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Urinary CXCL-10, a prognostic biomarker for kidney graft injuries: a systematic review and meta-analysis

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Abstract

The challenges of long-term graft survival and the side effects of current immunosuppressive therapies in kidney transplantation highlight the need for improved drugs with fewer adverse effects. Biomarkers play a crucial role in quickly detecting post-transplant complications, with new biomarkers showing promise for ongoing monitoring of disease and potentially reducing the need for unnecessary invasive biopsies. The chemokines such as C-X-C motif chemokine ligand 10 (CXCL10), are particularly promising protein biomarkers for acute renal rejection, with urine samples being a desirable source for biomarkers. The aim of this review is to analyze the literature on the potential role of urinary CXCL10 protein in predicting kidney graft injuries. The results of this study demonstrate that evaluating urinary CXCL10 levels is more successful in identifying post-transplant injuries compared to assessing the CXCL10/Cr ratio.

Keywords Urine, CXCL10, Biomarker, Kidney graft, Meta-analysis

Introduction

Kidney allograft transplantation is the best treatment for end-stage renal disease (ESRD), but long-term graft survival and adverse effects of current immunosuppressive regimens remain significant challenges [1, 2]. Laboratory tests, including serum urea, creatinine, and proteinuria, play a crucial role in monitoring kidney transplants. While histopathological analysis of graft biopsies remains the gold standard for diagnosing post-transplant injuries, it has limitations due to its invasive nature, potential sampling errors, and high costs. Consequently, this method is impractical for continuous graft monitoring over time [3, 4]. Therefore, exploring novel biomarkers for early detection of post-transplant injuries holds promise for reducing unnecessary biopsies [4, 5]. Considering these facts, urine samples, which directly reflect allograft function and are minimally affected by systemic inflammation, represent an optimal source for biomarkers in this context [5].

Based on the search results provided, the primary new biomarkers being studied for the detection of kidney transplant complications are urinary C-X-C motif chemokine ligand 9 (CXCL9) and 10 (CXCL10) [6]. Additionally, the analysis of urinary mRNA transcripts such as $CD3^+$, perforin, granzyme B, CD103, and CXCR3, has been conducted [6, 7]. Urinary perforin and granzyme B and CD103, can serve as screening tools for acute rejection. Moreover, elevated levels of donor-derived cell-free DNA (dd-cf DNA) in the blood or urine may indicate acute rejection, while declining levels could signal recovery from rejection [6–10]. In conclusion, urinary and

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blood transcriptomics are emerging as promising biomarkers in the field of kidney transplantation, offering valuable insights into the status of kidney allografts. The identification of specific mRNAs and microRNAs associated with rejection episodes has proven beneficial in detecting T cell-mediated rejection (TCMR) and antibody-mediated rejection (ABMR), thereby enhancing our understanding of the immunological processes involved in kidney transplant rejection [11]. Some of mentioned biomarkers such as the CXCL9 and CXCL10, seems to be more promising for kidney graft problems early detection and ongoing disease monitoring. These chemokines recruit T cells to inflammatory sites and have shown potential as biomarkers for diagnosing rejection [6]. A multicenter prospective study found that urinary CXCL9 and CXCL10 protein levels were significantly higher in patients with acute rejection compared to stable graft conditions, and low urinary CXCL9 protein levels could be used to rule out acute rejection with a high negative predictive value (NPV). Furthermore, CXCL10 levels have been shown to increase up to 30 days before the biopsy, which can help identify patients at risk for acute rejection [6]. CXCL9 is also a promising biomarker, but CXCL10 has a more robust and consistent association with graft complications, making it a more reliable indicator [12]. CXCL10 is a member of the CXC chemokine family also known as IFNγ-induced protein 10 (IP-10). It is an 8.7 kDa protein encoded by the CXCL10 gene located on human chromosome 4q21. The CXCL10 gene consists of 4 exons and 3 introns and elicits its effects by binding to the cell surface chemokine receptor CXCR3. This chemokine secreted by monocytes, endothelial cells and fibroblasts in response to IFNγ and recruit immune cells to sites of inflammation. It also plays roles in anti-tumor activity, adhesion of T cells, and inhibition of angiogenesis and bone marrow colony formation [13, 14]. Studies have demonstrated that CXCL10 is directly involved in the development of kidney conditions through its chemoattractant properties and effects on cell proliferation [14]. CXCL10 or its ratio to creatinine has been more extensively studied and validated as a biomarker for kidney allograft rejection and can predict early rejection risk and longer-term graft survival [5, 6, 15–20]. This chemokine, is detected as a urinary biomarker for both TCMR and ABMR. Low levels of CXCL10 are associated with immunological quietness, making it ideal for ruling out rejection and identifying transplant recipients at low immunological risk [21].

Integrating the urinary CXCL10 biomarker with clinical indicators such as serum urea, creatinine, and proteinuria holds promise for reducing unnecessary invasive biopsies and improving patient outcomes [22].

Aim of this review The aim of this systematic review and meta-analysis is to examine the existing literature to determine the potential role of urinary CXCL10 protein in predicting kidney graft injuries.

Materials and methods

Literature search

This review is conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23]. The objectives of the study, the search strategy, inclusion and exclusion criteria, and study evaluation method were carefully designed, refined, and unanimously approved by all contributing authors well in advance. Pubmed, Scopus, Web of Sciences, EMBASE electric databases were searched from 6 March 2022 to 2 October 2023. The medical subject headings (MeSH) and their entry terms used in the literature search included: ((“Renal Transplantation*”) or (“Kidney Transplantation*”) or (“Kidney Graft*”) or (“Renal Graft*”)) and ((“Chemokine CXCL10”) or (“Interferon-Inducible Protein 10”) or (“Small Inducible Cytokine B10”) or (“IFN-gamma-Inducible Protein, 10 kDa”)). We applied no restrictions regarding the language or the publication date of the sources. Furthermore, a manual search of references in review articles was conducted to uncover additional relevant studies.

Selection process and data extraction

In the preliminary phase of the eligibility assessment, the screening of titles and abstracts was conducted independently by two investigators (A.A., S.J.). This initial review aimed to identify original research articles that investigated the utility of urinary CXCL10, either singularly or in combination with creatinine, in the prediction of kidney injuries post-transplantation.

In the course of our study, we excluded abstracts, reviews, and research focusing on CXCL10 derived from sources other than urine, such as blood samples or histological stains. Studies that primarily evaluated different outcomes, including infections or allograft survival, were also excluded. Subsequently, in the inclusion phase, the selected articles underwent an independent full-text review by two researchers (A.A., S.J.), ensuring a comprehensive and rigorous evaluation of the relevant literature. Discrepancies in the assessments made by the two investigators were deliberated upon and resolved through consultative discussions involving the entire authorial team. Data extraction from the included studies was carried out using a pre-defined spreadsheet and an extraction table, collaboratively developed and refined by all authors. The extracted data encompassed a range of variables, including, authors, years of enrollment, exposure, protein cut-off, outcome, sensitivity, specificity, and measures of diagnostic accuracy such as True Positive (TP),

False Negative (FN), False Positive (FP), True Negative (TN), and the Area Under the Receiver Operating Characteristic Curve (AUC) for protein. These variables were systematically tabulated for descriptive analysis. Two independent investigators conducted a thorough review of eligible publications, meticulously extracting relevant data into a standardized format. This rigorous selection process involved an initial review of titles and abstracts, followed by a detailed examination of the full texts. Any discrepancies encountered during this process were effectively resolved through consultation with a third reviewer.

Quality assessment

In the present meta-analysis, the integrity and robustness of the included studies were rigorously assessed using the Newcastle Ottawa Scale (NOS), a bespoke tool for the evaluation of nonrandomized studies. The NOS framework awards up to nine points, distributed across three critical dimensions: the selection process of study participants (maximum of 4 points), the comparability of the study groups (maximum of 2 points), and the accuracy and reliability of outcome assessment (maximum of 3 points). Studies achieving a score of 7 to 9 are classified as high quality, indicating lower risk of bias. Those garnering 4 to 6 points are categorized as having a high risk of bias, while a score of 0 to 3 suggests a very high risk of bias, potentially impacting the reliability of their findings.

Statistical analysis

In the initial phase of our analysis, we computed the natural logarithms (Ln) of the Relative Risks (RRs) along with their 95% Confidence Intervals (CIs) to derive the summary Effect Size (ES). To assess the comparative impact of the highest versus lowest categories, we implemented a random-effects model, specifically chosen to adequately account for the variability among studies (between-study heterogeneity). Furthermore, this model was instrumental in calculating I^2 values, which serve as quantitative measures of heterogeneity. We considered I^2 values exceeding 50% as a threshold for significant between-study heterogeneity. Upon encountering substantial heterogeneity, our analytical strategy included conducting subgroup analyses, with a particular focus on differing outcomes, to elucidate potential sources of variability among the included studies.

Results

Summary of searches and study selection process

Upon conducting a comprehensive search of the relevant database, a total of 878 articles were initially retrieved. Rigorous deduplication procedures resulted in removing 224 articles. A cursory examination of titles and abstracts facilitated the exclusion of 587 articles, which primarily consisted of review articles, conference proceedings, and additional publications by the same author. A more in-depth evaluation led to the further exclusion of 23, 31 and 4 articles in three steps due to reasons including the assay techniques, the use of non-urinary sample types, and the inability to extract complete data sets. Consequently, a final selection of 9 articles [18, 20, 24–30], representing 10 studies (with one article encompassing two studies), was made [27] (Fig. 1).

The basic characteristics of literatures

The fundamental characteristics of the selected publications are systematically cataloged in Table-S1. From each study, we meticulously extracted key data components, encompassing the first author's name, country of research, publication date, exposure details, protein cut-off values, and the primary diagnostic metrics, including the number of true positives, false positives, false negatives, and true negatives.

Quality evaluation results

The result of quality assessment using NOS is shown in Fig. 2. The quality assessment of the 9 selected articles was performed using Stata14 (metareg), as illustrated in Fig. 3. Overall, the quality of the included literature was deemed satisfactory. Each study adopted a case-control design, with the unanimous gold standard for diagnosis across all experiments being the pathological results post-transplantation. An analysis of quality scores in relation to sensitivity revealed that the study quality did not significantly influence the sensitivity outcomes. The pertinent data and findings from this analysis are detailed in Table 1.

Statistical analysis results

In this meta-analysis, Stata 14 was utilized as the primary statistical software. Due to significant heterogeneity observed in the initial results, indicated by an I2 value exceeding 50%, comprehensive subgroup analyses and meta-regression were undertaken to delve deeper into the data. The subgroup analysis was specifically tailored based on the study outcomes, with a particular focus on the methodologies used for CXCL10 quantification (isolated CXCL10 measurement versus the CXCL10/Creatinine ratio). The heterogeneity analysis revealed that the I^2 values for sensitivity and specificity, when utilizing the CXCL10 only measurement approach, were 63.4% ($p=0.027$) and 80.4% ($p=0.000$) respectively, as illustrated in Fig. 4. In contrast, the I^2 values for sensitivity and specificity with the CXCL10/Creatinine ratio method were 0% ($p=0.454$) and 97.6% ($p=0.000$) respectively, detailed in Fig. 5.

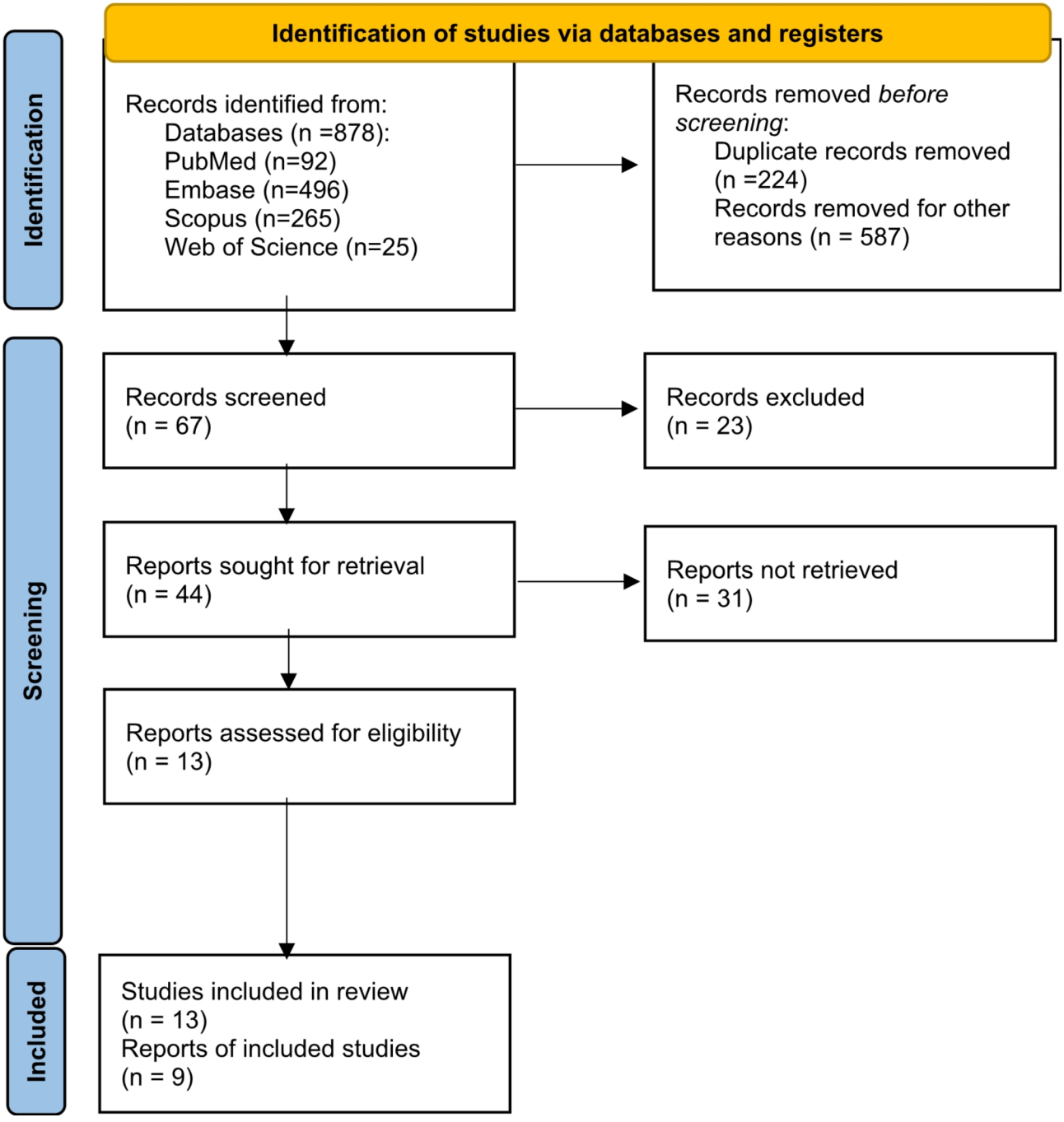

Fig. 1 Flow diagram for screening related articles; a total of 878 articles were initially retrieved and finally after removing deduplication (224), incompatibility of titles and abstracts)587(, further exclusion of 23, 31 and 4 articles due to the assay techniques, use of non-urinary sample types, and the inability of extracting data, resulted in 9 articles

Publication bias test

Funnel plots are commonly used in meta-analysis to assess publication bias and small-study effects. Asymmetric funnel plots can indicate the presence of such biases, but they can also be caused by other factors such as the choice of the plotted effect size, the presence of a moderator correlated with the study effect and size, or chance. These plots add contours of statistical significance to the funnel plot to aid interpretation. Stata 14 was used to draw funnel plot. As displayed in Fig. 6, it had a moderate asymmetry.

Discussion

Previous research underscores the significance of CXCL10 as a biomarker in the prognosis of kidney graft injuries (acute rejection (AR), TCMR, ABMR), examining

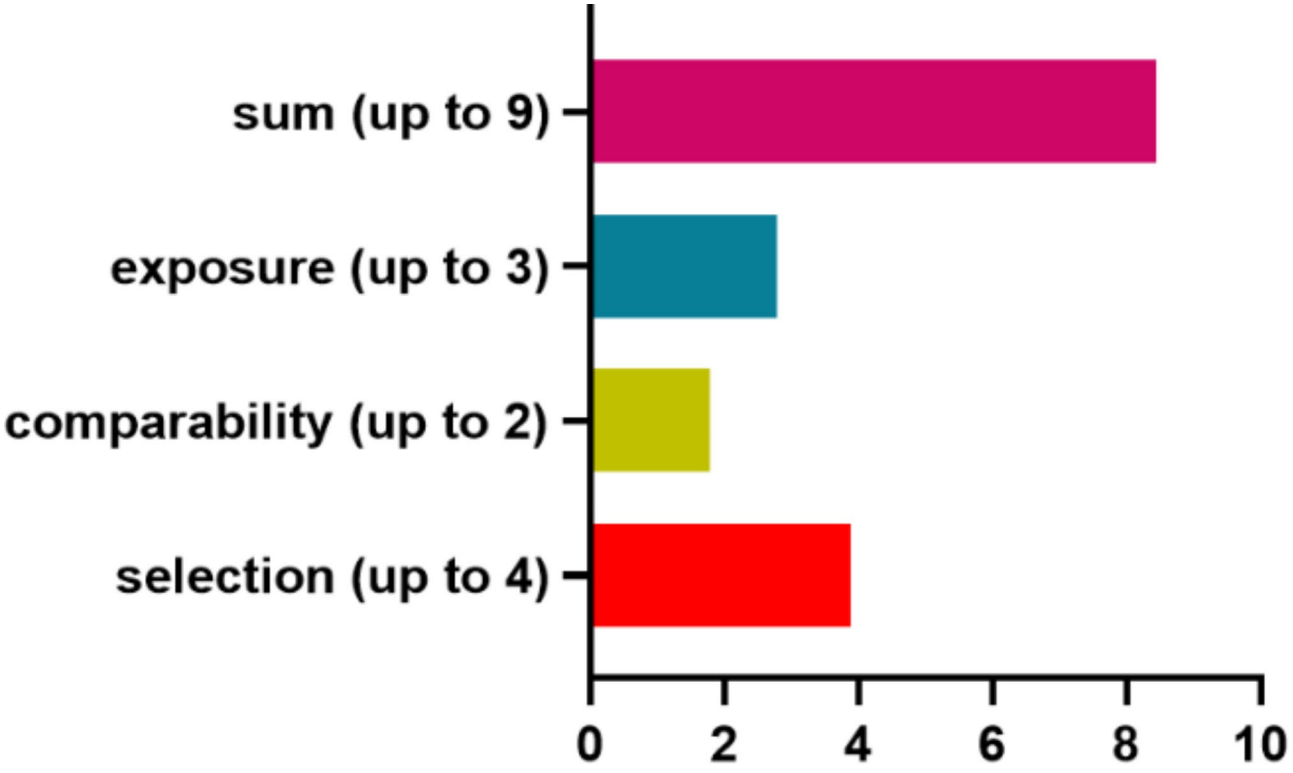

Fig. 2 The quality assessment of included studies using the Newcastle-Ottawa Scale (NOS); The NOS evaluates studies on their selection of groups, comparability of groups, and ascertainment of exposure or outcomes, represented in the star ratings displayed in X-axis

its presence in both serum and urinary assays. Investigations have not only focused on CXCL10 as an isolated marker but have also encompassed its correlative studies with serum creatinine levels.

These studies propose that CXCL10 may serve as an integral biomarker, offering predictive insights into the functional status of renal transplants [5, 6, 15–17, 20]. Rabant et al. suggested that low levels of urinary CXCL10 could predict immunological quiescence, or a low risk of acute rejection, as early as one month into stable graft conditions [31]. The study by Mühlbacher J et al. highlighted that the association of urinary CXCL10/Cr ratio with donor-specific antibodies (DSA) significantly improved the identification of ABMR and the prediction of graft loss. Their finding emphasizes the potential of CXCL10 as a biomarker in transplant medicine [19]. Earlier research, demonstrated that measuring the serum level of CXCL10 before kidney transplantation could be a predictor of acute rejection which suggest that CXCL10 levels could serve as an important indicator for preemptive measures in transplant recipients [32]. Finally, Jackson et al. concluded that CXCL10 levels don't seem to distinguish between AR and BK virus infection. They both show elevated levels of this chemokine, although diagnostic certainty is still possible when combined with other tests like a creatinine assay [33]. This study presents a comprehensive systematic review and meta-analysis that focuses on the clinical validation and comparison of CXCL10 and CXCL10/Cr urinary levels in the detection of post-kidney transplantation injuries. The analysis encompasses data from 10 studies (9 articles) involving a total of 3035 kidney transplant recipients. The findings indicate that CXCL10 protein level demonstrated a sensitivity of 0.78 (0.69–0.89) and a specificity of 0.82 (0.72–0.94), while CXCL10/Cr level exhibited a sensitivity of 0.77 (0.72–0.81) and a specificity of 0.73 (0.60–0.90). These results indicate that assessing the sensitivity and specificity of CXCL10, as opposed to CXCL10/Cr, may offer greater efficacy in predicting injuries in kidney transplant recipients. It may be related to notable variations in urinary creatinine excretion rates (uCER) among kidney transplant recipients. For instance, those with delayed graft function may have values below 300 mg/day, while patients showing prompt graft function can exceed 2,100 mg/day [34]. These differences can be influenced by several factors, including age, sex, race [35], daily changes in creatinine production, levels of physical activity, dietary habits, emotional stress, muscle mass, and overall health condition [36]. Research indicates that urinary creatinine can fluctuate significantly even within an individual, with intraindividual coefficients of variation (CVs) reported to be between 10.5% and 14.4%. Additionally, creatinine excretion may vary throughout the day and across different days [37].

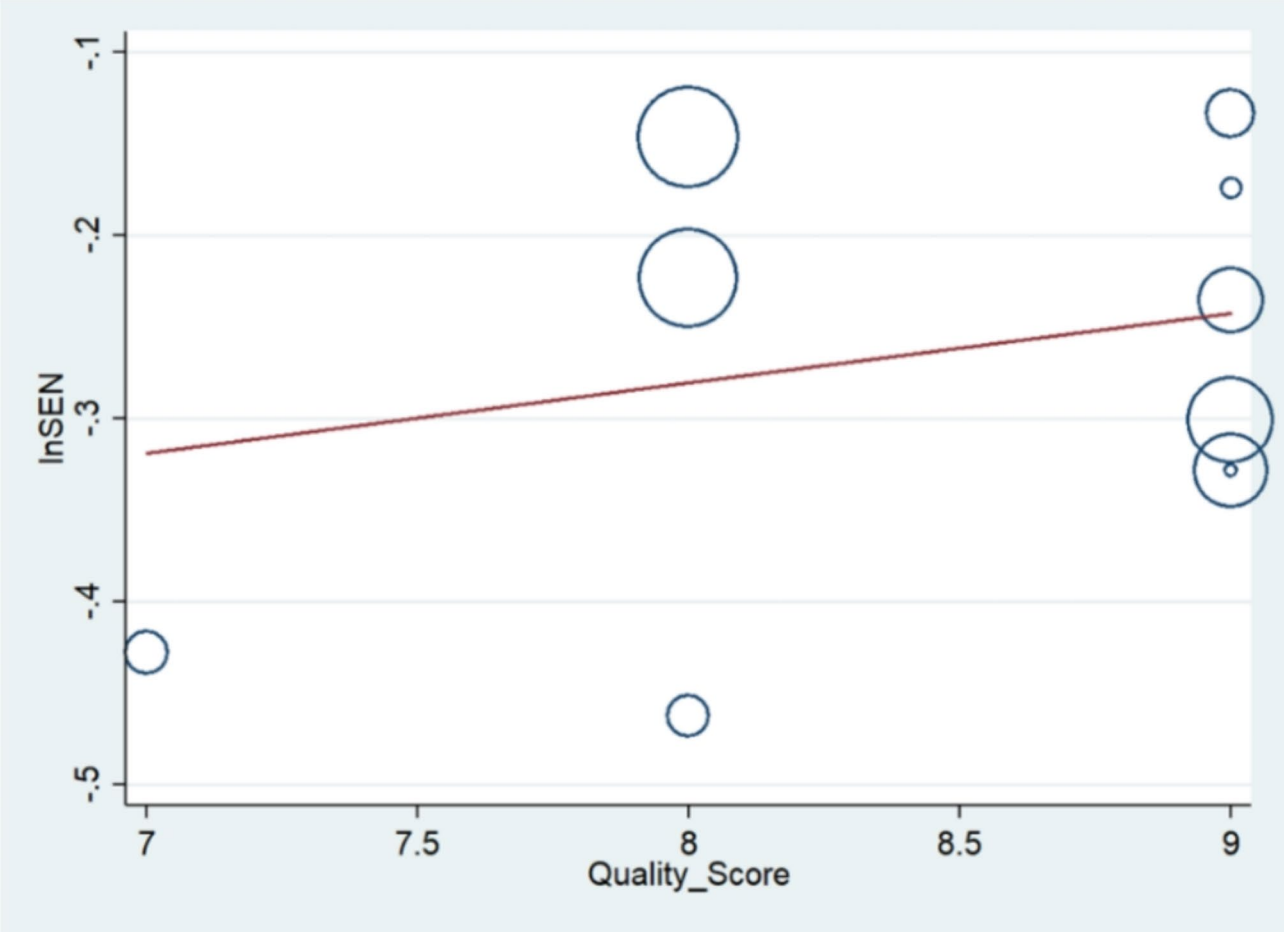

Fig. 3 The metareg plot evaluating the quality of included studies in the meta-analysis; This plot visually displays the relationship between the study quality scores based on sensitivity

Table 1 The results of the quality score analysis of the included studies in relation to sensitivity; this analysis evaluates the quality scores based on the sensitivity of the included studies and its results showed that the quality of studies were not critical factors in sensitivity outcomes

lnSEN	SEN	*p* value	95% conf. Interval
Quality_Score	0.0380267	0.544	-0.1005241 to 0.1765775
_cons	-0.5848578	0.284	-1.75863 to 0.5889142

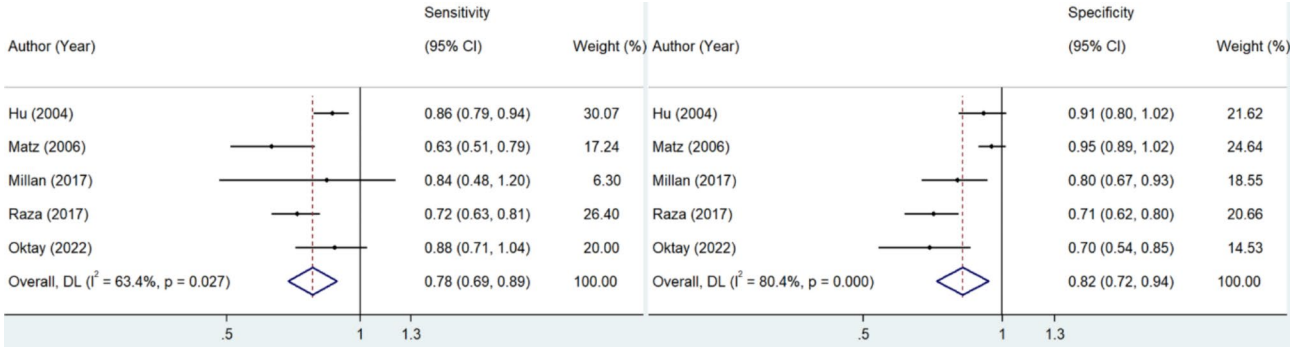

Fig. 4 Forest plots; show the 5 included studies heterogeneity and estimated exposures, sensitivity (left) and specificity (right), with urinary CXCL10 as outcome

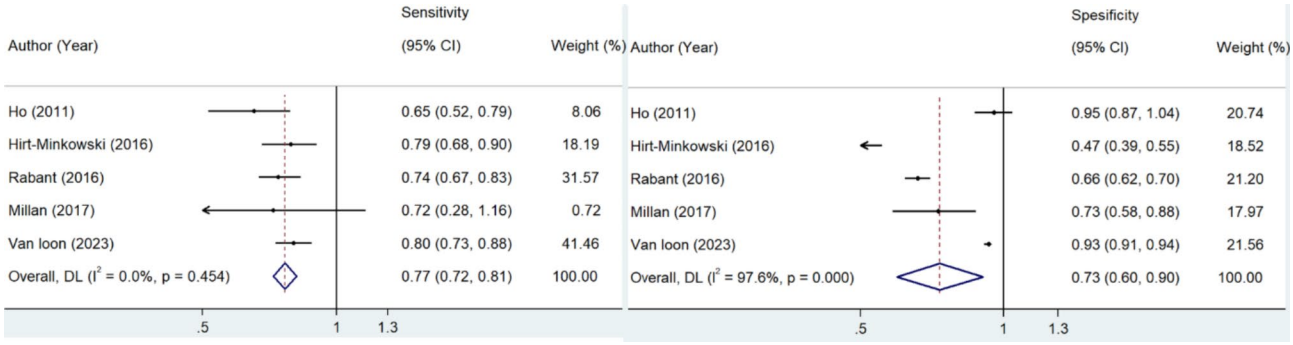

Fig. 5 Forest plots; show the 5 included studies heterogeneity and estimated exposures, sensitivity (left) and specificity (right), with urinary CXCL10/Cr as outcome

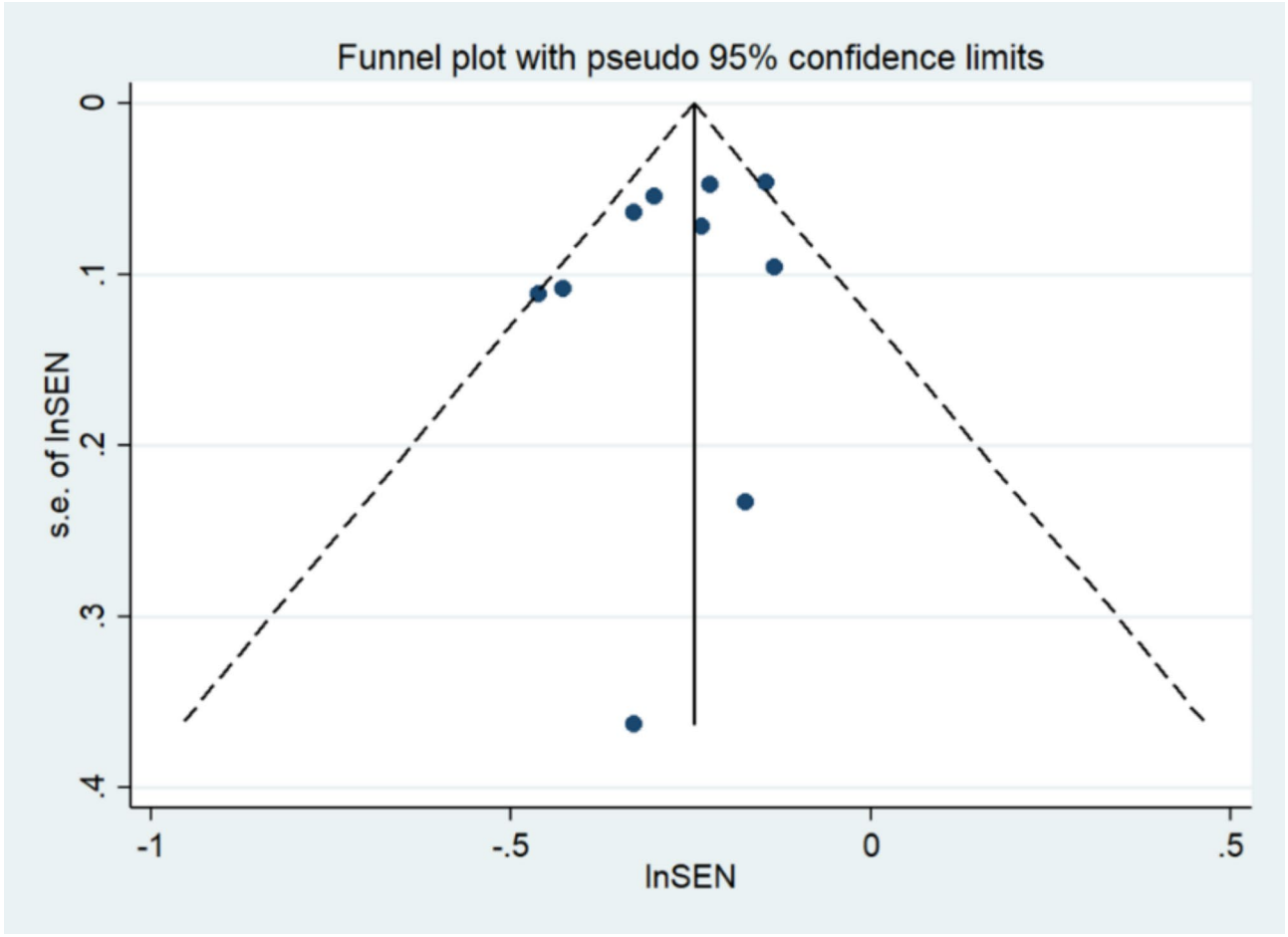

Fig. 6 The funnel plot; used to assess the potential for publication bias among the included studies for sensitivity as the exposure

Some studies have found that normalizing urinary biomarker values to creatinine, such as in the case of neutrophil gelatinase-associated lipocalin (NGAL), can help lower these intraindividual CVs [38, 39]. Waikar et al. noted that kidney injury molecule-1(KIM-1) excretion and uCER have different responses during acute disease states [34], suggesting that normalizing to creatinine is not always appropriate. Therefore, the appropriateness of normalizing urinary creatinine depends significantly on the specific research objectives, the biomarker involved, and the clinical context of the patients being studied [40].

This review encompassed nine articles [18, 24–31], five of which examined urinary CXCL10 protein levels, [25–27, 29, 30] while one included two groups [27]. The first group exclusively evaluated urinary CXCL10 protein levels, while the second group measured urinary CXCL10

to serum Cr ratio. The other four articles in the review explored urinary CXCL10 to urinary Cr ratio as a biomarker under study [18, 24, 28, 31].

Moreover, Matz et al. conducted a study involving two groups, acute cellular rejection and borderline rejection (BR), which were assessed at three different time points (2/3, 4/5, and 6/7 days) prior to rejection. The study reported varying sensitivities of 0.47, 0.62, and 0.71, with a consistent specificity of 0.95 for all time points, focusing on early post-transplant urinary CXCL10 protein levels after kidney transplantation. These data were subsequently aggregated for inclusion in the final evaluation, yielding a combined sensitivity and specificity of 0.63 and 0.95, respectively [29].

The other study that was pooled is Rabant et al. that examined urinary samples collected at three time points post-kidney transplantation 10 days, 1 month, and 3 months. The study focused on measuring the CXCL10/Cr ratio in recipients with ABMR, TCMR, and mixed rejection. The reported sensitivities for these time points were 0.57, 0.83, and 0.53, with specificities of 0.52, 0.51, and 0.76, respectively. Upon combining the data from these time points, the resulting sensitivity and specificity were 0.74 and 0.66, respectively [31].

The last study that was pooled for including in meta-analysis is Van loon et al. [24] who assessed the CXCL10/Cr protein level through an automated immunoassay method at three distinct thresholds (5%, 16%, and 25%) derived from a 5-parametere model for the non-invasive detection of acute rejection. The sensitivities reported at theses thresholds were 0.882, 0.392, and 0.248, with corresponding specificities of 0.314, 0.9, and 0.96. When the data of these threshold were combined the resulting sensitivity and specificity were 0.8 and 0.93, respectively.

The detection methods used for urinary CXCL10 in the included studies were based on assessing protein expression levels. All studies detected this urinary protein using ELISA, except for Hu [30] and Van loon [24] who used luminex assay and automated immunoassay, respectively. Across all included studies, an increased level of urinary CXCL10 was associated with a type of kidney graft injury. All urinary samples were collected post-transplantation and almost always before biopsy procedures (Table S1). Finally, it is worth noting that measuring urinary protein levels based on antibody-using tests such as ELISA is currently one of the most reliable and accurate existing methods.

The injuries related to the included studies in this review encompassed 14 different types of dysfunctions of kidney grafts. These included AR, TCMR, ABMR, mixed rejection (MR), BR, subclinical rejection (SR), clinical rejection (CLR), acute vascular rejection (AVR), BK virus nephropathy (BKVN), acute tubular necrosis (ATN), chronic rejection (CHR), late clinical rejection, graft functional decline, and graft loss. This review discusses the potential role of urinary CXCL10 assessment before performing an invasive biopsy procedure in identifying high-risk kidney transplant recipients who were developing at least one of the 14 different types of dysfunctions. Therefore, serial urinary CXCL10 monitoring in the weeks and months following transplantation may help accelerate clinical diagnosis of recipients at risk for rejection or graft loss which might help in reducing the number of biopsies. Accordingly, CXCL10 shows promise as a marker for identifying post-kidney transplant injuries, particularly rejection, further comprehensive studies are essential. These studies should focus on standardizing factors such as study design, sample type, evaluation methods, types of post-transplant injuries, and patient monitoring for a minimum of 6 months before and after transplantation. Moreover, combining the clinical data of CXCL10 with indicators like serum urea, creatinine, and proteinuria could lead to more precise models for predicting various potential injuries following kidney transplantation.

This manuscript is subject to several limitations. Firstly, numerous articles were excluded from the analysis due to insufficient information for calculating effect size. Additionally, a standardized method for grouping patients was not available, resulting in the comparison of studies with vastly different study groups, making it impossible to merge their results. Moreover, the articles employed two distinct approaches - studying CXCL10 levels and CXCL10/Cr ratios - which are not compatible for combination. These factors led to a significant decrease in the number of studies included in the meta-analysis.

Conclusion

The identification of specific and sensitive biomarkers could potentially reduce unnecessary biopsies, leading to more individualized treatment plans and improved health outcomes. While urinary CXCL10 levels have been studied as an important inflammatory chemokine in kidney post-transplant outcomes, relying solely on CXCL10 is insufficient for determining graft complications. Therefore, considering other critical clinical parameters alongside CXCL10 may facilitate early detection and intervention in graft-related complications. Notably, urinary CXCL10 assessment appears more effective in detecting post-transplant injuries than measuring the CXCL10/Cr ratio.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03728-2.

Supplementary Material 1

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"The study concept and design, data acquisition and analysis, drafting of manuscript and critical revision of the manuscript were done by S. J., A. A., R.Y., and J. R."

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Data availability
"All data generated or analyzed during this study are included in this published article and its supplementary information file."

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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