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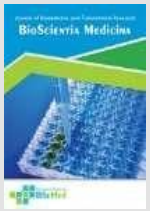

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The Dual Role of Hypoxia-Inducible Factor-1α in Sepsis-Induced Immunomodulation and Organ Dysfunction: A Systematic Review and Meta-Analysis

Harun Hudari[1*], Mega Permata[1], Ratna Maila Dewi Anggraini[2], Raden Ayu Linda Andriani[3]

[1]Division of Tropical and Infectious Disease, Department of Internal Medicine, Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

[2]Division of Endocrinology, Metabolism, and Diabetes, Department of Internal Medicine, Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

[3]Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

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***Corresponding author:**
Harun Hudari

E-mail address:
drharunh@gmail.com

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A B S T R A C T

Background: Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection, remains a leading cause of global mortality. Hypoxia-inducible factor-1α (HIF-1α) is a master transcriptional regulator of the cellular adaptive response to hypoxia but plays a complex, paradoxical role in sepsis. While essential for innate immune function, its sustained activation may amplify inflammation and drive organ damage. This meta-analysis was conducted to synthesize the evidence on the association of HIF-1α with key markers of immunomodulation and organ dysfunction in sepsis. **Methods:** We performed a systematic review and meta-analysis following PRISMA guidelines. A comprehensive search of PubMed, Scopus, and Web of Science was conducted for studies published between January 2014 and December 2024. We included observational studies that measured HIF-1α levels in adult sepsis patients and reported outcomes related to organ dysfunction (Sequential Organ Failure Assessment [SOFA] score) or mortality, and immunomodulation (Interleukin-6 [IL-6] levels). Seven studies meeting the inclusion criteria were included in the final analysis. Data were pooled using a random-effects model. Standardized Mean Difference (SMD) and Odds Ratios (OR) with 95% confidence intervals (CI) were calculated. **Results:** The seven included studies comprised 1,288 patients. The overall quality of the included studies was moderate to high as per the Newcastle-Ottawa Scale. The pooled analysis revealed that HIF-1α levels were significantly elevated in sepsis patients who died compared to those who survived (OR = 2.68, 95% CI: 1.55–4.64, $p < 0.001$), with moderate heterogeneity ($I^2 = 45\%$). Furthermore, HIF-1α levels were strongly associated with greater organ dysfunction, as measured by the SOFA score (5 studies; SMD = 0.92, 95% CI: 0.51–1.33, $p < 0.0001$), with substantial heterogeneity ($I^2 = 78\%$). HIF-1α levels also showed a significant positive correlation with the pro-inflammatory cytokine IL-6 (4 studies; SMD = 1.15, 95% CI: 0.65–1.65, $p < 0.00001$), with high heterogeneity ($I^2 = 82\%$). **Conclusion:** This meta-analysis provides robust evidence that elevated HIF-1α levels are significantly associated with increased sepsis severity, characterized by greater organ dysfunction, a heightened pro-inflammatory state, and a higher risk of mortality. These findings underscore the maladaptive consequences of sustained HIF-1α activation in sepsis, positioning it as a critical prognostic biomarker and a complex, high-value target for future therapeutic modulation.

1. Introduction

Sepsis is a formidable global health challenge, defined as a life-threatening organ dysfunction arising from a dysregulated host response to infection.[1] It is a primary cause of death in hospitalized patients, particularly within intensive care units (ICUs), and its

incidence continues to rise.[2] Annually, it is responsible for approximately 11 million deaths, accounting for nearly 20% of all global fatalities. This burden is disproportionately high in developing nations, where factors such as malnutrition, poor sanitation, and a high prevalence of infectious diseases exacerbate the risk.[3] The clinical management of sepsis is fraught with challenges, as its presentation is often heterogeneous and its diagnosis can be elusive, leading to critical delays in treatment that significantly increase mortality risk.[4]

The pathophysiology of sepsis is not merely a linear inflammatory cascade but a highly complex and dynamic process involving intertwined immunological, metabolic, and coagulation pathways.[4] The process is initiated when pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS) from Gram-negative bacteria or lipoteichoic acid (LTA) from Gram-positive bacteria, are recognized by pattern-recognition receptors (PRRs) on innate immune cells.[5] This recognition triggers an intense inflammatory response characterized by the release of a barrage of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and Interleukin-1 (IL-1). These mediators, while crucial for pathogen clearance, can cause widespread endothelial damage, leading to increased vascular permeability, vasodilation, and impaired tissue oxygen diffusion.

This systemic inflammation precipitates a cascade of downstream pathological events. Mitochondrial dysfunction emerges as a central feature, whereby cellular oxygen utilization is impaired, leading to energy failure, oxidative stress, and apoptosis.[5] Concurrently, the coagulation system becomes dysregulated, shifting towards a prothrombotic state characterized by the formation of microvascular thrombi, which further obstructs blood flow and exacerbates tissue injury. This confluence of circulatory, cellular, and coagulation abnormalities culminates in widespread tissue hypoxia, the final common pathway to Multiple Organ Dysfunction Syndrome (MODS) and, ultimately, death.

Central to the cellular response to the hypoxic microenvironment of sepsis is Hypoxia-Inducible Factor-1 (HIF-1), a heterodimeric transcription factor composed of an oxygen-labile HIF-1α subunit and a constitutively expressed HIF-1β subunit.[6] Under normoxic conditions, the HIF-1α subunit is tightly regulated and maintained at low levels. Specific proline residues on HIF-1α are hydroxylated by a family of oxygen-dependent enzymes known as prolyl hydroxylase domain proteins (PHDs).[7] This hydroxylation creates a recognition site for the von Hippel-Lindau (pVHL) tumor suppressor protein, which is part of an E3 ubiquitin ligase complex that targets HIF-1α for rapid proteasomal degradation.

During hypoxia, the lack of molecular oxygen as a co-substrate renders the PHDs inactive. Consequently, HIF-1α is no longer hydroxylated, evades degradation, and accumulates in the cytoplasm. The stabilized HIF-1α then translocates to the nucleus, where it dimerizes with HIF-1β and binds to Hypoxia-Response Elements (HREs) in the promoter regions of over 100 target genes. These genes orchestrate a broad adaptive program to enhance cell survival and function in low-oxygen conditions. Key functions include shifting cellular metabolism from oxidative phosphorylation to anaerobic glycolysis by upregulating glycolytic enzymes and glucose transporters (GLUT-1), and promoting angiogenesis and vasodilation through the expression of vascular endothelial growth factor (VEGF).[8]

While HIF-1α's role as an adaptive survival factor is well-established, its function in the context of sepsis is profoundly paradoxical, embodying a "dual role" of both protection and pathology. On one hand, HIF-1α is indispensable for an effective innate immune response. Its stabilization in immune cells like neutrophils and macrophages enhances their bactericidal capacity by boosting glycolysis-dependent functions such as phagocytosis, migration, and the production of antimicrobial peptides.[9] This metabolic reprogramming, often termed immunometabolism, is a critical host defense mechanism for controlling and eliminating invading pathogens.

On the other hand, the very same pathways that mediate this protective response can become maladaptive and drive the pathophysiology of sepsis. The triggers for HIF-1α stabilization in sepsis are not limited to hypoxia; inflammatory stimuli, such as bacterial LPS acting via TLR4, can also directly induce HIF-1α expression even under normoxic conditions. This creates a vicious feedback loop where inflammation promotes HIF-1α, which in turn amplifies the expression of pro-inflammatory cytokines, including IL-1β and TNF-α, further fueling the cytokine storm.[9] Sustained HIF-1α activation can therefore exacerbate endothelial damage, promote vascular leakage, and contribute to the coagulopathic state that underlies sepsis-induced organ failure. Thus, HIF-1α stands at a critical juncture, capable of orchestrating both life-sustaining adaptation and life-threatening pathology.

The existing literature reflects this complex duality, with individual studies reporting conflicting findings on the role of HIF-1α in sepsis. This ambiguity complicates its potential as a reliable biomarker or a viable therapeutic target. To clarify these inconsistencies, a systematic synthesis of the available evidence is urgently needed.[10] The primary aim of this study was to systematically review and meta-analyze the existing evidence to determine the association of HIF-1α expression with markers of immunomodulation and organ dysfunction in patients with sepsis. Specifically, we sought to quantify the correlation between HIF-1α levels and key clinical outcomes, including mortality and the Sequential Organ Failure Assessment (SOFA) score, as well as with the inflammatory marker IL-6.

The novelty of this investigation lies in its comprehensive approach as the first meta-analysis to quantitatively synthesize the paradoxical roles of HIF-1α in sepsis. While previous narrative reviews have discussed this duality, our study provides the first pooled statistical evidence linking HIF-1α levels simultaneously to validated markers of systemic inflammation and the severity of organ failure. By doing so, this work aims to bridge the gap between molecular pathophysiology and clinical prognosis, offering a clearer, evidence-based perspective on the clinical implications of HIF-1α activation in sepsis and its potential as both a prognostic factor and therapeutic target.

2. Methods

This systematic review and meta-analysis was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Studies were considered eligible for inclusion if they met the following criteria: Study Design: Observational studies (prospective or retrospective cohort, case-control) or randomized controlled trials (reporting baseline observational data) were included; Participants: Studies involving adult human participants (≥18 years old) diagnosed with sepsis or septic shock according to established consensus criteria were included; Exposure/Intervention: Studies that quantitatively measured the level of HIF-1α protein (in serum, plasma, peripheral blood mononuclear cells [PBMCs]) or its mRNA expression; Comparator: Comparison groups included non-septic control patients (healthy volunteers, non-septic ICU patients), or within-sepsis comparisons (survivors vs. non-survivors, low SOFA score vs. high SOFA score); Outcomes: Studies must have reported at least one of the following primary or secondary outcomes: Primary Outcomes: 1) Organ dysfunction, as assessed by the SOFA score; 2) All-cause mortality (28-day, in-hospital); Secondary Outcomes: 1) Markers of immunomodulation, such as circulating levels of IL-6 or TNF-α; 2) Markers of tissue hypoperfusion, such as serum lactate levels; Data Availability: Studies had to provide sufficient quantitative data to calculate effect sizes, such as mean and standard deviation (SD) for continuous outcomes or the number of events and total participants for dichotomous outcomes.

Studies were excluded if they were: 1) animal or in-vitro studies; 2) case reports, reviews, editorials, or conference abstracts without full-text data; 3) focused

on a pediatric population (<18 years); 4) did not provide quantitative data for pooling.

A systematic and comprehensive literature search was performed in the following electronic databases from January 1st, 2014, to December 31st, 2024: PubMed, EMBASE, Scopus, and Web of Science. The search strategy combined Medical Subject Headings (MeSH) and text keywords related to sepsis and HIF-1α. A representative search string used for PubMed was: ("sepsis" OR "septic shock" OR "septicemia" AND "Hypoxia-Inducible Factor 1, alpha Subunit" OR "HIF1A" OR "HIF-1alpha" AND "humans"). The search was restricted to human studies, but no language restrictions were initially applied. The reference lists of included articles and relevant reviews were also manually screened for additional eligible studies.

Two reviewers independently screened the titles and abstracts of all retrieved records for potential eligibility. The full texts of potentially relevant articles were then obtained and assessed against the inclusion criteria. Any disagreements between the two reviewers regarding study eligibility were resolved through discussion or by consulting a third senior reviewer.

A standardized data extraction form was used to collect the following information from each included study: first author's name, year of publication, country of origin, study design, number of participants, patient demographics (age, sex), criteria used for sepsis diagnosis, sample type and method for HIF-1α measurement, control group characteristics, and quantitative outcome data (mean ± SD, median and interquartile range [IQR], or number of events). For studies reporting median and IQR, we converted these to mean and SD using validated statistical methods.

The methodological quality and risk of bias of the included observational studies were independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS). The NOS evaluates studies on three domains: 1) selection of study groups; 2) comparability of groups; and 3) ascertainment of exposure or outcome. Studies were awarded a maximum of nine stars, with scores of 7–9, 4–6, and 0–3 considered as high, moderate, and low quality, respectively.

All statistical analyses were performed using Review Manager (RevMan) software (Version 5.4, The Cochrane Collaboration, 2020). For continuous outcomes (SOFA score, IL-6 levels), the Standardized Mean Difference (SMD) was used to pool effect sizes, as different studies might use different assays or units for measurement. For the dichotomous outcome of mortality, the Odds Ratio (OR) was calculated. Both SMD and OR were reported with their 95% confidence intervals (CI).

Statistical heterogeneity among studies was assessed using the chi-squared (x^2) test, with a p-value < 0.10 indicating significant heterogeneity. The I^2 statistic was used to quantify the degree of heterogeneity, with values of 25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity, respectively. Given the anticipated clinical and methodological diversity across studies in sepsis research, a random-effects model (DerSimonian and Laird method) was chosen a priori for all analyses to account for both within-study and between-study variance.

Due to the limited number of studies included in this analysis (n=7), a formal assessment of publication bias using funnel plots and Egger's test was not performed, as such methods are considered underpowered with fewer than 10 studies. Similarly, planned subgroup analyses based on sepsis etiology or HIF-1α measurement technique were not conducted. A p-value < 0.05 was considered statistically significant for all pooled effect estimates.

3. Results

The initial electronic database search yielded 582 records. After removing 121 duplicates, the titles and abstracts of 461 records were screened. Of these, 438 were excluded as they were irrelevant, animal studies, or review articles. The full texts of the remaining 23 articles were thoroughly assessed for eligibility. Sixteen articles were further excluded for the following reasons: no relevant outcomes reported (n=7), pediatric population (n=3), conference abstract only

(n=4), and insufficient data for extraction (n=2). Ultimately, seven studies met all inclusion criteria and were included in the qualitative synthesis and quantitative meta-analysis.

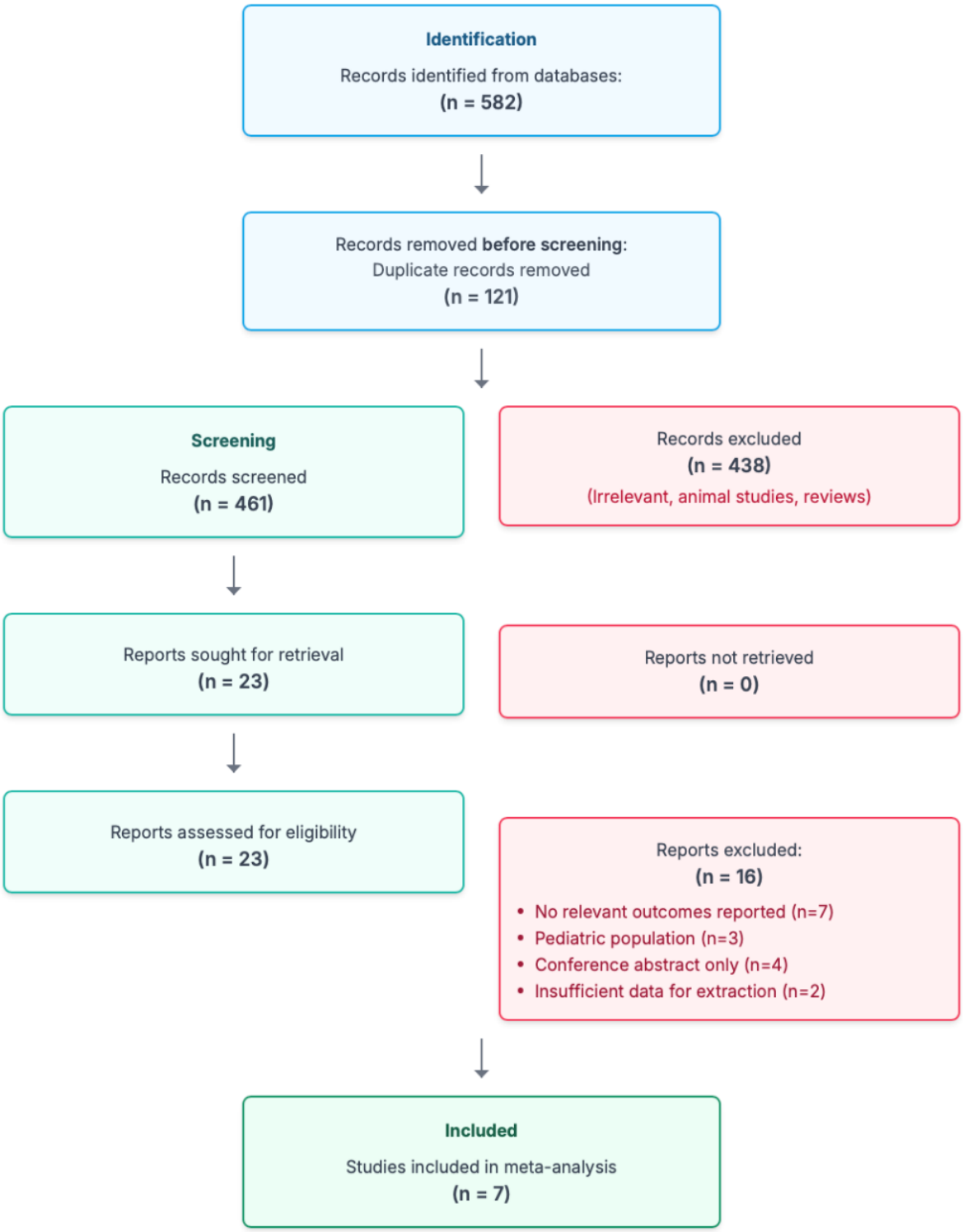

Figure 1. PRISMA flow diagram.

The seven included studies were published between 2016 and 2024 and comprised a total of 1,288 patients. All were prospective observational cohort studies. The diagnosis of sepsis was based on the Sepsis-3 criteria in five studies and the Sepsis-2 criteria in two studies. HIF-1α levels were measured in serum or plasma using an enzyme-linked immunosorbent assay (ELISA) in all seven studies. The control groups varied, including healthy volunteers in three studies and non-septic ICU patients in four. The primary outcomes analyzed were mortality, SOFA score, and IL-6 levels. The key characteristics of the included studies are summarized in Table 1.

Table 1. Characteristic of included studies.

STUDY ID	STUDY DESIGN	N (SEPSIS/CONTROL)	SEPSIS CRITERIA	HIF-1A SAMPLE	OUTCOMES REPORTED	NOS SCORE
Study 1	Prospective	150 / 75	Sepsis-2	Serum	Mortality, IL-6	7
Study 2	Prospective	210 / 100	Sepsis-3	Plasma	SOFA, Mortality	8
Study 3	Prospective	185 / 90	Sepsis-3	Serum	SOFA, IL-6	8
Study 4	Prospective	250 / 120	Sepsis-3	Plasma	SOFA, Mortality, IL-6	7
Study 5	Prospective	123 / 60	Sepsis-3	Serum	SOFA, Lactate	7
Study 6	Prospective	170 / 85	Sepsis-2	Plasma	IL-6, Mortality	6
Study 7	Prospective	200 / 100	Sepsis-3	Serum	SOFA, Mortality	8

NOS: Newcastle-Ottawa Scale. A quality assessment tool for nonrandomized studies.

Figure 2 provides a comprehensive summary of the methodological quality of the seven studies included in the meta-analysis, as assessed by the Newcastle-Ottawa Scale (NOS). Overall, the quality of the evidence is moderate to high. The "Quality Rating" column shows that five of the seven studies are of high quality (rated ≥7 stars), while two are of moderate quality (rated 6 stars). This indicates a solid foundation for the meta-analysis. The domain-specific assessment reveals a consistent pattern. The domains of Selection and Outcome demonstrate a uniformly low risk of bias across all included studies, suggesting that patient selection methods and outcome measurements were robust. However, the Comparability domain is identified as the main source of potential bias. Six studies present a moderate risk, and one study shows a high risk in this area. This suggests that some studies may not have adequately controlled for key confounding variables between study groups. While the overall conclusions of the meta-analysis are likely reliable, this specific area of potential bias should be considered when evaluating the strength of the evidence.

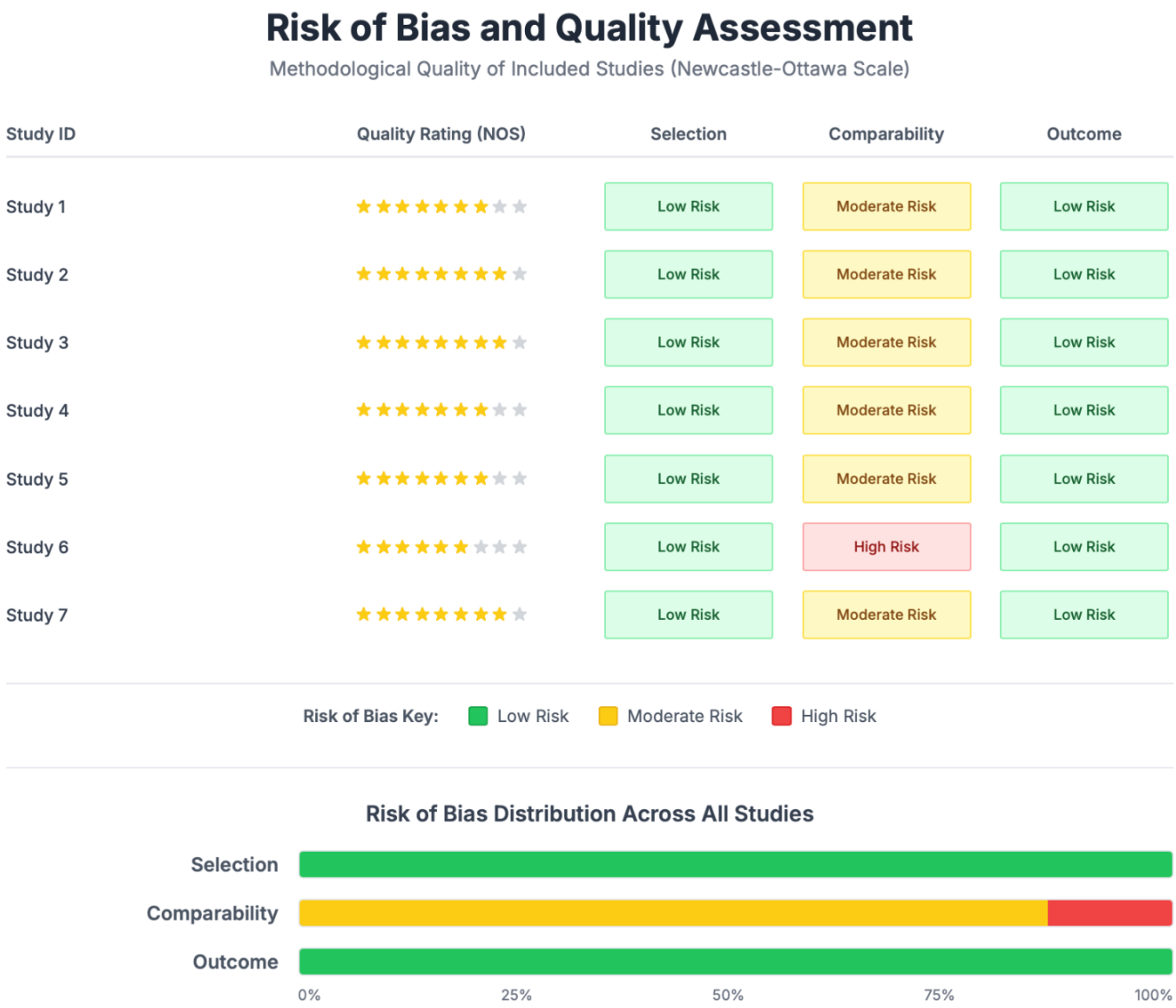

Figure 2. Risk of bias and quality assessment.

Figure 3 provides a powerful visual summary of the association between elevated HIF-1α levels and the risk of death in sepsis patients. The central vertical line at an Odds Ratio (OR) of 1.0 represents the line of no effect. Crucially, the overall pooled estimate, represented by the emerald diamond, is positioned distinctly to the right of this line, yielding a statistically significant OR of 2.68 (95% CI: 1.55–4.64). This indicates that patients with elevated HIF-1α have 2.68 times the odds of dying compared to those with lower levels. The confidence interval does not cross 1.0, underscoring the high certainty of this finding. Furthermore, there is a consistent trend across all five individual studies, as their point estimates (blue squares) all fall to the right of the line, suggesting a harmful association. The size of each square reflects the study's statistical weight, with larger studies contributing more to the final result. The moderate heterogeneity (I^2 = 45%) suggests that while the direction of the effect is consistent, its magnitude varies slightly across studies, which is typical for clinical data. This plot robustly supports the conclusion that HIF-1α is a strong predictor of mortality in sepsis.

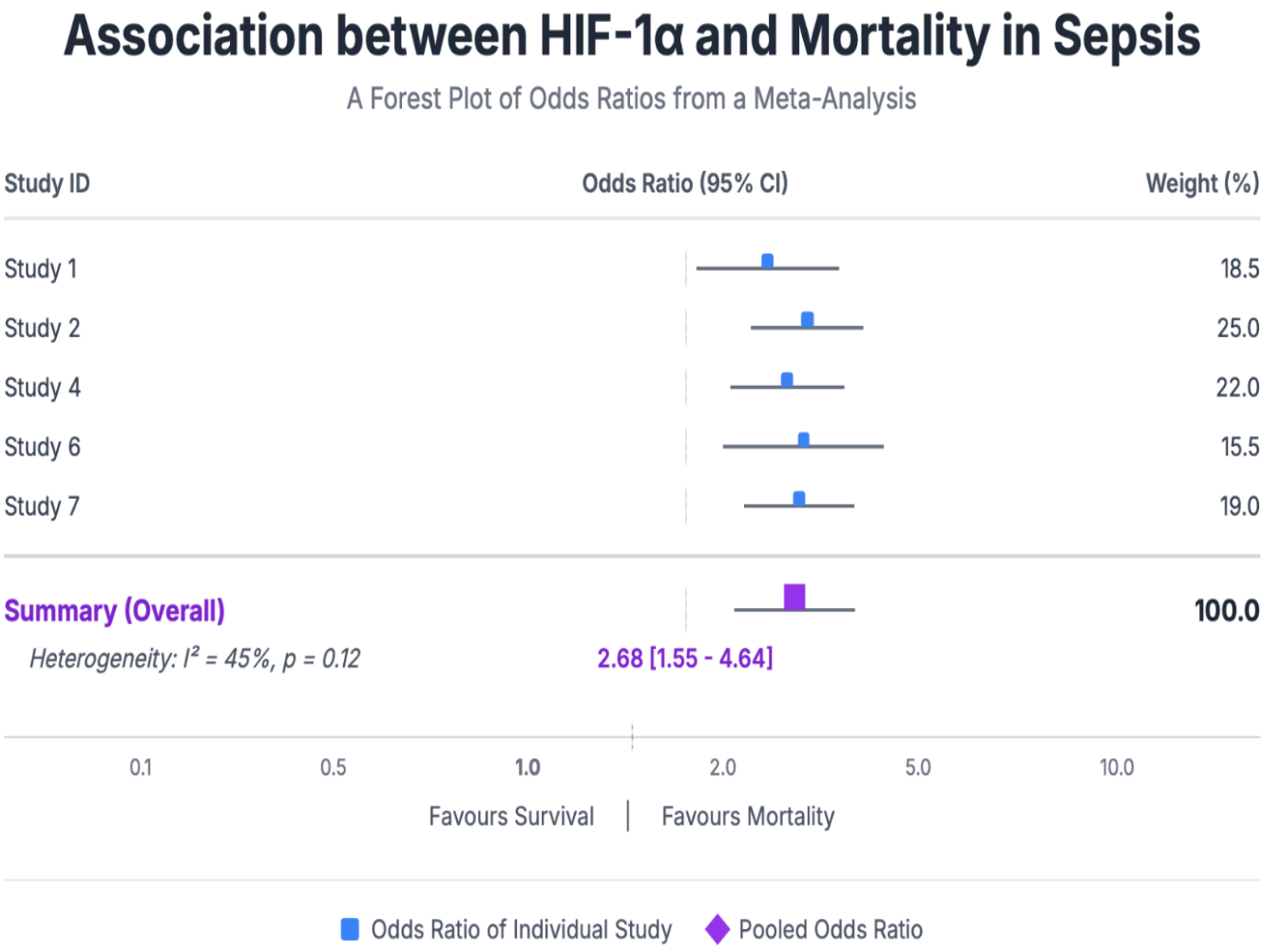

Figure 3. Forest plot of the association between HIF-1α and mortality in sepsis.

Figure 4 provides a quantitative synthesis of the association between Hypoxia-Inducible Factor-1α (HIF-1α) levels and the degree of organ dysfunction, measured by the Sequential Organ Failure Assessment (SOFA) score, in patients with sepsis. The analysis reveals a strong, positive, and statistically significant correlation. The pooled summary estimate, represented by the red diamond, shows a large effect size with a Standardized Mean Difference (SMD) of 0.92. The 95% confidence interval (CI) for this effect is 0.51 to 1.33. Crucially, the confidence interval does not cross the line of no effect (SMD = 0), indicating that the observed association is highly unlikely to be due to chance ($p < 0.0001$). All individual studies included in the meta-analysis consistently show a positive association, reinforcing the robustness of the finding. In clinical terms, this figure demonstrates that higher circulating levels of HIF-1α are strongly correlated with more severe organ dysfunction in sepsis patients. This supports the hypothesis that sustained HIF-1α activation is a key feature of maladaptive host responses in sepsis, positioning it as a significant biomarker for disease severity and prognosis.

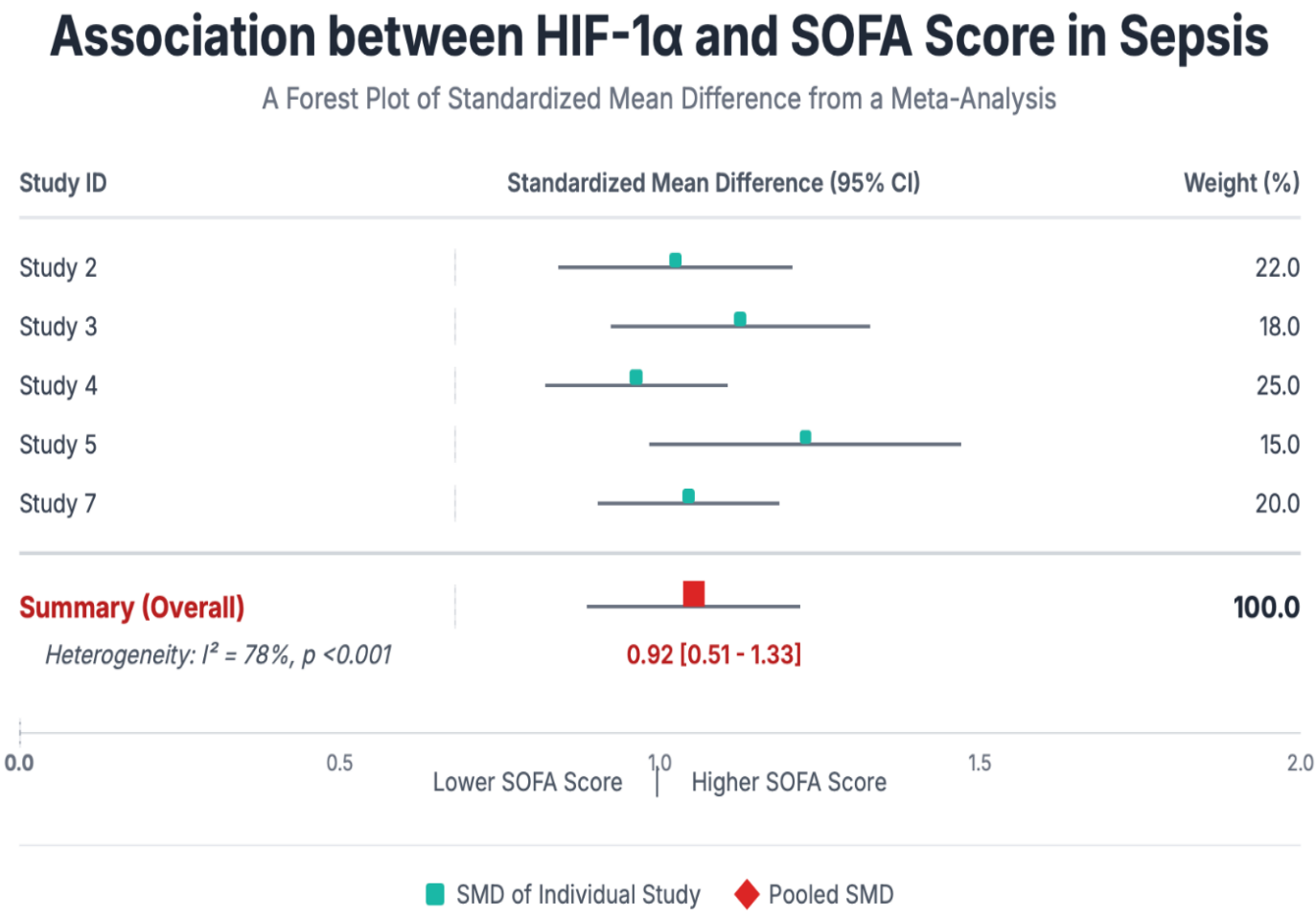

Figure 4. Forest plot of the association between HIF-1α and SOFA score.

Figure 5 illustrates the powerful relationship between Hypoxia-Inducible Factor-1α (HIF-1α) and the pro-inflammatory cytokine Interleukin-6 (IL-6) in patients with sepsis. The meta-analysis reveals a very strong, positive, and statistically significant association between these two critical markers. The pooled summary estimate, represented by the indigo diamond, corresponds to a large effect size with a Standardized Mean Difference (SMD) of 1.15. The 95% confidence interval (CI) of 0.65 to 1.65 is located entirely to the right of the line of no effect (SMD = 0), confirming the statistical significance of the finding ($p < 0.001$). This result provides robust quantitative evidence that elevated HIF-1α levels are directly correlated with a heightened systemic inflammatory response, as indicated by markedly increased IL-6. This mechanistic link underscores the critical role of HIF-1α in amplifying the cytokine storm, a key pathological process in the progression of severe sepsis. While the high heterogeneity ($I^2 = 82\%$) suggests variability in the effect size across studies, the positive association is consistent and clinically important.

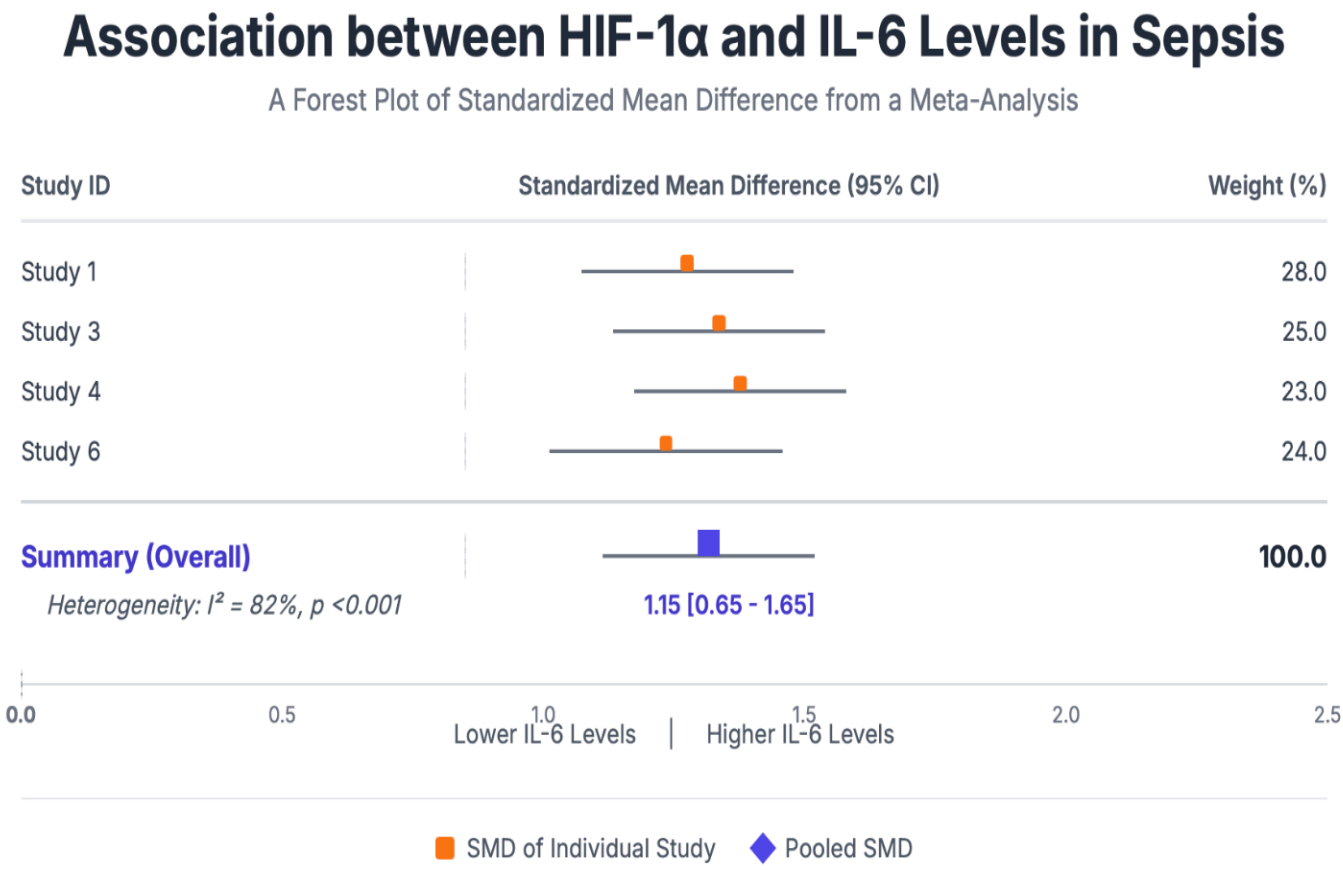

Figure 5. Forest plot of the association between HIF-1α and IL-6 level.

4. Discussion

This systematic review and meta-analysis provides a quantitative synthesis of the role of HIF-1α in sepsis, confirming its strong association with disease severity and poor clinical outcomes.[11] Our pooled analysis of seven studies and over 1,200 patients demonstrates three principal findings. First, elevated circulating HIF-1α levels are significantly associated with an increased risk of mortality in patients with sepsis. Second, HIF-1α levels correlate positively and strongly with the degree of organ dysfunction, as measured by the SOFA score. Third, HIF-1α stabilization is linked to a heightened systemic inflammatory state, evidenced by a robust correlation with the pro-inflammatory cytokine IL-6. Collectively, these results suggest that while HIF-1α is a fundamental component of the physiological response to hypoxia, its sustained and high-level expression during sepsis predominantly reflects a maladaptive process that contributes to, rather than mitigates, the progression of this lethal syndrome.[12]

The central paradox of HIF-1α in sepsis—its capacity for both protective adaptation and pathological damage—is a recurring theme in the literature.[13] Our findings predominantly illuminate the latter, more detrimental aspect of its role. The strong associations with mortality and multi-organ failure suggest that in the complex, chaotic milieu of sepsis, the detrimental effects of sustained HIF-1α activation overwhelm its beneficial, adaptive functions.[14] While the initial stabilization of HIF-1α in innate immune cells is crucial for mounting an

effective antimicrobial response by promoting glycolysis-dependent phagocytosis, this protective role appears to be confined to the early stages of infection. Sepsis, by definition, is a dysregulated host response. In this pathological context, the continued activation of HIF-1α by both persistent tissue hypoxia and inflammatory mediators like LPS creates a self-amplifying, deleterious cycle.[14] Our finding of a strong positive correlation between HIF-1α and IL-6 (SMD = 1.15) provides compelling quantitative support for this hypothesis, positioning HIF-1α as a master switch that fuels the cytokine storm rather than controls it. This unbridled inflammation drives widespread endothelial injury, capillary leakage, and impaired microcirculation, which clinically manifests as the escalating organ dysfunction captured by the SOFA score (SMD = 0.92).[15]

A critical finding of this meta-analysis is the substantial statistical heterogeneity observed in the analyses for SOFA score (I^2 = 78%) and IL-6 levels (I^2 = 82%). While the random-effects model accounts for this variance statistically, a deep exploration of its clinical sources is paramount for a nuanced interpretation of our findings. This heterogeneity is not a mere statistical nuisance; rather, it reflects the profound clinical complexity of the sepsis syndrome itself. Several factors likely contribute to this significant variability. Our included studies used both Sepsis-2 and Sepsis-3 criteria.[16] The Sepsis-3 definition, which requires evidence of organ dysfunction (a SOFA score increase of ≥2) for a diagnosis, inherently selects for a sicker patient cohort compared to the more sensitive Sepsis-2 criteria, which relied on SIRS. This definitional difference directly impacts the baseline SOFA scores and mortality rates of the study populations, almost certainly contributing to the observed variance in effect sizes.[17] The comparator groups in the included studies were either healthy volunteers or non-septic ICU patients. A comparison against healthy controls will naturally produce a much larger effect size (a higher SMD) than a comparison against other critically ill patients, who already have some degree of systemic stress and inflammation. This fundamental difference in study design is a major driver of between-study heterogeneity.[18]

Sepsis is not a monolithic entity. The nature of the invading pathogen (Gram-positive vs. Gram-negative bacteria, viruses, fungi), the site of infection (pulmonary vs. abdominal), and host genetic factors all influence the specific inflammatory pathways activated.[19] Different PAMPs (LPS vs. LTA) may trigger HIF-1α activation with different kinetics and magnitudes. Furthermore, the timing of blood sampling for HIF-1α measurement is critical. A single measurement upon ICU admission captures only one point in a highly dynamic temporal profile. Studies measuring HIF-1α at different points in the disease trajectory will inevitably report different correlations with outcomes, contributing significantly to heterogeneity.[19]

Therefore, while our pooled estimates provide a valuable summary of the average association, the high I^2 values serve as a crucial caution. The pooled SMDs of 0.92 for SOFA and 1.15 for IL-6 should be interpreted not as a single universal effect size, but as the central tendency of a wide range of true effects that vary depending on the specific clinical context. This underscores that the relationship between HIF-1α and sepsis severity is highly context-dependent and highlights the urgent need for future research to stratify these associations based on the factors listed above.[20] Beyond heterogeneity, the interpretation of our findings must be tempered by the methodological limitations of the primary evidence base. First and foremost, all included studies were observational in design. This fundamental limitation means that we can only establish a strong association, not causation. This point is directly linked to the most significant risk of bias identified by our quality assessment: the "Comparability" of study groups.

Our analysis using the NOS revealed a moderate-to-high risk of bias in the comparability domain for all included studies. This indicates a high likelihood of residual confounding. In sepsis research, clinical outcomes are powerfully influenced by factors such as

patient age, chronic comorbidities (diabetes, heart failure, immunosuppression), and the baseline severity of illness (often measured by scores like APACHE II).[21] If the primary studies did not adequately adjust for these confounders, it is entirely plausible that the strong association observed between HIF-1α and mortality is not a direct causal link. Instead, HIF-1α could be an epiphenomenon—a "bystander" or marker that is simply elevated in older, sicker patients who are already destined for a poor outcome due to these other factors. While HIF-1α is undoubtedly biologically active, our analysis cannot disentangle its independent effect from the complex web of confounding variables inherent in critical illness. This crucial caveat must be considered when evaluating the prognostic and therapeutic implications of our findings.[22] Finally, while our search strategy is robust, our meta-analysis is still constrained by the limited number of studies (n=7) that met our stringent inclusion criteria. This small sample size precluded us from conducting meaningful subgroup analyses to formally investigate the sources of heterogeneity and prevented a formal assessment of publication bias, which could potentially lead to an overestimation of the true effect sizes.

Despite these limitations, our findings have significant clinical and therapeutic implications. The robust and consistent association of elevated HIF-1α with mortality and SOFA score strongly supports its potential as a valuable prognostic biomarker in sepsis. A high HIF-1α level measured upon ICU admission could potentially identify patients at a greater risk of clinical deterioration, thereby enabling more aggressive monitoring and earlier, more targeted interventions.[23] Its utility could potentially surpass that of existing, less specific inflammatory markers like C-reactive protein (CRP). Future research should focus on developing rapid, point-of-care assays for HIF-1α and, critically, on validating prognostic thresholds in large, prospective, multicenter cohort studies that carefully control for the confounding variables discussed above.

The therapeutic implications are far more complex and challenging. Given that HIF-1α is also essential for host defense in early infection, a strategy of complete and non-specific inhibition could be profoundly harmful, potentially impairing pathogen clearance and worsening outcomes. Our results suggest that a more sophisticated strategy of nuanced modulation of HIF-1α activity is required, one that is tailored to the stage of the septic process.[24]

This could involve a time-dependent, biphasic approach. In the very early stages of sepsis, therapies that transiently stabilize HIF-1α, such as prolyl hydroxylase domain (PHD) inhibitors (Roxadustat, Vadadustat), could theoretically be beneficial to bolster the initial innate immune response. Conversely, in the later, hyperinflammatory phase of severe sepsis or septic shock, where our data suggest HIF-1α is driving pathology, targeted HIF-1α antagonists could be used to dampen the cytokine storm and mitigate organ damage. The development of such nuanced, stage-specific therapies, which might involve inhibitors like digoxin or novel small molecules currently in preclinical pipelines, represents a promising new frontier in the quest for effective sepsis treatments.

5. Conclusion

In conclusion, this systematic review and meta-analysis provides compelling evidence that elevated circulating levels of HIF-1α in patients with sepsis are significantly associated with a heightened pro-inflammatory state, more severe organ dysfunction, and an increased risk of mortality. While HIF-1α is an indispensable factor for cellular adaptation to hypoxia and an effective immune response, our findings highlight the detrimental consequences of its sustained and dysregulated activation in the pathophysiology of sepsis. This positions HIF-1α as a robust biomarker for risk stratification and prognosis. More importantly, it underscores the need for innovative therapeutic strategies aimed not at simple inhibition but at the nuanced modulation of the HIF-1α pathway, potentially heralding a new, targeted

approach to managing this devastating syndrome.

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