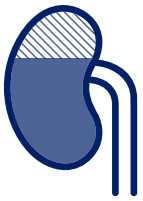
Impact and Implications of Hematuria in Glomerular Disease

Despite being a principal symptom of glomerular diseases, hematuria is often overlooked[1]

Hematuria is a frequent symptom in patients with glomerular diseases; it is present in

70-100%



patients with IgAN[2]

87%

patients with C3G (either C3GN or DDD)[3]

50%

patients with MCD, MGN, FSGS[1]

- Despite its frequency, hematuria is often overlooked because of[1]
  - **Non-specificity:** Hematuria is a non-specific finding and is not exclusive to glomerular pathology
  - **Diagnostic challenges:** Differentiating glomerular hematuria from nonglomerular causes is difficult in routine clinical practice, particularly in the absence of standardized detection methods
  - **Overlap with benign conditions:** Hematuria frequently occurs in healthy individuals and is often transient or benign, further limiting its specificity for identifying significant renal disease

Although hematuria has traditionally been considered a benign finding, it is a common symptom in many glomerular diseases[1]

- IgA Nephropathy
- Lupus Nephritis
- ANCA-associated vasculitis

- Disorders of Collagen IV α345
- C3G
- Other Primary Glomerulopathies

Delay in the diagnosis of glomerular diseases may lead to faster progression to ESRD[4-7]

Best practices from the 2021 KDIGO Clinical Practice Guidelines for the Management of Glomerular Diseases[8]

- Routine evaluation of urine sediment for erythrocyte morphology and the presence of red cell casts and/or acanthocytes is indicated in all forms of glomerular disease
- Monitoring of hematuria (magnitude and persistence) may have prognostic value in many forms of glomerular disease, which is particularly applicable to IgAN and IgA vasculitis

Monitoring hematuria may identify patients with rare glomerular disease sooner and might serve as a monitoring consideration for risk of progression[1,8]

*Patients with negative or minimal hematuria (TA-hematuria of 0.2 [0–31] red blood cells per high-power field [RBC x hpf]; n=66) and those with persistent hematuria (TA-hematuria of 24.7 [13–71] RBC x hpf; n=46) during follow-up. † In this study, IC-MPGN (n = 19) and C3G (C3GN: n = 87; DDD: n = 19) between 1995 and 2020 enrolled in the GLOSEN study. ‡ Defined as <5 RBC/hpf. § Defined as eGFR <15 mL/min/1.73 m^2, need for dialysis or transplantation.

ANCA, antineutrophil cytoplasmic antibodies; C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; CKD, chronic kidney disease; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FSGS, focal and segmental glomerulosclerosis; hpf, high-power field; IC-MPGN, immune complex membranoproliferative glomerulonephritis; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease Improving Global Outcomes; MCD, minimal change disease; MGN, membranous glomerulonephritis; RBC, red blood cell; TA, time-averaged.

References: 1. Moreno JA et al. *Int J Mol Sci.* 2019; 20(9):2205. **2.** Coppo R, Fervenza FC. *J Am Soc Nephrol.* 2017;28(10):2831–2834. **3.** Ravindran A et al. *Mayo Clin Proc.* 2018; 93(8): 991–1008. **4.** Caravaca-Fontán F, Praga M. *Nephrol Dial Transplant*, 2024;39:1529–1532. **5.** Nune M et al. *J Am Soc Nephrol.* 2023; 34:266 (abstract #TH-PO627). **6.** Kwon CS et al. *J Health Econ Outcomes Res.* 2021;8(2):36-45. **7.** Pitcher D et al. *Clin J Am Soc Nephrol.* 2023;18(6):727-738. **8.** Rovin BH et al. *Kidney International.* 2021;100(4):S1-S276. doi: 10.1016/j.kint.2021.05.021. **9.** Sevillano AM et al. *J Am Soc Nephrol.* 2017; 28(10):3089-3099. **10.** Moreno JA et al. *Clin J Am Soc Nephrol.* 2012;7(1):175-184. **11.** Rubio-Navarro A et al. *J Pathol.* 2018;244(3):296-310.

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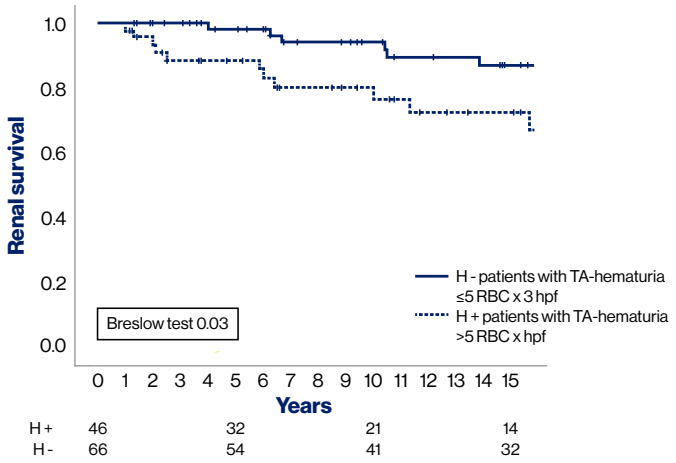
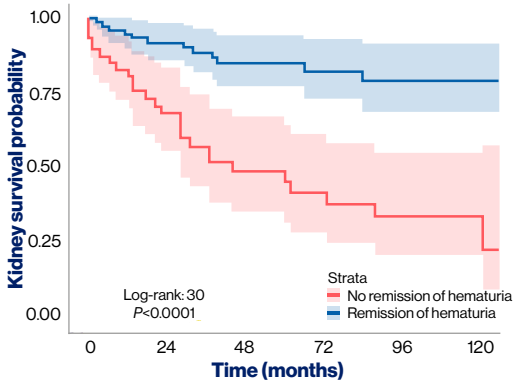
Observed Association Between Hematuria and Renal Survival

Observation of Time-Averaged (TA) Hematuria and Renal Survival in IgAN[9]



- Cohort study of 112 IgAN patients followed for 14 ±10.2 years
- Patients categorized into 2 groups*: 1) TA-hematuria negative or minimal hematuria or 2) persistent hematuria. Clinical and analytic risk factors were regularly tested
- Those with little or no hematuria progressed to ESRD slower than patients with persistent hematuria
- Study was limited to a relatively small number of patients

Presence of Hematuria and Kidney Survival Observed in C3G and IC-MPGN[4]

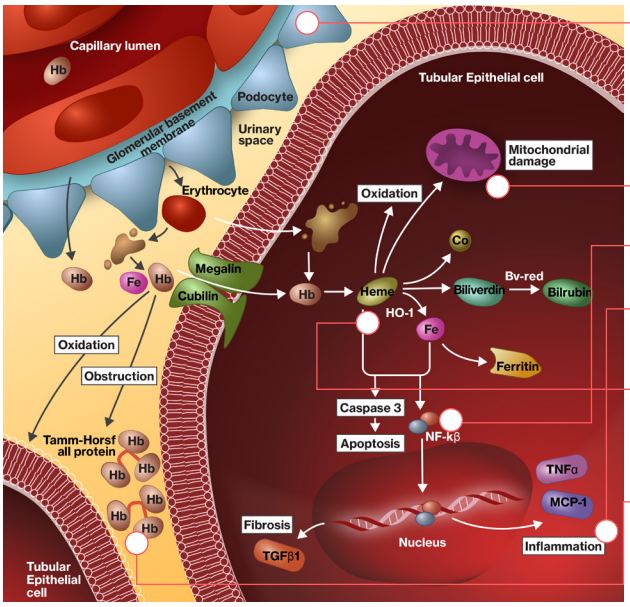


Number at risk

No remission of hematuria	48	26	15	11	5	3
Remission of hematuria	77	61	40	28	22	17

- Retrospective, longitudinal, multicenter, observational cohort data of 125 patients† with IC-MPGN and C3G
- At a median follow-up of 48 months, 17% of patients with hematuria remission‡ at last follow-up reached kidney failure§ compared to 53% of patients without hematuria remission (P<0.001)‖
- Limitations of the study are its retrospective nature, which prevents establishing casual relationships, and the degree of microscopic hematuria was not centrally evaluated

Glomerular hematuria mediates renal damage by promoting AKI and progression to CKD[1,10]



Preclinical studies suggest **podocytes** are also cellular **targets of hemoglobin-mediated renal damage**[11]

Direct tubular toxic effects of hemoglobin and heme produced after red blood cell rupture in the tubular lumen:

- Oxidative stress: triggers lipid peroxidation, protein oxidation and aggregation, and DNA damage
- Inflammatory cytokine secretion: MCP-1, TNF-α, and NF-κB activation
- Pro-inflammatory cascade: TLR-4 may recognize the heme group and trigger pathways like c-Jun kinases, p38, MAPK, and NF-κB

Glomerular inflammation due to heme-related cytotoxic and proinflammatory effects

Direct tubular damage due to intratubular obstruction of the blood cell casts

Hematuria may contribute to glomerular inflammation due to renal damage, which may lead to further disease progression[1,4,9]

Adapted from Moreno et al, 2012 with permission.

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AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic antibodies; Bv-red, reduced biliverdin; C3G, C3 glomerulopathy; CKD, chronic kidney disease; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; hpf, high-power field; Fe, iron; Hb, hemoglobin; HO, heme oxygenase; hpf, high-power field; IC-MPGN, immune complex membranoproliferative glomerulonephritis; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease Improving Global Outcomes; MAPK, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor kappa B; RBC, red blood cell; TGFB1, transforming growth factor beta 1; TNF, tumor necrosis factor; TLR, toll like receptor.

References: 1. Moreno JA et al. *Int J Mol Sci*.2019; 20(9):2205. **2.** Coppo R, Fervenza FC. *J Am Soc Nephrol*. 2017;28(10):2831–2834. **3.** Ravindran A et al. *Mayo Clin Proc*. 2018; 93(8): 991–1008. **4.** Caravaca-Fontán F, Praga M. *Nephrol Dial Transplant*, 2024;39:1529-1532. **5.** Nune M et al. *J Am Soc Nephrol*. 2023; 34:266 (abstract #TH-PO627). **6.** Kwon CS et al. *J Health Econ Outcomes Res*. 2021;8(2):36-45. **7.** Pitcher D et al. *Clin J Am Soc Nephrol*. 2023;18(6):727-738. **8.** Rovin BH et al. *Kidney International*. 2021;100(4):S1-S276. doi: 10.1016/j.kint.2021.05.021. **9.** Sevillano AM et al. *J Am Soc Nephrol*. 2017;28(10):3089-3099. **10.** Moreno JA et al. *Clin J Am Soc Nephrol*. 2012;7(1):175-184. **11.** Rubio-Navarro A et al. *J Pathol*. 2018;244(3):296-310.

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