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ARTICLE

Clinical Characteristics and Prognostic Factors of Nephrotic Syndrome after Allogeneic Hematopoietic Stem Cell Transplantation

Yan Tu[1], Mengni Yan[2], Mingming Zhang[3], Yi Luo[3], Jimin Shi[3], Yanmin Zhao[3], Rending Wang[4], Huiping Wang[5], Huarui Fu[3,*], Yamin Tan[6,*]

[1]Department of Hematology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, Zhejiang, China
[2]Department of Hematology, The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People's Hospital, Quzhou, Zhejiang, China
[3]Department of Hematology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China
[4]Department of Nephrology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China
[5]Department of Pathology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China
[6]Department of Hematology, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Hangzhou, Zhejiang, China
*Correspondence: fhr1984@163.com (Huarui Fu); tan_yamin@163.com (Yamin Tan)

Abstract

Aims/Background Although the incidence of nephrotic syndrome (NS) following allogeneic hematopoietic stem cell transplantation (allo-HSCT) is relatively low, it can significantly affect patients' quality of life and may even be life-threatening. Therefore, it is essential to investigate the clinical manifestations and prognosis of patients with NS after allo-HSCT, as well as to identify potential high-risk factors associated with this condition.

Methods We investigated the incidence rate of NS in 1457 patients who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) at the First Affiliated Hospital, Zhejiang University School of Medicine between June 2007 and March 2020. Among these, we identified 12 patients who developed NS after allo-HSCT (NS group). For comparison, we selected a control group of 48 patients matched by gender and transplantation time who did not develop NS. Univariate and multivariate logistic regression analyses were performed using SPSS software, version 25.0 (IBM Corp., Armonk, NY, USA) to identify independent risk factors for NS.

Results Among the 1457 patients, 12 (0.82%) developed post-transplantation NS, with a median onset time of 14.99 months (range: 5.39–48.43 months) after transplantation. Univariate analysis indicated that the occurrence of post-transplantation NS was significantly correlated with total cholesterol (TC) levels at 6 months post-transplantation (p = 0.041), triglycerides (TG) and TC levels at 1 year post-transplantation (p = 0.004 and p = 0.011, respectively), and cytomegalovirus (CMV) infection (p = 0.002). Multivariate analysis revealed that CMV infection (p = 0.004, odds ratio = 15.871; 95% confidence interval: 2.465–102.194) was independently associated with the development of NS.

Conclusion After allo-HSCT, NS may manifest as a form of chronic graft-versus-host disease. CMV infection is a risk factor for developing NS. Effective management through the administration of calcium inhibitors and corticosteroids can enable long-term survival in these patients.

Key words: allogeneic; hematopoietic stem cell transplantation; graft-versus-host disease; nephrotic syndrome

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Introduction

Hematopoietic stem cell transplantation (HSCT) is the only curative treatment for hematologic malignancies; however, chronic graft-versus-host disease (cGVHD) is a major complication that can significantly impair both quality of life and lifespan. cGVHD is induced when the donor's allogeneic T cells attack the recipient's target organs, making it one of the most common late complications following allogeneic hematopoietic stem cell transplantation (allo-HSCT), occurring in 40–80% of patients. Its clinical presentations are diverse, primarily affecting the skin, oral cavity, liver, gastrointestinal tract, joints, and fascia. However, renal involvement secondary to cGVHD is relatively uncommon, typically arising more than 100 days after transplantation and manifesting as acute renal failure, chronic kidney disease, nephrotic syndrome (NS), or proteinuria (Roy et al, 2023). The primary pathological subtypes are membranous nephropathy (MN) and minimal change disease (MCD), with MN accounting for approximately two-thirds of cases (Stylianou et al, 2010; Terrier et al, 2007) and MCD for roughly one-quarter (Silva et al, 2007). Nephrotic syndrome (NS) can significantly reduce patients' quality of life and may even be life-threatening (Hölttä and Jalanko, 2020).

Currently, it is hypothesized that the emergence of NS following allo-HSCT may be related to cGVHD, the reduction or discontinuation of immunosuppressive agents, and cytomegalovirus (CMV) infections (Brukamp et al, 2006). However, the precise causative mechanisms and underlying pathophysiology of NS development in this context remain largely unclear, with significant variations in clinical manifestations and prognoses among different patients. Furthermore, there is a lack of systematic research data and analysis. Therefore, identifying the clinical characteristics and risk factors of post-transplantation NS is crucial for preventing and treating this complication. This project aims to retrospectively analyze the clinical data of patients who developed NS after allo-HSCT to elucidate their clinical features and risk factors, thereby providing valuable reference data for clinicians to develop more effective prevention and treatment strategies. Additionally, this investigation will offer foundational data for further in-depth research, aiding in the understanding of the pathological mechanisms and treatment approaches for post-transplantation NS.

Methods

Study Subjects

From June 2007 to March 2020, 1457 patients who survived over 100 days after undergoing allo-HSCT at the Bone Marrow Transplantation Center of the First Affiliated Hospital, Zhejiang University School of Medicine were included in this retrospective study. We collected basic patient information and laboratory test results (including blood and urine tests) and divided the patients into two groups based on the occurrence of NS after surgery. Given the limited number of NS cases, we included 48 patients in the control group, resulting in 12 patients in the NS group (N = 12) and 48 patients without NS in the control group (N = 48).

The inclusion criteria for the study were: (1) Patients diagnosed with acute or cGVHD who were treated with allo-HSCT; (2) Patients whose primary disease was in remission before undergoing allo-HSCT; (3) Patients who survived more than 100 days after transplantation; (4) Patients who met the diagnostic criteria for NS; and (5) The control group was individually matched to the NS group at a ratio of 1:4, with matching criteria including identical sex, an age difference of no more than 5 years, and a transplantation date within 6 months; (6) Follow-up was complete for the full five years.

The exclusion criteria were: (1) Patients who had abnormal urine tests or impaired liver or kidney function before transplantation; (2) Patients with autoimmune diseases, diabetes, or other underlying conditions; (3) Patients with severe mental or cognitive impairments that prevented them from understanding or complying with the study requirements; and (4) Pregnant or lactating women.

All procedures in this study adhered to the ethical principles outlined in the Declaration of Helsinki. Since all patient data involved in the study were anonymized and did not include any private patient information, informed consent was waived. The waiver of informed consent and the ethical approval (Approval No.: 0598, 2024) were granted by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine.

Transplantation Method and Pretreatment Protocol

In 60 cases, different conditioning regimens were applied based on factors such as disease type, disease status, organ function levels, and donor-recipient relationships. Among these, 55 patients received a myeloablative conditioning (MAC) regimen that included busulfan (Bu) and cyclophosphamide (Cy) with or without antithymocyte globulin (ATG), methotrexate (MTX), and cytarabine as the core components. The remaining 5 patients received a reduced-intensity conditioning (RIC) regimen based on fludarabine ± Bu, ATG, and Velcade.

GVHD Prevention and Diagnostic Criteria

The GVHD prophylactic strategy consisted of mycophenolate mofetil combined with cyclosporine A (CsA) and a short course of MTX. Acute and cGVHD were diagnosed according to the Seattle criteria (Huang and Wu, 2020).

CMV Virus Monitoring and Prevention

Fluorescence quantitative polymerase chain reaction (FQ-PCR) was employed to measure *CMV* DNA levels in peripheral blood, with a threshold of $\geq 5 \times 10^2$ copies/mL defining as CMV antigenemia. As preventive measures against viral infections following stem cell infusion, oral acyclovir and intravenous immunoglobulin were administered. FQ-PCR testing was conducted weekly during the first 3 months to closely monitor *CMV* DNA levels. Once test results were negative, the frequency of FQ-PCR monitoring was adjusted to every 2–4 weeks until there was a reduction or discontinuation of immunosuppressant agents. For patients with CMV infection, antiviral treatment with ganciclovir or foscarnet was administered.

Diagnosis and Efficacy Criteria for NS after allo-HSCT

(1) Diagnostic criteria:

a. Clinical presentation: Massive proteinuria, hypoproteinemia, hyperlipidemia, and edema.

b. Laboratory tests: A 24-hour urine protein level of ≥3.5 g and a serum albumin concentration of ≤30 g/L.

c. Renal pathology: Diagnosis confirmed by glomerular nephritis (Brukamp et al, 2006).

(2) Treatment principle: Corticosteroids combined with cyclosporine or tacrolimus. If there is no significant improvement in 24-hour urine protein levels after 2 weeks, the dose of cyclosporine or tacrolimus should be increased to the baseline dose.

(3) Efficacy criteria:

• Complete remission (CR): Defined as a post-treatment 24-hour urine protein level of ≤0.3 g.

• Partial remission (PR): Defined as a reduction of 50% or more in the 24-hour urine protein output compared to the onset.

• No response (NR): No improvement or worsening in the 24-hour urine protein measurements before and after treatment.

Pathological Examination

Using the Logiq E9 ultrasound (General Electric Healthcare, Chicago, IL, USA) guided percutaneous renal biopsy technique, kidney tissue samples were obtained. The biopsy samples were immediately fixed in 10% neutral buffered formalin (Sigma-Aldrich, St. Louis, MO, USA), followed by routine paraffin embedding and sectioning. The tissues were sectioned into 4-μm slices and stained using the Periodic Acid-Schiff (PAS) staining kit (C0142S, Beyotime, Shanghai, China). Pathological changes in glomeruli, tubules, interstitium, and vessels were observed under a Leica DM2500 light microscope (Leica Microsystems, Wetzlar, Germany).

For immunofluorescence staining, the treated sections were incubated overnight at 4 °C with anti-Immunoglobulin G (IgG) antibody (ab218427, 1:800, Abcam, Cambridge, UK). The sections were then washed three times with Phosphate-Buffered Saline (PBS, Lot NO. E607008, Sangon Biotech, Shanghai, China) and incubated with Goat Anti-Rabbit IgG H&L (Alexa Fluor® 488) (ab150077, 1:500, Abcam, Cambridge, UK) at 37 °C for 2 hours. After washing, the sections were stained with 4′,6-diamidino-2-phenylindole (DAPI, Lot D1306, Thermo Fisher Scientific, Waltham, MA, USA) solution for 3 minutes and mounted with anti-fade mounting medium (Beyotime, Shanghai, China). The deposition sites and types of immune complexes were observed under a Nikon Eclipse 80i fluorescence microscope (Nikon Corporation, Tokyo, Japan). The ultrastructure of glomeruli, including changes in the basement membrane, foot processes, and electron-dense deposits, was observed under a Hitachi H-7650 transmission electron microscope (Hitachi High-Tech Corporation, Tokyo, Japan).

Table 1. Clinical data of 12 patients with NS after allo-HSCT.

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Gender	Male	Female	Female	Male	Female	Female	Female	Female	Male	Female	Female	Male
Age (year)	40	20	15	32	39	34	29	21	51	18	39	45
Diagnosis	Anaplastic T lymphoma	AML	T lymphoblastic lymphoma	AML	ALL	AML	T lymphoblastic lymphoma	CML	MM	ALL	AML	ALL
Unrelated complete HLA match	Unrelated complete HLA match	Unrelated complete HLA match	Haploidentical	Unrelated complete HLA match	Haploidentical	Haploidentical	Haploidentical	Unrelated complete HLA match	Haploidentical	Unrelated complete HLA match	Haploidentical	Haploidentical
Preprocessing scheme	MAC	MAC	MAC	MAC	MAC	MAC	RIC	MAC	RIC	MAC	MAC	MAC
aGVHD	Skin	None	None	None	None	None	None	None	Skin	Skin	None	Skin
cGVHD	Skin oral cavity	Skin oral cavity	None	Skin liver	None	None	None	Skin oral cavity	Skin oral cavity	Skin liver	Skin oral cavity	None
CMV infection	Positive	Positive	Positive	Positive	Negative	Negative	Negative	Positive	Positive	Positive	Negative	Positive
Immunosuppressant reduction time (month)	7	12	5	6	6	6	7	6	6	6	12	6
HSCT to NS occurrence time (month)	20.22	34.29	5.39	12.62	15.95	48.43	15.98	14.04	23.70	10.32	13.55	8.38
Organ GVHD accompanied by NS	Yes	Yes	No	No	No	No	No	No	No	Yes	No	No
Immunosuppressants used when NS occurs	FK506+Prednisone	No	FK506+Prednisone	CsA+ Prednisone	No	No	No	No	No	FK506+Prednisone	CsA	No
Quantitative urine protein (g/24 h)	13.93	5.1	4.46	15.85	4.01	3.91	3.62	4.63	21.74	3.85	3.61	2.08

Table 1. Continued.

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Alb (g/L)	13.3	12.4	26	19.3	30.3	20.2	14	12.8	16.3	24	29.1	25.9
Creatine (umol/L)	75	33	55	75	54	56	78	62	80	64	52	75
GFR (mL/min)	92.6	150.09	132.84	92.6	114.7	113.15	87.54	106.45	73.8	98.3	114.43	104.57
Autoantibody	P-ANCA, ANA	ANA	Negative	ANA	ANA	Negative	Negative	ANA	ANA	Negative	Negative	ANA
Pathological type	MN	MN	MCD	MN	MN	MN	MN	MN	MN	Unpierced	Unpierced	FSGS
Pathological Antibody	IgG, IgM	IgG	IgM	IgG, IgM	IgG, IgM	IgG	IgG	IgG, IgM	IgG, IgM, IgA	/	/	IgM
Treatment	FK506+ Prednisone	CsA+ Prednisone	FK506+ Prednisone	CsA+ Prednisone	CsA+ Prednisone	FK506+ Prednisone	FK506+ Prednisone	CsA+ Prednisone	CsA+ Prednisone	FK506+ Prednisone	FK506+ Prednisone	CsA+ Prednisone
NS to efficacy evaluation time (month)	45.17	51.98	11.61	22.29	4.67	4.14	6.12	41.16	4.41	9.50	8.75	9.80
Efficacy evaluation	NR	CR	CR	CR	CR	CR	CR	CR	PR	CR	CR	CR
Outcome	Renal failure death	Death with recurrence and remission, esophageal cancer	Survive	Remission after recurrence survive	Remission after recurrence survive	Survive	Survive	Survive	Pulmonary infection to death	Survive	Survive	Survive

Abbreviations: NS, nephrotic syndrome; allo-HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukemia; ALL, Acute Lymphoblastic Leukemia; CML, Chronic myelogenous leukemia; MM, Multiple myeloma; HLA, Human leukocyte antigen; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; CMV, cytomegalovirus; HSCT, Hematopoietic stem cell transplantation; GVHD, graft-versus-host disease; FK506, tacrolimus; CsA, cyclosporine A; Alb, albumin; GFR, Glomerular Filtration Rate; P-ANCA, Perinuclear Anti-Neutrophil Cytoplasmic Antibodies; ANA, antinuclear antibodies; MN, membranous nephropathy; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; NR, No response; CR, Complete remission; PR, Partial remission; IgG, Immunoglobulin G; IgM, Immunoglobulin M; IgA, Immunoglobulin A.

Statistical Methods

All data were processed using IBM SPSS Statistics (version 25.0, IBM Corp, Armonk, NY, USA). Count data were expressed as n (%). Comparisons between groups were made using the chi-square test. When the expected value (T) $\geq$5, the Pearson chi-square test was used to evaluate differences between groups. For expected values where T $<$ 5, the likelihood ratio chi-square test was applied. Measurement data were assessed for normality using the Shapiro-Wilk test. Normally distributed data were presented as mean $\pm$ standard deviation and compared using an independent sample *t*-test. Non-normally distributed data were presented as median (range), and comparisons between groups were made using the Mann-Whitney U test.

A univariate analysis was conducted to identify factors with significant differences between the case and control groups. Significant factors were then included in a multivariate logistic regression analysis to investigate independent risk factors, with results reported as odds ratios (OR) with 95% confidence intervals (CI). Survival analysis was performed using the Kaplan-Meier method, with the *p*-value calculated using the log-rank test. Statistical significance was set at $p < 0.05$.

Results

General Information on NS Patients

In this project, 12 patients developed NS after transplantation, with an incidence rate of 0.82% (12/1457). Detailed clinical data are presented in Table 1. The median age of onset in the NS group was 33 years (range: 15–51), with 8 patients experiencing CMV infection. In the Non-NS group, the median age was also 33 years (range: 16–50), with 9 patients experiencing CMV infection. There was a statistically significant difference between the two groups ($p < 0.05$), as shown in Table 2.

In the NS group, there were 4 males and 8 females. Human leukocyte antigen (HLA) typing results included 7 with half-matched HLA, and 5 with fully mismatched HLA. Four patients developed acute GVHD, and 7 had other organ cGVHD. Massive proteinuria, hypoproteinemia, and edema were observed in 10 patients. Seven patients tested positive for antinuclear antibodies (ANA), including one with Perinuclear Anti-Neutrophil Cytoplasmic Antibodies (P-ANCA) positivity, while none had elevated serum immunoglobulins (Ig). Additionally, 8 out of 12 patients (66.7%) with NS had a history of CMV infection before the onset of NS. None of the twelve patients had underlying kidney diseases prior to transplantation. The follow-up period for all patients ended on 1 June 2021, or at the time of the patient's death, whichever came first. The median time to onset of NS after allo-HSCT was 14.99 months (range: 5.39–48.43).

Pathological Features

To identify the pathological types of NS in patients, we performed pathological tests. Two of the 12 patients did not undergo renal biopsy due to thrombocytopenia. Among the remaining 10 patients, 8 were diagnosed with membranous

Table 2. Univariate analysis of NS after allo-HSCT.

HSCT patient (N = 60)	NS group (N = 12)	Non-NS group (N = 48)	$\chi^2/t/Z$	*p*-value
Gender, n (%)			0.000	1.000
Male	4 (33.3)	16 (33.3)		
Female	8 (66.7)	32 (66.7)		
Age (years)	33 (15–51)	33 (16–50)	0.104	0.747
Donor and recipient blood type, n (%)			0.070	0.791
Match, n (%)	7 (58.3)	30 (62.5)		
Mismatch, n (%)	5 (41.7)	18 (37.5)		
HLA match, n (%)			4.449	0.108
Unrelated, n (%)	5 (41.7)	17 (35.4)		
Haploidentica (half-matched), L, n (%)	2 (16.6)	22 (45.8)		
Fully matched (HLA), n (%)	5 (41.7)	9 (18.8)		
Diagnosis, n (%)			10.161	0.071
ALL	3 (25.0)	22 (45.8)		
AML	4 (33.4)	17 (35.4)		
CML	1 (8.3)	2 (4.2)		
T lymphoma	3 (25.0)	1 (2.1)		
MDS	0	5 (10.4)		
Others	1 (8.3)	1 (2.1)		
Preprocessing scheme, n (%)			1.163	0.281
MAC	10 (83.3)	45 (93.8)		
RIC	2 (16.7)	3 (6.2)		
aGVHD, n (%)			0.283	0.595
Yes	4 (33.3)	20 (41.7)		
No	8 (66.7)	28 (58.3)		
cGVHD, n (%)			0.067	0.795
Yes	7 (58.3)	26 (56.3)		
No	5 (41.7)	22 (43.7)		
CMV infection, n (%)			9.925	0.002
Positive	8 (66.7)	9 (18.8)		
Negative	4 (33.3)	39 (81.2)		
Outcome, n (%)			2.053	0.152
Survival	7 (58.33)	38 (79.17)		
Death	5 (41.67)	10 (20.83)		
Immunosuppressant reduction time (month)	6 (5–12)	7 (3–36)	0.938	0.333
TG before transplantation (mmol/L)	1.60 (0.79–7.72)	1.12 (0.48–4.41)	1.446	0.173
TC before transplantation (mmol/L)	4.20 (2.51–6.77)	4.09 (2.24–7.17)	1.163	0.256
Half a year after transplantation TG (mmol/L)	1.55 (0.91–4.28)	1.64 (0.57–3.81)	1.140	0.260
Half a year after transplantation TC (mmol/L)	5.30 (3.13–11.49)	4.59 (2.65–9.95)	2.369	0.041
1 year after transplantation TG (mmol/L)	2.11 (1.11–3.91)	1.39 (0.43–2.90)	3.493	0.004
1 year after transplantation TC (mmol/L)	5.91 (3.27–10.17)	4.20 (2.56–9.19)	3.050	0.011

Abbreviations: HSCT, Hematopoietic stem cell transplantation; NS, nephrotic syndrome; HLA, Human leukocyte antigen; ALL, Acute Lymphoblastic Leukemia; AML, acute myeloid leukemia; CML, Chronic myelogenous leukemia; MDS, Myelodysplastic Syndromes; MAC, myeloablative conditioning; RIC, reeduced-intensity conditioning; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; CMV, cytomegalovirus; TG, triglycerides; TC, total cholesterol.

nephropathy (MN). PAS staining revealed blue nuclei, with red staining of the basement membrane and glomerular mesangial matrix (Fig. 1A). Electron microscopy showed electron-dense deposits on the epithelial side, widespread foot process fusion, and thickening of the basement membrane (Fig. 1B). Immunofluorescence demonstrated granular deposits of IgG along the capillary walls (Fig. 1C).

In one case, minimal glomerular lesions were observed, including occasional segmental mesangial proliferation, but no segmental sclerosis, tubular atrophy, or interstitial fibrosis, leading to a diagnosis of MCD (Fig. 2A). Electron microscopy revealed fusion of podocyte foot processes in the visceral layer of the glomerulus, without electron-dense deposits (Fig. 2B). Immunofluorescence results were negative. Another case exhibited focal segmental glomerulosclerosis (FSGS).

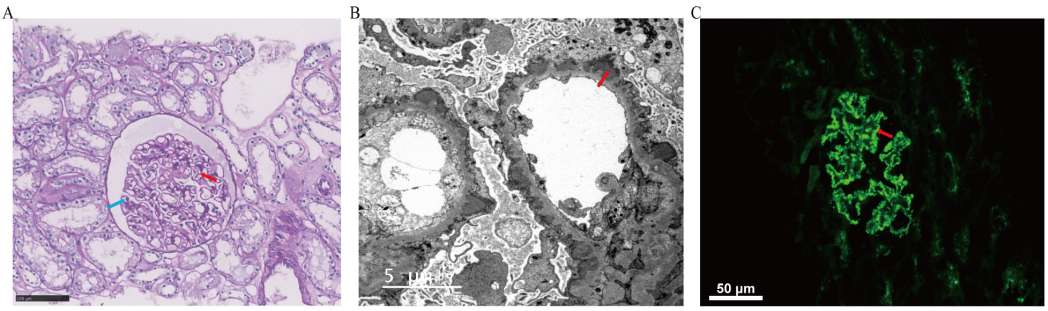

Fig. 1. Renal pathology examination of patients with membranous nephropathy. (A) Periodic Acid-Schiff (PAS) staining, with blue arrows indicating blue nuclei and red arrows indicating the red basement membrane and mesangial matrix. The scale bar represents 100 μm. (B) Electron microscopy, with red arrows indicating electron-dense deposits on the epithelial side. The scale bar represents 5 μm. (C) Immunofluorescence staining, with red arrows indicating granular IgG deposits along the capillary walls. The scale bar represents 50 μm.

Analysis of Risk Factors Related to the Development of NS after allo-HSCT

To identify the risk factors for NS after allo-HSCT, a univariate analysis was conducted. The analysis revealed that gender, age, donor gender, donor-recipient blood type compatibility, HLA typing matching degree, acute and chronic GVHD, duration of immunosuppressant reduction, as well as triglyceride (TG) and total cholesterol (TC) levels before and 6 months after transplantation, did not show statistical significance ($p > 0.05$). However, CMV infection ($p = 0.002$), TC at 6 months after transplantation ($p = 0.041$), TG at 1 year post-transplantation ($p = 0.004$), and TC at 1 year post-transplantation ($p = 0.011$) were statistically significant related to the occurrence of NS (Table 2).

Subsequently, we conducted a multivariate analysis of the selected risk factors based on the findings from Table 2. Prior to this, we checked for collinearity among the four indicators by calculating the variance inflation factor (VIF) and found no issues of collinearity (see Table 3). The univariate analysis further revealed that CMV infection was an independent risk factor for NS ($p = 0.004$, OR (95% CI) = 15.871 (95% CI: 2.465–102.194), Table 3).

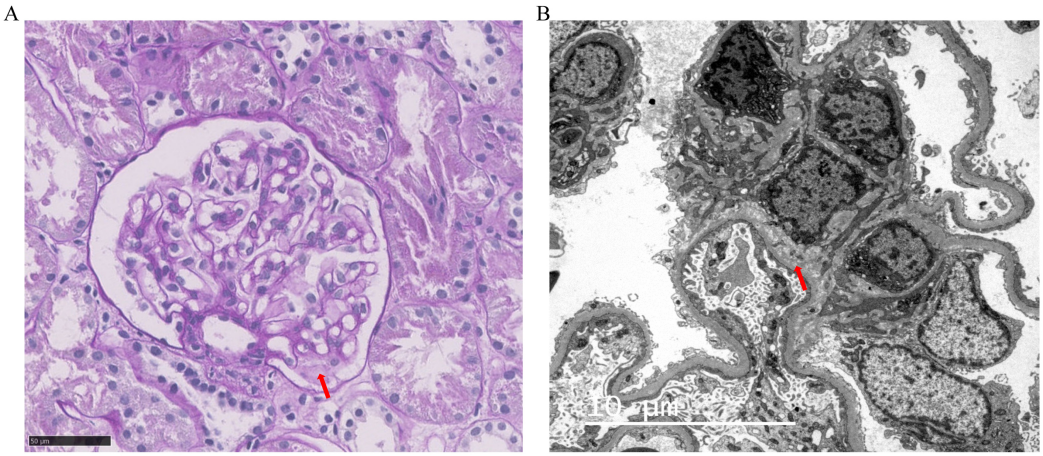

Fig. 2. Renal pathology examination of patients with minimal change disease. (A) Periodic Acid-Schiff (PAS) staining, with red arrows indicating minor glomerular lesions, occasional segmental mesangial proliferation, and the absence of segmental sclerosis, tubular atrophy, and interstitial fibrosis. The scale bar represents 50 μm. (B) Electron microscopy, with red arrows indicating podocyte foot process effacement in the glomerulus and the absence of electron-dense deposits. The scale bar represents 10 μm.

Table 3. Multivariate analysis of NS after allo-HSCT.

	β	SE	OR	95% CI	p-value	VIF	Wald χ^2
CMV infection (Positive/Negative)	2.765	0.950	15.871	2.465–102.194	0.004	1.241	8.464
Half year after transplantation TC	0.020	0.311	1.021	0.555–1.876	0.948	2.151	0.004
1 year after transplantation, TG	–0.504	0.339	0.604	0.311–1.175	0.138	1.549	2.296
1 year after transplantation TC	–1.023	0.675	0.360	0.096–1.350	0.130	1.930	2.205

Abbreviations: SE, standard error; OR, odds ratios; CI, confidence intervals; VIF, variance inflation factor.

Efficacy and Outcome of Treatment in NS Patients

After treatment with calcineurin inhibitors (CNIs) combined with glucocorticoids, 10 out of 12 patients (83.33%) achieved CR, with a median time to CR of 9.69 months (range: 4.14–51.98 months). One patient reached PR but succumbed to a pulmonary infection, and one patient proved resistant to treatment, progressing to end-stage renal disease that required hemodialysis and ultimately resulting in death from chronic renal failure.

As of 1 June 2021, among the 10 patients who achieved CR, 1 experienced a relapse of the blood disease but later attained remission again, although this patient eventually died of esophageal cancer. The remaining 9 CR patients survived, with 7 experiencing no recurrence of blood disease and 2 experiencing relapses but eventually regaining remission. The median follow-up time was 58.93 months (range: 19.82–163.82 months).

Kaplan-Meier survival analysis indicated that the estimated 5-year overall survival rate was 90.0% for the NS group compared to 77.6% for the control group (Fig. 3). Before 65.62 months, the survival rate of the NS group was higher than

that of the control group. After 65.62 months, the survival rate of the NS group was lower than that of the control group. The estimated 5-year survival rate without malignant blood disease was 60.2% for the NS group versus 76.3% for the control group (Fig. 4). Before 27.68 months, the progression-free rate of the NS group was higher than that of the control group. After 27.68 months, the progression-free rate of the NS group was lower than that of the control group. No statistically significant difference was observed between the two groups.

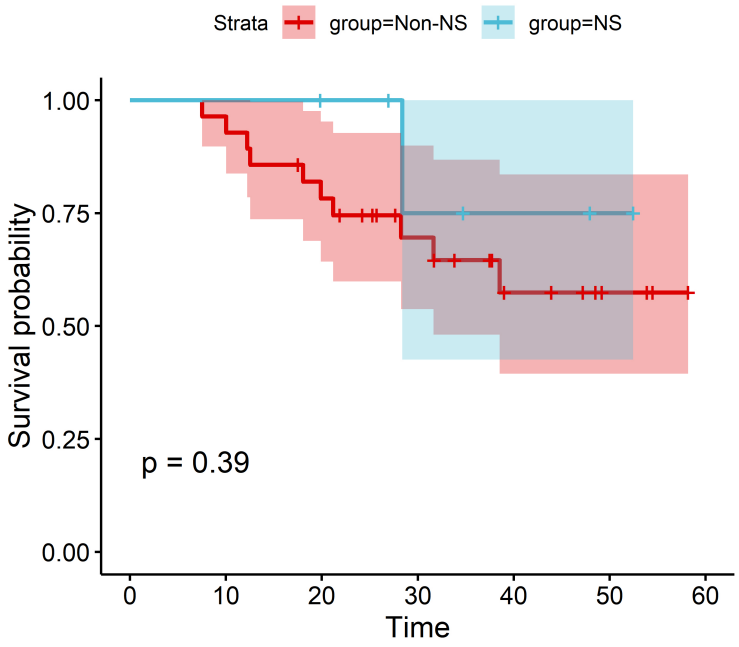

Fig. 3. Kaplan-Meier survival curve for overall survival.

Discussion

NS is recognized as an uncommon and rare late complication following allo-HSCT, with an incidence ranging from 0.6% to 4.3% across various studies (Huang and Wu, 2020; Abudayyeh and Wanchoo, 2022; Brukamp et al, 2006; Chen et al, 2011). In allo-HSCT-related NS, renal biopsy results commonly reveal MN as the primary pathological diagnosis (65.5%), followed by MCD as the second most common cause (19%). The incidence of NS in our study was 0.82%, with 8 cases diagnosed with MN, which aligns with previous findings. Moreover, our study found that the median time to onset of post-transplantation NS was 14.99 months, and 58.3% of NS patients developed the condition concurrently with chronic GVHD. Previous research reported that the median time to onset of NS after allo-HSCT was 19.5 months (range: 3.9–84 months), with a high incidence of prior chronic GVHD among NS patients (Wong et al, 2016). Additionally, other studies have indicated a median onset time of 20.5 months (range: 3–174 months) post-HSCT, with 87.2% cases having experienced acute or chronic GVHD at the time of NS onset (Beyar-Katz et al, 2016). This suggests that NS often represents a manifestation or complication of chronic GVHD (Brukamp et al, 2006).

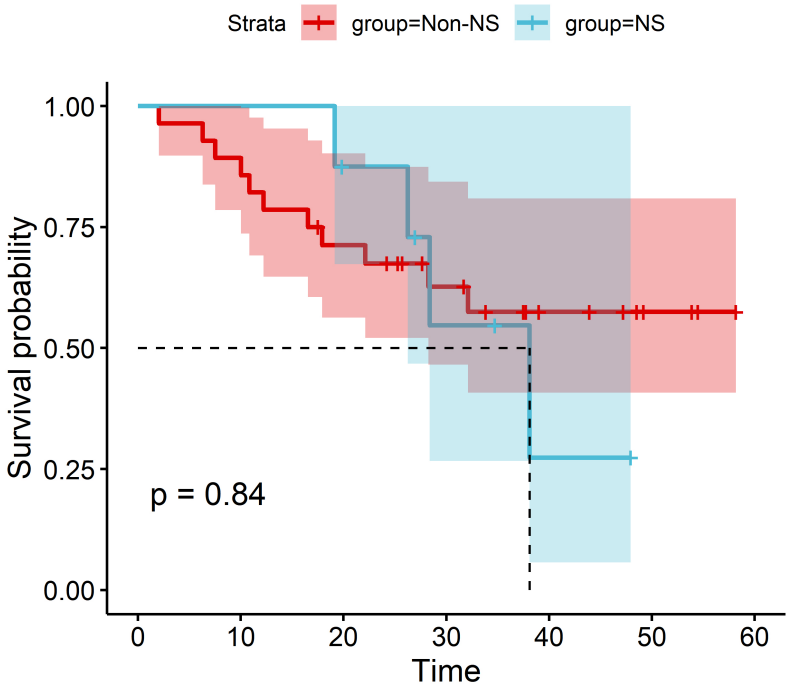

Fig. 4. Kaplan-Meier survival curve for progression-free survival.

We investigated the risk factors associated with NS after allo-HSCT and found significant correlations with TC at 6 months post-transplantation, TG and TC at 1 year post-transplantation, and CMV infection. Notably, CMV infection emerged as an independent risk factor for post-HSCT NS.

A meta-analysis has suggested that congenital NS can be a common clinical manifestation of congenital CMV infection, though the exact causal relationship remains unclear (Huang and Wu, 2020; Abudayyeh and Wanchoo, 2022; Nematollahi et al, 2023). CMV infection can trigger a broad immune response, including the activation of T and B cells. T cell-mediated vascular hyperpermeability increases protein permeability in the glomerular capillaries, leading to proteinuria and hypoalbuminemia (Garin, 2000; Tamura, 2021). The activation of immune cells may result in the deposition of immune complexes in the glomeruli, causing glomerular damage and inflammatory reactions, which contributes to the development of NS (Karakus et al, 2022). Additionally, inflammatory factors such as TNF-α and interleukin-1 have been shown to alter lipid metabolism in glomerular cells (Teshima et al, 2002). Thus, T cells activated by CMV can release large amounts of pro-inflammatory cytokines, inducing changes in glomerular permeability and leading to proteinuria (Cho et al, 2019).

Letermovir is currently effective in preventing cytomegalovirus infection in HSCT. The wide 95% confidence interval observed for CMV in our multivariate analysis suggests a high degree of uncertainty in our estimates. This variability may be attributed to the relatively small sample size, which limits the statistical power and precision of our findings. Future studies with larger cohorts are needed to confirm these results and provide more robust estimates.

The incidence of abnormal blood lipids significantly increases after HSCT, with over 70% of patients developing hyperlipidemia (Blaser et al, 2012). Studies have highlighted the substantial impact of serum total TC and TG on renal function. Lipid accumulation in the renal parenchyma can drive inflammation and fibrosis. This lipid deposition leads to the accumulation of lipid vacuoles in mesangial and tubular epithelial cells, provoking endoplasmic reticulum oxidative stress and activating a cascade of inflammatory factors.

In our project, TC (6 months post-transplantation), TG (1 year post-transplantation), and TC (1 year post-transplantation) were all associated with the occurrence of NS. However, multivariate analysis did not identify TC or TG levels as independent risk factors for NS after allo-HSCT. Therefore, further research and larger case studies are needed to better understand the relationship between hyperlipidemia after HSCT and the development of NS.

Currently, there are no established standards for the prevention and treatment of nephrotic syndrome (NS) following HSCT. Proteinuria, a key marker of kidney disease progression, is associated with reduced post-transplant survival rates, highlighting the importance of routine urinalysis using dipsticks.

B-cell depletion with anti-CD20 monoclonal antibodies, such as rituximab, has shown efficacy in managing nephrotic syndrome (Reddy et al, 2006). Chinese researchers have reported a case where a patient with NS post-allo-HSCT, initially unresponsive to corticosteroids and cyclosporine, achieved CR following treatment with CD20 monoclonal antibodies. Additionally, another case documented CR through mesenchymal stem cell (MSC) therapy after failure of treatment with CsA, prednisone, and rituximab. It was hypothesized that MSCs might regulate post-transplant NS by inhibiting B cell proliferation, inducing regulatory B cells (Bregs) and regulatory T cells (Tregs), and reducing the production of inflammatory cytokines by monocytes and natural killer (NK) cells, thereby offering therapeutic benefits for patients with this complication (Zhang et al, 2017).

In this investigation, the Kaplan-Meier survival curves for NS patients exhibited crossing, which may be attributed to several factors:

(1) Sample Size: The relatively small sample size in this study can lead to increased statistical fluctuations, resulting in the crossing of survival curves at certain time points. This underscores the need for larger sample sizes in future studies to achieve more stable and reliable survival curves.

(2) Baseline Characteristics and Disease Variability: Significant differences in baseline characteristics, disease severity, and responses to treatment among patients can contribute to the crossing of survival curves. Variability in early and late treatment responses and disease progression can impact survival outcomes.

(3) Response Patterns: Patients may exhibit different response patterns during treatment. Some may have better survival rates in the early stages, with rates decreasing over time, while others may not show significant treatment effects initially but improve later. These varying response patterns can lead to the observed crossing of survival curves.

This study explored the pathology of patients with NS and provided a detailed description of the pathological features. The findings are directly relevant to clini-

cal practice, highlighting the potential importance of screening for CMV infection in NS patients. Early identification of high-risk patients and prompt intervention could improve patient outcomes.

However, several limitations should be noted. Firstly, despite including a relatively large number of patients, the actual number with NS was small, which may affect the statistical power of the results. Future studies with larger sample sizes are needed to validate these findings. Secondly, the follow-up period in this study was relatively short, and we were unable to assess the long-term impact of CMV infection on the prognosis of NS. Extending the follow-up period in future research would provide a more comprehensive understanding of these effects. Finally, as this project is retrospective, there may be unknown confounding variables that could influence the study results.

Conclusion

In summary, this study retrospectively analyzed 1457 patients who survived more than 100 days after receiving allogeneic hematopoietic stem cell transplantation at our hospital over a 13-year period. The study found that the incidence of post-transplant NS was 0.82% (12 cases), with a median onset time of 14.99 months after transplantation. Univariate analysis revealed significant associations between post-transplant NS and TC at 6 months post-transplant, TG and TC at 1 year post-transplant, and CMV infection. Multivariate analysis confirmed CMV infection as an independent risk factor for NS. However, the wide confidence intervals indicate considerable uncertainty, highlighting the need for further research with larger sample sizes to validate these findings. The research suggests that NS may be a manifestation of chronic graft-versus-host disease following allogeneic hematopoietic stem cell transplantation, with CMV infection identified as one of its risk factors. The use of CNIs and corticosteroids is crucial in managing NS, potentially improving long-term survival rates. These findings provide new insights into understanding and managing post-transplant NS and offer significant guidance for clinical practice. Future research should further explore the pathogenesis and treatment strategies for NS to enhance patient outcomes.

Key Points

- The study found that the incidence of post-transplant nephrotic syndrome (NS) was 0.82% (12 cases), with a median onset time of 14.99 months after transplantation.
- Univariate analysis revealed significant associations between post-transplant NS and total cholesterol at 6 months post-transplant, triglycerides and total cholesterol at 1 year post-transplant, and CMV infection.
- Multivariate analysis confirmed that CMV infection was an independent risk factor for NS.
- The use of calcineurin inhibitors and corticosteroids is crucial in managing NS and may improve long-term survival rates.

Availability of Data and Materials

The data in the current study are available from the corresponding authors on reasonable request.

Author Contributions

YT, MY, YMT and HF were responsible for conceptualization. YMT, MZ, YL, JS, YZ and HF handled data collection. RW and HW were in charge of data analysis. YT and MY drafted the manuscript. YMT, MY, YT and HF were responsible for writing, review, and editing. All authors contributed to important editorial changes of important content in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All procedures in this study adhered to the ethical principles outlined in the Declaration of Helsinki. Since all patient data involved in the study were anonymized and did not include any private patient information, informed consent was waived. The waiver of informed consent and the ethical approval (Approval No.: 0598, 2024) were granted by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine.

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Conflict of Interest

The authors declare no conflict of interest.

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