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Endoluminal Complement Accessibility as a Spatial Determinant of Glomerular Injury: A Systematic Review with Integrated Narrative Analysis

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Endoluminal Complement Accessibility as a Spatial Determinant of Glomerular Injury: A Systematic Review with Integrated Narrative Analysis

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Abstract

Purpose: The anatomical relationship between glomerular complement deposition and inflammatory injury remains incompletely defined. Although complement activation is often interpreted as downstream of immune-complex deposition, whether complement localisation helps shape lesion architecture is less clear. We tested whether endothelial accessibility of glomerular complement deposition to circulating neutrophils is associated with the compartmental localisation of inflammatory injury.

Methods: A structured review of human renal biopsy studies was conducted across four disease arms selected to test this spatial hypothesis: lupus nephritis (LN) and post-infectious/infection-related glomerulonephritis (PIGNI), representing complement-depositing diseases with endothelial-accessible deposits; ANCA-associated vasculitis (AAV), representing a pauci-immune glomerular comparator; and membranous nephropathy (MN), representing abundant glomerular complement deposition confined to an abluminal compartment. Data were synthesised using a compartment-based framework focused on complement localisation, neutrophil distribution, temporal deposition patterns, NET-marker localisation, and karyorrhexis.

Results: Endothelial-accessible complement deposition in LN and PIGNI was consistently associated with endocapillary neutrophil-rich lesions and karyorrhexis. By contrast, AAV showed predominantly extraglomerular or vessel-wall neutrophil-associated injury, while MN served as the critical internal comparator separating complement presence from endothelial accessibility. Temporal biopsy data suggested that C3c tracks active complement deposition more closely than C3d, which may persist after prior activity. NET-marker studies and karyorrhexis distribution were compatible with interface-localised neutrophil lytic injury, but did not establish lesion-level mechanism.

Conclusions: These findings support a spatial model in which complement accessibility, rather than glomerular complement deposition alone, helps define the architecture of inflammatory glomerular injury. Endoluminal complement may mark and amplify an actively arrested endothelial-interface lesion, but lesion-level co-localisation studies are required for direct validation. The model generates falsifiable predictions for multiplex biopsy analysis and suggests that fragment-specific complement assessment may improve biopsy interpretation and biomarker-guided therapeutic stratification.

Keywords: *lupus nephritis; post-infectious glomerulonephritis; ANCA-associated vasculitis; membranous nephropathy; neutrophil extracellular traps; diapedesis;*

Statements and Declarations

Competing Interests: The authors declare no competing interests.

Systematic Review

INTRODUCTION

Glomerulonephritis encompasses a spectrum of immune-mediated injuries in which neutrophil accumulation in glomerular capillaries is a well-recognised histologic feature, yet its mechanistic basis remains incompletely explained [1,2]. In both lupus nephritis (LN) and post-infectious or post-streptococcal glomerulonephritis (PIGNI/PSAGN), endocapillary neutrophil accumulation and associated nuclear debris have been incorporated into disease classification and activity scoring systems for decades [3–5]. However, the fundamental question of why these neutrophils remain within glomerular capillaries rather than completing transendothelial migration into the renal interstitium has not been systematically examined.

The classical model of neutrophil recruitment describes a sequential adhesion and transmigration cascade culminating in paracellular passage through endothelial junctions, involving molecules such as PECAM-1, CD99, JAM-A, and JAM-C [6]. This final step requires active endothelial participation. An activated endothelium differs from a quiescent one not only by upregulating ICAM-1, E-selectin, and VCAM-1, but also by executing the cytoskeletal and membrane-recycling events required for junction opening, including VE-cadherin endocytosis and lateral border recycling compartment mobilisation. In principle, therefore, neutrophil arrest at the endothelial surface and successful transmigration are separable events. The observation that LN and PIGNI show prominent endocapillary neutrophil accumulation without comparably prominent interstitial neutrophilic infiltration raises the possibility that this final endothelial junction-opening step may be impaired in these diseases [3,4,7].

The central hypothesis of this review is that endoluminal complement at the glomerular endothelial surface is a marker of this stuck transmigration state. The claim is not that complement is the sole cause of diapedesis failure, nor that it is a passive bystander. Rather, we hypothesise that endoluminal complement identifies glomerular capillary segments in which neutrophil transmigration has been initiated but not completed, and that complement at this interface may also participate in maintaining and amplifying the arrested state through mechanisms such as iC3b/CR3-mediated adhesion and C5a/C5aR1 activation. Within this framework, systemic hypocomplementaemia can be interpreted as a readout of the cumulative burden of active interface lesions across the glomerular microvasculature. The upstream causes of junctional dysfunction may vary by disease, but the spatial lesion pattern and its complement signature may be shared.

This model generates a specific and testable spatial prediction: the characteristic lesion should form only when complement reaches the endoluminal endothelial surface. Two natural comparators test this prediction directly and were pre-specified as control arms in this review.

First, pauci-immune ANCA-associated vasculitis (AAV) has minimal or absent immune complex and complement deposition in glomerular vessels [8,9]. If endothelial-accessible complement is a defining feature of the characteristic endocapillary lesion pattern, then AAV should lack that lesion pattern and instead show neutrophil associated injury in extraglomerular compartments, providing a pauci-immune glomerular-deposition comparator.

Second, membranous nephropathy (MN) has substantial immune complex and complement deposition within glomeruli, but specifically in the subepithelial compartment on the podocyte side of the glomerular basement membrane [1,10]. In this setting, C3a and C5a are generated albuminally and do not directly access the endothelial luminal interface where circulating neutrophils are located. If the model is correct, MN should lack endocapillary neutrophil accumulation and karyorrhexis despite robust complement deposition within the glomerulus. The reported absence of endocapillary hypercellularity, neutrophil-rich exudative lesions, karyorrhexis, and fibrinoid

necrosis in MN is consistent with this prediction [1,10].

A further implication of the model is that neutrophils retained at this interface may undergo lytic NET-associated injury rather than completing orderly transmigration. In this framework, NETosis is not assumed to be the initiating event, but may function as a downstream response to persistent endothelial arrest [11]. Release of MPO, elastase, chromatin, and other neutrophil products at the capillary wall would be expected to amplify local endothelial and glomerular basement membrane injury, providing a potential explanation for the endocapillary localisation of karyorrhexis and fibrinoid necrosis in complement-depositing glomerulonephritides. This remains a mechanistic interpretation to be tested against the biopsy literature rather than a settled conclusion.

Accordingly, this systematic review was conducted to determine whether the published renal biopsy literature, interrogated through five pre-specified research questions across four disease arms, is consistent with this spatial model. A parallel narrative review was undertaken to situate the biopsy findings within the molecular biology of leukocyte extravasation, endothelial junction opening, complement signalling, and disease-specific upstream triggers.

Two prior publications provide mechanistic context for the model examined here. A case report of atypical haemolytic uraemic syndrome suggested that failed complement receptor internalisation at arrested neutrophils may be associated with in situ NET-associated injury and heparan sulfate–PF4–TLR4-mediated microthrombus formation as downstream consequences of a stuck-interface state [12]. A separate scoping review of APOL1 G1/G2 variants in lupus nephritis identified disruption of the APOL3/PI4KB/NCS-1 complex as one possible upstream mechanism by which endothelial junction-opening competence may be impaired [13]. The present paper is self-contained: it tests whether the systematic biopsy literature across four pre-specified disease arms is consistent with the stuck-interface model independently of the mechanistic substrate responsible for any individual upstream disease process.

To test the proposed spatial model, the review was structured around five pre-specified research questions: (1) How are neutrophils anatomically distributed across the four disease arms? (2) Is the location of complement deposition associated with the compartment of neutrophil-associated injury? (3) Do temporal biopsy data, including the distinction between C3c and C3d, differentiate active from residual complement deposition? (4) How are NET-associated markers spatially distributed across complement-depositing and pauci-immune disease patterns? (5) Does the spatial distribution of karyorrhexis support or weaken its current interpretation within glomerular activity lesions?

METHODS

Study Design, Registration, and Control Arm Logic

This study was designed and reported in accordance with the PRISMA 2020 statement [14]. The protocol was submitted prospectively to PROSPERO before formal review conduct and is registered as CRD420261368198. Four disease arms were pre-specified, each intended to test a different aspect of the spatial model under investigation.

LN and PIGNI were designated the primary arms, as complement-depositing glomerulonephritides with endoluminally accessible deposits expected to show endocapillary neutrophil accumulation, karyorrhexis, and related activity lesions. AAV was designated the pauci-immune glomerular-deposition comparator arm: in pauci immune AAV, glomerular immune-complex deposition is minimal or absent on routine biopsy, and this arm was included to assess whether the characteristic endocapillary lesion pattern requires glomerular immune complex/complement deposition at the endothelial interface. MN was designated the spatial specificity

comparator arm: immune complex and complement deposition are abundant within glomeruli but localised predominantly to the subepithelial compartment on the podocyte side of the glomerular basement membrane. This arm was included to assess whether endoluminal accessibility of complement-related inflammatory signals is specifically required, rather than complement presence within the kidney alone.

Together, the four-arm comparison: endothelial-accessible complement present (LN, PIGNI), pauci-immune glomerular deposition minimal or absent (AAV), and complement present but abluminal (MN) was designed to isolate the anatomical relationship between complement deposition and the endothelial interface as the key variable of interest. A parallel narrative synthesis of the mechanistic literature was pre-specified and is presented as an integrated mechanistic interpretation.

Data Sources and Search Strategy

Systematic electronic searches were conducted in PubMed/MEDLINE and Cochrane Library in April 2025. No language restrictions or date limits were applied. Supplementary searches were conducted in Google Scholar, and forward citation searching was performed on five anchor papers [15–19]. The three identification sources together yielded 240 total records: 210 from databases and 30 from other methods. After removal of 30 duplicate records, 210 unique records were screened at title and abstract.

The PubMed search used a single consolidated string across all four disease arms structured in three Boolean blocks: (1) disease and population terms; (2) biopsy and tissue methodology terms; and (3) outcome terms covering endocapillary hypercellularity, karyorrhexis, complement markers, and deposit compartments. Case reports were excluded using a publication type filter. The Cochrane Library was searched using equivalent keyword terms. The full search strings are provided as Supplementary Appendix 1.

Title and abstract screening was conducted independently by two reviewers (G.N.Z. and S.A.T.) with disagreements resolved by discussion. Of 210 records screened, 144 were excluded at title and abstract stage. The remaining 66 records were retrieved for full-text assessment. No full texts were unobtainable. Forty-two full-text articles were excluded with reasons: no extractable biopsy histological data relevant to pre-specified outcomes (n=30), wrong disease or population (n=5), animal study (n=4), and wrong outcome reported (n=3). Twenty-four studies were included in the final review. The PRISMA 2020 flow diagram is provided as a related file with this submission.

Eligibility Criteria

Included studies were primary human renal biopsy cohorts or case series (minimum n=3) involving adults aged ≥18 years with biopsy-proven LN (ISN/RPS classification), PIGNI/PSAGN (clinicopathologic diagnosis), AAV (2012 CHCC criteria), or MN (primary or secondary), reporting at least one of: neutrophil prevalence or localisation; presence or absence of endocapillary hypercellularity; complement deposition by immunofluorescence or immunohistochemistry; activity lesion scores including neutrophil-related components; or NET-associated immunostaining. For MN, authoritative biopsy-based pathology studies and mechanistic pathology reviews were also eligible when they clearly defined the characteristic lesion pattern and its spatial relationship to complement deposition. Exclusion criteria: animal studies; non-biopsy-based studies; studies lacking complement or neutrophil data interpretable by pre-specified compartment definitions; and reviews without

primary biopsy data relevant to the corresponding research question.

Data Extraction and Outcome Definitions

Neutrophil localisation was extracted according to: endocapillary/intraluminal, subendothelial/interface associated, mesangial, interstitial/extravasated, and peritubular capillary intravascular compartments. Complement findings were recorded by marker (C3, C3c, C3d, C1q, C4d, C5b-9/MAC), detection method, and localisation. The distinction between C3c and C3d was extracted explicitly where reported. Studies using generic anti-C3 antibodies were recorded separately with that limitation acknowledged. NET-related data were extracted by marker (MPO, H3Cit, PAD4), tissue compartment, and whether co-localisation studies were performed. Because included studies varied substantially in staining methods and reporting granularity, spatial patterns were synthesised narratively using pre-specified compartment-based categories.

Outcomes

The primary outcome was the prevalence and anatomical localisation of neutrophil accumulation across all four disease arms, with particular attention to endocapillary versus interstitial distribution and to the presence or absence of an endocapillary lesion pattern in MN. Secondary outcomes were: spatial relationship between complement deposit location and neutrophil accumulation; the relationship of C3c versus C3d to active lesions on serial biopsy; temporal patterns linking complement deposition with active versus resolving lesions; NET marker localisation relative to complement and neutrophil compartments; and evidence bearing on the attribution of karyorrhexis.

Quality Assessment

Study quality was assessed to contextualise evidential weight rather than to exclude studies by rigid quantitative thresholds. Biopsy cohort studies were evaluated using a light Newcastle–Ottawa-style framework adapted for cross-sectional designs, focusing on cohort selection, diagnostic clarity, lesion definition, and adequacy of outcome reporting. Immunohistochemistry-based studies were additionally assessed for antibody validation, staining consistency, compartment definition, and scoring methodology. Quality assessment was performed independently by two reviewers (G.N.Z. and S.A.T.) with disagreements resolved by discussion.

RESULTS

Twenty-four studies were included across the four pre-specified disease arms. Detailed study characteristics, extracted biopsy findings, complement markers, NET-marker data, timing data, and quality assessments are provided in Supplementary Table 1.

RQ1: Neutrophil Prevalence and Anatomical Localisation Across All Four Arms

Overview

The primary aim of RQ1 was to assess whether neutrophil accumulation localises preferentially to endocapillary, capillary loop–associated, or interstitial compartments across the four disease arms, and whether this distribution tracks with endoluminal accessibility of complement-related inflammatory signals. In LN and PIGNI/PSAGN, where complement deposition is reported in endocapillary-accessible compartments, neutrophils are described predominantly within glomerular capillary lumina or in immediate capillary loop–associated locations [4,7,15,17,20,21]. In contrast, in AAV, where glomerular immune deposits are absent or minimal, neutrophil associated injury is reported predominantly in interstitial, perivascular, and necrotising compartments [8,18,22,23]. MN provides a spatial specificity comparator: despite abundant glomerular complement deposition, deposits are subepithelial and therefore spatially segregated from the endothelial–luminal interface, and endocapillary neutrophil accumulation is not characteristic of typical MN [1,10,24]. This pattern separates glomerular complement deposition from endothelial-luminal accessibility within the comparative framework.

Lupus Nephritis

The largest identified LN cohort, reported by Querin et al. (n=194), found neutrophils/karyorrhexis in 58.2% of

biopsies and endocapillary hypercellularity in 72.7%, with a strong correlation between these lesions (Spearman r=0.78, p<0.0001) [15]. In the cross-disease immunohistochemical study by Kimura et al., MPO-positive neutrophils in LN localised predominantly to the margins of glomerular tufts, particularly in association with wire loop lesions; interstitial MPO-positive and H3Cit-positive signals were limited [17]. This glomerular inflammatory pattern is also consistent with studies demonstrating increased glomerular ICAM-1 expression in proliferative glomerulonephritides, with significant correlations between ICAM-1, endocapillary proliferation, mesangial proliferation, and leukocyte infiltration [25].

Post-Infectious Glomerulonephritis

In PIGNI/PSAGN, neutrophil localisation was even more consistently endocapillary. In the C3-dominant PIGN subgroup reported by Khalighi et al. (n=13), exudative glomerulonephritis was present in 84.6% of biopsies [7]. Kimura et al. further supported this pattern by demonstrating neutrophils within glomerular capillary lumina on electron microscopy in PSAGN, without accompanying interstitial inflammation [17]. In the IgA-dominant infection-related glomerulonephritis series reported by Koo et al. (n=7), intracapillary neutrophils were present in all cases, whereas the interstitial infiltrate was predominantly lymphocytic [20]. Larger adult series of acute post infectious glomerulonephritis similarly describe a diffuse proliferative glomerular pattern with dominant C3 deposition [4,21]. Across the post-infectious spectrum, the available evidence supports a predominantly intraluminal or endocapillary neutrophil distribution rather than a tissue-invasive interstitial neutrophilic pattern [4,20,21].

ANCA-Associated Vasculitis

AAV showed a contrasting pattern. In the series reported by Kamijo et al. (n=50), H3Cit-positive cells were identified in the interstitium in 84% of cases, and interstitial H3Cit positivity correlated with urinary β2-microglobulin; H3Cit-positive staining was also present in all arteritic lesions examined [18]. In the study by Kimura et al., interstitial MPO-positive and H3Cit-positive signals were significantly greater in microscopic polyangiitis than in the complement-depositing comparator diseases [17]. These findings support the conclusion that the dominant neutrophil-associated pattern in AAV is not endocapillary neutrophil retention but rather extraglomerular or tissue-invasive inflammation [17,18,22].

Membranous Nephropathy

Membranous nephropathy serves as a spatial specificity comparator in which complement deposition is present within glomeruli but localised predominantly to the subepithelial compartment [1,10]. Endocapillary hypercellularity and neutrophil-rich exudative lesions are not characteristic features of typical MN and, when prominent, should prompt consideration of a superimposed or secondary process [1]. Supportive studies further suggest that inflammatory cell accumulation in MN is not centred within the glomerular capillary lumen [24]. Thus, although complement deposition is present within glomeruli, it is not associated with the characteristic endocapillary neutrophil-rich inflammatory lesion seen in proliferative immune-complex glomerulonephritides [1,24].

Synthesis Across All Four Arms

Across the four disease arms, neutrophil localisation followed a consistent compartmental pattern. LN and PIGNI/PSAGN showed predominantly endocapillary neutrophil accumulation in the setting of endothelial accessible complement deposition [4,7,15,17,20,21]. In contrast, AAV showed predominantly interstitial and vessel wall neutrophil-associated injury [8,18,22,23], while MN lacked a characteristic endocapillary neutrophil rich lesion despite glomerular complement deposition [1,10,24]. Taken together, these findings indicate that endocapillary neutrophil accumulation tracks more closely with endothelial accessibility of inflammatory signals than with glomerular complement deposition alone. The comparative spatial pattern is summarised in Table 1 and Figure 1.

Disease	Complement in glomerulus	Complement location	Endoluminal complement access	Dominant neutrophil compartment	Endocapillary hypercellularity	Karyorrhexis (endocapillary)	Predomin ant lesion pattern
Lupus nephritis (LN)	Present	Subendothelial/ capillary loop / mesangial	Yes	Endocapillary (capillary loop–associated)	Present (≈72.7%)	Present (≈58.2%)	Endocapillary neutrophil rich inflammatory pattern
Post infectious GN (PIGNI/PSAGN)	Present	Capillary wall (subendothelial) / mesangial	Yes	Endocapillary (intracapillary 'exudative')	Present (≈80–85%)	Present	Endocapillary exudative inflammatory pattern
ANCA associated vasculitis (AAV)	Absent (pauci immune)	Not applicable	No	Interstitial / perivascular / vessel wall	Absent	Absent (endocapillary)	Predominantly extraglomerular neutrophil associated pattern
Membranous nephropathy (MN)	Present	Subepithelial (abluminal)	No	Absent (no neutrophil rich lesion)	Absent	Absent	Non proliferative complement -associated glomerular pattern

Table 1. Spatial localisation of complement and neutrophil-associated injury across four disease arms.

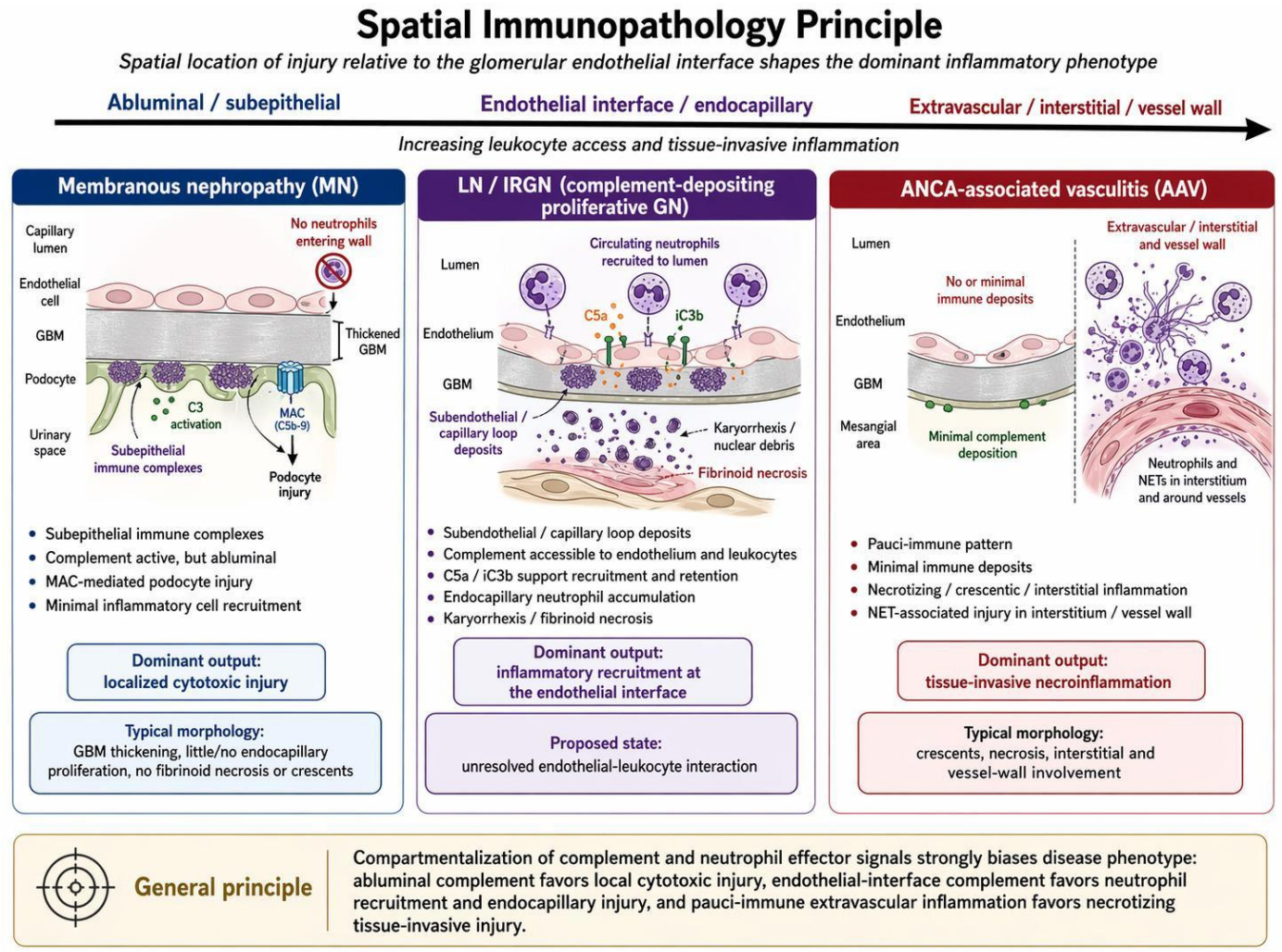


Figure 1. Spatial immunopathology principle across glomerulonephritides.

RQ2: Complement Deposit Location and Neutrophil Spatial Coupling

RQ2 examined whether complement localisation, rather than complement presence alone, was associated with the compartment of neutrophil-associated injury. The comparison focused on three spatial conditions: endothelial accessible complement deposition in LN/PIGNI, pauci-immune glomerular deposition in AAV, and abluminal subepithelial complement deposition in MN.

C4d and Karyorrhexis/Fibrinoid Necrosis in LN

Ding et al. reported glomerular C4d positivity in 98.2% of biopsies (n=325). Biopsies with peritubular capillary or tubular basement membrane C4d positivity showed higher karyorrhexis/fibrinoid necrosis scores and higher overall activity indices than C4d-negative cases [3]. An important qualification is that glomerular C4d in LN is subtype-dependent: class V disease may show strong glomerular C4d despite relative absence of endocapillary inflammatory lesions, indicating that complement positivity alone does not predict lesion type without reference to anatomical compartment [3,16].

Complement in PIGNI and Temporal Coupling

In PIGNI/PSAGN, available studies support coupling between capillary wall complement deposition and acute neutrophil-rich glomerular injury. Miquelestorena-Standley et al. documented C3 deposits in all 27 biopsies from

patients with IgA-dominant infection-related glomerulonephritis: diffuse or global capillary wall C4d staining was associated with acute histologic patterns [21]. Khalighi et al. reported capillary wall and mesangial C3 deposition coexisting with intracapillary neutrophils in 85% of C3-dominant post-infectious cases [7]. Matsell et al. showed that plasma SC5b-9 levels were highest near disease onset, declined with increasing time from onset (r=−0.59, p=0.0008), and co localised with C3 in capillary loops on biopsy, indicating that terminal complement complex formation is temporally concurrent with the acute neutrophil exudation phase [19].

MN as a Spatial Specificity Comparator

MN provided the spatial specificity comparator. In typical MN, complement is present within glomeruli but confined predominantly to the subepithelial compartment, spatially separated from circulating neutrophils at the endothelial-luminal interface [1,10]. The characteristic biopsy pattern lacks the endocapillary neutrophil-rich lesion seen in proliferative immune-complex glomerulonephritides [1,24].

RQ3: Temporal Relationships and the C3c/C3d Distinction

PSAGN: Temporal Coupling

Sorger et al. described early-phase biopsies (weeks 1–3) characterised by finely granular capillary wall C3 and IgG deposition in a 'starry sky' pattern, corresponding to peak endocapillary neutrophil exudation [26]. As disease progresses, the immunofluorescence pattern transitions to a predominantly mesangial distribution, coinciding with reduction in endocapillary hypercellularity. Serum complement kinetics parallel these findings, with C3 reduced in the majority of patients during early disease and normalising over subsequent weeks [19,26]. This temporal coupling is consistent with infection-related glomerulonephritis cohorts in which acute exudative and capillary wall complement-positive patterns are most prominent close to disease onset [4,21,19].

LN: Differential Persistence of Complement Fragments

Wilson and Pickering et al., in a study of serial LN biopsies (n=57), demonstrated that C3c — an early and labile complement cleavage fragment — clears from tissue over days to weeks, whereas C3d persists for months and C5b-9 for longer durations [16]. In this cohort, C3c deposition correlated significantly with the proportion of glomeruli demonstrating active disease and with crescent formation, whereas C3d and C5b-9 did not show similar associations [16].

Interpretation: Active Versus Residual Complement Deposition Because standard immunofluorescence using anti-C3 antibodies primarily detects C3d, tissue C3 positivity may represent residual deposition rather than ongoing complement activation [16]. Detection of C3c appears to more closely reflect currently active complement deposition. This distinction provides a potential explanation for the observed dissociation between serum complement levels and histologic findings in LN: serum complement reflects current consumption, while tissue staining may reflect prior activity [16]. In PSAGN, complement deposition and endocapillary inflammatory lesions decline in parallel over time, consistent with a self-limited disease course [19,26]. In LN, complement deposition persists within tissue despite clinical or biochemical improvement, reflecting the prolonged retention of C3d and C5b-9 [16].

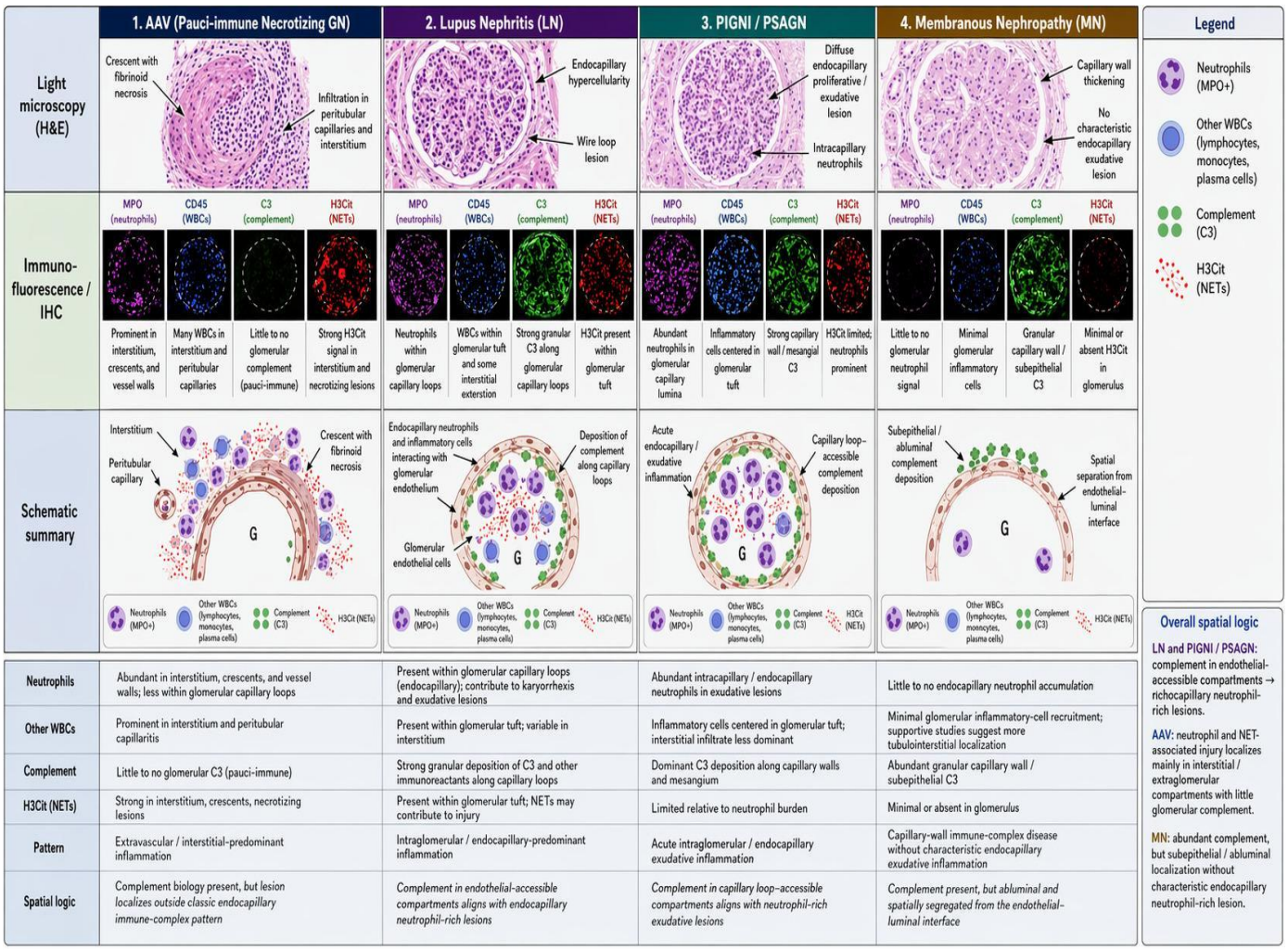
RQ4: NET Marker Spatial Distribution

In the cross-disease immunohistochemical study by Kimura et al., H3Cit-positive staining was significantly lower in complement-depositing diseases including class IV LN, PSAGN, and Henoch–Schönlein purpura nephritis than in microscopic polyangiitis. Interstitial H3Cit-positive staining was minimal, and extracellular NET material was absent or not clearly discernible in these groups. PSAGN showed the highest MPO-positive neutrophil burden but the lowest H3Cit-positive frequency, indicating that neutrophil accumulation and NET marker detectability do not

necessarily track in parallel [17]. Kamijo et al. reported H3Cit-positive cells in the interstitium in 84% of AAV biopsies, with H3Cit positivity correlating with tubular injury markers; H3Cit-positive staining was also present in all arteritic lesions examined [18]. For MN, no biopsy study specifically evaluating NET marker localisation was identified.

RQ5: Karyorrhexis Attribution and Spatial Distribution

Existing morphologic descriptions do not definitively distinguish apoptotic nuclear fragmentation from NET associated nuclear injury in routine biopsy material [15,17]. Kimura et al. demonstrated H3Cit-positive, MPO positive neutrophils at wire-loop margins in class IV LN, providing partial support for a neutrophil-associated chromatin injury pattern in active endocapillary lesions [17]. However, no biopsy study identified in this review directly compared MPO, H3Cit, and activated caspase-3 within the same endocapillary lesion. Accordingly, current biopsy evidence does not permit definitive assignment of karyorrhexis to either apoptosis or NETosis on immunophenotypic grounds alone. This uncertainty remains notable because established histopathologic activity indices in lupus nephritis incorporate karyorrhexis, fibrinoid necrosis, and endocapillary hypercellularity as core active lesions [3,15].



	1. AAV (Pauci-immune Necrotizing GN)	2. Lupus Nephritis (LN)	3. PIGNI / PSAGN	4. Membranous Nephropathy (MN)
Neutrophils	Abundant in interstitium, crescents, and vessel walls; less within glomerular capillary loops	Present within glomerular capillary loops (endocapillary); contribute to karyorrhexis and exudative lesions	Abundant intracapillary / endocapillary neutrophils in exudative lesions	Little to no endocapillary neutrophil accumulation
Other WBCs	Prominent in interstitium and peritubular capillaritis	Present within glomerular tuft; variable in interstitium	Inflammatory cells centered in glomerular tuft; interstitial infiltrate less dominant	Minimal glomerular inflammatory-cell recruitment; supportive studies suggest more tubulointerstitial localization
Complement	Little to no glomerular C3 (pauci-immune)	Strong granular deposition of C3 and other immunoreactants along capillary loops	Dominant C3 deposition along capillary walls and mesangium	Abundant granular capillary wall / subepithelial C3
H3Cit (NETs)	Strong in interstitium, crescents, necrotizing lesions	Present within glomerular tuft; NETs may contribute to injury	Limited relative to neutrophil burden	Minimal or absent in glomerulus
Pattern	Extravascular / interstitial-predominant inflammation	Intraglomerular / endocapillary-predominant inflammation	Acute intraglomerular / endocapillary exudative inflammation	Capillary-wall immune-complex disease without characteristic endocapillary exudative inflammation
Spatial logic	Complement biology present, but lesion localizes outside classic endocapillary immune-complex pattern	Complement in endothelial-accessible compartments aligns with endocapillary neutrophil-rich lesions	Complement in capillary loop–accessible compartments aligns with neutrophil-rich exudative lesions	Complement present, but abluminal and spatially segregated from the endothelial–luminal interface

Figure 2. Integrated histological and schematic comparison across four glomerulonephritis phenotypes

DISCUSSION

The Four-Arm Pattern

This systematic review examined whether published renal biopsy data across four pre-specified disease arms are consistent with the hypothesis that endoluminal complement at the glomerular endothelial surface is a marker and participant of an actively stuck transmigration interface. Across all five research questions, the available biopsy evidence is consistent with this model and supports a spatially structured interpretation of complement-associated glomerular injury.

The logical structure of the four-arm comparison is the central evidential contribution of this review. LN and PIGNI, in which complement is present in endoluminally accessible compartments, show endocapillary neutrophil accumulation, karyorrhexis, and hypocomplementaemia [3,4,7,15,19,21,26]. AAV, in which glomerular immune complex deposition is minimal or absent on routine biopsy, lacks a comparable endocapillary lesion and instead shows neutrophil-associated injury and NET marker localisation predominantly in interstitial and vessel wall compartments [8,9,17,18,22,23]. MN, in which complement is present but confined to the abluminal subepithelial compartment, shows no endocapillary neutrophil accumulation, no karyorrhexis, and generally normal serum complement [1,10,24].

The importance of the MN arm is that it breaks the most obvious confounding argument. In a two-arm comparison between LN/PIGNI and AAV alone, the association between complement deposition and endocapillary neutrophil rich lesions could be dismissed as a downstream correlate of general disease activity. MN removes that explanation: complement is present in abundance, the disease is active, podocyte injury is substantial, yet endocapillary neutrophil accumulation and karyorrhexis are absent [1,10].

The absence of a characteristic endocapillary neutrophil-rich lesion in MN therefore argues against a model in which complement presence alone is sufficient to generate endocapillary inflammation. Instead, MN supports the more constrained interpretation that complement must be anatomically accessible to the endothelial-luminal interface to participate in, or mark, the lesion architecture described in LN and PIGNI/PSAGN [1,10,24]. The AAV arm completes the argument from the opposite direction: in the absence of a glomerular complement deposition pattern comparable to LN or PIGNI, neutrophils are not retained in an endocapillary lesion pattern and NET-associated injury is identified in interstitial and vessel wall compartments [8,18,22,23]. The stronger AAV complement studies sharpen rather than weaken this point: complement activation is present in AAV, but its biopsy-linked correlates are focal necrosis and interstitial infiltration, not a classic endocapillary exudative lesion [9,18].

The C3c/C3d Distinction and its Clinical Implications

The distinction between C3c and C3d is one of the most practically important findings in this review and remains underappreciated in routine nephrology practice. The serial biopsy data summarised here indicate that C3c, an early and labile cleavage fragment, tracks active lesions, whereas C3d and C5b-9 persist substantially longer and do not show the same relationship to currently active disease [16].

A biopsy showing C3c at the capillary wall indicates complement is being deposited in the active phase of injury. By contrast, C3d may remain in tissue long after the active cycle has resolved [16]. Standard immunofluorescence using generic anti-C3 antibodies does not distinguish between these fragments. A biopsy reported simply as 'C3 positive, capillary wall pattern' is therefore temporally ambiguous. This distinction provides a plausible explanation for the longstanding dissociation between serum complement levels and histologic remission: serum C3 reflects current consumption at active lesion sites, whereas tissue C3 positivity (if driven largely by persistent C3d) may instead reflect prior activity [16]. Persistent isolated C3 hypocomplementaemia has been identified as a

strong predictor of progression to end-stage kidney disease in lupus nephritis [27], supporting fragment specific complement assessment as a clinically testable improvement to biopsy interpretation.

Karyorrhexis and the Four-Arm Spatial Distribution Argument

The case against a settled apoptosis attribution for karyorrhexis is strengthened most by the spatial distribution analysis rather than by direct co-staining evidence alone. Karyorrhexis appears specifically in endocapillary inflammatory lesions in complement-depositing glomerulonephritides [3,7,15,21], is absent in MN despite abundant complement deposition [1,10], and is not a characteristic endocapillary lesion in AAV despite clear evidence of neutrophil-associated injury and NET marker positivity in extraglomerular compartments [8,18,22,23]. This distribution is more compatible with the interpretation that karyorrhexis reflects a form of neutrophil-associated chromatin injury linked to a specific lesion architecture than with the view that it is simply a nonspecific apoptotic phenomenon. The decisive validation experiment remains lesion-level co-staining for MPO, H3Cit, and activated caspase-3 in the same endocapillary LN biopsies. Until then, the apoptosis attribution embedded in current classification systems should be regarded as incompletely validated rather than established [3,15,17].

A further possibility is that the contrast between LN and IRGN reflects not only lesion topology but also differences in host handling of released nuclear material. In SLE/LN, impaired degradation and elimination of extracellular nuclear material has been described, providing a plausible background in which NET-associated chromatin may persist once released [28]. By contrast, equivalent evidence for a predisposing clearance-defect phenotype is not established in IRGN.

Falsifiable Predictions of the Stalled-Interface Model

The present framework generates several falsifiable predictions. First, within individual active capillary loop lesions, MPO-positive neutrophils should spatially overlap with fragment-specific complement deposition, particularly C3c and/or C5b-9, at the endothelial-luminal interface. This overlap should be strongest in proliferative LN and PIGNI/PSAGN and should be weak or absent in typical MN. Second, active endocapillary lesions should show evidence of endothelial-interface disturbance, including altered VE-cadherin distribution or junctional marker organisation. Third, C3c should correlate more closely with endocapillary hypercellularity, neutrophil accumulation, karyorrhexis, or fibrinoid necrosis than C3d. Fourth, karyorrhexis should map preferentially to endothelial-accessible complement lesions rather than to complement deposition in general.

Frequent endocapillary karyorrhexis in typical MN, or a classic endocapillary exudative pattern in pauci-immune AAV without local glomerular complement deposition, would argue against the spatial model.

Translational and Therapeutic Implications

If the relevant lesion is an actively arrested endothelial-interface state rather than complement deposition in general, treatment selection should distinguish between patients with currently active endoluminal complement accessible lesions, patients with residual complement deposition but little ongoing interface activity, and patients whose dominant neutrophil injury pattern is extraglomerular [3,8,9,16,18,22,23]. Fragment-specific complement assessment, particularly C3c versus generic C3 positivity, may have value not only for biopsy interpretation but also for identifying patients most likely to benefit from complement-directed therapy [16].

The model organises interventions into three mechanistic levels: therapies targeting the upstream endothelial or cytoskeletal defect, therapies targeting complement as an amplifying interface signal, and therapies targeting downstream NET-associated injury once neutrophils are retained at the capillary wall. This framework remains hypothesis-generating, but it is already translationally useful for biomarker-enriched trial design and therapeutic matching across mechanistically heterogeneous forms of immune glomerulonephritis [16,17,18]. The AAV data

are especially important here: they indicate that complement-directed therapy may be rational even in pauci immune disease, but the relevant biology is alternative-pathway amplification linked to necrotising and interstitial injury [8,9,18,22,23] — a different complement lesion, not an absence of complement biology.

Limitations

Several limitations should be emphasised. The NET marker evidence base remains small and was not designed specifically to test the present hypothesis [17,18,29]. The interpretation of complement as a marker and participant of a stuck transmigration interface remains inferential and has not yet been validated by functional human data. Direct experimental evidence showing that selective interruption of endoluminal complement signalling prevents the lesion while preserving immune complex deposition is not currently available.

Search completeness is limited by the exclusion of Embase owing to lack of institutional access; Google Scholar was used as a supplementary source but lacks the controlled vocabulary and comprehensive indexing of Embase and may have introduced retrieval bias, particularly for older or non-English literature. The current cross-disease comparison is assembled from studies using different staining platforms, compartment definitions, and scoring schemes, and the literature lacks a large biopsy series comparing LN, PIGNI, MN, and AAV using the same markers and analytic framework. The PSAGN biopsy literature is subject to biopsy indication bias toward atypical or severe presentations [19,26,4].

CONCLUSIONS

The renal biopsy literature across four pre-specified disease arms supports a spatial interpretation of complement associated glomerular injury in which endoluminal accessibility of complement-related signals is associated with endocapillary neutrophil-rich lesion formation. The MN comparator indicates that complement presence alone is insufficient: the key variable is whether complement-related inflammatory signals are positioned in an endothelial accessible compartment. The AAV comparator indicates that neutrophil-associated injury can proceed outside the

glomerular lumen despite complement activation, but in a different spatial context from immune-complex glomerulonephritides. The C3c/C3d distinction suggests that fragment-specific complement staining may improve discrimination between active and residual disease, and the spatial distribution of karyorrhexis indicates that its current classification attribution remains incompletely validated. Together, these findings define a coherent, testable framework for future mechanistic and translational studies of glomerular inflammation

Mechanistic Interpretation and Disease-Specific Upstream Triggers

The sections below outline mechanistically plausible pathways that could give rise to the spatial lesion state identified in Part 1. They are not presented as established causal mechanisms. Each pathway is supported by published molecular and cell-biological evidence, but none has been directly validated in intact human glomerular tissue in the disease context to which it is applied. The purpose of this synthesis is to situate the biopsy findings within a biologically coherent framework that generates testable predictions, not to assert that the model is confirmed.

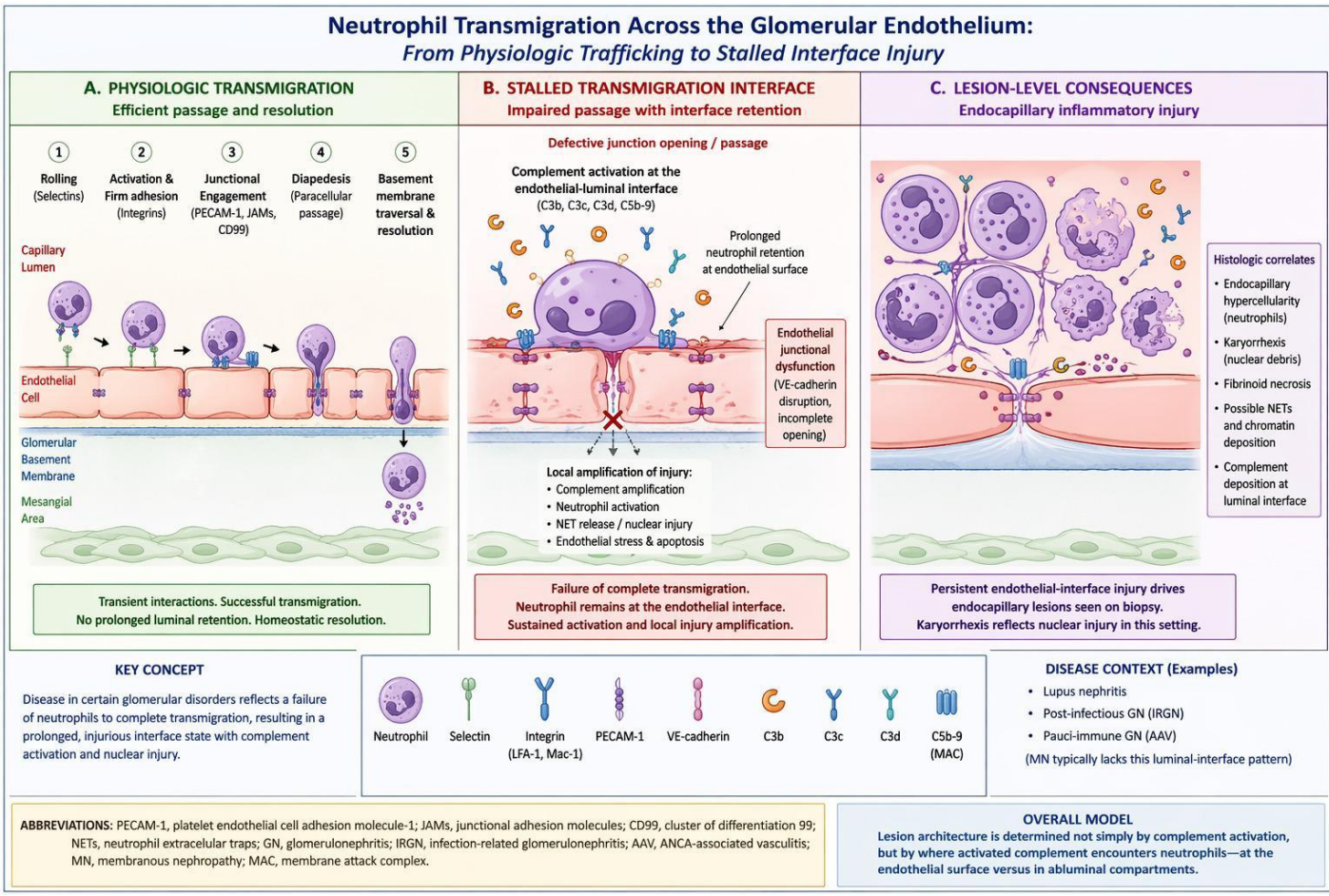


Figure 3. Proposed model of neutrophil transmigration and stalled endothelial-interface injury.

1. THE LEUKOCYTE ADHESION CASCADE AND THE JUNCTION OPENING STEP

Transendothelial migration is classically described as a multistep adhesion cascade consisting of selectin-mediated rolling, chemokine-triggered integrin activation, firm arrest via LFA-1 and Mac-1 engagement with ICAM-1 and ICAM-2, intraluminal crawling, and paracellular diapedesis through endothelial junctions involving molecules such as PECAM-1, CD99, JAM-A, and JAM-C [6,30]. A key distinction for the present framework is that endothelial activation and endothelial junction-opening competence are not identical processes. Upregulation of ICAM-1, E-selectin, and VCAM-1 reflects activation, but successful diapedesis also requires the endothelial cell to execute the cytoskeletal and membrane-recycling events required for junction opening, including VE-cadherin endocytosis and lateral border recycling compartment mobilisation [30–32].

In principle, an endothelium may be activated in surface presentation and capable of capturing neutrophils, yet still be impaired in the machinery required to open junctions and complete transmigration. In such a state, neutrophils would be predicted to arrest normally but fail to pass through efficiently — a stuck-interface state rather than a failure of recruitment. The biopsy evidence supporting glomerular ICAM-1 upregulation in proliferative glomerulonephritides is compatible with this distinction [25].

2. COMPLEMENT AT THE ENDOLUMINAL SURFACE: MARKER AND PARTICIPANT OF THE STUCK-INTERFACE STATE

Within this framework, complement at the endoluminal endothelial surface is interpreted as both a marker of the active lesion and a potential participant in its persistence. Once neutrophils are retained at the endothelial interface, iC3b deposited on the endothelial surface may engage CR3/Mac-1 (CD11b-CD18) on neutrophils in sustained high-avidity adhesion [33,34], while C5a/C5aR1 signalling may promote continued neutrophil activation and arrest signalling [35–37]. These interactions would not necessarily constitute the initiating defect. Rather, they would be expected to amplify and stabilise a lesion that has already formed because junction-opening competence is impaired. This is a model of pathological amplification, not a causal claim that complement initiates the lesion. In this interpretation, complement is neither the sole cause of the lesion nor a passive bystander; it is a contextual signal whose pathological significance depends on the state of the endothelial barrier — a distinction that cannot yet be validated by direct functional evidence in human glomerular tissue.

The AAV comparator helps define this boundary. In ANCA-associated glomerulonephritis, complement activation is now well supported, particularly through the alternative pathway and C5a-amplification axis [35,36,38]. However, the dominant lesion is not one of glomerular immune-complex deposition at an endothelial interface comparable to LN or PIGNI. Instead, the available biopsy evidence is more consistent with neutrophil injury localising to interstitial, necrotising, and vessel wall compartments [8,9,18,22,23]. In this setting, complement remains mechanistically important, but its role is better understood as part of a circulating and tissue-invasive amplification loop than as a marker of a glomerular endoluminal deposition-defined interface lesion.

3. ENDOTHELIAL CYTOSKELETAL MECHANISMS OF JUNCTIONAL FAILURE

The junction-opening step depends on coordinated endothelial cytoskeletal dynamics. PI(4,5)P2-dependent actin polymerisation and VE-cadherin endocytic recycling are central to junction remodelling, and both depend on adequate PI4P supply at the endothelial plasma membrane [32,39]. On mechanistic grounds, depletion of endothelial plasma membrane PI4P would therefore be predicted to impair both actin remodelling and VE-cadherin recycling, producing an endothelium that remains inflammatory in surface presentation but is less able to execute controlled junction opening [13,32,39]. This mechanistic prediction has not been directly tested in glomerular endothelial cells under the specific conditions of immune complex deposition; the following subsections describe how upstream insults might plausibly converge on this state through distinct disease-specific pathways.

3.1 APOL1 G1/G2 Variants and Endothelial Cytoskeletal Failure in Lupus Nephritis

The relationship between APOL1 risk variants and endothelial junctional failure has been reviewed in detail elsewhere [13]. In this proposed pathway, APOL1 G1/G2 variants increase binding to APOL3, disrupt the APOL3/PI4KB/NCS-1 trans-Golgi complex, and reduce Golgi and plasma membrane PI4P availability [39,40]. The downstream effect, if this pathway operates in glomerular endothelial cells as it does in podocytes and other cell types studied to date, would be predicted to include impaired VE-cadherin recycling and defective actin reorganisation, particularly under interferon-I signalling states in which APOL1 expression is increased [13,39,40]. Whether this pathway is operative in glomerular endothelial cells under lupus nephritis conditions has not been directly demonstrated. Endoluminal complement at these sites would then be interpreted as marking where that defect is currently active rather than serving as the original cause of failure.

3.2 Streptococcal Mechanisms and the Stuck-Interface Signature in PSAGN

In PSAGN, streptococcal factors may plausibly contribute to the proposed stuck-interface state through two partially separable mechanisms: perturbation of complement handling and perturbation of host cytoskeletal organisation. Streptococcal inhibitor of complement (SIC) can interfere with terminal complement complex formation and has also been shown to enter host cells and bind ezrin and moesin, proteins that link the plasma membrane to the actin cytoskeleton [41,42]. Nephritis-associated plasmin receptor (NAPlr) can localise to glomerular structures and promote alternative pathway complement activation [43,44]. Streptococcal pyrogenic exotoxin B (SPeB) may further alter complement regulation through cleavage of complement components including C3 and properdin [45–47]. Sublytic MAC deposition on endothelial membranes may promote endothelial activation and cytoskeletal stress rather than coordinated junction opening [48].

If these mechanisms operate together; and this convergence has not been directly demonstrated in intact human glomerular tissue, PSAGN would be predicted to produce an activated but junctionally impaired glomerular endothelium. PSAGN is particularly informative because it is usually self-limited: clearance of streptococcal antigens would be expected to reduce complement activation and relieve upstream endothelial perturbation, allowing the interface lesion to resolve. This sequence is compatible with the temporal observations summarised in Part 1, in which the capillary wall 'starry sky' pattern shifts toward mesangial localisation as the acute exudative phase subsides [19,26].

3.3 HCV Cryoglobulinemic GN

HCV-associated cryoglobulinemic glomerulonephritis provides a chronic viral comparator to the acute bacterial course of PSAGN. In PSAGN, the upstream trigger is exogenous and usually time-limited; in HCV-associated disease, the upstream trigger is persistent viral infection with sustained immune-complex formation and recurrent capillary-wall deposition [49]. HCV RNA has been detected in renal biopsies from HCV-infected patients, including tubular and capillary endothelial cells [50], and laser-capture microdissection studies have demonstrated HCV RNA in 65% of sampled glomeruli from chronically infected patients with glomerulopathies [51].

This matters mechanistically because HCV is known to reorganise host PI4P-dependent membrane biology during replication, depending on phosphatidylinositol 4-kinase IIIα (PI4KA) with PI4P enrichment at virus-induced membranous webs [52–54]. Although the strongest PI4P data derive from hepatocyte-lineage replication systems rather than renal endothelium, the renal-detection studies reduce the concern that HCV is only a distant hepatic driver [50,51]. Within the present model, HCV cryoglobulinemic GN can be interpreted as a chronic viral setting in which immune-complex/complement deposition at the glomerular capillary wall may coexist with viral membrane-trafficking stress in renal compartments. Compared with PSAGN, HCV-associated disease provides a useful temporal and mechanistic contrast: PSAGN should resolve as streptococcal antigens clear, whereas HCV associated renal disease may persist because the upstream viral driver can continuously regenerate immune complex deposition. This interpretation remains inferential; direct evidence that HCV hijacks PI4P signalling specifically in glomerular endothelial cells is not established.

3.4 Complement at the Endoluminal Surface: Marker and Participant — Summary

The narrative synthesis is compatible with a model of glomerular injury in which the primary lesion involves impaired endothelial junction-opening competence arising from disease-specific upstream mechanisms. The upstream cause may vary substantially across diseases — APOL1-associated PI4P dysregulation in LN [13,39,40], SIC- and NAPlr-associated endothelial perturbation in PSAGN [42,43], MAC-associated endothelial contraction in HCV cryoglobulinemic GN [48,51], or failed complement receptor internalisation in aHUS [12]. What these mechanisms may share is not a single trigger, but a common downstream state in which endothelial activation is preserved while junction-opening competence is impaired.

Within such a state, endoluminal complement would be interpreted not as the sole cause of failed transmigration, but as a marker of the active lesion and a participant in its persistence. Complement deposited at the endothelial surface could identify sites where diapedesis is failing and, once present, may further stabilise neutrophil arrest through iC3b/CR3-mediated adhesion and C5a/C5aR1 signalling [33–36]. In this interpretation, C3c would be expected to mark currently active lesions more closely than C3d, while systemic hypocomplementaemia would reflect the aggregate burden of active complement-consuming interfaces across the glomerular microvasculature [16].

MN remains the key spatial comparator because complement is abundant but abluminal, reinforcing that the proposed interface lesion depends on anatomical accessibility rather than complement deposition alone [1,10,24]. The final layer of the model is that neutrophils retained at this interface may undergo lytic NET-associated injury rather than completing transmigration. In that setting, release of chromatin and granular enzymes at the capillary wall could amplify local endothelial and basement membrane injury, providing one possible explanation for the endocapillary localisation of karyorrhexis and fibrinoid necrosis in complement-depositing glomerulonephritides [3,11,15,17]. This interpretation is the most inferential element of the model; it is consistent with the spatial pattern identified in Part 1 and provides a mechanistically testable account of how endothelial-interface arrest might transition into destructive lesion formation, but it has not been directly validated in human glomerular tissue.

Statements and Declarations

Ethics approval and consent to participate

Not applicable. This study is a systematic review of previously published data and did not involve human subjects, animal subjects, or identifiable personal data.

Consent for publication

Not applicable.

Availability of data and materials

All data supporting the conclusions of this article are included in the published studies referenced in the bibliography. No new datasets were generated. The full PubMed and Cochrane search strings are provided in Supplementary Appendix 1.

Competing interests

The authors declare no competing interests.

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Authors' contributions

G.N.Z. conceived and designed the review, conducted literature searching, performed title/abstract and full-text screening jointly with S.A.T., extracted data, conducted quality assessment jointly with S.A.T. S.A.T. conducted independent title/abstract screening and quality assessment and reviewed the manuscript. Both authors read and approved the final manuscript.

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Table 1. Spatial localisation of complement and neutrophil-associated injury across four disease arms.

Summary of complement presence, anatomical localisation, neutrophil compartment, and associated lesion patterns. Columns 3–8 are based on findings from included renal biopsy studies.

Disease	Complement in glomerulus	Complement location	Endoluminal complement access	Dominant neutrophil compartment	Endocapillary hypercellularity	Karyorrhexis (endocapillary)	Predomin ant lesion pattern
Lupus nephritis (LN)	Present	Subendothelial/ capillary loop / mesangial	Yes	Endocapillary (capillary loop–associated)	Present (≈72.7%)	Present (≈58.2%)	Endocapillary neutrophil rich inflammatory pattern
Post infectious GN (PIGNI/PSAGN)	Present	Capillary wall (subendothelial) / mesangial	Yes	Endocapillary (intracapillary 'exudative')	Present (≈80–85%)	Present	Endocapillary exudative inflammatory pattern
ANCA associated vasculitis (AAV)	Absent (pauci immune)	Not applicable	No	Interstitial / perivascular / vessel wall	Absent	Absent (endocapillary)	Predominantly extraglomerular neutrophil associated pattern
Membranous nephropathy (MN)	Present	Subepithelial (abluminal)	No	Absent (no neutrophil rich lesion)	Absent	Absent	Non proliferative complement -associated glomerular pattern

Figure legends

Figure 1. Spatial immunopathology principle across glomerulonephritides Schematic representation of the relationship between complement localisation and neutrophil-associated injury across LN, PIGNI/PSAGN, AAV, and MN. The horizontal axis represents increasing proximity of complement related inflammatory signals to the endothelial-luminal interface and leukocyte accessibility. LN and PIGNI/PSAGN show endothelial-accessible complement deposition with endocapillary neutrophil-rich injury. MN shows subepithelial, abluminal

complement deposition without characteristic endocapillary inflammation. AAV shows a pauci-immune glomerular pattern with neutrophil-associated injury localising predominantly to interstitial and vessel wall compartments. Data correspond to Table 1.

Figure 2. Integrated histological and schematic comparison across four glomerulonephritis phenotypes Representative light microscopy, immunofluorescence/immunohistochemistry, and schematic summaries are shown for ANCA-associated vasculitis (AAV), lupus nephritis (LN), post-infectious/infection-related glomerulonephritis (PIGNI/PSAGN), and membranous nephropathy (MN). AAV demonstrates a pauci-immune glomerular pattern with predominantly interstitial and vessel wall neutrophil-associated injury. LN and PIGNI/PSAGN demonstrate endothelial-accessible complement deposition with endocapillary neutrophil-rich inflammatory lesions. MN demonstrates subepithelial complement deposition with a non-proliferative capillary wall pattern and absence of characteristic endocapillary neutrophil-rich injury. The schematic row summarises the compartmental relationship between complement localisation and inflammatory phenotype.

Figure 3. Proposed model of neutrophil transmigration and stalled endothelial-interface injury

Schematic illustrating the proposed relationship between endothelial junction-opening competence, complement deposition, and neutrophil-associated glomerular injury. In physiological transmigration, neutrophils complete adhesion, junctional passage, and resolution without prolonged luminal retention. In the proposed stalled-interface state, neutrophils arrest at the endothelial surface but fail to complete transmigration, while endoluminal complement may amplify retention through iC3b/CR3 engagement and C5a/C5aR1 signalling. Persistent neutrophil-endothelial interface interaction is hypothesised to contribute to endocapillary hypercellularity, karyorrhexis, fibrinoid necrosis, and possible NET-associated injury. The model proposes that lesion architecture is shaped by whether complement-related inflammatory signals are accessible to neutrophils at the endothelial surface.

Supplementary Files

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