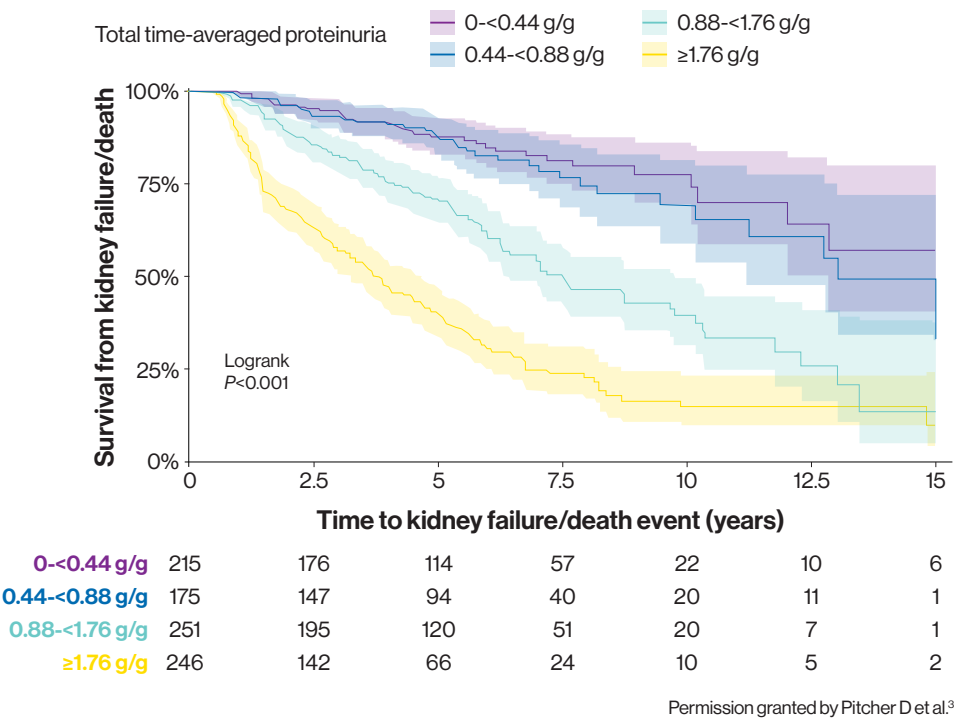


Kaplan-Meier Survival Curves of Time to Kidney Failure/Death Event on the Basis of Total Follow-Up Time-Averaged Proteinuria in a UK Retrospective Cohort³



- Data from retrospective cohort of 2299 adults and 140 children with IgAN in the UK National Registry of Rare Kidney Diseases (RaDaR)
- Patients enrolled had a biopsy-proven diagnosis of IgAN plus proteinuria >0.5 g/day or eGFR <60 mL/min/1.73 m² at any time in the history of their disease
- Analyses of kidney survival were conducted using Kaplan-Meier and Cox regression
- Availability of patient medication and blood pressure data was a limiting factor in this study
- 0.88 g/g is approximately equivalent to 1 g/day

KDIGO recommends assessing estimated glomerular filtration rate and proteinuria as the only valid prognostic biomarkers and to monitor treatment outcomes²¹

KDIGO 2025 guidelines state that proteinuria should be maintained at a minimum of <0.5 g/d (or equivalent); ideally at <0.3 g/d (or equivalent) as disease management goals. Guidelines are evolving with emerging information regarding disease state and treatment modalities²¹

Patients with proteinuria are at increased risk for developing kidney failure³

References: 1. Rizk DV et al. *Front Immunol*. 2019;10:504. 2. Lai KN et al. *Nat Rev Dis Primers*. 2016;2:16001. 3. Pitcher D et al. *Clin J Am Soc Nephrol*. 2023;18(6):727-738. 4. Kwon CS et al. *J Health Econ Outcomes Res*. 2021;8(2):36-45. 5. Lafayette RA, Kelepouris E. *Am J Nephrol*. 2018;47(suppl 1):43-52. 6. Penfold RS et al. *Int J Nephrol Renovasc Dis*. 2018;11:137-148. 7. Xie J et al. *PLoS One*. 2012;7(6):e38904. 8. Reich HN et al. Toronto Glomerulonephritis Registry. *J Am Soc Nephrol*. 2007;18(12):3177-3183. 9. Makhammajanov Z et al. *Nephrol Dial Transplant*. 2024;39(4):589-599. 10. Suzuki H et al. *J Am Soc Nephrol*. 2011;22(10):1795-1803. 11. Maillard N et al. *J Am Soc Nephrol*. 2015;26(7):1503-1512. 12. Barratt J et al. *Kidney Int*. 2023;104(2):254-264. 13. Kohan D et al. *Kidney Int Rep*. 2023;8(11):2198-2210. 14. Ruggenenti P et al. *J Am Soc Nephrol*. 2012;23(12):1917-1928. 15. Nakayama M et al. *Kidney Int Rep*. 2022;7(12):2726-2729. 16. Stefan G et al. *Kidney Int Rep*. 2024;9(2):356-369. 17. Thurman JM et al. *Clin J Am Soc Nephrol*. 2016;11(10):1856-1866. 18. Cortinovis M et al. *Front Med*. 2024;11:1478697. 19. Huang G et al. *Biochem Biophys Res*. 2022;33:101417. 20. Zhuang Y et al. *J Biol Chem*. 2014;289(36):25101-25111. 21. KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV). *Kidney Int*. 2025;108(4S):S1-S71.

Proteinuria—a key prognostic biomarker for patients with IgA nephropathy

IgA nephropathy is a heterogeneous, progressive autoimmune disease characterized by glomerular injury, inflammation, and scarring, leading to chronic kidney disease¹⁻⁶

It contributes significantly to the global burden of CKD and kidney failure¹⁻⁶

Up to 50% of patients with IgA nephropathy progress to kidney failure* within 10 to 20 years of diagnosis^{3,4,7}

In a retrospective study of patients with IgA nephropathy in the UK, data suggest that high-risk patients (ie, with total time-averaged proteinuria >0.88 g/g) **progress more quickly** to kidney failure³

However, even patients with **less severe proteinuria may still experience progression**^{3,8}



~30%

of patients with time-averaged proteinuria of 0.44-0.88 g/g will experience kidney failure within 10 years of diagnosis³

Proteinuria ≥0.5 g/day (or equivalent) is a predictor of increased risk of disease progression in IgA nephropathy²¹

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*Defined by the need for renal replacement therapy (dialysis or transplantation).
CKD, chronic kidney disease; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease: Improving Global Outcomes.



Proteinuria is a consequence of glomerular damage, **but it can also be a cause of tubular damage and progression of kidney disease through several mechanisms**⁹

Preclinical disease models

Immune complexes with Gd-IgA1 can induce cultured mesangial cells to proliferate and secrete extracellular matrix, which can then alter glomerular permeability¹⁰

Urinary proteins in patients with nephrotic syndrome induce inflammatory and cytotoxic responses in tubular epithelial cells in vitro, and this is thought to contribute to interstitial fibrosis¹⁸

Damage to the glomerular filtration barrier and podocyte injury can occur via:



Complement activation^{1,11,12}



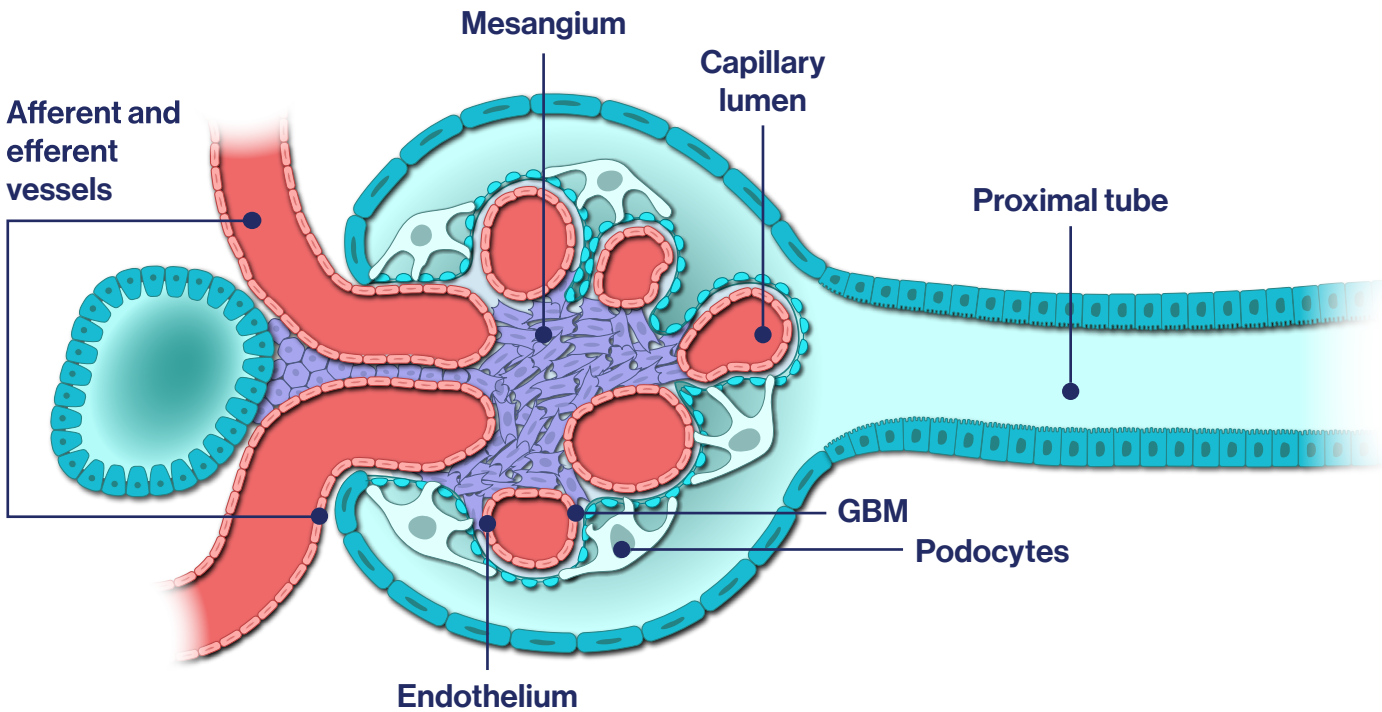
Increased proinflammatory cytokines^{10,12}



ET_A receptor activation¹³



Podocyte dysfunction¹⁴



IC deposition in the mesangium leads to glomerular damage and proteinuria



High levels of proteinuria may induce inflammation in the proximal tubule

Permission granted by Thurman JM et al.¹⁷

Proteinuria may activate tubular inflammation via:



Increased ER stress and ROS in proximal tubule epithelial cells⁹



NLRP3 inflammasome activation^{19,20}



ET_A receptor activation¹³



Complement activation^{9,12}

Clinical observations



High Gd-IgA1 deposition in the mesangium is associated with the presence of inflammatory lesions (E1, C1) and increased proteinuria¹⁵



A systematic literature review of 34 studies found that tissue staining for C3 and C4 is associated with higher MEST-C scores¹⁶



Strong ET_A receptor staining in the tubule and glomerulus is linked to proteinuria¹³



NLRP3 is upregulated in patients with chronic kidney disease and proteinuria^{19,20}

C3, complement 3; C4, complement 4; ER, endoplasmic reticulum; ET_A, endothelin A; GBM, glomerular basement membrane; Gd-IgA1, galactose-deficient immunoglobulin A1; IC, immune complex; MEST-C, mesangial(M) and endocapillary hypercellularity(E), segmental sclerosis(S), interstitial fibrosis/tubular atrophy(T), and crescents(C); NLRP3, NLR family pyrin domain containing 3; ROS, reactive oxygen species.