cardiovascular risk factors. Third, the prominence of SGLT2 inhibitor-associated cases establishes this drug class as a key risk factor requiring enhanced monitoring and patient education. These

insights should inform updated clinical guidelines for both emergency department protocols and SGLT2 inhibitor prescribing practices.

This systematic review aggregated all the known case reports on this subject in the literature, in order to provide a comprehensive, up-to-date assessment of the relationship between DKA and ACS. However, this study still has some limitations that should be considered, including the inherent biases of the study design. A case report was the best available option to address this issue, given the rarity of concurrent DKA and ACS, higher-level evidence, such as cohort studies or RCTs, is not feasible. Additional limitations included heterogeneity in the diagnostic criteria and management protocols, publication bias, a small sample size, and a lack of control groups and long-term follow-up. Thus, larger-scale observational prospective or retrospective studies are required to address these limitations.

5. Conclusion

In conclusion, our review highlights the bidirectional association between DKA and ACS. Clinicians should maintain a low threshold for suspicion of concurrent DKA in patients presenting with ACS, particularly when traditional DKA symptoms (polyuria, polydipsia, nausea) are absent. Routine ECG, troponin assessment and echocardiography are essential to differentiate between true ischemia and metabolic mimicry. Ultimately, early recognition, standard treatment and use of coronary angiography are pivotal to optimizing outcomes.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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Authors Contribution

AE handled conceptualization, data curation, validation, methodology, reference management, and writing of the original draft, while AFG provided resources, data curation, validation, methodology, and writing of the original draft. MH was responsible for data curation, validation, and writing of the original draft, and LMA managed data curation, methodology, and writing of the original draft. MYE, MM, and AAA oversaw data curation, validation, methodology, and preparation of tables. AH supervised the work and contributed to writing, review, and editing.

Data Availability

All studies used in the research are available in various databases.

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Original Article

Esophageal Stenting and Endoscopic Vacuum Therapy for Esophageal Defects: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Spontaneous esophageal perforation, particularly Boerhaave syndrome, is a life-threatening condition associated with high morbidity and mortality. Traditional surgical management is increasingly being supplemented by minimally invasive approaches, including esophageal stenting and endoscopic vacuum therapy (EVT). However, the optimal treatment strategy remains debated due to variations in reported outcomes and the lack of randomized controlled trials. This systematic review and meta-analysis aim to evaluate the efficacy and safety of esophageal stenting and EVT in managing esophageal defects by specifically assessing sealing rates, failure rates, and mortality.
Methods: A comprehensive literature search was conducted in PubMed, Scopus, and the Cochrane Library up to March 29, 2025. The primary outcomes were the pooled sealing rate, failure rate, and mortality for esophageal stenting and the closure rate for EVT. Data were analyzed using a random-effects model, and heterogeneity was assessed using the I^2 statistic.
Results: Fourteen studies on esophageal stenting demonstrated a pooled sealing rate of 86.1% (95% CI: 80.2–92.0%) with a failure rate of 14.9% (95% CI: 8.5–21.3%). Mortality associated with stenting was 7.4% (95% CI: 3.5–11.4%). EVT studies reported a closure rate ranging from 80% to 94%.
Conclusion: Both esophageal stenting and EVT show high efficacy in sealing esophageal defects. Although EVT exhibits promising closure rates, further comparative studies are needed to establish definitive treatment guidelines.

1. Introduction

Spontaneous esophageal perforation—commonly known as Boerhaave syndrome or barogenic rupture—is an infrequent yet life-threatening condition. It arises from a sudden surge in pressure within the distal esophagus while the upper esophageal sphincter remains closed, a scenario frequently precipitated by forceful vomiting or esophageal spasms. Although Mackler's triad of vomiting, chest pain, and subcutaneous emphysema is considered characteristic, nearly one-third of cases exhibit atypical clinical features that can delay diagnosis [1]. The rupture is most often localized to the left side of the lower intrathoracic esophagus [2]. And without prompt recognition and intervention, mortality rates can range from 15% to 42% [3]. Conventional treatment strategies involve emergency surgical procedures—such as primary repair, T-tube insertion, or esophageal resection and diversion—with early surgery correlating with improved outcomes [4, 5, 6, 7].

Esophageal leaks, perforations, and Boerhaave syndrome continue to pose significant clinical challenges given their high morbidity and mortality. While invasive surgical methods have traditionally been the mainstay of treatment, there has been a notable shift over the past two decades towards minimally invasive techniques. Approaches such as esophageal stenting and endoscopic vacuum therapy (EVT) have emerged as promising alternatives, offering the benefits of re-establishing gastrointestinal continuity, facilitating the drainage of infected areas, and optimizing resuscitative efforts. These interventions may reduce the duration and invasiveness of traditional surgeries, thereby enhancing patient recovery. In fact, a comprehensive review that analyzed 66 studies on the use of esophageal stents for anastomotic leaks and benign perforations reported a technical success rate of 96% and a clinical success rate of 87% [8, 6].

Esophageal stenting, in particular, provides a less invasive option with the potential for rapid defect closure and lower procedural morbidity, while EVT has attracted attention for its effectiveness in promoting tissue healing and controlling sepsis in complex

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esophageal defects [9, 1]. Despite their increasing utilization, the optimal treatment strategy remains debatable due to the variability in reported outcomes and the current lack of randomized controlled trials (RCTs).

The existing evidence is primarily derived from observational studies and case series, which are subject to inherent biases and confounding factors. Although recent reviews have contributed valuable insights into endoscopic stenting, they have generally not included EVT in their analyses [6]. More recent pivotal studies by Wannhoff et al. [10] and Anundsen et al. [11] have begun to integrate EVT data, offering further perspective on managing Boerhaave syndrome. This structured review is designed to systematically evaluate and synthesize the current literature, addressing the variability in clinical outcomes and establishing a robust foundation for decision-making in this high-risk patient population.

While a recent meta-analysis by Vohra et al. (2025) [12] provided important insights into the efficacy of EVT in esophageal luminal defects, our review differs significantly in scope and focus. We expand upon this foundation by directly comparing EVT and esophageal stenting, integrating recent studies, and analyzing additional outcomes, including mortality and failure rates. This broader comparative approach aims to inform treatment selection in a wider range of clinical contexts, including Boerhaave syndrome.

The primary objective of this systematic review and meta-analysis is to assess the sealing efficacy, failure rates, and mortality associated with esophageal stenting and EVT in patients with esophageal leaks, perforations, and particularly Boerhaave syndrome. Specifically, we aim to: (1) quantify the pooled sealing rate, failure rate, and mortality rate associated with esophageal stenting from various observational studies; (2) evaluate the efficacy of EVT in achieving defect closure while exploring the sources of heterogeneity and potential publication bias in the existing literature; and (3) compare the clinical outcomes of esophageal stenting and EVT to inform clinical practice and pinpoint priorities for future research.

2. Methods

2.1. Study Design and Literature Search

We performed a systematic review and meta-analysis to evaluate the efficacy and safety of esophageal stenting and EVT for various esophageal conditions, including anastomotic leaks, iatrogenic perforations, and Boerhaave syndrome. In light of the absence of randomized controlled trials (RCTs) in this field, our analysis was restricted to observational studies and case series. This review was conducted following the PRISMA 2020 guidelines (see flowchart in **(Figure 1)**), registered in PROSPERO, and the methodological quality was further ensured by adherence to the A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR2) criteria [13]. A comprehensive literature search was carried out across PubMed/MEDLINE, Scopus, and the Cochrane Library from their inception until the 22nd of March 2025, using a combination of keywords and Medical Subject Headings (MeSH) including “esophageal stenting,” “endoscopic vacuum therapy,” “esophageal leak,” and “esophageal perforation.” No language restrictions were applied, and additional studies were identified through manual screening of reference lists. A detailed search strategy is available from Supplementary File S1. A PRISMA checklist is also added as a supplement. This systematic review was first registered with the International Prospective Register of Systematic Reviews (PROSPERO) on March 16, 2025, under the registration number CRD420251012734 (accessible at: https://www.crd.york.ac.uk/PROSPERO/view/CRD420251012734).

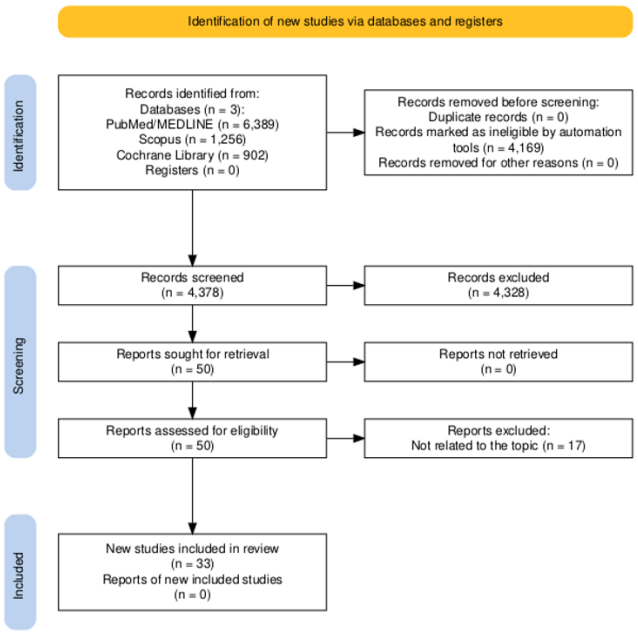

Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA flowchart).

2.2. Eligibility Criteria and Study Selection

Studies were eligible for inclusion if they reported on the use of esophageal stents or EVT in patients with esophageal conditions. Although our inclusion criteria did not exclude randomized controlled trials (RCTs), our search identified no eligible RCTs that met the criteria for evaluating esophageal stenting or EVT in this context. As a result, the analysis was necessarily based on observational studies and case series. For stenting studies, outcomes of interest included sealing rates, failure rates, and mortality. EVT studies were required to report sealing success, treatment duration, and sponge change frequency. Two independent reviewers screened titles, abstracts, and full texts to determine eligibility, resolving any discrepancies through consensus. Study quality and risk of bias were assessed using the MINORS (Methodological Index for Non-Randomized Studies) scale [14] (available in **(Table 1)** and **(Table 3)**). A separate table detailing the MINORS score for each study is available in Supplementary file S1.

2.3. Data Extraction and Outcome Measures

Data were independently extracted by two reviewers using a standardized extraction form. For esophageal stenting studies, the extracted variables included publication year, study design, MINORS score, stent types used, patient numbers, incidence of delayed presentation/treatment (>24 hours), sepsis incidence, and procedural details (e.g., concomitant drainage, additional drainage, endoscopic reinterventions, final sealing, failure, surgical conversion, and mortality). For EVT studies, we collected information on study design, country, conditions treated, MINORS score, number of patients, closure rate, mean treatment duration, and average sponge changes.

The primary outcomes for esophageal stenting included the sealing rate, defined as the proportion of patients achieving successful closure of the esophageal defect; the failure rate, defined as the proportion of cases in which stent therapy was unsuccessful and required surgical intervention; and the mortality rate, representing the proportion of patients who died in association with the esophageal condition or its treatment. For EVT, the primary outcome was

Table 1: Summary of studies on esophageal stenting for esophageal conditions

Author et al	Design	MINORS Score	Stent Types	Patients	Delayed Presentation/Treatment (>24h)	Sepsis Incidence
Wannhoff 2025 [10]	Retrospective	10	–	57	–	–
Anundsen 2024 [11]	Retrospective	10	WallFlex, EndoFlex, Hanaro	17	6/17 (35%)	–
Chiu 2023 [16]	Retrospective	10	Wallflex	5	5/5 (100%)	3/5 (60%)
Hauge 2018 [17]	Retrospective	8	Ultraflex, Wallflex, SX-ELLA, Niti-S, Polyflex	15	9/15 (60%)	–
Aloreidi 2018 [18]	Retrospective	9	Wallflex	6	4/6 (67%)	6/6 (100%)
Huh 2018 [19]	Retrospective	10	Hanarostent, Choo stent	4	–	–
Glatz 2016 [20]	Prospective	11	Ultraflex, Leufen	16	4/16 (25%)[1]	6/16 (38%)
Wu 2016 [21]	Retrospective	10	Nanjing	19	16/19 (84%)	5/19 (26%)
Gubler 2014 [22]	Retrospective	10	Niti S, Rusch, Ultraflex, Hanarostent	7	–	–
Persson 2014 [23]	Retrospective	10	CSEMS	23	–	–
Schweigert 2013 [24]	Retrospective Comparative	14	Polyflex, Ultraflex	13	–	9/13 (69%)
Darrien 2013 [25]	Retrospective	10	Ultraflex, Polyflex	5	2/5 (40%)	5/5 (100%)
Koivukangas 2012 [26]	Retrospective	9	Hanarostent, Nanjing	14	7/14 (50%)	7/14 (50%)
Freeman 2009 [27]	Prospective Observational	12	Polyflex	19	–	3/19 (16%)[2]
Salminen 2009 [28]	Retrospective	8	Hanarostent	3	3/3 (100%)	–
Kim 2008 [29]	Retrospective	9	Montgomery Salivary Bypass Stent	4	4/4 (100%)	4/4 (100%)
Fischer 2006 [30]	Retrospective	8	Ultraflex	5	1/5 (20%)	4/5 (80%)
Prichard 2006 [31]	Retrospective	7	CSEMS	5	5/5 (100%)	–
Siersema 2003 [32]	Retrospective	10	Flamingo, Ultraflex	5	4/5 (80%)	–
Chung 2001 [33]	Retrospective	8	Song, Niti S	3	3/3 (100%)	–

the sealing rate, which indicated the successful closure of the esophageal defect following treatment.

2.4. Statistical Analysis

Meta-analyses were conducted using OpenMeta Analyst software [15] under a random-effects model to account for inter-study variability. Pooled proportions were calculated using the Freeman-Tukey double arcsine transformation to stabilize variance. Heterogeneity was assessed with the I^2 statistic, τ^2, and Cochran's Q test. Publication bias was evaluated using the Eggers test, and sensitivity analyses were performed where significant bias was detected to test the robustness of our findings. A two-tailed p-value of less than 0.05 was considered statistically significant.

3. Results

Our systematic search did not identify any eligible RCTs evaluating esophageal stenting or endoscopic vacuum therapy EVT. Consequently, all included studies were either observational studies or case series. In our study, the summary of studies on esophageal stenting is tabulated in **(Table 1)**. **(Table 2)** tabulates the procedural interventions and additional outcomes. **(Table 3)** summarizes the studies on endoscopic vacuum therapy for esophageal conditions. A total of 15 studies, comprising 413 patients, were included in the analysis of EVT sealing outcomes.

Further analysis is presented below under the subheadings for each analysis.

3.1. Forest Plot for Sealing Rate with Esophageal Stent Therapy

Fourteen studies[11, 16, 33, 25, 30, 27, 20, 22, 17, 19, 29, 28, 32, 21] were pooled to assess the sealing success of esophageal stenting. In total, 106 successful sealing events were observed among 127 patients, yielding a pooled sealing rate of 86.1% (95% CI: 80.2%–92.0%) under a random-effects model. Heterogeneity was minimal ($I^2 = 8.26\%$, $p = 0.362$). An Eggers test for publication bias produced a non-significant result ($p = 0.42$), suggesting no evidence of small-study effects as shown in **(Figure 2)**.

3.2. Forest plot failure of stent therapy

Seventeen studies[18, 11, 16, 33, 25, 30, 27, 20, 17, 29, 26, 23, 31, 28, 24, 32, 21] contributed data regarding stent therapy failure, with 28 failures recorded in 177 patients. The overall failure rate was 14.9% (95% CI: 8.5%–21.3%). Moderate heterogeneity was detected ($I^2 = 40.78\%$, $p = 0.041$). The Eggers test did not indicate significant publication bias ($p = 0.37$) as shown in **(Figure 3)**.

3.3. Forest plot Mortality with esophageal stenting

Data from the same set of studies [18, 11, 16, 33, 25, 30, 27, 20, 17, 29, 26, 23, 31, 28, 24, 32, 21] were used to evaluate mortality, with 15 deaths occurring among 154 patients. The pooled mortality

Table 2: Procedural interventions and additional outcomes

Year, Author et al.	Concomitant Drainage	Additional Drainage	Endoscopic Reinterventions	Final Sealing	Failure	Surgical Conversion	Mortality
Anundsen 2024 [11]	15/17 (88%)	14/17 (82%)	8/17 (47%)	16/17 (94%)	1/17 (6%)	0 (0)	1/17 (6%)
Chiu 2023 [16]	5/5 (100%)	1/5 (20%)	0 (0)	5/5 (100%)	0 (0)	0 (0)	0 (0)
Hauge 2018 [17]	14/15 (93%)	4/15 (27%)	5/15 (33%)	13/15 (87%)	2/15 (13%)	0 (0)	2/15 (13%)
Aloreidi 2018 [18]	6/6 (100%)	0 (0)	3/6 (50%)	–	0 (0)	0 (0)	0 (0)
Huh 2018 [19]	–	–	–	4/4 (100%)	–	–	–
Glatz 2016 [20]	15/16 (94%)	11/16 (69%)	5/16 (31%)	11/16 (69%)	6/16 (38%)	4/16 (25%)	2/16 (13%)
Wu 2016 [21]	19/19 (100%)	–	0 (0)	16/19 (84%)	1/19 (5%)	0 (0)	1/19 (5%)
Gubler 2014 [22]	–	–	–	5/7 (71%)	–	–	–
Persson 2014 [23]	–	–	–	–	3/23 (13%)[1]	–	–
Schweigert 2013 [24]	13/13 (100%)	11/13 (85%)	–	–	2/13 (15%)	0 (0)	2/13 (15%)
Darrien 2013 [25]	5/5 (100%)	4/5 (80%)	4/5 (80%)	2/5 (40%)	1/5 (20%)	0 (0)	1/5 (20%)

Table 3: Summary of studies on endoscopic vacuum therapy for esophageal conditions

Author et al.	Study Type	Country	Conditions Assessed (n)	MINORS Score	N of Pa tie	Closure Rate (%)	Mean Duration of EVT (days)	Average Sponge Changes
Wedemeyer 2008 [34]	Case series	Germany	AL (2)	10	2	100.0	15.0	4.0
Loske 2011 [35]	Case series	Germany	AL (8); IP (3); BS (1); O (1)	10	14	92.9	12.0	4.0
Brangewitz 2013 [36]	Retrospective	Germany	AL (32)	8	32	84.4	23.0	7.0
Schneiwind 2013 [37]	Retrospective	Germany	AL (17)	10	17	Not available	57.0	Not available
Bludau 2013 [38]	Retrospective	Germany	AL (8); IP (3); BS (2); O (1)	9	14	86	12.1	3.9
Kuehn 2016 [39]	Retrospective	Germany	AL (11); IP (8)	10	21	90	15.0	5.0
Laukoetter 2017 [40]	Prospective	Germany	AL (39); IP (9); BS (4)	10	52	94	22.0	6.0
Bludau 2018 [41]	Retrospective	Germany	BS (6); IP (12); AL (59)	14	77	77	11.0	2.75
Alakkari 2019 [42]	Case series	UK	AL (1); BS (1)	10	2	100	6.0	8.5
Mastoridis 2022 [43]	Prospective	UK	AL (3); BS (3)	8	7	85	13.0	3.0
Richter 2022 [44]	Observational	Germany	AL (69); IP (9); BS (7); O (17)	9	10	91	27.5	7.55
Luttikhold 2023 [45]	Retrospective	Sweden	IP (16); BS (9); TP (2)	7	27	89	12.0	1.0
Wannhoff 2024 [10]	Retrospective	Germany	BS	10	57	80	–	–

AL – Anastomotic leak; IP – Iatrogenic perforation; BS – Boerhaave syndrome; O – Other; TP – Traumatic perforation; EVT – Endoscopic vacuum therapy.

rate was 7.4% (95% CI: 3.5%–11.4%), and no heterogeneity was observed ($I^2 = 0\%$, $p = 0.903$). Egger's test results ($p = 0.56$) further supported the absence of publication bias in this analysis, as shown in **(Figure 4)**.

3.4. Forest plot sealing rate with endoscopic vacuum therapy

Fifteen studies [42, 11, 41, 38, 36, 39, 40, 35, 45, 43, 44, 37, 10, 34] were analyzed for EVT sealing outcomes. Overall, 125 events were observed among 413 patients, resulting in a pooled sealing rate of 54.1% (95% CI: 34.8%–73.4%) using a binary random-effects model. Substantial heterogeneity was present ($I^2 = 98.24\%$, $p < 0.001$). Moreover, the Eggers test for this analysis was significant ($p = 0.01$), indicating potential publication bias and small-study effects as shown in **(Figure 5)**.

The sensitivity analysis shows a substantial change after removing some influential studies [11, 41, 36, 40, 44, 10], the pooled sealing rate for EVT is now 89.6% (95% CI: 83.9–95.3%), with no heterogeneity ($I^2 = 0\%$, $p = 0.998$). This suggests that those studies were major contributors to the significant publication bias and overall heterogeneity in the initial analysis, as shown in **(Figure 6)**. The large variability in reported outcomes likely reflects differences in patient selection, EVT protocols, and the quality of study design.

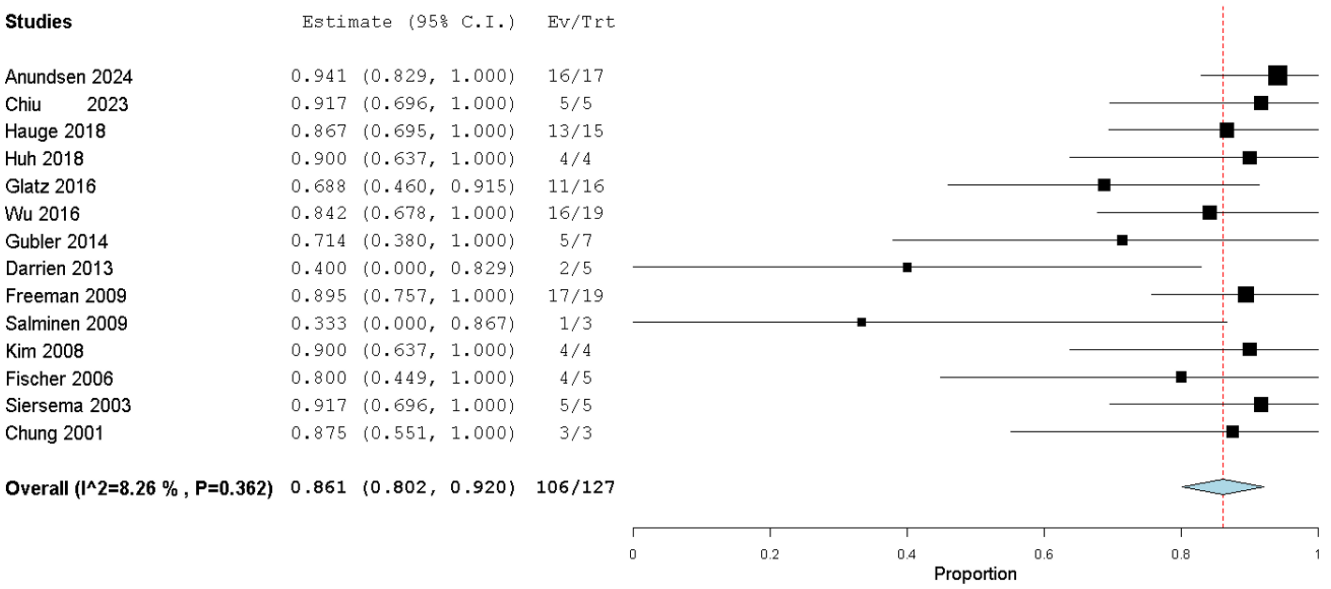

Figure 2: Forest plot of sealing success from 14 studies (106 events/127 patients) showing a pooled rate of 86.1% (95% CI: 80.2–92.0%) with minimal heterogeneity ($I^2 = 8.26\%$, $p = 0.362$) and no publication bias (Eggers test, $p = 0.42$).

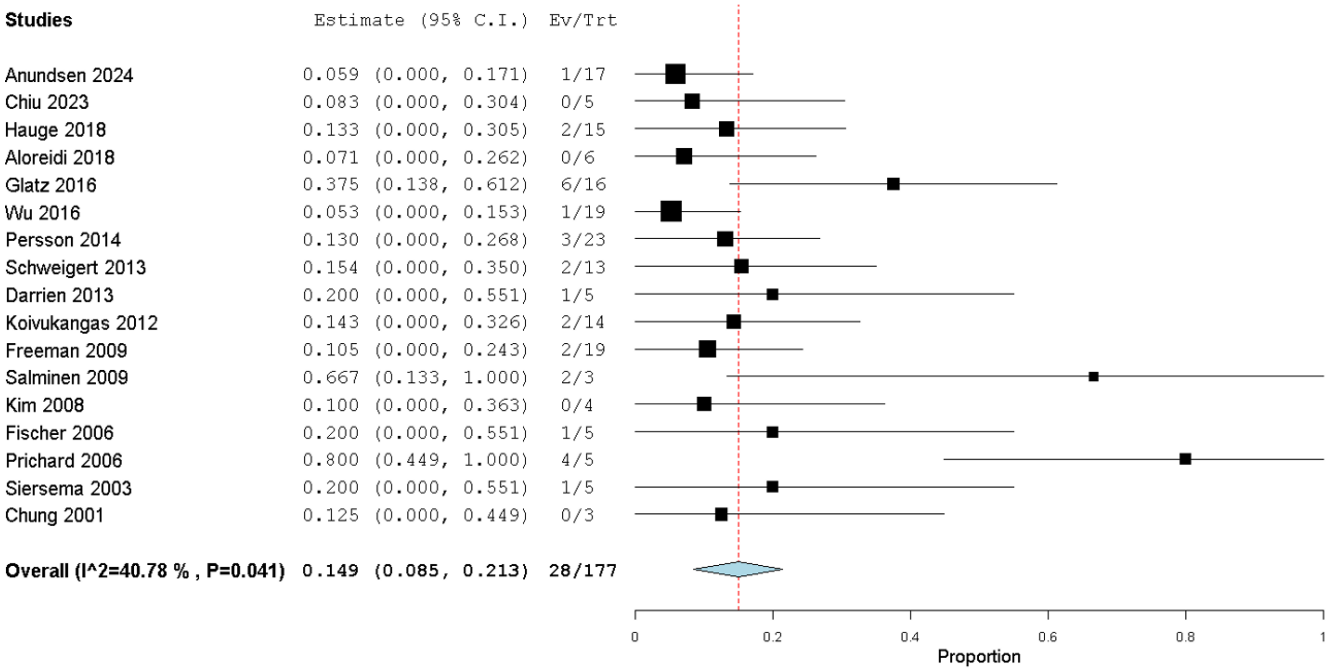

Figure 3: Forest plot of stent therapy failure from 17 studies (28 failures/177 patients), showing an overall failure rate of 14.9% (95% CI: 8.5–21.3%) with moderate heterogeneity ($I^2 = 40.78\%$, $p = 0.041$) and no significant publication bias (Eggers test, $p = 0.37$).

4. Discussion

Our study sought to deepen our understanding of the role of minimally invasive therapies, specifically esophageal stenting and EVT, in the treatment of complex esophageal defects. When we pooled data from 14 observational studies, esophageal stenting emerged with a notably high sealing success rate of 86.1% (95% CI: 80.2%–92.0%), a failure rate of 14.9% (95% CI: 8.5%–21.3%), and a mortality rate of 7.4% (95% CI: 3.5%–11.4%). These results are in strong agreement with earlier reports by Margaris et al. [6], who demonstrated that stents function as an effective bridge, maintaining continuity in the esophagus while allowing the defect to heal and preventing further contamination of the mediastinum and pleural space. This temporary "bridging" is especially important in the context of Boerhaave syndrome and other perforations, where the risk of sepsis is high. By avoiding the need for major surgical intervention—which is both physiologically taxing and carries inherent risks—stenting offers an appealing option for

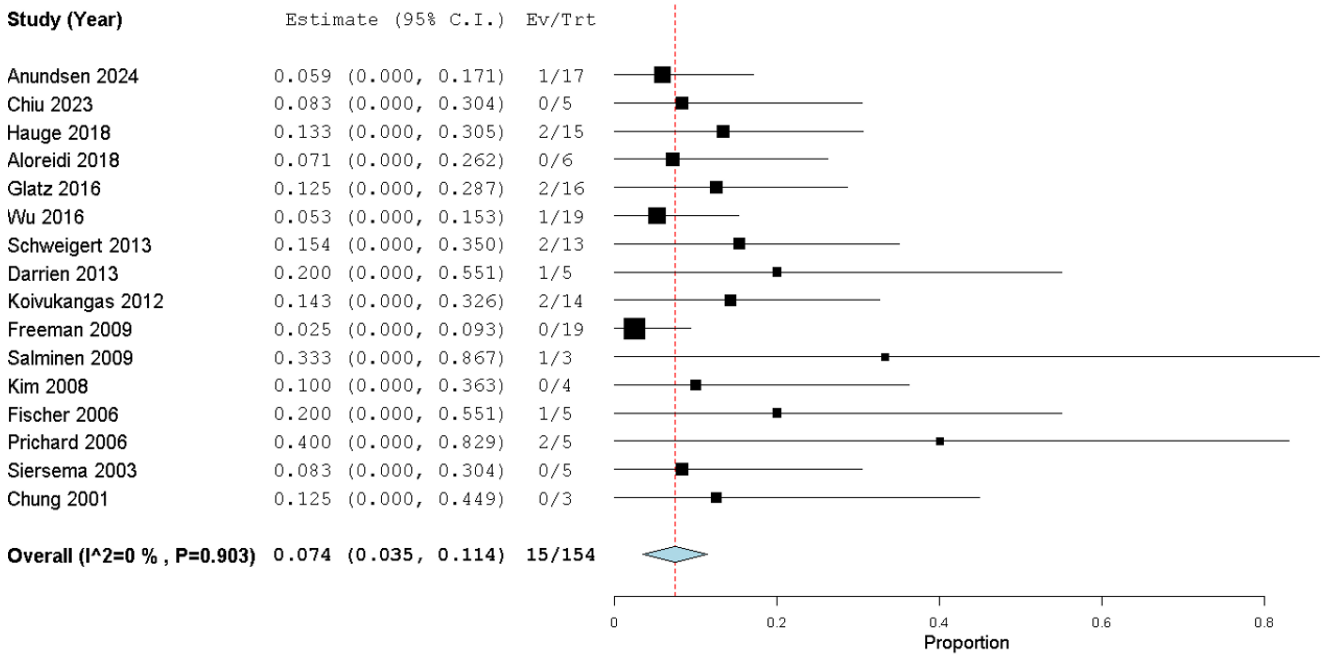

Figure 4: Forest plot of mortality from esophageal stenting studies (15 deaths/154 patients) showing a pooled mortality rate of 7.4% (95% CI: 3.5–11.4%) with no heterogeneity ($I^2 = 0\%$, $p = 0.903$) and no publication bias (Eggers test, $p = 0.56$).

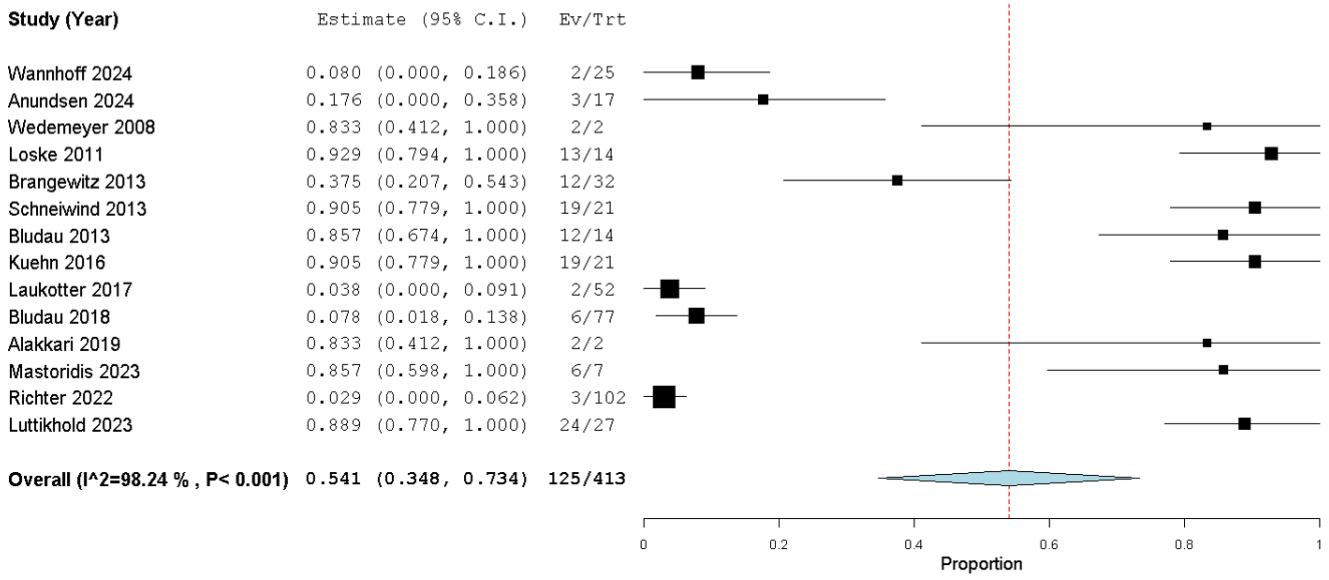

Figure 5: Forest plot of endoscopic vacuum therapy sealing outcomes from 15 studies (125 events/413 patients) showing a pooled sealing rate of 54.1% (95% CI: 34.8–73.4%) with substantial heterogeneity ($I^2 = 98.24\%$, $p < 0.001$) and significant publication bias (Eggers test, $p = 0.01$).

patients with multiple comorbidities or those deemed poor surgical candidates[5, 6, 46]. Equally significant is the role of concomitant drainage procedures; our review and other studies [5, 6, 46] highlight that proper drainage, when combined with stenting, is critical to controlling infection and facilitating recovery.

Our findings build upon those of Vohra et al. [12], whose work focused exclusively on EVT outcomes. While they reported pooled closure rates across various studies, our study additionally includes mortality, failure, and procedural outcomes and compares EVT with esophageal stenting across similar patient populations to provide a more comprehensive clinical perspective.

In contrast, our initial evaluation of EVT outcomes was far more variable. Across 15 studies, the pooled sealing rate for EVT was only 54.1% (95% CI: 34.8%–73.4%), accompanied by substantial heterogeneity ($I^2 = 98.24\%$, $p < 0.001$) and indications of publication bias (Eggers test, $p = 0.01$). This inconsistency likely reflects the diverse patient populations, differing defect characteristics, and the lack of standardized treatment protocols that currently

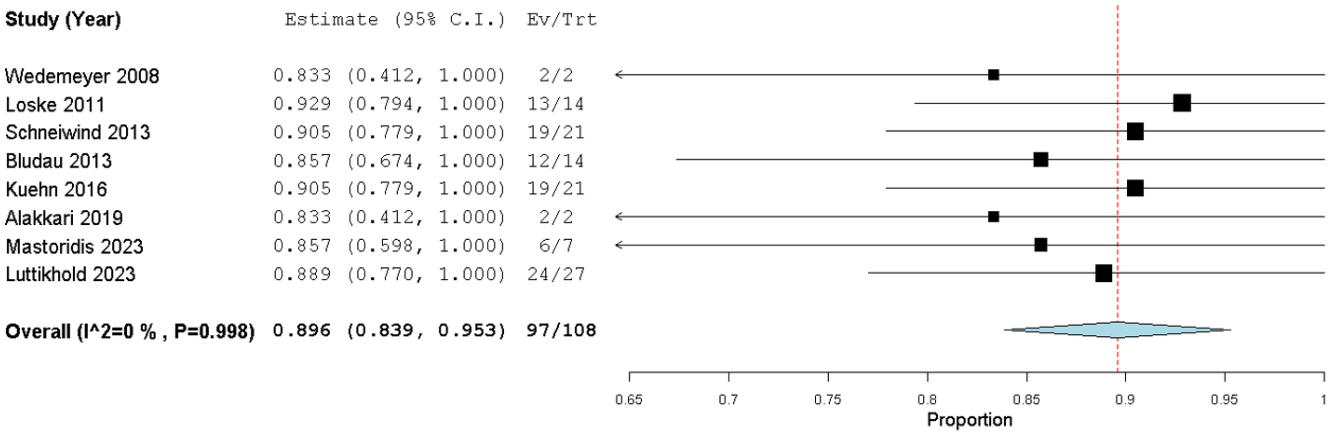

Figure 6: Sensitivity analysis of endoscopic vacuum therapy sealing outcomes after excluding 6 outlier studies showing a pooled sealing rate of 89.6% (95% CI: 83.9–95.3%) with no heterogeneity ($I^2 = 0\%$, $p = 0.998$).

characterize EVT use. The dramatic improvement in EVT sealing rates from 54.1% to 89.6% in the sensitivity analysis highlights the influence of outlier studies and inconsistent reporting. Studies, such as those by Wannhoff et al. [10] and Bludau et al. [41], while important, may have introduced heterogeneity due to their unique patient populations, the inclusion of more complex defects, or variations in treatment protocols. Once these outliers were removed, the more consistent data revealed that EVT can achieve sealing rates comparable to those of stenting when applied under standardized, well-controlled conditions. This underscores the importance of protocol harmonization and careful patient selection when evaluating EVT outcomes. Early experiences—such as those described by Wedemeyer et al. [34]and further documented by Alakkari et al. [42]—demonstrated that EVT could serve as a vital rescue treatment after conventional surgery and stenting had failed. These pioneering reports provided the initial evidence that EVT not only promotes rapid wound closure but also minimizes the duration of hospital stays by facilitating continuous drainage of contaminated collections.

What is particularly intriguing is how subsequent studies have refined our understanding of EVT. For instance, Brangewitz et al. [36] and Schneiwind et al. [37] provided evidence that EVT could achieve higher closure rates and reduce mortality compared to stenting, especially in patients with severe systemic inflammation. Laukoetter et al. [40] reported healing in over 94% of patients treated solely with EVT—a result that initially seemed at odds with the pooled average in our analysis. Recognizing the heterogeneity in EVT outcomes, we performed a sensitivity analysis that excluded several influential outlier studies. This analysis dramatically improved the pooled sealing rate to 89.6% (95% CI: 83.9%–95.3%) and completely eliminated statistical heterogeneity ($I^2 = 0\%$, $p = 0.998$). This finding strongly suggests that when EVT is applied in a more uniform manner—perhaps through standardized protocols and careful patient selection —its efficacy may well be comparable to, if not exceed, that of stenting. For instance, Schneiwind et al. [37] reported that in systemically ill patients with similar APACHE II scores, those treated with EVT experienced markedly improved results, with a mortality rate of only 12%, as opposed to 50% for surgery and 83% for stenting ($p = 0.01$ and $p = 0.0014$, respectively). In a separate study, Laukoetter et al. [40] demonstrated that EVT alone was sufficient to heal 94.2% of 52 patients, eliminating the necessity for any further interventions.

This observed heterogeneity highlights the need to tailor EVT use based on specific clinical scenarios. For instance, EVT appears especially beneficial in patients with large, complex leaks or significant mediastinal contamination—cases where continuous drainage and active defect healing are critical. Patients with systemic sepsis or those who have failed prior stent therapy may also derive greater benefit from EVT. Conversely, individuals with small, contained perforations or limited access to experienced endoscopy teams may be better served by stenting or conservative management. Moreover, because EVT requires multiple endoscopic interventions, it may not be ideal for critically ill patients who cannot tolerate repeated procedures or for centers lacking the infrastructure for close monitoring and frequent sponge changes. These considerations underscore the importance of individualized patient selection when applying EVT in clinical practice.

Yet, no therapy is without its drawbacks. EVT, while promising, presents practical challenges: it necessitates frequent endoscopic reassessments and sponge exchanges, which can prolong hospital stays and increase costs. There are also complications to consider, such as sponge dislocation, bleeding during the exchange, and the development of strictures. Some authors have debated whether the strictures observed are a direct consequence of EVT or are related to the complex nature of the esophageal pathology itself [41, 38, 36, 40, 6]. In our view, these issues underscore the importance of further refining EVT protocols and implementing rigorous training and standardization across centers.

It is also essential to acknowledge the limitations inherent in our analysis. All the data we synthesized come from observational studies and case series, with modest methodological quality as indicated by average MINORS scores in the range of 9–10. Such study designs are susceptible to biases—selection bias, lack of blinding, and uncontrolled confounding—which means that our findings, though informative, should be interpreted with cautious optimism. The absence of randomized controlled trials in this field is a significant gap, one that future prospective studies or multicenter registries must address to provide clearer guidance for clinical practice. Additionally, it is noteworthy that a substantial proportion of EVT studies included in this analysis originate from Germany. This geographic concentration may reflect regional differences in clinical expertise, institutional familiarity with EVT, and earlier

adoption of the technique. Such concentration introduces a limitation in terms of generalizability, as the outcomes and protocols observed in German centers may not fully represent practices in other countries with different healthcare infrastructures, reimbursement systems, or procedural training. As EVT continues to gain global interest, future multicenter studies involving more diverse geographic regions will be essential to validate these findings and optimize external applicability.

In practical terms, our findings support a personalized approach to managing esophageal defects. For patients with high surgical risk or extensive comorbidities, esophageal stenting appears to offer a reliable, less invasive solution with a high success rate. Meanwhile, EVT holds considerable promise as an alternative or adjunct treatment, especially in settings where stenting has failed or is contraindicated. The evolution of EVT, as illustrated by improved outcomes in sensitivity analyses, suggests that uniform protocols and better patient selection can substantially enhance its effectiveness. Ultimately, both therapies are important tools in the endoscopist's arsenal, and the choice between them should be guided by individual patient factors, available expertise, and institutional resources.

Several limitations must be acknowledged in interpreting the results of this meta-analysis. First, the absence of RCTs significantly limits the strength of the evidence. All included studies were observational in nature, either retrospective cohorts or case series, which are inherently prone to selection bias, unmeasured confounding, and lack of standardized outcome definitions. Second, substantial heterogeneity was observed in the analysis of EVT, which reflects variability in patient selection, treatment protocols, and institutional expertise. Although sensitivity analysis helped mitigate this issue, the initial inconsistency underscores the need for standardization across centers. Third, most EVT studies originated from Germany, potentially limiting the generalizability of findings to other regions where practice patterns, resources, and clinical thresholds may differ. Additionally, the relatively small sample sizes in many included studies, as well as the lack of uniform reporting on adverse events and long-term follow-up, further constrain our ability to draw definitive conclusions about comparative efficacy and safety. Finally, despite comprehensive database searches, the possibility of publication bias cannot be fully excluded.

In conclusion, our meta-analysis reinforces the notion that both esophageal stenting and EVT are viable, minimally invasive options for treating esophageal leaks and perforations. While stenting shows consistently high sealing rates and low mortality, EVT demonstrates significant potential when applied under standardized conditions. Future research should focus on conducting high-quality prospective studies and cost-effectiveness analyses to refine treatment protocols and establish clearer criteria for patient selection, thereby improving outcomes for this challenging and high-risk patient population.

5. Conclusion

Both esophageal stenting and EVT are effective, minimally invasive strategies for managing esophageal defects, with stenting showing consistently high sealing rates and low mortality, while EVT exhibits promising efficacy, especially when standardized protocols are applied. Despite the inherent limitations of observational data, these findings underscore the importance of individualized treatment approaches that incorporate adjunctive drainage and supportive care to optimize outcomes.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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None

Authors Contribution

MS led the conceptualization, methodology, data curation, formal analysis, writing of the original draft, and supervision. MM contributed to the investigation, formal analysis, review, and editing of the manuscript, and visualization. MK and SK were responsible for software development, validation, data curation, and review and editing. MK handled resources, data curation, review and editing, and project administration. SK contributed to validation, visualization, review, and editing. MM assisted with review and editing and provided resources. All authors have read and approved the final manuscript.

Data Availability

All the data is publicly available.

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ASIDE Internal Medicine

Original Article

Migraine Headache in Patients with Allergic Rhinitis: A Systematic Review and Meta-Analysis of Observational Studies

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ABSTRACT

Background: Migraine is a condition characterized by recurrent episodes of unilateral headache. Allergic rhinitis (AR) is an IgE-mediated inflammatory condition of the nasal mucosa that is triggered by exposure to allergens. Migraine and AR may share underlying immunological mechanisms, including histamine release and mast cell activation. Despite the growing interest in the immunological interplay between allergic conditions and neurological symptoms, the specific relationship between AR and migraine remains underexplored.
Methods: PubMed, Scopus, and Web of Science were systematically searched to identify relevant studies. Pooled odds ratio (OR) and pooled risk ratio (RR) were calculated with 95% confidence intervals (CI) using a random-effects model. The Newcastle-Ottawa Scale (NOS) was used for quality assessment. Heterogeneity assessment and subgroup analysis were also performed.
Results: Eleven studies involving 4,704,591 participants were included. The pooled OR for migraine in individuals with AR was 2.94 (95% CI: 2.02–4.29; $p < 0.0001$; $I^2 = 95.62\%$). The pooled RR from two cohort studies was 2.27 (95% CI: 1.10–4.65; $p = 0.026$; $I^2 = 99.72\%$). Subgroup analysis revealed significant differences in the pooled OR regarding the source of individuals with AR and the method of AR assessment, with a higher pooled OR in hospital patients (OR = 7.32) and when using skin tests (OR =6.93).
Conclusion: Migraine headaches are significantly associated with AR, particularly in hospital settings andwhenobjectivemethodsareusedforARdiagnosis.Thefindingsofthisstudyshouldbeinterpreted cautiously owing to the high heterogeneity.

1. Introduction

Migraine is a prevalent and disabling neurological disorder characterized by recurrent episodes of moderate to severe unilateral headache, frequently accompanied by nausea, vomiting, photophobia, and phonophobia [1, 2]. It is ranked among the leading causes of years lived with disability worldwide, particularly affecting individuals in their most productive years of life [3]. According to recent estimates, migraine affected over 1.1 billion people globally in 2021, representing a 58.15% increase in prevalence since 1990 and underscoring its substantial and growing public health burden [4, 5]. Allergic rhinitis (AR) is an IgE-mediated inflammatory condition of the nasal mucosa triggered by exposure to allergens. While commonly perceived as a localized upper airway disease, AR has been increasingly associated with systemic inflammatory processes and a variety of comorbidities [6]. Its prevalence ranges from 10% to 30% in adults, with even higher rates reported in pediatric populations [7]. Given the immunological basis of both AR and migraine, a potential pathophysiological link has been proposed. Several shared mechanisms may underpin the relationship between AR and migraine, including mast cell activation, histamine release, and cytokine-mediated neuroinflammation, which can contribute to the sensitization of the trigeminovascular system —a central pathway implicated in migraine pathogenesis [8]. However, recent genetic evidence from Mendelian randomization analyses does not support a causal relationship, suggesting that previously reported associations may be confounded by environmental or diagnostic factors [9]. Moreover, an association between migraine and other allergic conditions, including atopic dermatitis, was observed [10]. Given these conflicting observations, a comprehensive synthesis of the available literature is warranted. While previous meta-analyses, such as the one by Yang et al., have explored the association between atopic dermatitis and headache disorders, no prior study has

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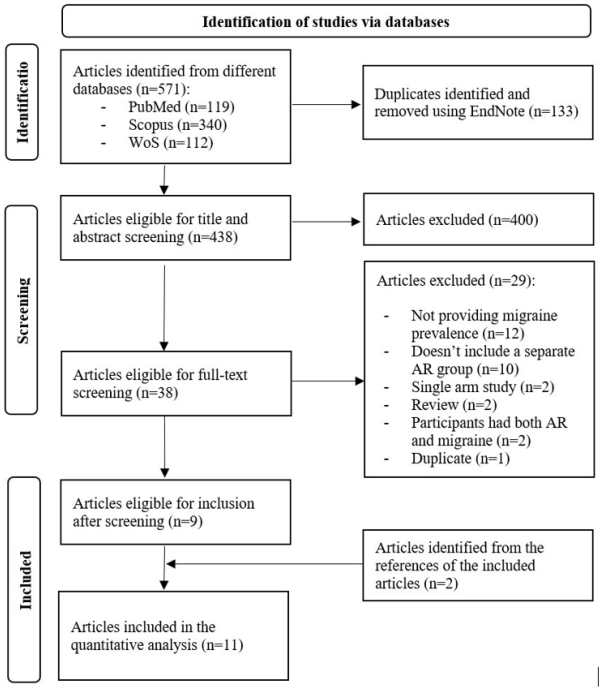

Figure 1: PRISMA flowchart for the database searching and screening process.

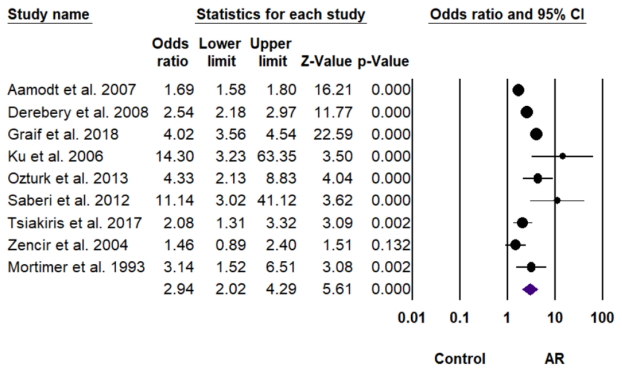

Figure 2: Pooled OR of migraine in AR compared to controls.

quantitatively assessed the specific relationship between allergic rhinitis (AR) and migraine headaches using pooled odds ratios compared to healthy controls. Therefore, this systematic review and meta-analysis were undertaken to estimate the pooled odds ratio of migraine in individuals with AR and to evaluate the strength and consistency of this association across observational studies.

2. Methods

2.1. Identification of eligible studies

This systematic review and meta-analysis study was conducted to explore the association between allergic rhinitis (AR) and migraine headaches based on observational studies providing estimates of migraine in individuals with AR compared to non-AR controls. A comprehensive search strategy was developed to identify all relevant articles with terms related to AR (allergic rhinitis OR allergic rhinopathy OR atopic rhinitis OR rhinitis allergica OR allergic rhinitides OR pollen sensitivity OR pollen allergy OR pollen allergies OR hay fever OR hayferver OR pollinosis OR seasonal rhinitis OR respiratory allergy OR and IgE-mediated rhinitis) and migraine headache (migraine OR migraine headache OR hemicrania OR cephalgia OR cephalagia OR vascular headache OR aura). A search syntax was developed and applied for three different databases: PubMed, Scopus, and Web of Science. Filters for the English language and articles were used when appropriate. Medical subject headings (MeSH) for migraine disorders and allergic rhinitis were added to the search syntax for PubMed. All identified articles from conception up to the date of database searching (February 25, 2025) were collected.

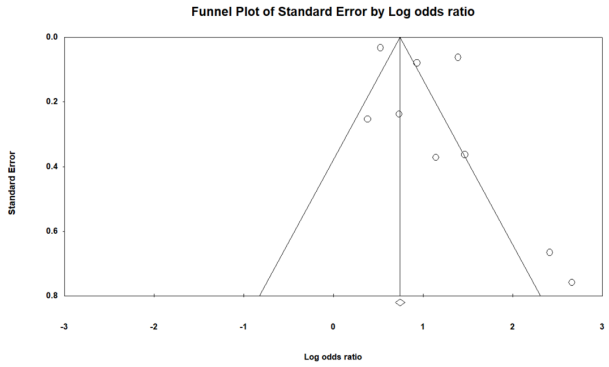

Figure 3: Funnel plot for the pooled OR of migraine in AR compared to controls.

2.2. Evaluation of eligible studies

For a study to be included in the meta-analysis, it must [1] be observational in design (cohort, cross-sectional, or case-control), [2] be available in full-text format, [3] have both an allergic rhinitis group and a healthy control group, and [5] provide data regarding the occurrence of migraine in both groups for calculation of odds ratio (OR) or risk ratio (RR). Studies were excluded if they [1] were not related to migraine or AR, [2] were not available in English, [3] were of an inappropriate study design (reviews, editorials, case series, clinical trials, or book chapters), or [5] didn't provide sufficient data for the calculation of OR or RR of migraine in individuals with AR compared to controls. The screening process was conducted by the PRISMA flowchart, adhering to the established inclusion and exclusion criteria [11]. Prior to the screening process, articles from the three databases were collected, with duplicates being removed by EndNote software. The remaining articles were exported into an Excel spreadsheet. Four authors working in pairs (KK&AE) and (AAL&MM) independently assessed each article for eligibility and extracted relevant data from eligible studies. Discrepancies in the screening and data extraction were resolved by a third author (AT).

2.3. Data extraction and quality assessment

Data extraction was conducted independently by two authors using a standardized and pre-defined data extraction form designed to collect information on study characteristics, population details, diagnostic methods, effect sizes, and outcomes. The data extraction form was piloted on three studies to ensure clarity and consistency before being applied to all included studies. Discrepancies between reviewers were resolved through discussion or consultation with a third author.

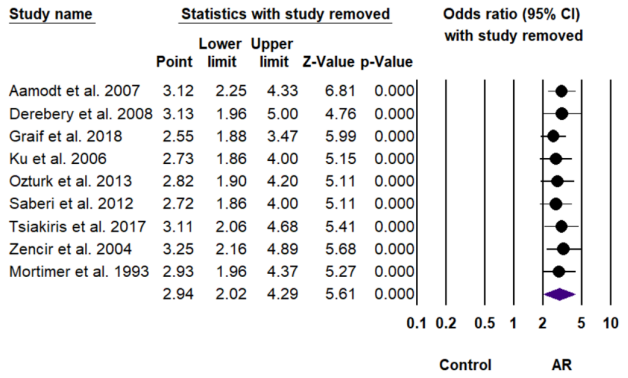

Figure 4: Sensitivity analysis for the pooled OR of migraine in AR compared to controls.

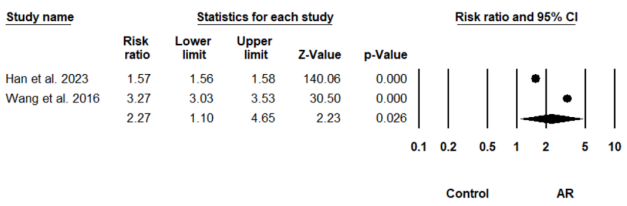

Figure 5: Pooled Risk Ratio of migraine in AR compared to controls.

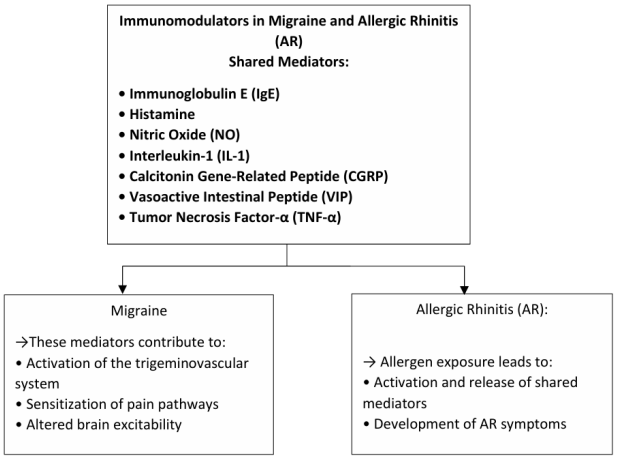

Figure 6: This flowchart illustrates the common mediators activated in both migraine and allergic rhinitis, as well as their roles in both pathways.

In this review, grey literature sources such as conference abstracts, theses, and preprints were explicitly excluded. This decision was based on the need to include only peer-reviewed, full-text articles to ensure methodological rigor and data completeness. While grey literature can reduce publication bias, many sources lack standardized diagnostic criteria or sufficient data for meta-analysis, which was essential for our pooled estimates.

The Newcastle-Ottawa Scale (NOS) was used for assessing the quality of the included studies [12]. The NOS evaluates each article according to eight questions within the selection, comparability, and outcomes domains, with slight variations in the questions depending on the study design. The NOS scale total score ranges from 0 to 9, with higher scores indicating higher quality. The total score is obtained from adding the scores of the three domains, and based on it, studies are classified into low-quality (<5 points), intermediate-quality (5-7 points), and high-quality (>7 points) studies [13].

2.4. Statistical analysis

The outcomes of this study were pooled OR and RR for migraine in AR patients compared to controls. Pooled OR and RR were calculated with 95% confidence intervals (CI). Heterogeneity was assessed using the I^2 statistic, with higher percentages reflecting greater heterogeneity [14]. A random-effects model was used for all statistical analyses, as this model accounts for variations in the study populations [15]. Sensitivity analysis was done by sequentially removing one study and observing its impact on the pooled estimate. Publication bias was assessed by funnel plots and the corresponding Egger's test p-value, with values <0.05 indicating the presence of publication bias. Subgroup analyses were conducted for different categorical variables, including region, age group, source of study participants, study design, study quality, AR sample size, and method of AR and migraine diagnosis, to investigate the role of these variables on the pooled estimates. All statistical analyses were performed using the Comprehensive Meta-Analysis (CMA) software (Biostat, Englewood, NJ, USA version 3). A p-value of 0.05 was used as a threshold for statistical significance across all analyses.

3. Results

3.1. Study screening and selection

A PRISMA flowchart illustrating the process of article identification, screening, and inclusion is shown in **(Figure 1)**. A total of 571 articles were identified from the three databases. A total of 133 articles were identified as duplicates and removed prior to the screening process, leaving a final count of 438 articles. After title and abstract screening, 400 articles were excluded for being irrelevant to our study. The full texts of the remaining 38 articles were retrieved and assessed. 29 articles were excluded for different reasons, leaving nine studies as eligible [16, 17, 18, 19, 20, 21, 22, 23, 24]. Additionally, two articles were identified through manual searching of the references of the included articles [25, 26]. Thus, the final number of articles included in the quantitative analysis is 11.

3.2. Characteristics of the included studies

(Table 1) shows the characteristics of the included studies. The 11 included studies had 944,125 Individuals with AR and 3,760,466 non-AR controls from nine different countries, including Norway, the USA, Israel, Korea, Turkey, Iran, Sweden, Taiwan, and the UK. Nine studies were either cross-sectional or case-control studies, thus eligible for OR calculation; the remaining two articles were cohort studies, which were eligible for RR calculation [19, 20, 21, 22, 23, 24]. Studies were classified according to the age group of participants into three groups: the first is studies with participants <18 years, the second is for participants >18 years, and the third group is for studies including participants from both groups. Eight studies were conducted in community settings targeting individuals from the general population, and the remaining three studies were conducted in hospital settings for patients referred to hospital-based clinics. There were variations in the diagnosis of AR and migraine in cross-sectional and case-control studies. Only three studies diagnosed AR using skin tests, with the remaining studies relying

Table 1: Summary of included studies on migraine and allergic rhinitis (AR)

Study ID	Country	Migraine Diagnosis	AR Diagnosis	Population	Age Group	Study Design	Migraine/AR	Migraine/Control	Quality
Aamodt et al. 2007 [16]	Norway	IHS criteria	self-report	general population	>18 years	Cross-sectional	1561/8969	4225/38061	7
Derebery et al. 2008 [17]	USA	self-report	self-report	general population	Both groups	Cross-sectional	663/3831	243/3193	5
Graif et al. 2018 [18]	Israel	previous diagnosis	previous diagnosis	general population	<18 years	Cross-sectional	331/5239	1789/108432	9
Han et al. 2023 [19]	Korea	ICD-10 code G43	ICD-10 codes J301-J304	general population	>18 years	Cohort	95607/463510	412756/3144089	8
Ku et al. 2006 [20]	USA	IHS criteria	positive skin tests with positive history and examination findings	Patients from hospital-based clinics	Both groups	Case-control	26/76	2/57	7
Ozturk et al. 2013 [21]	Turkey	IHS criteria	Skin tests and serum IgE levels	Patients with AR from ENT clinic and age-matched healthy controls	Both groups	Case-control	40/80	15/80	5
Saberi et al. 2012 [22]	Iran	IHS criteria	Clinical signs and symptoms, positive skin tests	patients referred to the ENT clinic	>18 years	Cross-sectional	17/46	3/60	5
Tsiakiris et al. 2017 [23]	Sweden	previous diagnosis	previous diagnosis	general population	>18 years	Cross-sectional	23/298	111/2876	6
Wang et al. 2016 [24]	Taiwan	ICD-9-CM code 364	ICD-9-CM code 477	general population	<18 years	Cohort	2823/461850	860/460718	9
Zencir et al. 2004 [26]	Turkey	IHS criteria	previous diagnosis	general population	<18 years	Cross-sectional	20/144	187/1885	7
Mortimer et al. 1993 [25]	UK	previous diagnosis	previous diagnosis	general population	<18 years	Cross-sectional	10/82	43/1015	5

AR, allergic rhinitis; ENT, ear, nose, and throat; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10, International Classification of Diseases, 10th Revision; IgE, immunoglobulin E; IHS, International Headache Society; UK, United Kingdom; USA, United States of America.

on self-reports or the presence of previous AR diagnoses. Five studies diagnosed migraine in accordance with the International Headache Society (IHS) criteria, while the remaining studies used either self-report or the presence of a previous migraine diagnosis. The two cohort studies relied on International Classification of Diseases (ICD) codes from patient records for the diagnosis of AR and migraine headaches, excluding those diagnosed with migraine at the beginning of the follow-up period. Based on the total NOS score, three studies were of high quality, while the remaining eight studies were of intermediate quality. None of the included studies was of low quality.

A total of nine case-control or cross-sectional studies, including 18,765 individuals with allergic rhinitis and 155,659 controls, were included in the meta-analysis to estimate the pooled odds ratio (OR) for migraine. As illustrated in**(Figure 2)**, the pooled OR for migraine among individuals with allergic rhinitis was 2.94 (95% CI: 2.02–4.29; $p < 0.0001$), indicating a statistically significant association. Substantial heterogeneity was observed across studies ($I^2 = 95.62\%$). Assessment of publication bias using a funnel plot **(Figure 3)** and Egger's test yielded a p-value of 0.2655, suggesting no significant evidence of publication bias. Sensitivity analysis, presented in **(Figure 4)**, demonstrated that no single study had a disproportionate influence on the overall effect estimate.

(Table 2) shows the results of the subgroup analysis for the pooled OR of migraine in AR compared to controls based on different categorical variables. Regarding the source of participants, a significantly higher pooled OR for AR patients recruited from hospitals (OR=7.32 (95% CI: 3.18–16.84)) compared to studies that recruited individuals with AR from the community (OR=2.35 (95% CI: 1.56–3.54)) was observed. All age groups showed a statistically significant pooled OR for migraine in AR compared to healthy controls. Although studies including participants from all age ranges showed higher pooled estimates compared to studies involving only those younger or older than 18 years, the differences between the groups were not statistically significant. Subgrouping in accordance with different methods for AR and migraine

Table 2: Subgroup analysis of included studies

Subgroup analysis	Category	Studies (n)	I^2 (%)	OR	95% CI	p-value (within)	p-value (across)
Source of participants	General population	6	96.99	2.35	1.56–3.54	<0.001	0.016
	Hospital patients	3	32.32	7.32	3.18–16.84	<0.001	
Age group	<18 years	3	86.93	2.70	1.44–5.08	0.002	0.601
	>18 years	3	77.11	2.50	1.28–4.87	0.007	
	Both	3	71.60	3.99	1.97–8.09	<0.001	
Region	Asia	4	83.08	3.46	2.01–5.94	<0.001	0.387
	Europe	3	42.97	2.11	1.19–3.75	0.011	
	North America	2	80.47	3.67	1.65–8.14	0.001	
AR diagnosis	Previous diagnosis	4	85.86	2.59	1.73–3.88	<0.001	0.022
	Self-report	2	95.63	2.06	1.28–3.33	0.003	
	Skin tests	3	32.32	6.93	3.35–14.35	<0.001	
Migraine diagnosis	IHS criteria	5	82.47	3.03	1.75–5.25	<0.001	0.949
	Previous diagnosis	3	73.22	3.03	1.63–5.63	<0.001	
	Self-report	1	0.00	2.54	0.95–6.77	0.062	
Study design	Case-control	2	50.28	6.28	2.35–16.81	<0.001	0.102
	Cross-sectional	7	96.52	2.59	1.73–3.87	<0.001	
AR sample size	<100 patients	4	40.54	5.53	2.79–10.96	<0.001	0.030
	>100 patients	5	97.57	2.25	1.45–3.50	<0.001	

AR, allergic rhinitis; CI, confidence interval; IHS, International Headache Society; OR, odds ratio.

diagnosis showed a statistically significant pooled OR for all the methods with significant differences between the methods of AR diagnosis, whereas studies using skin tests for AR confirmation had higher pooled estimates of 6.93 (95% CI: 3.35–14.35) compared to studies relying on previous diagnosis (2.59 (95% CI: 1.73–3.88)) or self-report (2.06 (95% CI: 1.28–3.33)). Both cross-sectional and case-control studies had a statistically significant pooled OR, with no significant differences in the pooled estimates regarding study design. Grouping the studies according to the AR sample size showed a statistically significantly higher pooled OR for studies conducted on less than 100 individuals with AR (OR=5.53 (95% CI: 2.79–10.96)) compared to those conducted on more than 100 individuals with AR (OR=2.25 (95% CI: 1.45–3.5)).

(Figure 5) shows the pooled RR of migraine in AR compared to controls. As calculated from two studies with 925,360 individuals with AR and 3,604,807 non-AR controls, the pooled RR was 2.27 (95% CI: 1.10–4.65), $p = 0.026$, $I^2 = 99.72\%$.

4. Discussion

The link between different atopic conditions and headache has been studied in previous literature, and meta-analyses have investigated the association between atopic conditions and headache. However, to our knowledge, this is the first meta-analysis to focus on studying the prevalence of co-occurrence of allergic rhinitis (AR) and migraine headache. This systematic review and meta-analysis investigated 11 observational studies with a total of 4,704,591 participants. Our primary finding indicated a significant association between AR and migraine headache, with an odds ratio of 2.94. Subgroup analysis demonstrated a stronger association between migraine headache and allergic rhinitis in the hospital setting compared to the general population. Remarkably, the accurate diagnosis of AR appeared to affect the association between the two conditions significantly. Our results also showed comparable associations between both conditions within different age groups and geographical regions.

Although the exact mechanism of the coexistence of migraine headache and AR has not yet been fully determined, previous research suggests common immunological mechanisms [27, 28, 29, 30], as well as responses to the same medications [31, 32, 33]. This flowchart summarizes key mediators currently believed to be involved in the development of both conditions **(Figure 6)**. This flowchart illustrates the common mediators activated in both migraine and allergic rhinitis, as well as their roles in both pathways.

The role of histamine in both conditions has been repeatedly studied in previous literature; a study by Lassen et al. showed that histamine infusion provoked migraine attacks, and those attacks could be blocked by pretreatment with pyrilamine maleate but not with placebo [34]. Histamine was hypothesized to modulate hypothalamic function and activity, which may have a major role in migraines and influence the severity of migraine attacks [35]. Moreover, whole blood from migraineurs was found to have significantly elevated levels of histamine compared to the control group [28]. A study by Forcelini et al. on pediatric populations suggests that the inflammatory response associated with AR is believed to contribute to the development and worsening of migraines by activating immune mechanisms [36]. Symptoms such as nasal congestion, discharge, and sneezing in AR involve heightened trigeminal nerve transmission, which is linked to migraine [36]. Suggesting a mutual relationship between both conditions rather than a one-way association. These results indicate a wide area of overlap between the two conditions, both in pathogenesis and management [28, 32, 36, 37]. A study by Zencir et al. failed to demonstrate a significant association between migraine and allergic rhinitis in pediatric patients [26], highlighting the need for further research to investigate the complex interplay between these conditions.

In addition to the stated common inflammatory mediators between allergic rhinitis and migraine, different confounding factors that affect both conditions have been identified in previous literature. [6, 5] Psychological factors, including anxiety and depression, as well as sleep disturbances, have been repeatedly linked to both migraine and allergic disease. [6, 8, 7] Additionally, dietary mediators pose a notable confounder; biogenic amines, such as histamine and tyramine, present in aged cheeses, cured meats, fermented products, and certain beverages, are well-documented migraine triggers due to their vasoactive and neuromodulatory properties. [4, 9, 5] These dietary factors also have the potential to provoke allergic-like responses via mast cell activation and histamine release, thereby confounding migraine–allergy associations. [10] Considering the divergent selection of the population, our analysis revealed a notable association between hospitals and patients. The odds ratio is 7.32 for hospital patients compared to 2.35 for the general population. This discrepancy may be partly explained by Berkson's bias, which arises when both the exposure and the disease increase the likelihood of hospitalization, thereby inflating the observed association in hospital-based samples [11]. In this context, patients with more severe disease are more likely to seek or require hospital care, leading to an overrepresentation of severe cases and potentially related comorbid conditions. This is supported by Derebery et al. [17, 25], who observed that patients with moderate to severe rhinitis tend to have more comorbidities than those with mild disease. The following reason could be the cause:

A selection bias that occurs when hospital-based populations are used. People with multiple conditions (e.g., both migraine and AR) are more likely to be hospitalized, making comorbidities seem more common than in the general population. Patients with more severe or complex symptoms are more likely to be referred to tertiary care centers (e.g., specialty clinics or hospitals). This means the population in hospital-based studies isn't representative of the general population. In tertiary care, patients are often thoroughly evaluated, so multiple conditions are more likely to be diagnosed—this inflates the observed association between two diseases like AR and migraine.

Similarly, Aamodt et al. observed that the frequency of migraine attacks was positively correlated with the association with all types of asthma-related disorders [16], further contributing to the differential representation in hospital settings.

Another reason for the higher association observed in hospital-based populations is what Aamodt et al. described as "personality trait", which means that patients who report their AR symptoms are more likely to report headache symptoms once they develop it [16]. Also, the fact that most studies on the general population relied on self-report or previous diagnosis of one or more conditions may question the accuracy of the diagnosis [38].

Furthermore, considering the effect of diagnostic accuracy, we analyzed the results according to the diagnostic system used in each study for both AR and migraine. Interestingly, when the skin prick test (SPT) was used for diagnosing AR, the results showed a significant association with migraine, with an odds ratio of 6.93, compared to 2.59 and 2.06 for previous diagnosis and self-report, respectively. SPT is believed to be the gold standard in AR diagnosis [35], likely contributing to more accurate assessment and higher diagnostic rates [36, 39], thereby amplifying the observed association. This finding underscores the importance of diagnostic precision in elucidating the relationship between migraine and AR. It also underlines the necessity of utilizing standardized diagnostic procedures in future research to ensure consistency and reliability. Notably, different diagnostic methods of migraine showed statistically significant results that are consistent across variables. However, whereas many studies relied on self-report or previous migraine diagnosis, it is of fundamental importance to note that applying the International Headache Society (IHS) classification system had a pivotal role in the results. Eross et al. concluded in their study that 86% of patients with a self-diagnosis and/or physician diagnosis of "sinus headache" have migraine (63%) or probable migraine (23%) as defined by the IHS Classification Criteria [40]. A finding replicated by Cady and Schreiber, who found in their study that 90% of physicians and/or self-diagnosed sinus headaches meet IHS criteria for migraine [40]. Another study by Schreiber assessed more than 2000 patients with reported sinus headaches and found that 80% had migraine [41]. These findings indicate that the actual number of migraine cases is significantly underestimated in existing records, and further prospective studies are needed to assess the effect of using the IHS criteria as a standard of migraine diagnosis and its impact on the results of future research. Subgroup analysis within different age groups, geographic regions, and study designs demonstrated a statistically significant relationship between AR and migraine. However, it is important to note that the consistently elevated odds ratios associated with these factors reinforce the robustness of the association between the two conditions and may reflect an underlying biological link. Overall, the subgroup analysis enhances our understanding of the complex dynamics of AR and migraine headache, considering the accuracy of diagnosis, the selection of population, and the sample size as important factors affecting their co-occurrence.

In this systematic review, we conducted a meta-analysis based on a systematic evaluation of previous research results, resulting in a relatively large sample size and confirming the link between AR and migraine. This meta-analysis also explored more precise connections between migraine and AR by considering age, regional variations, distinctions in study populations, and diverse diagnostic approaches for AR and migraine. The results of this investigation need further validation and exploration. Despite its limitations, the study results still provide preliminary clues about the potential connection between AR and migraine.

5. Strengths and Limitations

Several reasons contribute to the strength of this study. First, as a comprehensive analysis, we applied systematic review and meta-analysis methods, integrating data from 11 studies that encompassed more than 4 million participants, to investigate the association between AR and migraine. Second, extensive subgroup analysis has enabled a deeper understanding of the nuanced dynamics between the two conditions and a better understanding of the variable association between the AR and migraine in different populations. Third, it highlighted the potential effect of diagnostic accuracy and questioned the need for standardized diagnostic systems, thereby providing direction for future research. The study also has certain limitations. First, the study's limited causality is a result of its observational design; therefore, it can only determine the association between the two conditions, rather than assessing the causal effect or determining the pathogenesis of both conditions. Second, substantial heterogeneity was observed among studies, likely reflecting variability in sample demographics, diagnostic methods of both conditions, and study designs. This limits the generalizability of our findings and underscores the need for more uniform study designs and diagnostic methods in future research. Additionally, tests for publication bias are underpowered when based on fewer than 10 studies and should be interpreted with

caution. Despite the heterogeneity between the two cohort prospective studies, which can be attributed to differences in population characteristics, age groups, diagnostic coding, and sample size, both studies contributed to a pooled risk ratio of 2.27 (95% CI: 1.10–4.65, p = 0.026). This suggests a statistically significant association between AR and the development of migraine. As prospective studies, these findings imply that AR can be a contributing risk factor for migraine rather than being only a co-existing condition. Additionally, higher effect sizes observed in smaller studies may indicate potential small-study bias, which warrants cautious interpretation of the findings and highlights the need for larger, high-quality investigations. Also, many included studies relied on self-reported or historical diagnoses, introducing potential misclassification bias

6. Conclusion

Our findings demonstrate a significant association between allergic rhinitis (AR) and migraine. This relationship appears particularly relevant in cases where sinus headache symptoms persist or are resistant to typical explanations. Further research is warranted to clarify the nature of this association, ideally through prospective cohort studies with consistent diagnostic criteria and better control of confounding variables. Further high-quality prospective research is required before changes to screening or management practices can be recommended. In addition, the causal relationship between both conditions and the potential response of AR and migraine to the same management protocol is an insightful area that requires future research.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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None

Authors Contribution

AT was responsible for conceptualization, project administration, statistical analysis, preparing tables, drafting the manuscript, and review. KK contributed to screening, data extraction, and risk of bias assessment. AAL and AEH participated in screening and data extraction. MM was involved in screening, data extraction, and risk of bias assessment. MA contributed to writing the discussion section. MW and SME drafted the manuscript.

Data Availability

All studies used in the research are available in various databases.

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