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Review

Urinary Biomarkers of Renal Involvement in Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis: Diagnosis, Disease Activity and Relapse Prediction

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Abstract

Kidney involvement largely determines prognosis in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), yet serum creatinine, proteinuria and haematuria cannot reliably separate active vasculitis from chronic damage or flare mimics, and kidney biopsy is invasive and rarely repeated. Unlike recent systematic reviews, which assessed a few soluble serum and urinary markers of overall disease activity, this structured narrative review covers the full range of urinary markers of renal involvement, organises them by clinical question and grades the evidence for each. A PubMed search identified 77 clinical studies. Urinary soluble CD163 is the most extensively validated marker; an accredited assay identified renal flare with an area under the curve of 0.95 in a prospective multicentre cohort. Urinary CD4+ T cells discriminate active glomerulonephritis and, in one prospective study, predicted six-month renal relapse with high specificity but modest sensitivity. Persistent haematuria after induction is the most consistently replicated predictor of renal relapse, whereas persistent proteinuria or albuminuria mainly predicts kidney failure. Urinary MCP-1 supports within-patient monitoring, and complement fragments and markers of tubular injury and fibrosis mainly add prognostic information. No urinary marker is yet ready for routine use, and the validation needed is outlined.

Keywords: ANCA-associated vasculitis; glomerulonephritis; urinary biomarkers; soluble CD163; monocyte chemoattractant protein-1; urinary T cells; complement; relapse; disease activity; diagnostic accuracy

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1. Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA) and renal-limited vasculitis, necrotising small-vessel vasculitides with few or no immune deposits [1–4]. Pauci-immune necrotising crescentic glomerulonephritis (GN) develops in up to 70% of patients and is the main determinant of prognosis; roughly one quarter of those affected progress to kidney failure despite modern immunosuppression [5–7].

AAV is a relapsing–remitting disease. Relapse is more frequent with proteinase 3 (PR3)-ANCA and GPA, each renal flare adds irreversible nephron loss [8–10], and decisions to extend or stop maintenance rituximab rest on an imprecise estimate of relapse risk [11–14].

Clinicians therefore face three recurring questions: is new kidney injury caused by vasculitis, is the kidney still inflamed after induction, and is a patient in remission about to relapse?

Current tools answer these questions poorly. Serum creatinine rises late and cannot separate inflammation from scarring, drug toxicity or infection; proteinuria persists as a marker of damage; and microscopic haematuria may persist in remission and also occurs in non-renal flares [15,16]. A rise in ANCA predicts relapse only modestly and mainly in renal disease [17,18], and the Birmingham Vasculitis Activity Score (BVAS) relies on the same urinalysis and creatinine items [19]. Kidney biopsy remains the reference standard [20,21], but it is invasive, cannot be repeated frequently, and samples few glomeruli.

Urine, by contrast, is collected non-invasively, can be sampled serially and is in direct contact with the inflamed glomerulus and tubulointerstitium. Molecules shed by infiltrating leukocytes, products of complement activation and proteins released by injured tubules therefore reach the urine in proportion to intrarenal activity, often before serum creatinine changes. Over the past two decades, urinary soluble CD163, monocyte chemoattractant protein-1, urinary T cells, complement activation products, markers of tubular damage and repair, and multimarker proteomic classifiers have emerged as the leading candidates.

Three systematic reviews have recently addressed biomarkers in this field. Baas et al. assessed the diagnostic accuracy of four soluble markers (CD163, CD206, CD25 and MCP-1), measured in serum or urine, for overall disease activity in 20 studies [22]; Renson et al. combined blood-based and urinary markers of activity and damage across all organ manifestations of AAV [23]; and Davies et al. examined proteomic and metabolomic studies across glomerulonephritis [24]. This review differs in four respects. First, it covers the full range of urinary markers of renal involvement, from conventional urinalysis to cellular, complement, tubular, fibrotic and omics markers, in 77 studies. Second, it organises the evidence around the decisions clinicians face: diagnosis of active renal vasculitis, monitoring of activity and treatment response, prediction of renal relapse and long-term kidney prognosis. Third, it grades the strength of evidence for each marker and application. Fourth, it uses conventional urinalysis and the established clinical and histological scores as the benchmark against which new markers are judged. Confounding conditions, pre-analytical issues and validation gaps are also discussed.

2. Materials and Methods

2.1. Design and Reporting

This is a structured narrative review prepared in line with the SANRA (Scale for the Assessment of Narrative Review Articles) criteria [25]. A systematic review with meta-analysis was not undertaken because the available studies differ widely in markers, designs, reference standards and assays; the aim was instead to map and grade the evidence across clinical applications. The literature search was nevertheless structured and reproducible, and study selection is reported with the PRISMA 2020 flow diagram for transparency [26]. Accordingly, the protocol was not registered and a formal risk-of-bias assessment was not performed.

2.2. Information Sources and Search Strategy

PubMed/MEDLINE was searched for English-language articles published from January 2000 to October 2026, a period covering standardised ANCA testing and modern immunoassay, flow cytometry and mass spectrometry platforms; the search was last updated in October 2026. Earlier landmark papers and other publications cited as background, such as randomised trials (for example, the CLEAR trial [27]), guidelines, classification systems and studies in other kidney diseases, were identified separately and were not counted among the included studies.

Three complementary queries were run (Table S1). The main query combined AAV terms (the MeSH term Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis and free-text terms for ANCA, granulomatosis with polyangiitis, Wegener, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis and pauci-immune) with urine terms (the MeSH term Urine; urine; urinary). Biomarker terms were omitted to keep the search sensitive. A second query captured records not indexed with the AAV MeSH term (for example, Churg–Strauss, renal vasculitis or small-vessel vasculitis), and a third captured studies of conventional urinalysis by combining AAV terms with urinalysis, haematuria or urine sediment and with relapse, activity, flare, biomarker or prognosis. Three recent systematic reviews [22–24] were used for context and were not included.

2.3. Eligibility Criteria

Studies were eligible if they met all of the following criteria:

1. Population: patients of any age with AAV defined by the 2012 Chapel Hill Consensus Conference nomenclature, the 2022 ACR/EULAR classification criteria or equivalent clinical and histological criteria [1,3,4].
2. Index test: at least one urinary marker (soluble, cellular, proteomic, vesicular, nucleic-acid or metabolic) or conventional urinalysis parameter, evaluated as the index test rather than only as a covariate.
3. Reference standard or comparison: clinical renal activity (BVAS renal items or clinician-defined renal flare), kidney biopsy, renal relapse or kidney outcome, or comparison with patients in remission, patients with non-renal AAV, disease controls or healthy controls.
4. Outcome: renal activity (defined clinically, by BVAS renal items or by biopsy), discrimination from flare mimics, treatment response, renal relapse, histological lesions or long-term kidney outcome.
5. Design: original research, including cohort, cross-sectional, case–control and diagnostic accuracy studies and post hoc analyses of clinical trials.
6. Publication: peer-reviewed full-text article in English, published from January 2000 to October 2026.

Studies were excluded if they met any of the following criteria:

1. Fewer than 10 patients with AAV.
2. Mixed cohorts in which data for AAV were not reported separately, or studies in which AAV was included only as a disease-control group.
3. Markers measured only in serum, plasma or kidney tissue.
4. Urinary parameters used only as covariates, without evaluation against a renal outcome.
5. No outcome related to renal involvement.
6. Case reports and case series of fewer than 10 patients; reviews, editorials, letters, comments, study protocols and consensus statements without original data.
7. Animal or in vitro studies without data from patients.
8. Full text not available.

Animal and serum-only studies were not counted as included studies; they are cited only where they explain the biology of a urinary marker or provide a comparison for urinary findings.

2.4. Study Selection

Records were exported from PubMed and de-duplicated by PubMed identifier (PMID). Records indexed as case reports, reviews, editorials, letters, comments or news, or as animal studies without human data, were excluded using PubMed publication-type and MeSH

tags. The remaining titles and abstracts were screened, and potentially eligible records were assessed in full text, retrieved from PubMed Central where available. Screening and eligibility assessment were performed by both authors (M.M. and M.A.) with the assistance of a generative AI tool (Claude Opus 5.5, Anthropic), and every decision was verified by the authors: for each record, the tool proposed an inclusion or exclusion decision with a reason, which the authors checked against the title, abstract or full text before accepting or overriding it. The complete screening log, with the reason for each exclusion, is provided in Table S3. The included studies were also cross-checked against the studies reported in three recent systematic reviews [22–24]; this identified no additional eligible study.

The three queries identified 1335 records (642, 526 and 167, respectively). After removal of 470 duplicates and one record whose bibliographic data could not be retrieved, 864 records were screened. Of these, 473 were excluded on publication type (381 case reports; 80 reviews, editorials, letters or comments; and 12 animal studies), and 305 after title and abstract review: no urinary marker evaluated in relation to renal involvement (144); population not AAV or AAV data not reported separately (100); case report or case series of fewer than 10 patients (39); animal or in vitro study only (13); and not original research (9). Of 86 reports sought, 4 could not be retrieved. Of 82 reports assessed in full text, 5 were excluded: AAV data not reported separately (2), no urinary marker evaluated against a renal outcome (2) and AAV included only as a disease-control group (1). In total, 77 studies were included (Figure S1; Table S2). Table 1 summarises the twelve studies that provide the principal evidence for the markers graded A or B in Table 2, selected as those with a defined reference standard and, where available, a multicentre or prospective design; all included studies are discussed in Sections 4–9 and graded in Table 2.

Table 1. Key clinical studies of urinary biomarkers of renal involvement in ANCA-associated vasculitis.

Study	Design and Setting	Population	Reference Standard	Marker and Cut-Off	Main Performance	Cut-Off Derivation
O'Reilly 2016 [28]	Multicentre; inception cohort with internal and external validation	177 SVV (inception)	Clinical activity (BVAS renal items)	usCD163 > 0.3 ng/mmol Cr (research ELISA)	Sens 83%, spec 96%, LR+ 20.8 (CI —)	Derived in inception cohort; applied in validation cohorts
Dekkema 2019 [29]	Two cohorts (inception, validation)	154 AAV (72 active renal)	Clinical activity	usCD163 alone; decision tree usCD163 + usCD25 + serum sCD25	usCD163: sens 72% (60–82) †, spec 98% (91–100) †; tree: sens 85% (74–92) †, spec 95% (88–99) †	Derived in same data
Aendekerk 2020 [30]	Single-centre biopsy cohort	95 AAV; 125 biopsies (58 repeat)	Kidney biopsy	usCD163 (24 h urine)	High in 87% (80–93) † of active vs. 7% of inactive biopsies; repeat biopsy sens 0.94, spec 0.91 (CI —)	Derived in same data
Moran 2020 [31]	VCRC longitudinal, multicentre	88 AAV; 320 visits (39 renal flares)	Clinical renal flare	usCD163 72.9 ng/mmol; uMCP-1 10.0 pg/mmol	usCD163 sens 80% (64–91) †, spec 67% (61–73) †; uMCP-1 sens 54% (37–70) †, spec 82% (77–86) †; combined tree spec 98%, LR+ 19.2	Derived in same data

Table 1. *Cont.*

Study	Design and Setting	Population	Reference Standard	Marker and Cut-Off	Main Performance	Cut-Off Derivation
Villacorta 2021 [32]	Prospective, two centres	47 AAV-GN; 156 samples	BVAS; clinical relapse	usCD163 (serial)	Relapse: AUC 0.96 (0.91–1.00); sens 100%, spec 89% for a 20% relative rise; correlated with BVAS	Derived in same data
Moran 2021 [7]	Real-world cohort + prospective multicentre flare cohort	405 AAV (cohort 1); 84 suspected flares (31 true)	Adjudicated renal flare	usCD163 250 ng/mmol Cr (accredited ELISA)	AUC 0.978 (cohort 1); prospective AUC 0.95, sens 97% (83–100) †, spec 87% (75–95) †, NPV 98% (89–100) †	Derived in cohort 1; pre-specified in prospective cohort
Lieberthal 2013 [16]	VCRC longitudinal	50 AAV (20 renal flare)	Clinical renal flare	uMCP-1 ≥ 1.3-fold rise from own remission baseline	Sens 94% (74–100), spec 89% (81–93), AUC 0.93; NGAL/KIM-1/AGP AUC 0.71–0.75	Derived in same data (Youden index)
Sonnemann 2023 [33]	Multicentre (four centres), proof of concept	95 AAV + 8 controls	Clinical activity; 21 biopsies	Urinary CD3+ T cells, Treg (flow cytometry)	AUC: CD3+ 0.95, Treg 0.92, MCP-1 0.82, sCD163 0.78; dipstick haematuria 0.98 (CI —)	None (AUC only)
Prskalo 2024 (PRE-FLARED) [34]	Prospective multicentre; patients in remission, 6-month follow-up	102 AAV (10 renal relapses)	Clinical renal relapse	Urinary CD4+ T cells ≥ 490/100 mL	AUC 0.88; sens 60% (26–88) †, spec 97.8% (92–100) †	Derived in same data
Almaani 2023 [35]	VCRC longitudinal	60 AAV (21 renal flare, 19 non-renal flare, 20 remission)	Clinical flare	Urine Ba 12.53 ng/mg Cr	AUC 0.76; sens 76% (53–92) †, spec 68% (51–82) †; plasma Ba unchanged	Derived in same data
Rhee 2018 [15]	Post hoc analysis of RAVE and WGET trials	149 AAV	Clinical renal relapse	Persistent haematuria after induction	sHR 3.99 (1.20–13.25)	Fixed definition (persistence ≥6 months)
Wu 2018 [36]	Single-centre cohort	173 active, 143 remission AAV	ESKD or 30% eGFR decline	Urinary EGF/Cr (continuous)	Adjusted HR 0.61 (0.45–0.83)	Continuous (no cut-off)

Abbreviations: AAV, ANCA-associated vasculitis; AGP, alpha-1 acid glycoprotein; AUC, area under the receiver operating characteristic curve; BVAS, Birmingham Vasculitis Activity Score; Cr, creatinine; EGF, epidermal growth factor; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GN, glomerulonephritis; HR, hazard ratio; LR+, positive likelihood ratio; NPV, negative predictive value; sens, sensitivity; sHR, subdistribution hazard ratio; spec, specificity; SVV, small-vessel vasculitis; Treg, regulatory T cells; VCRC, Vasculitis Clinical Research Consortium. Values in parentheses are 95% confidence intervals as reported in the original publication; †, 95% confidence interval calculated by the authors (exact Clopper–Pearson method) from the reported percentages and group sizes (per study visit for Moran 2020 [31]); CI —, confidence interval neither reported in the sources consulted nor derivable from reported counts. "Derived in same data" indicates that the cut-off was chosen and evaluated in the same patients, which tends to overestimate accuracy.

Table 2. Strength of evidence for urinary biomarkers of renal involvement in ANCA-associated vasculitis, by clinical application.

Main Limitations	Key References	Prognosis	Relapse	Monitoring	Diagnosis	Source/ Pathway	Biomarker
Non-specific; persists in remission; long lead time to relapse	[15,16,37–42]	C	B	B	B	Glomerular bleeding; leukocyturia	Haematuria and urinary sediment
Mixes activity and chronic damage	[38,43–47]	B	C	C	C	Glomerular barrier damage	Proteinuria and albuminuria
Elevated in other crescentic GN; false positives in nephrotic proteinuria; 17–28% of active cases missed; assay-specific cut-offs	[7,28,30–32]	C	C	B	A	Crescent macrophages	sCD163
One study (two Japanese cohorts)	[48]	C	—	—	C	Infiltrating myeloid cells	CD11b
Non-specific; elevated in many CKD causes and some non-renal flares	[16,31,49–52]	C	C	B (within-patient change)	B	Injured renal cells; monocyte recruitment	MCP-1 (CCL2)
Small single-centre cohorts; serum levels more informative	[53–55]	C	—	C	C	Neutrophils and monocytes	Calprotectin (S100A8/A9), S100A12
Requires fresh urine and flow cytometry; few relapse events	[33,34,56]	C	C	C	B	Infiltrating T cells	CD4+ effector memory T cells
Few studies; serum component needed	[29]	—	—	C	C (with sCD163)	Activated T cells	sCD25 (sIL-2Rα)
Single study; levels fall rather than rise in active disease	[57]	—	—	C	C	Immune checkpoint pathway	PD-1, PD-L1, PD-L2
Mostly MPO-AAV; ex vivo instability; rise with proteinuria in any GN	[35,58–61]	C	—	C	B	Alternative and terminal complement pathways	Ba, Bb, C3 fragments, C5a, sC5b-9
Reflect tubular injury from any cause	[16,62–66]	B	—	C	C	Tubular injury	NGAL, KIM-1, NAG, α1-microglobulin
Single-centre Chinese cohorts	[67,68]	—	—	C	C	Intrarenal renin–angiotensin system; cell injury	Angiotensinogen, mitochondrial DNA
Reflect damage rather than activity	[36,69–72]	B	—	C	—	Tubular repair; matrix remodelling and fibrosis	EGF, endotrophin, MMP-7
Single cohorts without independent validation	[50,73–81]	C	C	C	C	Inflammation; fibrosis; glomerular permeability	Other mediators (IL-6, TWEAK, PTX3, activin A, FABP4, gremlin, suPAR, IgM)
Two small cohorts; different assays	[82,83]	—	—	C	C	NETs/necrosis	HMGB1
Specialised processing; small studies	[84,85]	C	—	—	C	Glomerular and tubular cell shedding	Podocyte mRNA and tubular epithelial cells
Specialised platform; limited external validation	[86]	—	C	C	C	Multiple, including neutrophil proteases	Peptide classifier (CE-MS)

Table 2. *Cont.*

Main Limitations	Key References	Prognosis	Relapse	Monitoring	Diagnosis	Source/ Pathway	Biomarker
Discovery stage only	[87]	—	—	—	D	Glomerular and tubular cells	uEV microRNAs
Animal or pilot data; diet and GFR confounding	[88–91]	—	D	D	D	Metabolic profile	Metabolomics and spectroscopy

Evidence grades: A, consistent findings in at least two independent cohorts including prospective multicentre validation with a pre-specified cut-off; B, consistent findings in at least two independent cohorts, without prospective validation of a pre-specified cut-off; C, a single cohort or research group, or inconsistent findings in small studies; D, discovery-phase or predominantly experimental data; —, not studied. Independent cohorts are those from different centres or research groups without overlapping patients; criteria adapted from the phases of biomarker development [92]. Diagnosis, diagnosis of active renal involvement; Monitoring, monitoring of activity and treatment response; Relapse, prediction of renal relapse; Prognosis, prediction of kidney failure or decline in eGFR. Abbreviations: CE-MS, capillary electrophoresis–mass spectrometry; CKD, chronic kidney disease; EGF, epidermal growth factor; FABP4, fatty acid-binding protein 4; GFR, glomerular filtration rate; KIM-1, kidney injury molecule-1; MMP-7, matrix metalloproteinase-7; NAG, N-acetyl-β-D-glucosaminidase; PD-1, programmed death-1; PTX3, pentraxin-3; suPAR, soluble urokinase plasminogen activator receptor; TWEAK, TNF-like weak inducer of apoptosis; uEV, urinary extracellular vesicle.

2.5. Data Extraction

Data were extracted with a standardised form and checked against the original publications: first author, year and country; design and setting; numbers of patients and samples; ANCA specificity (MPO or PR3); disease phase; reference standard for renal activity or relapse; urine sample type, timing and handling; assay and normalisation method; cut-off; and performance measures, including sensitivity, specificity, AUC, predictive values, likelihood ratios and hazard ratios with 95% confidence intervals where reported.

2.6. Evidence Grading and Synthesis

Because designs, populations, reference standards, assays and cut-offs differed widely, findings were synthesised narratively without meta-analysis. Studies were grouped by the pathway that each marker reflects (Section 3) and by clinical application. The strength of evidence for each marker and application was graded A to D using pre-specified criteria adapted from the phases of biomarker development [92] (Table 2), based on the number of independent cohorts, prospective multicentre validation and pre-specification of the cut-off. Cohorts were considered independent only when they came from different centres or research groups without overlapping patients; studies from the same cohort or group, such as the Vasculitis Clinical Research Consortium (VCRC) longitudinal cohort [16,31,35] and the Irish usCD163 cohorts [7,28], were counted as a single source of evidence. Grades were assigned jointly by both authors, and disagreements were resolved by discussion. The grades reflect the number, independence and design of the studies and the validation of cut-offs; they do not incorporate a formal assessment of risk of bias. Table S2 lists, for each included study, the design, sample size, reference standard and the cohort or research group under which it was counted. Table 1 gives 95% confidence intervals as reported in the original publications or, where they were not reported but the underlying counts could be derived, as calculated by the authors (exact Clopper–Pearson method), and indicates whether each cut-off was pre-specified or derived in the same data. The limitations of this approach are summarised in Section 11.5.

3. Pathophysiology of ANCA-Associated Glomerulonephritis: The Basis for Urinary Biomarkers

A useful urinary biomarker should reflect a defined step in the injury cascade of ANCA-associated GN: neutrophil activation, complement amplification, monocyte–macrophage and T-cell infiltration, and tubulointerstitial injury and repair. Each step leaves a distinct molecular footprint in the urine (Figure 1).

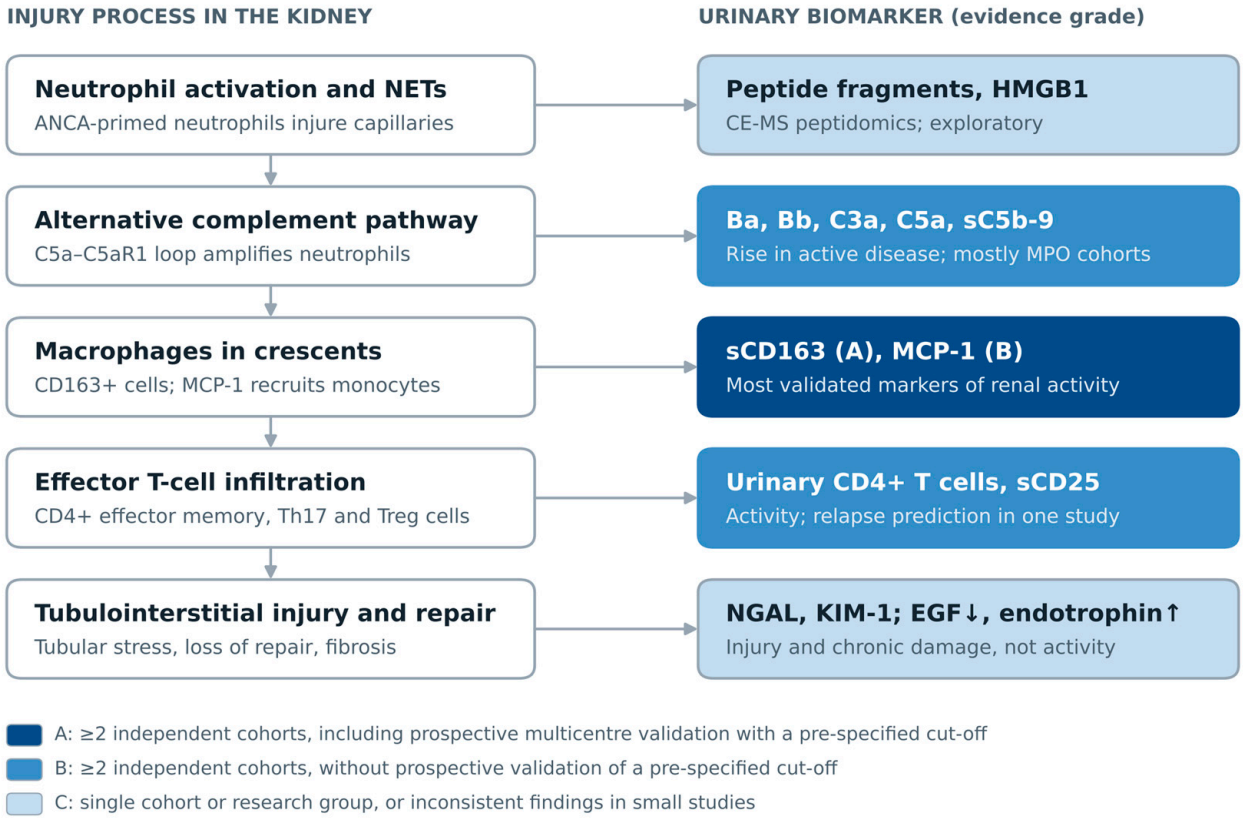


Figure 1. Sources of urinary biomarkers along the injury cascade of ANCA-associated glomerulonephritis. ANCA-activated neutrophils and neutrophil extracellular traps (NETs) damage glomerular capillaries and activate the alternative complement pathway (urinary Ba, Bb, C3a, C5a, sC5b-9). Recruited monocytes/macrophages in crescents shed sCD163 and are attracted by MCP-1. Effector memory CD4+ T cells and regulatory/Th17 subsets migrate into the urinary space and shed sCD25. Tubular injury releases KIM-1 and NGAL, whereas loss of epidermal growth factor (EGF) and release of endotrophin mark chronic damage. Neutrophil proteases generate urinary peptide fragments detected by proteomics. The shading indicates the strength of evidence for diagnosis of active renal involvement, graded as in Table 2 (darker = stronger). Original figure created by the authors.

3.1. Neutrophil Activation and Neutrophil Extracellular Traps

ANCA directed against myeloperoxidase (MPO) or PR3 activate cytokine-primed neutrophils, causing degranulation, release of reactive oxygen species and formation of neutrophil extracellular traps (NETs) within glomerular capillaries [2,93,94]; passive transfer of anti-MPO IgG is sufficient to cause crescentic GN in mice [93]. Neutrophil proteases also generate peptide fragments that can be detected by urinary peptidomics (Section 9).

3.2. The Alternative Complement Pathway

Although lesions are pauci-immune, ANCA-stimulated neutrophils activate the alternative complement pathway, and mice lacking factor B or C5 are protected from anti-MPO

GN [95]. The anaphylatoxin C5a primes further neutrophils through the C5a receptor (C5aR1, CD88), creating a self-sustaining loop [96], a pathway targeted clinically by the C5aR1 antagonist avacopan, although its pivotal Phase 3 ADVOCATE trial was subsequently retracted due to post-unblinding endpoint adjudication issues [97]. Split products such as Ba, Bb, C3a, C5a and soluble C5b-9 (sC5b-9) are therefore logical urinary readouts.

3.3. Monocytes and Macrophages

Monocytes and macrophages dominate crescents and periglomerular infiltrates. Macrophages expressing the scavenger receptor CD163 are abundant even in early lesions [98], CD163 mRNA is more highly expressed in ANCA-associated GN than in other glomerular diseases [28], and $CD163^{+}CD206-$ macrophages predominate in glomeruli, whereas CD206+ cells are mainly tubulointerstitial [99]. Shedding of CD163 into Bowman's space explains why urinary soluble CD163 (usCD163) tracks crescentic activity. The chemokine monocyte chemoattractant protein-1 (MCP-1, CCL2), produced by injured residenT cells, recruits these monocytes.

3.4. T Lymphocytes

Autoreactive CD4+ effector T cells cause glomerular injury independently of ANCA in experimental anti-MPO GN [100], and activated, clonally expanded CD4+ and CD8+ T cells with a cytotoxic gene profile infiltrate the kidney in patients [101]. Urinary T cells differ in composition from blood T cells, indicating migration from tissue rather than haematuria alone [33].

3.5. Tubulointerstitial Injury and Repair

Periglomerular inflammation and peritubular capillaritis extend injury to the tubulointerstitium, where injured tubules release kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL). Loss of the tubular repair signal epidermal growth factor (EGF) and release of fibrosis-derived fragments such as endotrophin reflect chronic damage [36,69]. These markers indicate injury rather than vasculitic activity, but they help separate inflammation from scarring.

4. Conventional Urinary Parameters and Their Limitations

4.1. Haematuria and Urinary Sediment

Glomerular haematuria, identified by dysmorphic erythrocytes, acanthocytes and red blood cell casts on microscopy of fresh urine [102], remains the cornerstone of clinical assessment, but casts are insensitive and observer-dependent, and dipstick haematuria is non-specific. In a longitudinal Vasculitis Clinical Research Consortium (VCRC) cohort, dipstick haematuria was present in 83% of active renal episodes but also in 43% of non-renal flares and 25% of remission samples [16].

Persistent haematuria nevertheless carries prognostic information. In a post hoc analysis of 149 patients from the RAVE and WGET trials, persistent haematuria after induction was associated with renal relapse (subdistribution hazard ratio [sHR] 3.99; 95% CI 1.20–13.25), with risk increasing for each additional month of haematuria, although the median time to relapse was 22 months and persistent proteinuria was not associated with relapse [15]. Similar associations were found in 86 patients after a first renal flare (hazard ratio [HR] 4.15) [37], in 571 patients from five European trials (adjusted sHR 2.16) [38] and at 12 months in 113 patients with GPA (HR 1.91) [39]. At suspected relapse, reappearance of haematuria accompanied histologically active disease on repeat biopsy in 80% of cases, whereas a rise in proteinuria did not [40], and resolution of haematuria usually parallels remission [103].

The morphology of the sediment adds information. Erythrocyte casts and more than 40 erythrocytes per high-power field at diagnosis predicted crescentic histology [41]; in PR3-ANCA GN, leukocyturia and haematuria were associated with focal and extensive rupture of Bowman's capsule, respectively [104]; and predominantly isomorphic erythrocytes in MPO-AAV were associated with lower eGFR and more frequent kidney failure, although not independently of other risk factors [42]. Conversely, minor abnormalities do not exclude renal vasculitis: 69% of 13 ANCA-positive patients with minimal proteinuria and haematuria had renal vasculitis on biopsy [105].

4.2. Proteinuria

Proteinuria at diagnosis reflects both active inflammation and established damage. After remission, it usually represents nephron loss, and new proteinuria may also arise from infection, hypertension or drug toxicity. After induction, however, proteinuria is a robust prognostic marker. In the five-trial analysis, a urine protein-to-creatinine ratio of 0.05 g/mmol or more was associated with death or kidney failure (adjusted HR 3.06; 95% CI 1.09–8.59) [38], and an albumin-to-creatinine ratio above 300 mg/g at six months predicted kidney failure independently of histological class and eGFR (HR 6.53) [43]. Similar associations were reported for dipstick proteinuria [44] and for the protein-to-creatinine ratio, which modestly improved the ANCA Kidney Risk Score [45] and was the only activity marker that added to eGFR in another cohort [46]. At diagnosis, proteinuria correlates with sclerotic rather than active lesions [47], and nephrotic-range, non-selective proteinuria in MPO-ANCA GN is associated with crescents and a poorer prognosis [106].

The composition of proteinuria may be more informative than its quantity: a higher urinary IgG-to-albumin ratio and N-acetyl-β-D-glucosaminidase (NAG) predicted response to cyclophosphamide [62], urinary IgM excretion predicted kidney failure [73], and urinary α1-microglobulin correlated with tubulointerstitial lesions [63].

Taken together, haematuria and proteinuria cannot reliably separate active vasculitis from chronic damage, from flare mimics or from non-renal activity. New markers must therefore add discriminatory value to urinalysis, serum creatinine and ANCA rather than merely correlate with them, and they should be compared directly with dipstick haematuria, which discriminated active renal AAV from remission with an AUC of 0.98 in one cohort [33].

5. Monocyte and Macrophage Biomarkers

5.1. Urinary Soluble CD163

usCD163 is the most extensively validated urinary marker of active renal vasculitis (Table 1). O'Reilly et al. showed that CD163 is the most highly expressed macrophage marker in glomeruli of ANCA-associated GN and, in an inception cohort of 177 patients with internal and external validation, a cut-off of 0.3 ng/mmol creatinine identified active renal vasculitis with 83% sensitivity and 96% specificity; levels remained low in remission, active non-renal AAV and other causes of acute kidney injury (AKI) [28]. In 125 biopsies, high usCD163 was found in 87% of biopsies with active GN versus 7% of those without, correlated with cellular crescents ($\rho = 0.70$) and identified relapsing GN with a sensitivity of 0.94 and specificity of 0.91 [30].

Accuracy is lower when flares are mild. In the VCRC cohort (88 patients, 320 visits), median usCD163 was 162 ng/mmol during renal flare versus 44 ng/mmol in remission and 38 ng/mmol in active extrarenal disease, but the optimal cut-off gave 79.5% sensitivity and 67.3% specificity, and a decision tree adding urinary MCP-1 (uMCP-1) or new proteinuria reached 97.9% specificity at the cost of 41% sensitivity [31]. In a Spanish prospective cohort, usCD163 correlated with BVAS during follow-up and rose at renal relapse [32].

Moran et al. then developed an accredited clinical ELISA in 405 patients (cut-off 250 ng/mmol creatinine; AUC 0.978). In a prospective multicentre cohort of 84 patients with possible renal flare, it identified adjudicated flares with an AUC of 0.95, a sensitivity of 96.8%, a specificity of 86.8% and a negative predictive value of 97.9%, while remaining low in non-vasculitic AKI, sepsis and isolated haematuria. False-positive results in nephrotic-range proteinuria were largely corrected by normalising to urinary protein [7].

Important limitations remain. Between 17% and 28% of active cases fall below the cut-off [28,29]; thresholds are assay-specific and differ by almost three orders of magnitude between assays [7,28]; levels are also raised in lupus nephritis and other crescentic GN [107]; and a systematic review of 20 studies reported sensitivities of 0.72–1.00 and specificities of 0.67–0.98 [22]. Data under rituximab maintenance are sparse; in a small exploratory cohort, usCD163 was only marginally higher before relapse and did not predict it on its own [108]. usCD163 is therefore a marker of active glomerular inflammation in a patient known to have AAV, not a diagnostic test for AAV.

Related myeloid markers add prognostic rather than diagnostic information. Serum soluble CD206 did not improve on usCD163, but rising levels were associated with kidney failure and death [99], and urinary CD11b correlated with tubulointerstitial infiltration and predicted recovery of eGFR in two Japanese cohorts [48]. Combining pathways helps: a model of serum calprotectin, usCD163 and haematuria reached 97% sensitivity and 90% specificity in the inception cohort and 78% and 94% on validation [53].

5.2. Urinary Monocyte Chemoattractant Protein-1 (MCP-1/CCL2)

Tam et al. reported higher uMCP-1 in active renal vasculitis than in inactive or non-renal disease, with levels falling after treatment [49]. In two Swedish cohorts, uMCP-1 remained elevated in stable disease, and higher levels were associated with adverse events, severe outcome and renal damage [50,51].

In the VCRC cohort, a 1.3-fold rise from an individual's remission baseline detected active renal disease with 94% sensitivity and 89% specificity (AUC 0.93), but uMCP-1 also rose in half of apparently non-renal flares [16], and in absolute terms it was less sensitive than usCD163 for subtle flare (54% vs. 80%) [31]. Because injured tubules release MCP-1 in many kidney diseases, its strength lies in within-patient monitoring. uMCP-1 also responds to therapy: in the CLEAR trial, avacopan reduced it faster than high-dose prednisone [27] and in autoimmune GN including AAV, uMCP-1, transforming growth factor-β1 and sC5b-9 paralleled activity [52].

5.3. Neutrophil-Derived Proteins: Calprotectin and S100A12

Calprotectin (S100A8/A9) and S100A12 are released by activated neutrophils and monocytes. In 42 patients with MPO-AAV, serum and urinary levels were higher in active disease and correlated with severity [54]. In a Spanish cohort, urinary calprotectin was lower with sclerotic histology, whereas serum calprotectin during remission was associated with later decline in renal function [55]. Urinary calprotectin did not enter the best-performing model in a larger cohort [53], and neither serum calprotectin nor usCD163 predicted relapse during rituximab maintenance [108]. Evidence for the urinary form is limited, and serum measurement currently appears more informative.

6. T-Cell Biomarkers

6.1. Urinary CD4+ Effector Memory T cells

Abdulahad et al. showed by flow cytometry that CD4+ effector memory T cells are the dominant urinary T-cell population in active renal AAV, with low numbers in remission and non-renal disease [56]; the same approach was later applied to lupus nephritis [109]. In

95 patients from four centres, Sonnemann et al. found that urinary CD3+ T cells (AUC 0.95) and regulatory T cells (Treg; AUC 0.92) discriminated active renal AAV better than MCP-1 and sCD163, although dipstick haematuria performed at least as well (AUC 0.98) [33]. Different Treg proportions in urine and blood supported migration from the kidney, higher urinary Treg and Th17 counts were associated with faster renal response, and the three patients who relapsed within six months had high urinary Th17 and undetectable Treg counts, a hypothesis-generating observation [33]. Cell-based assays require fresh urine processed within hours, flow cytometry and exclusion of infection and menstruation, which currently restricts them to specialised centres.

6.2. Prediction of Renal Relapse: The PRE-FLARED Study

To our knowledge, PRE-FLARED is the first prospective multicentre study designed to predict renal relapse with a urinary marker [34]. Of 102 patients in remission followed for six months, ten relapsed. Baseline urinary CD4+ T cells predicted relapse with an AUC of 0.88, and a threshold of 490 cells per 100 mL gave a specificity of 97.8% but a sensitivity of 60%; adding PR3-ANCA levels improved prediction in PR3-ANCA-positive patients [34]. With so few events, confidence intervals are wide, and the authors acknowledged that higher AUCs than haematuria or ANCA do not establish superiority, proposing a multimodal model instead [110]. Elevated urinary T cells in quiescent patients may also reflect undetected smouldering activity rather than a true prediction.

6.3. Soluble CD25 (Soluble Interleukin-2 Receptor α)

Soluble CD25 is shed by activated T cells. In 154 patients from two cohorts, urinary and serum sCD25 were higher in active renal AAV and identified patients with normal usCD163; combining them with usCD163 raised sensitivity from 72% to 85% at 95% specificity [29].

6.4. Immune Checkpoint Molecules

Urinary programmed death-1 (PD-1) and PD-L2 were lower than in healthy controls, and urinary PD-L2 was lower in acute disease than in remission in both a discovery and a validation cohort, suggesting loss of local checkpoint signalling during active nephritis [57]. These data are preliminary but point to an immunoregulatory dimension that activation markers do not capture.

7. Complement Activation Products

7.1. Clinical Evidence

Because complement split products are generated locally, their urinary excretion should reflect intrarenal activity more directly than plasma levels [95–97]. In MPO-ANCA GN, urinary Bb, C3a, C5a and sC5b-9 were higher in active disease than in remission, and glomerular Bb correlated with crescents and tubulointerstitial injury [58]. Urinary C5a was higher in active AAV, with downregulation of renal C5aR1, but did not differ from lupus nephritis [59]. In 60 VCRC patients, urine Ba rose at renal but not at non-renal flare, whereas plasma Ba was unchanged (AUC 0.76), supporting an intrarenal origin [35].

Urinary complement also carries prognostic information: high urinary C3a and C5a at diagnosis or relapse were associated with kidney failure or death in 57 patients [60], and urinary C3 fragments correlated strongly with BVAS in 22 patients with MPO-AAV ($r = 0.79–0.90$) [61]. However, urinary complement fragments rise with proteinuria in every form of GN, and terminal-pathway products are not higher in AAV than in other glomerulopathies [52,111], so values must be interpreted against the degree of proteinuria. Plasma Bb, C3a, C5a and sC5b-9 are also elevated and may remain so in remission [112,113],

and low serum C3 at presentation has been associated with mortality but not with kidney survival [114].

7.2. Limitations and Opportunities

Most data come from single-centre cohorts of predominantly MPO-ANCA patients; fragments are unstable ex vivo and require cold, prompt processing; and no study has tested urinary complement prospectively for relapse prediction. With avacopan now approved and in clinical use, it is plausible, but untested, that urinary complement profiles could identify patients most likely to benefit from C5aR1 blockade and monitor their response, including in severe renal impairment [115].

8. Tubular Injury, Damage and Repair Markers and Other Soluble Mediators

8.1. Tubular Injury Markers: NGAL, KIM-1 and Related Molecules

NGAL and KIM-1 rise during renal flares but discriminate activity poorly. In the VCRC cohort, urinary NGAL, KIM-1 and alpha-1 acid glycoprotein yielded AUCs of only 0.71–0.75, inferior to uMCP-1 [16], and they reflect tubular stress from any cause. They are more useful for prognosis: urinary NGAL was associated with crescents and poor renal prognosis in 134 patients [64], and urinary NGAL and trehalase independently predicted kidney failure in 88 patients (AUC 0.85–0.86) [65]. Urinary KIM-1 correlated with chronicity but not with glomerular lesions or relapse in MPA [66]. In a two-stage cohort of 94 patients, urinary angiotensinogen correlated with cellular crescents, outperformed albuminuria for crescentic GN (AUC 0.88 vs. 0.73) and fell after treatment [67], and urinary mitochondrial DNA correlated with NGAL, eGFR and the crescentic class [68].

8.2. Markers of Chronic Damage, Repair and Fibrosis

Markers of repair and fibrosis address how much residual abnormality is irreversible. In 316 patients, urinary EGF was higher in remission than in active disease, correlated with eGFR and independently predicted kidney failure or a 30% fall in eGFR (adjusted HR 0.61) [36]. Endotrophin, measured by the PRO-C6 assay, rose with interstitial fibrosis and tubular atrophy [69], and urinary matrix metalloproteinase-7 (MMP-7) independently predicted kidney failure in a two-stage study of 150 patients with MPO-AAV (adjusted HR 3.79) [70]. Single cohorts have also linked a five-marker fibrosis panel [71], urinary MMP-2 and tissue inhibitor of metalloproteinases-1 [72] and urinary gremlin [74] with tubulointerstitial damage or outcome, whereas connective tissue growth factor was informative in plasma rather than urine [116]; these markers are summarised in Table 2.

8.3. High-Mobility Group Box 1 (HMGB1)

High-mobility group box 1 (HMGB1), a damage-associated molecule released by necrotic and NETosing cells, was higher in the urine of patients with active nephritis, fell in remission and correlated with urinary effector memory T cells, although HMGB1 was measured semi-quantitatively by Western blot [82]. A larger ELISA-based cohort confirmed higher levels in active disease but only a weak correlation with BVAS ($r = 0.35$) [83].

8.4. Cytokines, Chemokines and Other Mediators

Other mediators have each been studied in a single cohort, and few have been tested against usCD163 or urinary T cells [23]; they are summarised in Table 2. Urinary interleukin-6 (IL-6) and IL-8 [50,75], TNF-like weak inducer of apoptosis (TWEAK) [76], pentraxin-3 [77], activin A [78] and fatty acid-binding protein 4 [79] correlated with activity, cres-

cents or outcome, whereas urinary soluble urokinase plasminogen activator receptor (suPAR) [80,81] and IL-18 [117] added little beyond their plasma or serum levels. None has been independently validated, and their likely role is within multiplex panels.

8.5. Urinary Cells and Podocyte-Derived mRNA

Urine also contains shed podocytes and tubular cells. Urinary podocin mRNA correlated with crescents and recovery of eGFR in 19 patients [84], and flow-cytometric counts of distal tubular epithelial cells distinguished AKI from glomerular disease in cohorts including 110 patients with AAV [85]. Both approaches, like urinary T-cell assays, require fresh urine and specialised processing.

9. Omics-Based Approaches

9.1. Urinary Proteomics and Peptidomics

Haubitz et al. used capillary electrophoresis–mass spectrometry (CE-MS) to derive a urinary peptide classifier that distinguished active renal AAV from controls and other glomerular diseases, normalised in remission and identified relapse; several peptides were plausibly generated by neutrophil proteases [86]. It has not been validated in independent prospective cohorts. Proteomics of urinary extracellular vesicles (uEVs) identified changes in renal AAV, whereas whole-urine results were dominated by proteinuria [118], and small samples and lack of external validation remain the main barriers to translation [24].

9.2. Extracellular Vesicles and MicroRNAs

Urinary EVs protect proteins and nucleic acids from degradation. Five microRNAs were markedly elevated in uEVs from patients with AAV, with predicted targets in pathways of podocyte cytoskeletal assembly [87], and circulating microRNAs associated with active AAV-GN [119] are logical candidates for urinary testing.

9.3. Metabolomics and Spectroscopy

In experimental vasculitis, nuclear magnetic resonance urinary metabolite profiles separated active from inactive disease, and the myo-inositol:citrate ratio tracked renal activity; human data from that study remain limited [88]. In a human pilot study, citric acid cycle intermediates were lower in active disease [89], whereas infrared and Raman spectroscopy of urine discriminated less well than plasma or tissue [90,91]. Metabolites are cheap and stable but strongly affected by diet, kidney function and drugs.

9.4. Integration and Machine Learning

The main strength of omics is breadth and the main weakness is overfitting: classifiers derived from thousands of features in small cohorts give optimistic performance. Future studies should pre-register analyses, use independent validation cohorts, follow TRIPOD+AI guidance [120] and report performance against urinalysis plus usCD163.

10. Urinary Biomarkers by Clinical Application

Different markers suit different clinical questions. Table 2 grades the evidence for each marker and application, and Figure 2 maps these grades onto the course of the disease. Independent systematic reviews reached similar conclusions: usCD163 is the most reliable single marker, and large prospective validation is lacking [22,23].

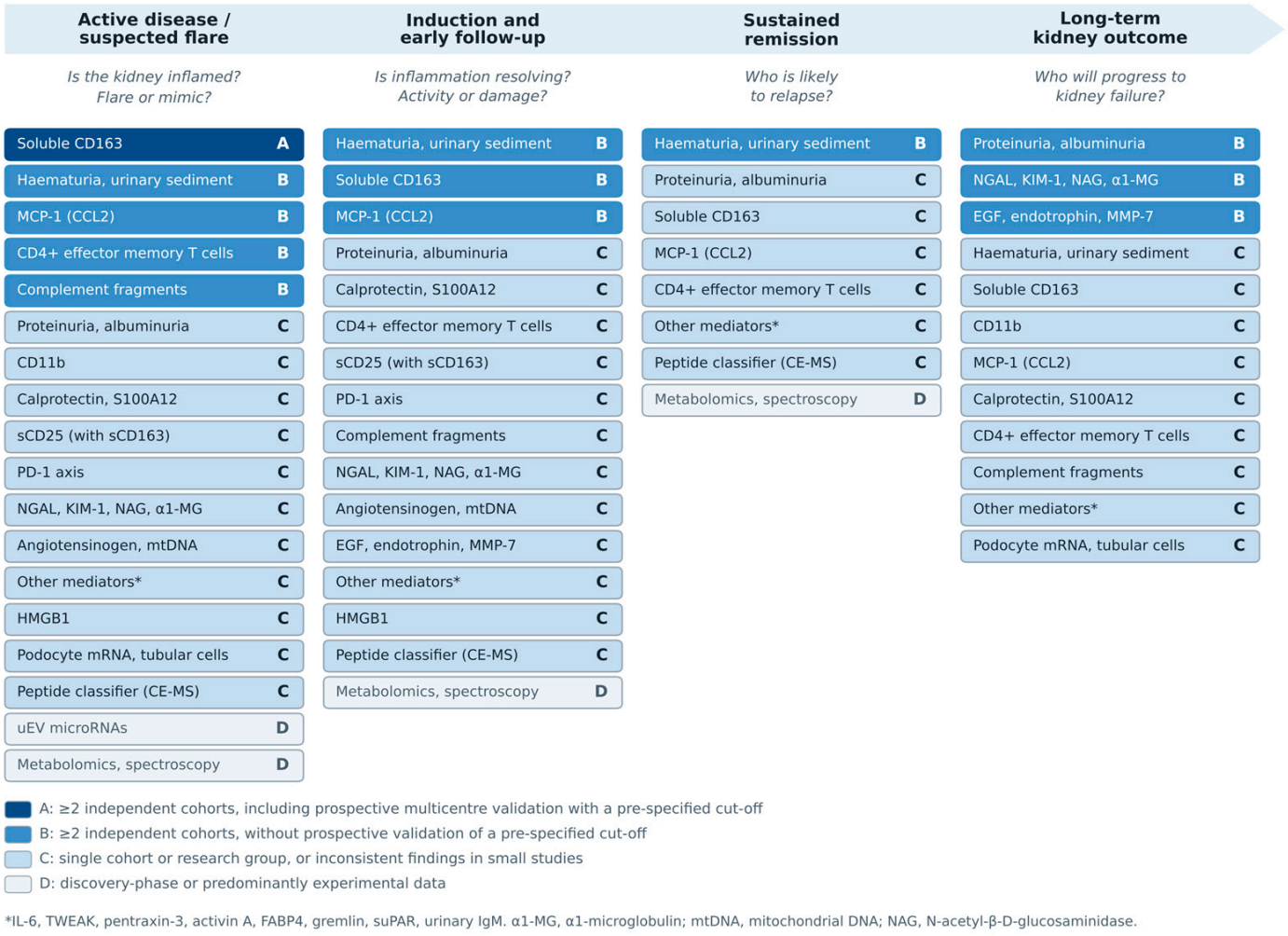


Figure 2. Evidence map of urinary biomarkers across the course of ANCA-associated renal disease. For each clinical phase, from active disease to long-term kidney outcome, the question that a urinary biomarker could address is shown, together with the markers studied in that setting and the strength of evidence, graded as in Table 2. Markers of tubular injury and fibrosis mainly inform kidney prognosis rather than activity. The map summarises current evidence and is not intended as a clinical algorithm. Original figure created by the authors. CE-MS, capillary electrophoresis–mass spectrometry; EGF, epidermal growth factor; FABP4, fatty acid-binding protein 4; KIM-1, kidney injury molecule-1; MMP-7, matrix metalloproteinase-7; PD-1, programmed death-1; suPAR, soluble urokinase plasminogen activator receptor; TWEAK, TNF-like weak inducer of apoptosis; uEV, urinary extracellular vesicle.

10.1. Diagnosis of Active Renal Involvement

No urinary biomarker diagnoses AAV itself; ANCA serology and kidney biopsy remain essential [10,14]. The realistic role is to confirm active renal involvement in known or suspected AAV and to separate flare from mimics. Here, usCD163 has the strongest evidence, including a negative predictive value of 98% in a prospective flare cohort in which 37% of patients had an adjudicated flare [7]; predictive values will differ where flare is more or less common. Urinary T cells and peptide classifiers may add discrimination but require validation [33,86].

The benchmark for any new marker is the urinalysis already available at the bedside, yet few studies have compared the two directly. In a multicentre cohort, dipstick haematuria discriminated active renal AAV at least as well as urinary T cells (AUC 0.98 vs. 0.95) [33], and in the VCRC cohort it was positive in most renal flares but also in 43% of non-renal

flares [16]. The added value of usCD163 lies mainly in specificity: it remained low in patients with isolated haematuria without vasculitic flare [7], and models combining it with haematuria and serum calprotectin [53] or with uMCP-1 and new proteinuria [31] achieved higher accuracy or specificity than single markers. Studies reporting the incremental value of a new marker over urinalysis, creatinine and ANCA in the same patients are needed.

10.2. Monitoring Disease Activity and Treatment Response

usCD163, urinary T cells and uMCP-1 fall with successful induction [30,32,33,49], and for uMCP-1, change from an individual baseline outperforms absolute values [16]. Persistent elevation after induction may identify smouldering activity and could, in future, inform decisions about re-biopsy or escalation.

10.3. Prediction of Renal Relapse

Relapse prediction is the least mature application. Persistent haematuria after induction is the most consistently replicated, if non-specific, predictor, with four independent cohorts including a pooled analysis of five trials, but its lead time is long [15,37–39]. Urinary CD4+ T cells predicted relapse within six months with high specificity [34], whereas evidence that usCD163 rises before clinical relapse is limited [30,32,108]. Combining urinary markers with ANCA kinetics, particularly in PR3-ANCA disease, appears most promising [34]. Evidence for proteinuria is inconsistent: a protein-to-creatinine ratio of 0.05 g/mmol or more after induction was associated with renal relapse in the five-trial analysis [38] but not in the RAVE and WGET analysis [15].

10.4. Distinguishing Activity from Chronic Damage

Markers of inflammation (usCD163, urinary T cells, complement fragments) should normalise in remission despite residual damage, whereas proteinuria, low urinary EGF and high endotrophin reflect nephron loss and fibrosis [36,69]. A low usCD163 with persistent urinary abnormalities may therefore support continuing rather than escalating therapy, although this has not been tested prospectively. For long-term kidney outcome, proteinuria or albuminuria after induction and urinary MMP-7, NGAL and EGF are the best-supported markers [36,38,43,65,70].

10.5. Urinary Biomarkers Alongside Clinical and Histological Scores

Urinary markers are best interpreted alongside, not instead of, the established clinical and histological scores. Clinically, the BVAS captures renal activity through haematuria, proteinuria and creatinine items [19], so markers that merely correlate with it add little. usCD163 correlated with the BVAS during follow-up [32], as did urinary C3 fragments ($r = 0.79–0.90$) [61], TWEAK [76] and pentraxin-3 [77], whereas urinary HMGB1 correlated only weakly ($r = 0.35$) [83]. Histologically, the Berden classification [20] and the ANCA renal risk score [21] remain the main prognostic tools, and several urinary markers map onto them. Erythrocyte casts and heavy haematuria predicted the crescentic class [41]; urinary T cells [33], usCD163 [71] and urinary mitochondrial DNA [68] were highest in the crescentic class; usCD163 correlated with cellular crescents and fibrinoid necrosis [30]; and urinary DKK-3 and endotrophin were highest in the sclerotic class [71]. Urinary KIM-1 correlated with the Mayo Clinic Chronicity Score [66], and proteinuria at diagnosis was most marked in the sclerotic class and in the high-risk category of the renal risk score [47]. For prognosis, albuminuria after induction predicted kidney failure independently of the Berden class [43], and the protein-to-creatinine ratio after induction modestly improved the ANCA Kidney Risk Score [45], whereas in another cohort neither the Berden class nor the renal risk score outperformed eGFR [46]. Urinary markers may therefore add most where

they reflect what the scores capture poorly, such as ongoing glomerular macrophage or T-cell activity after induction, when repeat biopsy is rarely performed.

10.6. Implications for Current Practice

On current evidence, no urinary biomarker can replace kidney biopsy or be recommended for routine use in all patients, but several practical points emerge. Careful urinalysis remains essential at every visit, and persistent haematuria after induction identifies patients who merit closer follow-up for renal relapse [15,38]. Where an accredited usCD163 assay is available, a low value in a patient with suspected renal flare makes active vasculitis less likely and may help avoid unnecessary escalation, whereas a high value supports biopsy or treatment [7]. This reassurance rests on a negative predictive value from a single prospective cohort with a flare prevalence of 37%, and it will be weaker where flare is more common [7]. Proteinuria or albuminuria after induction should be interpreted mainly as a prognostic marker rather than as evidence of ongoing activity [38,43]. Other urinary markers should currently be used only in research settings.

11. Challenges, Limitations and Future Directions

11.1. Pre-Analytical and Analytical Issues

Urinary biomarker results depend on sample type, time to processing, storage temperature, freeze–thaw cycles and protease inhibition, particularly for complement fragments and cells. Creatinine normalisation is distorted by changing kidney function and muscle mass, and in nephrotic-range proteinuria normalisation to total protein may be preferable [7]. Research ELISAs with different antibodies and calibrators explain much of the variation in cut-offs; only usCD163 has an accredited diagnostic-grade assay [7].

11.2. Reference Standards and Study Design

Definitions of active renal vasculitis vary (biopsy, BVAS renal items, clinician judgement or treatment escalation), and all are imperfect. Histological activity should be graded with established classifications [20,21], diagnostic accuracy studies should follow STARD [121], and each marker should be placed within the recognised phases of biomarker development [92]. Spectrum bias is common: markers derived in highly active new disease perform worse in mild, ambiguous flares, where they are needed most [31]. Relapse studies have few events, and most compare novel markers with single urinalysis parameters rather than testing added value over a multivariable clinical model.

PR3-ANCA disease, EGPA, children, kidney transplant recipients and non-European populations are under-represented [23]. Data from Saudi Arabia and the Gulf region are limited to small retrospective series [122–124]: renal involvement was present in 43.8% of 48 patients in a Saudi tertiary cohort [122], and 39% of 28 patients with ANCA-associated GN in Qatar progressed to kidney failure [123]. To the authors' knowledge, urinary biomarkers have not been evaluated in these populations, and we identified no study that evaluated a urinary biomarker specifically in EGPA, in children or in kidney transplant recipients with AAV.

11.3. Confounding Conditions and Specificity

Most candidate markers are not specific to vasculitis. usCD163 is also raised in proliferative lupus nephritis and other crescentic GN [107] and, through non-selective protein leakage, in nephrotic-range proteinuria and primary podocytopathy [7]; MCP-1, NGAL and KIM-1 are released by injured tubules in many kidney diseases; and urinary complement fragments rise with proteinuria in every form of GN [52,111]. Urinary tract infection and haematuria from other causes can raise cellular and inflammatory markers, and advanced

chronic kidney disease distorts creatinine normalisation. Because this review relies on published data, these confounders could not be controlled statistically; instead, the main specificity limitation of each marker is given in Table 2. Only usCD163 has been tested prospectively against common flare mimics, including non-vasculitic acute kidney injury, sepsis and isolated haematuria, and it remained low in these settings [7]. Most other markers were compared with remission, non-renal AAV or healthy controls, and only a few studies included other glomerular or kidney diseases as comparators [28,48,58,59,74,86]. In practice, urinary markers should be interpreted only in patients with known AAV, after excluding urinary tract infection, with normalisation to urinary protein when proteinuria is heavy, and together with eGFR and the degree of proteinuria. Future studies should include patients with these mimics and with advanced chronic kidney disease as comparison groups.

11.4. From Biomarker Performance to Clinical Impact

Good diagnostic accuracy does not guarantee better outcomes. The decisive evidence will come from strategy studies in which biomarker results guide biopsy or the escalation, de-escalation or extension of maintenance therapy, analogous to the ANCA- and B-cell-tailored approach of MAINRITSAN2 [12], supported by health-economic analyses.

11.5. Limitations of This Review

This review has several limitations. First, only PubMed was searched and only English-language articles were included, so relevant studies indexed elsewhere or published in other languages may have been missed, although cross-checking against three recent systematic reviews identified no additional eligible study [22–24]. Second, as a structured narrative review, it did not include a meta-analysis or a formal risk-of-bias assessment, and the evidence grades reflect the number, independence and design of studies rather than their methodological quality. Third, the grading system was developed for this review and has not been validated. Fourth, screening was assisted by a generative AI tool; although every decision was verified by the authors, selection errors cannot be excluded. Fifth, the included studies were heterogeneous in populations, reference standards, assays, normalisation methods and cut-offs, and several drew on overlapping cohorts, which limits direct comparison. Finally, most accuracy estimates come from studies that derived and tested cut-offs in the same data, which tends to overestimate performance, and studies with positive results are more likely to have been published.

11.6. Research Priorities

1. Harmonised procedures for urine collection, processing and storage across vasculitis registries and biobanks.
2. Prospective multicentre validation of usCD163 and urinary T cells in suspected flare and stable remission, including under rituximab maintenance and avacopan.
3. Multimarker models combining macrophage, T-cell, complement and damage markers with ANCA kinetics, with external validation.
4. Head-to-head comparisons in the same samples, with pre-specified cut-offs and dipstick haematuria as the minimum comparator.
5. Inclusion of PR3-ANCA disease, EGPA, children, transplant recipients and non-European populations.
6. Randomised biomarker-strategy trials with renal relapse, cumulative immunosuppression and kidney function as outcomes.

12. Conclusions

Urinary biomarkers offer a non-invasive window onto intrarenal inflammation in AAV that urinalysis, serum creatinine and ANCA titres cannot provide. usCD163 is the most mature candidate: it reflects crescentic macrophage infiltration, distinguishes renal flare from common mimics and is available as a diagnostic-grade assay, although it misses roughly one in five active cases and its cut-offs are assay-specific. Urinary CD4+ T cells discriminate active GN and are, to our knowledge, the first urinary marker to predict renal relapse prospectively, albeit in a single small study. uMCP-1 is suited to within-patient monitoring, complement products link urinary findings to a therapeutically targetable pathway, and markers of tubular injury, repair and fibrosis mainly inform prognosis. For relapse prediction, the best-supported criterion is persistent haematuria after induction, which was associated with renal relapse in four independent cohorts (hazard or subdistribution hazard ratios 1.91–4.15), although relapse occurred a median of almost two years later. A baseline count of at least 490 urinary CD4+ T cells per 100 mL predicted renal relapse within six months with a specificity of 97.8% but a sensitivity of 60% in a single study, and adding PR3-ANCA levels improved this prediction in PR3-ANCA-positive patients. No urinary marker has yet been shown to predict relapse well enough to guide maintenance therapy. Persistent proteinuria or albuminuria after induction, by contrast, mainly predicts kidney failure. No single marker is sufficient; validated multimarker panels, tested in prospective strategy trials that show an impact on relapse, treatment burden and kidney survival, are the most likely way forward.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/diagnostics16223794/s1, Table S1: Search strategies and results; Figure S1: Flow diagram of the literature search and study selection; Table S2: Studies included in the review ($n = 77$); Table S3: Complete screening log (Excel).

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Abbreviations

The following abbreviations are used in this manuscript: AAV, ANCA-associated vasculitis; AGP, alpha-1 acid glycoprotein; AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic antibody; AUC, area under the curve; BVAS, Birmingham Vasculitis Activity Score; C5aR1, C5a receptor 1; CE-MS, capillary electrophoresis–mass spectrometry; EGF, epidermal growth factor; EGPA, eosinophilic granulomatosis with polyangiitis; GN, glomerulonephritis; GPA, granulomatosis with polyangiitis; HMGB1, high-mobility group box 1; KIM-1, kidney injury molecule-1; MCP-1, monocyte

chemoattractant protein-1; MPA, microscopic polyangiitis; MPO, myeloperoxidase; NETs, neutrophil extracellular traps; NGAL, neutrophil gelatinase-associated lipocalin; NPV, negative predictive value; PR3, proteinase 3; RBC, red blood cell; sC5b-9, soluble C5b-9; sCD25, soluble CD25; sHR, subdistribution hazard ratio; Treg, regulatory T cell; uEV, urinary extracellular vesicle; uMCP-1, urinary MCP-1; usCD163, urinary soluble CD163; VCRC, Vasculitis Clinical Research Consortium.

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