

Clinical Manifestations and Prognosis of Chronic Kidney Disease after Hematopoietic Stem Cell Transplantation

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Keywords

Chronic kidney disease · Hematopoietic stem cell transplantation · Thrombotic microangiopathy · Graft-versus-host disease

Abstract

Introduction: Kidney disease is a common complication of hematopoietic stem cell transplantation (HSCT). However, there is limited research on the clinical pathology and prognosis of patients who develop chronic kidney disease (CKD) after HSCT. **Methods:** A retrospective analysis was conducted on 50 patients diagnosed with CKD through kidney biopsy between September 2008 and May 2024. The patients were categorized based on their pathological presentations into groups with thrombotic microangiopathy (TMA) or membranous nephropathy (MN). **Results:** The renal pathological results revealed that TMA was the most prevalent pathological type, accounting for 40% of cases, followed by MN at 32%, and mesangial proliferative glomerulonephritis at 16%, among others. Clinically, patients with TMA predominantly presented with renal insufficiency, whereas those with MN mainly exhibited nephrotic syndrome. Patients with MN showed favorable responses to treatment, achieving complete and

partial response rates of 14.3% and 71.4%, respectively. Among the 50-patient cohort, 45 remained alive, corresponding to a 5-year overall survival rate of 87.8%. The 5-year renal survival rate was observed to be 78.8%, with 3 patients (6.98%) requiring kidney replacement therapy. **Conclusion:** TMA and MN are the two most common pathological findings in patients with CKD following HSCT. Both conditions exhibit favorable responses to combined steroids and immunosuppressant therapy. Notably, patients with MN demonstrate a higher overall response rate and superior treatment outcomes compared to those with TMA.

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Published by S. Karger AG, Basel

Introduction

Hematopoietic stem cell transplantation (HSCT) is an established therapeutic intervention for hematologic malignancies, and over the past 2 decades, it has significantly improved survival rates for patients with hematological disorders [1]. However, renal impairment is a prevalent complication associated with HSCT, encompassing both acute kidney injury (AKI) and chronic kidney disease (CKD). Previous studies indicate that the

incidence of AKI following autologous transplantation is approximately 10%, while in allogeneic transplantation, the rates of AKI range from 50% to 73%, and the incidence of CKD varies from 7% to 48% [2]. Despite kidney biopsy being the definitive diagnostic tool for kidney disease, it poses considerable risks to HSCT patients. Kidney disease following HSCT is associated with increased mortality and may arise from high-dose chemotherapy and/or radiation therapy administered during HSCT pretreatment, the use of calcineurin inhibitors (CNIs) during transplantation, nephrotoxic antibiotics, infections, and graft-versus-host disease (GVHD) [3]. Currently, there is limited research on the clinical pathology of CKD induced by HSCT [3, 4], and studies evaluating treatment outcomes in these patients are insufficient. Consequently, this study aimed to analyze the clinical and pathological manifestations, as well as treatment outcomes, of patients with CKD following HSCT.

Methods

Patients

This study is a single-center retrospective analysis conducted at the National Clinical Research Center of Kidney Diseases, Jinling Hospital. It includes patients who underwent HSCT between September 2008 and May 2024 and subsequently received kidney biopsies due to renal injury, with comprehensive clinical data available. Kidney biopsies were performed in patients exhibiting any of the following characteristics: proteinuria >1 g/day, significant renal impairment (defined as $>50\%$ increase in serum creatinine (SCr) from baseline level or $\text{eGFR} < 60$ mL/min/1.73 m^2 on two occasions), unexplained renal hypoplasia, multiorgan functional involvement, or lack of improvement after treatment. Proteinuria was assessed using 24-h timed collection, in accordance with standard practice at our center. Pathological assessments revealed kidney disease in 50 cases. The majority of these cases were attributed to TMA and MN, prompting a focused analysis of TMA and MN cases. This study protocol was reviewed and approved by Jinling Hospital Ethics Committee.

Clinical Data and Pathological Data

The clinical data encompassed patient demographics, such as gender, age, donor type, donor-recipient HLA typing, and stem cell source. Additionally, the occurrence of GVHD and the affected organs, incidence of hemorrhagic cystitis, timing of kidney biopsy,

presence of peripheral edema, and hematuria were recorded. Clinical manifestations of GVHD included damage to various organs. Skin manifestations included rash (with or without itching), congestion, hyperpigmentation, and skin hardening. Gastrointestinal symptoms included prolonged diarrhea and abdominal pain. Oral manifestations comprised mouth ulcers, dry mouth, oral mucositis, and pain. Liver abnormalities were characterized by elevated liver enzymes and abnormally high bilirubin levels. Eye manifestations included dry eyes, corneal ulcers. Pulmonary symptoms included an increased susceptibility to infections, particularly those caused by aspergillus and other fungi. Laboratory data consisted of quantitative measurements for urine protein, hemoglobin levels, serum albumin, SCr, total cholesterol, uric acid, urea nitrogen, immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin A (IgA), among others. Treatment and follow-up data encompassed details on therapeutic agents, duration of therapy, treatment efficacy, and patient outcomes. All patients underwent percutaneous kidney biopsy under ultrasound guidance. Kidney tissue samples were obtained and subjected to immunofluorescence staining for IgG, IgA, IgM, complement component 3 (C3), complement component 1q (C1q), κ light chain, and λ light chain, followed by examination using light microscopy and electron microscopy. In cases of membranous nephropathy, additional staining for phospholipase A2 receptor (PLA2R) was performed.

Definition

Patient follow-up commenced from the date of kidney biopsy and continued until May 31, 2024. In our study, AKI in HSCT was defined as an abrupt decline in kidney function due to damage causing structural or functional changes in the kidneys, manifested by: (1) an absolute increase in SCr of ≥ 0.3 mg/dL (26.4 $\mu\text{mol/L}$) over 48 h, (2) a $\geq 50\%$ increase in SCr within 7 days (1.5 times the baseline), or (3) an increase in urine output < 0.5 mL/kg/h for more than 6 consecutive hours. CKD was defined as an eGFR of < 90 mL/min per 1.73 m^2 at ≥ 2 measurements over a period of at least 3 months (KDIGO stage G2 or lower) and/or albuminuria (KDIGO stage A2). CKD was defined as structural or functional abnormalities of the kidneys for > 3 months. Acute graft-versus-host disease and chronic graft-versus-host disease were classified based on whether the condition developed before or after the 100th day post-transplantation. Study endpoints included adverse kidney outcomes: eGFR decline of $\geq 50\%$ or doubling of

SCr, progression to end-stage renal disease, and the need for kidney replacement therapy (hemodialysis, peritoneal dialysis, or kidney transplantation).

Evaluation of Efficacy

The efficacy of interventions for MN and other pathological types was classified into complete remission (CR), partial remission (PR), and no remission (NR) [5]. CR was defined as a 24-h urine protein quantification of ≤ 0.5 g/day with normal serum albumin (≥ 3.5 g/dL) and stable renal function (SCr levels of < 1.24 mg/dL); PR was defined as a decrease in proteinuria to < 2.5 g/day or a $\geq 50\%$ decrease from baseline and serum albumin ≥ 3 g/dL with stable renal function and SCr that was either within normal limits or had increased by no more than 25% from the baseline value. Failure to meet CR or PR criteria was classified as NR. The efficacy of interventions for TMA was also classified into CR, PR, and NR [6, 7]. CR was defined as normalization of hematologic values (a normal platelet count and lactate dehydrogenase level), normalization or improvement of kidney function (proteinuria < 0.5 g/day, normal albumin and SCr, no requirement for maintenance dialysis, and no new initiation of dialysis). PR was defined as normalization of hematologic values with any of the following kidney function criteria: a $> 50\%$ decrease in proteinuria from baseline to < 3.0 g/day with albumin > 30 g/L and stable SCr (an increase of SCr $\leq 25\%$ baseline value) with no requirement for maintenance dialysis and no new initiation of dialysis, a decrease of SCr $> 50\%$ for patients with a baseline SCr > 219.2 $\mu\text{mol/L}$, decrease of SCr to below 109.6 $\mu\text{mol/L}$ for patients with a baseline SCr ranging from 109.6 $\mu\text{mol/L}$ to 219.2 $\mu\text{mol/L}$. Failure to meet CR or PR criteria was classified as NR. The optimal time to remission was defined as the period during which the lowest 24-h urine protein level, and the lowest SCr level were recorded throughout the follow-up period. Relapse was defined as an increase in urinary protein-to-creatinine ratio to > 3.5 g/day after remission, an increase of at least twofold after remission, surpassing the urine protein value at diagnosis, or an increase of at least twofold SCr levels after remission on two occasions.

Statistical Analysis

Data processing was conducted using SPSS version 25.0 statistical software. For continuous measurement data, a normality test was performed. Data conforming to a normal distribution were expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$). Variables that did not

conform to a normal distribution were described using the median and interquartile range (M [Q1, Q3]). Categorical data were expressed as frequencies and percentages.

Results

Patient Characteristics

The study included a total of 50 patients, consisting of 39 males (78%) and 11 females (22%), with a median age of 46 years (31.25, 50.75). The median interval from HSCT to kidney biopsy was 18.5 months (12.34, 24.63). Within the cohort, 12 patients (24%) developed nephrotic syndrome (NS), while 30 patients (60%) exhibited proteinuria and 14 patients (28%) exhibited hematuria of a non-nephrotic nature. Additionally, 35 patients (70%) were diagnosed with CKD. At the time of HSCT, a greater proportion of patients with TMA had haploidentical donors and HLA haploidentical matches compared to those with MN. Conversely, the MN group demonstrated a higher prevalence of liver cGVHD (Table 1). Clinical manifestations of GVHD were accompanied by other organ damage during renal biopsy. 8 patients (16%) had oral involvement, 12 patients (24%) had gastrointestinal symptoms, 15 patients (30%) had skin lesions, 11 patients (22%) showed abnormal liver function, 4 patients (8%) had eye involvement, and 16 patients (32%) had lung infections.

In the context of baseline kidney biopsy characteristics, patients with MN demonstrated significantly greater peripheral edema and elevated levels of hemoglobin, 24-h urine protein, white blood cells, total cholesterol, and IgM compared to those with TMA (Table 2). Conversely, MN patients exhibited significantly lower levels of albumin, creatinine, uric acid, and urea nitrogen.

Pathological Features

Among the cases studied, 20 (40%) predominantly exhibited features consistent with TMA, 14 cases (28%) were characteristic of MN, 8 cases (16%) presented with mesangial proliferative glomerulonephritis, and 3 cases (6%) displayed acute interstitial nephritis (AIN), and 2 cases (4%) were diagnosed with BK virus-associated nephropathy. Additionally, there was 1 case (2%) each of chronic interstitial nephritis, IgA nephropathy, and hypertensive nephropathy. In 14 patients with MN, there was a predominant deposition of subepithelial immune complexes and the formation of "spikes" on the epithelial side, accompanied by extensive fusion of foot processes

Table 1. Baseline characteristics of patients at HSCT

Characteristics	All patients (N = 50)	TMA (N = 20)	MN (N = 14)
Age at HSCT, median (IQR), years	43 (29.25–48.25)	43.5 (35.25–47.75)	46 (34.75–50.25)
Gender, <i>n</i> (%)			
Males	39 (78)	15 (75)	10 (71.4)
Females	11 (22)	5 (25)	4 (28.6)
Underlying hematological disorders, <i>n</i> (%)			
ALL	13 (26)	3 (15)	3 (21.4)
AML	13 (26)	3 (15)	7 (50)
Lymphoma	3 (6)	2 (10)	0 (0)
MDS	6 (12)	3 (15)	1 (7.1)
CML	3 (6)	1 (5)	2 (14.3)
AA	11 (22)	7 (35)	1 (7.1)
Mixed phenotype leukemia	1 (2)	1 (5)	0 (0)
Type of donor*, <i>n</i> (%)			
Autologous donor	2 (5.13)	2 (12.5)	0 (0)
Matched sibling donor	20 (51.23)	6 (37.5)	9 (75)
Matched unrelated donor	5 (1.82)	1 (6.3)	3 (25)
Haploidentical donor	12 (30.77)	7 (43.8)	0 (0)
Donor-recipient HLA match*, <i>n</i> (%)			
Perfect congruence	24 (64.86)	8 (53.3)	11 (100)
Half-matched	13 (35.14)	7 (46.7)	0 (0)
Stem cell source*, <i>n</i> (%)			
Bone marrow transplant	7 (33.33)	1 (20)	4 (40)
Peripheral blood stem cell transplant	12 (57.14)	3 (60)	6 (60)
Both	2 (9.52)	1 (20)	0 (0)
GVHD prophylaxis*, <i>n</i> (%)			
CNI	17 (43.59)	7 (46.7)	4 (33.3)
CNI + steroids	17 (43.59)	6 (40)	7 (58.3)
CNI + ATG + steroids	2 (5.13)	0 (0)	1 (8.3)
Other prophylaxis	3 (7.69)	2 (13.3)	0 (0)
Conditioning regimen*, <i>n</i> (%)			
MeCCNU + cytarabine + busulfan + cyclophosphamide	6 (33.33)	2 (40)	1 (11.1)
Busulfan + cyclophosphamide	7 (38.89)	1 (20)	6 (66.7)
MeCCNU + cytarabine + busulfan + cyclophosphamide + ATG	1 (5.56)	0 (0)	1 (11.1)
Cyclophosphamide + TBI	2 (11.1)	0 (0)	1 (11.1)
Carmustine + etoposide + cytarabine + cyclophosphamide	1 (5.56)	1 (20)	0 (0)
Fludarabine + cyclophosphamide + ATG	1 (5.56)	1 (20)	0 (0)
Incidence of acute GVHD, <i>n</i> (%)			
Skin	9 (18)	2 (10)	5 (35.7)
Gastrointestinal tract	12 (24)	3 (15)	4 (28.6)
Liver	4 (8)	0 (0)	3 (21.4)
Incidence of chronic GVHD, <i>n</i> (%)			
Oral cavity	8 (16)	2 (10)	4 (28.6)
Liver	7 (14)	0 (0)	5 (35.7)
Skin	6 (12)	3 (15)	0 (0)
Eye	4 (8)	2 (10)	0 (0)
Hemorrhagic cystitis	6 (12)	2 (10)	0 (0)

TMA, thrombotic microangiopathy; MN, membranous nephropathy; IQR, interquartile range; HSCT, hematopoietic stem cell transplantation; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; CML, chronic myelogenous leukemia; AA, aplastic anemia; HLA, human leukocyte antigen; CNI, calcineurin inhibitor; ATG, anti-thymocyte globulin; TBI, total body irradiation; GVHD, graft-versus-host disease. *The overall number of people is not 50, based on the known number of people and that some patients' data were not measured or were missing.

Table 2. Baseline characteristics of patients at kidney biopsy

Characteristics	All patients (N = 50)	TMA (N = 20)	MN (N = 14)
Age at kidney biopsy, median (IQR), years	46 (31.25–50.75)	47 (36–51)	48 (38–51)
Time to kidney biopsy from HSCT, median (IQR), months	18.5 (12–34.63)	18.5 (12.5–31.5)	15 (14–40)
Peripheral edema, n (%)	16 (32)	3 (15)	8 (57.1)
Hematuria, n (%)			
Visible hematuria	4 (8)	0 (0)	2 (14.3)
Non-visible hematuria	9 (18)	3 (15)	3 (21.4)
Hemoglobin, mean±SD, g/dL	107.82±23.74	102.5±16.3	120.6±18.1
Serum creatinine, median (IQR), mg/dL	1.54 (1.13–1.97)	1.61 (1.37–2.00)	0.75 (0.63–0.92)
eGFR*, median (IQR), mL/min/1.73 m ²	55 (38–69)	47 (38–59)	95 (76–129)
eGFR categories at biopsy*, n (%)			
≥90 mL/min/1.73 m ²	6 (15.4)	0 (0)	4 (50)
60–89 mL/min/1.73 m ²	8 (20.5)	3 (15.8)	3 (37.5)
30–59 mL/min/1.73 m ²	23 (59)	15 (78.9)	1 (12.5)
15–29 mL/min/1.73 m ²	1 (2.6)	1 (5.3)	0 (0)
<15 mL/min/1.73 m ²	1 (2.6)	0 (0)	0 (0)
24-h urine protein, median (IQR), g/day	1.2 (0.73–2.93)	0.99 (0.58–1.44)	4.755 (2.84–13.07)
Serum albumin, median (IQR), g/L	38.3 (29.7–41.9)	40.9 (38.1–42.2)	25.3 (22.1–30.0)
White blood cell, median (IQR), ×10 ⁹ /L	5.58 (4.67–7.6)	5 (4.15–6.75)	8.1 (5.27–8.80)
Urea nitrogen, median (IQR), mg/dL	22.47 (16.87–29.5)	23.33 (19.87–32.70)	15.12 (12.00–25.05)
Uric acid, mean±SD, μmol/L	268.97±95.67	399.87±116.60	336.21±98.51
Total protein, median (IQR), g/L	58.8 (52.1–62.4)	60.4 (57.9–63.3)	39.3 (35.7–57.3)
Total cholesterol, median (IQR), mmol/L	4.9 (4.16–8.37)	4.52 (3.87–4.90)	8.175 (5.11–10.00)
IgG, mean±SD, g/L	8.70±4.17	9.37±3.62	7.34±4.75
IgA, median (IQR), g/L	0.71 (0.52–1.37)	0.7 (0.47–1.29)	0.713 (0.60–1.28)
IgM, median (IQR), g/L	0.80 (0.51–1.23)	0.61 (0.39–0.84)	1.03 (0.58–1.77)

TMA, thrombotic microangiopathy; MN, membranous nephropathy; IQR, interquartile range; HSCT, hematopoietic stem cell transplantation; eGFR, estimated glomerular filtration rate; SD, standard deviation; IgG, immunoglobulin G; IgM, immunoglobulin M; IgA, immunoglobulin A. *The overall number of people is not 50, based on the known number of people and that some patients' data were not measured or were missing.

(Fig. 1a, b, c). Among these patients, 6 underwent PLA2R staining of kidney tissue, all of which yielded negative results. In 20 cases of TMA, there was focal or diffuse mesangial dissolution and widening of the mesangial area in the glomeruli, along with segmental fusion of foot processes (Fig. 1d, e, f).

Treatment Regimen

Regarding treatment regimens, the remission rates for the three groups were 62.5%, 63.6%, and 75% (Table 3), respectively. Patients receiving a combination of steroids and immunosuppressants exhibited the highest remission rate, whereas those treated solely with steroids demonstrated the lowest organ remission rate.

Among the cohort, 8 patients were treated exclusively with steroids, primarily prednisone or methylprednisolone, supplemented by supportive therapies such as angiotensin receptor blockers. Eleven patients received immunosuppressants alone, the majority of whom were treated with tripterygium glycosides, with a few receiving agents such as mycophenolate mofetil or tacrolimus.

The remaining 20 patients were managed with a combination regimen of steroids and immunosuppressants. Commonly used combinations included steroids with tripterygium glycosides, mycophenolate mofetil, tacrolimus, or cyclosporine. All treatment decisions were made based on the patient's condition, with steroid doses generally ranging from 10 to 50 mg/day.

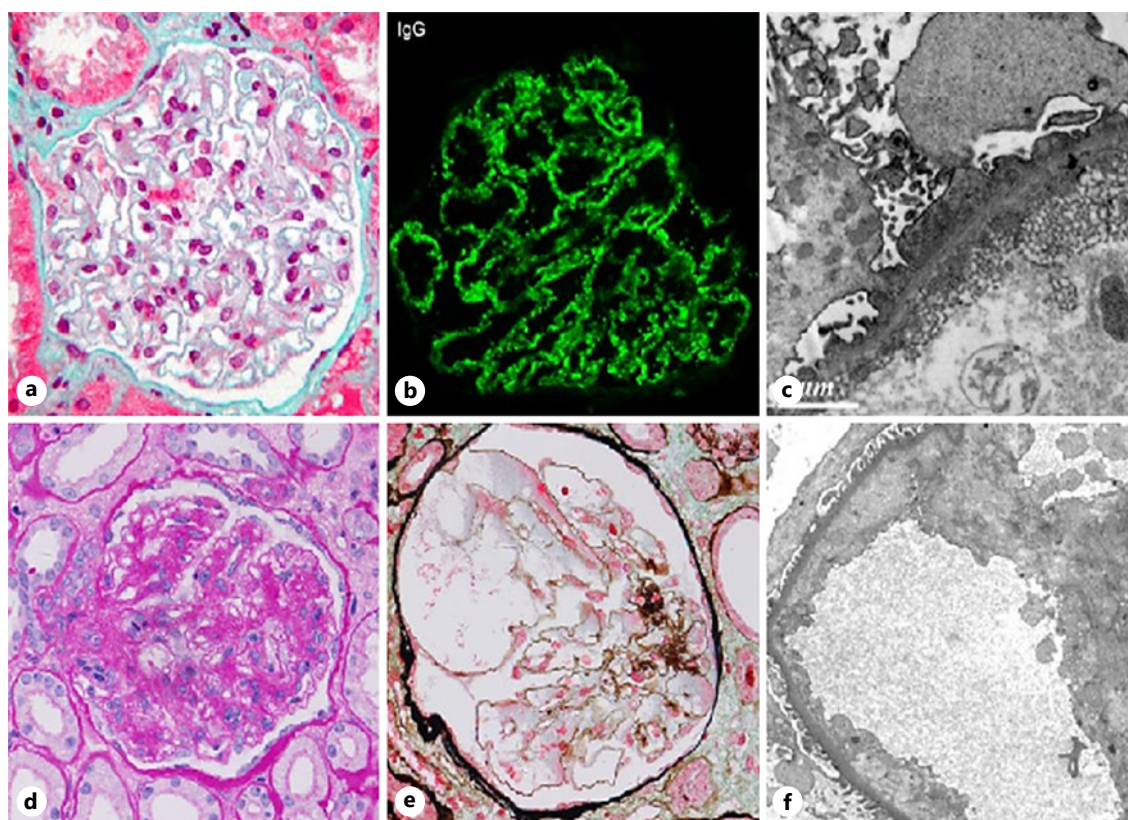


Fig. 1. HSCT-associated MN and TMA. **a** Mesangial area widening with deposition of immune complexes on the epithelial side (PASM-Masson. $\times 400$). **b** IgG3+ granular deposits in the capillary loops (IF. $\times 400$). **c** Electron-dense deposits on the epithelial side of the glomerulus with widespread fusion of foot processes (EM). **d** Severe mesangial area widening with GBM stratification (HE. $\times 400$). **e** Diffuse mesangial dissolution, marked expansion of the peripheral loops, and red blood cell aggregation in the dilated loops (PASM. $\times 400$). **f** Widened subendothelial areas, mesangial matrix insertion, and segmental fusion of foot processes (EM).

Table 3. Organ response of patients

Organ response	Pathological type				Treatment regimens			
	all patients (N = 41)	TMA (N = 17)	MN (N = 14)	other pathological types (N = 10)	all patients (N = 39)	cortisol (N = 8)	immunosuppressant (N = 11)	combined use (N = 20)
ORR, % (n)	68.2% (28/41)	52.9% (9/17)	85.7% (12/14)	70% (7/10)	69.2% (27/39)	62.5% (5/8)	63.6% (7/11)	75% (15/20)
CR, % (n)	26.8% (11/41)	29.4% (5/17)	14.3% (2/14)	40% (4/10)	25.6% (10/39)	25% (2/8)	36.4% (4/11)	20% (4/20)
PR, % (n)	41.4% (17/41)	23.5% (4/17)	71.4% (10/14)	30% (3/10)	43.6% (17/39)	37.5% (3/8)	27.3% (3/11)	55% (11/20)
NR, % (n)	31.7% (13/41)	47.1% (8/17)	14.3% (2/14)	30% (3/10)	30.8% (12/39)	37.5% (3/8)	36.4% (4/11)	25% (5/20)

TMA, thrombotic microangiopathy; MN, membranous nephropathy; ORR, objective response rate; CR, complete remission; PR, partial remission; NR, no remission.

Treatment Outcomes

Based on the pathological classification, out of 41 patients, 28 (68.2%) achieved remission, with 11 (26.8%) attaining complete remission and 17 (41.4%) achieving PR. In comparison to patients with MN, those with TMA exhibited a lower overall remission rate but a higher rate of complete remission. Conversely, MN patients demonstrated a higher rate of PR (Table 3).

A total of 29 patients were evaluated for disease progression and optimal remission outcomes. One patient persistently failed to achieve remission and ultimately requiring dialysis. The median duration to achieve optimal remission was 5 months (2.5–20). Fourteen cases exhibited sustained renal remission, with a median duration to sustained remission of 24 months (6.75–53.25). Following the initial remission of proteinuria, clinicians gradually tapered the steroid doses, maintaining patients on 5 mg/day of steroids in conjunction with a low dose of immunosuppressants after 6 months.

Fifteen patients experienced a relapse after reaching optimal remission, with the median time to relapse of 6 months (3–18). Among the 6 patients who did not experience relapse and were treated exclusively with immunosuppressive agents, only 1 patient discontinued treatment, while the remaining patients were maintained on low-dose maintenance therapy. Of the 7 patients who did not relapse and were treated solely with steroids, only 2 eventually discontinued steroid use. Among the patients who relapsed, 2 progressed to dialysis, 2 succumbed to their condition, and the remainder exhibited stable disease. For eligible patients, clinicians recommended monoclonal antibody therapy. During the follow-up, 1 patient was treated with rituximab.

The median follow-up duration was 53 months (32.5–65.5). As of the study endpoint, the median time to kidney survival and overall survival had not been reached. During our follow-up, relapse of the primary disease occurred in 2 patients, while 48 patients remained relapse-free. 5 patients (10%) succumbed to causes unrelated to kidney injury. It has been established that the deaths of 5 patients were confirmed to be unrelated to renal causes. The precise cause of death remains unidentified in 2 cases; 1 patient succumbed to hypertension, 1 patient succumbed to COVID-19 pneumonia, and 1 patient succumbed to hepatic complications. The overall survival rate was 100% at 1 year and 87.8% at 5 years. Three patients (6%) required dialysis, with a 1-year kidney survival rate of 87.5% and a 5-year survival rate of 78.8%.

Discussion

The pathogenesis of kidney disease following HSCT remains both unclear and multifactorial. Contributing factors to AKI encompass chemotherapy-induced toxicity, BK virus infection, antibiotic use, various medications, tumor lysis syndrome, high-dose conditioning regimens, hepatic sinusoidal obstruction syndrome, total body irradiation, and calcium-phosphorus enzyme inhibitors [8]. In contrast, post-transplant risk factors for CKD are typically associated with prior episodes of AKI, advanced age, hypertension, transplantation from an unrelated donor, CNI use, total body irradiation, and cGVHD [9, 10]. Among these, cGVHD is the most prevalent risk factor. Previous research has indicated that the mechanism underlying the occurrence of TMA is likely associated with endothelial cell injury and complement activation, potentially manifesting as GVHD. In normal endothelium, podocytes produce vascular endothelial growth factor, which binds to receptors on endothelial cells to maintain the integrity of the microvasculature. In TMA, endothelial injury and activation occur, leading to the expression of tissue factor on the cell surface. Tissue factor binds to factor VIIa and von Willebrand factor, promoting thrombus formation with activated platelets. Additionally, activated complement generates the membrane attack complex, which induces cell lysis [11]. A three-hit hypothesis has been proposed and widely accepted [12]. Post-HSCT GVHD, the use of CNIs, radiotherapy, and chemotherapy has been implicated in causing endothelial cell damage. In the context of non-GVHD, endothelial injury may arise from circulating inflammatory cytokines secondary to systemic inflammation, activation of the coagulation pathway, and decreased levels of vascular endothelial growth factor. Conversely, in cGVHD, endothelial cells are considered direct targets of cytotoxic donor T lymphocytes [13, 14]. Beyar-Katz et al. [15] demonstrated that the development of NS is associated with both acute and chronic GVHD, which is considered the glomerular manifestation of cGVHD and may be linked to direct mesangial injury and substantial immune complex deposition. Bruijn et al. [16] found that the infusion of allogeneic lymphocytes into mice resulted in the formation of anti-glomerular basement membrane antibodies, which caused clinical NS with renal histology similar to MN. Although formal criteria for defining renal GVHD have not yet been established, accumulating evidence suggests an association between GVHD and renal injury following HSCT.

Our study highlights that TMA and MN were the most prevalent pathological findings among patients undergoing kidney biopsy following HSCT, consistent with the findings of Yap et al. [4]. In addition to TMA and MN, prior research has identified various forms of glomerular pathology, including minimal change disease, focal segmental glomerulosclerosis, MsPGN, membranoproliferative glomerulonephritis, and IgA nephropathy [4, 15, 17, 18]. Consequently, the range of kidney injuries following HSCT is extensive, presenting significant challenges for accurate diagnosis and effective management. Kidney biopsy remains the gold standard for diagnosing kidney injuries post-HSCT, particularly for cases involving unexplained AKI, new-onset CKD, or significant proteinuria.

It is noteworthy that our findings indicate that TMA patients demonstrated more severe clinical manifestations. Furthermore, our study revealed that patients with HSCT-associated MN exhibited clinical manifestations akin to those observed in patients with idiopathic MN. Six patients underwent PLA2R staining of kidney tissue, all of which yielded negative results. At the same time, these patients tested negative for serum PLA2R antibody, and the rest of the patients also showed no antibodies present in the serum, thereby confirming that the antigens targeted in HSCT-associated MN differ from those in idiopathic MN. Protocadherin FAT1 (FAT1) has emerged as a novel protein, potentially serving as a specific antibody target for allogeneic HSCT-associated MN [19]. Nevertheless, our study was unable to fully determine the antibody target due to technical limitations. Notably, 25% of patients with HSCT-associated TMA exhibited normal SCr and hemoglobin levels, with the highest recorded SCr level being only 2.29 mg/dL. Furthermore, none of the patients exhibited overt neurological symptoms, which could lead to an oversight in diagnosing atypical HSCT-associated TMA based solely on clinical manifestations. This observation aligns with the findings of Changsirikulchai et al. [13], emphasizing the crucial role of kidney biopsy in patients with renal disease following HSCT. However, Troxell ML et al. [20] reported that the kidney biopsy rate among patients with renal disease following HSCT ranges from 0.5% to 4.3%, potentially leading to delays in diagnosis and treatment. There remains a critical need for the early identification of diagnostic and prognostic markers for this condition, such as Ba protein, soluble urokinase plasminogen activator receptor, and growth differentiation factor-15 [21–23]. Complement component 4d (C4d)-positive renal arterioles serve as a reliable

marker of complement system activation and a valuable diagnostic tool for TA-TMA [24]. It has been demonstrated that diffuse (>50% of the tissue specimen) or focal (10%–50%) arteriolar C4d staining is more prevalent in TA-TMA specimens [25]. We acknowledge that the absence of C4d staining in our study may have impacted the depth of our pathological analysis, particularly in distinguishing specific features of TA-TMA. Arteriolar C4d deposition could serve as a pathological indicator of TA-TMA, suggesting localized complement activation in HSCT recipients who develop kidney disease due to small vessel damage. Further research aimed at better understanding the mechanisms behind the preferential arteriolar C4d staining may help pinpoint a specific renal compartment affected by injury, potentially shedding light on the severe hypertension observed in TA-TMA cases.

Currently, there is no standardized treatment protocol for CKD following HSCT, and reports on available treatment options are limited. Moreover, the heterogeneity of patient populations contributes to substantial variability in treatment regimens. Our findings suggest that corticosteroids and immunosuppressive agents are effective in achieving remission in most cases. For cases where kidney biopsy reveals MCD, corticosteroid therapy is initiated. However, MCD occurring post-HSCT may exhibit greater resistance compared to non-HSCT patients, necessitating the use of additional immunomodulatory agents, such as CNIs [15]. MN following HSCT demonstrates a lower response rate to corticosteroids alone, necessitating combination therapy with additional agents. Wang et al. [26] reported a case of post-transplant NS that exhibited a poor response to treatment with a combination of three immunosuppressants, suggesting more severe activity of cGVHD. Intravenous immunoglobulin has demonstrated immunomodulatory effects and efficacy in the treatment of refractory GVHD-related NS [26]. Several therapeutic strategies have been proposed for the management of TA-TMA following HSCT. These strategies include the reduction or discontinuation of CNIs, the administration of corticosteroids, therapeutic plasma exchange, rituximab, defibrotide, vincristine, pravastatin, and eculizumab [27–32]. Due to medical constraints, monoclonal antibody therapies and other advanced interventions were not administered to our patients.

In our study, for patients presenting with hypertension and proteinuria, in addition to the administration of immunosuppressive agents, we also explored the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the management of CKD

following HSCT. Notably, patients with MN have shown favorable responses to these interventions. The literature indicates that most cases of NS following HSCT exhibit a slow disease progression, a favorable response to immunosuppressive treatment, and a low incidence of relapse. Given the efficacy of steroids and calcineurin phosphatase inhibitors in treating GVHD, the prognosis for NS post-HSCT is generally positive when aggressive immunosuppressive therapy is employed. Beyar-Katz [15] also reported a favorable overall prognosis for NS, with a remission rate of 63.5% and a high likelihood of preserved renal function. George et al. [33] documented a cohort of patients who exhibited characteristic clinical manifestations of TMA, with a mortality rate of 75% within 3 months of post-diagnosis. In contrast, our study demonstrated a remission rate of 52.9% among patients who received treatment, underscoring the significant discrepancies between pathological and clinical diagnoses of TMA as assessed by hematologists based on historical presentations. While the majority of patients received a regimen combining multiple immunosuppressive drugs, monotherapy with steroids proved adequate in certain instances.

Overall, these therapeutic approaches yielded positive outcomes, characterized by high rates of renal and overall survival in our study. It has been established that the deaths of 5 patients were unrelated to renal causes. This finding underscores the necessity of recognizing adverse effects on other organs resulting from HSCT. Previous studies, though limited, have indicated that TA-TMA is associated with a lower overall survival rate and a higher non-relapse mortality rate compared to patients without TA-TMA [34, 35]. However, these studies also reported a 2-year renal survival rate of 95.7% and a 5-year survival rate of 87.5% [2]. The existing literature on survival outcomes in CKD following HSCT is limited. Our study contributes to this body of knowledge by affirming that the long-term prognosis of CKD post-HSCT is moderate.

However, this study has certain limitations. Being retrospective in nature, it suffers from significant data loss, and comprehensive follow-up data regarding renal survival and overall survival have not been obtained. Therefore, an extended follow-up period for the cohort is warranted. The limited sample size precluded our ability to distinguish between CKD resulting from autologous versus allogeneic stem cell transplantation, as well as AKI associated with HSCT. Future research should involve larger sample size through multicenter collaboration to facilitate more comprehensive analyses. Additionally, the therapeutic interventions were restricted to steroids and

immunosuppressive agents, without the incorporation of novel treatment modalities.

In conclusion, we present a case series comprising 50 patients with CKD following HSCT and analyze their clinical and pathological manifestations, as well as the treatment strategies employed. MN and TMA represent the two predominant pathological classifications. Furthermore, our findings indicate that patients with CKD exhibit a favorable response to a therapeutic regimen combining corticosteroids and immunosuppressive agents. This treatment approach is generally associated with a positive prognosis and a high survival rate.

Statement of Ethics

This study protocol was reviewed and approved by Jinling Hospital Ethics Committees, Approval No. 2019NZKYKS00601. Prior to the participation in the study, all patients provided written informed consent.

Conflict of Interest Statement

Xianghua Huang was a member of the journal's Editorial Board at the time of submission.

Funding Sources

This research was supported by the National Natural Science Foundation of China (82270767) and the Key Research and Development Plan Project of Jiangsu Province – Social Development Projects (BE2023797).

Author Contributions

All authors contributed to each of the following aspects of the study: Yu Zhang and Xianghua Huang designed the study and wrote manuscript. Guisheng Ren and Wencui Chen collected the data. Jinzhou Guo and Xiaomei Wu were responsible for data analysis and statistical analysis. Weiwei Xu and Xianghua Huang managed patients and revised the manuscript critically. All authors reviewed and approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author, please contact hxhszb@163.com.

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