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Review Article

Prognostic value of inflammatory cytokine detection for sepsis patients in ICU: a meta-analysis

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Abstract: Objective: To explore the prognostic effect of cytokine levels such as IL-6 (interleukin), IL-8 and TNF (tumor necrosis factor)-α on patients with sepsis in intensive care units (ICUs) by Meta-analysis. Methods: We systematically searched PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang, and other databases up to May 2023 to retrieve clinical research articles on cytokine testing for predicting sepsis prognosis in ICU settings. Relevant indicators were extracted and recorded in Excel. Meta-analyses were performed using RevMan 5.3. Results: A total of 25 studies were finally included in this Meta-analysis: 21 investigated IL-6, 6 examined IL-8, 11 addressed IL-10, 12 reviewed TNF-α, and 6 focused on IL-1β. Meta-analysis results demonstrated that cytokine levels (IL-6, IL-8, IL-10, TNF-α and IL-1β) in survival groups were substantially lower than those in non-survival groups (ALL $P < 0.00001$). Specific findings include significant differences in IL-6 [SMD = -25.32, 95% CI (-27.14, -23.49), $P < 0.00001$], IL-8 [SMD = -140.48, 95% CI (-154.32, -126.64), $P < 0.00001$], IL-10 [SMD = -54.10, 95% CI (-56.74, -51.47), $P < 0.00001$], TNF-α [SMD = -8.67, 95% CI (-9.82, -7.52), $P < 0.00001$], and IL-1β [SMD = -3.71, 95% CI (-4.11, -3.30), $P < 0.00001$]. The funnel plots for IL-6, IL-8, IL-10, TNF-α, and IL-1β displayed roughly symmetrical distributions, suggesting minimal bias and high reliability of the findings. Conclusion: Cytokine levels such as IL-6, IL-8, and TNF-α are valuable prognostic indicators for patients with sepsis in the ICUs. Early testing of these cytokines can guide clinical interventions and enable targeted treatments for high-risk patients to reduce the likelihood of adverse outcomes.

Keywords: Sepsis, cytokines, intensive care, prognosis, IL-6, IL-8, TNF-α

Introduction

Sepsis (Sep), an acute clinical syndrome, arises from an infection leading to a dysregulated immune response and exacerbated hemodynamic disorders. This condition precipitates varying degrees of organ dysfunction and evolves rapidly with a grave prognosis, posing a significant mortality risk in intensive care units (ICUs) [1-3]. Annually, nearly 50 million cases of sepsis are reported worldwide, with over 20% resulting in death. The mortality risk can escalate to 50% if shock occurs [4, 5]. Early identification and prognostic prediction through biomarker tests are crucial in managing sepsis, yet no gold standard biomarker currently exists, making the discovery of efficient, convenient, and reproducible biomarkers vital for enhancing clinical outcomes and reducing mortality rates.

Pathogen detection remains the gold standard for diagnosing infections. However, in sepsis, approximately 40% of the microbial test results are false negatives, undermining their reliability for sepsis diagnosis. The search for effective sepsis biomarkers is thus a key focus of clinical research. Sepsis involves complex interactions within the human immune and adaptive systems, with significant changes in cytokine expression levels during its onset, progression, and treatment. Pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-8, and tumor necrosis factor-alpha (TNF-α) play critical roles [6-8]. This study utilizes meta-analysis to explore the relationship between these cyto-

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kines and the prognosis of sepsis patients in ICUs.

Materials and methods

Literature search strategies

A comprehensive search was conducted in English-languages databases including PubMed, Embase, Web of Science, and Cochrane Library using terms such as "Sepsis", "Pyemia", "TNF-α", "TNF-α", "Interleukin-2", "Interleukin-6", "Interleukin-2", "Interleukin-6", "Interleukin-8", and "cytokine". Similarly, searches were performed in Chinese databases such as China Knowledge Network (CNKI), Wan Fang Data, and other relevant platforms using terms like "Sep", "sepsis", "Cyt", "calcitoninogen", "interleukin", and "cytokine". These searches also included specific terms such as "TNF-α", "IL-2", "IL-6", "IL-8", and "prognosis". The literature search spanned from the inception of each database until May 2023, focusing on all published literature.

Inclusion and exclusion criteria

Criteria for inclusion: (1) Studies with subjects clearly diagnosed with Sepsis; (2) Studies with subjects aged ≥ 18 years; (3) Studies using survival status as prognostic outcome, with subjects grouped for comparison of cytokine levels; (4) Studies with complete and available cytokine levels tested before receiving treatment; (5) Chinese or English literature; (6) Studies with cytokine levels reported as means and standard deviation, median and quartiles.

Criteria for exclusion: (1) Literature published as reviews, Meta-analyses, and conference abstracts; (2) Studies with non-human subjects such as animal testing or cell experiments; (3) Duplicated literature; (4) Studies with incomplete data; and (5) Studies where the full content of the literature was not available.

Literature screening and information extraction

Literature screening: Two researchers collaborated to independently review and extract data from the literature. They utilized the reference management software ENDNOTE X9 to organize their findings. The screening process was structured as follows: (1) Exclude any duplicated published literature; (2) Perform an initial screening by reviewing titles and abstracts to exclude reviews, meta-analyses, and other irrelevant literature; (3) Conduct a detailed reading of the full content of each article to perform a thorough screening. Discrepancies were resolved through discussion and analysis. If a consensus could not be reached, a third-party researcher was consulted to make a final decision on the inclusion of the literature.

Extraction of information: The final included literature underwent a detailed information extraction. The extracted data included: (1) Bibliographic details such as authors and publication dates. (2) Clinical data from the study subjects, including sample size, age, and gender. (3) Outcome measures, specifically pre-treatment cytokine levels in subjects who survived and those who did not, were presented as means and standard deviations.

For literature where accurate data were not readily available, contacting the authors is an option. The researchers documented relevant data in an Excel spreadsheet, ensuring to standardize units across different clinical literature to address inconsistencies often seen in studies from various countries and regions. Two researchers independently extracted and input data into the spreadsheet. Any discrepancies in the data were addressed by re-extracting the information. If disagreements persisted, a third-party researcher was consulted for a final resolution. Additionally, this study implemented standardization of outcome measure units across the clinical literature to further mitigate the issue of inconsistencies due to regional variations.

Literature risk of bias assessment

The risk of bias in the collected literature was evaluated using the Cochrane Risk of Bias Assessment Tool. Each study was categorized into one of three risk levels: low risk, unclear, or high risk. Two researchers independently assessed the risk and compared their findings. In cases of disagreement, they discussed the results to find a resolution. If a consensus still could not be reached, a third-party researcher was consulted for the final assessment.

Statistical analysis

Meta-analysis was conducted using RevMan 5.3 software. Pre-treatment cytokine levels in

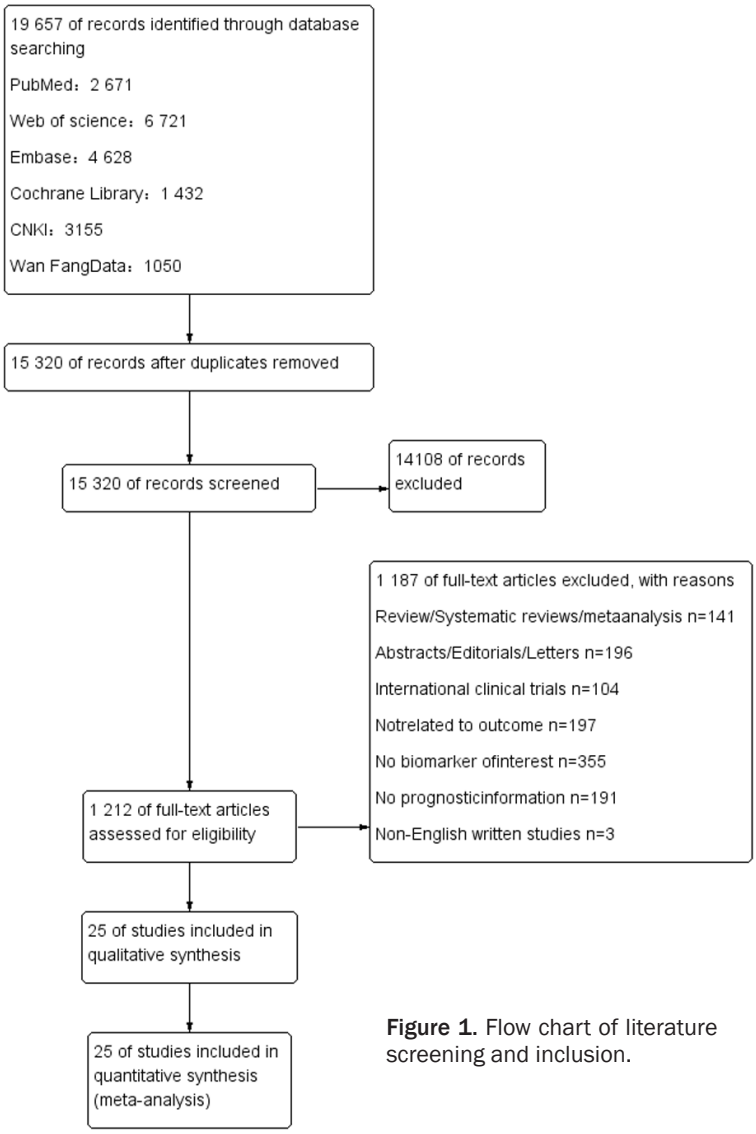

Figure 1. Flow chart of literature screening and inclusion.

patients who survived and those who did not were analyzed, with results expressed as mean difference (MD) or standard mean difference (SMD). For studies providing medians and quartiles, medians were converted into means, quartile ranges into standard deviations, and the 95% confidence interval (CI) was calculated.

Heterogeneity among studies was evaluated using the I^2 statistic and the *P*-value. $I^2 < 50\%$ or $P > 0.1$ indicates negligible heterogeneity, prompting the use of a fixed-effects model. Conversely, an I^2 value of 50% or higher, or a *P*-value of 0.1 or less, signifies substantial heterogeneity, necessitating a random-effects model. Publication bias was assessed using a funnel plot. A symmetrical distribution in the funnel plot suggests lower publication bias, enhancing the reliability of the results. A *p*-value of less than 0.05 was considered statistically significant in all analyses.

Results

Results of literature search

After database pooling, a total of 19,657 records were initially identified. Following a meticulous screening process, which included removing duplicates, reviewing titles and abstracts, and conducting a detailed examination of the full texts against the established inclusion and exclusion criteria, 25 documents were ultimately selected for inclusion (**Figure 1**).

Basic characteristics of included literature and quality assessment

Among the 25 papers finally included, there were 14 papers in English and 11 papers in Chinese, of which 21 papers reported IL-6 levels, 6 papers reported IL-8 levels, 11 papers reported IL-10 levels, 12 papers reported TNF-α levels, and 6 papers reported IL-1β levels. **Table 1** outlines the essential characteristics of these papers, while **Figure 2** provides an evaluation of their quality.

Relationship between IL-6 levels and prognosis of ICU Sepsis patients

The relationship between interleukin-6 (IL-6) levels and the prognosis of sepsis patients in ICU was analyzed in 21 studies. Given the Chi-squared value of 819.29 and an I^2 of 98%, there was significant heterogeneity among the studies, which warranted the selection of a random effects model for the analysis (**Figure 3A**). The results demonstrated that IL-6 level mea-

Table 1. Basic characteristics of the included literature

No.	Included studies	Type of study	Number of samples		Age		Indicators of outcome
			Survival group	Non-survival group	Survival group	Non-survival group	
1	Bozza FA [9], 2007	Forward-looking	31	29	-	-	IL-6, IL-8, IL-10, TNF-α, IL-1β
2	Chen YY [10], 2014	Retrospective	22	36	-	-	IL-6, TNF-α
3	Garnacho-Montero J [11], 2020	Forward-looking	41	14	-	-	IL-1β
4	Kohro S [12], 2006	Forward-looking	9	15	-	-	IL-6, IL-8, IL-10
5	Lekkou A [13], 2014	Forward-looking	28	22	-	-	IL-6, IL-8, IL-10, TNF-α
6	Liu J [14], 2021	Forward-looking	49	17	-	-	IL-6
7	Liu S [15], 2021	Retrospective	186	78	52.05±12.97	55.06±11.51	IL-6
8	Li X [16], 2021	Forward-looking	119	42	-	-	IL-6, IL-10, TNF-α
9	Lorente L [17], 2017	Forward-looking	197	98	-	-	IL-10, TNF-α
10	Seol CH [18], 2020	Retrospective	102	43	-	-	IL-6, IL-8, IL-10, TNF-α
11	Tsai WH [19], 2013	Forward-looking	39	27	-	-	IL-6, IL-8
12	Walborn A [20], 2020	Retrospective	88	15	-	-	IL-6, IL-8
13	Wu HP [21], 2011	Forward-looking	23	12	-	-	IL-6, IL-10, TNF-α, IL-1β
14	Yang Y [22], 2020	Forward-looking	38	16	-	-	IL-6, IL-10
15	Yu Suhuai [23], 2021	Forward-looking	53	31	-	-	IL-1β
16	Liu Jun [24], 2020	Forward-looking	60	18	-	-	IL-6, TNF-α
17	Sun Rong [25], 2022	Forward-looking	92	38	58.48±7.84	56.43±6.12	IL-6, TNF-α, IL-1β
18	Chao Yiqun [26], 2021	Forward-looking	39	37	69.4±7.6	76.8±7.5	IL-6, TNF-α
19	Li Ying [27], 2018	Forward-looking	36	22	-	-	IL-6
20	Wang Ting [28], 2020	Forward-looking	24	16	-	-	IL-6, IL-10
21	Wang Hai [29], 2021	Forward-looking	101	45	-	-	IL-6
22	Fan Hao [30], 2023	Retrospective	192	183	69.8±7.7	75.2±7.4	IL-6, IL-8, IL-10, TNF-α
23	Chen Chen [31], 2016	Forward-looking	60	37	-	-	IL-10, TNF-α
24	Chen Xide [32], 2020	Forward-looking	62	44	64.80±10.82	66.40±12.16	IL-6
25	Ma Dongpu [33], 2015	Forward-looking	63	21	60.4±5.2	57.9±3.7	IL-6, TNF-α

Note: IL is for interleukin; TNF is for tumor necrosis factor.

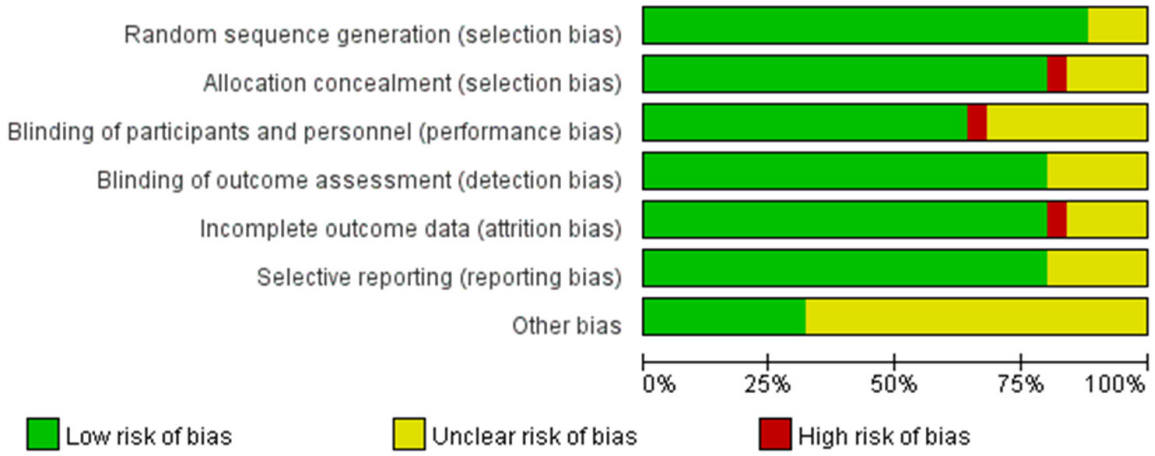

Figure 2. Assessment of risk of bias for included studies.

surement could be a critical cytokine marker for predicting the prognosis of these patients. The standardized mean difference (SMD) was -25.32 with a 95% confidence interval (CI) ranging from -27.14 to -23.49, and a highly significant *p*-value ($P < 0.00001$). Additionally, the funnel plot for IL-6 showed a roughly symmetrical distribution, suggesting low publication bias and increasing confidence in these findings (**Figure 3B**). Notably, IL-6 levels were lower in

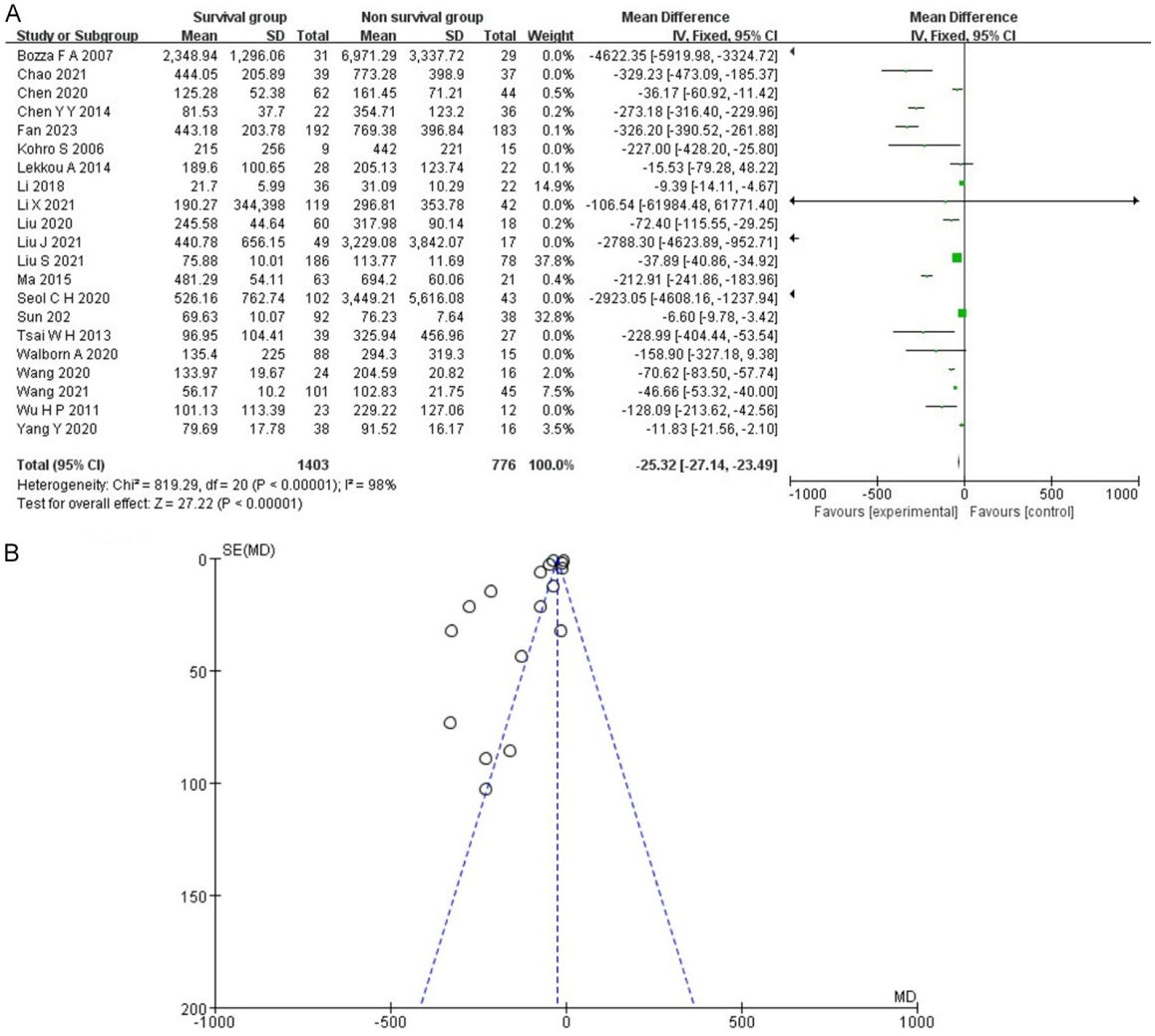

Figure 3. Forest plot of IL-6 levels and prognosis of ICU Sepsis patients.

the survival group compared to the non-survival group, highlighting its potential as a prognostic marker in critical care settings.

Relationship between IL-8 levels and prognosis of ICU Sepsis patients

The relationship between IL-8 levels and the prognosis of ICU Sepsis patients was analyzed in six studies. The heterogeneity of the studies was significant, with a Chi-squared value of 47.16 and an I^2 of 89%, necessitating the use of a random effects model (**Figure 4A**). The results revealed that IL-8 level could serve as a cytokine marker for predicting the prognosis of sepsis patients in ICU [SMD = -140.48, 95% CI (-154.32, -137.87), P < 0.00001]. Furthermore, the IL-8 funnel plot showed a roughly symmetrical distribution, indicating a low study publication bias and high confidence in the results (**Figure 4B**).

Relationship between IL-10 levels and prognosis of ICU Sepsis patients

The relationship between IL-10 levels and the prognosis of IUC Sepsis was analyzed in 11 studies. High heterogeneity among the studies was evident, as reflected by a Chi-squared value of 491.02 and an I^2 of 98%, prompting the use of a random effects model (**Figure 5A**). It was shown that IL-10 level could serve as a cytokine marker to predict the prognosis of ICU sepsis patients [SMD = -54.10, 95% CI (-56.74, -51.47), P < 0.00001]. Moreover, the funnel plot for IL-10 indicated a roughly symmetrical

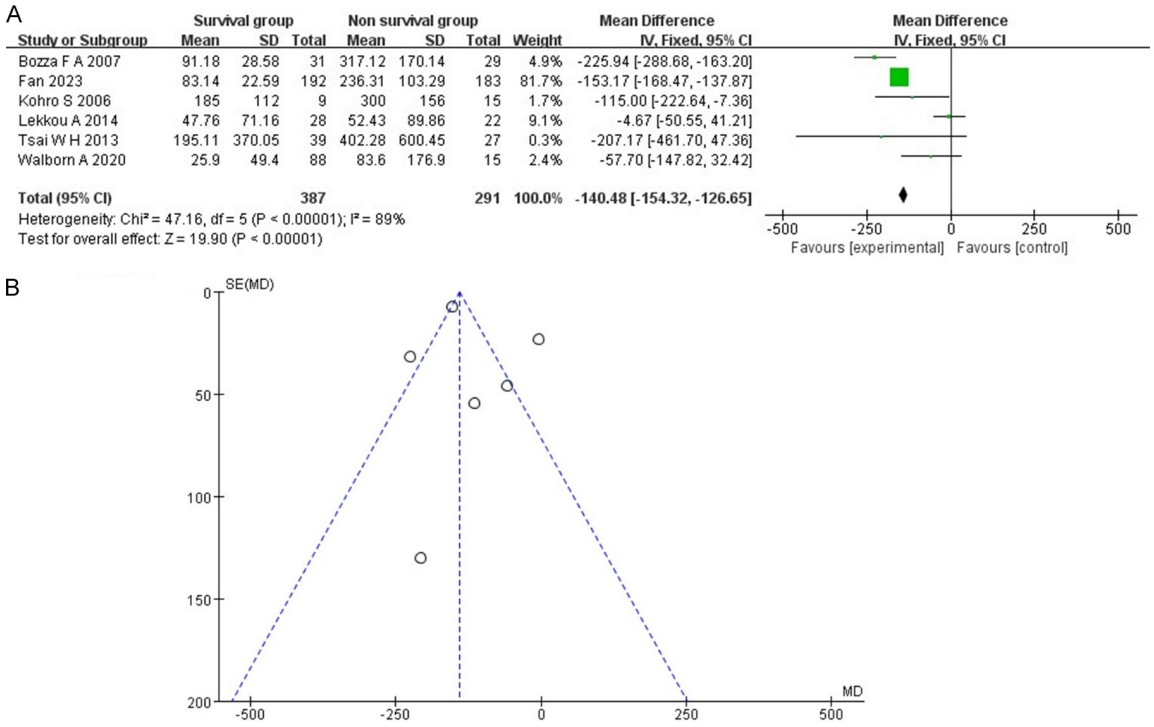

Figure 4. Forest plot of IL-8 levels and prognosis of ICU Sepsis patients.

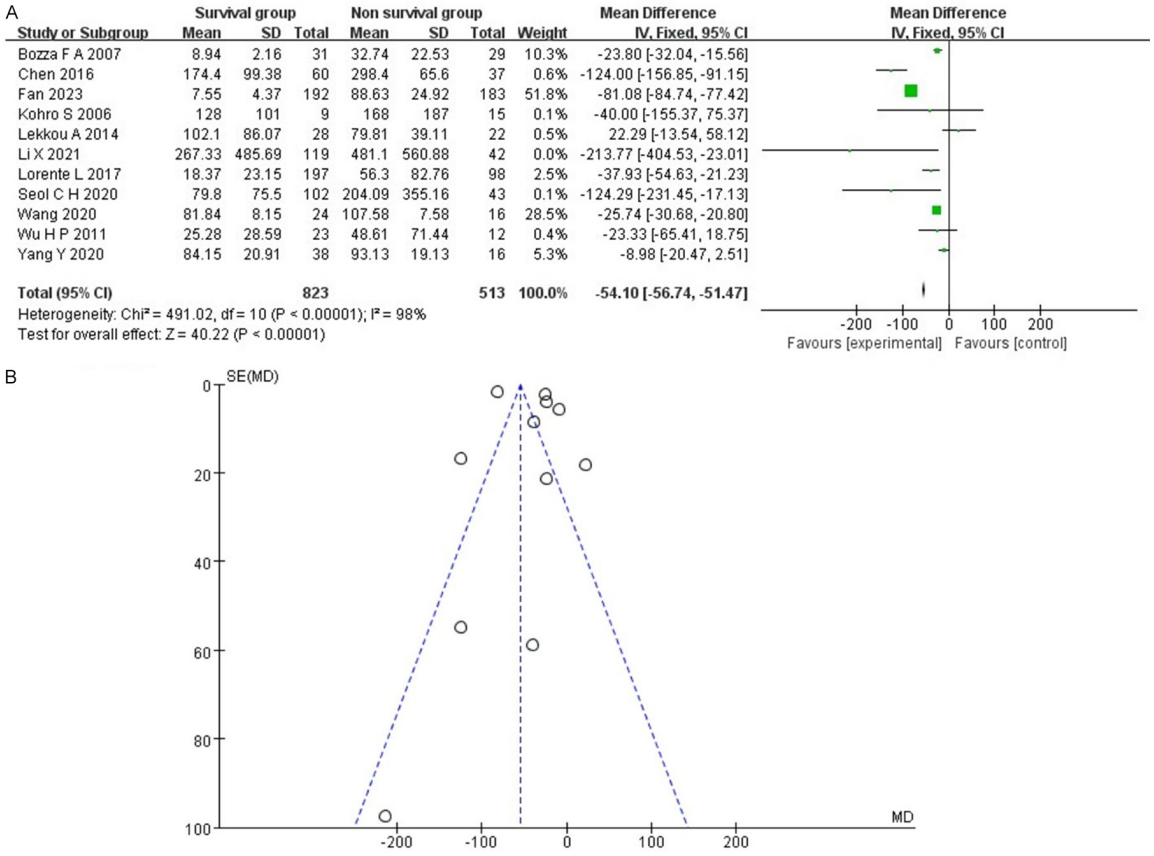

Figure 5. Forest plot of IL-10 levels and prognosis of ICU Sepsis patients.

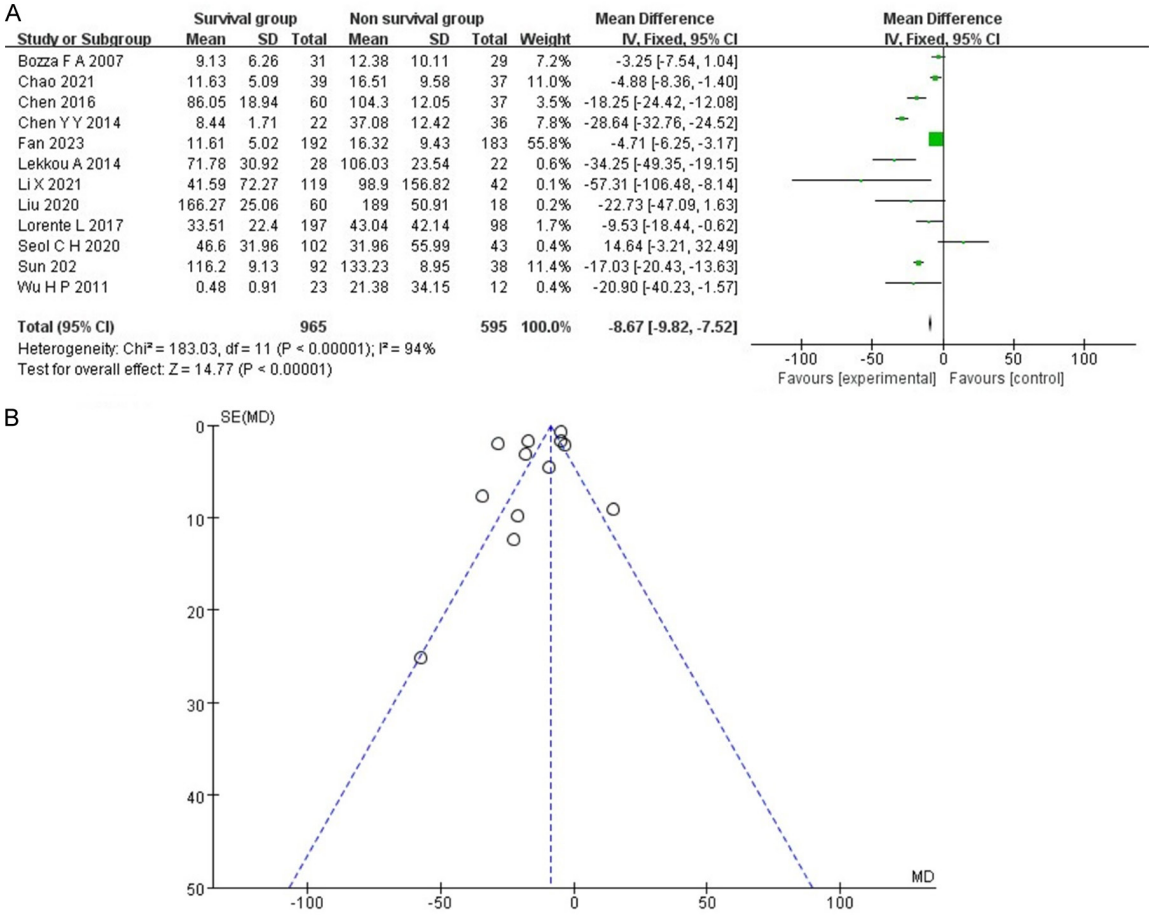

Figure 6. Forest plot of TNF-α level and prognosis of ICU Sepsis patients.

distribution, suggesting minimal publication bias and thus increasing the reliability of the results (**Figure 5B**).

Relationship between TNF-α levels and prognosis of ICU Sepsis patients

The relationship between TNF-α levels and the prognosis of sepsis patients in ICU was investigated in 12 studies. Heterogeneity was assessed with a Chi-squared value of 183.03 and an I^2 of 94%, indicating significant heterogeneity ($P < 0.00001$), thus a random effects model was chosen (**Figure 6A**). The results showed that TNF-α level could serve as a cytokine marker for predicting the prognosis of sepsis patients [SMD = -8.67, 95% CI (-9.82, -7.52), $P < 0.00001$]. The TNF-α funnel plot showed a roughly symmetrical distribution, indicating a low study publication bias and a high degree of confidence in the results (**Figure 6B**).

Relationship between IL-1β levels and prognosis of ICU Sepsis patients

The relationship between IL-1β levels and the prognosis of ICU Sepsis patients was reported in 6 studies. Heterogeneity was assessed with a Chi-squared value of 157.63 and an I^2 of 97%, indicating significant heterogeneity ($P < 0.00001$), thus a random effects model was chosen (**Figure 7A**). Results showed that IL-1β levels could serve as a cytokine marker for predicting the prognosis of sepsis patients in ICU [SMD = -3.71, 95% CI (-4.11, -3.30), $P < 0.00001$]. The IL-1β funnel plot showed a roughly symmetrical distribution, indicating a low study publication bias and high confidence in the results (**Figure 7B**).

Discussion

The mortality rate of sepsis is as high as 20%, which is related to inflammatory damage to tis-

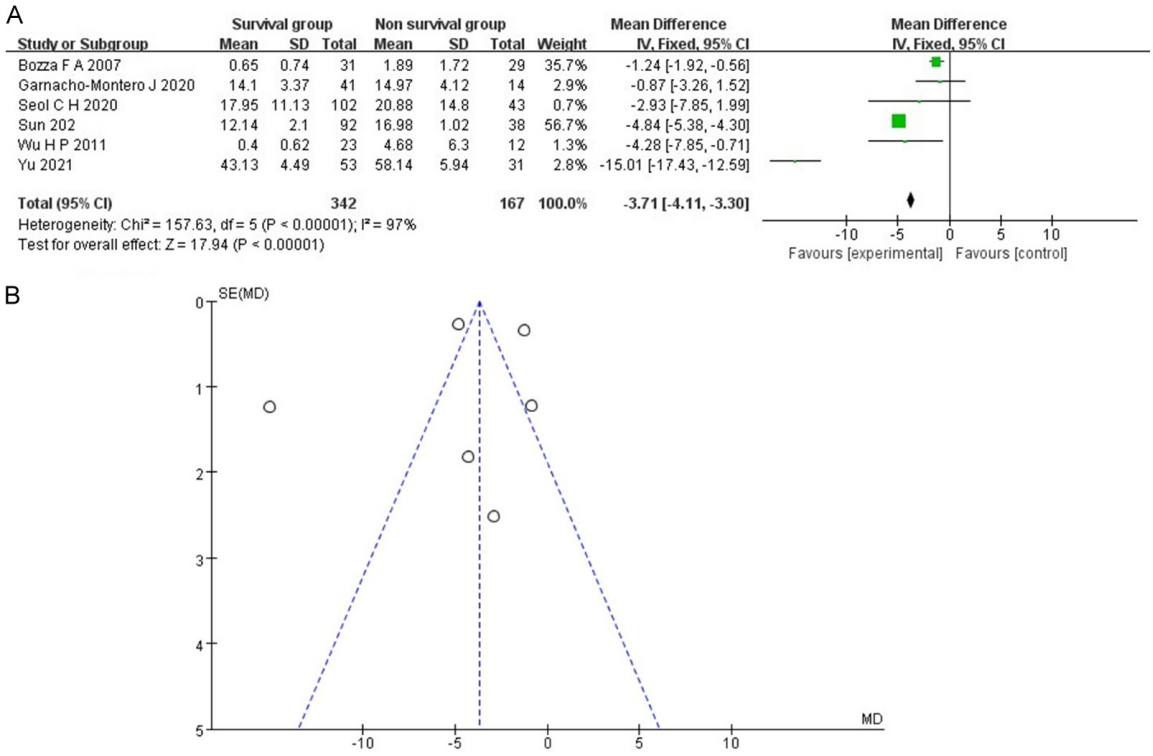

Figure 7. Forest plot of IL-1β levels and prognosis of ICU Sepsis patients.

sues and organs and suppression of immune function in patients resulting from prolonged immunosuppression and a hyperinflammatory response. As the disease progresses to an advanced stage, it can trigger an inflammatory storm or even immune paralysis, potentially raising the mortality rate to 60%. Early determination of the prognosis through the detection of cytokines, and targeted therapeutic interventions for patients at a high risk of death can significantly reduce the clinical mortality rates. Research [27] has highlighted the value of serum biochemical marker tests in the early diagnosis, disease management, and prognosis prediction of sepsis. Currently, more than 200 biomarkers have been analyzed in clinical studies for determining the prognosis of sepsis patients. In this study, a meta-approach was used to comprehensively analyze the cytokine tests involved in previous studies, aiming to identify the most significant biomarkers.

IL-6 and TNF-α are classic pro-inflammatory cytokines that mediate the initial response of the innate immune system to injury and infection. They play a crucial role as mediators of inflammatory reactions. Upon invasion or stimulation by bacteria or other microorganisms, monocytes are activated, releasing large amounts of IL-6 and TNF-α in a cascading burst. This release pattern accumulates at the site of injury and distant organs, triggering systemic inflammatory response syndrome (SIRS), causing dysregulation of the body's immune function, ultimately leading to organ damage, failure, and death [32]. Nest et al. [26] also emphasized that IL-6 and TNF-α are prognostic risk factors for mortality in sepsis patients. As the condition of sepsis patients worsens, inflammatory mediators increasingly invade various organs, exacerbating damage. This organ damage further increases the release of inflammatory mediators, resulting in elevated levels of IL-6 and TNF-α in the body. Changes in IL-6 level are associated with many diseases. In this study, 21 of the 25 papers analyzed compared IL-6 levels, underscoring its broad acceptance and utility in prognostic assessments of sepsis. Although the IL-6 funnel plot displays symmetrical distribution, its upper scatter points are unevenly concentrated around the mean, likely due to variations in the methodologies of the 21 papers and factors like the ages of study subjects. Similarly, TNF-α, which is rapidly produced in large quantities upon infection, has a shorter peak time. It is used not only to assess

the severity of infection in sepsis patients but also for prognosis prediction. In this meta-analysis, 12 papers confirmed the utility of this indicator in predicting outcomes for ICU sepsis patients, demonstrating low bias and high confidence.

In the management and prognosis of sepsis, IL-8 acts as a key cytokine involved in the systemic inflammatory response and catalyzes the pro-inflammatory response [34]. IL-10, an anti-inflammatory factor, plays an inter-regulatory role with TNF-α, helping suppress and terminate the inflammatory response; its level fluctuates with the change of the level of TNF-α during the infection [31]. IL-1β, a core inflammatory factor, regulates and counteracts with anti-inflammatory factors such as IL-10. Reported literature on these cytokines varies, with IL-8, IL-10, and IL-1β being studied in 8, 11, and 6 papers respectively, indicating a lesser focus on IL-1β. Meta-analysis results showed that IL-8, IL-10, IL-1β can be used to predict the prognostic outcomes of patients with sepsis in ICU, with funnel showing symmetry and scatter concentrated near the mean, suggesting high reliability.

In conclusion, for patients with sepsis in ICU, pre-treatment levels of IL-10, IL-1β, IL-8, TNF-α and IL-6 levels can provide a preliminary assessment of their prognostic risk, aiding in targeted clinical treatment strategies. This study focuses on "inflammatory cytokines", with its scope limited to IL-6, IL-8, IL-10, TNF-α, and IL-1β due to meta-analysis constraints. The exclusion of some cytokines due to insufficient literature underscores a limitation of the study. To overcome this, prospective studies with adequate participant numbers are recommended, which would enable a more comprehensive analysis of inflammatory cytokines.

Disclosure of conflict of interest

None.

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