SYSTEMATIC REVIEWS

Prognostic Value of IL-6 for Mortality in ICU Patients with Sepsis: A Systematic Review and Meta-Analysis

Maulitia Neny Yusuprihastuti[*], Juniarti[*], Linda Weni[*], Diniwati Muchtar[*], Hari Hendriarto Satoto[**]

[*]Department of Biomedic, Faculty of Medicine, Universitas Yarsi, Jakarta, Indonesia
[**]Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Universitas Diponegoro/RSUP Dr.Kariadi, Semarang, Indonesia

✉Correspondence: mollytia888@gmail.com

ABSTRACT

Objectives: To evaluate the prognostic value of interleukin-6 (IL-6) for mortality in intensive care unit (ICU) patients with sepsis.

Study design: This study was conducted as a systematic review and meta-analysis of observational studies. Study quality was assessed using the Quality in Prognosis Studies (QUIPS) tool, and adjusted hazard ratios (HRs) were pooled using a random-effects model.

Data sources: A comprehensive literature search was performed in PubMed, Scopus, Cochrane Library, and ScienceDirect for studies published up to March 2026. Reference lists of relevant articles were also screened to identify additional eligible studies.

Data synthesis: Eighteen studies were included in the qualitative synthesis, and six studies were included in the meta-analysis. Elevated IL-6 levels were consistently higher in non-survivors across studies. The pooled analysis demonstrated that increased IL-6 levels were significantly associated with higher mortality risk (HR = 1.39, 95% CI 1.14–1.70; p = 0.001), with moderate heterogeneity (I^2 = 70%), likely reflecting differences in study populations, measurement timing, and study design. Sensitivity analysis excluding one large multicenter study reduced heterogeneity (I^2 = 0%) while maintaining statistical significance (HR = 1.29, 95% CI 1.13–1.47; p < 0.001), confirming the robustness of the findings.

Conclusions: Elevated IL-6 is significantly associated with increased mortality in ICU patients with sepsis. Despite heterogeneity, the findings are consistent and support the role of IL-6 as a prognostic biomarker, particularly when integrated with other clinical and laboratory parameters.

Registration: The protocol for this systematic review was prospectively registered in PROSPERO.

Keywords: intensive care unit; interleukin-6; mortality; prognosis; sepsis

INTRODUCTION

Sepsis remains a major global health burden, being one of the leading causes of death among critical patients admitted to the intensive care unit (ICU). Sepsis is characterized as disorder in which there is an abnormal inflammatory response to an infectious agent resulting in organ dysfunction, caused by several factors such as systemic inflammation, immune dysregulation, endothelial injury, and metabolic disorders.[1] despite with the advances development of supportive and early identification methods, mortality levels in patients with sepsis admitted to the ICU have remained relatively high, underscoring the need for improved early risk stratification.[2]

Present methods for prognosis mainly depend on scoring systems like the Sequential Organ Failure Assessment (SOFA) score, where organ failure is quantified but does not account for the biological mechanisms behind the development of illness. Considering the fact that inflammation plays a vital role in the pathology of sepsis, an increasing focus has been placed on identifying biomarkers that reflect how the body's immune system responds to an infection and provide more precise prognostic information.[3]

Interleukin-6 (IL-6) is a type of inflammatory protein that the body makes during infection. It has an important role in the early immune response, especially in the acute phase. IL-6 is released quickly when the body detects pathogens.[4] In the immune system, IL-6 regulates the activities of immune cells, vascular permeability, and hepatic protein production. Conversely, excessive amounts of IL-6 may have adverse effects on the inflammatory process rather than positive outcomes. Excessive production of IL-6 leads to vascular damage, poor microcirculation, and ultimately organ failure, which are typical characteristics of sepsis.[5]

There has been a large number of studies demonstrating an association between high IL-6 concentration and the severity and adverse outcome in sepsis patients. The studies show that non-survivors tend to have much higher levels of IL-6 than survivors and that there is a strong correlation between IL-6 concentration and organ dysfunction score and the inflammatory response in general.[6,7,8] Additionally, there seems to be a relationship between disease course and changes in IL-6 concentration over time.

However, the role of IL-6 as a predictive marker is still debated despite the biological relevance associated with it. Though numerous cohort studies adjusted for their sample size and potential confounders to independently correlate high IL-6 levels with mortality[9,10], some research findings were insignificant even after accounting for clinical severity and other factors, as highlighted by Karampela et al. (2024). Such discrepancies could be attributed to patient heterogeneity, sampling variability, and differences in methodology, among others.[11]

Because of these limitations and no clear agreement so far, it is important to combine and review the existing evidence in a more structured way. Therefore, this systematic review and meta-analysis were done to assess the prognostic value of IL-6 for mortality in ICU patients with sepsis.

This study pooled adjusted HRs from observational studies, with the aim of reducing confounding factors and making the results more comparable across different clinical settings, even though the conditions between studies are quite varied.

METHODS

This study was performed using a systematic review and meta-analysis to assess the predictive capacity of IL-6 in critically ill patients with sepsis for mortality risk. The methodology employed in the analysis adhered to set protocols to ensure the scientific validity of the study.

The literature search was performed on four electronic databases, including PubMed, Scopus, Cochrane Library, and ScienceDirect. The search, which was performed until March 2026, was confined only to those papers that were published during the last ten years. It was also limited to only those papers that were available in English. The following combination of search terms was used: ("Sepsis"[Mesh] OR sepsis OR "septic shock") AND (IL-6 OR "interleukin-6") AND ("Mortality"[Mesh] OR mortality OR prognosis OR "treatment outcome") AND ("Intensive Care Units"[Mesh] OR ICU) for pubmed, TITLE-ABS-KEY ((sepsis OR "septic shock") AND ("interleukin-6" OR "IL-6") AND (mortality OR prognosis OR outcome) AND ("intensive care" OR ICU)) for scopus, sepsis AND IL-6 AND (mortality OR prognosis OR outcome) AND ("intensive care" OR ICU) for ScieneDrirect, and sepsis OR "septic shock" in Title Abstract Keyword AND "interleukin-6" OR IL-6 in Title Abstract Keyword AND mortality OR prognosis OR outcome OR "treatment outcome" in Title Abstract Keyword AND "intensive care" OR ICU in Title Abstract Keyword for cohrane library.

To improve the search results, the reference lists of relevant articles were also checked manually, so additional studies that were not found in the first database search could be included.

All records that were found were collected and screened in two steps. First, the titles and abstracts were reviewed to remove studies that were clearly not relevant. After that, the full-text articles were checked based on the predefined inclusion criteria. The selection process was done independently, and any disagreements were discussed until an agreement was reached.

Search results included 1,218 citations. Excluding duplicates (n = 346), 872 papers underwent screening. Out of which, 332 were dropped at the level of title and abstract review. In total, 40 full-text papers were reviewed, 22 of which were dropped for reasons including no data to extract, non-specific IL-6 measurements, or non-ICU patients. Eventually, 18 papers were included in the qualitative synthesis, while 6 met the quantitative inclusion criteria.

Studies that qualified for inclusion had to meet the following criteria: (1) adult patients with sepsis or septic shock admitted to the ICU, (2) studies where IL-6 was used as a predictor, (3) mortality as one of the study outcomes, adjusted hazard ratio estimates and/or confidence intervals for HRs. Excluded were studies on pediatric patients, those not conducted in the ICU environment, and those without enough data on outcome measures. (e.g., HRs and corresponding confidence intervals).

The relevant data were systematically abstracted according to an established scheme. Abstracted information encompassed study features, patients' characteristics, IL-6 test features, outcomes definition, and effect sizes. For situations where several models were present, the model with comprehensive adjustment was used in order to prevent

possible confounding effects. Study features and effect sizes from the included studies are described in Table 1 and Table 2.

Methodological quality of the selected studies was appraised using the Quality in Prognosis Studies (QUIPS) tool. It identifies possible sources of biases within six domains, such as study participants, incomplete data, exposure and outcome measurements, confounders, and statistics. Based on this analysis, each study was classified as low, moderate, or high risk. Results of the assessment are shown in Table 3.

The main outcome of interest was all-cause mortality. The meta-analysis included only those studies that provided HRs (adjusted for relevant covariates). To ensure consistency in effect estimates and account for time-to-event outcomes.

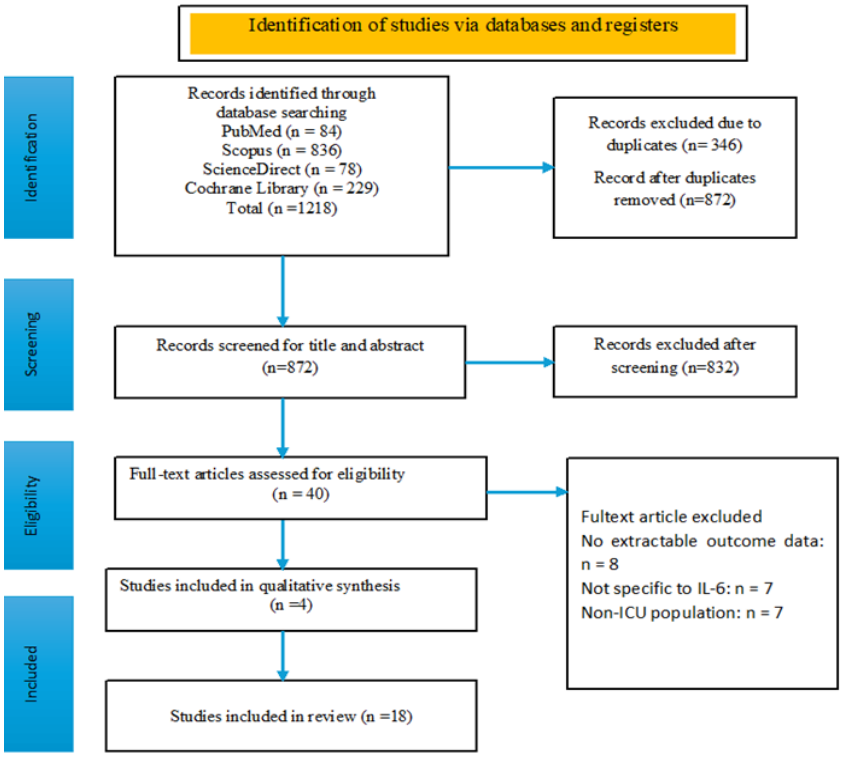

Figure 1. Flowchart of the search strategy following the PRISMA 2020 guidelines for systematic review and meta-analyses

Pooled effect sizes were calculated using a random-effects model with the inverse-variance approach, applying log-transformed HRs and their corresponding standard errors. The presence of statistical heterogeneity was evaluated using the I^2 statistic and Cochran's Q-test. An I^2 statistic higher than 50% was deemed to represent a significant level of heterogeneity. Sensitivity analysis was carried out via stepwise exclusion of individual studies to determine the reliability of pooled effect sizes and possible causes of heterogeneity. The publication bias test was not conducted due to the limited number of studies (less than 10).

Table 1. Characteristics of included studies

Author	Year	Country	Design	Population	N	Biomarker	Outcome	Key Findings	Meta-analysis
Chen et al.[12]	2025	China	Prospective cohort	ICU patients with sepsis & septic shock	143	IL-6, DcR3, CRP, PCT	28-day mortality	IL-6 associated with mortality; DcR3 significant predictor	yes
Karampela et al.[13]	2022	Greece	Prospective cohort	ICU patients with sepsis/septic shock	102	Chemerin, IL-6	28-day mortality	Chemerin independently predicts mortality; IL-6 is also independently associated	yes
Karampela et al.[11]	2024	Greece	Prospective cohort	ICU patients with new-onset sepsis/septic shock	102	Lactate-to-Albumin Ratio, IL-6	28-day mortality	LAR independently predicts mortality; IL-6 is not significant in the multivariate model	yes
Picod et al.[9]	2022	France/Belgium	Prospective multicenter cohort	Critically ill ICU patients (septic & non-septic)	2,076	IL-6, CRP	90-day mortality	High IL-6 is independently associated with mortality (aHR 1.92)	yes
Siddiqui et al.[10]	2019	Singapore	Observational cohort	ICU patients with severe sepsis/septic shock	198	IL-6, IL-10, TNF-α	28-day mortality	IL-6 is associated with mortality (HR 1.46); the effect varies by ethnicity	yes
Shimazui et al.[14]	2025	Japan	Retrospective cohort	ICU patients with sepsis	519	IL-6	28-day mortality	IL-6 is associated with mortality in non-elderly but not elderly patients	yes
Aktaş et al.[15]	2025	Türkiye	Prospective cohort	ICU patients with suspected bacteremia/sepsis	132	IL-6, CRP, PCT, SAA, endotoxin	Mortality (timeframe not specified), sepsis development	IL-6 is independently associated with mortality (OR≈4.1); CRP & PCT are significant predictors of sepsis; combined biomarkers improve diagnostic and prognostic performance	no
Ameen et al.[16]	2025	India	Prospective observational	ICU patients with sepsis (qSOFA ≥2)	72	IL-6	ICU mortality	IL-6 is independently associated with ICU mortality (OR≈28); strong correlation with	no

							SOFA score and organ dysfunction; combined IL-6 + SOFA improves mortality prediction	
Costa et al.[8]	2019	Brazil	Prospective observational	ICU patients with sepsis/septic shock	104	IL-6, IL-8, IL-10, IL-17, IL-21, TNF-α, G-CSF, others	Hospital mortality (also 28-day mortality reported)	IL-6 and IL-8 higher in non-survivors; IL-6 predictive of hospital mortality (AUROC >0.7 at D7/D14); cytokine patterns correlated with SOFA and organ dysfunction	no
Gamarra-Morales et al.[17]	2024	Spain	Prospective analytical	ICU patients with septic shock	28	IL-6 (with CRP, PCT, and lactate comparison)	28-day mortality	IL-6 is significantly higher in non-survivors; good prognostic accuracy (AUC≈0.83); early decrease over 72h reflects treatment response; correlates with lactate and severity markers	no
Jiang et al.[6]	2019	China	Prospective observational	ICU patients with sepsis	198	IL-6 (with anemia-related biomarkers)	28-day mortality	IL-6 is significantly higher in non-survivors; independently associated with mortality (OR>1); moderate predictive value (AUC≈0.76); correlated with hepcidin, ferritin, RDW, and SOFA score	no
Jiang et al.[18]	2025	China	Retrospective observational	ICU patients with sepsis (Sepsis-3)	578	IL-6 (part of SCIS score)	28-day mortality	IL-6 >150 pg/mL independently predicts mortality (adjusted OR 4.06); incorporated into SCIS with excellent	no

							predictive performance (AUC ≈ 0.86–0.96)	
Khan et al.[19]	2023	USA	Prospective observational cohort	ICU patients with delirium (≥1 week stay)	178	IL-6 (dynamic change), IL-10, others	In-hospital mortality	Increase in IL-6 over time (Day 1 → Day 8) associated with higher mortality; IL-10 higher quartiles also predictive	no
Liu et al.[7]	2021	China	Prospective observational cohort	ICU patients with sepsis/septic shock (within 24h of admission)	66	IL-6 (baseline), NT-proBNP, INR	28-day mortality	IL-6 is significantly higher in non-survivors; independently associated with mortality; best performance in the combination model	no
Lei et al.[20]	2022	China	Prospective cohort (single-center)	ICU patients (mixed, many with sepsis ± delirium)	52	IL-6, TNF-α, immune cells, gene expression	28-day mortality	IL-6 is higher in non-survivors; independently associated with mortality in a multivariable model	no
Ríos-Toro et al.[21]	2017	Spain	Prospective observational	ICU patients with severe sepsis/septic shock	50	IL-6, PCT, CRP, sTREM-1, sCD14, sCD163	28-day mortality	IL-6 is higher in severe cases and correlates with severity; a dynamic decrease (day 0–5) is associated with survival	no
Tsai et al.[22]	2025	Taiwan	Retrospective ICU cohort	Sepsis (ICU, Sepsis-3)	165	IL-6, leptin, cytokine panel	28-day & 90-day mortality	IL-6 predicts mortality; effect modified by leptin (high leptin weakens IL-6 impact)	no
Chen et al.[23]	2020	China	Prospective observational ICU study	Sepsis & septic shock	80 (40 sepsis, 40 shock)	NDMPs, IL-6, TNF-α, sTREM-1	28-day mortality	NDMPs strongly associated with mortality and correlate with IL-6	no

Table 2. Summary of outcomes and effect estimates

Author	Year	Effect type	HR	95% CI	Log (HR)	SE	Notes
Chen et al.	2025	HR	1.153	(0.811–1.639)	0.142	0.180	Adjusted Cox model; IL-6
Karampela et al.	2022	HR	1.46	(1.02–2.09)	0.378	0.183	Adjusted Cox IL-6
Karampela et al.	2024	HR	1.06	(0.76–1.48)	0.058	0.17	Adjusted Cox IL-6
Picod et al.	2022	HR	1.92	(1.63–2.26)	0.653	0.083	Adjusted Cox model; IL-6
Siddiqui et al.	2019	HR	1.46	(1.11–1.92)	0.378	0.140	Adjusted Cox; IL-6 (log-transformed)
Shimazui et al.	2025	HR	1.29	(1.03–1.61)	0.255	0.113	Combined elderly + non-elderly

Table 3. Risk of bias assessment using the QUIPS tool

Study	Study participation	Study attrition	Prognostic factor measurement (IL-6)	Outcome measurement (Mortality)	Confounding	Statistical analysis & reporting	Overall risk
Aktaş 2025	Low	Low	Low	Low	Moderate	Low	Moderate
Ameen 2025	Moderate	Low	Low	Low	Moderate	Low	Moderate
Costa 2019	Low	Moderate	Low	Low	Moderate	Moderate	Moderate
Jiang 2019	Low	Low	Low	Low	Moderate	Low	Moderate
Jiang 2025	Low	Low	Low	Low	Moderate	Low	Moderate
Khan 2023	Moderate	Moderate	Moderate	Low	High	Moderate	High
Liu 2021	Moderate	Low	Low	Low	Moderate	Low	Moderate
Lei 2022	Moderate	Moderate	Moderate	Low	High	Moderate	High
Ríos-Toro 2017	Low	Moderate	Low	Low	Moderate	Moderate	Moderate
Tsai 2025	Moderate	Low	Moderate	Low	High	Moderate	High
Chen 2020	Low	Low	Low	Low	Moderate	Low	Moderate
Gamarra-Morales 2024	Moderate	Low	Low	Low	Moderate	Low	Moderate
Chen 2025	Low	Low	Low	Low	Moderate	Low	Moderate
Karampela 2022	Low	Moderate	Low	Low	Moderate	Low	Moderate
Karampela 2024	Low	Moderate	Moderate	Low	Moderate	Low	Moderate
Picod 2022	Low	Low	Low	Low	Low	Low	Low
Shimazui 2025	Low	Low	Low	Low	Moderate	Low	Moderate
Siddiqui 2019	Moderate	Low	Moderate	Low	High	Moderate	High

RESULTS

The literature search identified 1,218 records, of which 872 remained after removal of duplicates. Following title and abstract screening, 40 full-text articles were assessed for eligibility. Eighteen studies met the inclusion criteria for qualitative synthesis, and six studies were included in the quantitative meta-analysis.

The included studies came from different countries, such as China, Greece, France, Belgium, Singapore, Japan, the United States, India, Brazil, Spain, Taiwan, and Türkiye. Most of the studies used observational designs, either prospective or retrospective cohorts. The sample size was quite varied, from 28 to 2,076 patients. All studies included adult patients treated in the ICU with sepsis or septic shock. IL-6 levels were usually measured during ICU admission. The outcomes reported were different between studies, including 28-day mortality, ICU mortality, in-hospital mortality, and 90-day mortality.

In all eighteen papers, IL-6 was significantly higher in non-survivors compared to survivors, which shows that IL-6 is a good predictor of patients' survival or death. Six papers met the inclusion criteria for meta-analysis; most of them had shown positive correlations between IL-6 and death risk. Positive independent associations were reported in studies by Karampela et al. (2022), Picod et al. (2022), Siddiqui et al. (2019), and Shimazui et al. (2025), while Chen et al. (2025) found a positive correlation after controlling for confounders, but this was not statistically significant. In Karampela et al.'s (2024) study, IL-6 showed no independent association with mortality after multivariate analysis in combination with the lactate to albumin ratio. Of particular note is the paper by Picod et al. (2022) with a large sample size (n=2076).

The 12 studies not incorporated into the meta-analysis due to variations in the effect measure also consistently provided supportive evidence. Some studies found significant relationships with the use of odds ratios, such as the study by Ameen et al. (2025), which showed a significantly increased risk of ICU mortality, and Jiang et al. (2025), which found IL-6 to be an independent predictor of mortality, showing high discrimination. The study by Aktaş et al. (2025) found IL-6 to be an independent predictor of mortality and showed improvements in mortality prediction when used in combination with other biomarkers. In relation to predicting accuracy, studies that performed the ROC analysis, such as Costa et al. (2019), Gamarra-Morales et al. (2024), and Jiang et al. (2019), found moderate-to-good accuracy with an area under the curve value greater than 0.7.

Moreover, several studies emphasized the dynamics and contextual influence of IL-6. Thus, as stated by Khan et al. (2023), elevated IL-6 levels with time increased mortality risk, and, as found by Ríos-Toro et al. (2017), declining IL-6 levels contributed to better survival rates. Moreover, Tsai et al. (2025) revealed that the prognostic impact of IL-6 depended on leptin levels, and Shimazui et al. (2025) identified IL-6 as a mortality predictor in non-elderly individuals only. Some research, such as Liu et al. (2021), Lei et al. (2022), and Chen et al. (2020), proved the increased predictive value of IL-6 when applied together with other biomarkers and clinical features.

Six studies provided an estimate of the hazard ratio and were thus included in the meta-analysis. The results obtained from meta-analysis showed that high levels of IL-6 were significantly linked to mortality (HR = 1.39, 95% CI 1.14-1.70; p = 0.001). On the other hand, there was considerable

heterogeneity between the selected studies (I2 = 70%, p = 0.001). IL-6 was primarily analyzed as a continuous or log-transformed variable across studies, and no consistent cutoff value was identified, reflecting variability in measurement and analytical approaches.

In order to analyze the origin of heterogeneity, a sensitivity analysis was conducted by excluding the study of Picod et al. (2022). After exclusion of the aforementioned study, the pooled effect was still significant (HR = 1.29, 95% CI 1.13–1.47; p < 0.001), but heterogeneity was significantly minimized (I^2 = 0%, p = 0.56). It is worth mentioning that Picod et al.'s research study was the major factor causing interstudy heterogeneity due to the larger number of participants and the multicenter nature of the study. However, the relationship between IL-6 and mortality remains consistent and significant.

The risk of bias analysis conducted using the QUIPS framework revealed that many studies had a low risk of bias in areas such as recruitment, assessment of the prognostic factor, and outcomes' measurement. Moderate risk of bias was prevalent in the confounding area, due to inconsistencies in adjusting for clinical severity, among others. High risk of bias was observed in some studies, especially where the areas were those of confounding and statistics. Notably, the study by Picod et al. (2022) presented a low risk of bias despite its heterogeneity.

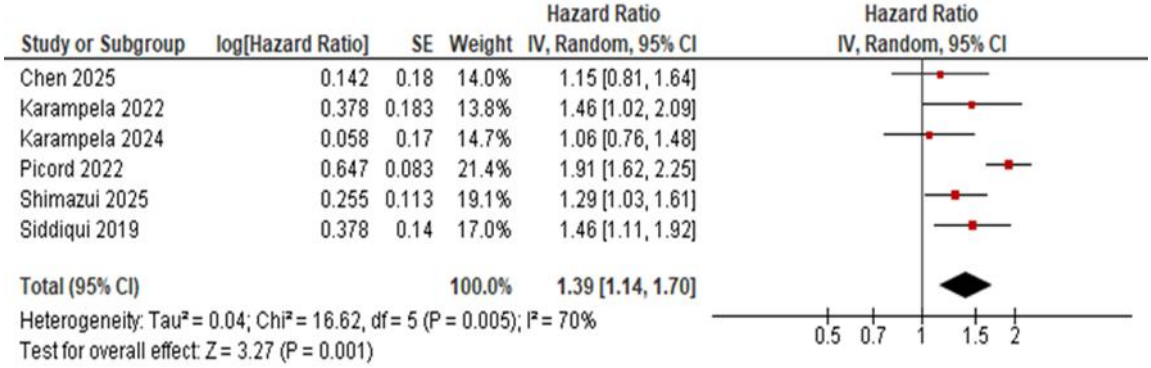

Figure 2. Forest plot of the association between IL-6 levels and mortality in ICU patients with sepsis

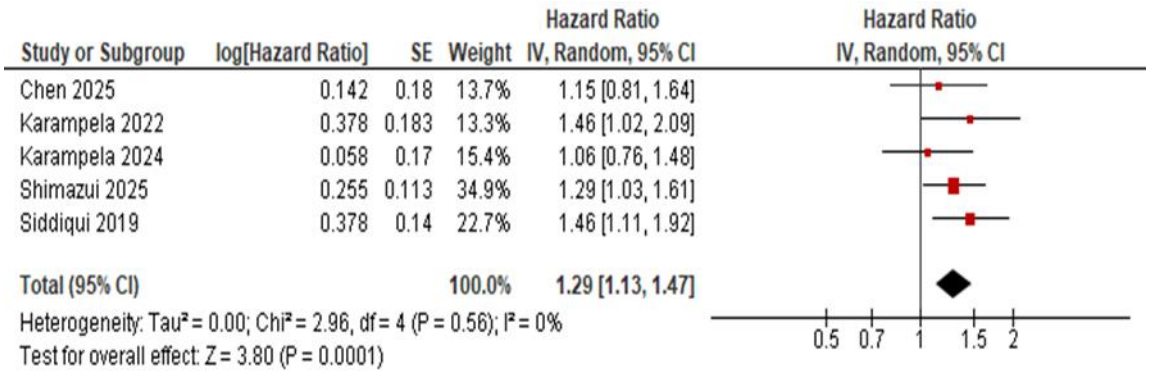

Figure 3. Sensitivity analysis excluding the study by Picod et al**.**

DISCUSSION

The current study provides evidence that high levels of IL-6 significantly predict mortality among ICU patients with sepsis. The adjusted hazard ratio results show a 39% increase in mortality risk, indicating that IL-6 may serve as an important prognostic biomarker. Consistent with other findings included in the literature review, the present study found increased levels of IL-6 among non-surviving patients with sepsis.

It is worth acknowledging the strong biological rationale behind the role of IL-6 as a potential predictor of mortality. Indeed, IL-6 is one of the most critical elements involved in the inflammatory response related to sepsis. More specifically, the presence of high levels of IL-6 contributes to endothelial dysfunction, increased vascular permeability, and altered regulation of the immune system, resulting in organ dysfunction. Many of the studies used for this review provide a lot of evidence that IL-6 levels correlate with organ dysfunction and disease progression.[6,7,8]

Nevertheless, there is evidence of heterogeneity in effect sizes despite the general consistency in results. This variability may be partly explained by differences in study design, patient populations, timing of IL-6 measurement, and analytical approaches. Importantly, no universal cutoff value for IL-6 could be established across studies. Most included studies evaluated IL-6 as a continuous or log-transformed variable rather than defining a fixed threshold.

Although some individual studies have proposed clinically relevant cutoff values, for example, Jiang et al. (2025) identified IL-6 levels >150 pg/mL as an independent predictor of mortality. These thresholds vary considerably across studies and clinical contexts. This wide variability limits the applicability of a single cutoff value and suggests that IL-6 should be interpreted as a dynamic and continuous biomarker, where increasing levels correspond to progressively higher mortality risk.

In addition, methodological quality may have contributed to the observed variability. Moderate risk of bias was common in the confounding domain due to inconsistent adjustment for clinical severity and comorbidities. Some studies also showed high risk of bias in statistical analysis, particularly where adjustment for key prognostic factors was limited, or reporting was incomplete, which may have influenced the reliability of effect estimates.[24]

Further sensitivity analysis revealed that the identified heterogeneity was mainly attributable to one single large-scale multicenter study, which showed higher effect sizes and encompassed a wider critical patient population. Exclusion of this study from the meta-analysis led to the disappearance of heterogeneity while preserving the statistical significance of IL-6 effects on mortality. This clearly indicates that heterogeneity was mainly attributed to methodological and participant differences rather than any kind of bias.

Moreover, there is evidence that the predictive power of IL-6 is dependent on certain contextual factors. First of all, the prediction efficiency may depend on such patient-related variables as age and metabolic status. Additionally, the timing of IL-6 measurements has also been proven to affect its prognostic significance. Furthermore, a significant importance has been attributed to dynamics, as persistently high or rising

levels predicted poor prognosis, whereas a decrease in the concentrations indicated a favorable course of the disease [19,21,22]

Finally, it is worth noting the possible benefits of combining IL-6 with other markers in terms of improving the prediction. Indeed, the integration of this cytokine into various scoring systems that incorporate parameters of organ dysfunction, inflammation, or metabolic imbalance allowed obtaining more accurate estimates.[7,15,16,18]

IL-6 presents multiple benefits from a clinical point of view. This cytokine is rapidly produced when the body gets infected; therefore, its production indicates real inflammation at the moment. Furthermore, its relationship with the severity and mortality rate proves that IL-6 can be a valuable predictor for other scores that are currently used by clinicians.

There are several limitations associated with the current research. First, only six articles were included in the meta-analysis, which limits statistical power and precludes a formal assessment of publication bias. Second, all selected articles were observational, and thus some biases cannot be ruled out even after adjustment for potential confounders. Third, differences in measurement timing, methods of assessing IL-6, and outcome definitions may account for the observed heterogeneity. Moreover, variations in patient populations and clinical settings limit the generalizability of the findings. In addition, variability in IL-6 measurement and analysis across studies limited the ability to establish a standardized cutoff value for clinical use. Finally, several articles used different types of effect measures, which prevented their inclusion in the quantitative synthesis.

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