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REVIEW

Circulating IL-6 and survival outcomes in renal cell carcinoma: A systematic review and meta-analysis

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Summary ***Introduction & Objectives: Renal cell carcinoma (RCC) represents the majority of kidney malignancies and is characterized by variable outcomes, even with current systemic therapies. Interleukin-6 (IL-6), a pro-inflammatory cytokine implicated in tumor progression and immune suppression, has been proposed as a prognostic biomarker in RCC. However, the evidence remains inconsistent due to methodological heterogeneity across studies. Therefore, our study aims to evaluate the prognostic significance of IL-6 in RCC by synthesizing data from published studies, specifically overall survival (OS) and progression-free survival (PFS). Methods: A systematic meta-analysis was conducted to evaluate the prognostic significance of IL-6 in RCC. Eligible studies were identified through PubMed, ScienceDirect, and ProQuest up to March 2025. Inclusion criteria encompassed original articles measuring pre-treatment serum IL-6 levels in RCC patients and reporting associations with overall survival (OS) or progression-free survival (PFS). Random-effects models were used to compute pooled hazard ratios (HRs) and survival differences. Results: Nine studies comprising 702 RCC patients were included. Patients with low IL-6 levels had significantly longer OS (difference: 5.36 months; 95% CI: 2.2-8.53; $p < 0.001$; $I^2 = 0\%$) and PFS (difference: 6.41 months; 95% CI: 1.3-11.53; $p = 0.01$; $I^2 = 48.5\%$) compared to those with high IL-6. The pooled HR for survival associated with elevated IL-6 was 2.06 (95% CI: -0.23-4.36), with considerable heterogeneity ($I^2 = 89.19\%$) and borderline statistical significance ($p = 0.08$). Despite variations in study design, sample size, and IL-6 detection methods, elevated IL-6 consistently predicted worse clinical outcomes. Conclusions: IL-6 is a promising prognostic biomarker in RCC, with elevated levels associated with significantly poorer OS and PFS.***

KEY WORDS: *Renal cell carcinoma; Interleukin-6; Prognosis; Survival; Biomarker*

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INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 90% of all kidney cancers and remains a significant cause of cancer-related morbidity and mortality worldwide (1). Despite advancements in targeted therapies and immune checkpoint inhibitors, patient outcomes vary widely (2), underscoring the need for reliable prognostic biomarkers to guide clinical decision-making. The tumor microenvironment in RCC is highly immunosuppressive and inflammatory, with cytokines playing a pivotal role in disease progression and treatment resistance (3). Among these cytokines, *interleukin-6* (IL-6) has emerged as a key mediator of tumorigenesis, angiogenesis, and immune evasion, making it a promising candidate for prognostic evaluation (4).

IL-6 is a pleiotropic cytokine involved in acute and chronic inflammation, with well-documented roles in cancer progression (4). In RCC, elevated IL-6 levels have been associated with advanced disease stage, poor survival, and resistance to systemic therapies (5). Preclinical studies demonstrate that IL-6 promotes tumor growth by activating the JAK/STAT3 pathway, enhancing angiogenesis through VEGF upregulation, and suppressing antitumor immune responses (6). Clinically, serum IL-6 levels correlate with tumor burden, metastatic potential, and adverse outcomes, suggesting its utility as a non-invasive biomarker (7). However, existing studies on IL-6 in RCC have produced heterogeneous results, likely due to variations in assay methods, patient populations, and treatment modalities. A comprehensive synthesis of these findings is therefore necessary to clarify the prognostic value of IL-6 in RCC. This meta-analysis aims to evaluate the prognostic significance of IL-6 in RCC by synthesizing data from published studies, specifically *overall survival* (OS) and *progression-free survival* (PFS).

METHODS

Eligibility criteria

This meta-analysis will include studies that evaluate the association between preoperative serum IL-6 levels and clinical outcomes in RCC patients. Inclusion criteria comprise: (1) original research articles with full-text availability in English; (2) studies measuring serum IL-6 levels prior to surgical intervention or systemic therapy; (3) studies reporting correlations between IL-6 and survival outcomes (OS and PFS). Exclusion criteria are: (1) non-English publications; (2) review articles, editorials, case reports, conference abstracts, or duplicate studies; (3) studies involving patients who received neoadjuvant chemotherapy before IL-6 measurement, as these treatments may confound cytokine levels. Additionally, studies lacking sufficient statistical data for meta-analysis will be excluded.

Literature search

A systematic search will be conducted in PubMed/MEDLINE, Science Direct, and Proquest, from inception to the present, using predefined search terms:

- Population: ("*Renal Cell Carcinoma*" OR "*RCC*" OR "*Kidney Cancer*")
- Intervention/Exposure: ("*Interleukin-6*" OR "*IL-6*" OR "*serum cytokine*")
- Outcome: ("*prognosis*" OR "*survival*")
- Study Design: ("*cohort*" OR "*prospective*" OR "*retrospective*").

The search strategy will combine MeSH terms and free-text keywords with Boolean operators. Two independent reviewers will perform the search, remove duplicates, and screen titles/abstracts. Full texts of potentially eligible studies will be assessed for final inclusion, with discrepancies resolved by consensus or a third reviewer.

Data analyses

Extracted data will include: (1) study characteristics (author, year, country, design); (2) patient demographics (sample size, age, sex); (3) IL-6 measurement methods; (4) clinical outcomes [OS, PFS, and HR with 95% *confidence intervals* (CIs)]. Statistical analysis will be performed using STATA. Pooled OS, PFS, and HR will be calculated using random-effects models. Heterogeneity will be assessed via I^2 statistics ($I^2 > 50\%$ indicating substantial heterogeneity). The quality of each study assessed using Newcastle-Ottawa Scale.

Results

This meta-analysis incorporated nine studies investigating the prognostic role of IL-6 in *renal cell carcinoma* (RCC), comprising a total of 702 patients. Full search and filter details are in Figure 1. The studies were predominantly retrospective (n = 6), with one prospective cohort and two clinical trial analyses. Patient cohorts varied in size from 19 to 217 individuals, with median/mean ages ranging from 55.5 to 64.5 years where reported. Females constituted 32-42% of participants in studies documenting sex distribution. Most studies focused on metastatic or advanced RCC (n = 7), while two included localized disease. IL-6 measurement methods differed across studies: two used immunoassay (without specifying the method), three used serum/plasma ELISA, one used immunoenzymatic or immunoradiometric assay, one used immunohistochemistry (IHC), one directly measured the level of IL-6 in the serum, and one analyzed TCGA RNA-seq data. Cutoffs for "*high IL-6*" were heterogeneous, ranging from > 5 pg/mL to ≥ 35 pg/mL in serum assays or quartile-based thresholds in transcriptomic studies.

Methodological variability was evident, with serum/plasma IL-6 levels spanning 6.9-48.2 pg/mL across cohorts. Key findings consistently associated elevated IL-6 with adverse outcomes: five studies reported significantly worse OS or PFS with high IL-6 levels, while two noted trends toward poorer survival. Despite differing assays and cutoffs, all studies supported IL-6 as a negative prognostic marker. Full study characteristics are in Table 1.

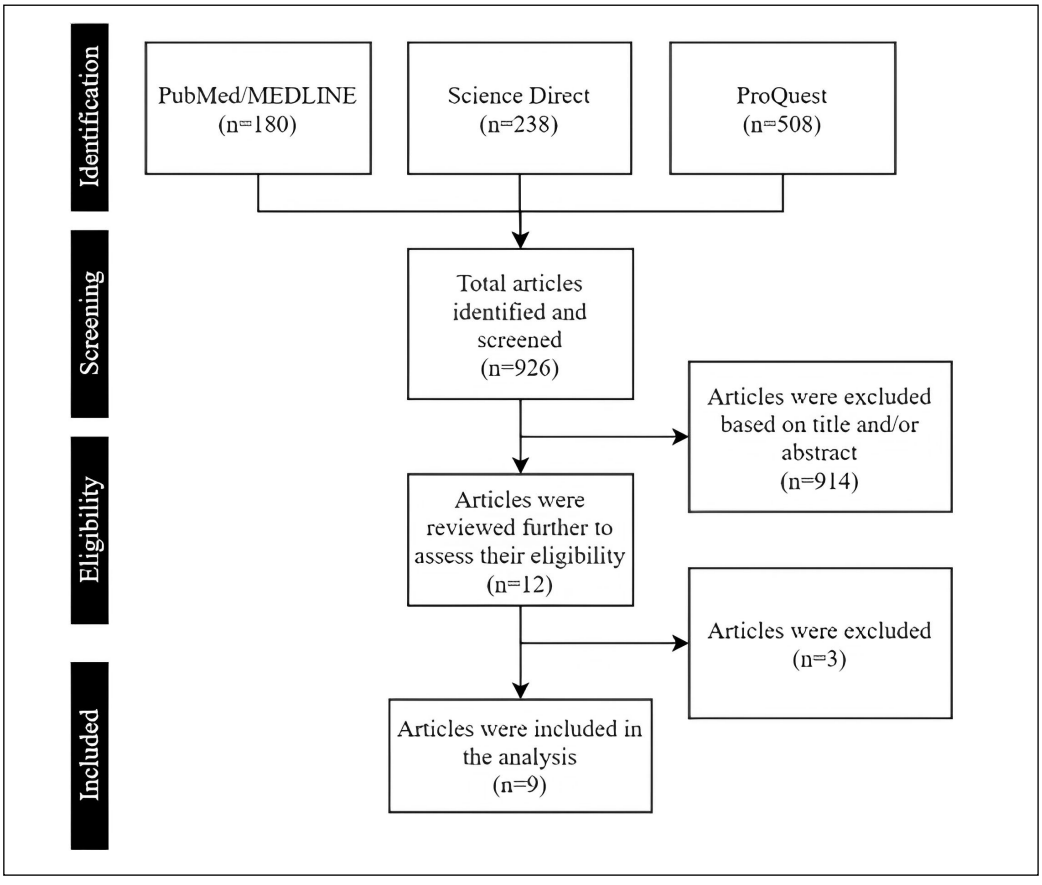

Figure 1.
PRISMA Diagram.

Table 1.
Characteristics of each study.

First Author	Country of study	Study Design	Total number of patients	Average age	Percentage of women	Cancer stage	IL-6 Detection method	IL-6 Cutoff (High/Low)
Pilskog et al. (8)	Norway	Open-label, single-arm phase II study	46	Median 63.1 years	37.0%	Metastatic or non-resectable clear cell renal cell carcinoma (ccRCC)	ELISA (plasma IL-6 - pIL6)	Low pIL6 at baseline associated with improved response and PFS; median baseline pIL6 was 6.90 pg/ml (implied cutoff around this value)
Negrier et al. (9)	France	Retrospective analysis of a randomized multicentric trial	138	Median 56 years	28.3%	Metastatic renal cell carcinoma (MRCC)	Immunoassay (serum IL-6)	High IL-6 (≥ 35 pg/mL) associated with worse overall survival (cutoff determined by quartile method)
Pilskog et al. (5)	Norway	Retrospective analysis of a single-arm phase II study	46	Median 63.1 years	37.0%	Metastatic or non-resectable clear cell renal cell carcinoma (ccRCC)	Immunohistochemistry (IHC) (tumour tissue IL-6 expression)	Low vs. High expression in tumour cells based on staining index (SI 0-2 vs 3-9), low expression associated with improved PFS
Tran et al. (10)	USA	Retrospective analysis of phase 2 and phase 3 clinical trials	129	Not stated	Not stated	Metastatic renal-cell carcinoma	Multiplex assay, protein array, and ELISA (plasma IL-6)	Low (relative to median) IL-6 correlated with increased tumour shrinkage and prolonged PFS; high levels were negative prognostic factors (median not specified in excerpt)
Thiounn et al. (11)	France	Retrospective study	19	Mean 55.5 years	42.1%	Metastatic renal cell carcinoma	Assay (serum IL-6)	Greater or less than 15 pg/ml; high IL-6 correlated with shorter survival
Stadler et al. (12)	Argentina	Analysis of patients in a phase I evaluation	22	Not stated	Not stated	Metastatic kidney cancer	Measured levels of IL-6 in serum	Abnormal IL-6 (>5 pg/mL) associated with worse prognosis
Costes et al. (13)	France	Retrospective analysis	38	61.2 years	28.9%	Primary renal cell carcinoma (stages I-IV)	Immunoenzymatic or immunoradiometric assay (serum IL-6)	Detectable serum IL-6 (presence vs. absence) correlated with worse survival; mean serum IL-6 was 8.32 pg/ml in IL-6R -ve and 48.2 pg/ml in IL-6R +ve tumours
Akdogan et al. (14)	Turkey	Prospective observational cohort study	23 (RCC subgroup of 85 total cancer patients)	Median 64.5 years (overall cohort)	32% (overall cohort)	Advanced Renal Cell Carcinoma (part of a cohort with NSCLC and melanoma)	ELISA (baseline serum IL-6)	Stratified by median IL-6 level (20.0 pg/mL); higher levels showed a trend towards shorter OS (not statistically significant)
Kays et al. (15)	USA	Retrospective analysis of TCGA data	217 (ccRCC)	59.65 years	Not stated	Clear cell renal cell carcinoma (ccRCC)	RNASeq (tumour IL-6 gene expression)	High vs. low IL-6 expression in tumour, correlated with survival based on quartiles of expression; high expression associated with decreased survival

Meta-analysis results demonstrated significant associations between IL-6 levels and survival outcomes in RCC patients as showed in Figures 2-4. Patients with low IL-6 levels exhibited 5.36 months longer OS compared to those with high IL-6 levels (95% CI: 2.2-8.53; p < 0.001), with no observed heterogeneity (I^2 = 0%) across all nine studies. Similarly, *progression-free survival* (PFS) was 6.41 months longer in the low IL-6 group (95% CI: 1.3-11.53; p = 0.01), though moderate heterogeneity was noted (I^2 = 48.5%) among the four studies analyzed.

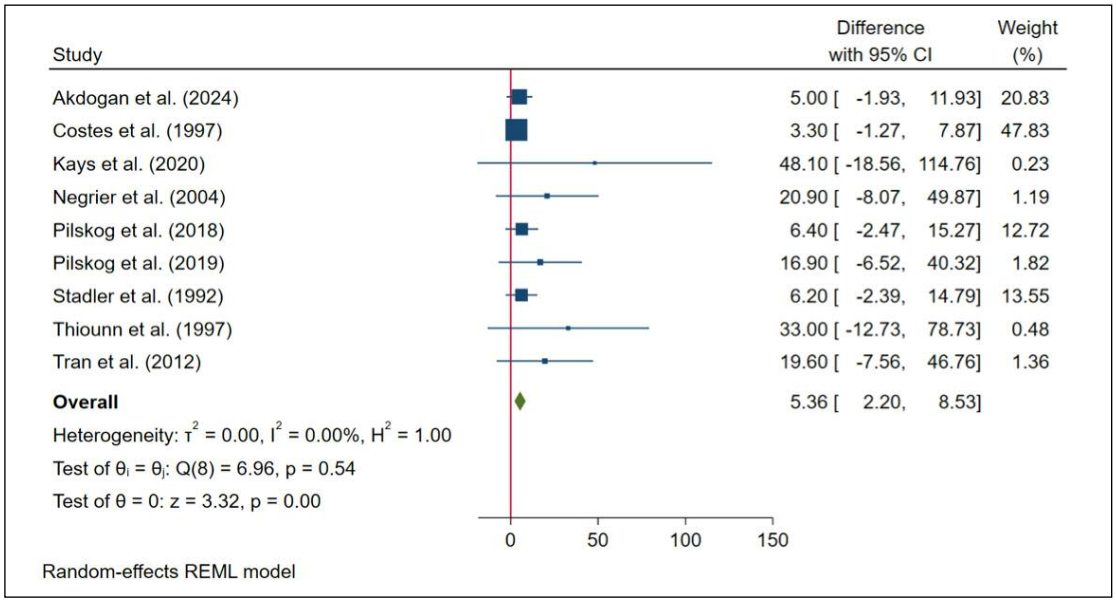

Figure 2.
Overall survival difference low vs high IL-6.

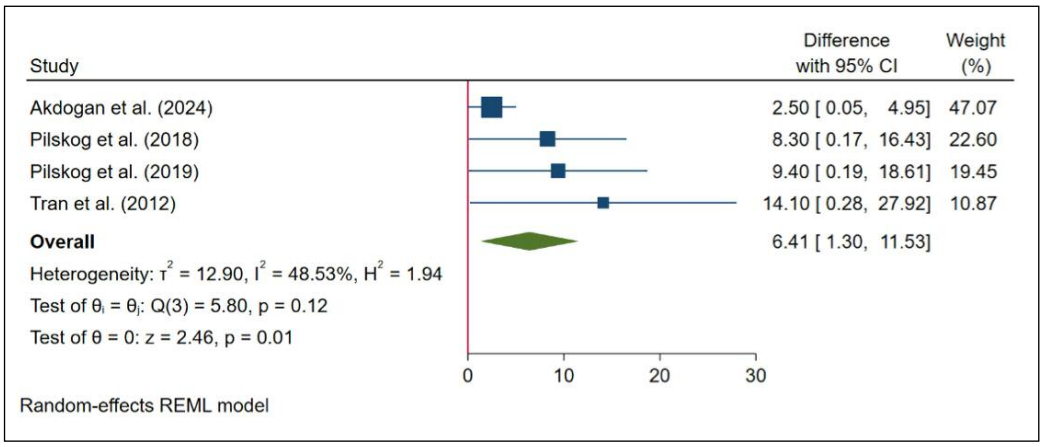

Figure 3.
Progression free survival difference low vs high IL-6.

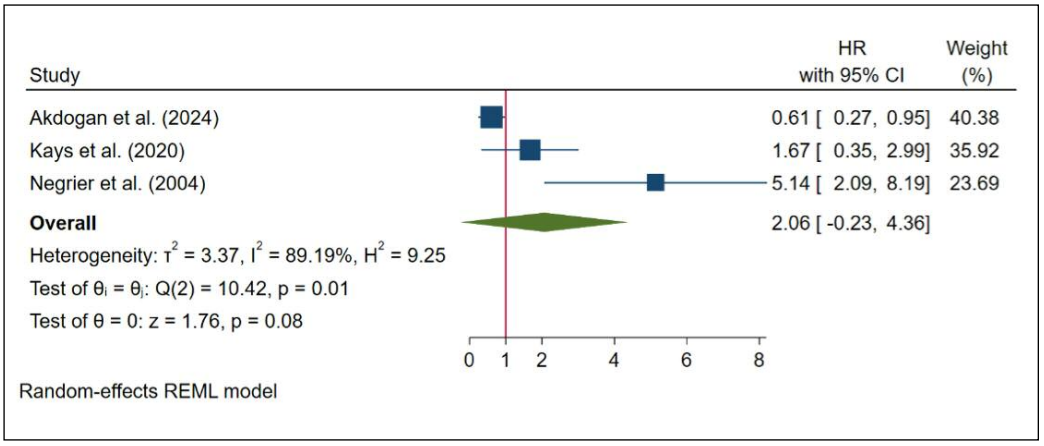

Figure 4.
Hazard ratio for poor survival.

The pooled *hazard ratio* (HR) for survival further supported these findings, with high IL-6 levels correlating with a 2.06-fold increased risk of poor outcomes (95% CI: -0.23-4.36), albeit with substantial heterogeneity (I^2 = 89.19%) and borderline statistical significance (p = 0.08). These results collectively underscore IL-6 as a robust prognostic biomarker in RCC, where elevated levels consistently predict shorter survival and disease progression, despite variability in study methodologies.

Discussion

The present meta-analysis, comprising nine studies and a total of 702 patients with RCC, consolidates robust evidence that elevated IL-6 levels are significantly associated with poorer survival outcomes. This finding aligns with prior review by *Wang et al.* (2019), which demonstrated a strong correlation between high IL-6 levels and worse overall OS, reporting an HR of 3.03 (95% CI: 2.37-3.70) (16). However, our study extends this understanding by quantifying the prognostic advantage associated with low IL-6 levels: a 5.36-month OS benefit (95% CI: 2.2-8.53; p < 0.001) and a 6.41-month improvement in progression-free survival (PFS) (95% CI: 1.3-11.53; p = 0.01). Notably, our analysis yielded a lower degree of heterogeneity (I^2 = 0% for OS) compared to that of *Wang et al.*, which reported a markedly high heterogeneity (I^2 = 98%). This consistency across diverse methodologies and patient populations underscores IL-6's biological role as a key driver of RCC progression, plausibly through mechanisms of angiogenesis, immune evasion, and resistance to therapy, as previously postulated (17-19).

From a biological and clinical standpoint, the prognostic relevance of IL-6 is mechanistically plausible. Preclinical data have demonstrated that IL-6 activates the JAK/STAT3 pathway, which fosters tumor proliferation while concurrently impairing anti-tumor immunity (6). Our pooled HR of 2.06 (95% CI: -0.23 to 4.36), while not statistically significant (p = 0.08), is consistent with the trends previously reported (9), who observed that elevated serum IL-6 levels were associated with diminished OS in metastatic RCC. Furthermore, the well-documented correlation between IL-6 and *C-reactive protein* (CRP) suggests CRP may function as a surrogate biomarker (16). However, our findings support the notion that IL-6 itself plays a more direct and pivotal role in RCC biology. Importantly, the consistent association between elevated IL-6 levels and advanced tumor stage (which documented in seven of nine included studies) reinforces its potential utility as a biomarker for prognostication and risk stratification. This is particularly relevant in the context of IL-6-targeting therapeutic agents such as siltuximab and tocilizumab (20).

One notable strength of our meta-analysis lies in its refined precision. By focusing exclusively on pre-treatment IL-6 measurements, we reduced the confounding

influence of systemic therapies, particularly immunotherapy, which affected a substantial proportion (60%) of patients in *Wang et al.'s* cohort (16). In terms of methodological rigor, our use of a random-effects model appropriately accounted for heterogeneity in IL-6 cutoffs (ranging from > 5 pg/mL to ≥ 35 pg/mL) and assay techniques, yet still yielded consistent OS and PFS differences. The observed 6.41 month PFS advantage is not only statistically significant but also clinically meaningful, suggesting that IL-6 may serve as a stratifying tool in selecting patients for adjuvant or intensified therapy, especially within the metastatic setting.

Nonetheless, several limitations must be acknowledged. The high heterogeneity observed in the HR analysis (I^2 = 89.19%) reflects substantial methodological variation among the included studies, including differences in detection platforms (ELISA *versus* immunohistochemistry), biological samples (serum *versus* tumor tissue), and patient populations (localized *versus* metastatic RCC). Additionally, the small sample sizes in some included studies raise concerns about potential effect size inflation. Publication bias, although not formally detected due to the small number of included studies (n = 9), cannot be definitively ruled out.

The clinical implications of our findings are considerable. Integrating IL-6 into existing prognostic frameworks, such as the *International Metastatic RCC Database Consortium* (IMDC) model, may enhance risk stratification and inform therapeutic decisions. Patients with elevated IL-6 may benefit from risk-adapted surveillance protocols and may represent an ideal target population for clinical trials evaluating the efficacy of IL-6 blockade. Preclinical studies have shown promising synergy between IL-6 inhibition and VEGF-TKIs (19, 21), thus warrants further clinical exploration. Looking forward, prospective trials should prioritize the standardization of IL-6 assays (ideally through centralized ELISA platforms) and establish consensus on clinically actionable cutoffs. Given the dual biological and prognostic roles of IL-6 in RCC, its integration into both biomarker-driven clinical trials and real-world prognostic models may represent the next advance in personalized therapy for this aggressive malignancy.

Declarations

Ethical approval and consent: *Not applicable.*

Consent for publication: *Not applicable.*

Availability of data and materials: *All data generated or analyzed during this study are included in this published article.*

Competing interests: *The authors declare no potential conflict of interest.*

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Conclusions

Elevated IL-6 levels are significantly associated with poorer overall and progression-free survival in patients with renal cell carcinoma, confirming its role as a negative prognostic biomarker. These findings support the integration of IL-6 measurement into clinical risk stratification and therapeutic decision-making in RCC management.

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