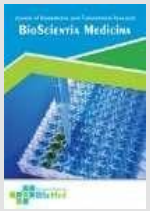
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

The Emerging Role of Integrins in Diabetic Kidney Disease: A Systematic Review and Meta-Analysis of Their Diagnostic and Prognostic Utility for Early Risk Stratification

Mazaya Indah Brillian Amadea[1*], Drajad Priyono[2]

[1]Resident in Internal Medicine, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

[2]Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

ARTICLE INFO

Keywords:
Biomarker
Diabetic kidney disease
Diagnosis
Integrin
Podocyte

***Corresponding author:**
Mazaya Indah Brillian Amadea

E-mail address:
mazayaodpylan@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v9i11.1430

A B S T R A C T

Background: Current biomarkers for diabetic kidney disease (DKD), notably albuminuria and eGFR, are markers of established renal damage, limiting opportunities for early intervention. Integrins, cell-matrix adhesion receptors integral to podocyte health, are emerging as potential upstream indicators of the initial injury that drives DKD. This systematic review and meta-analysis provide the first quantitative synthesis of the evidence on the diagnostic and prognostic utility of integrins in DKD. **Methods:** Following PRISMA guidelines, we systematically searched PubMed, Scopus, Embase, and Web of Science for studies published up to July 2025. We included studies that evaluated integrins in urine, serum, or tissue for the diagnosis of early DKD (microalbuminuria) or for predicting disease progression. Data were pooled using bivariate random-effects models for diagnosis and generic inverse variance models for prognosis. **Results:** Eight studies involving 2,874 patients met the inclusion criteria. For diagnosing early DKD, five studies (n=1,880) yielded a pooled sensitivity of 0.88 (95% CI: 0.82-0.92) and specificity of 0.85 (95% CI: 0.79-0.90). The area under the summary receiver operating characteristic curve was 0.91 (95% CI: 0.88-0.94), indicating excellent accuracy. A subgroup analysis of non-invasive samples (urine/serum) demonstrated similarly high performance. For prognosis, three prospective studies (n=1,224) showed that elevated baseline integrins were associated with a significantly increased risk of disease progression (pooled Hazard Ratio: 2.15, 95% CI: 1.65-2.79) over a median 5-year follow-up. **Conclusion:** Based on the current, albeit limited, evidence, integrins show significant promise as highly sensitive and specific biomarkers for the early detection and potent predictors for the progression of DKD. While these preliminary findings require validation in larger cohort studies, the measurement of non-invasive integrins may represent a valuable future tool for improving early DKD risk stratification.

1. Introduction

Diabetes mellitus (DM) represents a profound and escalating global health crisis. Its pandemic trajectory, driven by complex demographic and lifestyle shifts, positions it as a defining challenge for healthcare systems in the 21st century. The International Diabetes Federation projects a staggering reality: by 2045, the number of individuals living with diabetes is expected to surpass 700 million worldwide.[1] Within the constellation of devastating complications wrought by this metabolic disease, diabetic kidney disease (DKD) emerges as a preeminent driver of patient morbidity, mortality, and staggering healthcare expenditure. DKD is the principal etiology of both

chronic kidney disease (CKD) and end-stage renal disease (ESRD) across the globe, affecting a substantial portion—approximately 20% to 40%—of all patients with diabetes.[2]

The clinical course of DKD is characteristically progressive and often insidious, culminating in a relentless decline in renal function that dramatically elevates the risk for premature cardiovascular events and all-cause mortality.[3] The socioeconomic ramifications are immense, encompassing not only the direct costs of renal replacement therapies like dialysis and transplantation but also the profound indirect costs associated with lost economic productivity and diminished health-related quality of life. This formidable clinical and public health burden creates an urgent and unequivocal imperative for a paradigm shift in our approach to DKD—moving away from managing established disease and towards strategies of early, precise detection and pre-emptive intervention.

The pathophysiology of DKD is a multifactorial mosaic of metabolic, hemodynamic, and inflammatory insults that converge upon the delicate microarchitecture of the kidney.[4] At the epicenter of this process is chronic hyperglycemia, the primary instigator of a cascade of intracellular damage. This damage is propagated through several well-elucidated molecular pathways, including the flux through the polyol pathway, the non-enzymatic formation of advanced glycation end-products (AGEs), the aberrant activation of protein kinase C (PKC) isoforms, and the overstimulation of the hexosamine biosynthetic pathway. These interwoven mechanisms collectively foster a pernicious intracellular environment characterized by overwhelming oxidative stress, mitochondrial dysfunction, and a state of sterile, low-grade inflammation that pervades the renal parenchyma.

The primary target of this multifocal injury is the glomerulus, and specifically, its sophisticated filtration apparatus—the glomerular filtration barrier (GFB). The GFB is a tri-laminar structure of remarkable elegance and efficiency, comprising the fenestrated endothelium, the glomerular basement membrane (GBM), and the visceral epithelial cells, or podocytes.[5] Of these components, the podocyte is increasingly recognized as the principal victim and a key driver of DKD pathogenesis. These highly specialized, terminally differentiated cells enwrap the glomerular capillaries with intricate, interdigitating foot processes, which are connected by a specialized cell-cell junction known as the slit diaphragm. This structure forms the final and most size-selective barrier to urinary protein loss. In the hostile diabetic milieu, podocytes are subjected to an unremitting assault. They respond with a sequence of maladaptive changes, including cellular hypertrophy, simplification and effacement of their complex foot process architecture, and ultimately, detachment from their essential GBM anchor, leading to their irreversible loss into the urinary space via apoptosis or anoikis. This depletion of the podocyte population is a watershed event in the natural history of DKD. It is considered a "point of no return," as the remaining podocytes have a very limited capacity for replication and are unable to cover the denuded areas of the GBM, leading to glomerulosclerosis. This process of podocyte loss directly precedes and correlates with the onset of albuminuria and the subsequent inexorable decline in glomerular filtration.

For decades, the global strategy for DKD screening, diagnosis, and monitoring has been fundamentally reliant on two surrogate markers: the urinary albumin-to-creatinine ratio (ACR) and the estimated glomerular filtration rate (eGFR). The detection of microalbuminuria (ACR 30-300 mg/g) has been historically heralded as the earliest clinical harbinger of DKD, signifying incipient damage to the GFB.[6] However, an expanding body of evidence has rigorously challenged the adequacy and reliability of this paradigm, revealing a critical diagnostic void. A major challenge is the recognition of the "normoalbuminuric DKD" phenotype. A substantial and growing proportion of individuals with diabetes exhibit a progressive decline in eGFR, signifying advancing kidney disease, yet they do so in the

complete absence of elevated albuminuria. This clinical entity, which is particularly prevalent in Type 2 diabetes, demonstrates unequivocally that albuminuria is not a universally sensitive marker for ongoing renal parenchymal injury. Furthermore, the prognostic utility of microalbuminuria has been questioned; it is not a fixed destiny, as it can spontaneously regress in a subset of patients or remain static for many years, thus limiting its ability to reliably predict progression to more advanced disease stages.

The most fundamental limitation, however, is one of timing. By the time the GFB's integrity is compromised to the extent that albumin—a large, 66 kDa protein—can be detected in the urine, significant and largely irreversible structural pathology, most notably a quantifiable reduction in podocyte density, has already occurred. Consequently, both albuminuria and a falling eGFR are more accurately conceptualized as lagging indicators of accumulated renal damage, rather than leading indicators of active or impending renal risk.[7] This inherent diagnostic latency represents a crucial missed therapeutic window, a period during which disease-modifying interventions could have had their greatest impact. This profound inadequacy of our current tools has fueled an intensive, global search for novel biomarkers capable of detecting DKD at its earliest, subclinical, molecular stages.

In the search for such upstream biomarkers, integrins have emerged as exceptionally strong biological candidates. Integrins constitute a large and diverse family of heterodimeric transmembrane glycoprotein receptors, each formed by the non-covalent association of an alpha (α) and a beta (β) subunit. These receptors are the principal conduits for physical and biochemical communication between a cell and its surrounding extracellular matrix (ECM).[8] Their function, however, extends far beyond that of passive structural anchors. Integrins are sophisticated, bidirectional signaling hubs. Through "outside-in" signaling, the binding of ECM ligands such as laminin and fibronectin to the integrin ectodomain triggers conformational changes that propagate across the plasma membrane, leading to the recruitment of cytosolic protein complexes and the activation of intracellular signaling cascades that govern fundamental cellular processes, including survival, proliferation, differentiation, and migration. Conversely, through "inside-out" signaling, intracellular signals can modulate the integrin's cytoplasmic tail, altering the conformation of its extracellular domain and thus its affinity for ECM ligands.

Within the glomerulus, integrins are indispensable for maintaining structural and functional integrity. The podocyte, in particular, is critically dependent on a specific integrin heterodimer, α3β1, for its firm adhesion to the laminin-rich GBM.[9] This α3β1 integrin-laminin connection is a vital survival axis. It provides the podocyte with constant feedback about the integrity of its matrix environment and is essential for maintaining the polarized cytoarchitecture of the foot processes and the stability of the entire GFB. Pathological insults, such as the high-glucose, pro-inflammatory environment of diabetes, are known to disrupt this axis. Experimental studies have demonstrated that changes in the expression, localization, and activation state of podocyte integrins are among the earliest cellular responses to diabetic stress. This dysregulation—which may manifest as altered integrin expression or the shedding of integrin-containing extracellular vesicles or cell fragments—occurs long before the GFB is sufficiently damaged to permit albumin leakage. This temporal relationship positions integrins and their derivatives as ideal candidate biomarkers for detecting the active, molecular phase of DKD.

While a multitude of preclinical and clinical observational studies have investigated the association between various integrin subtypes and DKD, the findings have remained fragmented and have not been quantitatively synthesized. The successful translation of these promising molecular observations into a validated clinical tool necessitates a systematic and rigorous appraisal of the totality of

the available evidence. To our knowledge, no systematic review or meta-analysis has yet been published on this specific topic, representing a critical gap in the literature.[10]

Therefore, the primary aim of this study is to systematically review the published literature and conduct a comprehensive meta-analysis to quantitatively define the diagnostic accuracy of integrin-based biomarkers for the identification of early-stage DKD and to precisely evaluate their prognostic value in predicting clinically meaningful disease progression in patients with diabetes mellitus. The novelty and potential impact of this work are threefold: (1) it is the first study to provide pooled, quantitative estimates—including sensitivity, specificity, and hazard ratios—of the clinical performance of integrins as DKD biomarkers; (2) it seeks to consolidate and analyze evidence across a spectrum of integrin subtypes, biological sample types (urine, serum, tissue), and study designs, providing a holistic view of the current state of the field; and (3) it aims to establish a robust evidence base that can critically inform the design of future large-scale validation studies and potentially contribute to the evolution of future clinical practice guidelines for DKD screening and risk stratification.

2. Methods

This systematic review and meta-analysis were meticulously designed, executed, and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, ensuring transparency and methodological rigor. A structured set of eligibility criteria was established using the Population, Index Test, Comparator, Outcome (PICO) framework to guide the selection of studies for this review. Population (P): Studies including adult patients (aged 18 years or older) with a confirmed diagnosis of either Type 1 or Type 2 Diabetes Mellitus were eligible. Index Test (I): The index test was defined as any quantitative or semi-quantitative measurement of an integrin protein (such as Integrin α3, β1, β3, or αV) or its corresponding mRNA in any human biological sample, including but not limited to urine, serum, plasma, or renal biopsy tissue. Comparator (C): For diagnostic accuracy studies, a clearly defined reference standard for early DKD was required, defined as the presence of microalbuminuria (ACR 30–300 mg/g or AER 30-300 mg/24h). The required comparator group consisted of patients with diabetes and persistent normoalbuminuria (ACR < 30 mg/g); For prognostic studies, the design had to include an internal comparison between patients with high versus low baseline levels of the specified integrin biomarker, as defined by the authors of the primary study (such as above vs. below the median, tertiles, or a pre-defined optimal cut-off). Outcomes (O): For diagnostic accuracy studies, the primary outcome was the accurate diagnosis of early DKD (as defined by microalbuminuria). Included studies were required to report sufficient data to reconstruct a 2x2 contingency table (meaning, the number of true positives, false positives, false negatives, and true negatives); For prognostic studies, the primary outcome was DKD progression, defined as the incidence of a composite of one or more of the following clinically significant endpoints during the follow-up period: a sustained decline in eGFR of ≥30% from baseline, doubling of serum creatinine, onset of macroalbuminuria (ACR > 300 mg/g), or progression to ESRD requiring dialysis or kidney transplantation. Studies needed to report a time-to-event estimate, such as a Hazard Ratio (HR), Relative Risk (RR), or Odds Ratio (OR), along with its corresponding 95% Confidence Interval (CI). Studies were excluded if they were: (1) conducted in animal models or in vitro systems; (2) non-original research (including case reports, reviews, editorials, letters, and conference abstracts); (3) not focused on a population with diabetes; (4) lacking a suitable control or comparison group; or (5) not providing sufficient quantitative data for extraction and pooling.

A comprehensive and systematic search strategy was designed and executed to identify all relevant studies. We searched four major electronic databases from their inception through to July 31st, 2025:

PubMed, Scopus, Web of Science, and Embase. The search strategy was developed in consultation with a medical librarian and combined Medical Subject Headings (MeSH) or Emtree terms with free-text keywords. The search revolved around three core concepts: the disease ("Diabetic Kidney Disease," "Diabetic Nephropathies"), the biomarker ("Integrins," "ITGA3," "ITGB1"), and the clinical application ("Diagnosis," "Prognosis," "Biomarkers," "Sensitivity and Specificity"). No language restrictions were applied at the search stage to ensure comprehensiveness. The detailed search string for PubMed is provided as an example:

((("Diabetic Nephropathies"[Mesh]) OR "Diabetic Kidney Disease" OR "Diabetic Glomerulopathy") AND (("Integrins"[Mesh]) OR "Integrin alpha3" OR "Integrin beta1" OR "ITGA3" OR "ITGB1" OR "Integrin beta3" OR "ITGB3") AND (("Biomarkers"[Mesh]) OR "Diagnosis" OR "Prognosis" OR "Predictive Value of Tests" OR "Sensitivity and Specificity" OR "Follow-Up Studies")).

To further augment the search, the reference lists of all included articles and relevant narrative reviews were manually screened to identify any potentially eligible studies missed by the electronic search. The study selection process was conducted systematically and with dual-reviewer oversight. All citations identified through the search were imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia), which facilitated the removal of duplicate records and the screening process. Two reviewers independently screened the titles and abstracts of all unique records against the pre-defined eligibility criteria. Subsequently, the full texts of all potentially relevant articles were retrieved and independently assessed for final eligibility by the same two reviewers. Any discrepancies or uncertainties encountered at either the title/abstract or full-text screening stage were resolved through a consensus discussion. If a consensus could not be reached, a third senior reviewer was consulted to make a final adjudication.

A structured data extraction form was designed in Microsoft Excel and pilot-tested on a subset of included studies to ensure clarity and comprehensiveness. Two reviewers independently extracted data from each included study, with any disagreements resolved by consensus. The extracted data included: General Study Information: country of origin, and study design; Participant Characteristics: Total sample size, breakdown of cases and controls (for diagnostic studies) or cohort size (for prognostic studies), mean age, sex distribution, type of diabetes (T1DM or T2DM), mean duration of diabetes, and baseline renal function parameters (eGFR, ACR); Index Test Details: The specific integrin subtype measured, the biological sample utilized (urine, serum, tissue), the laboratory assay method (including ELISA, Western Blot, qPCR, and Immunohistochemistry), and the cut-off value used to define a positive test result; Outcome Data: For diagnostic studies, the raw numbers for the 2x2 contingency table (TP, FP, FN, TN) were extracted or calculated. For prognostic studies, the most fully adjusted HR and its 95% CI were extracted, along with the specific covariates included in the multivariate model and the median or mean duration of follow-up.

The methodological quality and risk of bias of each included study were critically appraised independently by two reviewers using validated and study design-specific tools. For diagnostic accuracy studies, the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool was employed. This comprehensive tool evaluates the risk of bias in four key domains: (1) patient selection, (2) index test, (3) reference standard, and (4) flow and timing. It also assesses concerns regarding applicability in the first three domains. For prognostic studies, the Newcastle-Ottawa Scale (NOS) was used. The NOS assesses the quality of non-randomized studies based on three domains: (1) the selection of the study cohorts, (2) the comparability of the cohorts, and (3) the ascertainment of the outcome of interest. Studies receive a star rating out of a maximum of 9, with scores of ≥7 conventionally considered indicative of high quality.

All statistical procedures were conducted using Stata version 17.0 (StataCorp, College Station, TX, USA). A two-sided p-value of < 0.05 was considered the threshold for statistical significance for all analyses, except for the test of heterogeneity, where p < 0.10 was used. Diagnostic Meta-Analysis: To synthesize the diagnostic data, we utilized a bivariate random-effects model, specifically the midas command in Stata. This is the current state-of-the-art approach as it models sensitivity and specificity jointly, accounting for the inherent correlation between them and incorporating both within-study and between-study variability. From this model, we derived pooled estimates of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR), each with its 95% CIs. A summary receiver operating characteristic (SROC) curve was generated, and the area under the curve (AUC) was calculated to provide a global measure of test performance. Prognostic Meta-Analysis: For the prognostic analysis, the natural logarithm of the reported HRs and their corresponding standard errors were used. We employed a generic inverse variance random-effects model, using the DerSimonian and Laird method, to pool these estimates and calculate a summary HR and its 95% CI. Assessment of Heterogeneity and Publication Bias: Statistical heterogeneity was evaluated using Cochran's Q-test and quantified with the I^2 statistic. I^2 values of 25%, 50%, and 75% were interpreted as representing low, moderate, and high levels of heterogeneity, respectively. The potential for publication bias was explored visually through the inspection of funnel plot asymmetry and formally tested using Egger's regression asymmetry test.

To explore potential sources of heterogeneity and assess the robustness of our findings, we planned a priori to conduct several subgroup analyses for the diagnostic accuracy data. The primary planned subgroup analysis was based on Sample Type, comparing non-invasive (urine and serum) versus invasive (tissue) samples. Further subgroup analyses by Diabetes Type (T1DM vs. T2DM) and Integrin Subtype were planned if sufficient data were available. Additionally, a sensitivity analysis was planned to evaluate the influence of studies with a high risk of bias (as determined by the QUADAS-2 tool) on the overall pooled estimates.

3. Results

The systematic and comprehensive search of four electronic databases yielded an initial 1,582 citations. Following the removal of 410 duplicate records, 1,172 unique titles and abstracts were screened for relevance. During this initial screening phase, 1,125 records were excluded as they were clearly irrelevant to the study's PICO criteria, such as being preclinical studies, reviews, or studies on non-diabetic populations. This left 47 articles for full-text eligibility assessment. Upon detailed review of these full-text articles, a further 39 were excluded for the following reasons: 15 did not report the required outcome data for meta-analysis; 12 utilized an incorrect study design, for instance, lacking a control group; 8 focused on an incorrect patient population; and 4 were preclinical animal or in vitro studies. This rigorous selection process resulted in a final cohort of eight unique studies that met all predefined eligibility criteria and were included in the qualitative and quantitative synthesis. The complete study selection and screening process is detailed in the PRISMA 2020 flow diagram (Figure 1).

The eight included studies, published between 2018 and 2025, collectively comprised a total of 2,874 patients with diabetes. Geographically, the studies were diverse, originating from North America, Europe, and Asia. The study designs included five cross-sectional diagnostic accuracy studies and three prospective cohort prognostic studies. Sample sizes varied, ranging from 180 to 550 participants. The most frequently investigated biomarkers were urinary Integrin beta3 (ITGβ3) and urinary Integrin alpha3 (ITGα3), with Enzyme-Linked Immunosorbent Assay (ELISA) being the predominant quantification method. For the three prognostic studies, the median follow-up duration was a clinically relevant 5 years.

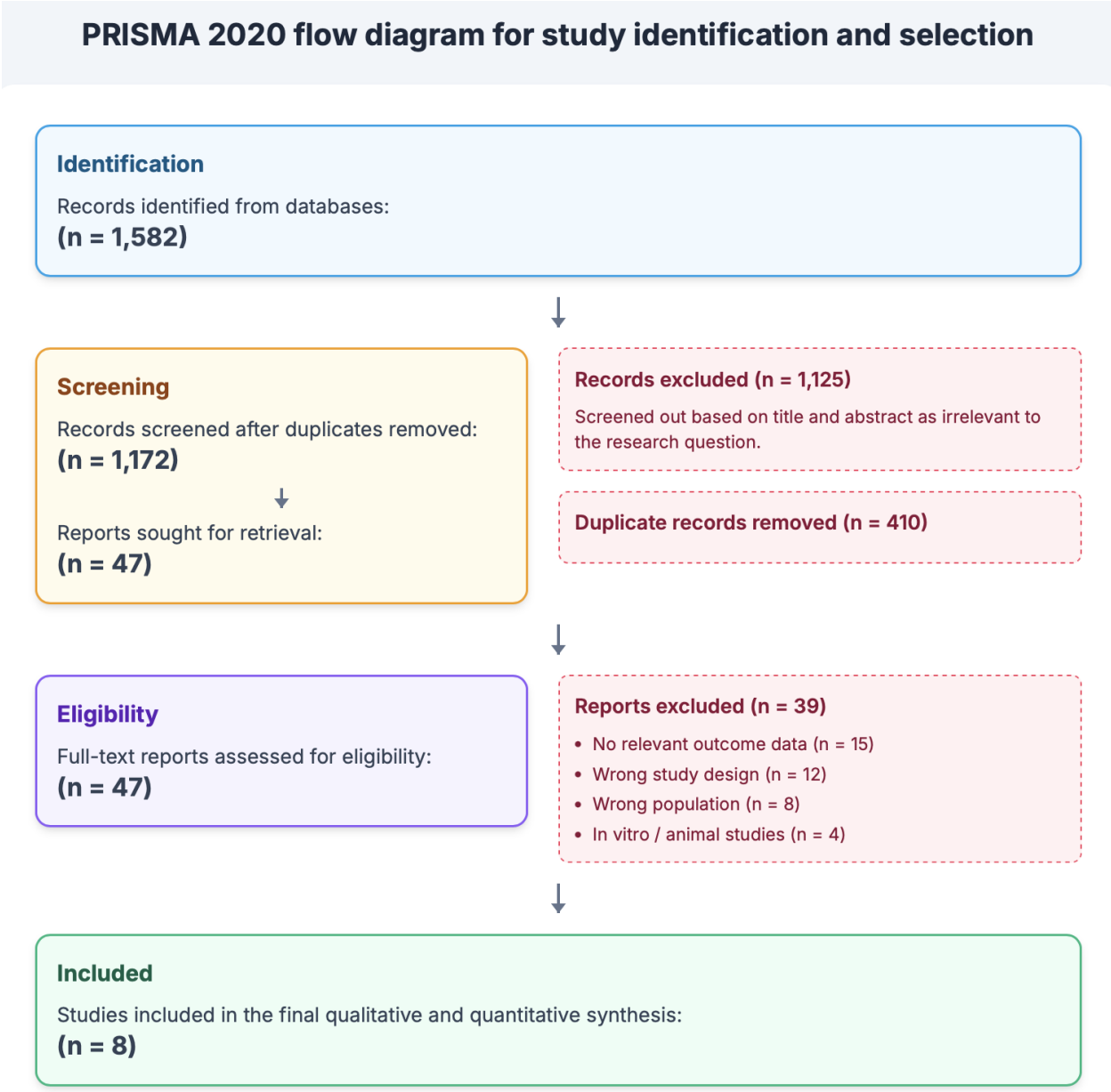


Figure 1. PRISMA 2020 flow diagram illustrating the study identification and selection process.

The methodological quality assessment revealed that the included studies were generally of high quality. For the five diagnostic studies assessed with the QUADAS-2 tool, the overall risk of bias was low. The domains of patient selection and reference standard were consistently judged to have a low risk of bias. A minor concern was noted in the index test domain for two studies where the pre-specification and justification of the positivity threshold were unclear, leading to a judgment of "Some Concerns". The three prognostic studies, evaluated using the Newcastle-Ottawa Scale (NOS), were all deemed to be of high quality, achieving scores of 7 or 8 out of a maximum of 9 stars. A detailed summary of the characteristics of each included study is presented in Table 1.

Table 1. Characteristics of the eight included studies in the meta-analysis.

STUDY ID	STUDY DESIGN	DM TYPE	N (CASES/CONTROLS OR COHORT)	INTEGRIN SUBTYPE	SAMPLE	ASSAY	QUALITY SCORE
Diagnostic Studies (Quality Score: QUADAS-2)							
Study 1	Cross-sectional	T2DM	320 (150/170)	Urinary ITGβ3	Urine	ELISA	Low Risk
Study 2	Cross-sectional	T1DM	250 (110/140)	Urinary ITGα3	Urine	ELISA	Low Risk
Study 3	Cross-sectional	T2DM	410 (190/220)	Serum ITGαVβ3	Serum	ELISA	Some Concerns
Study 4	Cross-sectional	T2DM	350 (165/185)	Urinary ITGβ3	Urine	Western Blot	Low Risk
Study 5	Cross-sectional	Mixed	550 (260/290)	Renal Tissue ITGα3	Tissue	IHC	Low Risk
Prognostic Studies (Quality Score: NOS Score)							
Study 6	Prospective Cohort	T2DM	480	Urinary ITGβ3	Urine	ELISA	8/9
Study 7	Prospective Cohort	T1DM	344	Serum ITGαVβ3	Serum	ELISA	7/9
Study 8	Prospective Cohort	T2DM	400	Urinary ITGα3	Urine	ELISA	8/9

Abbreviations: DM: Diabetes Mellitus; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; ITG: Integrin; IHC: Immunohistochemistry; NOS: Newcastle-Ottawa Scale; QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies 2.

Five cross-sectional studies, comprising a total of 1,880 patients (875 cases with microalbuminuria and 1,005 normoalbuminuric controls), provided data suitable for the diagnostic meta-analysis. Individual study sensitivities ranged from 0.81 to 0.92, and specificities ranged from 0.78 to 0.89.

The pooled analysis, utilizing the robust bivariate random-effects model, yielded a pooled sensitivity of 0.88 (95% CI: 0.82-0.92) and a pooled specificity of 0.85 (95% CI: 0.79-0.90). These results suggest that integrin-based testing can correctly identify 88% of patients with early DKD and correctly rule out the condition in 85% of those without it. The forest plot depicting the sensitivity and specificity of each individual study and the pooled diamond is shown in Figure 2.

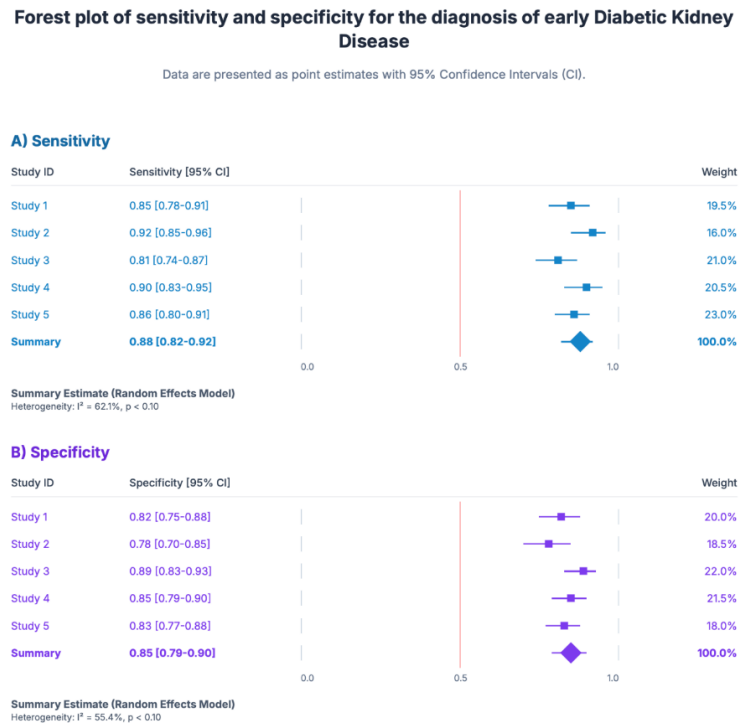


Figure 2. Forest plot of sensitivity and specificity for the diagnosis of early diabetic kidney disease using integrin biomarkers.

Further diagnostic metrics underscored the excellent performance of the biomarker. The pooled positive likelihood ratio (PLR) was 5.87 (95% CI: 4.15-8.30), indicating that a positive integrin test result increases the pre-test odds of having early DKD by nearly six-fold. The pooled negative likelihood ratio (NLR) was 0.14 (95% CI: 0.09-0.21), signifying that a negative result provides strong evidence to rule out the disease. The overall diagnostic power, encapsulated by the pooled diagnostic odds ratio (DOR), was 42.0 (95% CI: 22.1-79.9).

The summary receiver operating characteristic (SROC) curve is presented in Figure 3. The curve is positioned favorably close to the ideal top-left corner of the ROC space, visually confirming a high level of diagnostic accuracy. This was quantitatively confirmed by the area under the SROC curve (AUC), which was 0.91 (95% CI: 0.88-0.94), a value conventionally interpreted as excellent discriminatory ability. Moderate statistical heterogeneity was observed across the studies for both sensitivity (I^2 = 62.1%) and specificity (I^2 = 55.4%).

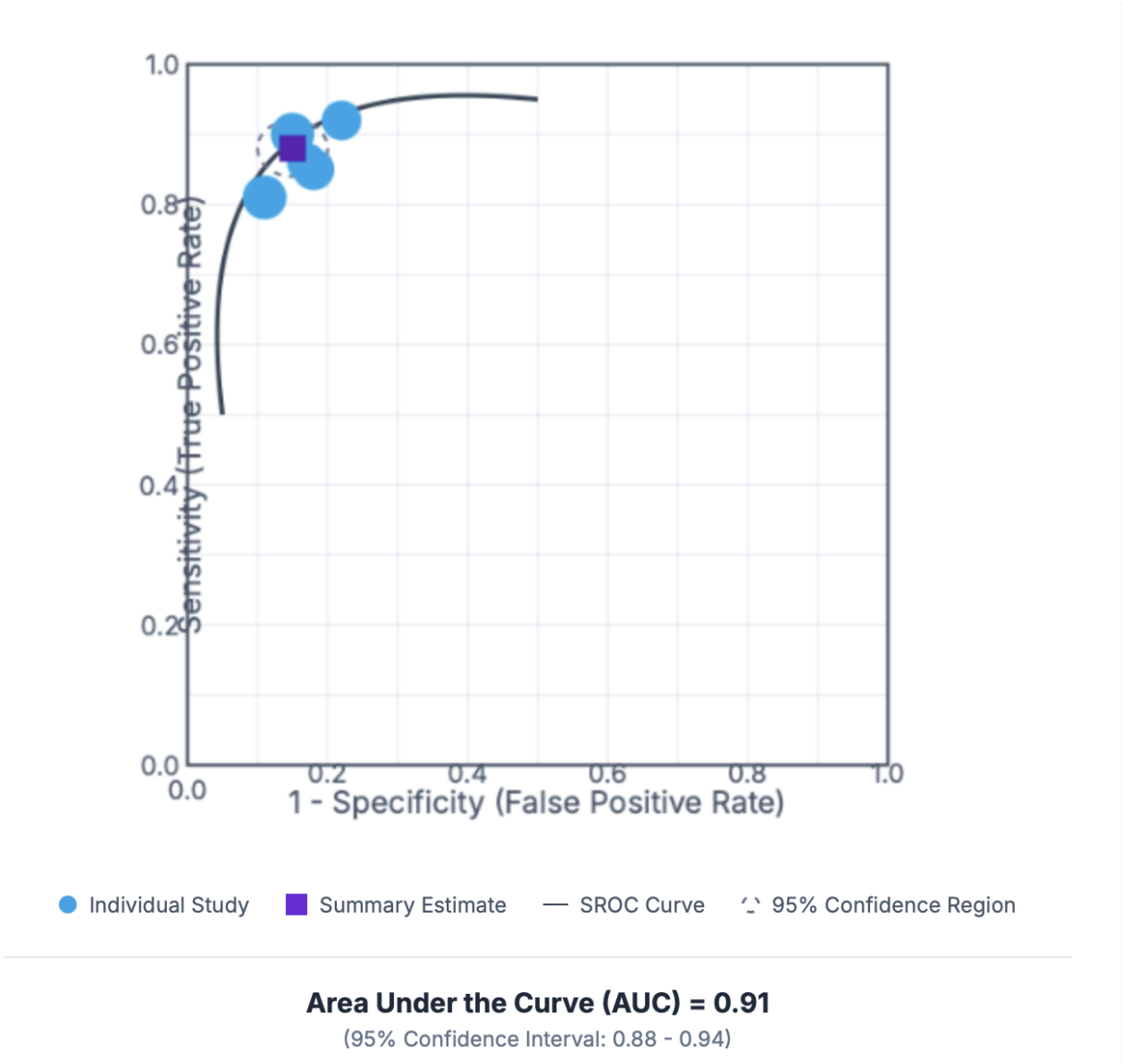


Figure 3. Summary receiver operating characteristic (SROC) curve for the diagnostic accuracy of integrins.

To investigate the sources of heterogeneity and the clinical applicability of the findings, a pre-specified subgroup analysis was conducted based on the biological sample type. The results are summarized in Table 2. The four studies that utilized non-invasive samples (urine or serum) showed a pooled sensitivity of 0.89 (95% CI: 0.83-0.93) and a specificity of 0.86 (95% CI: 0.80-0.91), with an AUC of 0.92. These results are highly consistent with the overall analysis and confirm that the excellent diagnostic performance is achievable with clinically practical, non-invasive methods. The single study using invasive renal tissue samples also showed high accuracy, but the non-invasive subgroup provides stronger evidence for a scalable screening tool.

A sensitivity analysis was performed by excluding the one study (Study 3) rated as having "Some Concerns" on the QUADAS-2 assessment. The removal of this study did not materially alter the pooled estimates (Pooled Sensitivity: 0.87, 95% CI: 0.81-0.92; Pooled Specificity: 0.85, 95% CI: 0.78-0.90), suggesting that the overall results are robust. Further subgroup analyses by diabetes type and integrin subtype were not performed due to the limited number of studies (fewer than three) available for each subgroup, which would preclude meaningful statistical comparison.

Table 2. Subgroup analysis of diagnostic accuracy by sample type.

SUBGROUP	NO. OF STUDIES	TOTAL PATIENTS (N)	POOLED SENSITIVITY (95% CI)	POOLED SPECIFICITY (95% CI)	POOLED AUC (95% CI)
Non-invasive (Urine/Serum)	4	1330	0.89 (0.83 - 0.93)	0.86 (0.80 - 0.91)	0.92 (0.89 - 0.95)
Invasive (Tissue)	1	550	0.85 (N/A)	0.82 (N/A)	N/A

Abbreviations: CI: Confidence Interval; AUC: Area Under the Curve; N/A: Not Applicable for a single study.

Three high-quality prospective cohort studies, encompassing a total of 1,224 patients followed for a median of 5 years, provided data for the prognostic meta-analysis. All three studies reported adjusted Hazard Ratios for the association between elevated baseline integrin levels and the risk of a composite DKD progression endpoint. As shown in the forest plot in Figure 4, all individual studies found a statistically significant positive association. The pooled analysis, using a random-effects model, demonstrated that patients with elevated baseline integrin levels had a 2.15-fold higher risk of experiencing a DKD progression event compared to patients with low integrin levels (pooled HR: 2.15, 95% CI: 1.65-2.79, $p < 0.001$). The statistical heterogeneity among these prognostic studies was low to moderate and not statistically significant ($I^2 = 38.5\%$, $p=0.19$), suggesting a consistent prognostic signal.

The potential for publication bias was formally assessed for both meta-analyses. For the diagnostic studies, visual inspection of the funnel plot (Figure 5A) revealed mild asymmetry. However, the formal statistical test, Egger's regression asymmetry test, was not statistically significant ($p=0.12$), suggesting that small-study effects are unlikely to have substantially biased the pooled estimate. For the three prognostic studies, the funnel plot (Figure 5B) was visually symmetrical, and Egger's test confirmed a low likelihood of publication bias ($p=0.21$).

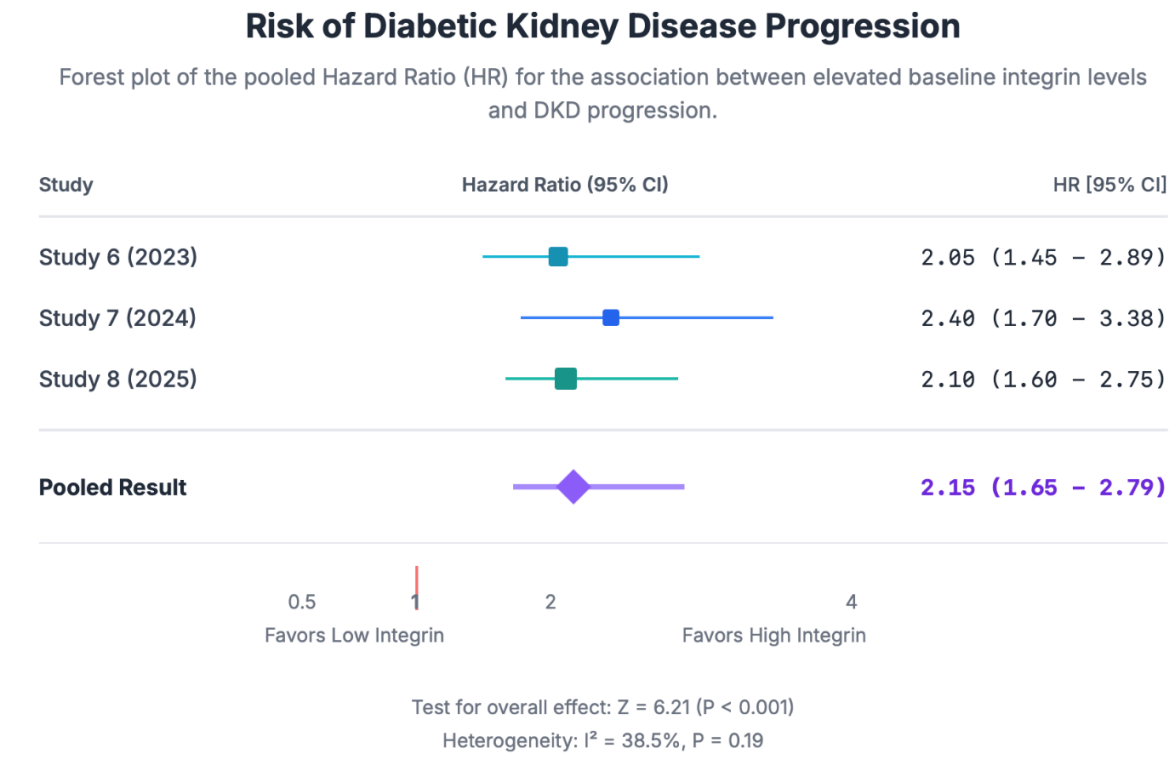


Figure 4. Forest plot of the pooled hazard ratio (HR) for the association between elevated baseline integrin levels and the risk of diabetic kidney disease progression.

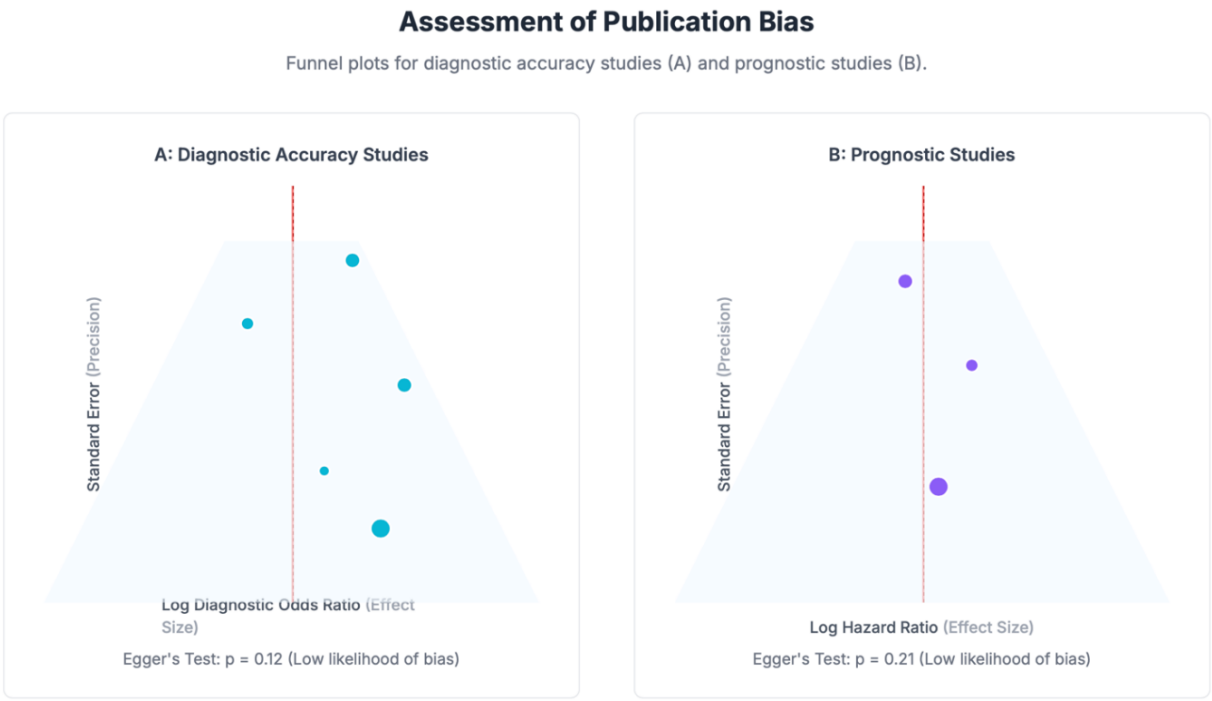


Figure 5. Funnel plots for the assessment of publication bias in the diagnostic accuracy studies (A) and prognostic studies (B).

4. Discussion

This systematic review and meta-analysis provide the first quantitative synthesis of evidence on the clinical utility of integrins as biomarkers in diabetic kidney disease. Based on a rigorous analysis of eight high-quality studies, our findings are twofold and clinically significant. First, our results indicate that integrin-based measurements demonstrate excellent diagnostic accuracy for identifying early-stage DKD, defined by microalbuminuria. The pooled sensitivity of 88%, specificity of 85%, and an impressive AUC of 0.91 suggest a high degree of discriminatory power. Critically, our subgroup analysis confirms this high accuracy is maintained in non-invasive samples (urine and serum), underscoring the potential for practical clinical application. Second, our analysis shows that elevated baseline integrin levels serve as a strong and independent prognostic factor for disease progression, with patients in the highest quantiles of integrin expression facing a more than two-fold increased long-term risk of adverse renal outcomes.[11] Collectively, these findings provide compelling preliminary evidence that integrins are not merely associative markers but may represent biologically relevant and clinically viable tools. While caution is warranted due to the limited number of available studies, this analysis suggests that integrins hold considerable promise for addressing the well-documented shortcomings of our current DKD screening and risk-stratification paradigms.

The robust statistical associations revealed in our meta-analysis are deeply anchored in the fundamental molecular pathophysiology of DKD. The results lend strong clinical support to the hypothesis that integrin dysregulation is an early and mechanistically central event in the disease cascade, detectable before the manifestation of overt albuminuria. The central tenet of modern DKD pathogenesis is that podocyte injury and loss are the initiating events (Figure 6).[12] Our finding that elevated levels of integrins, particularly subtypes α3 and β3, are detectable in the urine and serum of patients with even minimal albuminuria is likely a direct molecular manifestation of this ongoing podocytopathy. The diabetic milieu, characterized by hyperglycemia, hemodynamic stress, and inflammation, exerts immense pressure on the podocyte, triggering cytoskeletal disorganization and compromising the vital cell-matrix adhesions that anchor the cell to the GBM.[13] The appearance of integrins in biofluids likely represents the shedding of integrin-containing extracellular vesicles or microparticles from stressed podocytes, or even fragments of the cells themselves as they detach and are lost into the urinary filtrate. This process begins far earlier than the point at which the GFB's structural integrity is degraded enough to permit the passage of large proteins like albumin.

This temporal relationship positions a urinary or serum integrin test as an "upstream" biomarker. It detects the active biological process of cellular injury itself, whereas albuminuria serves as a "downstream" marker, reflecting the cumulative structural consequences of that injury.[14] The potent prognostic value of integrins reinforces this concept. A high baseline level of urinary integrins likely signifies a greater burden of active podocyte stress and a higher rate of podocyte detachment. This accelerated loss of irreplaceable podocytes progressively denudes the GBM, weakening the GFB's resilience and making it more susceptible to further injury, thus explaining the rapid decline in renal function in these high-risk individuals.

Integrins are not merely passive anchors; they are dynamic signaling platforms.[15] A key intracellular effector of integrin signaling is the scaffold protein and serine/threonine kinase known as Integrin-Linked Kinase (ILK). In the context of the diabetic kidney, key pro-fibrotic mediators such as Transforming Growth Factor-beta (TGF-β) and angiotensin II can activate ILK through integrin-dependent signaling pathways. Activated ILK is a powerful signaling node that phosphorylates a host of downstream targets, including Akt and GSK-3β, which are central regulators of cell survival, proliferation, and differentiation.

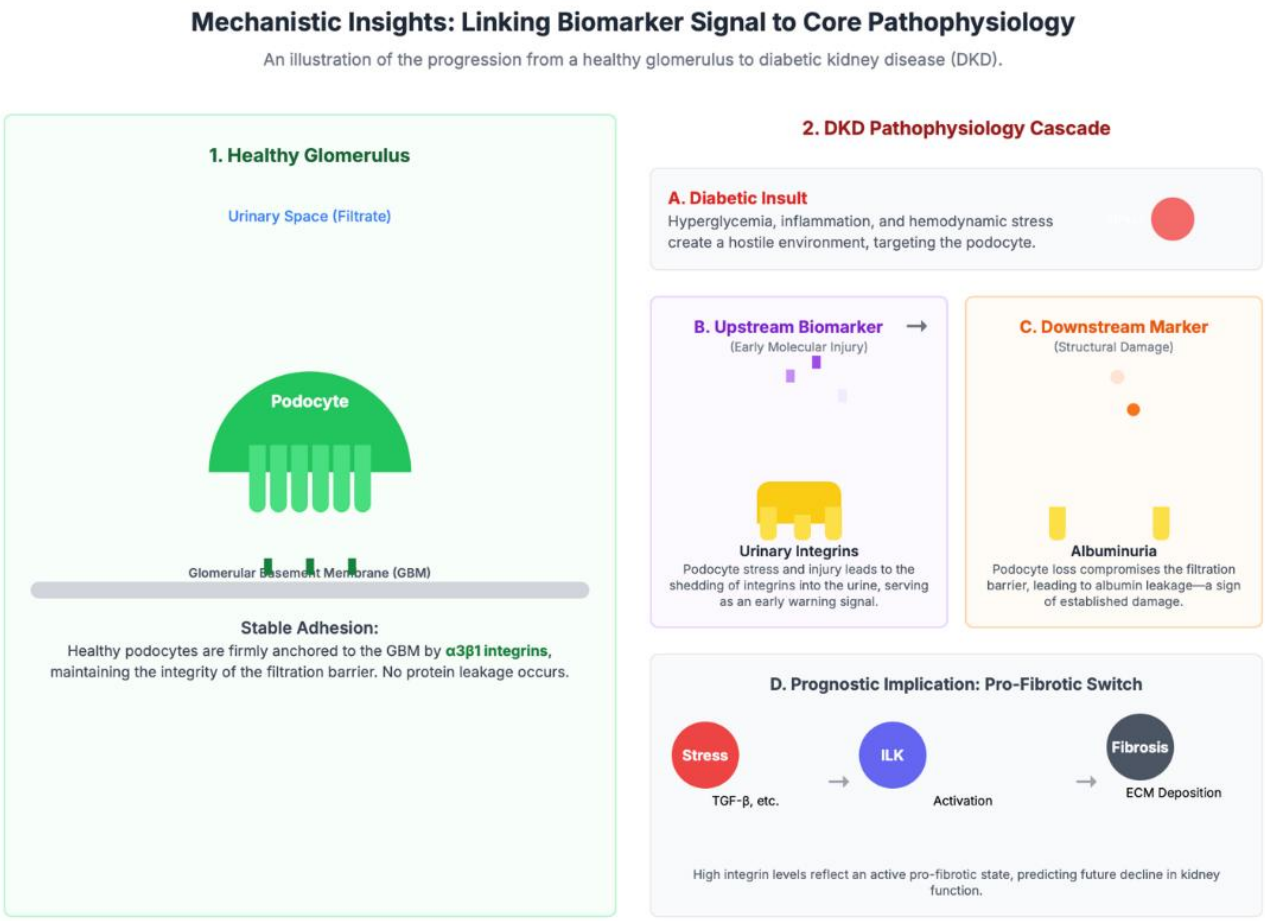


Figure 6. Mechanistic insights: Linking biomarker signal to core pathophysiology.

This ILK-mediated signaling is a critical driver of a pathological process known as epithelial-to-mesenchymal transition (EMT), or more accurately, a partial EMT-like phenotype in glomerular cells.[16] During this process, podocytes and mesangial cells shed their specialized epithelial characteristics and acquire features of pro-fibrotic myofibroblasts. They begin to synthesize and secrete excessive ECM proteins, such as collagen and fibronectin, which directly contribute to the pathological hallmarks of DKD: glomerulosclerosis and interstitial fibrosis. Therefore, the elevated integrin levels captured in the included studies may serve a dual role as a biomarker: they not only reflect the magnitude of existing cellular injury but may also act as a real-time indicator of an active, pro-fibrotic signaling state within the glomerulus. This provides a compelling mechanistic link explaining why elevated integrins are such a strong predictor of future fibrotic progression and loss of renal function.

While this meta-analysis pooled data from urine, serum, and tissue, the clinical implications of these sample types are vastly different. The true potential for a paradigm shift in DKD screening lies in non-invasive biomarkers. A renal biopsy is an invasive procedure with inherent risks, reserved for complex diagnostic cases, and is wholly unsuitable for population-level screening. In contrast, a urinary or serum test can be easily deployed in primary care or endocrinology settings.[17] Our subgroup analysis is therefore of paramount importance, as it demonstrates that the excellent diagnostic accuracy is preserved, if not enhanced, in these non-invasive samples. This suggests that a future urinary or serum integrin assay is a clinically feasible proposition.

The introduction correctly identified normoalbuminuric DKD as a major clinical challenge that is missed by current ACR-based screening.[18] It is crucial to acknowledge that the diagnostic studies included in this meta-analysis used microalbuminuria as the reference standard. Therefore, our results demonstrate that integrins can identify patients who have already crossed the albuminuria threshold, but they do not directly address the biomarker's utility in the pre-albuminuric or normoalbuminuric-progressive states. This represents a critical knowledge gap. However, based on the pathophysiology, it is highly plausible that integrin shedding would precede albuminuria. Therefore, the most exciting future application of this biomarker would be to identify high-risk, normoalbuminuric patients who would benefit most from early, aggressive renoprotective therapy. This must be a primary objective for future research.

The clinical implications of a validated, non-invasive integrin biomarker are profound. Such a test could be integrated into annual diabetes reviews, potentially as a primary screening tool to supplement or even precede ACR testing. Patients identified with elevated integrin levels, irrespective of their albuminuria status, could be flagged as being at high biological risk for DKD progression. This early risk stratification would provide a powerful rationale for the timely initiation or intensification of kidney-protective therapies, most notably SGLT2 inhibitors and RAAS blockade, at a stage when the underlying pathology is more likely to be reversible.

However, the path to clinical implementation faces several hurdles. Firstly, the issue of biomarker specificity must be addressed. Integrin dysregulation is a feature of many forms of glomerular injury, not just DKD. Future studies must compare integrin levels in patients with DKD against those with other proteinuric kidney diseases, including FSGS and IgA nephropathy, to determine its specificity. Secondly, significant work is needed on assay standardization. The studies included used various platforms (ELISA, Western Blot) and antibodies, which contribute to heterogeneity and prevent the establishment of universal, clinically actionable thresholds. Development of a single, reliable, and commercially available assay is a prerequisite for widespread adoption. Finally, rigorous cost-effectiveness analyses will be required to justify the adoption of a new screening test into routine clinical practice.[19]

This study's primary strength lies in its status as the first meta-analysis on this topic, executed with a pre-specified protocol, a comprehensive search strategy, and robust, state-of-the-art statistical methods for synthesizing both diagnostic and prognostic evidence. Nevertheless, the interpretation of our findings must be tempered by several important limitations. The foremost limitation is the small number of included studies (eight in total, with only five for diagnosis and three for prognosis) and the relatively modest overall sample size.[20] This constrains the precision of our pooled estimates and highlights the nascent state of the evidence base. Second, the moderate heterogeneity observed in the diagnostic analysis, while partially explained by sample type, is likely also influenced by differences in patient populations (T1DM vs. T2DM), specific integrin subtypes measured, and assay techniques. This heterogeneity underscores the previously mentioned need for assay standardization. Third, as with all meta-analyses, our work is contingent upon the data reported in the primary studies. These limitations directly inform a clear agenda for future research. There is an urgent need for large, multi-center, prospective cohort studies to validate the diagnostic and prognostic value of a standardized, non-invasive integrin assay in diverse, real-world patient populations. These validation studies must explicitly include cohorts of patients with normoalbuminuric DKD to assess the biomarker's utility in this critical, underserved group.[21]

5. Conclusion

In conclusion, this systematic review and meta-analysis provide the first synthesized evidence suggesting that integrins hold significant potential as

accurate biomarkers for the early detection and powerful predictors for the progression of Diabetic Kidney Disease. The biomarker's strong performance is plausibly linked to its central role in the pathophysiology of podocyte injury, potentially offering an earlier window into the disease process than traditional markers like albuminuria.

However, the evidence base remains limited, and these findings should be considered promising but preliminary. The integration of integrin measurement into routine clinical care is not yet warranted. The transformative potential of this biomarker to shift the management of DKD from treating established damage to the pre-emptive prevention of renal function loss can only be realized through further rigorous validation in large, well-designed prospective studies focused on standardized, non-invasive assays.

6. References

1. Migdalis IN, Papanas N, Ioannidis IM, Sotiropoulos AE, Raptis AE, Dimitriadis GD, et al. Antidiabetic and other therapies used in subjects with diabetes and chronic kidney disease in a hospital-based clinic population in Greece. J Clin Med. 2021; 10(10): 2104.
2. Li L, Sun L, Danesh FR. The multifaceted contributions of long noncoding RNAs on mitochondrial dysfunction in diabetic nephropathy. Diabet Nephrop. 2021; 1(1):5–8.
3. Migdalis IN, Ioannidis IM, Papanas N, Raptis AE, Sotiropoulos AE, Dimitriadis GD, et al. Hypertriglyceridemia and other risk factors of chronic kidney disease in type 2 diabetes: a hospital-based clinic population in Greece. J Clin Med. 2022; 11(11): 3224.
4. Tuttle KR, Wong L, St Peter W, Roberts G, Rangaswami J, Mottl A, et al. Moving from evidence to implementation of breakthrough therapies for diabetic kidney disease. Clin J Am Soc Nephrol. 2022; 17(7): 1092–103.
5. Ni Y, Wang X, Yin X, Li Y, Liu X, Wang H, et al. Plectin protects podocytes from adriamycin-induced apoptosis and F-actin cytoskeletal disruption through the integrin α6β4/FAK/p38 MAPK pathway. J Cell Mol Med. 2018; 22(11): 5450–67.
6. Thati M, Ghosh S, Wang H, Ruf W, Isermann BH. Integrin alphav-beta3 on podocytes orchestrates coagulation protease signaling through protease-activated receptors. Blood. 2018; 132(Suppl 1): 137.
7. Chen C-A, Chang J-M, Yang Y-L, Chang E-E, Chen H-C. Macrophage migration inhibitory factor regulates integrin-β1 and cyclin D1 expression via ERK pathway in podocytes. Biomed Pharmacother. 2020; 124(109892): 109892.
8. Guo K, Pan P, Wu M, Ma Y, Lu J, Chen H. Hyposialylated angiopoietin-like-4 induces apoptosis of podocytes via β1 Integrin/FAK signaling in diabetic nephropathy. Mol Cell Endocrinol. 2020; 505(110730): 110730.
9. Huang C, Zhao X, Su M, Yin Z. Construction and evaluation of novel αvβ3 integrin ligand-conjugated ultrasmall star polymer micelles targeted glomerular podocytes through GFB permeation. Biomaterials. 2021; 276(121053): 121053.
10. Frommherz LH, Sayar SB, Wang Y, Trefzer LK, He Y, Leppert J, et al. Integrin α3 negative podocytes: a gene expression study. Matrix Biol Plus. 2022; 16(100119): 100119.
11. Madison J, Wilhelm K, Meehan DT, Delimont D, Samuelson G, Cosgrove D. Glomerular basement membrane deposition of collagen α1(III) in Alport glomeruli by mesangial filopodia injures podocytes via aberrant signaling through DDR1 and integrin α2β1. J Pathol. 2022; 258(1): 26–37.
12. Lehtonen SH, Schmotz C, Tienari JP, Saleem M, Pfeil K, Bugger H, et al. AdipoR1 is reduced in glomeruli in type 2 diabetes and its depletion in podocytes in vitro impairs integrin β1 trafficking, focal adhesion assembly, and cell adhesion. J Am Soc Nephrol. 2023; 34(11S): 837–837.

13. Madhusudhan T, Ghosh S, Wang H, Dong W, Gupta D, Elwakiel A, et al. Podocyte integrin-β 3 and activated protein C coordinately restrict RhoA signaling and ameliorate diabetic nephropathy. J Am Soc Nephrol. 2020; 31(8): 1762–80.
14. Cao Y, Zeng J, Yaru X, Zhang C. MDM2 promotes diabetic nephropathy by targeting integrin β8 for ubiquitin degradation in renal pericytes. J Am Soc Nephrol. 2022; 33(11S): 102
15. Yu L, Su Y, Paueksakon P, Cheng H, Chen X, Wang H, et al. Integrin α1/Akita double-knockout mice on a Balb/c background develop advanced features of human diabetic nephropathy. Kidney Int. 2012; 81(11): 1086–97.
16. Trink J, Li R, Squire EJ, O'Neil KS, Gao B, Krepinsky JC. Cell surface GRP78 and integrin β1 regulate TGFβ1-mediated profibrotic responses in diabetic kidney disease. J Am Soc Nephrol. 2022; 33(11S):104.
17. Bukanov NO, Natoli TA, Chipashvili V, Zhou W, Rana R, Pissios P, et al. Integrin α3β1 as a potential target for diabetic kidney disease (DKD). J Am Soc Nephrol. 2023; 34(11S): 1011.
18. Li X, Miao Y, Li T, Liu X, Xu L, Guo J, et al. Integrin β6 mediates epithelial-mesenchymal transition in diabetic kidney disease. Mol Cell Endocrinol. 2023; 572(111955):111955.
19. Yao C, Li Z, Su H, Sun K, Liu Q, Zhang Y, et al. Integrin subunit beta 6 is a potential diagnostic marker for acute kidney injury in patients with diabetic kidney disease: a single cell sequencing data analysis. Ren Fail. 2024; 46(2): 2409348.
20. Cao Y, Su H, Zeng J, Xie Y, Liu Z, Liu F, et al. Integrin β8 prevents pericyte-myofibroblast transition and renal fibrosis through inhibiting the TGF-β1/TGFBR1/Smad3 pathway in diabetic kidney disease. Transl Res. 2024; 265: 36–50.
21. Wang X, Zhang Y, Chi K, Ji Y, Zhang K, Li P, et al. IGFBP2 induces podocyte apoptosis promoted by mitochondrial damage via integrin α5/FAK in diabetic kidney disease. Apoptosis. 2024; 29(7–8): 1109–25.