BMC Nephrology

RESEARCH Open Access

Short- and long-term outcomes in critically ill patients with primary glomerular disease: a case–control study

Nicoli Ferri Revoredo Coutinho[1] and Alexandre Braga Libório[1*]

Abstract

Introduction Glomerular diseases, encompassing primary and secondary forms, pose significant morbidity and mortality risks. Despite their impact, little is known about critically ill patients with primary glomerulopathy admitted to the intensive care unit (ICU).

Methods We conducted a case–control study of patients with primary glomerulopathy using the Medical Information Mart for Intensive Care IV database. Demographic, clinical, and outcome data were collected. Logistic regression and mediation analysis were performed to identify predictors of hospital and long-term mortality.

Results Among 50,920 patients, 307 with primary glomerulopathy were included. Infectious and cardiovascular-related causes were the main reasons for ICU admission, with sepsis being diagnosed in more than half of the patients during their ICU stay. The hospital mortality rate was similar to that of the control group, with a long-term mortality rate of 29.0% three years post-ICU discharge. Reduced urine output and serum albumin were identified as independent predictors of hospital mortality, while serum albumin and the Charlson comorbidity index were significantly associated with long-term mortality. Notably, although acute kidney injury was frequent, it was not significantly associated with mortality. Additionally, reduced urine output mediates nearly 25% of the association between serum albumin and hospital mortality.

Conclusion Critically ill patients with primary glomerulopathy exhibit unique characteristics and outcomes. Although hospital mortality was comparable to that of the control group, long-term mortality remained high. The serum albumin concentration and Charlson Comorbidity Index score emerged as robust predictors of long-term mortality, highlighting the importance of comprehensive risk assessment in this population. The lack of an association between acute kidney injury and mortality suggests the need for further research to understand the complex interplay of factors influencing outcomes in this patient population.

Keywords Glomerulopathy, Critically ill, Nephrotic syndrome, Hypoalbuminemia, Mortality

*Correspondence:
Alexandre Braga Libório
alexandreliborio@yahoo.com.br
[1]Medical Sciences Postgraduate Program, Universidade de Fortaleza-UNIFOR, Fortaleza, Ceará, Brazil

Introduction

Glomerular diseases can manifest in primary or secondary forms, with the latter arising in the context of systemic autoimmune diseases, infections, medication usage, or malignancies. Primary glomerular diseases include various disorders, including minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), immunoglobulin A nephropathy (IgAN), and certain types of membranoproliferative glomerulonephritis (MPGN). Additionally, glomeruli can be affected secondarily, where the involvement of other organs is minimal or absent, such as in pauci-immune kidney-limited vasculitis, and in cases where endocapillary proliferation in the glomerulus is secondary to sometimes unnoticed infections. In these patients, renal involvement is considered primary [1].

Glomerular disease can manifest as several syndromes, frequently with overlap, primarily nephrotic or nephritic syndrome, with its most severe form being rapidly progressive glomerulonephritis [2]. The main systemic consequences of glomerular disease include edema, hypoalbuminemia, chronic kidney disease with a progressive reduction in the glomerular filtration rate, accelerated atherosclerosis with a high burden of cardiovascular disease, and infection-prone complications due to immunosuppressive therapy and urinary loss of immunoglobulin and complement system fragments [3]. All these characteristics help to explain the increased mortality in this population—2.7-fold greater for primary glomerular disease than for the general population [4].

Although associated with substantial morbidity and mortality rates, primary glomerulopathy is an uncommon condition [5]. Studies evaluating hospitalization rates are scarce, and most data come from epidemiologic cohort studies evaluating chronic kidney disease in advanced stages [6]. To the best of our knowledge, there are no studies available on critically ill patients with primary glomerulopathy. Due to the aforementioned glomerulopathy-specific complications, comprehensive data regarding admission causes, severity, in-hospital deaths, and long-term outcomes of patients with primary glomerulopathy admitted to the intensive care unit (ICU) can assist healthcare professionals and medical services in providing more rational care to these patients.

In this study, we used a large, detailed and prospectively collected electronic database to design a case–control study to assess the main causes at admission, severity, and short- and long-term outcomes of critically ill patients with primary glomerulopathy. Additionally, we aimed to determine prognostic factors related to glomerulopathy.

Methods

Medical Information Mart for Intensive Care IV database and data collection

The Medical Information Mart for Intensive Care (MIMIC-IV) project is managed by the Massachusetts Institute of Technology Laboratory for Computational Physiology and houses data on patients admitted to Beth Israel Deaconess Medical Center from 2008 to 2019 [7, 8]. The MIMIC-IV database is publicly available, and researchers who agree to the data use agreement and have completed "protecting human subjects training" can request access. The MIMIC database was approved by the institutional review boards of the Beth Israel Deaconess Medical Center (2001-P-001699/14) and the Massachusetts Institute of Technology (No. 0403000206) in accordance with the Declaration of Helsinki, which waived the requirement for individual patient consent because the datasets contained deidentified information.

We included all adult patients (aged > 18 years) with a diagnosis of glomerulopathy according to the International Classification of Diseases (ICD) versions 9 and 10 with intensive care unit (ICU) admission (see Supplementary Table S1). Patients who met the following criteria were excluded: baseline serum cretinine > 4 mg/dL; estimated glomerular filtration rate (eGFR) < 15 ml/min/1.73m^2 - calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation – 2021 [9], considering the lowest serum creatinine during the hospital stay; maintenance hemodialysis before hospital admission; previous renal transplantation; identifiable secondary glomerulopathies through medical notes and associated diagnosis. Patients with a hospital length of stay (LOS) < 24 h were excluded. If a patient had multiple ICU admissions during the study period, only the first admission was considered.

For each patient with primary glomerulopathy, we selected one matched control patient who had no glomerular disease. We used a hierarchical matching scheme prioritizing the following factors in order: age (within 5 years), sex, baseline estimated glomerular filtration rate (within 5 ml/min/1.73 m2), Charlson comorbidity index within 1 score), angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) use, main ICU admission reason, and Sequential Organ Failure Assessment score [10] without the renal component (nonrenal SOFA) in the first 24 h of ICU admission (within 1 score) to account for these potential confounders. We were able to match patients and controls 1:1.

Demographic and clinical variables

Patient demographic characteristics (age and sex), main reason for ICU admission, glomerulopathy diagnosis, lowest serum creatinine, Charlson comorbidity index, ACEI or ARB use, immunosuppressive agents, nonrenal

SOFA score and serum albumin were extracted up to the first 24 h of ICU admission. Additionally, higher proteinuria and higher hematuria grade were recorded during the hospital stay. Proteinuria data were collected as the time at which urine was collected or the urine protein/creatinine ratio was measured, and the values were converted to g/24 h [11]. For hematuria, urine samples collected up to 48 h after the passage of indwelling urinary catheters were not considered. Other variables were collected during the ICU stay: suspicion of infection (defined as antibiotic use and collection of cultures), sepsis defined according to the Sepsis-3 criteria [12], use of nephrotoxic drugs (aminoglycoside, vancomycin, and amphotericin), contrast administration, need for kidney replacement therapy (KRT), use of vasoactive drugs and need for high-flow nasal cannula, and noninvasive or invasive mechanical ventilation. Hospital and ICU length of stay data were collected. During the ICU stay, patients were classified according to the KDIGO criteria: stage 1 AKI was defined as a 6-hour mean urine output less than 0.5 mL/kg/h or a peak-to-baseline serum creatinine difference of at least 0.3 mg/dL within a 48-hour time frame or a peak-to-baseline serum creatinine ratio of 1.5 to 1.9; stage 2 AKI was defined as a 12-hour mean urine output less than 0.5 mL/kg/h or a peak-to-baseline serum creatinine ratio of 2.0 to 2.9; and stage 3 AKI was defined as a 24-hour mean urine output less than 0.3 mL/kg/h or a 12-hour period of anuria or a peak-to-baseline serum creatinine ratio of at least 3.0, a serum creatinine level of at least 4.0 mg/dL or KRT initiation [13]. The baseline renal function was considered the lowest serum creatinine during the hospital stay. After 48 h of ICU stay, 48-hour and 7-day sliding windows were used to define dynamic baselines. Finally, the number of hospital and ICU admissions during the study period was recorded. Patients were also classified according to the main glomerular syndrome when possible: nephritic or nephrotic.

Outcomes

The outcomes were AKI during the ICU stay and hospital and long-term mortality up to three years after hospital discharge.

Statistical analysis

The descriptive characteristics of the study population are presented as proportions for categorical and binary variables, means with standard deviations (SDs) for normally distributed continuous variables, and medians with interquartile ranges (IQRs) for skewed variables. Differences between categorical variables were assessed using chi-square tests, and continuous variables were compared using t tests or Wilcoxon signed-rank tests, as appropriate.

Clinically relevant covariates identified in univariate analysis with $P<0.25$ were included in the initial logistic binary regression model to determine independent predictors of hospital and long-term mortality in primary glomerulopathy patients and controls separately. Stepwise logistic regression using backward elimination was performed using an α-critical value of 0.10 for the exit from the previous model. Because AKI stage was not associated with either outcome in patients with primary glomerulopathy (see below), we analyzed the lowest urine output in each 24-h block and AKI according to the serum creatinine criteria as independent variables.

When appropriate, mediation analyses were performed based on the logistic regression results to assess the hypothesized associations of clinical and laboratory variables with hospital mortality. Specifically, the mediation analysis was performed when (1) the exposure was significantly correlated with the mediator and outcome (after adjustment for confounders) and (2) the mediator was significantly correlated with the outcome. Indirect effects and confidence intervals were estimated by bootstrapping with 5000 resamples using the PROCESS Statistical Package for SPSS (PROCESS version 2—note that version 3 does not run dichotomous outcomes and SPSS, version 20.0, 2011; SPSS Inc., Chicago, IL) [13]. Statistically significant mediation is established when the indirect effect is significantly different from zero. To construct a directed acyclic graph (DAG) [14], we propose a model that maintains the temporal causal assumption. All mediation models were adjusted for the covariates identified in univariate analysis with $P<0.25$. A p value <0.05 was considered to indicate statistical significance. All analyses were conducted using SPSS (version 20.0; IBM, Armonk, NY, USA) and the abovementioned package.

Results

Patient characteristics

The MIMIC-IV database contains the records of 50,920 patients admitted to the ICU, 545 of whom had a diagnosis of glomerulopathy. Among these patients, 122 were excluded because they had ESRD or previous renal transplantation, 81 because they had secondary glomerulopathy, 26 because they had missing data and 9 because they had an ICU stay of less than 24 h. After all, 307 patients remained in the final analysis (Fig. 1).

The mean age was 61.4±15.2 years, and most patients were male ($n=175$, 57.0%). The most common glomerular syndromes were nephritic ($n=175$, 57.0%) and nephrotic syndrome ($n=93$, 30.3%), and almost half of the patients ($n=153$, 49.8%) received immunosuppressive therapy. The most common etiology was acute glomerulonephritis ($n=161$, 52.4%). In patients with nephrotic syndrome, the most common identified etiology was MN ($n=25/93$, 26.9%). The mean serum albumin concentration was

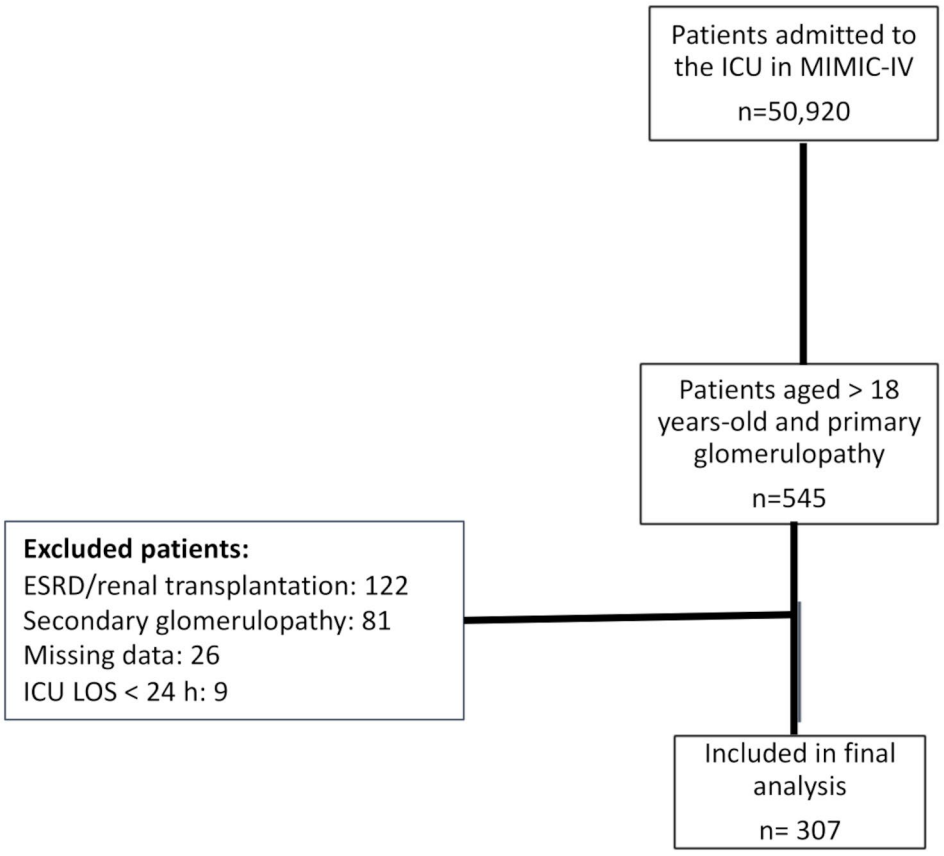


Fig. 1 Flowchart of patients and exclusion criteria

2.6±0.7 g/dL, and the urine protein excretion rate during the hospital stay was 1.5 [IQR 0.5–4.1] g/24 h. As expected, the control group had comparable values for all measured baseline characteristics, except for the serum albumin concentration (Table 1).

Patient clinical parameters at ICU admission and their ICU management

As shown in Table 2, the main causes at ICU admission were infection (n=68, 22.1%) and cardiovascular disease (n=66, 21.5%). Kidney-related complications were the main reason for ICU admission in 26 (8.5%) patients. At ICU admission, the median nonrenal SOFA score was 3 [IQR 1–5]. During the ICU stay, 18 (5.9%) patients required high-flow nasal oxygen therapy or noninvasive ventilation, and 105 (34.2%) patients required invasive mechanical ventilation. Infection was suspected, antibiotics were initiated in 217 (70.7%) patients, and 168 (54.7%) patients had sepsis. Additionally, 89 patients (29.0%) received vasoactive drugs. No significant difference was observed in these characteristics between patients with primary glomerulopathy and those in the control group. AKI occurred in 266 (86.7%) patients with primary glomerulopathy. Although no difference in AKI incidence was observed among the control group, patients with primary glomerulopathy had more stage 3 AKI and needed KRT (Table 2). Among patients with primary glomerulopathy, 33/266 (2.4%) met only the urine output criterion, 43/266 (16.2%) met only the serum creatinine criterion, and 190/266 (71.4%) met both criteria.

Factors associated with acute kidney injury

In patients with primary glomerulopathy, the use of a vasopressor, the need for mechanical ventilation and serum albumin were associated with stage 3 AKI according to univariate analysis. After stepwise backward logistic regression, only serum albumin and vasopressor use were independently associated with stage 3 AKI (Table 3). In the control group, the Charlson comorbidity index and nonrenal SOFA score were independently associated with stage 3 AKI (Supplementary Table S2).

Outcomes

The median ICU LOS was 2.2 [IQR 1.3–4.8] days. Among 307 patients, 21 died in the ICU, for a mortality rate of 6.8%, which was very similar to that of the control group. Among the patients who were discharged from the hospital, the three-year survival probability after ICU

Table 1 Baseline characteristics of the study population

Variables	Primary glomerulopathy patients (*n* = 307)	Control group (*n* = 307)	*p*
Age, mean ± *SD, years*	61.4 ± 15.2	62.0 ± 14.7	0.66
Male, n (%)	175 (57.0)	175 (57.0)	-
Glomerular syndrome, n(%)		-	-
Nephritic syndrome	175 (57.0)		
Nephrotic syndrome	93 (30.30)		
Chronic glomerulopathy	35 (11.4)		
No classified	4 (1.3)		
Baseline eGFR, mean ± SD, ml/min/1.73m^2	87.0 ± 32.0	85.4 ± 29.3	0.18
Use of ACEI/ARB, n(%)	101 (32.9)	101 (32.9)	-
Immunosuppressive drug, n (%)			
Corticosteroids	94 (30.6)	-	-
Calcineurin inhibitors	21 (6.8)		
Mycophenolate	15 (4.9)		
Rituximab	9(2.9)		
mTOR inhibitors	4 (1.3)		
Serum albumin, mean ± SD, g/dL	2.6 ± 0.7	3.0 ± 0.7	0.48
24 h-protein excretion, median [IQR], mg*	1,500 [500-4,100]	-	-
Microscopic hematuria, n (%) *	100 (46.1)	-	-
Charlson Index, median [IQR]	5 [3–7]	5 [3–7]	0.91

*n = 217. eGFR = estimated glomerular filtration rate; ACEIs: angiotensin-converting–enzyme inhibitors; ARBs: angiotensin receptor blockers; mTOR: mammalian target of rapamycin

Table 2 Clinical variables, support and outcomes during the ICU stay

Variable	Primary glomerulopathy patients (*n* = 307)	Control group (*n* = 307)	*p*
ICU admission reason			-
Infectious disease	68 (22.1)	68 (22.1)	
Cardiovascular disease	66 (21.5)	66 (21.5)	
Surgical	43 (14.0)	43 (14.0)	
Respiratory complication	28 (9.1)	28 (9.1)	
Renal-related complication	26 (8.5)	26 (8.5)	
Neurologic-related complication	27 (8.8)	27 (8.8)	
Liver complication	14 (4.6)	14 (4.6)	
Other	35 (11.4)	35 (11.4)	
Nonrenal SOFA, median [IQR]	3 [1–5]	3 [1–5]	0.90
Suspicion of infection, n (%)	217 (70.7)	202(65.8)	0.22
Sepsis, n (%)	168 (54.7)	163 (53.1)	0.75
Need of vasoactive drugs, n (%)	89 (29.0)	77 (25.1)	0.32
Invasive ventilatory support, n (%)	105 (34.2)	114 (37.1)	0.50
Use of nephrotoxic drugs, n (%)	189 (61.6)	177 (57.7)	0.87
AKI stage*, n (%)			< 0.001
No-AKI	41 (13.4)	42 (13.7)	
AKI stage 1	54 (17.6)	78 (25.4)	
AKI stage 2	81 (24.4)	127 (41.4)	
AKI stage 3	131 (42.7)	60 (19.5)	
Need of KRT, n (%)	28 (9.1)	3 (1.0)	< 0.001
ICU LOS, median [IQR], days	2.2 [1.2–4.8]	2.4 [1.1–4.8]	0.74
Hospital Mortality, n (%)	21 (6.8)	22 (7.2)	1.0

*Using both the serum creatinine and urine output criteria. ICU; intensive care unit; SOFA: sequential organ failure Assessment; AKI: acute kidney injury; KRT: kidney replacement therapy; LOS: length of stay

Table 3 Unadjusted and adjusted odds ratios for acute kidney injury in patients with primary glomerulopathy

	Unadjusted Analysis	Adjusted Analysis
Age, per 10years	0.98 (0.94–1.03)	-
Charlson	0.88 (0.92–1.08)	-
Serum albumin, per g/dL	0.51 (0.34–0.76)	0.53 (0.36–0.80)
Nonrenal SOFA	1.06 (0.98–1.15)	-
Mechanical Ventilation	1.52 (0.95–2.46)	-
Vasopressor	1.90 (1.16–3.14)	1.70 (1.02–3.10)

SOFA: sequential organ failure Assessment

discharge was less than that in the control group (66.1 vs. 74.0, $p=0.04$). This population had a greater frequency of ICU readmission: more than half of the patients (51.7%) had at least one other ICU admission out of 21.3% in the control group ($p<0.001$), and 33.9% had at least 2 other ICU admissions out of 6.0% in the control group ($p<0.001$).

Factors predicting hospital mortality

In patients with primary glomerulopathy, univariate analysis revealed that hospital mortality was significantly associated with age, the Charlson comorbidity index, the serum albumin concentration, the nonrenal SOFA score at admission, the need for invasive mechanical ventilation, the use of vasopressors and the need for KRT during the ICU stay. Surprisingly, acute kidney injury according to the KDIGO criteria was not associated with in-hospital mortality (OR 1.38, 95% CI 0.86–2.20), but the lowest 24-h urine output was strongly associated with in-hospital mortality. Because AKI stage was not associated with either outcome, we analyzed the lowest urine output in each 24-h block and AKI according to the serum creatinine criteria as independent variables. Stepwise backward logistic regression revealed that only the lowest urine output at 24 h and the serum albumin concentration were independently associated with in-hospital mortality (Table 4). In the control group, AKI and serum albumin were independently associated with in-hospital mortality (see supplementary table S3).

In patients with primary glomerulopathy, all three variables (serum albumin before ICU admission, lowest urine output and hospital mortality) were significantly correlated with one another, and there was a temporal causal assumption. Therefore, we tested whether reduced urine output mediated the effects of serum albumin on hospital mortality. Because the association between the serum albumin concentration and in-hospital mortality remained significant after the lowest urine output was included, a total mediation of this association was excluded. However, we tested whether this association was partially mediated by the lowest urine output in a 24-h period. The indirect effect of serum albumin on hospital mortality through reduced urine output was significant and explained 23.4% of the total observed effect (Fig. 2). No significant indirect effect of serum albumin through AKI on in-hospital mortality was detected in the control group (indirect effect: -0.13, 95% CI: -0.54 to 0.06).

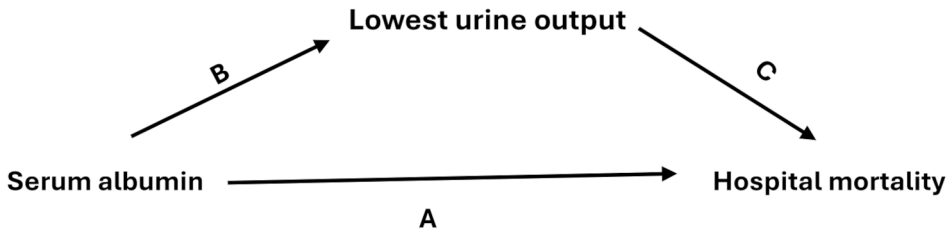
Predictive factors of long-term mortality

Among only patients who were discharged alive, only age, serum albumin concentration and the Charlson comorbidity index were significantly associated with three-year survival in both patients with primary glomerulopathy and in the control group (Table 4 and Supplementary Table S3). Because there was no association between these predictors, no mediation association was further explored. Because the serum albumin concentration was also a strong predictor of long-term survival and to further explore this association, we divided the patients according to the median serum albumin concentration. Figure 3 displays the adjusted survival curve for patients

Table 4 Unadjusted and adjusted odds ratios for hospital and three-year mortality for patients with primary glomerulopathy

	Hospital mortality		Three-year mortality	
	Unadjusted Analysis	Adjusted Analysis	Unadjusted Analysis	Adjusted Analysis
Age, per 10years	1.39 (1.05–1.75)	-	1.22 (1.06–1.38)	1.20 (1.0-1.40)
Charlson	1.39(1.18–1.62)	-	1.15 (1.07–1.24)	1.10 (1.01–1.21)
Serum albumin, per g/dL	0.26 (0.11–0.61)	0.27 (0.11–0.68)	0.69 (0.48–0.99)	0.61 (0.42–0.88)
Nonrenal SOFA	1.26 (1.12–1.43)	-	1.02 (0.95–1.10)	-
Mechanical Ventilation	2.25 (0.92–5.48)	-	0.81 (0.50–1.30)	-
Vasopressor	2.93 (1.20–7.18)	-	1.04 (0.63–1.68)	-
AKI stage- sCr criterion				
AKI stage 1	0.77 (0.54–2.38)	-	0.84 (0.47–1.64)	-
AKI stage 2	0.95 (0.69–3.09)		1.44 (0.68–3.08)	
AKI stage 3	1.39 (0.82–5.61)		1.21 (0.60–2.45)	
KRT	4.80 (1.7–9.6)	-	1.19 (0.55–2.59)	-
Lowest urine output 24 h, per 100 ml	0.77 (0.65–0.91)	0.79 (0.67–0.94)	1.00 (0.97–1.04)	-

SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; AKI: acute kidney injury; sCr: serum creatinine; KRT: kidney replacement therapy



Path	Effect	95%CI
A	-1.31	-2.24 to -0.38
BC	-0.40	-0.89 to -0.09

Fig. 2 Mediation analyses of the association between serum albumin and in-hospital mortality in patients with primary glomerulopathy. Path models and mediation analyses describe the mediation of the association between serum albumin and hospital mortality through the lowest urine output in a 24-h period. Path effects are reported as odds ratios of natural log-transformed values. Direct effects are labeled path A, and indirect effects are labeled letters B and C

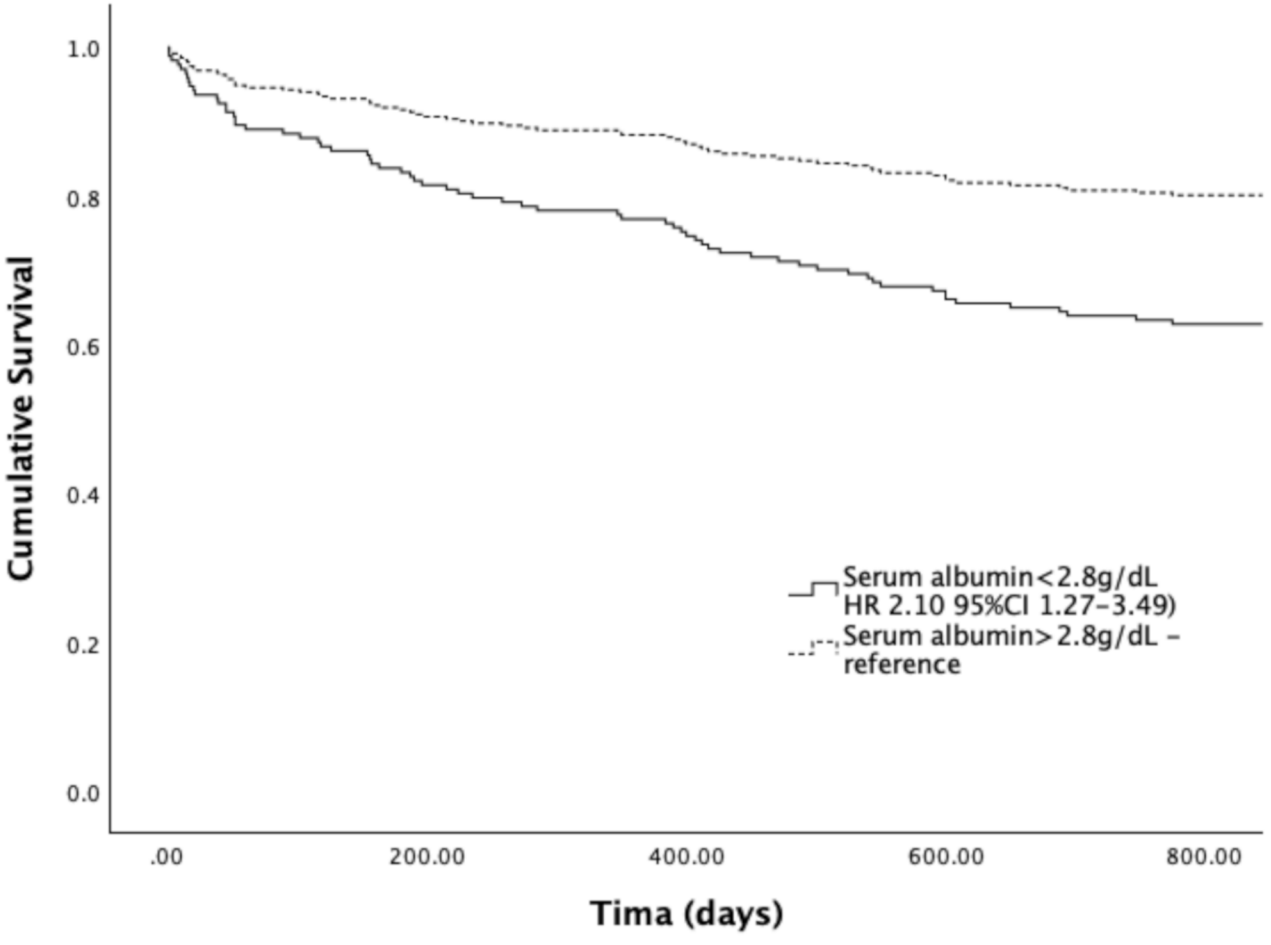


Fig. 3 Adjusted survival curves according to serum albumin concentration

with a serum albumin concentration greater than 2.8 g/dL among those with primary glomerulopathy.

Discussion

In the present research, for the first time, we described a large cohort of critically ill patients with primary glomerulopathy. Several findings need to be highlighted. These patients had nephritic syndrome as the main diagnosis, and they were admitted mainly because of infectious and cardiovascular-related complications. Compared with that of the control group, the hospital mortality rate was similar, but the rate of ICU readmission was greater. Although the incidence of AKI was comparable, patients with primary glomerulopathy had more stage 3 AKI than did those in the control group, but we did not observe any significant association between AKI stage and mortality in those patients, except when reduced urine output was used as the sole criterion. Finally, the serum albumin concentration was a strong predictor of both hospital and three-year mortality. Moreover, we revealed that reduced urine output is an important mediator of the association between serum albumin and in-hospital mortality.

To the best of our knowledge, the admission of patients with glomerular disease to the ICU remains an unexplored topic in the literature. Several intrinsic characteristics of patients with glomerulopathy limit the generalizability of critical population data validation for this specific group [15]. Susceptibility to infection due to the disease itself and the use of immunosuppressants, early and severe atherosclerosis, hypoalbuminemia, and structural and/or functional renal disease itself are factors that may modify the causes and outcomes of these critically ill patients [1]. In our dataset, infectious and cardiovascular causes were the primary reasons for ICU admission. Because we matched the control group to patients admitted to the ICU for reasons related to illness severity (nonrenal SOFA), it is difficult to determine differences in cardiovascular or infectious disease incidence from our data. However, the frequency of ICU admission due to cardiovascular disease appears to be similar to that of other ICU cohorts, and patients with primary glomerulopathy in this study appeared to have a higher rate of admission for infectious complications than patients in other studies of general ICU populations [16]. In our study, more than half of the patients were diagnosed with sepsis at some point. Moreover, renal causes for ICU admission were more common than previously reported [17]. This was an expected finding, especially in our cohort, where more than half of the patients were diagnosed with nephritic syndrome.

In this cohort, AKI exhibited several noteworthy features. First, we observed a greater frequency of severe AKI (stage 3) than in the control group. Even when both the serum creatinine and urine output criteria are used, the incidence of stage 3 AKI rarely exceeds 30% [18]. In the control group, the incidence of stage 3 AKI was less than half of that in patients with primary glomerulopathy. Patients with primary glomerulopathy had a near-normal baseline eGFR during hospitalization, supporting findings from the literature that structural damage, even in the absence of a reduced eGFR, can be a risk factor for AKI in critically ill patients [19–21].

Regarding hospital mortality, the control group was matched for age and comorbidities as determined by the Charlson index and severity score index at ICU admission, and there was no difference in hospital survival. However, patients with primary glomerulopathy had a higher rate of ICU readmission. Another point that differs from the literature regarding AKI in this population is the lack of a clear correlation with mortality. Upon further exploration of both criteria (serum creatinine and urine output), we were able to identify only reduced urine output as a predictor of hospital mortality. Previous studies have demonstrated that AKI was not associated with worse short-term outcomes when combined with CKD [22, 23], although these data are conflicting [24]. Considering that reduced urine output is associated with hospital mortality, we can speculate that a reduced renal reserve causes a significant increase in serum creatinine in patients with less severe renal damage. Subclinical tubular injuries caused by proteinuria may hinder the increase in tubular secretion of creatinine [25], leading to relatively greater increases in serum creatinine. However, this is speculative, and further studies are needed before any conclusions can be drawn.

In addition to initially describing a cohort of critically ill patients with primary glomerulopathy, a major finding of our study was the strong association of serum albumin levels before or at ICU admission with both hospital and three-year mortality. Hypoalbuminemia is a hallmark of glomerulopathy and is associated with quality of life, edema, and chronic damage [26, 27]. While studies in the general population have shown controversy about the role of hypoalbuminemia as a marker of mortality in specific groups of critically ill patients [28], it is widely accepted as a marker of hospital mortality in the general population, although its causality is still debated [29]. Compared with that in the control group, serum albumin in glomerulopathy patients had a greater impact on in-hospital mortality. For instance, in the control group, each 1 g/dL decrease in the serum albumin concentration was associated with a 75% increase in mortality, which is comparable to the findings of a previously cited study [28], whereas in patients with primary glomerulopathy, this increase was nearly 385%. Moreover, we found that, maintaining the temporal causal assumption, reduced urine output mediated 23.4% of the association between serum albumin and hospital mortality, accounting for

nearly one-quarter of the total effect. Several mechanisms can be suggested by which serum albumin may protect the kidney: albumin increased the survival of cultured renal tubular cells [30], a low albumin concentration in the perfusion media was found to decrease renal plasma flow and the GFR in the isolated perfused rat kidney [31], and the frequency of oliguria was reduced in patients receiving albumin in a randomized trial of patients who developed vascular leakage due to interleukin-2 [32]. To the best of our knowledge, although this causal pathway (hypoalbuminemia → reduced urine output → mortality) has biological plausibility, it remains an unexplored pathway in critically ill patients. A strong association with serum albumin was also observed for long-term outcomes. Even after three years of follow-up, each 1 g/dL decrease in the serum albumin concentration was associated with an HR of 1.64 for mortality.

Our study has several important limitations. First, due to its retrospective design, much information about primary glomerulopathy was retrieved from disease codes and discharge summaries and, consequently, is prone to imprecision, including a precise histologic diagnosis. Additionally, while not correlated with any outcomes, the 24-hour protein excretion rate had many missing data, as did serum cholesterol, a biomarker of glomerulopathies that was not included because only a few patients had such measurements. Moreover, we were unable to explore renal function after hospital discharge.

In conclusion, patients with primary glomerulopathy often require ICU admission for infectious and cardiovascular complications. The in-hospital mortality rate was similar to that of the control group; however, ICU readmissions and long-term mortality were elevated. AKI was a frequent event in this population but showed no association with mortality, except for urine output, which was independently associated with hospital mortality. The serum albumin concentration was a strong predictor of both hospital and three-year mortality. Additionally, we found that urine output mediated nearly one-quarter of the association between serum albumin and in-hospital mortality in this population.

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
CKD-EPI	Epidemiology Collaboration
DAG	Directed acyclic graph
eGFR	Estimated glomerular filtration rate (eGFR)
FSGS	Focal segmental glomerulosclerosis
ICD	International Classification of Diseases
ICU	Intensive care unit
IgAN	Immunoglobulin A nephropathy
KRT	Kidney replacement therapy
LOS	Length of hospital stay
MCD	Minimal change disease
MIMIC	Medical Information Mart for Intensive Care
MN	Membranous nephropathy
MPGN	Membranoproliferative glomerulonephritis
SOFA	Sequential Organ Failure Assessment

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03766-w.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Acknowledgements
A.B.L. was supported by Fundação Edson Queiroz.

Author contributions
A.B.L designed the study, analyzed data and wrote the main manuscript. N.F.R.C. collected data and revised manuscript.

Funding
A.B.L. was supported by Fundação Edson Queiroz and Conselho Nacional de Desenvolvimento Científico e Tecnológico (grant no. 306377/2022-5).

Data availability
Data can be accessed on MIMIC-IV database through https://mimic.mit.edu/.

Declarations

Ethics approval and consent to participate
The MIMIC-IV database is publicly available, and researchers who agree to the data use agreement and have completed "protecting human subjects training" can request access. The MIMIC database was approved by the institutional review boards of the Beth Israel Deaconess Medical Center (2001-P-001699/14) and the Massachusetts Institute of Technology (No. 0403000206) in accordance with the Declaration of Helsinki, which waived the requirement for individual patient consent because the datasets contained deidentified information.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Received: 27 April 2024 / Accepted: 19 September 2024
Published online: 08 October 2024

References

1. Rovin BH, Adler SG, Barratt J, et al. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. Kidney Int. 2021;100:S1–276. https://doi.org/10.1016/j.kint.2021.05.021
2. Joshi A, Mariani LH. Reaping the rewards of mechanistic discovery in glomerular disease. Nat Rev Nephrol. 2024;20:77–8. https://doi.org/10.1038/s41581-023-00804-y
3. Lassén E, Daehn IS. Insights into glomerular function and disease pathogenesis. Nat Rev Nephrol. 2023;19:85–6. https://doi.org/10.1038/s41581-022-00667-9
4. Wetmore JB, Guo H, Liu J, et al. The incidence, prevalence, and outcomes of glomerulonephritis derived from a large retrospective analysis. Kidney Int. 2016;90:853–60. https://doi.org/10.1016/j.kint.2016.04.026
5. Janphram C, Worawichawong S, Assanatham M, et al. Years of life lost and long-term outcomes due to glomerular disease in a southeast Asian cohort. Sci Rep. 2023;13:19119. https://doi.org/10.1038/s41598-023-46268-9
6. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl (2011). 2022;12:7–11. https://doi.org/10.1016/j.kisu.2021.11.003
7. Johnson AEW, Bulgarelli L, Shen L, et al. MIMIC-IV, a freely accessible electronic health record dataset. Sci Data. 2023;10:1. https://doi.org/10.1038/s41597-022-01899-x
8. Johnson A, Bulgarelli L, Pollard T, et al. MIMIC-IV (version 2.2). Physionet. 2023

9. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin c–based equations to estimate GFR without race. N Engl J Med. 2021;385:1737–49. https://doi.org/10.1056/NEJMoa2102953
10. Vincent J-L, Moreno R, Takala J, et al. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22:707–10. https://doi.org/10.1007/BF01709751
11. Raza A, Nawaz SH, Rashid R, et al. The correlation of spot urinary protein-to-creatinine ratio with 24-h urinary protein excretion in various glomerulopathies. World J Nephrol. 2023;12:159–67. https://doi.org/10.5527/wjn.v12.i5.159
12. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a new definition and assessing new clinical criteria for septic shock. JAMA. 2016;315:775. https://doi.org/10.1001/jama.2016.0289
13. Hayes A. Introduction to mediation, moderation, and conditional process analysis. New York, NY: Guilford. 2013:3–4.
14. Suttorp MM, Siegerink B, Jager KJ, et al. Graphical presentation of confounding in directed acyclic graphs. Nephrol Dialysis Transplantation. 2015;30:1418–23.
15. Dumas G, Arabi YM, Bartz R, et al. Diagnosis and management of autoimmune diseases in the ICU. Intensive Care Med. 2024;50:17–35. https://doi.org/10.1007/s00134-023-07266-7
16. Sakr Y, Jaschinski U, Wittebole X, et al. Sepsis in intensive care unit patients: worldwide data from the intensive care over nations audit. Open Forum Infect Dis. 2018;5. https://doi.org/10.1093/ofid/ofy313
17. Barrett ML, Smith MW, Elixhauser A et al. Utilization of intensive care services, 2011. 2006
18. Kellum JA, Sileanu FE, Murugan R, et al. Classifying AKI by urine output versus serum creatinine level. J Am Soc Nephrol. 2015;26:2231–8. https://doi.org/10.1681/ASN.2014070724
19. James MT, Grams ME, Woodward M, et al. A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. Am J Kidney Dis. 2015;66:602–12. https://doi.org/10.1053/j.ajkd.2015.02.338
20. James MT, Hemmelgarn BR, Wiebe N, et al. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. Lancet. 2010;376:2096–103. https://doi.org/10.1016/S0140-6736(10)61271-8
21. Grams ME, Astor BC, Bash LD, et al. Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury. J Am Soc Nephrol. 2010;21:1757–64. https://doi.org/10.1681/ASN.2010010128
22. Khosla N, Soroko SB, Chertow GM, et al. Preexisting chronic kidney disease. Clin J Am Soc Nephrol. 2009;4:1914–9. https://doi.org/10.2215/CJN.01690309
23. Mehta RL, Pascual MT, Gruta CG, et al. Refining predictive models in critically ill patients with acute renal failure. J Am Soc Nephrol. 2002;13:1350–7. https://doi.org/10.1097/01.ASN.0000014692.19351.52
24. Neyra JA, Mescia F, Li X, et al. Impact of acute kidney injury and CKD on adverse outcomes in critically ill septic patients. Kidney Int Rep. 2018;3:1344–53. https://doi.org/10.1016/j.ekir.2018.07.016
25. Garimella PS, Tighiouart H, Sarnak MJ, et al. Tubular secretion of creatinine and risk of kidney failure: the modification of diet in renal disease (MDRD) study. Am J Kidney Dis. 2021;77:992–4. https://doi.org/10.1053/j.ajkd.2020.09.017
26. Zabala Ramirez MJ, Stein EJ, Jain K. Nephrotic syndrome for the internist. Med Clin North Am. 2023;107:727–37. https://doi.org/10.1016/j.mcna.2023.03.006
27. Libório AB, Santos JPL, Minete NFA, et al. Proteinuria is associated with quality of life and depression in adults with primary glomerulopathy and preserved renal function. PLoS ONE. 2012;7:e37763. https://doi.org/10.1371/journal.pone.0037763
28. Thongprayoon C, Cheungpasitporn W, Radhakrishnan Y, et al. Impact of hypoalbuminemia on mortality in critically ill patients requiring continuous renal replacement therapy. J Crit Care. 2022;68:72–5. https://doi.org/10.1016/j.jcrc.2021.12.008
29. Goldwasser P, Feldman J. Association of serum albumin and mortality risk. J Clin Epidemiol. 1997;50:693–703. https://doi.org/10.1016/S0895-4356(97)00015-2
30. Iglesias J, Abernethy VE, Wang Z, et al. Albumin is a major serum survival factor for renal tubular cells and macrophages through scavenging of ROS. Am J Physiology-Renal Physiol. 1999;277:F711–22. https://doi.org/10.1152/ajprenal.1999.277.5.F711
31. Zamlauski-Tucker MJ, Cohen JJ. Effect of substrate-free albumin on perfused rat kidney function. Kidney Blood Press Res. 1987;10:352–60. https://doi.org/10.1159/000173144
32. Pockaj BA, Yang JC, Lotze MT, et al. A prospective randomized trial evaluating colloid versus crystalloid resuscitation in the treatment of the vascular leak syndrome associated with interleukin-2 therapy. J Immunother. 1994;15:22–8. https://doi.org/10.1097/00002371-199401000-00003

Publisher's note