

Increased risk of cardio-cerebrovascular disease after hematopoietic cell transplantation in patients with previous history

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Abstract

Background: The impacts of previous cardio-cerebrovascular disease (pre-CCVD) on the outcomes of hematopoietic cell transplantation (HCT) are not well described. Patients with pre-CCVD may often be poor candidates for HCT. This study aimed to investigate the impact of pre-CCVD on transplant outcomes.

Methods: A retrospective study was conducted between patients with and without pre-CCVD who consecutively received allogeneic or autologous HCT between November 2013 and January 2020 with a matching of age and disease status. The cardiovascular complications and HCT outcomes of the two groups were evaluated and compared. The primary endpoints were post-transplant cardio-cerebrovascular disease (post-CCVD) and non-relapse mortality (NRM). We used a multivariable Cox proportional hazard model and the Fine-Gray competing risk regressions for analyses to estimate the hazard ratios (HRs).

Results: The outcomes of 23 HCT recipients with pre-CCVD were compared with those of 107 patients in the control group. No significant differences were noted in terms of engraftment, overall survival (OS) (67.00% *vs.* 67.90%, $P = 0.983$), or relapse (29.78% *vs.* 28.26%, $P = 0.561$) between the pre-CCVD group and the control group. The cumulative incidences of 2-year NRM were similar between patients with pre-CCVD and the controls (14.68% *vs.* 17.08%, $P = 0.670$). However, pre-CCVD was associated with an increased incidence of post-CCVD (HR: 12.50, 95% confidence interval [CI]: 3.88–40.30, $P < 0.001$), which was an independent risk factor for increased NRM (HR: 10.29, 95% CI: 3.84–27.62, $P < 0.001$) and inferior OS (HR: 10.29, 95% CI: 3.84–27.62, $P < 0.001$).

Conclusions: These findings suggest that the existence of pre-CCVD before transplantation might not result in increased mortality directly but superpose the toxicity of the transplantation procedure, leading to a risk of post-CCVD. Post-CCVD was a powerful predictor for high NRM and inferior OS. Further risk stratification of pre-CCVD is needed to reduce NRM in various transplantation settings.

Keywords: Hematopoietic cell transplantation; Coronary artery disease; Cardiovascular diseases; Cerebrovascular disorders; Mortality

Introduction

Hematopoietic cell transplantation (HCT) is an established treatment for hematologic malignancies.^[1-3] The safety of HCT has greatly improved over the past decades, with its tolerance being attributed to the availability of improved supportive care practices and widespread adoption of the practice of careful evaluation of comorbidities before the transplantation.^[4] Cardio-cerebrovascular comorbidities have been well identified as risk factors for non-relapse mortality (NRM) following transplantation, their presence accounting for a score of 1 in the HCT-specific comorbidity

index (HCT-CI).^[5,6] At present, cardiovascular (CV) assessment is a core component in the evaluation of HCT.^[7] However, the physiological status and organ function of transplantation recipients with previous cardio-cerebrovascular disease (pre-CCVD) vary at the start of conditioning. The validity of HCT-CI needs to be refined, with emphasis on organ potentiality before transplantation.^[8]

Both autologous-HCT (auto-HCT) and allogeneic-HCT (allo-HCT) are known to lead to an increased potential risk for post-transplant cardio-cerebrovascular disease (post-CCVD) among long-term survivors. Conditioning, infec-

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tion, and non-infectious complications after transplantation exert extended periods of physiological stress and direct organ toxicity on the recipients.^[9] Chemotherapy, total-body irradiation (TBI), and the inflammation resulting from various complications may cause endothelial dysfunction that results in subclinical CV injury and early pathophysiologic events in the occurrence of CCVD.^[10] Although the recipients did not develop symptoms or signs of organ dysfunction in the early stage of transplantation, it has been shown that post-CCVD occurring late after HCT was the leading cause of long-term morbidity and mortality.^[10] The late effects of transplantation have drawn much attention in the last decade. In comparison with age- and sex-matched healthy controls, HCT recipients have an up to 5.6-fold increased risk of contracting CCVD, including coronary artery disease (CAD), cerebrovascular disease, and heart failure (HF) and a nearly 4.0-fold increased risk of CV-specific mortality.

Few patients with pre-CCVD had been indicated for transplantation in the last two decades. Along with advances in supportive care, the number of HCT recipients with pre-CCVD is increasing. Internationally, Kosugi *et al*^[11] first reported the successful application of reduced-intensity conditioning HCT to a 60-year myelodysplastic syndrome (MDS) patient with severe CAD in 2006. This suggested that the transplant-related mortality (TRM) of such patients may be overestimated. Stillwell *et al*^[9] retrospectively compared the outcomes of 69 patients with CAD and 1109 CAD-free recipients of transplantation during the same period and found no difference in the TRM between the two groups ($P = 0.777$). This large study focusing on the impact of pre-CCVD on transplantation showed that underlying CAD was not a contraindication for HCT. However, from the first HCT in 1964 in China to 2010, few patients with CCVD have received transplantation. Even in the past 20 years, such patients have typically been poor candidates for HCT; this fact indicates a significant departure from international practices.^[12] Therefore, we focused on HCT recipients with moderate to severe CCVD before conditioning and performed a retrospective study to assess the impact of pre-CCVD on transplant outcomes.

Methods

Ethical approval

This study was conducted in accordance with the guidelines of the *Declaration of Helsinki* and was approved by the Ethics Committee of the Chinese People's Liberation Army General Hospital (No. S2021-086-01). Because this was a retrospective study and the data analysis was performed anonymously, this study was exempt from informed consent from patients.

Study population

The objective of this study was to investigate the outcomes of patients with pre-CCVD who underwent HCT for hematological malignancies. We also included patients without pre-CCVD who received HCT during the same period as the control group. Through a retrospective selection of patients, the CV complications and HCT

outcomes of the two groups were observed and compared.^[13] To reduce the potential influences on the outcomes, the control group was matched with the study group according to disease status (complete remission/relapse) and age (± 3 years) before HCT. These two factors have been recognized to be closely related to NRM and CV complications.^[10,14,15] The eligibility criteria were as follows: (1) HCT performed between November 2013 and January 2020 at our center; (2) adult recipient of HCT; (3) availability of a pre-specified data set comprising disease characteristics, confirmed history of pre-CCVD (diagnosis and treatment), cardiovascular risk factors (CVRFs), pre-transplant risk assessment and information on transplantation; and (4) regular follow-up or report after transplant. The last follow-up was recorded on July 18, 2020. All eligible patients were included in the analysis to avoid bias.

For all patients included, demographic data, primary malignancy and disease status, the type of pre-CCVD, cardiac function (left ventricular ejection fraction [LVEF] and electrocardiography [ECG]), CVRFs (hypertension, hypercholesterolemia, diabetes, smoking history^[16]), and transplantation characteristics were assessed. All the above variations were evaluated for their impact on transplant outcomes, including post-CCVD, relapse of malignancy, NRM, disease-free survival (DFS), and overall survival (OS).

Patients' characteristics

A total of 23 consecutive patients with pre-CCVD who received HCT between November 2013 and January 2020 were enrolled. A total of 107 patients without pre-CCVD who received HCT during the same period were selected as the control group. The median ages of the pre-CCVD group and control group at transplantation were 51 (range: 30–65) years and 45 (range: 27–63) years, respectively ($P = 0.061$). There was no difference with respect to the distribution of acute myeloid leukemia/MDS *vs.* acute lymphocytic leukemia/T-cell lymphoblastic lymphoma *vs.* lymphoma, cycles of chemotherapy, allo-HCT *vs.* auto-HCT, busulfan (Bu)-based *vs.* TBI-based *vs.* other conditioning, and the number of graft cells infused. Patients in the pre-CCVD group presented with a higher prevalence of CVRFs (78.3% *vs.* 30.8%, $P < 0.001$) and abnormal ECG (47.8% *vs.* 22.4%, $P = 0.019$) before HCT than the control groups. Both groups were similar with respect to echocardiographic assessment before HCT. The LVEF of each recipient was $> 50.00\%$ [Table 1]. Subtypes and proportions of pre-CCVD in the 23 patients are summarized in Table 2.

All patients received peripheral blood stem cells (PBSCs) or PBSCs combined with bone marrow mobilized by recombinant human granulocyte colony-stimulating factor. Conditioning regimens were identified based on the type and status of the primary malignancy. Bu-based or TBI-based conditioning was used as a myeloablative regimen in patients with acute leukemia or MDS for allo-HCT.^[3,16] BEAM (carmustine, etoposide, cytarabine, melphalan) or CBV (cyclophosphamide, carmustine, etoposide) was used as a conditioning regimen in recipients of auto-HCT with CD20 + B-cell lymphoma, using rituximab. The antiplatelet and anticoagulant medications

Table 1: Comparison of characteristics between pre-CCVD group and the control group.

Characteristic	Pre-CCVD group (n = 23)	Control group (n = 107)	Statistical values	P
Male	17 (73.9)	65 (60.7)	0.55*	0.341
Age (years)	51 (44–55)	45 (35–53)	2.66†	0.064
Primary disease				
AML/MDS	10 (43.5)	57 (53.3)	1.23*	0.505
ALL/T-LBL	6 (26.1)	18 (16.8)		
Lymphoma	7 (30.4)	32 (29.9)		
Disease risk				
Standard	5 (21.7)	27 (25.2)	1.21*	1.000
High	18 (78.3)	80 (74.8)		
Disease stage before HCT				
CR	12 (52.2)	66 (61.7)	1.47*	0.483
Relapsed/refractory	11 (47.8)	41 (38.3)		
Total cycles of chemotherapy				
<6	12 (52.2)	53 (49.5)	0.90*	1.000
≥6	11 (47.8)	54 (50.5)		
HCT-CI				
≤1	13 (56.5)	65 (60.7)	1.19*	0.815
>1	10 (43.5)	42 (39.3)		
Conditioning regimen				
Bu-based	12 (52.2)	66 (61.7)	0.72*	0.622
TBI-based	2 (8.7)	8 (7.5)		
Others	9 (39.1)	33 (30.8)		
Source of graft				
Allogeneic	16 (69.6)	75 (70.1)	1.03*	1.000
Autologous	7 (30.4)	32 (29.9)		
HCT date				
<July 17, 2018	8 (34.8)	56 (52.3)	2.05*	0.168
≥July 17, 2018	15 (65.2)	51 (47.7)		
MNC infused (×10 ⁸ /kg)	10.63 ± 3.89	10.80 ± 3.92	0.87‡	0.859
CD34+ cells infused (×10 ⁶ /kg)	4.43 ± 4.09	4.06 ± 2.29	1.15‡	0.678
Major CVRFs	18 (78.3)	33 (30.8)	7.93*	<0.001
LVEF before HCT (%)	65.17 ± 2.99	64.34 ± 3.02	1.92‡	0.233
Echocardiographic abnormalities before HCT	9 (39.1)	34 (31.8)	1.38*	0.626
Abnormal ECG before HCT	11 (47.8)	24 (22.4)	3.14*	0.019

Data were presented as n (%) or mean ± standard deviation (SD) or median (interquartile range, IQR). χ^2 values. †Z values. ‡t values. Bu-based: modified busulfan and cyclophosphamide regimen. TBI-based: total body radiation and cyclophosphamide regimen. Others: including BEAM (carmustine, etoposide, cytarabine, melphalan) and CBV (cyclophosphamide, carmustine, etoposide) conditioning regimens in auto-HCT. Major CVRFs consisting of hypertension, hypercholesterolemia, diabetes, and smoking history. ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; Auto-HCT: Autologous hematopoietic cell transplantation; CR: Complete remission; CVRFs: cardiovascular risk factors; ECG: Electrocardiography; HCT: Hematopoietic cell transplantation; HCT-CI: HCT-specific comorbidity index; LVEF: Left ventricular ejection fraction; MDS: Myelodysplastic syndrome; MNC: Mononuclear cells; Pre-CCVD: Previous cardio-cerebrovascular disease; TBI: Total-body irradiation; T-LBL: T-cell lymphoblastic lymphoma.

that the patients with pre-CCVD took were discontinued when platelets count falls below $50 \times 10^9/L$ after the start of conditioning. The diagnostic criteria and treatments of all patients were based on the same guidelines.

Definitions of CCVD

Pre-CCVD was defined as a history of one of the following before transplantation: (1) cardiac disease: symptomatic arrhythmia (atrial fibrillation [AF] or atrial flutter [AFL], rapid ventricular arrhythmia, supraventricular tachycardia or sustained ventricular tachycardia); cardiomyopathy; congestive heart failure; valvular heart disease; or CAD: history of percutaneous coronary intervention or coronary artery bypass graft surgery, obstructive CAD, myocardial ischemia (abnormal ECG with clinical symptoms), or myocardial infarction (suppression of tumorigenicity [ST]-segment elevation myocardial infarction, non-ST-segment

elevation myocardial infarction, or troponin elevation); or (2) cerebrovascular disease: history of transient ischemic attack, cerebrovascular event (hemorrhagic/ischemic cerebral infarction), or cerebral artery stenosis (intra-cranial atherosclerotic stenosis/carotid atherosclerotic stenosis).^[9] All evaluations for pre-CCVD were updated within 2 weeks before the start of conditioning.

Post-CCVD was defined according to the Common Terminology Criteria for Adverse Events version 5.0. Post-CCVD included grade ≥2 cardiac complications, including symptomatic arrhythmia, myocardial infarction, HF, myocarditis, pulmonary valve disease, intra-cranial hemorrhage, and cerebrovascular ischemia.^[9,10,17] Post-CCVD caused by severe infection or multiple organ dysfunction syndromes (MODS) were excluded. Cardio-cerebrovascular complications were identified by a review of the electronic medical records.

Table 2: Diagnosis of pre-CCVD (*n* = 23).

Pre-CCVD characterization	Number of patients*
CAD	12 (52.2)
Myocardial infarction	3 (13.0)
Percutaneous coronary intervention	5 (21.7)
Obstructive CAD	2 (8.7)
Myocardial ischemia	9 (39.1)
Cardiac arrhythmia	3 (13.0)
Vascular heart disease	1 (4.3)
TIA	2 (8.7)
History of hemorrhagic/cerebral infarction	5 (21.7)
Cerebral artery stenosis	3 (13.0)

Data were presented as *n* (%). *The total percentage exceeded 100% because that a patient could have two or more types of pre-CCVD concurrently. CAD: Coronary artery disease; Pre-CCVD: Previous cardiovascular disease; TIA: Transient ischemic attack.

Statistical analysis

The primary endpoints were NRM and post-CCVD. The secondary endpoints were neutrophil and platelet engraftment, length of stay in the laminar flow ward, relapse, and OS. The demographic and transplant characteristics between the pre-CCVD and control group were compared using independent sample *t*-tests for continuous data or Chi-square tests for discrete variables. Neutrophil and platelet recovery, length of stay in the laminar flow ward, relapse, and NRM are presented using cumulative incidence curves with competing risks. NRM was defined as death for any reason other than the recurrence of malignancy. The Kaplan-Meier method was used to estimate OS, and the log-rank test was used to compare the survival curves. The cumulative incidence of post-CCVD was estimated with death without post-CCVD as the competing risk, and Gray test was used to compare cumulative incidences between groups. Variables evaluated by univariable analysis included factors related to demography (age and sex), disease (primary disease, status, and risk of disease, cumulative chemotherapy cycles), CV assessments before HCT (CVRFs, LVEF, and ECG), and transplantation (conditioning, graft source, and the number of cells infused). All factors with $P < 0.100$ in univariable analysis and the grouping variable (pre-CCVD group *vs.* control group) were included in the multivariable analysis. Cox hazards models were generated to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for each outcome. All analyses were performed using the statistical software “Easy R” (<http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html>),^[18] which is based on R commander and R software version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). $P < 0.050$ was considered to be the level of significance.

Results

Outcomes of transplantation

There was no difference in the median days of neutrophil (14 [10–24] *vs.* 12 [9–21] days, $P = 0.269$) and platelet (14 [8–55] *vs.* 14 [9–92] days, $P = 0.395$) engraftment between the pre-CCVD group and the control group. In the multivariable analysis, rapid neutrophil recovery was

associated with a greater number of infused CD34 + cells ($P = 0.016$) and disease status in remission ($P = 0.002$). Both groups were similar with respect to the length of stay in the laminar flow ward (45 [26–86] *vs.* 47 [23–104] days, $P = 0.569$). Receiving auto-HCT was associated with shorter hospital stay (HR: 5.32, 95% CI: 1.81–15.63, $P = 0.002$). At the time of the last follow-up, no statistically significant difference of survival was noted in patients with pre-CCVD compared with that in the control group (2-year OS: 67.00% *vs.* 67.90%, $P = 0.983$). Further, the cumulative incidences of 2-year relapse (29.78% *vs.* 28.26%, $P = 0.561$), NRM (14.68% *vs.* 17.08%, $P = 0.670$), and DFS (66.20% *vs.* 69.70%, $P = 0.485$) were also comparable between the two cohorts [Table 3]. Multivariable analysis revealed that patients with relapsed/refractory disease had inferior OS ($P = 0.001$) and DFS ($P = 0.013$) to those of patients in remission status. Allo-HCT was a stronger prognostic factor for inferior OS, higher NRM, and longer hospital stay ($P < 0.001$) than auto-HCT. There was no significant impact of pre-CCVD on major HCT outcomes in multivariable analysis [Table 4]. Given the significant effect of graft source (autologous/allogeneic) on the outcomes, subgroup analysis was conducted. However, pre-CCVD was not associated with these outcomes in either the auto-HCT subgroup or allo-HCT subgroup [Supplementary Tables 1 and 2, <http://links.lww.com/CM9/A603>].

Post-transplant cardio-cerebrovascular disease

The onset of 30 post-CCVD was observed in 18 patients. There were 21 cardiac events, seven cerebrovascular events, and two severe vascular events. One patient without pre-CCVD developed deep vein thrombosis (DVT) followed by pulmonary embolism (PE) after transplantation. After anticoagulation therapy, he survived until the end of the follow-up. Given the close relation to the CV system, this patient's DVT and PE were also recorded as post-CCVD. Among the 18 pre-CCVD patients, nine (9/18) experienced the onset of one post-CCVD, seven (7/18) presented with the onset of two post-CCVD, and the other two patients experienced the onset of three and four post-CCVD separately. The most common post-CCVD was arrhythmia (36.67%), the most common of which was AF (45.45%), followed by HF (26.67%). There was no difference in the distribution of post-CCVD between the pre-CCVD group and the control group (cardiac disease: 76.5% *vs.* 76.9%, cerebrovascular disease: 23.5% *vs.* 23.1%, $P = 1.000$). The frequencies and types of post-CCVD in the two groups are shown in Figure 1. The 2-year cumulative incidence of the first post-CCVD was significantly higher in the pre-CCVD group than that in the control group (42.26% *vs.* 9.67%, $P < 0.001$). This difference was still obvious in patients receiving allo-HCT or auto-HCT. In the auto-HCT setting, none of the 23 patients in the control group developed post-CCVD, but four of seven patients in the pre-CCVD group developed post-CCVD [Figure 2]. The first onset of post-CCVD appeared at a median of 136 days (range: 1–595 days) following HCT, much earlier than that of NRM (median: 227 [55–504] days). In multivariable analysis, pre-CCVD was the only independent risk factor for the

Table 3: Comparison of HCT outcomes between the pre-CCVD group and the control group.

Outcomes	Pre-CCVD group (n=23)	Control group (n=107)	Statistical values	P
Neutrophil engraftment (days)	14 (12–15)	12 (10–15)	1.22*	0.269
Platelet engraftment (days)	14 (13–18)	14 (11–17)	0.72*	0.395
Length of stay (days)	45 (34–58)	47 (39–58)	0.56*	0.569
Post-CCVD	9 (39.1)	9 (8.4)	6.84 [†]	<0.001
Death	7 (30.4)	35 (32.7)	0.90 [†]	1.000
Cumulative incidence of post-CCVD				
100 days	21.74 (9.68–44.60)	1.89 (0.48–7.34)	14.68*	<0.001
1 year	42.26 (24.31–66.10)	9.67 (5.13–17.86)		
2 years	42.26 (24.31–66.10)	9.67 (5.13–17.86)		
Cumulative incidence of NRM				
1 year	14.68 (3.70–32.90)	14.95 (9.00–22.40)	0.23*	0.670
2 years	14.68 (3.70–32.90)	17.08 (10.60–24.90)		
OS [‡]				
1 year	73.50 (65.40–82.60)	67.90 (48.80–94.40)	1.01 [†]	0.983
2 years	67.00 (58.30–77.10)	67.90 (48.80–94.40)		
Cumulative incidence of relapse				
1 year	18.70 (5.80–37.20)	22.46 (15.10–30.70)	0.52*	0.561
2 years	29.78 (9.10–54.20)	28.26 (19.80–37.30)		
DFS				
1 year	79.50 (53.90–91.80)	84.50 (75.60–90.40)	0.50 [†]	0.485
2 years	66.20 (31.60–86.30)	69.70 (58.40–78.50)		

Data were presented as *n* (%) or median (IQR) or incidence rate (95% confidence interval, CI). *Z values. [†] χ^2 values. [‡]Survival adjusted for major CVRFs and abnormal ECG before transplant, which is significantly different between the two groups. CI: Confidence interval; CVRFs: cardiovascular risk factors; DFS: Disease-free survival; ECG: electrocardiography; NRM: Non-relapse mortality; OS: Overall survival; Post-CCVD: Post-transplant cardio-cerebrovascular disease; Pre-CCVD: Previous cardio-cerebrovascular diseases.

occurrence of post-CCVD (HR: 12.50, 95% CI: 3.88–40.30, $P < 0.001$) [Table 4]. Subgroup analysis stratified by graft source showed that pre-CCVD was strongly associated with the occurrence of post-CCVD (HR: 8.50, 95% CI: 2.14–33.90, $P = 0.002$). This was not observed in the auto-HCT setting ($P = 0.997$). ECG before allo-HCT was another significant factor for the occurrence of post-CCVD ($P = 0.023$) [Supplementary Tables 1 and 2, <http://links.lww.com/CM9/A603>].

Correlation between post-CCVD and outcomes

Additional analyses were performed to examine the impact of post-CCVD on survival, which was evaluated by a Cox proportional hazard model with a time-dependent (TD) covariate.^[18] The first post-CCVD was treated as the TD covariate. Other prognostic covariates ($P < 0.100$) were included in the model except for the grouping factor (with or without pre-CCVD). The development of post-CCVD was independently associated with high NRM (HR: 10.29, 95% CI: 3.84–27.62, $P < 0.001$) and inferior OS (HR: 10.29, 95% CI: 3.84–27.62, $P < 0.001$). In addition, auto-HCT was significantly associated with superior OS (HR: 0.03, 95% CI: 0.01–0.16, $P < 0.001$) and reduced NRM (HR: 0.11, 95% CI: 0.02–0.85, $P = 0.034$). Subgroup analyses were then conducted, revealing that post-CCVD remained a strong risk factor for inferior OS (HR: 5.03, 95% CI: 2.20–11.49, $P < 0.001$) and high NRM (HR: 9.15, 95% CI: 3.19–26.29, $P < 0.001$) in allo-HCT recipients. However, post-CCVD was not significant for OS in the auto-HCT subgroup (HR: 12.32, 95% CI: 0.76–199.10, $P = 0.080$) [Table 5]. The effect of post-CCVD on

NRM in auto-HCT subgroup was not investigated since there was only one patient who died of a non-relapse cause.

Discussion

Accurate risk assessment of comorbidities is vital for reducing potential NRM after transplantation. Several transplant-related scoring systems concerning comorbidities and performance status have been used in decision-making in relation to suitable candidates for allo-HCT in the past two decades.^[8] However, the CCVD in these systems was broadly stratified, and the status of cardio-cerebrovascular pathology in these candidates varied. Some patients recovered well from their pre-CCVD before HCT, while some CCVD occurred only weeks before transplant. In this study, individuals who underwent HCT during the same period were matched with age and disease status to ensure similar basic performance status and organ functions under the same clinical protocol and supportive care. Our data showed that pre-CCVD was not a contraindication for HCT but was an independent risk factor for post-CCVD. In addition, the development of short-term post-CCVD (≤ 2 years after HCT) was independently associated with high NRM and inferior OS. Lin *et al*^[19] reported that all cerebrovascular accidents (intra-cranial hemorrhage and cerebrovascular infarction) occurred within 2 years after HCT with an incidence of 6.40% and found that the median OS of patients with post-transplant cardiovascular disease (CVD) was markedly lower than that of patients without post-transplant CVD. A retrospective study by Stillwell *et al*^[9] enrolled 69 patients with CAD who received HCT for hematologic malignancy. The results showed that there was

Table 4: Impacts of pre-CCVD on transplantation outcomes by multivariate analyses.

Outcomes	HR	95% CI	P
Neutrophil engraftment			
Study cohort			
Control group	Reference	Reference	–
Pre-CCVD group	0.750	0.471–1.193	0.224
CD34+			
<3.52 × 10 ⁶ /kg	Reference		
≥3.52 × 10 ⁶ /kg	1.570	1.090–2.262	0.016
Disease stage before HCT			
CR1/CR2	Reference		
Relapse/refractory	0.537	0.360–0.800	0.002
Platelet engraftment			
Study cohort			
Control group	Reference		
Pre-CCVD group	1.306	0.725–2.352	0.374
Length of stay in laminar-flow ward			
Study cohort			
Control group	Reference		
Pre-CCVD group	0.984	0.618–1.568	0.946
Source of graft			
Allo	Reference		
Auto	5.315	1.807–15.630	0.002
Post-CCVD after transplantation			
Study cohort			
Control group	Reference		
Pre-CCVD group	12.500	3.880–40.300	<0.001
Non-relapse mortality			
Study cohort			
Control group	Reference		
Pre-CCVD group	0.515	0.118–2.240	0.377
Source of graft			
Allo	Reference		
Auto	0.006	0–0.120	<0.001
OS			
Study cohort			
Control group	Reference		
Pre-CCVD group	0.656	0.281–1.534	0.331
Source of graft			
Allo	Reference		
Auto	0.064	0.015–0.279	<0.001
Disease stage before HCT			
CR1/CR2	Reference		
Relapse/refractory	3.098	1.559–6.157	0.001
DFS			
Study cohort			
Control group	Reference		
Pre-CCVD group	0.657	0.309–1.400	0.277
Disease stage before HCT			
CR1/CR2	Reference		
Relapse/refractory	2.084	1.169–3.713	0.013

CI: Confidence interval; CR: Complete remission; DFS: Disease-free survival; HCT: Hematopoietic cell transplantation; HR: Hazard ratio; OS: Overall survival; Post-CCVD: Post-transplant cardio-cerebrovascular disease; Pre-CCVD: Previous cardio-cerebrovascular disease.

no difference in NRM (5.60% vs. 4.90%, *P* = 0.777), mortality at 1 year (15.30% vs. 16.60%, *P* = 0.871), or length of stay (*P* = 0.195). However, cardiac events in the CAD group increased with a trend toward significance (*P* = 0.096). The patients in our study were younger (median age: 51 vs. 63 years) and the types of primary diseases were

more homogeneous than those in Stillwell’s study. Although the results from these two studies cannot be compared directly, their conclusion is consistent with ours.

The pre-CCVD had no direct impact on NRM. Nevertheless, post-CCVD was closely associated with high NRM.

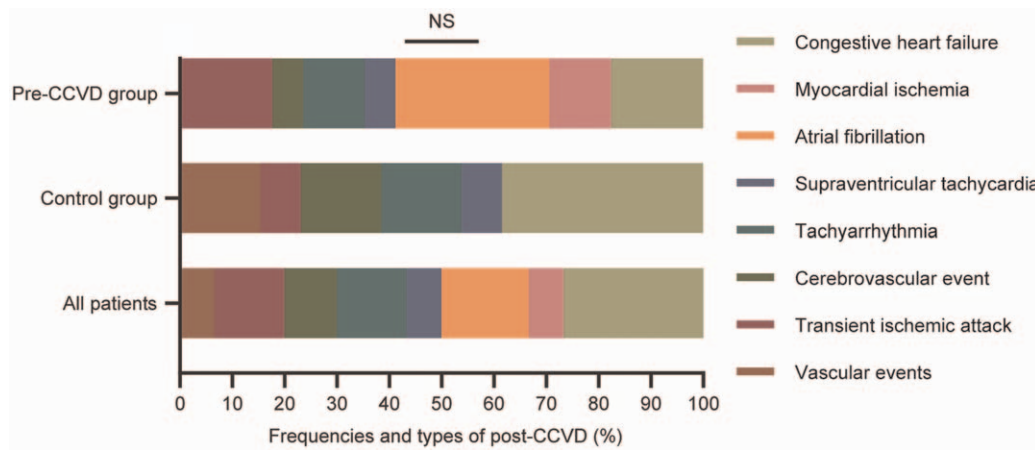


Figure 1: Characteristics of post-CCVD. There was no difference in the types and frequencies of post-CCVD among the pre-CCVD group, control group, and the entire studied population. NS: No significance; Post-CCVD: Post-transplant cardio-cerebrovascular disease; Pre-CCVD: Previous cardio-cerebrovascular disease.

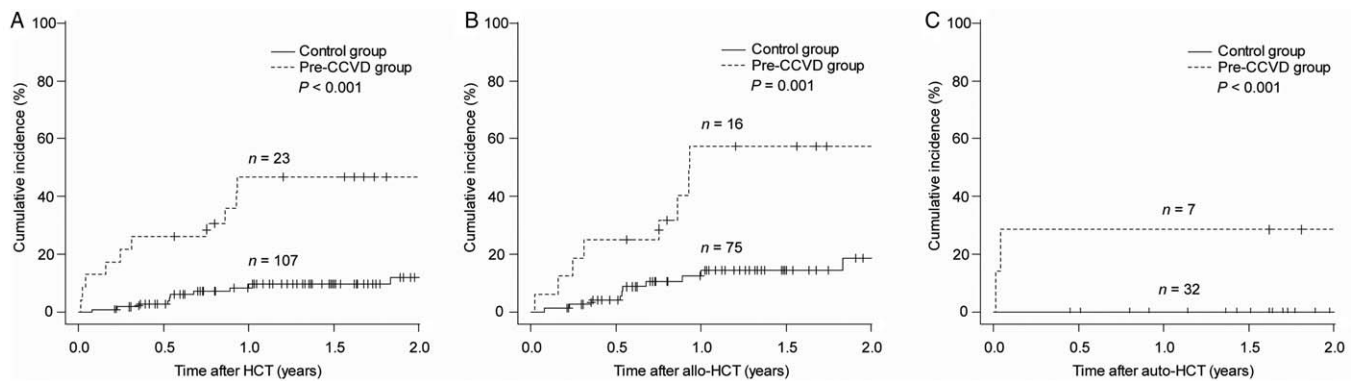


Figure 2: Higher post-CCVD incidence of the pre-CCVD group compared with the control group in patients who received HCT (A), allo-HCT (B), auto-HCT (C). The pre-CCVD group had a higher incidence of post-CCVD than the control group (42.26% vs. 9.67%, $P < 0.001$), and the difference between the two groups was significant in both the allo-HCT subgroup (57.40% vs. 18.80%, $P = 0.001$) and the auto-HCT subgroup (28.60% vs. 0%, $P < 0.001$). Allo-HCT: Allogeneic hematopoietic cell transplantation; Auto-HCT: Autologous hematopoietic cell transplantation; HCT: Hematopoietic cell transplantation; Post-CCVD: Post-transplant cardio-cerebrovascular disease; Pre-CCVD: Previous cardio-cerebrovascular disease.

Thus, we propose that post-CCVD is promoted by the combined effects of pre-CCVD and transplant toxicity. The reason could be that the current evaluation system for pre-transplant comorbidity is still reliable. In other words, patients with pre-CCVD can tolerate current myeloablative transplantation procedures with an HCT-CI score < 3 . However, transplant-related organ injury cannot be ignored. HCT-associated therapeutic exposure doubled the risk of endothelial damage and loss of organ functional reserve in recipients with underlying CV illness. Treatment-related toxicities were especially perceptible in the allo-HCT setting. A retrospective cohort study reported that the frequencies of CV complications within 12 months after auto-HCT and allo-HCT were 16.90%, and 27.30%, respectively.^[20] Among the 18 patients who developed post-CCVD in our study, 88.90% (16/18) underwent allo-HCT and only 11.10% (2/18) underwent auto-HCT. This data indicates that allo-HCT leads to higher CV toxicity than auto-HCT, suggesting that post-CCVD is a strong predictor for transplant-associated toxicity on survival. As organ damage resulting from HCT could be transient or irreversible, the prognostic value of post-CCVD needs to be evaluated dynamically. In addition, post-CCVD promoting NRM may be confounded in cases in which

post-CCVD was just one manifestation of NRM in patients before death. However, in the current study, post-CCVD caused by infections or MODS were not included for analysis. Furthermore, post-CCVD occurred much earlier than NRM after HCT. Therefore, our data suggest that post-CCVD might directly reduce the patient's tolerance to management within 2 years after transplantation leading to NRM. Compared with pre-CCVD, post-CCVD has much more direct impacts on outcomes.

CV complications can develop early or late after HCT, leading to morbidity, poor quality of life, and premature mortality. Post-CCVD remains a devastating complication in the modern era. The risk of developing post-CCVD after HCT depends on the patient's age, primary disease, vital organ function, the intensity of past treatment, previous comorbidity, and transplantation protocol.^[7,19] It should be noted that due to differences in the definitions of post-CCVD, the actual incidence of post-CCVD may be underestimated in some studies. The incidence of early fatal cardiotoxicity during the first 100 days post-transplant was reported to be 0.90% to 10.00%, of which the most common events were HF and arrhythmia.^[21] A recent meta-analysis revealed that the estimated

Table 5: Impacts of post-CCVD on transplantation outcomes by multivariate analyses.

Outcomes	HR	95% CI	P
Non-relapse mortality			
Post-CCVD			
No	Reference		
Yes	10.290	3.837–27.620	<0.001
Source of graft			
Allo	Reference		
Auto	0.112	0.015–0.849	0.034
OS			
Post-CCVD			
No	Reference		
Yes	6.530	3.090–13.800	<0.001
Disease stage before HCT			
CR1/CR2	Reference		
Relapse/refractory	3.928	1.907–8.092	<0.001
Source of graft			
Allo	Reference		
Auto	0.030	0.006–0.156	<0.001
Primary disease			
AML	Reference		
ALL	2.791	1.261–6.177	0.011
Non-relapse mortality in allo-HCT subgroup			
Post-CCVD			
No	Reference		
Yes	9.153	3.187–26.290	<0.001
Overall survival in allo-HCT subgroup			
Post-CCVD			
No	Reference		
Yes	5.031	2.203–11.490	<0.001
Cumulative chemotherapy cycles			
<6	Reference		
≥6	2.335	1.168–4.670	0.016
Primary disease			
AML	Reference		
ALL	2.791	1.261–6.177	0.011
Overall survival in auto-HCT subgroup			
Post-CCVD			
No	Reference		
Yes	12.320	0.762–199.100	0.077
Disease stage before HCT			
CR1/CR2	Reference		
Relapse/refractory	18.350	2.031–165.800	0.009

ALL: Acute lymphoblastic leukemia; Allo-HCT: Allogeneic hematopoietic cell transplantation; AML: Acute myeloid leukemia; Auto-HCT: Autologous hematopoietic cell transplantation; CI: Confidence interval; CR: Complete remission; HCT: Hematopoietic cell transplantation; HR: Hazard ratio; OS: Overall survival; Post-CCVD: Post-transplant cardio-cerebrovascular disease.

incidence of all types of arrhythmia following HCT was 7.20% (95% CI: 4.90–10.50), and the most common type was AF/AFL, with an estimated incidence of 4.20% (95% CI: 1.70–9.60).^[22] In our study, the most common post-CCVD were also HF and arrhythmia (6.02% and 5.26%, respectively). Late post-CCVD was reported to be associated with chemotherapy toxicity, CVRFs, chronic graft-*vs.*-host disease, and long-term physical inactivity.^[10] Recent data about the relevant risks of cardiotoxicity in transplantation recipients showed that age (older), creatinine (higher), and history of CAD were significantly correlated with the risk of post-transplant cardiac events.^[23] Our multivariable analysis showed that post-CCVD was significantly affected by pre-CCVD

($P < 0.001$). Alblooshi *et al*^[24] recently demonstrated that a history of CV disease, myocardial infarction, or CAD was the most important predictor of CV events in the first 100 days after HCT ($P = 0.00002$). A controlled study found that cardiac autonomic functioning was impaired 1 to 10 years after allo-HCT, which may be associated with post-CCVD. These patients showed a higher average heart rate ($P < 0.00010$) and lower parasympathetic control ($P < 0.001$) than the healthy group.^[25] Steuter *et al*^[26] retrospectively studied 516 patients who received auto-HCT and found that a history of arrhythmia was a risk factor for developing AF/AFL following HCT (odds ratio: 9.33, $P < 0.001$). However, the clinical impact of post-HCT arrhythmia needs to be further elucidated. Chow

et al^[27] found that transplant recipients experienced more CVD ($P < 0.010$) and were more likely to develop premature CVD death (adjusted incidence difference, 3.6 cases per thousand person-years [95% CI: 1.70–5.50]) than the general population. This indicates that there is a nearly four-fold increased risk of CVD death among HCT survivors (>2 years). Not surprisingly, the risk of late CVD-related mortality is significantly higher in HCT recipients. Our study showed that relatively early-onset post-CCVD (median days after HCT: 136 days [1–595 days]) were significantly associated with NRM and OS. This predictive role of post-CCVD was also observed in the allo-HCT subgroup, but not in the auto-HCT subgroup. A comparative study found that the risk of late arterial events after allo-HCT was significantly higher than that after auto-HCT (incidence at 15 years after HCT: 7.50% vs. 2.30%; $P = 0.009$)^[28] which may also suggest the different burdens between auto-HCT and allo-HCT. Considering the small number of post-CCVD ($n = 2$) following auto-HCT in our patients, the effect of early post-CCVD on auto-HCT needs to be further evaluated in a larger study.

The optimal time for CV screening after HCT has yet to be determined.^[10] Regular screening has not been widely conducted early in HCT recipients but mostly in long-term survivors.^[29] Early identification of post-CCVD may optimize HCT outcomes. Scott *et al*^[10] suggested that a combined evaluation of exercise testing, imaging, and blood markers could enable the detection of early post-CCVD and contribute to early intervention. Compared with conventional detection methods, biomarkers have the advantages of high sensitivity and accuracy. Multiple biomarkers are superior to a single biomarker for the prediction of CCVD.^[30] Specific biomarkers of CCVD include cardiac troponin, suppression of tumorigenicity-2, growth differentiation factor 15, N-terminal-pro-B-type natriuretic peptide, and homocysteine. In addition, some emerging biomarkers are shown to be associated with CCVD risk.^[31] Recent studies found that microRNA is very important to the proliferation, survival, and function of effector T cells in acute graft-*vs.*-host disease (aGVHD).^[32] aGVHD is also involved in the pathological process of early post-CCVD. Therefore, these biomarkers may provide new insights into the biological mechanism of post-CCVD. Metabonomic is promising in discovering new biomarkers of CCVD. Metabolites associated with CVD risk include several amino acids, carnitine, and lipid classes.^[33] The pathophysiology involved in CCVD after HCT is complex. Cooperation of conventional CV screening, biomarkers, and metabolites is promising for the early identification and prevention of post-CCVD. Based on our retrospective data, current HCT-specific recommendations for a yearly evaluation of CV risk should be implemented early in HCT patients, especially in the allo-HCT setting.

This study was limited by its retrospective nature and sample size. The conclusions require confirmation with prospective studies with larger sample sizes. Indeed, few patients with pre-CCVD have undergone the transplant procedure in the past 20 years, but this is expected to change following the conduction of additional studies. Furthermore, this result cannot be extrapolated to all HCT candidates with pre-CCVD. There are still no strict criteria

for the status of pre-CCVD patients who can undergo the transplant procedure.^[9,12,34] The benefits of HCT and the mortality risk of pre-CCVD for different statuses (stable or unstable) need to be assessed jointly by the cardiologist and the hematologist. However, there were patients with both pre-existing and recently developed pre-CCVD in our study. This population may not represent all HCT candidates with different pre-CCVD status, but rather those who have received HCT in the real world. Additionally, patients with multiple myeloma (MM) were not enrolled in the current study. These patients may develop cardiac amyloidosis, forming the pathologic basis of myocardial damage and HF.^[35] Therefore, the findings cannot be applied to patients with MM who received HCT. We believe that this study will help more CCVD patients, who are evaluated as poor candidates, to currently obtain access to HCT and contribute to the conduct of multicenter research.

In conclusion, patients with pre-CCVD could tolerate HCT well, but with an increased risk of early post-CCVD. Post-CCVD may be promoted by the combined effects of pre-CCVD and transplant toxicity. Post-CCVD was a powerful predictor of high NRM and inferior OS. The risk of pre-CCVD on the post-CCVD occurrence and that of early post-CCVD on outcomes need to be further stratified to reduce NRM in various transplantation settings.

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Conflicts of interest

None.

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