Interleukin-6 as a Risk and Prognostic Biomarker in Gastric Cancer: A Systematic Review and Meta-Analysis

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Abstract: *Introduction*: Gastric cancer (GC) is one of the leading causes of cancer-related mortality worldwide. Interleukin-6 (IL-6) has been implicated in its pathogenesis and progression, but its role as a prognostic biomarker remains controversial.

Objective: To evaluate the association between serum IL-6 levels and the risk or prognosis in patients with GC through a systematic review (SR) and meta-analysis.

Methods: A SR was conducted in PubMed, Scopus, EMBASE, and Web of Science. Inclusion criteria were studies in adults that assessed the risk or prognostic capacity of IL-6 in GC, with quantifiable association measures such as hazard ratio (HR) or relative risk (RR). Studies focusing on specific populations or lacking survival data were excluded. Methodological quality was assessed using the Newcastle-Ottawa Scale. A meta-analysis using a DerSimonian and Laird random-effects model was performed.

Results: Four studies (two case-control and two retrospective cohort studies) involving a total of 1,007 patients were included. The meta-analysis of cohort studies showed a significant association between elevated IL-6 levels and poorer prognosis (combined HR = 1.71, 95% CI: 1.21-2.43, p = 0.002). Heterogeneity was low (I^2 = 0%).

Discussion: The results suggest that elevated serum IL-6 is associated with a worse prognosis in GC. However, variability in IL-6 cut-off points and methodological differences between studies limit the generalizability of these findings. Larger, prospective, and standardized studies are needed to validate IL-6's role as a prognostic biomarker in GC and to establish clinically relevant cut-off points.

Keywords: Interleukin-6, Stomach Neoplasms, systematic review, meta-analysis (Source: MeSH).

INTRODUCTION

Gastric cancer (GC) represents a significant challenge to global public health, ranking fifth in frequency among all cancer types and as the fourth leading cause of cancer-related death worldwide [1,2]. Its incidence varies geographically, with a higher prevalence in East Asia and Europe. Moreover, a concerning trend has emerged, showing an increase in incidence among individuals under 50 years of age [3]. Given its substantial impact on global health, it is crucial to emphasize the importance of accurate and early diagnosis of GC [4].

Currently, the diagnostic arsenal for GC includes various tools such as endoscopy, serum markers, and biopsy. Among the serum markers, carbohydrate antigen 19-9 has been used specifically for GC. However, its diagnostic efficacy is limited by low sensitivity and specificity [5,6], underscoring the need to identify and validate new biomarkers that can enhance early detection and prognosis of GC.

In this context, IL-6 has emerged as a promising candidate. IL-6 is a glycoprotein mainly produced by monocytes and macrophages, playing crucial roles in various physiological processes, including reproduce-tion, immunity, metabolism, and inflammation [7]. Recent research has established a significant link between IL-6 and GC, suggesting that elevated expression of this molecule is associated with a chronic inflammatory state that could promote gastric carcinogenesis progression or serve as a prognostic indicator of survival [8-10].

Therefore, considering the growing evidence on these variables, the need for a systematic and comprehensive evaluation of the existing literature becomes evident. Thus, the aim of this study is to

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conduct a systematic review (SR) and meta-analysis to comprehensively evaluate both the risk and prognostic capacity of IL-6 in the context of GC.

METHODS

Design

This study was designed as a SR with meta-analysis, focusing on case-control and/or cohort studies that investigated the relationship between IL-6 and GC. The methodology strictly adhered to the guidelines set forth by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [11], ensuring transparency and reproducibility in our review process.

Search Strategy

An exhaustive and systematic exploration was conducted across four highly relevant academic databases: Web of Science, Scopus, Embase, and PubMed. The search period extended from March 18 to April 14, 2024, ensuring the inclusion of the most recent literature in the field. The key terms used in our search strategy were "Interleukin 6" and "Gastric cancer". These terms were combined using Boolean operators and adapted to the specificities of each database to optimize the sensitivity and specificity of the search. The detailed search formula for each database is available in Supplementary Appendix 1, allowing for the replicability of our strategy.

Selection Criteria

The inclusion of studies in our review was based on specific criteria designed to ensure the relevance and comparability of the data. Studies that specifically evaluated the prognostic or risk capacity of IL-6 in relation to GC and included patients over 18 years of age, considering the general population, were considered. A crucial inclusion criterion was the presence of quantifiable association measures, specifically the odds ratio (OR), relative risk (RR), or hazard ratio (HR).

Conversely, studies focusing on specific populations or subgroups were excluded to maintain the generalization of our findings to the general population of GC patients. Additionally, the decision was made to exclude studies that primarily focused on genetic polymorphisms related to IL-6. Although we recognize the potential importance of genetic factors in IL-6 expression and function, this aspect was considered beyond the scope of our current review.

Study Selection

The study selection process was carried out in several stages, using Rayyan software (https://rayyan.qcri.org) for managing and storing references obtained from the databases. Three independent reviewers examined the titles and abstracts of all manuscripts resulting from the search. Selection for a more detailed review required consensus from all three reviewers. In cases of disagreement between reviewers, a fourth reviewer acted as an arbitrator to make the final decision. Pre-selected manuscripts underwent a comprehensive full-text review. Using Microsoft Excel 2019, inclusion or exclusion decisions for each manuscript were documented, maintaining a transparent record of the selection process.

Data Extraction and Qualitative Analysis

Data extraction was meticulously performed for each included article using a standardized spreadsheet in Microsoft Excel 2019. Extracted data included author and year of publication, study design, sample size, prevalence of GC, details on IL-6 measurement, adjustment variables used in the analyses and reported association measures. This extraction process allowed for an initial qualitative synthesis of the findings from the included studies.

Risk of Bias Assessment

The methodological quality and risk of bias of the included studies were assessed using the Newcastle-Ottawa Scale (NOS), a widely recognized tool for evaluating non-randomized studies in systematic reviews. Specific versions of the NOS were applied [12]: one for case-control studies and another for cohort studies, thus ensuring an appropriate evaluation according to each study's design. The NOS assesses three main domains: the selection of study groups, comparability between groups, and determination of exposure (for case-control studies) or outcome assessment (for cohort studies).

Two independent reviewers conducted this assessment for each included study, using standardized NOS criteria. In case of discrepancies in the evaluations, a third reviewer intervened to resolve differences and reach a consensus. This peer evaluation process and discrepancy resolution were designed to minimize subjective bias in assessing study quality. The maximum possible score on the NOS is 9 stars, where a higher number of stars indicates better method-logical quality and lower risk of bias. This comprehensive

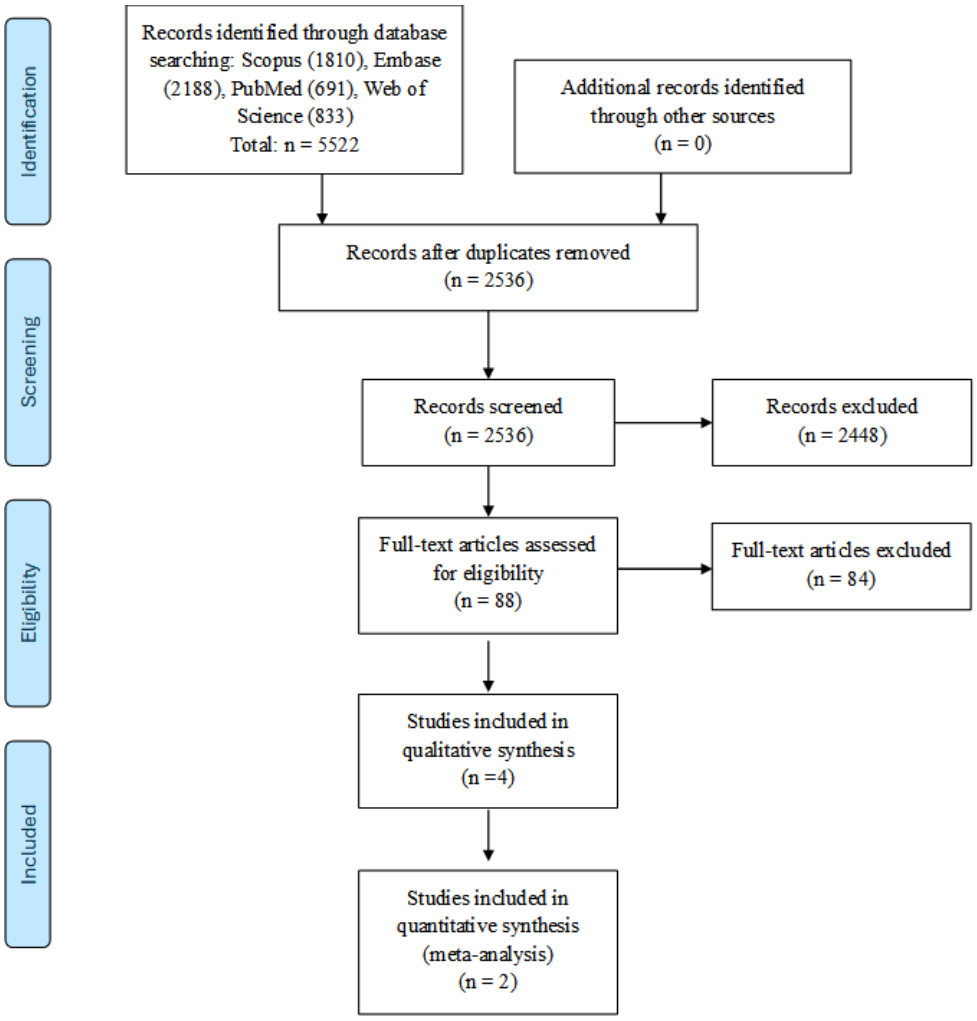


Figure 1: Flowchart of Study Selection.

evaluation allowed us not only to quantify the quality of each study but also to identify specific strengths and weaknesses in the methods employed, thus providing crucial context for interpreting the results of our SR and meta-analysis.

Quantitative Analysis

Quantitative analysis was performed using Review Manager 5.3 statistical software. The meta-analysis included all studies that provided sufficient data for the calculation of standardized effect measures. The total sample size and number of cases for each condition were extracted, allowing for the calculation of prevalences with their respective 95% confidence intervals (95% CI). The DerSimonian and Laird random-effects model was used for this purpose.

Heterogeneity between studies was assessed using the I^2 statistic. The interpretation of heterogeneity was based on Cochrane Handbook guidelines, considering different levels from potentially unimportant heterogeneity to considerable heterogeneity. Subgroup analyses were performed to explore possible sources of heterogeneity, considering factors such as study design, population characteristics, and IL-6 measurement methods.

This rigorous and multifaceted methodology allowed us to conduct a comprehensive and critical evaluation of the available evidence on the relationship between IL-6 and GC, providing a solid foundation for our conclusions and recommendations.

RESULTS

Study Selection

Initially, 5522 records were identified. After removing duplicates, 2536 unique records were screened, of which 2448 were excluded based on titles and abstracts. Subsequently, fifty full-text articles were assessed for eligibility, with 84 excluded for not meeting specific criteria. Ultimately, 4 studies were

included in the qualitative synthesis [13-16], while only 2 studies [15,16] were included in the quantitative meta-analysis.

Study Characteristics

Our SR identified four studies investigating the relationship between IL-6 and GC, published between 2008 and 2023 [13-16]. These studies encompass notable geographic diversity, with two conducted in China, one in Iran, and one in Taiwan, providing a varied perspective on the Asian population.

The studies are classified into two main categories based on their methodological design. Two utilized a case-control design, focusing on IL-6 as a risk factor for GC development. Hossein Nobakht *et al*. (2023) [13], in Iran, employed a case-control design with 180 participants, using the ELISA method to measure IL-6 as a continuous numerical variable. Their results showed an OR of 1.0004 (95% CI: 0.97-1.03). Hui-Lee Wong *et al*. (2011) [14], in China, adopted a nested case-control design with 423 participants, using the LINCOplex kit and categorizing IL-6 levels into three groups. They reported an OR of 1.73 (95% CI: 1.00-3.00) for IL-6 levels above 4.06 pg/mL.

The other two studies adopted a retrospective cohort design, focusing on the prognostic value of IL-6 in patients already diagnosed with GC. Pamping Liang *et al*. (2023) [15], China, included 249 participants and used an electrochemiluminescence immunoassay to measure IL-6. With a cut-off point of 5.51 pg/mL, they found an HR of 1.665 (95% CI: 1.026-2.703) for levels equal to or above this threshold. Wei-Chih Liao *et al*. (2008) [16], in Taiwan, analyzed a cohort of 155 participants, using the Quantikine Human IL-6 Immunoassay (ELISA) kit with a cut-off point of 13 pg/mL. They reported an HR of 1.77 (95% CI: 1.07-2.92) for levels above 13 pg/mL.

Differences in IL-6 measurement and analysis were observed across the studies. All used immunoassay techniques, but with specific variations in methods (ELISA, LINCOplex, electrochemiluminescence). The treatment of the IL-6 variable also differed: Nobakht *et al*. treated it as a continuous variable, Wong *et al*. categorized it into three levels, while Liang *et al*. [15] and Liao *et al*. [16] used single cut-off points, although different from each other.

Regarding specific methodological characteristics, Liao *et al*. [16] included an analysis of the -634G/C

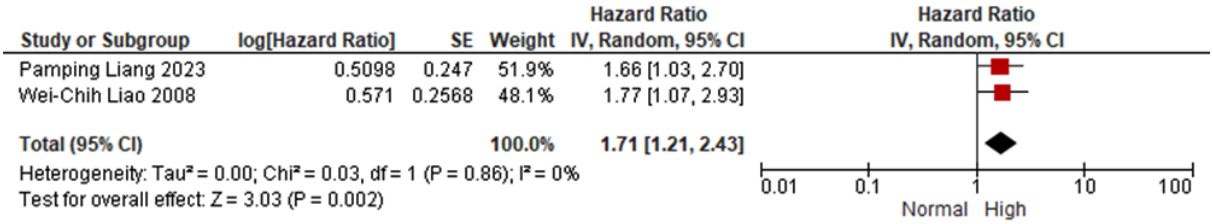
Table 1: Study Characteristics

Study	Country	Study Type	Sample	Age	IL-6 Evaluation Method	IL-6 Cut-off Point	GC Diagnosis	Association Measures	Adjustment Variables
Hossein Nobakht (2023)	Iran	Case-Control	180 participants (90 cases and 90 controls)	37.67 years	ELISA method (Platinum ELISA-811 kit). Blood obtained under fasting conditions, centrifuged at 2000rpm for 10 minutes.	Not specified	Self-report	OR=1.0004, 95% CI (0.97-1.03)	Age, Education, Smoking
Hui-Lee Wong (2011)	China	Nested Case-Control	423 participants (141 cases and 282 controls)	61 years	LINCOplex kit, samples collected in EDTA, processed within 6 hours, and stored at -70°C.	<1.76 pg/mL; 1.77–4.06 pg/mL; >4.06 pg/mL	Not clear, presumed by biopsy	<1.76 pg/mL (reference); 1.77–4.06 pg/mL, OR=1.07; >4.06 pg/mL, OR=1.73	Educational level
Pamping Liang (2023)	China	Retrospective Cohort	249 participants	60 years	Blood collected under fasting conditions, serum separated, IL-6 measured using ELISA (Sichuan University).	≤5.51 pg/mL; >5.51 pg/mL	Biopsy	IL-6 >5.51 pg/mL, HR=1.655, 95% CI: 1.026 – 2.703	T stage, N stage
Wei-Chih Liao (2008)	Taiwan	Retrospective Cohort	155 participants	62.3 years	Serum separated and stored at -80°C, IL-6 levels measured using ELISA (Quantikine Human IL-6 R&D Systems).	≤13 pg/mL; >13 pg/mL	Biopsy	IL-6 >13 pg/mL, HR=1.77, 95% CI: 1.07 – 2.92	Age, Sex, Metastasis, Depth of invasion, etc.

polymorphism, while Liang *et al*. (15) focused on constructing a new prognostic model. Liang *et al*. [15] explicitly compared their model with the TNM system and had a broader focus in terms of analyzed clinical indicators. Liao *et al*. [16], on the other hand, focused on evaluating IL-6 as an independent biomarker of survival.

These findings provide an overview of the different approaches and results obtained in research on the relationship between IL-6 and gastric cancer over the last 15 years, encompassing both risk and prognostic studies in Asian populations.

Meta-analysis of IL-6 as a Prognostic Marker for GC



A meta-analysis was conducted to quantitatively synthesize the evidence on the association between elevated IL-6 levels and mortality prognosis in patients with GC. This analysis included two retrospective cohort studies: Pamping Liang *et al*. (2023) [15] and Wei-Chih Liao *et al*. (2008) [16], both focused on evaluating overall patient survival.

The meta-analysis results showed a combined Hazard Ratio of 1.71 (95% CI: 1.21 - 2.43). This indicates that patients with elevated IL-6 levels have a 71% higher hazard of death compared to those with normal or low levels.

Notably, no significant heterogeneity was observed between the studies (I^2 = 0%, p = 0.86), despite differences in the cut-off points for IL-6 (5.51 pg/mL in Liang *et al*. and 13 pg/mL in Liao *et al*.). This consistency reinforces the robustness of the observed effect on survival. Additionally, the contribution of each study was balanced: Liang *et al*. (2023) [15] had a weight of 51.9% and Liao *et al*. (2008) [16] of 48.1%.

Bias Analysis of Selected Studies

Both studies differ in their Newcastle-Ottawa Scale scores; while both present a low risk level, it should be considered that the study by Nobakht *et al*. [13] did not adjust for additional variables, and both are unclear about their non-response rate.

On the other hand, both cohort studies show high methodological quality according to the Newcastle-Ottawa Scale, obtaining 8 stars each. Both studies do not meet the criterion of having a comparability group, as they are single-cohort studies.

DISCUSSION

Main Findings

The findings of this SR and meta-analysis, across the various studies analyzed, reveal a consistent pattern suggesting an association between elevated IL-6 levels and a worse prognosis in patients with GC. This relationship is maintained despite methodological and geographical variations among studies, reinforcing

Table 2: Bias Analysis Using the Newcastle-Ottawa Scale for Case-Control Studies

Authors, Year	Selection				Comparatibility		Outcome			Score	Overall Judgement
	Is the Case Definition Adequate?	Representa-tiveness of the Cases	Selection of Controls	Definition of Controls	Study Controls for the most Important Factor	Study Controls for any Additional Factor	Ascertainment of Exposure	Same Method of Ascertainment for Cases and Controls	Non-Response Rate		
Nobakht *et al.* (2023)	*	*	*	*	*		*	*		7	Low risk
Wong *et al.* (2011)	*	*	*	*	*	*	*	*		8	Low risk

*:Indicates that the study meets the specified criterion for this category.

Table 3: Bias Analysis Using the Newcastle-Ottawa Scale for Cohort Studies

Authors, Year	Selection				Comparability		Outcome			Score	Overall Judgement
	Representat-ivenes of the Exposed Cohort	Selection of the Non-exposed Cohort	Exposure Ascertainment	Outcome not Present at the Start of the Study	Study Controls for Sex and Age	Study Controls for any Additional Important Factor	Assessment of Outcome	Length of Follow-up	Adequacy of Follow up		
Liang *et al*. (2023)	*		*	*	*	*	*	*	*	8	Low risk
Liao *et al*. (2008)	*		*	*	*	*	*	*	*	8	Low risk

*: Indicates that the study meets the specified criterion for this category.

the robustness of this association. Particularly notable is the convergence of results between cohort studies, which, despite using different cut-off points for IL-6, show similar direction and magnitude of effect in terms of mortality risk. Additionally, the case-control studies, although not included in the quantitative meta-analysis, provide complementary evidence on the potential role of IL-6 as a risk factor in the development of GC. Collectively, these findings underscore the importance of IL-6 not only as a potential prognostic biomarker but also as a potential target for future therapeutic interventions in the management of GC.

Comparison with Existing Literature

Elevated IL-6 levels showed a connection to worse prognosis in gastric cancer. This matched earlier studies. Ashizawa *et al*. [17] reported findings in 2005. They noted that high serum IL-6 levels significantly correlated to advanced stages of GC and lower survival. Kim *et al*., in 2009, made similar observations [18]. Elevated IL-6 levels indicated a higher risk of metastasis along with a worse prognosis. Furthermore, ThongNgam *et al*. [19] research further supports this link by highlighting other inflammatory indicators related to patient outcomes.

Monitoring IL-6 levels proved crucial for assessing prognosis in GC patients. This finding stood out clearly. Inflammatory markers played a significant role in GC prognosis. In previous studies, C-reactive protein and the neutrophil-lymphocyte ratio also showed prognostic value [20]. The results aligned well with previous research, underscores the potential of IL-6 as a robust biomarker for managing gastric cancer. More research was needed to set standardized cut-off points. Evaluating its use alongside other established markers remained essential for further understanding its utility.

On the other hand, previous studies indicated that elevated IL-6 levels correlated with a worse prognosis. They also predict treatment response and disease recurrence [16,21]. For instance, Ikeguchi *et al*. [17] discovered that higher preoperative serum IL-6 levels were linked to lower overall and disease-free survival in gastric cancer patients. Also, measuring IL-6 might add value to patient risk stratification. It could complement traditional staging systems like TNM. This approach may provide a comprehensive understanding of patient outcomes. Further research is needed to solidify these findings and address existing hurdles in clinical practice. Therefore, the role of IL-6 presents opportunities for improving treatment strategies in gastric cancer despite the challenges faced in implementation.

Nashimoto *et al*. conducted a study in 2014. They suggested that combining IL-6 with other biomarkers like vascular endothelial growth factor could prognostic accuracy in advanced gastric cancer [22]. Yet, challenges remained for IL-6 to become a standard clinical biomarker. Standardization of measurement methods was one issue. Cutoff points also needed clarity, as Vainer *et al*. [23] pointed out in their systematic review from 2018 regarding IL-6 in gastrointestinal cancers. Longitudinal prospective studies were necessary to validate the utility of IL-6 across different populations and disease stages. This validation would be crucial for establishing IL-6 role in clinical settings effective. The need for further research was evident, especially considering the complexity of cancer diagnostics and treatment decisions involved.

Biological Mechanisms of IL-6 in Gastric Cancer

The association between elevated IL-6 levels and a worse prognosis in gastric cancer can be explained through several biological mechanisms. Primarily, IL-6 acts through the JAK/STAT3 signaling pathway, which plays a crucial role in tumor progression [24]. Persistent activation of STAT3 by IL-6 promotes cell proliferation, angiogenesis, and metastasis, while inhibiting apoptosis [25].

Recent studies have shown that IL-6 also induces epithelial-mesenchymal transition in GC cells, increasing their invasive and metastatic capacity [26]. Additionally, IL-6 modulates the tumor microenvironment, promoting chronic inflammation and immunosuppression. Johnson *et al*. demonstrated that IL-6 stimulates the differentiation of T helper 17 (Th17) cells and suppresses the activity of cytotoxic T cells, creating a favorable environment for tumor growth [27]. Interestingly, IL-6 also interacts with other cytokines and growth factors. For example, a synergy has been observed between IL-6 and vascular endothelial growth factor in promoting tumor angiogenesis [28].

Recently, Kinoshita *et al*. (2020) revealed that IL-6 induces PD-L1 expression in GC cells, contributing to immune evasion [29]. Furthermore, IL-6 appears to play a role in chemotherapy resistance, activating cell survival pathways such as PI3K/AKT [30]. These diverse mechanisms underscore the multifaceted role of IL-6 in GC biology and explain its association with an unfavorable prognosis.

Need for Standardization in IL-6 Measurement and Analysis

The review of studies in this meta-analysis showed significant variability in IL-6 measurement and analysis methods. This underscores the need for standardization in future research. Significant differences existed in the immunoassay techniques used. Techniques ranged from conventional ELISA to advanced methods like electrochemiluminescence. Such variations could impact the sensitivity and specificity of measurements. Also, there was no consensus on cut-off points to define "elevated" IL-6 levels. This lack of agreement hinders direct comparisons between studies. It also limited the clinical applicability of findings. For instance, Liang *et al*. Study presented different thresholds than others, complicating interpretations. Further complications arose from sample collection methods and storage conditions. These factors could introduce variability that affected results as well. Researchers faced challenges when trying to replicate findings across different settings.Moreover, some studies focused on specific populations, while others did not consider demographic differences. This inconsistency made it hard to generalize results across varied groups. The variability in measurement techniques and lack of standardization impacted the field significantly. The long-term implications could affect how IL-6 is utilized clinically for diagnosis or treatment decisions. A unified approach is essential for advancing the understanding and application of IL-6 research [13-16].

Different studies set different cut-off point points for IL6 levels. One study used a cut-off point of 5.51 pg/mL [15]. Another study by Liao *et al*. used 13 pg/mL [16]. This difference is significant for interpreting results. Such variability complicates evidence synthesis in meta-analyses. It also created implications when trying to apply research findings in clinical settings. Future studies crucial standardized protocols for sample collection and processing. Also, consistent methods for the measurement of IL6 were essential. Establishing an international consensus on preferred assay methods was a clinically relevant cut-off point. large-scale multicenter studies could help achieve this goal. The lack of standardization posed challenges that required attention from the scientific community. Researchers should focus on creating uniform guidelines to enhance the clarity and applicability of findings across various contexts.

The inclusion of quality controls inter-laboratory helped improve results. Calibration of assays with international standards also played a role. This way, different studies and centers could achieve better comparability. Standardization efforts were crucial for utilizing IL-6 as a prognostic biomarker in gastric cancer. This approach is aimed at facilitating its implementation in routine clinical practice. Only through these measures was it possible to unlock the full potential of IL-6.

Relevance of the Study for Clinical Practice

The study findings held significant implications for clinical practice. Elevated IL6 levels consistently linked to poor prognosis stood out. This biomarker could enhance patient risk stratification [16]. Clinicians might identify patients who benefit from intensive follow-up or aggressive treatment strategies [18]. For instance, those with high IL6 could be candidates for additional adjuvant therapies [17]. More frequent monitoring for relapses might be necessary as well. These insights aimed to refine clinical approaches in gastric cancer care [31].

IL6 measurement could integrate a role in clinical decisionmaking. It might complement traditional staging systems like TNM. This combination could provide an accurate prognostic assessment [24]. In personalized medicine, IL6 levels held potential for guiding targeted therapies. The development of IL6 inhibitors and their signaling pathways was significant here. Yet, challenges existed with using IL6 as a routine biomarker. Standardization in measurement remained crucial. Clinically relevant cutoff points required

validation, too [23]. These challenges complicated the implementation process. However, the future is promising for integrating IL6 into clinical practice. More research would likely clarify its utility and effectiveness in patient care [31].

The findings had limitations. However, they lay the groundwork for future clinical clinical trials. These could validate the use of IL6 in clinical practice. The potential exists for IL6 to incorporation as a biomarker. This could contribute to more personalized precise in gastric cancer management. Improved patient outcomes potentially improving from this approach. Overall, the groundwork was laid for further exploration and validation of IL6 role in clinical settings.

Strengths and Limitations of the Study

This study had significant strengths. It thoroughly synthesizes evidence on the relationship between IL6 and GC prognosis. This spanned over 15 years and included diverse Asian populations. Casecontrol studies and retrospective cohort studies were both included. This offered a wide perspective on IL6 as a risk factor and prognostic biomarker.Also, a random-effects model was used in the metaanalysis. This helped address differences among studies, which made findings stronger. The results remained consistent despite methodological differences in the included studies. Therefore, this reinforces the validity of the conclusions drawn from the research.

The analysis of IL-6 measurement methods was critical. It differences and established a solid foundation for future standardization efforts. The analysis on biological mechanisms was underlying. It also enhances potential clinical implications. This made the findings more relevant in the applicability of GC research. However, there were important limitations to this study. The main limitation of standardization efforts included in the meta-analysis was relatively small number. This restricts statistical power. Consequently, it hindered detailed subgroup analyses from perform effectively. In summary, while the study valuable insights into IL-6 measurements and their relevance, its important limitations acknowledged for a balanced perspective on its impact in research and management.

The heterogeneity in IL6 measurement methods created confusion. Different studies used different cut-off points. This made it hard to interpret results and compare them directly. Also, focusing mainly on Asian populations limited the findings' generalizability to other groups. The retrospective design of cohort studies raised concerns about selection and information biases. Furthermore, specific treatments affected interpretation of their impact on IL6 levels and prognosis. These limitations highlighted important limitation in drawing clear s from the research.

The lack of studies on the temporal of IL6 levels during the disease created gaps in understanding its utility as a follow-up biomarker. This absence was significant. It made it difficult to draw clear s. Larger and standardized prospective studies were necessary. They could confirm findings and expand knowledge on this topic. More research would clarify IL6 utility in monitoring disease progression or response to treatment. Therefore, addressing these limitations became crucial for future investigations into biomarker in clinical settings.

CONCLUSIONS AND RECOMMENDATIONS

This study provides evidence of the association between elevated IL-6 levels and a worse prognosis in patients with GC. Our meta-analysis, encompassing diverse studies in Asian populations, consistently demonstrates that patients with higher IL-6 levels have a significantly greater risk of adverse outcomes, with a combined hazard ratio of 1.71 (95% CI: 1.21 - 2.43). This finding underscores the potential importance of IL-6 as a prognostic biomarker in GC management. Despite these limitations, our findings represent a significant advance in understanding the joint role of both variables and suggest their potential as a tool for risk stratification and treatment personalization in clinical practice.

Based on the results of this study, we recommend several actions for future research and clinical applications. Firstly, it is crucial to develop and adopt standardized protocols for IL-6 measurement in GC, ideally through an international consensus. Large-scale, multicenter prospective studies that include diverse ethnic populations are needed to validate the prognostic value of IL-6 and establish clinically relevant cut-off points. Future studies should explore the combination of IL-6 with other biomarkers and staging systems to improve prognostic accuracy. It is also important to conduct longitudinal studies that assess changes in IL-6 levels over time to determine its utility in monitoring treatment response and early detection of recurrences. As more evidence accumulates, we suggest that professional organizations consider including IL-6 measurement in GC management guidelines. Finally, we recommend the development of standardized tests for IL-6 measurement and the

inclusion of this information in continuing medical education programs for oncologists and gastroenterologists.

AUTHORS' CONTRIBUTION

Joan A. Loayza-Castro: Conceptualization, Investigation, Methodology, Resources, Writing - Original Draft, Writing - Review & Editing

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Lupita Ana Maria Valladolid-Sandoval: Investigation, Methodology, Writing - Original Draft, Writing - Review & Editing

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Rafael Tapia-Limonchi: Validation, Visualization, Writing - Original Draft, Writing - Review & Editing

Víctor Juan Vera-Ponce: Methodology, Supervision, Funding acquisition, Writing - Review & Editing

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

INFORMED CONSENT

The primary study from which the database was obtained provided the required informed consent, however, for the present study it was not required.

DATA AVAILABILITY

Data are available upon request to the corresponding author.

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