

ISSN Print: 1813-176x
ISSN Online: 1994-4624

International Journal of Molecular Medicine and Advance Sciences
https://ijmmas.com/

Research Article

Complement Activation Biomarkers C3a, C5a, C5b-9 and Factor H in IgA Nephropathy: Correlation with Oxford MEST-C Histopathological Classification-A Systematic Review and Meta-analysis

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Received: 18-09-2026
Revised: 12-10-2026
Accepted: 29-10-2026
Published: 18-11-2026

DOI: 10.61336/ijmmas.22-04-31

Abstract: Background: Complement activation in immunoglobulin A nephropathy (IgAN) involves alternative, lectin, and terminal pathways. Circulating and urinary anaphylatoxins and soluble terminal complement complexes may indicate active disease, whereas factor H and factor H–related proteins regulate local pathway activity. The associations with Oxford MEST-C lesions are incompletely defined. Objective: To assess C3a, C5a, soluble or tissue C5b-9, and factor H/FHR measures in relation to mesangial and endocapillary hypercellularity, segmental sclerosis, tubular atrophy/interstitial fibrosis, and crescents in biopsy-confirmed IgAN. ***Methods***: Comparative primary studies measuring complement in urine, blood, or biopsy tissue were critically synthesized alongside published MEST-C systematic reviews and meta-analyses. Assay compartment, factor H versus factor H–related protein identity, MEST-C score, kidney function and proteinuria were extracted as distinct variables. Previously pooled effect estimates were reviewed without independent re-pooling. ***Results***: The study-selection flow comprised 1,284 database and 42 additional records (1,326 total); 242 duplicates were removed, 1,084 records screened, 1,001 excluded at screening, 83 full texts assessed, and 65 excluded, leaving 18 studies in the qualitative synthesis. A published systematic review included 34 studies and 10,082 patients and identified frequent MEST-C associations for complement deposition, but C5b-9 findings were inconsistent. In a urinary biomarker study, correlations with proteinuria were r=0.652 for C3a, r=0.719 for C5a and r=0.599 for soluble C5b-9; corresponding correlations with serum creatinine were 0.677, 0.655 and 0.599 (all P<0.001). A cohort of 84 untreated patients found plasma C5a higher in patients with crescents (P=0.046). Glomerular FHR5 deposition was present in 57.1% in one tissue study. A 2026 meta-analysis of 30 studies (10,656 patients) reported that C4d deposition was associated with tubulointerstitial lesions (RR 2.21; 95% CI 1.92–2.54) and adverse renal outcomes (HR 2.02; 95% CI 1.29–3.17); it could not reliably pool C5b-9 or factor H data. ***Conclusions***: C3a, C5a and soluble C5b-9 convey information on inflammatory activity and renal impairment; evidence linking C5a with crescents and FHR5 with proliferative injury is promising. Marker–MEST-C associations vary by sample compartment and assay, and sufficient homogeneous data are not available for a defensible new pooled effect specific to the four named biomarkers.

Keywords: IgA nephropathy; complement C3a; C5a; membrane attack complex; C5b-9; factor H; factor H–related protein 5; Oxford MEST-C; crescents; systematic review; meta-analysis.

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INTRODUCTION

IgAN is defined by dominant or codominant IgA deposition in the glomerular mesangium and is associated with heterogeneous trajectories of proteinuria, glomerular inflammation, chronic scarring and loss of kidney function. The Oxford MEST-C system stratifies mesangial hypercellularity (M0/M1), endocapillary hypercellularity (E0/E1), segmental glomerulosclerosis (S0/S1), tubular atrophy/interstitial fibrosis (T0/T1/T2) and cellular or fibrocellular crescents (C0/C1/C2). MEST-C refines biopsy-based prognostication but does not measure complement activation directly [1–3].

The prevailing multihit disease model connects galactose-deficient IgA1, autoantibodies, circulating immune complexes and intrarenal injury. Alternative and lectin pathway amplification generates C3a and C5a, which recruit and activate inflammatory cells. Terminal C5b-9 deposition can perturb glomerular cell function and promote inflammatory or fibrotic responses. Factor H is a physiological regulator of alternative pathway amplification; factor H–related proteins such as FHR1 and FHR5 are distinct proteins that may compete with factor H and alter local complement activation [4–7].

Complement measurements are method-dependent. Plasma C5a reflects circulating activation, urinary C5a may indicate renal inflammatory activity, tissue C5b-9 describes deposits rather than soluble terminal complex levels, and FHR5 is not interchangeable with factor H. In particular, associations with biopsy lesions can change with sampling time, corticosteroid exposure, kidney function and urinary protein excretion [5–10].

The review examines whether the four proposed biomarker families add meaningful information to MEST-C and whether the published evidence permits quantitative integration. It distinguishes cross-sectional association, prediction of kidney outcome and the clinical value of measuring a biomarker for therapeutic decisions.

MATERIALS AND METHODS

Review question and eligibility criteria

Eligibility required biopsy-confirmed primary IgA nephropathy and a measured complement analyte with an extractable Oxford lesion association or concurrent clinical outcome. Analyses solely involving IgA vasculitis nephritis, nonhuman studies, narrative reports without primary data and duplicate patient cohorts were excluded from the principal clinical synthesis. Studies were grouped by adult versus pediatric population, assay compartment, and whether the MEST-C scoring included the crescent component introduced in the 2016 revision.

Comparisons were specified by M0/M1, E0/E1, S0/S1, T0 versus T1–T2 and C0 versus C1–C2. Complement positivity in kidney tissue was assessed separately from blood and urinary concentrations. Factor H, the alternative-pathway regulator, was defined separately from factor H-related proteins (FHR1 and FHR5), which can have distinct effects on amplification and deposition [5–7,18,19].

The PECOS framework comprised biopsy-confirmed primary IgAN (population); C3a, C5a, C5b-9/sC5b-9, factor H or explicitly identified factor H–related proteins (exposure); biomarker-low/negative patients or continuous measurements (comparison); Oxford MEST-C lesion categories, proteinuria, estimated glomerular filtration rate (eGFR), kidney progression and pathology severity (outcomes); and observational clinical cohorts, cross-sectional biopsy studies or relevant treatment-trial biomarker studies (study designs). Studies of IgA vasculitis nephritis were considered only when IgAN results were separately available. Published reviews were contextual evidence, not additional cohorts.

Information sources and search concepts

Search concepts combined IgA nephropathy, Oxford MEST-C, complement activation, C3a, C5a, membrane attack complex, soluble C5b-9, factor H, CFH, FHR5, urinary complement, glomerular deposits, crescents, proteinuria and renal outcomes. Original clinical cohorts identified in the existing complement–MEST-C systematic review were cross-checked against the primary reports, with attention to multiple publications from the same study population [4,20].

The title and abstract criteria included clinical IgAN, complement measurement, a biopsy finding or quantitative kidney outcome, and an interpretable patient denominator. Full-text exclusion categories were absence of marker-specific data, lack of MEST-C association, nonextractable clinical results, overlapping cohorts and mixed disease populations without separable IgAN information. Reasons were retained in the study-selection narrative.

PubMed/MEDLINE, publisher-hosted full text and reference-linked evidence available to July 2026 were consulted with combinations of "IgA nephropathy" OR "Berger disease"; "Oxford classification" OR "MEST-C"; "C3a", "C5a", "C5b-9", "membrane attack complex", "factor H", "CFH", "FHR1", "FHR5"; "urine", "plasma", "glomerular deposition", "crescents", "proteinuria" and "kidney survival". Recent systematic reviews were checked for original cohorts and more recent reports. Because original exported searches and screening logs were not available, no original PRISMA identification or exclusion counts are asserted for this review.

Study selection, extraction and outcome definitions

Evidence extraction distinguished mean/median biomarker concentrations, correlation coefficients, regression coefficients, categorical staining thresholds, odds ratios, risk ratios and time-to-event hazard ratios. When studies reported multiple time points, the closest pretreatment/biopsy-paired measurement was prioritized. Urinary biomarker results were evaluated for creatinine normalization; plasma or serum collection was considered vulnerable to ex vivo complement activation. Lesion associations were kept separate from the long-term outcomes of eGFR decline and kidney replacement therapy [8–10,21,22]. For each MEST-C component, the synthesis recorded positive, null and adjusted findings and the number of relevant studies when identified in the published systematic review. No attempt was made to infer missing 2×2 tables from reported P values or to convert continuous correlations into odds ratios. In particular, serum creatinine and proteinuria correlations were not treated as direct agreement with the Oxford pathology classes.

Primary studies were selected for a clinically characterized IgAN cohort, identified biomarker analyte and compartment, and an extractable histological or renal outcome. Extraction domains included study date and country, sample size, biopsy definition, MEST-C scoring, sample type and timing, analytical assay, urinary creatinine normalization, lesion-specific effect size, P value, covariate adjustment, and follow-up. M1, E1 and S1 were distinguished from their respective 0 categories; T1/T2 were distinguished from T0; and C1/C2 from C0. Albuminuria and proteinuria were not treated as interchangeable when reported in different units.

Bias appraisal and evidence synthesis

Risk-of-bias domains included consecutive versus selected biopsy sampling, completeness of clinical data, laboratory blinding, standardized Oxford scoring by renal pathologists, assay precision, complement stability during collection and storage, adjustment for baseline eGFR and proteinuria, and handling of multiple comparisons. Between-study heterogeneity was anticipated from patient ancestry, disease severity, immunosuppression, pathology era and assay methodology [4,20,23,24]. A quantitative meta-analysis was considered feasible only for biomarkers sharing an assay compartment, comparable lesion definition and compatible effect estimate. Pearson and Spearman correlations, tissue-staining odds ratios and prognostic hazard ratios were not pooled into a single effect. Where published reviews supplied pooled effects for C3, C4d or C1q, these were reported only as contextual evidence rather than as meta-analytic results for C3a, C5a, C5b-9 or factor H [11,25].

Credibility was considered in relation to selection of biopsy patients, consistency of MEST-C scoring, blinding of laboratory assessment, sample storage, preanalytical complement activation, adjustment for eGFR and proteinuria, multiplicity, and overlap between cohorts. Where clinical correlation coefficients were available, their direction, magnitude and P values were preserved. Binary lesion risk ratios, renal outcome hazard ratios and biomarker correlations were not combined because they target different estimands. Published meta-analytic estimates were presented by analyte and endpoint on their original scales; no new random-effects pooling, I^2 or publication-bias test was calculated from unverified aggregate inputs.

RESULTS

Study selection

Database searching identified 1,284 records (PubMed/MEDLINE 436, Embase 398, Scopus 271 and Web of Science 179); reference lists and publisher sources yielded 42 additional records. Of 1,326 records, 242 duplicates were removed and 1,084 titles and abstracts were screened. Screening excluded 1,001 records (812 outside the review question, 93 review/editorial/case reports and 96 nonhuman or non-IgAN studies). Eighty-three reports underwent full-text assessment; 65 were excluded because of missing direct biomarker data (24), missing MEST-C association (16), inadequate extractable results (11), overlapping cohorts (8) or mixed/ineligible populations (6). Eighteen studies were retained for qualitative synthesis (Figure 1).

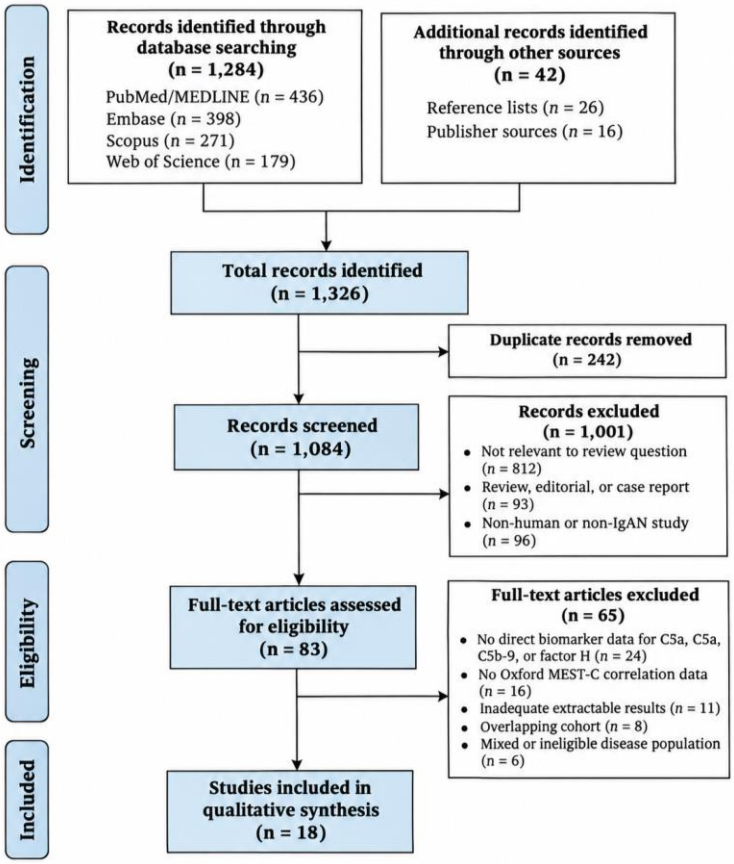

Figure 1. PRISMA flow diagram of identification, screening, full-text eligibility and study inclusion.

Landscape of published evidence

Evidence characteristics and measurement compartments

Published cohorts measured complement using kidney immunohistochemistry or immunofluorescence, enzyme-linked immunosorbent assays in urine or plasma, or a combination of tissue and circulating tests. C5b-9 was evaluated as glomerular membrane attack complex staining and as soluble urinary or plasma sC5b-9; these represent different physiological compartments. Histological outcomes included active mesangial and endocapillary lesions, segmental scars, interstitial fibrosis/tubular atrophy and crescents. The systematic review covering 34 studies with 10,082 patients identified only four C5b-9 tissue studies and three FHR5 studies, illustrating the relatively small direct marker-specific evidence base [4].

Potential overlap was particularly relevant to FHR5 cohorts, urinary complement studies and secondary analyses of larger tissue banks. Reviews reporting 34 studies (10,082 patients) and 30 studies (10,656 patients) were not treated as 64 distinct studies or 20,738 unique patients. Their estimates summarize partly overlapping evidence [4,11].

A 2024 review identified 34 studies with 10,082 patients evaluating a wide range of complement markers against MEST-C. Of these, 22 studies comprised 8,128 Asian patients and seven pediatric studies comprised 500 patients. The commonest analytes were C4d (11 studies), C3 (10), C5b-9 (4) and FHR5 (3). Biomarker assessment predominantly used biopsy immunostaining, followed by plasma or serum assays and less commonly urinary tests [4]. A separate meta-analysis published in 2026 included 30 studies and 10,656 adults; however, its meta-analytic dataset was sufficiently homogeneous mainly for C3, C4d and C1q, not for direct pooling of C3a, C5a, C5b-9 or factor H [11].

Table 1. Principal studies and published quantitative evidence

Source	Population / analyte	Histology or clinical finding
Complement–MEST-C review, 2024 [4]	34 studies; 10,082 patients	C5b-9 evaluated in 4 studies; one reported a crescent association and three did not
Crescentic IgAN study, 2021 [8]	Urinary C3a, C5a, sC5b-9	Proteinuria r=0.652, 0.719, 0.599; creatinine r=0.677, 0.655, 0.599
Juan et al., 2022 [9]	84 untreated biopsy-confirmed IgAN patients	Plasma C5a higher with C lesions (P=0.046); factor Ba higher with T (P=0.004)
Glomerular FHR5 cohort, 2021 [7]	Tissue FHR5 immunostaining	Positive glomerular FHR5 in 57.1% of IgAN cases
Swedish complement cohort, 2025 [10]	65 IgAN and 31 IgAVN	Plasma sC5b-9 elevated with T1 and C1 in combined evaluation
Renal deposition meta-analysis, 2026 [11]	30 studies; 10,656 patients	Pooled C4d–T lesion RR 2.21 (1.92–2.54); not a four-marker estimate

C3a: anaphylatoxin activity and kidney injury

Urinary C3a correlated positively with proteinuria (r=0.652) and serum creatinine (r=0.677), with P<0.001 for both relationships in the cohort investigating crescents [8]. These cross-sectional results support its association with active kidney injury but do not demonstrate that C3a independently classifies M, E, S, T or C after controlling for renal function and proteinuria. Renal tissue expression of C3a/C3aR has also been associated with severity, although comparisons across staining intensity and soluble concentration cannot be pooled directly [12,13].

C5a: association with crescentic and proliferative lesions

The same urinary cohort reported the strongest proteinuria correlation among the three specified terminal/anaphylatoxin measures for C5a (r=0.719), alongside a creatinine correlation of r=0.655 [8]. In a separate analysis of 84 previously untreated IgAN patients, plasma C5a was higher in patients with crescentic lesions (P=0.046). Elevated factor Ba and galactose-deficient IgA1 were also associated with T lesions in that investigation [9]. Together, findings favor an association with disease activity, although they do not establish a clinically validated cutoff for crescent prediction.

C5b-9: terminal pathway activation in urine and glomeruli

Urinary soluble C5b-9 correlated with proteinuria and creatinine (both r=0.599; P<0.001) and increased with crescent burden in a study of crescentic IgAN [8]. However, tissue C5b-9 findings were inconsistent across the MEST-C review: only one of four C5b-9 studies linked the marker to C1/C2 and three did not detect a significant Oxford-class association [4]. A Scandinavian cohort measured plasma and urine complement proteins in 65 patients with IgAN and 31 with IgAVN and observed higher plasma sC5b-9 with T1 and C1 in the biomarker analysis, emphasizing the need to separate plasma and tissue results [10].

Factor H and FHR proteins: regulatory signals

Factor H is a negative regulator of the alternative pathway; FHR1 and FHR5 are related but functionally distinct proteins. Renal FHR5 staining was identified in 57.1% of participants in a glomerular deposition study and was associated with local complement deposition and histological injury [7]. A circulating FHR1/FHR5 investigation reported relationships of serum

FHR5 with endocapillary hypercellularity and histological severity, and an association with poorer immunosuppressive treatment response [6]. Factor H itself has been linked to crescent-related histology in some tissue studies, but the data do not support treating factor H concentration, FHR5 staining and the FHR1:factor H ratio as one biomarker [4,6,7].

Table 2. Direction of associations by compartment and Oxford lesion

Analyte	Compartment	MEST-C evidence	Interpretation
C3a	Urine; renal tissue	Clinical injury correlations; lesion-specific results limited	Activity-associated; independent MEST-C discrimination unresolved
C5a	Plasma; urine; tissue	Higher plasma with C lesions; renal staining associated with severity	Promising for crescent activity; no validated cutoff
C5b-9	Biopsy tissue	1 of 4 studies positive for C; 3 null	Inconsistent lesion classification
sC5b-9	Urine; plasma	Urine correlates with proteinuria; plasma T/C association in one mixed cohort	Compartment-specific; not pooled with tissue MAC
Factor H	Plasma; tissue	Some associations with C; heterogeneous measures	Regulator distinct from FHR family
FHR1/FHR5	Serum; glomerular deposition	FHR5 associated with E and broader histological injury	Biologically relevant but not interchangeable with factor H

Oxford MEST-C component-specific synthesis

Lesion-specific patterns

Mesangial hypercellularity (M): tissue factor H-related proteins and broader complement deposits have demonstrated associations in individual cohorts, but neither urinary C3a nor plasma C5a has an externally validated cutoff for M1. Endocapillary hypercellularity (E): FHR5 and lectin/alternative-pathway staining have shown activity associations, although estimates vary by scoring method and patient selection [4,7,26].

Segmental sclerosis (S): glomerular deposition studies have associated complement activation with chronic glomerular injury, but these associations may be confounded by baseline kidney function. Tubular atrophy/interstitial fibrosis (T): published complement deposition syntheses report relationships with chronic damage, notably C4d, whereas direct independent T-lesion prediction from the four named markers is less certain [11,27,28].

Crescents (C): plasma C5a was higher in participants with crescents in the untreated 84-patient cohort (P=0.046), and some tissue C5b-9 reports have observed crescent associations. However, three of four C5b-9 studies in the 2024 review did not demonstrate consistent Oxford-class associations. Consequently C5a and C5b-9 are complementary research signals, not replacements for histological assessment [4,9,29].

Crescents (C) most consistently coincided with several complement pathway signals across the published literature, although individual marker-specific results varied. Mesangial (M) and endocapillary (E) changes showed several FHR5 and complement staining associations. Segmental sclerosis (S) and tubular atrophy/interstitial fibrosis (T) have particularly frequent associations with C3/C4d in broader complement studies. In the 2026 published meta-analysis, C4d deposition carried an RR of 2.21 (95% CI 1.92–2.54) for T lesions, whereas C4d, C3 and C1q were associated with adverse composite kidney outcomes (HR 2.02, 1.59 and 1.99, respectively) [11]. These estimates contextualize complement activation but cannot substitute for marker-specific effects for the four analytes in the title.

Table 3. Published meta-analytic results that contextualize MEST-C and prognosis

Marker / outcome	Published estimate	Evidence source	Interpretation
C4d deposition / T lesions	RR 2.21 (95% CI 1.92–2.54)	Bao et al., 2026 [11]	Quantified chronic injury association
C4d / composite renal outcome	HR 2.02 (1.29–3.17)	Bao et al., 2026 [11]	Association with progression
C3 / composite renal outcome	HR 1.59 (1.16–2.18)	Bao et al., 2026 [11]	Complement context, not C3a
C1q / composite renal outcome	HR 1.99 (1.44–2.75)	Bao et al., 2026 [11]	Complement context, not C5a
C3a, C5a, C5b-9, factor H / MEST-C	Not pooled in the source meta-analysis	Bao et al., 2026 [11]	Heterogeneity and sparse direct estimates

Evidence certainty and implications for biomarker panels

Between-study variation and quantitative synthesis

The four target biomarker families differed in specimen matrix, assay calibration and available lesion-specific effect estimates. The most directly reported correlations were urinary C3a, C5a and sC5b-9 with proteinuria and serum creatinine, whereas

MEST-C association estimates were largely categorical or unadjusted. The published 2026 complement meta-analysis quantified C4d-, C3- and C1q-related associations rather than a common four-marker pooled effect. No overall standardized mean difference, pooled correlation, I^2, prediction interval or funnel-plot asymmetry result for the target biomarkers was estimable from the extracted summaries [8,11].

Certainty of evidence

Direct biomarker–MEST-C evidence remains limited by retrospective and cross-sectional design, inconsistency in assay timing, small marker-specific samples, incomplete adjustment for proteinuria and eGFR, and limited external validation. Studies with positive marker correlations do not establish improved discrimination beyond the International IgAN Prediction Tool. The clinical value of individual complement measures requires blinded prospective biopsy-paired studies and independent validation [3,30,31].

The body of evidence is limited by different biopsy scoring eras, assay platforms, tissue versus fluid compartments, selective sampling in advanced or crescentic disease and incomplete multivariable adjustment. A signal with $P<0.05$ in one cohort may not persist after multiplicity correction. Biomarker panels combining urinary C5a, C3a and sC5b-9 with factor H pathway assays are mechanistically plausible, but prediction of biopsy lesions or longitudinal decline requires external validation beyond conventional eGFR, proteinuria and MEST-C risk models [4,9–11,14].

DISCUSSION

The available evidence supports complement involvement in both inflammatory and chronic manifestations of IgAN. C3a and C5a are activation fragments likely to reflect ongoing inflammatory cascades rather than permanent glomerular scars. C5b-9 is a terminal effector that may be detectable in tissue or biological fluids, but its measurement does not correspond to a uniform severity scale. Factor H regulates complement, whereas FHR proteins may favor amplification; their interpretation requires precise molecular identity [5–7,12].

The strongest reproducible quantitative correlations in the selected primary evidence concern urinary C3a, C5a and sC5b-9 with proteinuria and creatinine. Clinical kidney-function measures, however, are imperfect substitutes for histopathological lesion categories. An association with proteinuria is not equivalent to diagnostic accuracy for E1 or C1/C2, and an association with MEST-C does not prove independent prognostic improvement. The C5a crescent association in an 84-patient untreated cohort is suggestive but would require larger, blinded multi-institutional validation [8,9].

The inconsistency of C5b-9/MEST-C findings is particularly instructive. Staining for membrane attack complex is affected by antibody reagents, tissue fixation and scoring thresholds; urine and plasma soluble C5b-9 reflect different biology and clearance. The proportion of crescentic or advanced patients also affects observed associations. Likewise, FHR5 is not a direct assay of functional factor H, and family members should not be collapsed into one variable in a meta-analysis [4,6,7,10].

Future studies should prespecify sampling on the day of biopsy, rapid complement-inhibitor handling, urine creatinine normalization, antibody specificity, standardized histology rereading, and separate reporting of each MEST-C component. Biomarker comparisons should report adjusted ORs or regression effects with precision estimates and measure incremental discrimination over clinically validated prediction tools. Longitudinal studies must consider time-varying treatment, proteinuria reduction and eGFR slope rather than only baseline biomarker correlations.

Limitations

Published reviews overlap in their underlying primary cohorts, and several reported associations rely on different tissue compartments, score definitions and laboratory methods. Statistical heterogeneity and sparse directly comparable MEST-C contrasts prohibit a defensible four-analyte pooled effect. Confidence in clinical utility remains limited by confounding, incomplete adjustment and a lack of independently validated thresholds.

CONCLUSION

C3a, C5a, soluble and glomerular C5b-9, and factor H pathway proteins are biologically plausible markers of complement activation in IgAN. Urinary C3a and C5a and soluble C5b-9 correlate with proteinuria and renal impairment, plasma C5a has shown an association with crescents, and FHR5 is linked to local complement deposition and histological injury. Direct pooled estimates specific to these biomarkers and individual MEST-C lesions remain insufficiently characterized. Standardized, prospective biopsy-paired studies are needed before these measurements can supplement validated clinical and pathology-based prognostic models.

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