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Promoting Equity in Transplant Research by Addressing the Exclusion of Patients With Glomerular Disease

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Received 22 September 2025; accepted 29 September 2025; published online 10 October 2025

Kidney Int Rep (2025) **10,** 4277–4280; https://doi.org/10.1016/j.ekir.2025.09.042
KEYWORDS: clinical trials; equity; glomerular disease recurrence; kidney transplant; trial design

INTRODUCTION

Kidney transplantation remains the treatment of choice for patients with end-stage kidney disease (ESKD), offering superior survival and quality of life compared with dialysis.[1] Despite improvements in short-term kidney allograft outcomes, long-term success is often limited by challenges such as allograft rejection, metabolic and cardiovascular complications, immunosuppressive drug-related nephrotoxicity, and posttransplant recurrence of the native kidney disease that led to ESKD.[2,3] To address these challenges, the development of novel therapies with reduced toxicity is essential to improving kidney transplant outcomes. Glomerular

disease (GD) is the third leading cause of ESKD,[4] representing 17% of all adult kidney transplant recipients (KTRs) in the United States.[5] Moreover, patients with GD tend to be younger than those with other ESKD etiologies, which underscores the critical need to focus on improving long-term kidney allograft survival. Despite its impact, a significant disparity exists in the inclusion of patients with GD in clinical trials of KTRs. Owing to concerns about primary GD recurrence posttransplantation and its potential impact on trial outcomes, patients with GD may be excluded from participation. These exclusions are often based on historical and generalized assumptions, despite growing evidence supporting individualized risk stratification based on GD subtypes and phenotypic profiles.[6,7] Advances in understanding the pathophysiology and recurrence risk of specific GD subtypes challenge the rationale for blanket exclusions and highlight the need for more inclusive trial designs.

This study investigated the prevalence of excluding KTRs with primary GD from interventional clinical trials and offers guidance on recurrence risk stratification to promote equitable trial participation. By addressing these disparities, we aimed to enable evidence-based management strategies that improve outcomes for all KTRs, including those with GD.

RESULTS

The ClinicalTrials.gov registry was reviewed for interventional drug trials involving KTRs and waitlisted patients completed between September 2014 and 2024. Two independent investigators assessed trial eligibility criteria, and uncertainties were resolved by the Post-Transplant-Glomerular-Disease (TANGO) Consortium Committee.[8] Trials were evaluated for the exclusion of participants with primary GD. A detailed description of the methods is provided in the Supplementary Methods.

We identified 2119 trials related to kidney disease and transplantation registered on ClinicalTrials.gov. Of these, 298 were interventional pharmacological trials targeting KTRs or kidney transplant candidates on the waitlist. Twelve trials were specifically designed to study treatments for GD recurrence and were excluded from further analysis, because they could not inform patterns of exclusion. This left 286 trials for analysis. Further details of the trial selection process and inclusion or exclusion criteria are provided in Supplementary Figure S1 and described in the Supplementary Methods. Among the 286 trials, 40 (14%) explicitly excluded KTRs with GD or a specific GD subtype as the cause of their ESKD.

The most common exclusion criterion was any GD subtype (48%), followed by autoimmune diseases (24%) and focal segmental glomerulosclerosis (20%) (Figure 1a). Of the 8 trials excluding patients with focal segmental glomerulosclerosis, 7 specified primary focal segmental glomerulosclerosis, and 1 excluded all focal segmental glomerulosclerosis types. The proportion of trials excluding KTRs with GD remained relatively stable over the past decade; however, it increased to 24% among trials registered between 2023 and 2024 (Figure 1b). Notably, 24 of the 40 trials (60%) that excluded patients with GD focused on interventions involving immunosuppressants. These trials were predominantly conducted in North America (65%) and Europe (20%). No statistically significant differences were observed between trials that excluded patients with GD and those that did not, when comparing trial characteristics such as drug intervention type, trial phase, study population, funding source, enrollment size, geographic region, or start year. Further details of the trials are shown in Supplementary Tables S1 and S2.

DISCUSSION

Through our review of the ClinicalTrials.gov registry, we found that 14% of interventional pharmacological trials for KTRs or kidney transplant candidates explicitly excluded patients with any GD or a GD subtype. This practice raises equity concerns, because it limits opportunities for patients with GD to access potentially beneficial therapies and for clinicians to generate robust evidence that informs posttransplant care for this population. Although we acknowledge that some patients with GD face a high risk of GD recurrence, which could potentially be a confounder when assessing the safety and efficacy of an intervention, we advocate for a more evidence-based and hypothesis-driven approach to patient selection. Rather than blanket exclusions based solely on the presence of GD, we propose a risk classification model, detailed in Table 1,[9] to guide inclusion criteria. This model categorizes patients based on their underlying GD subtype into either a low, moderate, or high recurrence risk. We encourage trialists, as well as federal agencies, to refine their inclusion and exclusion criteria by considering the exclusion of only patients with high-risk patients with GD in smaller studies (pilot studies and phase 1 trials). In larger studies (phase 2, 3, and 4 trials), stratified randomization based on GD type and recurrence risk should be prioritized. This approach would facilitate subgroup analyses and minimize imbalances that could falsely suggest a new therapy's ineffectiveness. Given the high prevalence of GD among KTRs, ensuring a balanced representation of these patients

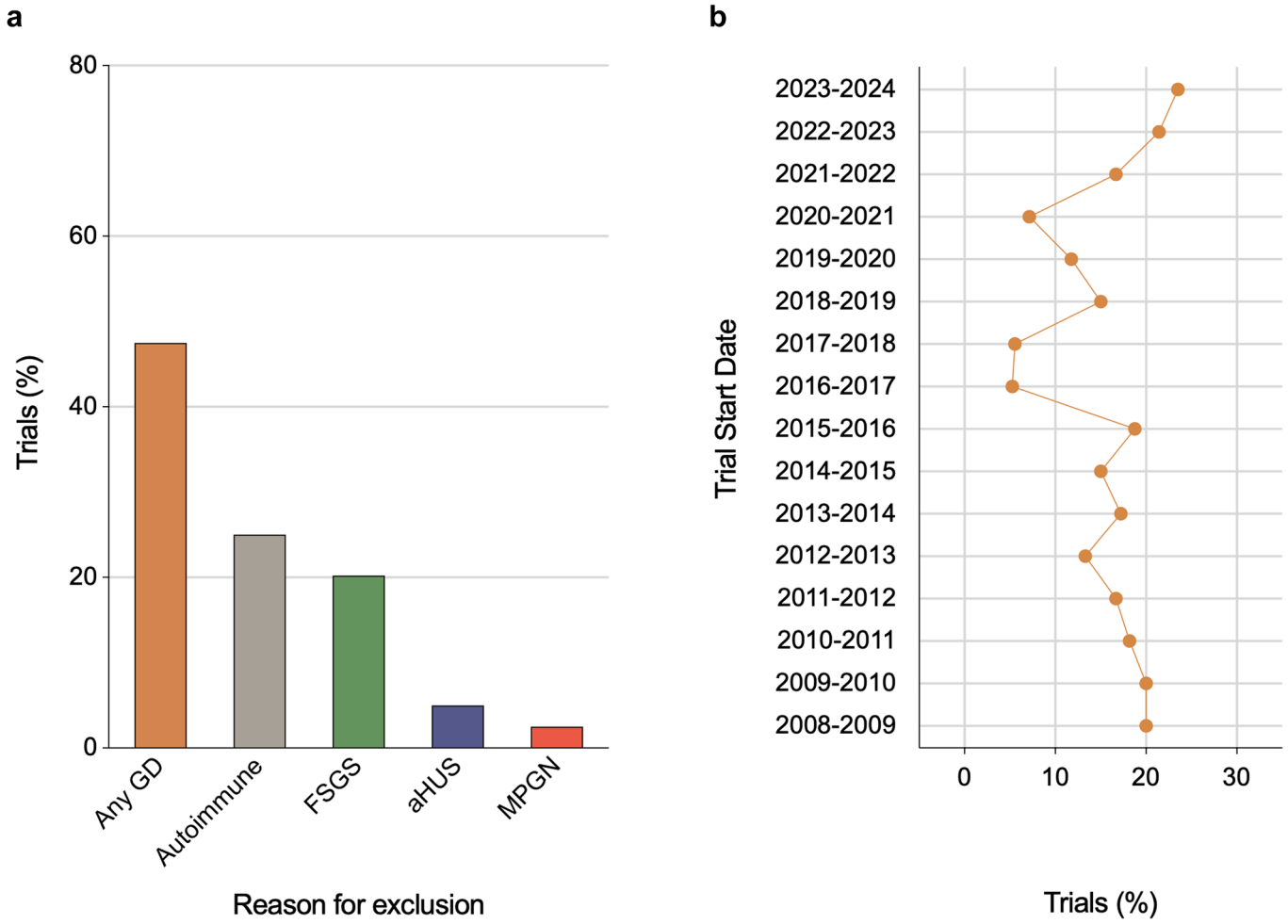

Figure 1. Reasons for excluding GD KTRs and trends in exclusion over time. (a) Reasons for the exclusion of KTRs and KT candidates with GD. (b) Trends in the proportion of KTR trials that exclude patients with GD over time. Trials are grouped by their trial start date, beginning from September 2008 to September 2009 and continuing in 1-year intervals. aHUS, atypical hemolytic uremic syndrome; FSGS, focal segmental glomerulosclerosis; GD, glomerular disease; KT, kidney transplant; KTRs, kidney transplant recipients; MPGN, membranoproliferative glomerulonephritis.

Table 1. Overview of glomerular and related autoimmune diseases categorized by recurrence risk after transplant

GD with low or no recurrence risk	GD with moderate recurrence risk	GD with high recurrence risk
Alport syndrome	IgA nephropathy	C3-glomerulonephritis
ANCA-associated vasculitis	Moderate risk for recurrent aHUS according to KDIGO guidelines[9]	Dense deposit disease
Anti-GBM disease	Primary MN with high pre-transplant anti-PLA2R antibody levels[6]	High risk for recurrent aHUS according to KDIGO guidelines[9]
APOL1-mediated FSGS		IC-MPGN
Genetic, familial or secondary FSGS		Primary FSGS or MCD with nephrotic range proteinuria and negative genetic testing
Low risk for recurrent aHUS according to KDIGO guidelines[9]		
Lupus nephritis		
Primary FSGS without recurrence in previous kidney transplant		
Primary MN with low or absent pre-transplant autoantibody titers		
Secondary TMA		
Thin basement membrane nephropathy		

aHUS, atypical hemolytic uremic syndrome; ANCA, antineutrophil cytoplasmic antibodies; APOL1, apolipoprotein L1; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; GD, glomerular disease; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; KDIGO, Kidney Disease: Improving Global Outcomes; MCD, minimal change disease; MN, membranous nephropathy; PLA2R, phospholipase A2 receptor; TMA, thrombotic microangiopathy.

across study arms is essential.[4,5] This strategy would foster more inclusive research and generate robust evidence to improve posttransplant care for all KTRs, while acknowledging the importance of adequately powered sample sizes to enable meaningful subgroup analyses.

DISCLOSURE

APdJ reports consultancy and lecture fees from Astellas, Chiesi, CSL Behring, Hansa, Neovvi, Novartis, Takeda, Sandoz, and Sanofi, all of which were to the employer LUMC and none to personal bank accounts. PV reports consultancy for Boehringer-Ingelheim funded by Viracor for principal investigator–initiated study. PC reports research support from Chinook Pharmaceuticals and Borealis Pharmaceuticals; and is consulting for Chinook Pharmaceuticals, Cerium Pharmaceuticals, and Roche. LVR reports a 1-time advisory board membership for Calliditas, Apellis, and Sanofi; and has received investigator-initiated research funding from CareDx, Natera, Visterra, AstraZeneca, and Veloxis. SAL reports being funded by a U2C/TL1 Harvard Kidney, Urology, and Hematology Training Institute Network Grant. All the other authors declared no competing interests

Funding

This study was supported in part by the Harold and Ellen Danser Endowed/Distinguished Chair in Transplantation at Massachusetts General Hospital, Harvard Medical School, Boston, MA. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding institution.

DATA AVAILABILITY STATEMENT

All clinical trial data were derived from the following resources available in the public domain: https://clinicaltrials.gov/.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Figure S1. Flowchart of the trial selection process.

Table S1. Characteristics of interventional pharmacological trials that exclude patients with GD.

Table S2. Characteristics of clinical trials excluding patients with GD.

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