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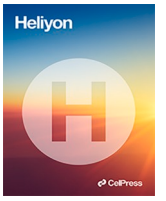

Review article

Diagnostic accuracy of interleukin-6 in multiple diseases: An umbrella review of meta-analyses

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ABSTRACT

Objective: This review aims to conduct a comprehensive study of the diagnostic accuracy of interleukin-6 (IL-6) for multiple diseases by utilizing existing systematic reviews and meta-analyses.

Methods: We performed a thorough search of Embase, Web of Science, PubMed, and Cochrane Database of Systematic Reviews up to April 2023 to gather meta-analyses that investigate the diagnostic accuracy of IL-6. To assess the methodological quality of the studies, we employed the Assessing the Methodological Quality of Systematic Reviews-2 and Grading of Recommendations, Assessment, Development and Evaluation criteria.

Results: We included 34 meta-analyses out of the 3024 articles retrieved from the search. These meta-analyses covered 9 categories of diseases of the International Classification of Diseases-11. Studies rated as "Critically Low" or "Very Low" in the quality assessment process were excluded, resulting in a total of 6 meta-analyses that encompassed sepsis, colorectal cancer, tuberculous pleural effusion (TPE), endometriosis, among others. Among these diseases, IL-6 demonstrated a relatively high diagnostic potential in accurately identifying TPE and endometriosis.

Conclusions: IL-6 exhibited favorable diagnostic accuracy across multiple diseases, suggesting its potential as a reliable diagnostic biomarker in the near future. Substantial evidence supported its high diagnostic accuracy, particularly in the cases of TPE and endometriosis.

1. Introduction

Interleukin-6 (IL-6) is a quadruple-helix cytokine with 184 amino acids synthesized by a wide range of cells that exerts its effects on various cell types via its unique receptor system and possessing an array of biological activities [1–3]. IL-6 was initially discovered in the 1970s by Kishimoto et al. as a soluble protein synthesized by T cells, inducing B-cell development [4,5]. Subsequently, the protein was demonstrated to exhibit a variety of biological activities and was first designated IL-6 in 1988 [4]. As a prototypical component of the IL-6 cytokine family, IL-6 is involved in modulating diverse normal biological and pathological events, including but not limited to inflammatory and immune responses, cellular growth, differentiation, apoptosis, and metabolic regulation [6]. When exposed to various stimuli, including toxins, cytokines, pathogens, and inflammatory stimuli, IL-6 is secreted by different types of cells during the

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disease process [1]. Following its heightened expression during inflammation and infection, IL-6 exerts its influence on the corresponding cell signaling pathways, ultimately resulting in a multitude of inflammatory responses and pathophysiological alterations [2].

The most commonly used specimens for detecting IL-6 are serum and tissue fluid, while the detection techniques primarily comprise enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorometric immunoassay (FIA) [7]. Normal serum IL-6 concentrations are less than 7 pg/mL, but after the onset of an inflammatory response, IL-6 levels can rise hundreds of times and peak at 2 h, earlier than other cytokines as well as C-reactive protein (CRP) and procalcitonin (PCT) [8–10]. Advancements in ambulatory and minimally invasive surgery have substantially reduced hospitalization durations. This has escalated the demand for short half-life biomarkers for disease diagnosis. It is widely acknowledged that the ongoing improvements in detection methodologies are expected to enhance the diagnostic significance of IL-6 in various disorders [11]. Therefore, the level of IL-6 *in vivo* may serve as a biomarker to aid in disease diagnosis and predict treatment efficacy.

Multiple published studies appraised the diagnostic accuracy of IL-6 testing for various infectious diseases, including sepsis, urinary tract infections, and gram-negative bloodstream infection [12–14]. Additionally, IL-6 is increasingly recognized as a significant biomarker in various malignancies, such as gastric, colorectal, and esophageal cancers [15–17]. Furthermore, its diagnostic accuracy has drawn the attention of several researchers in the context of respiratory, digestive, and urogenital system disorders [18–20]. However, despite numerous research studies confirming IL-6's diagnostic potential in various disorders, some conclusions lack sufficient evidence, while others present conflicting research outcomes [21–24]. As a result, there is a pressing need for a systematic and comprehensive assessment of IL-6 in the diagnosis of diverse ailments, which is not only imperative but also holds profound clinical significance.

In aggregate, quantifying IL-6 levels in patients has significant implications for clinical diagnosis and provides informative guidance for various decision-making processes, thanks to its unique role as a primary cytokine. While numerous meta-analyses focusing on the diagnostic role of IL-6 in various diseases have been published in recent decades, there is a lack of comprehensive evidence. Therefore, to assess the strength of evidence, potential bias, and diagnostic accuracy of IL-6 for multiple diseases, we systematically collected and integrated data from literature for this umbrella review.

2. Methods

2.1. Umbrella review approach

An umbrella review entails the systematic integration of current systematic reviews with the objective of providing a comprehensive and thorough picture of the given topic [25,26]. We systematically searched, extracted, and analyzed a large amount of data obtained from published systematic reviews and meta-analyses that investigated the diagnostic accuracy of IL-6 in diverse diseases. This review was conducted as previously described. Systematic reviews that did not include meta-analyses were excluded from this review because the accuracy of IL-6 diagnosis can be assessed in meta-analysis using metrics such as sensitivity and specificity. Our study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement [27]. It was prospectively registered in PROSPERO (CRD42023422842).

2.2. Literature search

A comprehensive literature search of the Web of Science, PubMed, Embase, and the Cochrane Database of Systematic Reviews databases was conducted up to April 2023 for studies published in English that evaluated the diagnostic accuracy of IL-6. We followed the SIGN guidance to retrieve the database using the following terms: "Interleukin-6", "IL-6", "Interleukin 6", "IL 6", "Diagnosis", "Sensitivity" "Specificity", "Systematic Review" and "Meta-Analysis" [28]. Supplementary Table S1provides a comprehensive and detailed search strategy. The titles and abstracts of the papers were independently assessed by two researchers, who then selected the preliminary eligible publications for further full-text evaluation. Any discrepancies between the two researchers' literature screening procedures were rectified by a third researcher. Furthermore, we conducted a manual search of the lists of references in all included publications to find any other pertinent research.

2.3. Eligibility criteria

We included meta-analyses that investigated the diagnostic value of IL-6 for various disorders. If multiple diagnostic studies on IL-6 related to a specific disease and its corresponding population existed, we selected the meta-analysis with the highest number of relevant studies to avoid inadvertent duplication of included data. In case where an equal number of studies were available, we chose the one with a higher quality rating according to Assessing the Methodological Quality of Systematic Reviews-2 (AMSTAR-2) [28]. If a disease-specific meta-analysis of IL-6 was conducted as part of the subgroup analysis in the included studies, we also incorporated it into our investigation. Meta-analyses lacking data related to diagnostic accuracy for outcome measures were excluded. Studies conducted on animals and articles published in languages other than English were also excluded. Furthermore, experimental investigations examining the correlation between IL-6 and disease or therapeutic outcomes, including their specific mechanisms and associated genetic polymorphisms, were excluded from our analysis as they fell outside the scope of our study.

2.4. Data extraction

The following data were independently extracted from the eligible articles by two researchers: (1) first author and publication year, (2) country, (3) population, (4) study design, (5) number of studies included and the number of participants in each study, (6) type of specimens, (7) IL-6 cut-off, (8) diseases, (9) reference standard, (10) diagnostic indexes such as the area under the curve (AUC), diagnostic odds ratio (DOR), specificity, sensitivity, negative likelihood ratio (NLR), and positive likelihood ratio (PLR), (11) effect model, (12) I^2 statistic value and P-value for Cochran's Q test, and (13) Egger's test P value. Any discrepancies were resolved by the third researcher.

2.5. Assessment of methodological strength and evidence grading

As a revised quality appraisal tool for systematic reviews, AMSTAR-2 contains a total of 16 items, including 7 key domains and 9 non-key domains, covering all aspects of systematic reviews [29–31]. Included articles were categorized as "Critically low," "Low," "Moderate," and "High." Additionally, the quality of the evidence for all results was graded using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, which assigns one of four grades to each outcome: "Very low," "Low," "Moderate," and "High [32]."

2.6. Data analysis

Pooled effects and 95% confidence intervals (CIs) were extracted from the included studies. When conducting both summary analysis and subgroup analysis for a specific category of studies within an article, summary data are employed. In scenarios where the meta-analysis encompasses multiple populations without consolidated results, information is extracted on a per-population basis. We used I^2 statistics and Cochran's Q test to estimate and quantify heterogeneity among meta-analyses. Publication bias estimates for each outcome were evaluated using Egger's regression test and Deeks' test [33,34]. We determined that a P value < 0.10 was statistically significant for the heterogeneity test. For other tests, we considered $P < 0.05$ to be significant.

3. Results

3.1. Characteristics of meta-analyses

The systematic procedure for conducting the literature search and selection in this study is presented in a flow chart in Fig. 1. A total of 3024 articles were identified from the four targeted databases, ultimately leading to the inclusion of 34 meta-analyses from 11 countries in the analysis. The included diseases were categorized into 9 distinct classifications based on the International Classification of Diseases-11 (ICD-11), encompassing the following disease categories: certain infectious or parasitic diseases (n = 10); neoplasms (n = 3); diseases of the blood or blood-forming organs (n = 1); diseases of the respiratory system (n = 3); diseases of the digestive system (n = 3); diseases of the genitourinary system (n = 4); certain conditions originating in the perinatal period (n = 4); injury, poisoning or

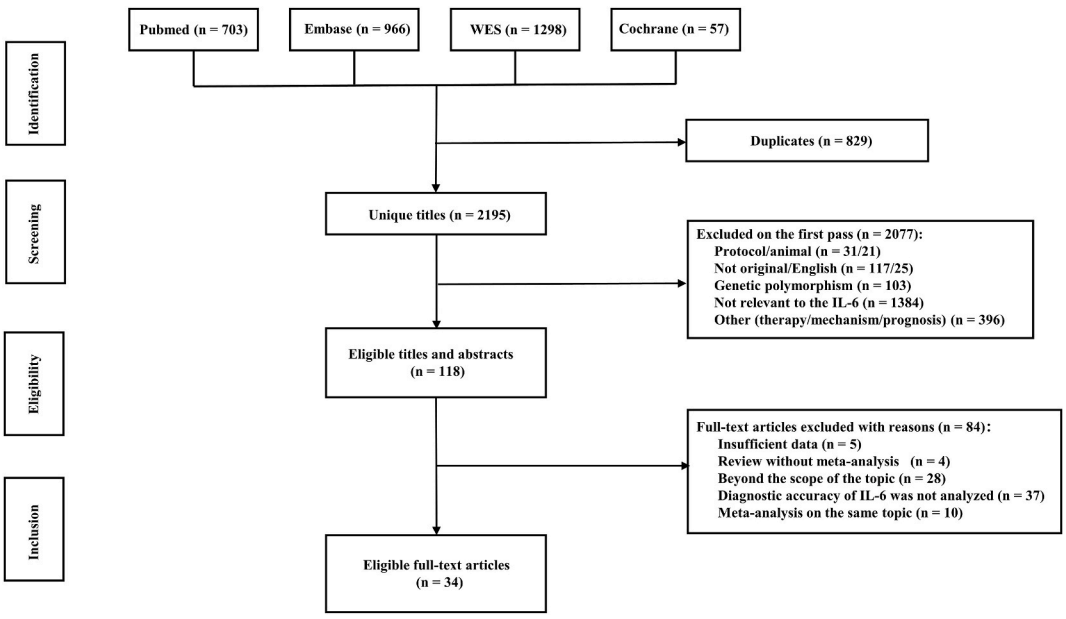

Fig. 1. Flowchart of the systematic search and selection process.

certain other consequences of external causes (n = 5); and mortality (n = 1) (Fig. 2). Table 1 presents the characteristics of the included meta-analyses with infectious diseases or cancer. The remaining characteristics of the included meta-analyses can be found in Supplementary Table S2.

3.2. Certain infectious

Table 2 displays the findings of meta-analyses examining the diagnostic accuracy indicators of IL-6 in infectious diseases and cancer. IL-6 was identified in several infectious diseases, including sepsis (n = 4), bacterial meningitis (n = 1), febrile urinary tract infection (n = 1), bacterial infection (n = 2), and gram-negative bloodstream infection (n = 1). The sensitivity and specificity of IL-6 in blood for sepsis in adult patients were found to be 0.72 (95% CI: 0.65, 0.78) and 0.70 (95% CI: 0.62, 0.76), respectively [13]. The corresponding DOR, AUC, PLR, and NLR were 6.00 (95% CI: 4.00, 9.00), 0.77 (95% CI: 0.73, 0.80), 2.40 (95% CI: 1.90, 3.00), and 0.40 (95% CI: 0.32, 0.51), respectively. Further analysis of serum samples showed a sensitivity and specificity of IL-6 in adult sepsis patients of 0.85 (95% CI: 0.80, 0.88) and 0.62 (95% CI: 0.55, 0.68), respectively. The PLR and NLR were 2.36 (95% CI: 1.16, 4.80) and 0.33 (95% CI: 0.23, 0.47), respectively [35]. In neonates, the corresponding sensitivity, specificity, PLR, and NLR were 0.77 (95% CI: 0.73, 0.81), 0.91 (95% CI: 0.86, 0.94), 7.78 (95% CI: 4.26, 14.22), and 0.25 (95% CI: 0.16, 0.39), respectively [35]. The sensitivity, specificity, AUC, PLR, and NLR of IL-6 in patients with systemic inflammatory response syndrome (SIRS) were 0.72 (95% CI: 0.63, 0.80), 0.73 (95% CI: 0.67, 0.79), 0.79 (95% CI: 0.75, 0.82), 3.41, and 0.60, respectively [36]. Among critically ill adult patients aged ≥18 years with suspected sepsis, the sensitivity and specificity of IL-6 were found to be 0.66 (95% CI: 0.60, 0.72) and 0.74, respectively [37]. The sensitivity, specificity, DOR, AUC, PLR, and NLR of serum IL-6 for bacterial infection in cirrhotic patients were 0.85 (95% CI: 0.64, 0.94), 0.91 (95% CI: 0.80, 0.96), 52.89 (95% CI: 15.21, 183.86), 0.94 (95% CI: 0.92, 0.96), 8.99 (95% CI: 4.13, 19.55), and 0.17 (95% CI: 0.07, 0.43), respectively [38]. In children and adults with febrile neutropenia, the sensitivity, specificity, DOR, AUC, PLR, and NLR of blood IL-6 to distinguish severe from nonsevere bacterial infections were 0.74 (95%CI: 0.65, 0.81), 0.80 (95% CI: 0.71, 0.87), 10.00 (95% CI: 5.50, 18.00), 0.76 (95% CI: 0.72, 0.79), 3.68 (95% CI: 2.41, 5.60), and 0.33 (95% CI: 0.23, 0.46), respectively [39]. The sensitivity, specificity, DOR, AUC, PLR, and NLR of IL-6 in the cerebrospinal fluid (CSF) for bacterial meningitis were 0.91 (95% CI: 0.81, 0.96), 0.93 (95% CI: 0.84, 0.97), 129.76 (95% CI: 41.48, 405.88), 0.97 (95% CI: 0.95, 0.98), 12.38 (95% CI: 5.42, 28.29), and 0.10 (95% CI: 0.04, 0.21), respectively [40]. In children and adolescents with febrile urinary tract infections, the sensitivity,

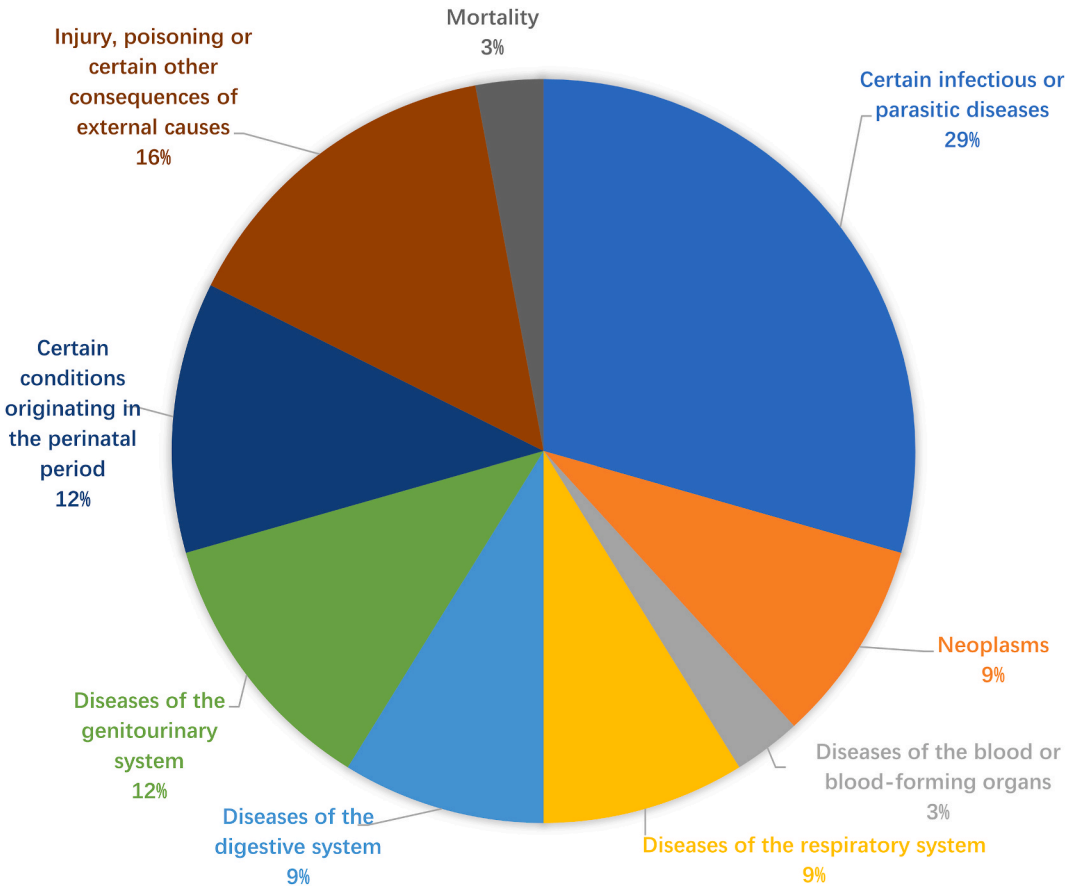

Fig. 2. Map of disease outcomes based on ICD-11 classification associated with IL-6 diagnosis.

Table 1
Characteristics of the included meta-analyses with infectious diseases or cancer.

Diseases	Study	Country	Study design of primary study	Population	No of participants/ studies	Type of specimen	Tool to assess risk of bias	Companion tested	Reference standard
Sepsis	Hou, 2015	China	Case-control	Neonate and adult	1311/6	Serum	NR	NR	NR
Sepsis	Liu, 2016	China	NR	Patients with SIRS	3450/22	NR	QUADAS	PCT, CRP, sTREM-1, Presepsin, LBP, CD64	ACCP/SCCM
Sepsis	Daniel, 2019	Spain	Diagnostic test	Critically ill adults aged 18 years or older under suspicion of sepsis	4192/23	Plasma	QUADAS-2	NR	1991 ACCP/SCCM; 2001 SCCM/ESICM/ ACCP/ATS/SIS; 2015 ESICM/SCCM
Sepsis	Cong, 2021	China	Prospective, retrospective	Adult patients	NR/16	Blood	QUADAS-2	Neutrophil CD64, PCT	Clinical diagnostic, blood culture
Bacterial meningitis	Yao, 2015	China	Diagnostic test	NR	825/9	Cerebrospinal fluid	QUADAS	IL-8	NR
Infection	Iwase, 2019	Japan	NR	Critically ill patients with suspected infection	527/6	Blood	QUADAS-2	NR	ACCP/SCCM, ISF and CDC/NHSN
Bacterial infection	Wu, 2016	China	Case-control, cohort	Cirrhotic patients	741/6	Serum	QUADAS-2	NR	NR
Serious bacterial infection	Wu, 2015	China	Prospective	Children and adult with febrile neutropenia	314/5	Blood	QUADAS	PCT, CRP	NR
Febrile urinary tract infection	Hosseini, 2022	Iran	Case-control, cross-sectional	Children and adolescents	NR/3	Serum, urine	QUADAS-2	IL-8	NR
Gram-negative bloodstream infection	Lai, 2020	China	Non case-control	Patients with suspected bloodstream infection	3455/5	Blood	QUADAS-2	PCT, CRP	Blood culture
Gastric cancer	Wang, 2021	China	Case-control	NR	794/4	Serum	QUADAS-2	NR	NR
Ovarian cancer	Amer, 2021	Australia	NR	NR	NR/12	Serum/plasma or peritoneal fluid	STROBE checklist	NR	NR
Colorectal cancer	Xu, 2016	China	Case-control	Patients with or without colorectal cancer	654/7	Serum	QUADAS	NR	Histologic assessment

NR, Not reported; SIRS, systemic inflammatory response syndrome; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; PCT, procalcitonin; CRP, C-reactive protein; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; LBP, lipopolysaccharide-binding protein; ACCP, American College of Chest Physicians; SCCM, Society of Critical Care Medicine; ESICM, European Society of Intensive Care Medicine; ATS, American Thoracic Society; SIS, Surgical Infection Society; IL-8, interleukin-8; ISF, International Sepsis Forum; CDC, Centers for Disease Control and Prevention; NHSN, National Healthcare Safety Network; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Table 2
Results of the IL-6 diagnostic accuracy indicators (meta-analyses with infectious diseases or cancer).

Disease	Study	Population	No of Participants/ Studies	Type of specimen/ IL-6 level pg/ml	Estimates(95%CI)						Effect model	Egger test P vaule	AMSTAR-2	Grade
					Sensitivity	Specificity	DOR	AUC	PLR	NLR				
Sepsis	Hou, 2015	Neonate	698/6	serum	0.77 (0.73, 0.81)	0.91 (0.86, 0.94)	NR	NR	7.78 (4.26, 14.22)	0.25 (0.16, 0.39)	Random	NR	Critically Low	Low
Sepsis	Hou, 2015	Adult	613/3	serum	0.85 (0.80, 0.88)	0.62 (0.55, 0.68)	NR	NR	2.36 (1.16, 4.80)	0.33 (0.23, 0.47)	Random	NR	Critically Low	Low
Sepsis	Liu, 2016	Patients with SIRS	3450/22	NR,138 (75, 220)[&]	0.72 (0.63, 0.80)	0.73 (0.67, 0.79)	NR	0.79 (0.75, 0.82)	3.41	0.60	Mixed	0.7	Low	Low
Sepsis	Daniel, 2019	Critically ill adults aged 18 years or older under suspicion of sepsis	4192/23	Plasma	0.66 (0.60, 0.72)	0.74	NR	NR	NR	NR	NR	NR	Low	Low
Sepsis	Cong, 2021	Adult patients	NR/16	Blood	0.72 (0.65, 0.78)	0.70 (0.62, 0.76)	6.00 (4.00, 9.00)	0.77 (0.73, 0.80)	2.40 (1.90, 3.00)	0.40 (0.32, 0.51)	Random	0.607	Critically Low	Very Low
Bacterial meningitis	Yao, 2015	NR	825/9	Cerebrospinal fluid	0.91 (0.81, 0.96)	0.93 (0.84, 0.97)	129.76 (41.48, 405.88)	0.97 (0.95, 0.98)	12.38 (5.42, 28.29)	0.10 (0.04, 0.21)	NR	0.21	Critically Low	Moderate
Infection	Iwase, 2019	Critically ill patients with suspected infection	527/6	Blood, 176*	0.73 (0.61,0.82)	0.76 (0.61, 0.87)	2.31 (1.20,3.48)	0.81 (0.78, 0.85)	NR	NR	Random	NR	Critically Low	Very Low
Bacterial infection	Wu, 2016	Cirrhotic patients	741/6	Serum	0.85 (0.64, 0.94)	0.91 (0.80, 0.96))	52.89 (15.21, 183.86)	0.94 (0.92, 0.96)	8.99 (4.13, 19.55)	0.17 (0.07, 0.43)	Mixed	0.481	Critically Low	Low
Serious bacterial infection	Wu, 2015	Children and adult with febrile neutropenia	314/5	Blood	0.74 (0.65, 0.81)	0.80 (0.71, 0.87)	10.00 (5.50, 18.00)	0.76 (0.72, 0.79)	3.68 (2.41, 5.60)	0.33 (0.23, 0.46)	NR	0.508	Critically Low	Very Low
Febrile urinary tract infection	Hosseini, 2022	Children and adolescents	NR/3	Serum, urine	0.77 (0.69, 0.83)	0.87 (0.80, 0.92)	22.00 [12,41]	NR	5.90 (3.8, 9.2)	0.27 (0.20, 0.36)	NR	0.59	Critically Low	Very Low
Gram-negative bloodstream infection	Lai, 2020	Patients with suspected bloodstream infection	3455/5	Blood	0.76 (0.58, 0.88)	0.79 (0.71, 0.85)	11.86 (3.95, 35.64)	0.83 (0.80, 0.86)	NR	NR	Mixed	NR	Critically Low	Low
Gastric cancer	Wang, 2021	NR	794/4	Serum	0.80 (0.57, 0.92)	0.86 (0.74, 0.94)	24.58 (14.14, 42.73)	0.90 (0.87, 0.93)	5.76 (3.49, 9.49)	0.23 (0.11, 0.51)	Mixed	NR	Critically Low	Very Low
Ovarian cancer	Amer, 2021	NR	NR/5	Peritoneal fluid	0.84 (0.71, 0.92)	0.74 (0.65, 0.83)	NR	NR	NR	NR	Random	NR	Critically Low	Moderate
Ovarian cancer	Amer, 2021	NR	NR/7	Serum/plasma	0.767 (0.71, 0.92)	0.72 (0.64, 0.79)	NR	NR	NR	NR	Random	NR	Critically Low	Moderate
Colorectal cancer	Xu, 2016	Patients with or without colorectal cancer	654/7	Serum	0.72 (0.46, 0.88)	0.74 (0.56, 0.86)	7.69 (4.40, 13.40)	0.79 (0.75, 0.82)	2.33 (1.74, 3.14)	0.33 (0.09, 1.25)	Random	>0.05	Low	Moderate

IL-6, interleukin-6; DOR, diagnostic odds ratio; AUC, area under the curve; PLR, positive likelihood ratio; NLR, negative likelihood ratio; AMSTAR-2, Assessing the Methodological Quality of Systematic Reviews-2; NR, Not reported; SIRS, systemic inflammatory response syndrome; &, data reported as median (25% percentiles, 75% percentiles); *, data reported as median.

specificity, DOR, PLR, and NLR of serum and urine IL-6 were 0.77 (95% CI: 0.69, 0.83), 0.87 (95% CI: 0.80, 0.92), 22.00 (95% CI: 12.00, 41.00), 5.90 (95% CI: 3.80, 9.20), and 0.27 (95% CI: 0.20, 0.36), respectively [14]. The sensitivity, specificity, DOR, and AUC of IL-6 in blood for gram-negative bloodstream infections were 0.76 (95% CI 0.58, 0.88), 0.79 (95% CI: 0.71, 0.85), 11.86 (95% CI 3.95, 35.64), and 0.83 (95% CI 0.80, 0.86), respectively [12]. Finally, the sensitivity, specificity, DOR, and AUC of serum IL-6 for the occurrence of infection in critically ill patients with suspected infection were 0.73 (95% CI: 0.61, 0.82), 0.76 (95% CI: 0.61, 0.87), 2.31 (95% CI: 1.20, 3.48), and 0.81 (95% CI: 0.78, 0.85), respectively [41].

3.3. Neoplasms

Tumors identified in this umbrella review included gastric, ovarian, and colorectal cancers. The sensitivity, specificity, DOR, AUC, PLR, and NLR of serum IL-6 for gastric cancer were 0.80 (95% CI: 0.57, 0.92), 0.86 (95% CI: 0.74, 0.94), 24.58 (95% CI: 14.14, 24.73), 0.90 (95% CI: 0.87, 0.93), 5.76 (95% CI: 3.49, 9.49), and 0.23 (95% CI: 0.11, 0.51), respectively [42]. In colorectal cancer, the sensitivity, specificity DOR, AUC, PLR, and NLR of serum IL-6 were 0.72 (95% CI: 0.46, 0.88), 0.74 (95% CI: 0.56, 0.86), 7.69 (95% CI: 4.40, 13.40), 0.79 (95% CI: 0.75, 0.82), 2.33 (95% CI: 1.74, 3.14), and 0.33 (95% CI: 0.09, 1.25), respectively [43]. The sensitivity and specificity of ascites IL-6 for ovarian cancer were 0.84 (95% CI: 0.71, 0.919) and 0.74(95% CI: 0.65, 0.83), respectively [44]. Also in ovarian cancer, the sensitivity and specificity of IL-6 in serum or plasma were 0.77 (95% CI: 0.71, 0.92) and 0.72 (95% CI: 0.64, 0.79), respectively [44].

3.4. Blood system

Results of diagnostic accuracy indicators for IL-6 (meta-analyses conducted without infectious diseases or cancer) are presented in Supplementary Table S3. Only one disease of IL-6 in the blood or hematopoietic organs was obtained: febrile neutropenia. In the group of children and young adults with cancer, the sensitivity and specificity of IL-6 with a cut-off value of >235 pg/ml for the adverse outcome documented infection in febrile neutropenia were 0.68 (95% CI: 0.15, 0.96) and 0.94 (95% CI: 0.84, 0.98), respectively [45]. In contrast, in the adverse outcome gram-negative bacteremia, utilizing a cut-off value of >235 pg/ml, the sensitivity and specificity of IL-6 were 0.78 (95% CI: 0.57, 0.91) and 0.96 (95% CI: 0.92, 0.99), respectively [45].

3.5. Respiratory system

IL-6 was detected in the respiratory system in a total of three diseases: acute respiratory distress syndrome (ARDS), tuberculous pleural effusion (TPE), and coronavirus disease 2019 (COVID-19). The DOR of IL-6 for adult ARDS was 2.37 (95% CI: 1.32, 4.26) [20]. In patients with pleural effusion, the sensitivity, specificity, DOR, PLR, and NLR of IL-6 for TPE were 0.87 (95% CI: 0.70, 0.95), 0.76 (95% CI: 0.72, 0.80), 22.09 (95% CI: 7.63, 63.91), 3.69 (95% CI: 3.04, 4.48), and 0.17 (95% CI: 0.06, 0.43), respectively [46]. Additionally, in COVID-19 patients, the sensitivity, specificity, and AUC for differentiating severe from non-severe were 0.67, 0.89, and 0.82 (95% CI: 0.68, 0.96), respectively [47].

3.6. Digestive system

The sensitivity and specificity of salivary IL-6 for the detection of periodontitis were 0.72 and 0.73, respectively [48]. In patients with acute pancreatitis, the sensitivity, specificity, DOR, AUC, PLR, and NLR of IL-6 were 0.91 (95% CI: 0.78, 0.97), 0.79 (95% CI: 0.72, 0.85), 23.35 (95% CI: 9.34, 58.37), 0.87 (95% CI: 0.84, 0.90), 3.72 (95% CI: 2.70, 5.13), and 0.20 (95% CI: 0.11, 0.37), respectively, for the discrimination between severe and non-severe cases on the first day [19]. Similarly, on the second day, the sensitivity, specificity, DOR, AUC, PLR, and NLR of IL-6 were 0.80 (95% CI: 0.59, 0.92), 0.86 (95% CI: 0.69, 0.95), 25.24 (95% CI: 7.75, 82.27), 0.90 (95% CI: 0.87, 0.93), 4.62 (95% CI: 2.17, 9.82), and 0.32 (95% CI: 0.17, 0.60), respectively. The data on the third day were similar to those of the previous day [19]. Moreover, IL-6 demonstrated a sensitivity of 0.73 (95% CI: 0.63, 0.86), specificity of 0.75 (95% CI: 0.61, 0.83), and DOR of 9.32 (95% CI: 3.88, 20.32) for the prediction of persistent organ failure [49].

3.7. Genitourinary system

IL-6 was detected in the genitourinary system for a total of three diseases: acute kidney injury (AKI), ovarian torsion, and endometriosis. The diagnostic accuracy of serum IL-6 between 75 and 188 pg/mg for AKI in children and adolescents was found to be 0.58 (95% CI: 0.37, 0.76), 0.87 (95% CI: 0.66, 0.96), 9.00 (95% CI: 4.00, 20.00), and 0.79 (95% CI: 0.75, 0.83) for sensitivity, specificity, DOR, and AUC(18). In children younger than 18 who underwent cardiac surgery, the sensitivity, specificity, DOR, AUC, PLR, and NLR of IL-6 were 0.52 (95% CI: 0.34, 0.69), 0.88 (95% CI: 0.66, 0.97), 8.26 (95% CI: 3.33, 19.80), 0.71 (95% CI: 0.63, 0.79), 4.48 (95% CI: 1.74, 11.5), and 0.54 (95% CI: 0.41, 0.71), respectively [50]. Moreover, the sensitivity, specificity, DOR, PLR, and NLR of serum IL-6 for ovarian torsion were 0.86 (95% CI: 0.65, 0.95), 0.84 (95% CI: 0.71, 0.92), 48.8 (95% CI: 8.00, 295.80), 5.60 (95% CI: 2.70, 11.30), and 0.18 (95% CI: 0.07, 0.48), respectively [51]. The sensitivity and specificity of blood IL-6 for endometriosis in women of childbearing age were 0.63 (95% CI: 0.52, 0.75) and 0.69 (95% CI: 0.57, 0.82), respectively [52].

3.8. Perinatal disease

The sensitivity, specificity, DOR, AUC, PLR, and NLR of IL-6 in the diagnosis of neonatal sepsis were 0.79 (95% CI: 0.74, 0.83), 0.84 (95% CI: 0.81, 0.87), 20.74 (95% CI: 10.83, 39.70), 0.89 (95% CI: 0.84, 0.94), 4.55 (95% CI: 3.27, 6.32), and 0.26 (95% CI: 0.18, 0.36), respectively [53]. In neonates with suspected sepsis but without other serious diseases, the sensitivity, specificity, DOR, AUC, PLR, and NLR of IL-6 for early neonatal sepsis were 0.82 (95% CI: 0.77, 0.86), 0.88 (95% CI: 0.83, 0.92), 29.54 (95% CI: 18.56, 47.04), 0.92 (95% CI: 0.89, 0.94), 7.03 (95% CI: 4.81, 10.26), and 0.20 (95% CI: 0.15, 0.26), respectively [54]. The sensitivity, specificity, DOR, AUC, PLR, and NLR of IL-6 in cord blood for early neonatal sepsis were 0.91 (95% CI: 0.82, 0.96), 0.90 (95% CI: 0.86, 0.93), 117.00 (95% CI: 21.90, 633.00), 0.96 (95% CI: 0.67, 0.99), 9.47 (95% CI: 3.86, 23.30), and 0.10 (95% CI: 0.05, 0.21), respectively [55]. The corresponding data of maternal serum IL-6 were relatively low [55]. In neonates with premature rupture of membranes, the sensitivity, specificity, DOR, AUC, PLR, and NLR of IL-6 for neonatal sepsis were 0.87 (95% CI: 0.77, 0.86), 0.88 (95% CI: 0.83, 0.92), 79.26 (95% CI: 23.42, 268.26), 0.95, 9.94 (95% CI: 4.27, 23.15), and 0.14 (95% CI: 0.06, 0.32), respectively [56].

3.9. The consequences of injury, poisoning or other external causes

The sensitivity, specificity, and AUC of synovial IL-6 as a diagnostic biomarker for periprosthetic joint infection (PJI) in patients who underwent arthroplasty were found to be 0.76 (95% CI: 0.65, 0.84), 0.91 (95% CI: 0.88, 0.94), and 0.93, respectively [57]. In patients undergoing hip and/or knee replacement, the sensitivity, specificity, DOR, AUC, PLR, and NLR of serum IL-6 for PJI were 0.76 (95% CI: 0.69, 0.81), 0.88 (95% CI: 0.82, 0.92), 22.00 (95% CI: 14.00, 36.00), 0.88 (95% CI: 0.85, 0.91), 6.20 (95% CI: 4.30, 9.00), and 0.28 (95% CI: 0.22, 0.35), respectively [58]. The data for the corresponding synovial IL-6 for PJI were 0.87 (95% CI: 0.75, 0.93), 0.90 (95% CI: 0.85, 0.93), 57.00 (95% CI: 21.00, 156.00), 0.94 (95% CI: 0.92, 0.96), 8.50 (95% CI: 5.30, 13.60), and 0.15 (95% CI: 0.08, 0.29), respectively [58]. In adults and children (<18 years) who underwent major abdominal gastrointestinal (GI) and hepatobiliary (HPB) surgeries, the sensitivity, specificity, and DOR of IL-6 for PJI were 0.84 (95% CI: 0.72, 0.92), 0.76 (95% CI: 0.68, 0.84), and 17.36 (95% CI: 7.10, 42.43), respectively [59]. The sensitivity, specificity, DOR, PLR, and NLR of IL-6 for persistent infection or treatment failure after secondary revision hip or knee replacement were 0.52 (95% CI: 0.33, 0.70), 0.92 (95% CI: 0.85, 0.96), 16.03 (95% CI: 1.01, 254.34), 7.90 (95% CI: 0.86, 72.61), and 0.52 (95% CI: 0.25, 1.10), respectively [60].

3.10. Mortality

In patients with COVID-19, the sensitivity, specificity, DOR, AUC, PLR, and NLR of IL-6 for mortality diagnosis was observed to be 0.15 (95% CI: 0.13, 0.17), 0.73 (95% CI: 0.65, 0.79), 1.28 (95% CI: 0.68, 2.42), 0.53 (95% CI: 0.45, 0.61), 1.16 (95% CI: 0.72, 1.18), and 0.93 (95% CI: 0.82, 1.05), respectively [61].

3.11. Heterogeneity

Heterogeneity in diagnostic accuracy indicators was reported in 44.1% of the 34 meta-analyses. Supplementary Table S4 contains the I^2 and p value of specific study data. DOR showed extremely high heterogeneity ($I^2 > 75\%$) in three studies, while moderate levels or higher heterogeneity ($I^2 > 50\%$) was evident in seven and nine meta-analyses for sensitivity and specificity, respectively. Furthermore, seven meta-analyses reported heterogeneity in AUC or PLR, as well as NLR.

3.12. Publication bias

16 meta-analyses reported no publication bias, and 11 of them provided accurate Egger's test values (Table 2). Statistically significant publication bias was observed in one study on AKI ($p < 0.001$) [18]. The remaining meta-analyses did not examine or report publication bias for specific outcomes, perhaps due to the limited number of studies included in the pooled analysis.

3.13. AMSTAR-2 and GRADE classification

Supplementary Table S5 presents the AMSTAR-2 results. Only 14.71% and 5.88% of articles received "Low" or "High" ratings, while the vast majority (79.41%) were rated as "Critically low" rating. This was mainly due to the inability to ascertain whether the research technique was established before implementation and the failure to provide a list of excluded literature, which are two essential components of AMSTAR-2. In the GRADE classification, 38.24% of the studies were categorized as "Very low", followed by 38.24% categorized as "Low", while 23.53% were deemed "Moderate", and no study received a "High" rating. Detailed GRADE scores for each outcome are provided in Supplementary Table S6.

4. Discussion

4.1. Main findings and possible explanations

We conducted an extensive review of the available evidence on the diagnostic accuracy of IL-6 across a wide range of disorders by synthesizing systematic reviews and meta-analyses. Finally, we obtained 34 meta-analyses from 3024 unique articles, covering 9

distinct diseases categorized by ICD-11. Meta-analyses were selected by excluding studies that received "Very Low" or "Critically Low" ratings in the quality assessment process, resulting in a total of 6 meta-analyses. The diseases involved sepsis, colorectal cancer, TPE, endometriosis, etc. Using the aforementioned diseases as a foundation, the ability of IL-6 to accurately diagnose TPE and endometriosis appears to be notably robust.

Our umbrella review provided strong evidence of the diagnostic accuracy of IL-6 in infectious and traumatic diseases, particularly in cases of sepsis. The diagnostic ability of IL-6 in infectious and traumatic diseases can be explained by the following mechanisms. In 1994, the first IL-6-deficient mice illustrated compromised innate and adaptive immunity in response to bacterial, parasitic, and viral infections, highlighting a crucial connection between IL-6 and the immune system [62]. In infectious lesions, IL-6 is produced as a soluble mediator stimulated by Toll-like receptors (TLRs) on macrophages as well as monocytes, signaling between cells and leading to the secretion of various chemokines [63]. Monocytes and/or macrophages are attracted to local lesions by inflammatory signals, which spread throughout the body and trigger the host's defense against infection, trauma, and other emergencies [64]. One of the major biological functions of IL-6 is its significant role in the production and secretion of acute-phase proteins. After the rapid induction of the acute-phase response that accompanies inflammation related to injuries, infections, and other stimuli, the IL-6-driven synthesis of acute-phase proteins in the liver assumes an essential role in immune defense against bacterial pathogens [65]. Moreover, the IL-6R, TLR4 signaling pathway, and complement component C5a receptor 1 (C5AR1) exhibit intricate interactions involving NF-κb and signal transducer and activator of transcription 3 (STAT3) and have been recognized as key regulators in the management of sepsis and bacteremia [66,67]. Furthermore, IL-6 enhances the expression of adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), in inflammatory sites and endothelial cells, consequently promoting angiogenesis [68]. As a clinically serious condition, sepsis can have grave consequences, including irreversible harm to the patient and even death due to the misdiagnosis of sepsis [69]. According to the current international definition, sepsis arises from impaired host defense against infection, resulting in the production of multiple cytokines, notably IL-6, via pathway-related molecular patterns [70]. Our study evaluated the diagnostic ability of IL-6 in sepsis in four distinct cohorts, and the results demonstrated that IL-6 in serum or plasma exhibits good levels of both sensitivity and specificity. Previous research has firmly established that concentrations of IL-6 are significantly elevated in the serum of septic patients and exhibit a robust association with the occurrence of shock as well as mortality outcomes [71]. Reinhart et al. observed a mortality rate of 56% in septic individuals with IL-6 levels exceeding 1000 pg/ml, whereas it declined to 40% for those below this threshold [72]. Therefore, taking the pathophysiology of sepsis into account, our findings suggest that measuring levels of IL-6 in the blood may aid in identifying sepsis and serve as a potential diagnostic biomarker for sepsis.

The use of cerebrospinal fluid IL-6 for diagnosing bacterial meningitis and synovial fluid IL-6 for diagnosing PJI exhibited higher accuracy compared to other diseases, as indicated by this umbrella review. Microglia and meningeal macrophages produce various proinflammatory cytokines, including IL-6, that attract leukocytes to the subarachnoid space and contribute to the development of bacterial meningitis [73]. PJI typically arises in the vicinity of diseased joints, and systemic damage is thought to occur only when synovial fluid becomes oversaturated with planktonic microorganisms [74]. Our perspective is supported by Ahmad et al., who suggested that the most effective diagnostic tests for ruling out PJI include synovial fluid cytology, serum IL-6 and CRP [75]. Mihalič et al. investigated a total of 49 joints in 48 individuals with PJI and suggested that synovial fluid IL-6 was not superior to white blood cell (WBC) count in synovial fluid and percentage of polymorphonuclear cells (%PMN) in detecting of PJI [24]. The limited sample size, combined with the potential risk of bias due to inconsistent criteria for defining PJI in relation to the indicators analyzed alongside IL-6, could potentially compromise the validity of the findings. In addition to conditions other than PJI, Qi et al. studied postoperative patients with colorectal cancer and found that peritoneal IL-6 levels were significantly higher in the colorectal anastomotic leakage (CAL) group 1–3 days postoperatively compared to the non-CAL group ($P = 0.0006$, 0.0002, 0.002), suggesting that peritoneal IL-6 levels might be used as a diagnostic indicator of CAL after colorectal surgery [76]. While our umbrella review covered the majority of infectious and injurious diseases (55.9%), only Yao et al. for bacterial meningitis and Shahkar et al. and Qiu et al. for neonatal sepsis received a "Moderate" rating in GRADE; all other meta-analyses were judged as "Low" or "Very low" in both GRADE and AMSTAR-2 [40,53,56]. Therefore, despite the relatively superior diagnostic capability of IL-6 in bacterial meningitis and PJI, it is noted that the methodological evaluations of these studies were not deemed satisfactory. Thus, caution must be exercised when interpreting the diagnostic accuracy of IL-6 in the aforementioned diseases.

Numerous research endeavors have revealed elevated concentrations of IL-6 in individuals with cancer, demonstrating its interdependency with the modulation of neoplasm growth and differentiation [77–79]. Our umbrella review uncovered that IL-6 exhibits robust diagnostic accuracy in tumors, especially in colorectal, ovarian, and gastric cancers. The role of IL-6 in tumors can be attributed to several mechanisms. In the tumor microenvironment, stromal cells and tumor cells produce IL-6, which subsequently interacts with its membrane receptor complex consisting of ligand binding (gp80) and signal transduction subunits (gp130) [80,81]. As an NF-κb-dependent tumor-promoting cytokine, IL-6 stimulates cancer cell growth through various signaling pathways, such as STAT3 activation to upregulate the levels of cell cycle proteins D1, D2, and B1, the elevation of telomerase activity to prevent cellular senescence, modulation of fructose metabolism, and activation of ERK1/2 and Rho proteins, thereby promoting tumor growth [82,83]. Additionally, IL-6 helps tumor cells evade stress and cytotoxic drug-induced cell death, promotes tumor angiogenesis and lymphangiogenesis, and induces epithelial–mesenchymal transition (EMT) to drive tumor growth and metastasis [84,85]. In our umbrella review, IL-6's accuracy in diagnosing tumors demonstrated satisfactory results, with all sensitivities and specificities measuring above 0.70. Other studies also supported the superiority of IL-6 in tumor diagnosis. Recent research findings have shown that the joint detection of IL-6 and free prostatic-specific antigen (fPSA)/total prostatic-specific antigen (tPSA) can enhance the diagnostic accuracy of prostate cancer (PCa), and it is suggested that IL-6 could serve as a potential risk factor for PCa [86]. Elmahgoub et al. proposed IL-6 as a salivary tool suitable for the early identification of oral cancer, while Aalten et al. found that IL-6 played a comparable role to alpha fetoprotein (AFP) in screening for hepatocellular carcinoma ($p = 0.66$) [87,88]. Despite the outstanding diagnostic accuracy of IL-6 in

ovarian cancer, as confirmed by our umbrella review, Fahmi et al.'s investigations were hindered by the small number of studies included, resulting in insufficient evidence to suggest that IL-6 assessed in ascites, tissue, and blood serves as a prognostic biomarker for epithelial ovarian cancer (EOC) [89]. Therefore, further research is imperative to elucidate the potential of IL-6 as a biomarker in malignancy, including its applicability in subpathological cancer variants.

In respiratory diseases, IL-6 demonstrated favorable diagnostic accuracy in ARDS, COVID-19, and TPE. Damaged pulmonary cells can emit pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), which stimulate alveolar macrophages and trigger the production of the proinflammatory cytokine IL-6 [90,91]. In patients with COVID-19 who develops ARDS, the concentrations of IL-6 and tumor necrosis factor (TNF) rise dramatically, leading to a cytokine storm and subsequent immune system overactivation [92]. In the previous century, Yokoyama et al. found that pleural IL-6 levels were helpful for differential diagnosis [93]. Now, studies have provided evidence supporting pleural effusion IL-6 levels as highly sensitive marker for differentiating between exudate and transudate fluid [94]. Furthermore, researchers have investigated the role of IL-6 in the differential diagnosis of TPE. Their findings indicate that IL-6 levels in the pleural effusion of patients with tuberculous empyema were lower than those in patients with tuberculous pleurisy, suggesting a potential indication for surgical intervention [95]. In addition, Ferreiro et al. used a predictive model that included IL-6, CRP, leukocytes, and neutrophil percentages. They demonstrated that the inclusion of IL-6 in the model significantly improved the accuracy in detecting pleural effusions extending to TPE, surpassing the predictive ability of a model excluding IL-6 [96]. Similarly, Zeng et al.'s meta-analysis of interleukin-based diagnostic power for TPE confirmed the good diagnostic accuracy of IL-6, as indicated by the pooled results from six studies [97]. Outside the scope of our umbrella review, the diagnostic capability of IL-6 in respiratory ailments has also garnered the interest of other researchers. Elshazli and colleagues have suggested a noteworthy correlation between increased concentrations of IL-6-related anti-inflammatory cytokines in individuals afflicted with severe COVID-19 and mortality(OR = 13.87) [98]. Similarly, Melo et al. have proposed that heightened concentrations of IL-6 and ferritin may act as cardinal biomarkers for systemic inflammation and adverse prognosis in COVID-19, notably among elderly patients and those with comorbidities [99]. Nevertheless, despite these promising findings, the efficacy of IL-6 as a measure of treatment response in COVID-19 remains unverified [21]. Furthermore, the current evidence is inadequate to substantiate the diagnostic efficacy of IL-6 in other respiratory ailments such as asthma or obstructive sleep apnea (OSA), which require further exploration [22,100].

IL-6 has also demonstrated encouraging results in digestive diseases, with sensitivity and specificity values exceeding 0.70. Furthermore, numerous clinical studies have consistently validated the significant elevation of IL-6 levels in pancreatitis. In patients with pancreatitis, IL-6 levels contemporaneously mirror disease progression, particularly in those who develop respiratory, circulatory, and renal failure, as well as MOF [101,102]. Acute pancreatitis typically presents as localized inflammation accompanied by leukocyte aggregation. IL-6 exerts its effects through the signal transducer gp130, which mediates the activation of MAPK [103]. The activation of immune cells and the secretion of proinflammatory mediators, such as IL-6 from pancreatic follicular cells, are now recognized as vital events determining the ultimate severity of the illness, even though the precise pathophysiological mechanisms are not entirely understood [104]. It's noteworthy that none of the meta-analyses on digestive disorders included in our study reported publication bias, so the results should be interpreted cautiously and considered in conjunction with an extensive body of clinical research to mitigate potential sources of bias.

Our umbrella review revealed significant associations between IL-6 and genitourinary disorders, including AKI, endometriosis, and ovarian torsion. Renal injury triggers a surge in IL-6 levels, promotes neutrophil infiltration, releases IL-6R, and activates STAT3 via *trans*-signaling to mitigate the progression of injury [105]. In endometriosis, dysregulation of IL-6 and its receptors has emerged as crucial for its pathogenesis, and may promote the expression of angiogenic factors in neutrophils to participate in the formation of its lesions [106]. The heightened levels of sIL-6R have amplified the biological function of IL-6, thereby exacerbating the disease [107]. Wang et al. observed a significant elevation in IL-6 levels among patients with endometriosis, and the ROC curve combined with miR-17 optimized the diagnostic power (AUC: 0.81) [108]. A recent cross-sectional study unveiled a significant elevation of IL-6 levels in the follicular fluid of endometriosis patients [109]. Furthermore, it was found that the level of IL-6 in stage III/IV patients was higher than that in stage I/II patients, and it was strongly correlated with the severity of the endometriosis [110]. A prospective study of IL-6 in seminal plasma from fertile and infertile men yielded similar IL-6 levels in both groups. However, a further subgroup, the male accessory gland infection (MAGI) group, exhibited significantly higher mean levels of IL-6 in the seminal plasma [111]. Amirian et al. discovered a significant elevation of serum IL-6 levels in pregnant women with gestational diabetes mellitus (GDM) compared to normal pregnant women. They proposed that serum IL-6 levels might replace the oral glucose tolerance test (OGTT) as a novel diagnostic biomarker for GDM [112]. Nevertheless, we must acknowledge the significant publication bias detected in the study by Yousefifard et al.. In addition, the majority of genitourinary meta-analyses included original studies on IL-6 and had small population sizes, which may result in a high risk of bias in terms of precision.

4.2. Strengths and limitations

Our umbrella review provides a comprehensive summary of the existing evidence regarding the diagnostic accuracy of cytokine IL-6 in various diseases, drawing from published meta-analyses. The methodology employed for this review involved a rigorous and systematic approach, including a comprehensive search of four databases, independent study selection, and data collection by two reviewers. Furthermore, we utilized AMSTAR-2 to evaluate the quality of the included meta-analyses, and we classified the evidence according to the GRADE classification. While most meta-analyses tested for potential publication bias, only the one on AKI yielded statistically significant evidence of bias.

Nonetheless, we must acknowledge several potential limitations in this study. First, it is worth acknowledging that certain diseases

not investigated in previous meta-analyses may have been disregarded, and our selection criteria could have led to the exclusion of certain studies. Although we included numerous studies overall, the number of studies incorporated in the meta-analysis for some diseases was low. Furthermore, this comprehensive review was limited to published articles only, which could result in the omission of unpublished or recently published meta-analyses, potentially introducing publication bias. Second, most meta-analyses had fewer than 10 studies, making it difficult to identify publication bias using Egger's test. Third, it is noteworthy that the majority of the evidence assessed through AMSTAR-2 and GRADE received low or very low quality ratings, and there was no statistical correlation between the two rating domains. Finally, the diagnostic accuracy of IL-6 in disease diagnosis may be affected by several confounding factors, including the reference standard, cut-off value, sample type, and measurement method. However, only a few investigations included in this umbrella review undertook subgroup analyses or made appropriate adjustments for potential confounding factors. Hence, it is not surprising that a substantial degree of heterogeneity exists in certain research studies.

5. Conclusion

The diagnostic accuracy of IL-6 across various disease types has been extensively evaluated in numerous meta-analyses. Our umbrella review covered a total of 9 categories of diseases classified according to ICD-11, including infectious, respiratory, gastrointestinal, genitourinary, blood, and traumatic diseases, as well as oncology. To ensure the quality of the meta-analyses, studies that received "Very low" or "Critically Low" ratings during the quality assessment process were excluded, resulting in a final count of 6 meta-analyses. The diseases involved were sepsis, colorectal cancer, TPE, endometriosis, and others. Based on the aforementioned diseases, the potential of IL-6 in accurately diagnosing TPE and endometriosis is relatively high. IL-6 levels have the potential to become a potent diagnostic biomarker in the future, serving as an auxiliary tool for disease-targeted therapy and prognosis prediction. Nonetheless, given the potential risks of bias, more large-scale prospective investigations are indispensable to establish the complete applicability of IL-6 as a biomarker in disease diagnosis.

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Data availability statement

The authors of this article will make available the raw data that supports the conclusions presented herein. No data related to our study has been deposited into a publicly available repository. Data related to our study are included in the article/supplementary materials and in the cited references.

Ethics approval and consent to participate

Review and/or approval by an ethics committee and informed consent were not needed for this study because it was a reanalysis of published papers, and no additional human subjects were involved.

CRediT authorship contribution statement

Zeyu Han: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Jin Li:** Visualization, Validation, Investigation, Formal analysis, Data curation. **Xianyanling Yi:** Visualization, Validation, Investigation, Formal analysis, Data curation. **Tianyi Zhang:** Supervision, Investigation, Formal analysis. **Dazhou Liao:** Methodology, Investigation, Formal analysis. **Jia You:** Visualization, Validation, Investigation. **Jianzhong Ai:** Writing – review & editing, Writing – original draft, Validation, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27769.

Abbreviations

IL-6	interleukin-6
ELISA	nzyme-linked immunosorbent assay
RIA	radioimmunoassay

FIA fluorometric immunoassay
PCT procalcitonin
CRP C-reactive protein
PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analysis
AMSTAR-2 Assessing the Methodological Quality of Systematic Reviews-2
DOR diagnostic odds ratio
AUC area under the curve
NLR negative likelihood ratio
PLR positive likelihood ratio
GRADE Grading of Recommendations, Assessment, Development and Evaluation
CIs confidence intervals
ICD-11 International Classification of Diseases-11
SIRS systemic inflammatory response syndrome
CSF cerebral spinal fluid
ARDS acute respiratory distress syndrome
COVID-19 coronavirus disease 2019
AKI acute kidney injury
PJI periprosthetic joint infection
GI gastrointestinal
HPB hepatobiliary
TLR4 toll-like receptor 4
C5AR1 C5a receptor 1
STAT3 signal transducer and activator of transcription 3
ICAM-1 intercellular cell adhesion molecule-1
VCAM-1 vascular cell adhesion molecule-1
TJA total joint arthroplasty
THA, TKA total hip or knee arthroplasty
WBC white blood cell
%PMN percentage of polymorphonuclear cells
CAL colorectal anastomotic leakage
EMT epithelial–mesenchymal transition
fPSA free prostatic-specific antigen
tPSA total prostatic-specific antigen
PCa prostate cancer
AFP alpha fetoprotein
EOC epithelial ovarian cancer
DAMPs danger-associated molecular patterns
PAMPs pathogen-associated molecular patterns
TNF tumor necrosis factor
OSA obstructive sleep apnea
MAGI male accessory gland infection
GDM gestaional diabetes mellitus
OGTT oral glucose tolerance test

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