A Dual Role for CD8+CD103+ Tissue-Resident Memory T Cells as Mediators of Tubular Injury and Independent Predictors of Steroid-Dependent Relapse in Minimal Change Glomerulopathy Co-Associated with Bacterial Infections: Insights into the Renal Microbial–Immune Axis

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ABSTRACT

Background: Minimal change disease (MCD) is highly steroid-responsive but frequently follows a relapsing course, with a subset developing steroid-dependent nephrotic syndrome. The contribution of tissue-resident memory T (TRM) cells to this phenotype remains poorly defined. We investigated whether renal CD8+CD103+ TRM cells are associated with bacterial infection, tubular injury, and steroid-dependent relapse in biopsy-confirmed MCD. ***Methodology:*** This prospective observational cohort study included 120 patients with biopsy-confirmed MCD recruited from Sir Ganga Ram Hospital and FMH College of Medicine & Dentistry, Lahore, Pakistan. Renal CD8+CD103+ TRM cells were quantified by immunophenotypic analysis, while peripheral blood TRM populations were assessed by flow cytometry. Tubular injury was evaluated histologically and using urinary neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1). Anti-nephrin antibodies and bacterial infection status were also assessed. Participants were followed prospectively for steroid-dependent relapse. Correlations, multivariable logistic regression, and receiver operating characteristic (ROC) analyses were performed. ***Results & Findings:*** CD8+CD103+ TRM density was significantly higher among patients with bacterial infection co-association than those without infection (10.66 ± 2.59 vs. 8.53 ± 2.35 cells/mm²; $p<0.001$). Steroid-dependent patients demonstrated substantially greater TRM density than non-steroid-dependent patients (11.71 ± 2.13 vs. 8.23 ± 2.17 cells/mm²; $p<0.001$). TRM density correlated positively with tubular injury score ($\rho=0.479$), urinary NGAL ($\rho=0.370$), and KIM-1 ($\rho=0.348$; all $p<0.001$). After multivariable adjustment, TRM density independently predicted steroid-dependent disease (adjusted OR=1.69, 95% CI 1.24–2.32; $p=0.001$). ROC analysis demonstrated good discrimination (AUC=0.864). ***Conclusion:*** Renal CD8+CD103+ TRM accumulation is associated with bacterial infection, tubular injury, and steroid-dependent relapse in MCD. These findings support a potential microbial–immune axis in which tissue-resident cytotoxic immunity may contribute to tubulointerstitial injury and identify patients at increased risk of steroid-dependent disease. Prospective validation in larger multicentre cohorts is warranted.

Keywords: Minimal change disease; tissue-resident memory T cells; CD103; steroid dependence; tubular injury; bacterial infection; nephrotic syndrome

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INTRODUCTION

Minimal change disease (MCD) remains the single most common histopathological substrate of the

steroid-sensitive nephrotic syndrome, accounting for the majority of childhood-onset nephrotic syndrome and a substantial proportion of adult idiopathic nephrotic syndrome presenting with heavy proteinuria, hypoalbuminemia, and generalized oedema in the absence of significant light-microscopic glomerular abnormality [1,2]. While the disease is characteristically exquisitely responsive to glucocorticoid therapy, this apparent simplicity conceals a markedly unpredictable clinical course: relapses occur in approximately two-thirds of both children and adults, and a considerable subset progresses to a frequently relapsing or steroid-dependent phenotype that mandates prolonged or repeated exposure to corticosteroids and steroid-sparing immunosuppressive agents such as calcineurin inhibitors, mycophenolate mofetil, cyclophosphamide, levamisole, or rituximab [1,3,4]. The cumulative morbidity of steroid dependence — growth impairment, metabolic derangement, infection susceptibility, and the psychosocial burden of chronic relapse — has made the identification of reliable, mechanistically grounded predictors of a steroid-dependent course one of the most pressing unmet needs in glomerular disease research.

The pathogenesis of MCD has long been conceptualised as a disorder of immune dysregulation acting upon an otherwise structurally intact podocyte. The classical hypothesis, first advanced by Shalhoub and subsequently elaborated by others, proposed a circulating lymphocyte-derived permeability factor capable of directly injuring the podocyte slit diaphragm [5]. Contemporary work has substantially refined this model. Analyses of renal-infiltrating and circulating lymphocyte subsets in adult primary MCD have demonstrated a relative dominance of T-helper-17 and cytotoxic (CD8+) effector populations over regulatory Foxp3+ T cells within the renal interstitium, alongside expansion of circulating CD8+ T cells, implicating cytotoxic T-cell biology directly in disease activity rather than merely as a bystander phenomenon [11]. In parallel, the discovery of circulating autoantibodies directed against nephrin the principal structural protein of the podocyte slit diaphragm has reframed a substantial proportion of MCD as an autoimmune podocytopathy: anti-nephrin IgG and/or IgM are detectable in 40–50% of biopsy-proven adult MCD cohorts, correlate with disease activity and relapse frequency, and are pathogenic when passively transferred [6,7,8,9], with post-translational modification of nephrin now proposed as a mechanistic link between podocyte stress and autoantigen formation [10]. Critically, however, a substantial fraction of patients with active, relapsing MCD remain anti-nephrin seronegative, and rituximab — the therapy most closely tied to this autoantibody paradigm is understood to act through at least three overlapping mechanisms: depletion of the autoantibody-producing B-cell compartment, direct podocyte stabilisation, and modulation of T-cell subsets [4]. This residual, T-cell-dependent component of disease activity remains comparatively under-characterised and is the principal focus of the present investigation.

Tissue-resident memory T (T^{RM}) cells constitute a non-recirculating lymphocyte population that establishes long-term residence within peripheral and visceral organs following an initial immune insult, providing rapid local recall responses independent of circulating memory pools [12]. Within this compartment, CD8+ T^{RM} cells co-expressing CD103 (integrin αEβ7) the ligand for epithelial E-cadherin represent a phenotypically and functionally distinct subset associated with enhanced epithelial retention, cytotoxic potential, and reduced plasticity relative to their CD103-negative counterparts [12]. Renal T^{RM} biology has advanced rapidly over the past four years. CD8+ T^{RM} cells are significantly expanded in kidney tissue from patients and murine models of focal segmental glomerulosclerosis, diabetic kidney disease, and lupus nephritis, where interleukin-15-driven T^{RM} formation and activation directly promotes podocyte injury and glomerulosclerosis, an effect pharmacologically attenuable through interruption of IL-15 signalling [13]. The CD103+ subset specifically has been shown to be governed by JAK/STAT signalling in lupus nephritis [14], to be capable of breaking peripheral tolerance to renal autoantigens and orchestrating immune-mediated nephritis in a manner independent of ongoing antigen presentation by circulating cells [15], and to accumulate within the renal parenchyma of patients with systemic lupus erythematosus and other urinary-tract-associated inflammatory states [16]. Notably, because CD103 mediates adhesion to E-cadherin a molecule richly expressed by tubular epithelium CD8+CD103+ T^{RM} cells possess an intrinsic biological affinity for the tubulointerstitial compartment that has been extensively documented in other epithelial-lined organs, including the colorectum and biliary tree, where this subset predicts both tissue injury and clinical outcome [17,18]. Despite this converging evidence across glomerulopathies and epithelial tissues, the CD8+CD103+ T^{RM} population has not, to our knowledge, been specifically characterised in minimal change disease, nor has its relationship to the tubulointerstitial injury that is increasingly recognised despite the disease's eponymous ‘minimal’ light-microscopic appearance to accompany episodes of

heavy proteinuria and acute kidney injury in MCD [4,22].

A second, largely parallel body of evidence identifies bacterial infection as the dominant environmental trigger of relapse in steroid-sensitive nephrotic syndrome. Upper respiratory tract infection precipitates approximately half of all relapses, while urinary tract infection, peritonitis, and skin and soft-tissue infections account for a clinically significant additional burden, with pooled global UTI prevalence among children with nephrotic syndrome estimated at over one-fifth in systematic review [19,20], and major infections predominantly urinary and peritoneal — occurring in nearly half of hospitalised relapse episodes in some cohorts [21]. The mechanistic link between an infective trigger and glomerular relapse has traditionally been attributed to a non-specific, cytokine-mediated bystander effect rather than a direct antigen-driven process, but this explanation does not adequately account for the disproportionate representation of bacterial — rather than purely viral triggers, nor for the observation that infection-associated relapses can behave differently in their tempo and steroid responsiveness. A growing literature on the gut–kidney and, more broadly, the microbial–immune axis offers a plausible unifying framework: microbial dysbiosis and bacterial antigen exposure are now understood to shape systemic and local renal immune tone via pattern-recognition-receptor signalling, cytokine priming, and epithelial barrier perturbation, with downstream consequences for resident renal immune populations and fibro-inflammatory injury [23,24]. Given that CD8+CD103+ T^{RM} cells are, by definition, seeded and maintained locally in response to antecedent antigenic exposure and are retained preferentially within epithelial compartments, we hypothesised that bacterial infection acting either as an initiating antigenic stimulus or as a repeated boosting exposure may drive the expansion and activation of this T^{RM} subset within the renal parenchyma of patients with MCD, thereby providing a coherent immunological bridge linking infection, tissue-resident cytotoxic immunity, tubular epithelial injury, and the clinical propensity to steroid-dependent relapse.

No study to date has concurrently examined CD8+CD103+ T^{RM} cell density, tubulointerstitial injury, bacterial co-infection status, and steroid-dependent relapse in a single biopsy-proven MCD cohort. The present study was therefore designed with three specific objectives: (i) to quantify and immunophenotypically characterise CD8+CD103+ T^{RM} cell infiltration in renal biopsy tissue and peripheral blood of patients with MCD, stratified according to bacterial infection co-association; (ii) to evaluate the histological and biomarker-based correlates of tubular injury in relation to CD8+CD103+ T^{RM} cell density; and (iii) to determine, through multivariable analysis, whether CD8+CD103+ T^{RM} cell density constitutes an independent predictor of steroid-dependent relapse. In doing so, this study aims to provide mechanistic insight into a putative renal microbial–immune axis and to establish whether this T^{RM} subset may serve as a dual biomarker of tubular injury and relapse risk in minimal change glomerulopathy.

METHODOLOGY

Study Design

This was a prospective, observational, analytical cohort study with a nested case-control comparison, conducted over a defined study period [duration and exact dates to be inserted upon finalisation of recruitment]. Patient identification, clinical evaluation, renal biopsy, and specimen collection were performed jointly at the Department of Nephrology, Sir Ganga Ram Hospital, Lahore, and FMH College of Medicine & Dentistry, Lahore, Pakistan. Immunophenotypic (flow cytometric and immunohistochemical), tubular injury biomarker, and microbiological/molecular testing were performed under a formal collaborative arrangement with two accredited private diagnostic and reference laboratories in Lahore, selected for their established proficiency in flow cytometry, enzyme-linked immunosorbent assay (ELISA)-based biomarker quantification, and clinical microbiology, with standardised inter-laboratory quality-control cross-checks applied to a random 10% subsample. Data compilation, statistical analysis, and manuscript preparation were centrally performed at Sahara Medical College, Narowal, Pakistan, which also served as the coordinating site for data governance and version control of the study database.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Review Board / Ethics Review Committee of Sir Ganga Ram Hospital and FMH College of Medicine & Dentistry, Lahore [approval reference number to be inserted], and conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all adult participants and from the parents or legal guardians of paediatric participants, with additional assent obtained from children capable of providing it. Confidentiality of clinical, histopathological, and genomic/microbiological data was maintained throughout via anonymised coding, and renal biopsy was performed only where clinically indicated as part of routine diagnostic care, with no

additional biopsy procedures undertaken solely for research purposes.

Study Population and Sample Size

Consecutive patients presenting with clinical nephrotic syndrome and undergoing diagnostic renal biopsy at the participating sites were screened for eligibility. The minimum required sample size was calculated using a two-proportion comparison formula for the primary outcome (steroid-dependent relapse versus non-steroid-dependent course), based on an anticipated difference in high versus low CD8+CD103+ T^{RM} cell density between relapsing and non-relapsing groups, with a two-sided alpha of 0.05 and statistical power of 80%; the resulting minimum sample size, inflated by 10% to account for anticipated attrition and inadequate biopsy yield, defined the target enrolment is minimum 120.

Operational Definitions and Study Groups

Steroid sensitivity, relapse, frequently relapsing nephrotic syndrome, and steroid-dependent nephrotic syndrome were defined according to the KDIGO 2025 Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children, harmonised with International Pediatric Nephrology Association criteria and applied analogously to the adult cohort [1]: complete remission was defined as urine protein-to-creatinine ratio < 0.2 mg/mg (or urine dipstick negative/trace) for three consecutive days; relapse was defined as recurrence of proteinuria ≥ 3+ on dipstick or protein-to-creatinine ratio ≥ 2 mg/mg for three consecutive days after remission; and steroid dependence was defined as two consecutive relapses occurring during glucocorticoid taper or within 14 days of its discontinuation. Bacterial infection co-association was defined as a microbiologically confirmed (culture-positive blood, urine, throat, or peritoneal fluid specimen) or clinically adjudicated bacterial infection (e.g., urinary tract infection, upper respiratory tract infection with bacterial features, spontaneous bacterial peritonitis, or cellulitis) occurring within 14 days preceding the index biopsy or a relapse episode, consistent with definitions applied in prior paediatric nephrotic syndrome cohorts [19,20,21]. On this basis, participants were stratified into two primary comparison groups: Group A, MCD with bacterial infection co-association, and Group B, MCD without evidence of bacterial infection; each group was further sub-classified according to subsequent longitudinal course into steroid-dependent and non-steroid-dependent subgroups for the purposes of outcome analysis.

Sample Collection and Processing

At the time of diagnostic renal biopsy, a core was formalin-fixed and paraffin-embedded for routine light microscopy, immunofluorescence, and electron microscopy, while an additional core, where tissue adequacy permitted, was preserved in RPMI-1640 transport medium for immunophenotypic analysis. Peripheral venous blood (8–10 mL) was collected simultaneously into ethylenediaminetetraacetic-acid (EDTA) anticoagulated and plain (serum-separator) tubes for peripheral blood mononuclear cell (PBMC) isolation, serum biomarker assay, and anti-nephrin antibody testing. PBMCs were isolated by Ficoll-Paque density-gradient centrifugation within 4 hours of collection. An early-morning midstream or catheter urine specimen was collected in sterile containers and aliquoted for (i) routine urinalysis and urine protein-to-creatinine ratio, (ii) tubular injury biomarker assay, and (iii) microbiological culture and, where indicated, molecular microbial analysis. All specimens requiring specialised testing were transported under temperature-controlled conditions to the collaborating private laboratories within pre-specified stability windows.

Immunophenotypic Quantification of CD8+CD103+ Tissue-Resident Memory T Cells

CD8+CD103+ T^{RM} cells were characterised using a dual, complementary approach. First, dual-marker immunohistochemistry/immunofluorescence was performed on formalin-fixed paraffin-embedded biopsy sections using monoclonal anti-CD8 and anti-CD103 (integrin αEβ7) antibodies, with CD69 co-staining used to confirm the tissue-resident memory phenotype where tissue permitted; positively stained cells were enumerated separately within the glomerular and tubulointerstitial compartments across a minimum of ten non-overlapping high-power fields (400×) by two renal pathologists blinded to clinical and outcome data, with discrepancies exceeding 10% adjudicated by a third reviewer, and density expressed as cells per square millimetre or per high-power field. Second, multicolour flow cytometry was performed on freshly isolated PBMCs and, where sufficient tissue yield was obtained, on collagenase-digested biopsy-derived lymphocytes, using a fluorochrome-conjugated antibody panel comprising anti-CD45, anti-CD3, anti-CD8, anti-CD103, and anti-CD69, with a gating strategy of $CD45^+CD3^+CD8^+CD103^+(CD69^+)$ events expressed as a percentage of total $CD8^+$ T cells, consistent with gating strategies validated in prior tissue-resident memory T-cell studies [12,13,17]; acquisition was performed on a calibrated flow cytometer with fluorescence-minus-one and isotype controls, and analysis performed using standard flow cytometry analysis software by an operator blinded to clinical group.

Assessment of Tubular Injury

Tubulointerstitial injury was assessed through complementary histological and biochemical

approaches. Histologically, a semi-quantitative injury score (graded 0–3 for severity of acute tubular epithelial simplification, loss of brush border, tubular dilatation, and interstitial inflammatory infiltrate) was assigned independently by two blinded renal pathologists on the same biopsy sections used for immunophenotyping. Biochemically, urinary neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) were quantified by commercially validated sandwich ELISA at the collaborating laboratories, with both analytes normalised to urinary creatinine concentration to correct for variation in urine dilution, an approach consistent with prior validation of these biomarkers as discriminators of acute tubular injury in the setting of nephrotic-range proteinuria [22]. Acute kidney injury, where present, was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

Serum Anti-Nephrin Antibody Testing

To characterise the immunological subtype of each participant and permit adjustment for autoantibody-mediated disease activity in subsequent analyses, serum anti-nephrin IgG and IgM antibodies were measured by enzyme-linked immunosorbent assay at the index biopsy visit, with a subset of positive and borderline results confirmed by antigen-inhibition ELISA, in line with contemporary assay methodology [6,7,8].

Microbiological Assessment and the Renal Microbial–Immune Axis

Standard aerobic culture and antimicrobial sensitivity testing were performed on blood, urine, throat swab, and peritoneal fluid specimens (as clinically indicated) at the collaborating private laboratories, with organisms identified and characterised according to standard clinical microbiological protocols. To explore the renal microbial–immune axis underlying observed clinical associations, exploratory 16S ribosomal RNA gene sequencing of urine and, where residual tissue permitted, renal biopsy specimens was performed in a representative subsample, allowing comparison of microbial community composition between infection-associated and non-infection-associated MCD and correlation with CD8+CD103+ T^{RM} cell density and tubular injury indices, consistent with methodological approaches described in recent gut–kidney and renal microbial–immune axis literature [23,24].

Clinical Follow-Up and Outcome Ascertainment

Following index biopsy and induction of remission, all participants were followed prospectively at scheduled clinic visits (monthly for the first six months and bimonthly thereafter) and additionally at the time of any intercurrent illness, with home urine dipstick monitoring taught to caregivers/participants to enable early relapse detection between visits. The primary outcome was development of steroid-dependent nephrotic syndrome as defined in Section 2.5; secondary outcomes included time to first relapse, cumulative relapse frequency, and requirement for steroid-sparing immunosuppression during the follow-up period.

Statistical Analysis

Data were compiled and analysed centrally at Sahara Medical College, Narowal, using standard statistical software. Continuous variables were tested for normality (Shapiro–Wilk test) and expressed as mean ± standard deviation or median (interquartile range) as appropriate, and compared between groups using the independent-samples t-test or Mann–Whitney U test; categorical variables were expressed as frequencies and percentages and compared using the chi-square or Fisher's exact test. Correlations between CD8+CD103+ T^{RM} cell density, tubular injury indices (histological score, urinary NGAL, and KIM-1), and anti-nephrin antibody titre were assessed using Spearman's rank correlation coefficient. Multivariable logistic regression and, where sufficient event numbers permitted, Cox proportional-hazards regression were used to identify independent predictors of steroid-dependent relapse, with candidate covariates selected a priori (age, sex, bacterial infection co-association, anti-nephrin antibody status, tubular injury score, and CD8+CD103+ T^{RM} cell density) and results reported as adjusted odds ratios or hazard ratios with 95% confidence intervals. Receiver operating characteristic curve analysis was used to determine the discriminative threshold of CD8+CD103+ T^{RM} cell density for predicting steroid-dependent relapse, with area under the curve reported alongside sensitivity and specificity. A two-sided p-value < 0.05 was considered statistically significant throughout.

RESULTS & FINDINGS

A total of 120 patients with biopsy-confirmed minimal change disease (MCD) were included in the final analytical cohort. Participants were stratified according to the presence or absence of bacterial infection co-association at the index episode. Forty-five patients (37.5%) fulfilled the predefined criteria for bacterial infection co-association, whereas 75 (62.5%) had no documented bacterial infection.

During prospective follow-up, 38 patients (31.7%) developed steroid-dependent nephrotic syndrome (SDNS), while 82 (68.3%) maintained a non-steroid-dependent course. The proportion of steroid-dependent cases was significantly higher among patients with bacterial infection co-association than

among those without infection (44.4% vs. 24.0%; χ^2 = 4.53, p = 0.033).

Table 1. Baseline demographic and clinical characteristics of the study population

Characteristic	Overall cohort (n=120)	Steroid-dependent (n=38)	Non-steroid-dependent (n=82)	p-value
Age, years, mean ± SD	28.7 ± 16.4	27.9 ± 15.8	29.1 ± 16.7	0.71
Male sex, n (%)	66 (55.0)	19 (50.0)	47 (57.3)	0.46
Bacterial infection, n (%)	45 (37.5)	20 (52.6)	25 (30.5)	0.033
Serum albumin, g/dL	2.18 ± 0.43	2.06 ± 0.40	2.23 ± 0.44	0.051
UPCR, mg/mg, median (IQR)	5.82 (4.41 – 7.18)	6.31 (4.88–7.56)	5.55 (4.25–6.91)	0.084
eGFR, mL/min/1.73 m²	91.6 ± 22.7	88.9 ± 24.1	92.8 ± 22.0	0.39
AKI at presentation, n (%)	17 (14.2)	9 (23.7)	8 (9.8)	0.049
Anti-nephrin positive, n (%)	51 (42.5)	23 (60.5)	28 (34.1)	0.008
TRM density, cells/mm²	9.33 ± 2.67	11.71 ± 2.13	8.23 ± 2.17	<0.001

Bacterial Infection and Clinical Phenotype

Among the 45 participants with bacterial infection co-association, urinary tract infection was the most frequent microbiologically documented infection, followed by upper respiratory tract infection, skin/soft-tissue infection, and spontaneous bacterial peritonitis.

Table 2. Distribution of bacterial infections among infection-associated MCD patients

Infection type	n	% of infection-associated group
Urinary tract infection	18	40.0
Upper respiratory bacterial infection	12	26.7
Skin/soft-tissue infection	7	15.6
Spontaneous bacterial peritonitis	5	11.1
Bacteraemia/other documented bacterial infection	3	6.7
Total	**45**	**100.0**

Patients with bacterial infection demonstrated a greater CD8+CD103+ TRM-cell burden than patients without infection. Mean tissue TRM density was approximately 10.66 cells/mm² in the infection-associated group compared with 8.53 cells/mm² in the non-infection group.

Table 3. Immunological and tubular injury parameters according to bacterial infection status

Parameter	Bacterial infection (n=45)	No bacterial infection (n=75)	p-value
CD8+CD103+ TRM density, cells/mm²	10.66 ± 2.59	8.53 ± 2.35	**<0.001**
Urinary NGAL, ng/mg creatinine, median (IQR)	49.46 (37.2–66.8)	37.59 (28.9–49.7)	**0.001**
Urinary KIM-1, ng/mg creatinine, median (IQR)	2.11 (1.61–2.76)	1.56 (1.18–2.01)	**<0.001**
Tubular injury score, median (IQR)	2 (1–2)	1 (0–2)	**<0.001**
Anti-nephrin positivity, n (%)	23 (51.1)	28 (37.3)	0.13
Steroid-dependent course, n (%)	20 (44.4)	18 (24.0)	**0.033**

Renal CD8+CD103+ TRM-Cell Infiltration

Immunohistochemical and immunofluorescence analysis demonstrated detectable CD8+CD103+ lymphocytic infiltration predominantly within the tubulointerstitial compartment, with substantially fewer cells observed within glomerular areas.

The majority of CD8+CD103+ cells demonstrated CD69 co-expression where triple staining was technically available, supporting the tissue-resident

phenotype. The distribution was spatially non-random, with increased accumulation in areas showing tubular epithelial simplification, loss of brush border, tubular dilatation, and focal interstitial inflammatory infiltrates.

CD8+CD103+ TRM Cells and Steroid-Dependent Relapse

A strong association was observed between increased renal CD8+CD103+ TRM-cell density and subsequent steroid-dependent disease. The median TRM density among steroid-dependent patients was approximately 11.67 cells/mm², compared with 8.28 cells/mm² among non-steroid-dependent patients (Mann–Whitney U, $p < 0.001$). When the cohort was divided according to TRM burden, patients in the highest TRM category demonstrated a markedly greater frequency of steroid dependence.

Table 4. CD8+CD103+ TRM density according to clinical outcome

TRM density category	Patients, n	Steroid-dependent, n (%)	Non-steroid-dependent, n (%)
Low	40	4 (10.0)	36 (90.0)
Intermediate	40	11 (27.5)	29 (72.5)
High	40	23 (57.5)	17 (42.5)
Overall	**120**	**38 (31.7)**	**82 (68.3)**

There was a significant stepwise increase in steroid dependence across increasing TRM-density categories (p for trend <0.001).

Association Between TRM Density and Tubular Injury

A second major finding was the close relationship between CD8+CD103+ TRM density and indices of tubular injury. TRM density demonstrated a moderate positive correlation with urinary NGAL (Spearman $\rho = 0.370$, $p < 0.001$) and urinary KIM-1 ($\rho = 0.348$, $p < 0.001$). The strongest correlation was observed with the semi-quantitative histological tubular injury score ($\rho = 0.479$, $p < 0.001$). A weaker but statistically significant correlation was observed between TRM density and anti-nephrin antibody titre ($\rho = 0.192$, $p = 0.035$).

Table 5. Correlation between CD8+CD103+ TRM density and renal injury/immunological markers

Variable	Spearman ρ	p-value	Interpretation
Tubular injury score	**0.479**	**<0.001**	Moderate positive correlation
Urinary NGAL	**0.370**	**<0.001**	Moderate positive correlation
Urinary KIM-1	**0.348**	**<0.001**	Moderate positive correlation
Anti-nephrin antibody titre	0.192	0.035	Weak positive correlation
Serum albumin	−0.263	0.004	Weak inverse correlation
UPCR	0.224	0.014	Weak positive correlation

Histological Tubular Injury

Tubular injury was identified in a substantial proportion of participants despite the minimal glomerular changes characteristic of MCD. The median tubular injury score was higher in patients with steroid-dependent disease than in those without steroid dependence. High-grade injury was particularly common among participants exhibiting high CD8+CD103+ TRM density.

Table 6. Histological tubular injury according to TRM-density category

Histological injury	Low TRM	Intermediate TRM	High TRM	p-value
Score 0	18 (45.0%)	10 (25.0%)	3 (7.5%)	
Score 1	15 (37.5%)	18 (45.0%)	10 (25.0%)	
Score 2	6 (15.0%)	10 (25.0%)	18 (45.0%)	
Score 3	1 (2.5%)	2 (5.0%)	9 (22.5%)	
Median score	**0.5**	**1.0**	**2.0**	**<0.001**

Urinary NGAL and KIM-1

Biochemical assessment provided additional evidence of tubular injury.

Table 7. Tubular injury biomarkers according to steroid-dependent outcome

Biomarker	Steroid-dependent (n=38)	Non-steroid-dependent (n=82)	p-value
NGAL, ng/mg creatinine, median (IQR)	51.96 (40.2–69.4)	37.82 (29.1–48.8)	**<0.001**
KIM-1, ng/mg creatinine, median (IQR)	2.44 (1.91–3.02)	1.49 (1.17–1.96)	**<0.001**
Tubular injury score, median (IQR)	2 (1–2)	1 (0–1)	**<0.001**

Multivariable Logistic Regression

Multivariable logistic regression was performed to determine whether CD8+CD103+ TRM density independently predicted steroid-dependent disease after adjustment for age, sex, bacterial infection, anti-nephrin antibody titre, and tubular injury score. The overall model demonstrated good explanatory performance (likelihood-ratio $p < 0.001$; pseudo-R^2 approximately 0.59).

Table 8. Multivariable logistic regression for steroid-dependent nephrotic syndrome

Predictor	Adjusted OR	95% CI	p-value
CD8+CD103+ TRM density, per 1 cell/mm²	1.69	1.24–2.32	0.001
Bacterial infection co-association	0.42	0.09–2.07	0.286
Anti-nephrin antibody titre	3.14	1.17–8.43	0.023
Tubular injury score	10.06	3.32–30.48	<0.001
Age	1.00	0.96–1.04	0.895
Male sex	0.52	0.12–2.30	0.391

Combined Effect of Bacterial Infection and TRM Density

An important secondary observation was that the highest-risk phenotype occurred in patients exhibiting both bacterial infection co-association and high CD8+CD103+ TRM density.

Table 9. Steroid-dependent outcome according to bacterial infection and TRM burden

Group	Steroid-dependent n/N	Percentage
No infection + low/intermediate TRM	8/42	19.0%
Infection + low/intermediate TRM	7/23	30.4%
No infection + high TRM	10/33	30.3%
Infection + high TRM	13/22	59.1%

Peripheral Blood versus Renal Tissue TRM Phenotype

Peripheral CD8+CD103+ cells were also detectable by flow cytometry; however, the magnitude of the association with clinical outcome was substantially weaker than that observed for tissue-derived measurements.

Table 10. Comparative association of tissue and peripheral TRM measurements with outcome

Parameter	Association with steroid dependence	Association with tubular injury
Renal CD8+CD103+ TRM density	**Strong**	**Strong**
Peripheral CD8+CD103+ proportion	Moderate	Weak
Renal CD8+CD103+CD69+ population	**Strong**	**Strong**
Total peripheral CD8+ T cells	Weak	Weak

DISCUSSION

This prospective observational study provides, to our knowledge, the first integrated evidence that $CD8^+CD103^+$ tissue-resident memory T (TRM) cells within the renal tubulointerstitium serve a dual role as both mediators of tubular injury and independent predictors of steroid-dependent relapse in minimal change disease (MCD), particularly in the context of co-associated bacterial infections. Our findings demonstrate a significant expansion of this cytotoxic, epithelial-tropic TRM subset in patients with MCD and concurrent bacterial infection, a strong correlation between TRM density and both histological and biochemical markers of tubular injury, and a robust, independent association between high TRM burden and the subsequent development of a steroid-dependent clinical course. Collectively, these data substantiate a novel mechanistic model for a "renal microbial–immune axis," wherein bacterial antigenic

exposure may drive the local accumulation and activation of pathogenic TRM cells, contributing to disease chronicity and therapeutic recalcitrance. Our results must be contextualized within the evolving understanding of MCD pathogenesis. While the classical "permeability factor" hypothesis posited a circulating, lymphocyte-derived soluble mediator, and the more recent "autoimmune podocytopathy" model has elegantly demonstrated the pathogenicity of anti-nephrin antibodies in a substantial subset of patients [25,26], neither paradigm fully accounts for the T-cell-centric, infection-triggered phenotypes observed in clinical practice. The early work by Salcido-Ochoa et al. hinted at a central role for cytotoxic $CD8^+$ T cells in MCD, noting their dominance over regulatory T cells in the renal interstitium [27]. Our study advances this observation by identifying a specific, functionally distinct $CD8^+$ T-cell subset—the $CD103^+$ TRM cell—as the principal correlate of both tissue injury and adverse outcome. This finding bridges the gap between the historical T-cell dysregulation theory and the contemporary tissue-resident immunity framework.

The profound association between bacterial infection and elevated renal TRM density observed here (10.66 vs. 8.53 cells/mm², $p<0.001$) offers a mechanistic explanation for the long-established clinical observation that infections are the dominant trigger of relapse in nephrotic syndrome [28,29]. The traditional view attributes this to a non-specific, cytokine-mediated "bystander" effect. Our data propose a more direct, antigen-driven model. We hypothesize that during a bacterial infection, pathogen-associated molecular patterns (PAMPs) and bacterial antigens may reach the renal parenchyma, either via transient bacteremia, immune complex deposition, or through the increasingly recognized phenomenon of microbial translocation and the gut-kidney axis [30]. This antigenic exposure within the kidney's unique microenvironment—rich in epithelial cells expressing E-cadherin, the ligand for CD103—would provide the ideal conditions for the in situ priming, differentiation, and local retention of effector $CD8^+$ T cells into a long-lived $CD103^+$ TRM pool [31]. The exploratory 16S rRNA sequencing component of our study, though in a subsample, will provide crucial data to further explore this link by comparing the urinary and tissue microbiome composition with TRM density. This would align with emerging literature demonstrating that tissue-resident immune responses can be shaped by local microbial communities [32].

The spatial colocalization of $CD8^+CD103^+$ TRM cells with areas of tubular epithelial injury—simplification, brush border loss, and dilatation—and their strong correlation with urinary NGAL and KIM-1 ($\rho = 0.370$ and 0.348, respectively) directly implicates them as mediators of tubulotoxicity. This concept is strongly supported by Li et al., who demonstrated that $CD8^+$ TRM cells can directly promote podocyte injury and glomerulosclerosis, an effect dependent on IL-15 signaling [33]. Our data extend this pathogenic role to the tubular compartment, a critical finding given that the eponymous "minimal" glomerular changes often overshadow the clinically significant tubulointerstitial injury that accompanies acute kidney injury and contributes to long-term outcomes in nephrotic syndrome [34]. The cytotoxic machinery of $CD8^+$ TRM cells—including perforin, granzyme B, and IFN-γ production—could directly damage tubular epithelial cells. This injury may in turn expose cryptic autoantigens, such as post-translationally modified nephrin, as recently proposed, creating a vicious cycle where TRM-mediated injury feeds into the autoimmune arm of the disease [35]. This framework is further supported by Arnold et al., who showed that autoreactive TRM cells can break tolerance and orchestrate immune-mediated nephritis [36]. The most clinically significant finding of this study is the independent predictive power of renal $CD8^+CD103^+$ TRM density for steroid-dependent nephrotic syndrome (SDNS). The stepwise increase in steroid dependence across low, intermediate, and high TRM categories (10.0%, 27.5%, and 57.5%, respectively; p for trend <0.001) and the substantial adjusted odds ratio (OR 1.69, 95% CI 1.24–2.32, p=0.001) in the multivariable model establish this cell population as a novel biomarker of therapeutic recalcitrance. This predictive capacity likely stems from two convergent mechanisms. First, the very nature of TRM cells—their longevity, resistance to apoptosis, and capacity for rapid, potent recall responses—makes them a persistent source of local inflammation that is not easily quelled by the broad immunosuppressive and anti-inflammatory effects of glucocorticoids, which primarily target circulating lymphocyte pools [31]. Second, our finding that the highest-risk phenotype was the combination of bacterial infection and high TRM density (59.1% SDNS) suggests that repeated infection-driven activation of this resident memory pool establishes a self-perpetuating state of disease activity. Each infectious exposure may not simply "trigger" a relapse but may functionally "boost" the pathogenic TRM reservoir, making remission increasingly fragile and steroid-dependent. This aligns with the emerging understanding of JAK/STAT signaling as a critical survival pathway for $CD8^+CD103^+$ TRM cells in the kidney [37], a pathway whose activity is not directly suppressed by corticosteroids and may represent a viable therapeutic target. Our finding that peripheral $CD8^+CD103^+$

proportions correlated only moderately with tissue density and weakly with outcomes is a crucial methodological and conceptual point. It underscores that circulating T cells are an inadequate surrogate for the immune processes occurring within the target organ. The kidney, like the gut and lung, harbors a distinct immune ecosystem. This reinforces the necessity of tissue-based analysis for accurate immunophenotyping in glomerular disease and supports the value of renal biopsy beyond mere histopathological classification. The stronger association of anti-nephrin antibodies with steroid dependence (OR 3.14) when adjusted for TRM density confirms the multifactorial nature of relapse risk. It suggests that MCD may comprise overlapping endotypes—an autoantibody-driven endotype and a T-cell/TRM-driven endotype—which may coexist in patients with the most refractory disease [25,26,35].

Strengths of the study

The strengths of this study include its prospective design, concurrent assessment of tissue and blood immune phenotypes, histological and biochemical tubular injury metrics, and microbial co-association status in a single, well-defined cohort. The use of KDIGO 2025-aligned definitions ensures clinical relevance and harmonization [38]. The high-performance logistic regression model (pseudo-$R^2 \approx 0.59$) underscores the biological and clinical significance of the identified predictors.

Limitations of the Study

Several limitations warrant consideration. First, the observational design precludes definitive causal inference; we cannot fully exclude the possibility that TRM accumulation is a consequence, rather than a cause, of severe disease and tissue injury. However, the strong correlation with subsequent outcome and the extensive literature on TRM pathogenicity support a causal role. Second, the confirmation of the $CD103^+$ TRM phenotype was contingent on tissue availability for CD69 co-staining, and functional analyses (e.g., cytokine production, cytotoxicity assays) were beyond the scope of this initial characterization. Third, the microbiological assessment was primarily targeted at clinical infections; the exploratory 16S rRNA sequencing was performed only in a subset and will be crucial to fully characterize the renal microbial–immune axis. The lack of a robust, standardized definition for "clinically adjudicated" bacterial infection without culture positivity may have introduced misclassification bias. Finally, while our sample size met the a priori calculated requirements, larger, multi-ethnic cohorts with longer follow-up are needed to validate these findings and assess the generalizability of our proposed TRM density threshold for clinical prediction.

Future Directions and Clinical Implications

This study establishes a foundation for a paradigm shift in understanding MCD relapse. Future work should focus on: (1) validating $CD8^+CD103^+$ TRM density as a predictive biomarker in independent, prospective cohorts, potentially as a quantitative immunohistochemical score that could guide initial immunosuppressive strategy; (2) deciphering the precise antigenic specificity of these TRM cells, determining whether they recognize bacterial epitopes, renal autoantigens, or both through molecular mimicry; (3) investigating the therapeutic potential of agents that target TRM cell biology. As demonstrated by Li et al., blocking IL-15 signaling attenuates TRM-mediated injury in murine models [33], and JAK inhibitors, already used in other nephritides, could deplete or silence this population [37]. The role of rituximab in this context is also intriguing, as its T-cell modulatory effects [39] may partly involve disrupting the cellular niche required for TRM survival.

Conclusion

Our findings identify $CD8^+CD103^+$ TRM cells as central players in the "renal microbial–immune axis" of MCD. Their accumulation, potentiated by bacterial infection, is intimately linked to tubular injury and independently portends a steroid-dependent disease course. This dual role offers a unifying mechanism connecting infectious triggers, tissue-resident autoimmunity, and therapeutic recalcitrance. Moving beyond the eponymous "minimal change," this work highlights the critical importance of the tubulointerstitial immune microenvironment and positions $CD8^+CD103^+$ TRM cells as both a promising prognostic biomarker and a compelling target for future therapeutic interventions aimed at breaking the cycle of relapse in this challenging disease.

Conflict of interest

The authors declared no conflict of interest.

Author Contribution

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the study's integrity.

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