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Incidence of Cardiovascular Events in Patients Receiving Hematopoietic Stem Cell Transplant (HSCT) In HCTM – (A Retrospective Cohort Study)

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Abstract

Background: Hematopoietic stem cell transplantation (HSCT) offers curative potential for hematologic malignancies but carries risks of cardiovascular events (CE). Existing data are predominantly from Western populations, with limited evidence from Asian centers.

Objectives: To determine the incidence of short-term (<100 days) and long-term (1-year) cardiovascular events post-HSCT at Hospital Canselor Tuanku Muhriz (HCTM), and to identify associated risk factors, including the usage CARE-BMT score in risk stratification.

Methods: This retrospective cohort study included adult patients who underwent autologous or allogeneic HSCT from 2000 to 2024 at HCTM. Data collected via manual and electronic medical records which included demographics, comorbidities, transplant type, conditioning regimens, and cardiovascular outcomes (heart failure, arrhythmia, myocardial infarction, stroke, cardiac death). Statistical analysis comprises of descriptive and unadjusted univariate tests.

Results: A total of 117 patients were included (63 allogeneic, 54 autologous). The 1-year incidence of cardiovascular events (CE) was 5.1% (6/117), with a higher rate among allogeneic recipients (9.3%) compared to autologous (1.6%). Unadjusted odds ratio (OR) analysis revealed that allogeneic transplant was associated with a higher, albeit nonsignificant, risk of CE (OR 3.84, 95% CI 0.42–34.95). Other factors with elevated but non-significant ORs included obesity (OR 2.91, 95% CI 0.32–26.72), hypertension (OR 2.57, 95% CI 0.28–23.95), and CARE-BMT intermediate/high risk score versus low (OR 7.68, 95% CI 0.86–68.28). Reduced baseline left ventricular ejection fraction (<50%) showed the highest estimated risk (OR 64.7, 95% CI 3.2–1304.8), but with a very wide confidence interval due to limited events. Most events occurred within 100 days post-transplant, and 83% of CE cases had intermediate/high CARE-BMT scores. However, multivariate analysis was limited by the small number

of events and wide confidence intervals.

Conclusions: The incidence of cardiovascular events post-HSCT in this Malaysian cohort was comparable to global data, with higher rates in allogeneic recipients and those with intermediate/high CARE-BMT scores. Most events occurred early post-transplant and in patients with traditional or transplant-specific risk factors. CARE-BMT score and baseline cardiac function may help stratify risk. Ongoing monitoring and tailored preventive strategies are necessary for this population. Future larger multi-center, prospective studies are required to confirm these trends and guide targeted cardio-oncology interventions for HSCT recipients in Malaysia.

1. Introduction

Hematopoietic stem cell transplant (HSCT) has emerged as a pivotal treatment for hematological malignancies such as leukemias, lymphomas, and multiple myeloma. Over the past two decades, therapeutics have advanced from conventional chemotherapy to HSCT, and newer cellular therapies (i.e., CAR-T) have significantly improved patient outcomes, including higher remission rates and longer progression-free survival, compared to salvage chemotherapy or palliative care (Hayek *et al*., 2024)[1]. In HSCT, the patient's bone marrow is first ablated with intensive conditioning chemotherapy, and then replaced with hematopoietic stem cells either from the patient (autologous HSCT) or from a donor (allogeneic HSCT). This process not only rescues marrow function but also confers a graft-versus-tumor effect in allogeneic transplants, which can eradicate residual cancer cells (Hayek *et al*., 2024). However, the high-dose chemotherapeutic agents used in conditioning (e.g., cyclophosphamide, busulfan, fludarabine, melphalan) are well-known for their toxicities and have been implicated as major contributors to cardiovascular complications post-transplant.

Despite the curative potential of HSCT, it is associated with considerable short- and long-term morbidity and mortality due to treatment-related toxicities. Cardiovascular events (CE) have become increasingly recognized among HSCT survivors both during therapy and in long-term follow-up. Common cardiovascular events observed include arrhythmias (particularly atrial fibrillation/flutter), heart failure, hypertension, myocardial infarction, stroke, and cardiac death (Vasbinder *et al*., 2023)[2]. The etiology of these post-HSCT cardiac events is multifactorial. Proposed mechanisms span direct cardiotoxic injury from conditioning chemotherapy, hyperinflammatory states during engraftment, and immune-mediated damage from graft-versus-host disease (GVHD). In addition, many HSCT patients have also been heavily pre-treated with cardiotoxic agents such as anthracyclines before transplant, compounding their risk. Furthermore, the prophylactic and therapeutic use of immunosuppressants to manage GVHD in allogeneic HSCT can lead to metabolic complications (such as dyslipidemia, hypertension, and insulin resistance), which in turn predispose patients to cardiovascular disease in the long run (Miller, 2002)[3].

Evidence to guide pre-transplant cardiovascular evaluation and post-transplant surveillance in HSCT patients is still evolving. Earlier studies identifying risk factors for cardiovascular outcomes largely involved pediatric or young adult cohorts and may not reflect current HSCT practices (Armenian *et al*., 2010)[4]. With the expansion of HSCT eligibility to older adults and those with comorbidities, contemporary cohorts present a different risk profile that requires updated risk stratification. In 2022, the

American Heart Association introduced a dedicated risk score known as CARE-BMT to aid in pre-HSCT cardiovascular risk assessment (Vasbinder *et al.*, 2024)[5]. The CARE-BMT score is a simple tool that stratifies transplant candidates based on factors like age, baseline cardiovascular risk factors, and transplant-related variables, aiming to predict post-transplant cardiovascular events. In theory, this score could help identify high-risk patients who require closer cardiac monitoring or preventive interventions. Unfortunately, to date, it has not been widely implemented in routine clinical practice, and its predictive value in real-world settings remains to be validated. This underscores the need for further research on the applicability of such risk models and the effectiveness of any interventional strategies guided by them.

In summary, while the overall incidence of cardiovascular events post-HSCT is reported to be relatively low, there is a growing body of evidence of higher long-term risk, especially among allogeneic HSCT recipients and those with pre-existing cardiovascular risk factors. Importantly, most published data are from Western populations – for example, an extensive cohort study by Vasbinder *et al.* (2023)[2] noted short-term (<100 days) incidence of 4.1% and long-term (1-year) incidence of about 10.2% in predominantly European patients, with arrhythmias and heart failure being the most common events. There is currently a paucity of data from Asian populations, including Malaysia, and it is unclear if the incidence and risk factor profile of post-HSCT cardiovascular events are similar in our local setting. Differences in patient demographics, prevalence of comorbidities, genetic factors, and treatment protocols may influence outcomes, making it impossible to directly extrapolate Western data to Asian cohorts.

Hence, this study aims to determine the incidence of cardiovascular events following HSCT in a Malaysian tertiary center and to explore associated risk factors in our patient population. The findings will help fill the gap in local data and could inform future patient care strategies, risk stratification, and long-term follow-up protocols for HSCT survivors in Malaysia.

2. Literature Review

Incidence of Cardiovascular Events Post-HSCT: Cardiovascular complications after HSCT can be broadly categorized into early (short-term, <100 days post-transplant) and late events (>100 days, often assessed at 1-year or beyond). Vasbinder *et al.* (2023)[2] conducted a cohort study of 3,354 adult HSCT patients and reported an overall incidence of cardiovascular events of 4.1% in the short term (within 100 days) and 10.2% in the long term (within the first year). Arrhythmias (particularly atrial fibrillation or flutter) were the most frequently observed events, followed by heart failure in their cohort. Interestingly, Vasbinder et al. noted no significant difference in short-term event rates between autologous and allogeneic transplants. However, certain conditioning regimens (notably fludarabine/busulfan-based) were associated with a higher short-term cardiovascular event rate of around 20%, especially in patients with pre-existing risk factors. In the same study, the long-term incidence (up to one year) of cardiovascular events was higher in allogeneic HSCT recipients compared to autologous recipients (16.8% vs 12.1%), although the incidence of major atherosclerotic events like myocardial infarction, stroke, or cardiovascular death remained very low (<1%). These findings emphasize that while transplant-related cardiac complications are relatively uncommon in the immediate phase, vigilance is

required in the longer term, particularly for allogeneic patients.

Risk Factors and Mechanisms: The pathophysiology behind post-HSCT cardiovascular events is complex and multifactorial. Early events (within 100 days) are often linked to the intense inflammatory and physiological stress of transplantation.

In allogeneic HSCT, acute graft-versus-host disease (GVHD) and engraftment syndrome may provoke a hyperinflammatory state, vascular endothelial injury, and a prothrombotic environment, which can manifest as arrhythmias or heart failure exacerbations in susceptible patients. Alblooshi *et al*. (2021)[6] specifically examined allogeneic transplant recipients during the first 100 days. They found that nearly all cardiovascular events in their series occurred early, often in conjunction with acute GVHD or infections. On the other hand, late-onset cardiovascular events (beyond day 100) are thought to be influenced by chronic GVHD, prolonged immunosuppressive therapy, and the development of metabolic syndrome features.

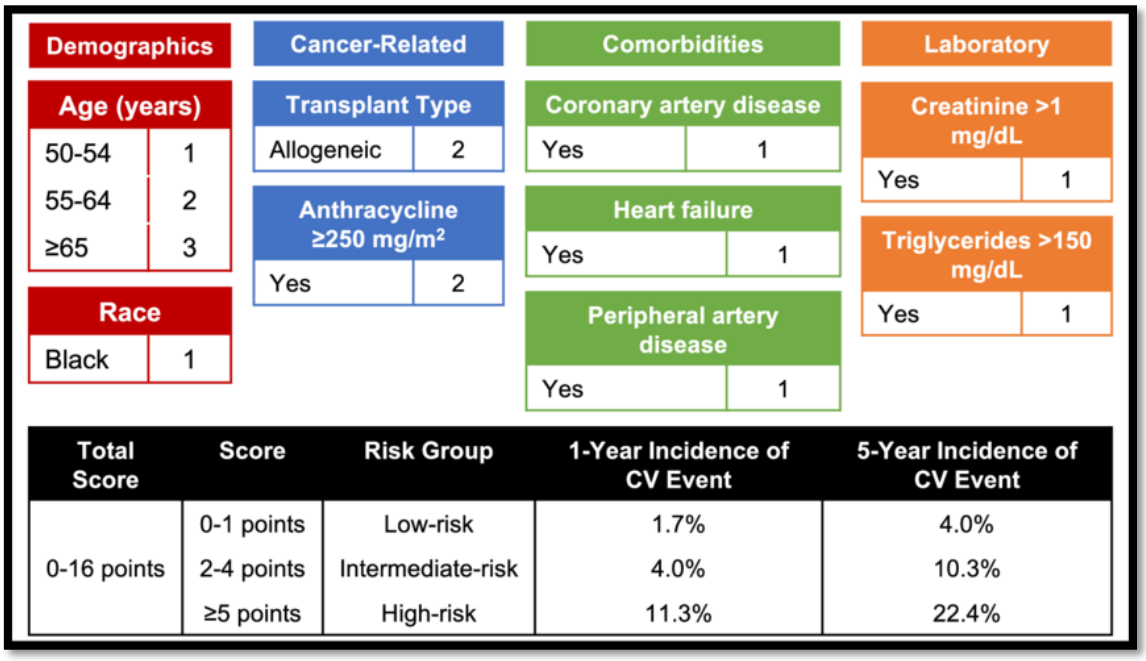
Chronic GVHD and its treatment (typically with corticosteroids and calcineurin inhibitors) contribute to hypertension, dyslipidemia, insulin resistance, and weight gain in survivors. Armenian *et al*. (2018)[7] reported that HSCT survivors have a high prevalence of traditional cardiovascular risk factors years after transplant, partly attributable to these effects, and these factors significantly predicted late cardiovascular disease outcomes in their cohort. Additionally, total body irradiation (TBI) used in some conditioning regimens has been linked to premature atherosclerosis and cardiomyopathy in long-term survivors (Armenian *et al*., 2010)[4], although TBI is less commonly used in adults now.

Allogeneic vs Autologous Transplant Outcomes: Several studies have observed differences in cardiovascular event profiles between autologous and allogeneic HSCT. Allogeneic recipients tend to have more complications overall due to the added immune-mediated issues. As noted, Vasbinder et al. observed a higher 1-year CV event rate in allogeneic patients (16.8%) relative to autologous (12.1%), though short-term rates were similar. Our literature search did not find a significant short-term difference in outcomes by transplant type in large cohorts, suggesting that immediate peri-transplant stress affects patients similarly regardless of graft source. In contrast, longer-term, allogeneic-specific factors, such as graft-versus-host disease (GVHD) and long-term immunosuppression, likely drive the divergence in risk.

For example, a European study by Alblooshi et al. (2021)[6] focusing on the first 100 days post-allogeneic HSCT reported an incidence of acute cardiac events around 6%, in line with general short-term rates, but highlighted that those with pre-existing cardiovascular risk factors had a disproportionately higher rate of heart failure and arrhythmias. Similarly, Armenian *et al*. (2018)[7] and others have noted that allogeneic transplant survivors are more prone to develop conditions like hypertension and dyslipidemia during follow-up, which could contribute to late cardiac events. In contrast, autologous transplant patients typically have shorter durations of therapy and immunosuppression, possibly explaining their lower long-term event rates.

Pre-transplant Cardiac Evaluation and Scoring Systems: Given the potential for serious cardiac complications, guidelines stress the importance of pre-transplant cardiac evaluation. Typically, this includes a thorough history and examination, assessment of traditional risk factors, and baseline cardiac imaging (such as an echocardiogram) to measure left ventricular ejection fraction (LVEF). Most transplant centers require a satisfactory LVEF (often >50%) and stable cardiac status before proceeding with HSCT. However, even patients with normal pre-HSCT cardiac function can experience events. In fact, in one analysis of our data, 5 of the 6 patients who had cardiovascular events post-HSCT had normal baseline LVEF >50%, indicating that preserved cardiac function prior to transplant does not guarantee immunity from post- transplant cardiac complications. This aligns with the notion that non-traditional factors (inflammation, endothelial damage) play a major role, as reported in prior studies (Armenian *et al*., 2018)[7]. To enhance risk stratification, Vasbinder et al. (2024)[5] proposed the CARE-BMT score. This scoring system incorporates patient age, baseline comorbidities (like hypertension, diabetes), type of transplant, and disease status to categorize patients into low, intermediate, or high risk for post-HSCT cardiovascular events. In the original development study, the high-risk group had a significantly greater incidence of early cardiovascular complications. However, external validation is needed. To date, no published studies have evaluated CARE-BMT in an Asian cohort. Our study therefore also provides an opportunity to observe the distribution of CARE-BMT scores in a local population and their relation (if any) to actual outcomes.

Figure 1: CARE-BMT risk score model



CARE-BMT risk score by Alexi Vasbinder et.al
Journal of the American Heart Association, Volume 13, Number 1.
https://doi.org/10.1161/JAHA.123.033599

In conclusion, the literature indicates that while cardiovascular events are not very common following HSCT, they are clinically important due to their potential impact on morbidity and mortality in survivors. Key risk factors identified include pre-existing cardiovascular conditions, older age,

allogeneic transplant (with its associated complications), and certain transplant regimens. Preventive strategies such as aggressive management of risk factors, cardioprotective interventions (e.g., beta-blockers or ACE inhibitors in high-risk patients, though evidence is limited), and close monitoring, especially in the first year post-transplant have been suggested (Hayek *et al*., 2024)[1]. Nonetheless, a clear understanding of incidence and predictors in our local context is lacking, which this thesis aims to address.

3. Methodology

3.1 Study Design and Setting

This research was designed as a single-centre retrospective cohort study. The study was conducted at Hospital Canselor Tuanku Muhriz (HCTM), which is the principal teaching hospital of Universiti Kebangsaan Malaysia (UKM) and a tertiary referral center for hematology and stem cell transplantation. The study period spanned from January 2000 to June 2024. All adult patients who underwent HSCT (either autologous or allogeneic) at HCTM during this period were considered for inclusion. The aim was to capture a comprehensive cohort over 20 years to ensure an adequate sample size and follow-up duration for observing post-transplant cardiovascular events. Ethical approval for the study was obtained from the UKM Research Ethics Committee prior to data collection, and the principles of confidentiality and anonymity were strictly adhered to (no personal identifiers are reported in this thesis).

Hypothesis: There is a notable gap in the literature regarding cardiovascular outcomes after hematopoietic stem cell transplantation (HSCT) in Asian populations, particularly concerning the incidence of cardiovascular events (CE) and their risk factors. To address this gap, the present study will investigate patients receiving HSCT at HCTM, focusing on both short-term (within 100 days post-transplant) and long-term (at one year post-transplant) adverse CEs. It will determine the overall incidence of CEs in this patient population and examine potential predictors of these events. In particular, a range of patient-specific, transplant-related, and cancer-related factors will be evaluated for their association with the development of CEs following HSCT. Additionally, the study will assess whether the CARE-BMT risk score is correlated with the occurrence of post-HSCT cardiovascular complications.

Based on current knowledge, it is hypothesized that the overall incidence of CEs among HSCT patients is low (below 5%)[2]. Furthermore, allogeneic HSCT recipients are expected to experience a higher incidence of CEs compared to autologous HSCT recipients. Finally, patients with traditional cardiovascular risk factors are anticipated to have an elevated risk of developing CEs following transplantation.

Research Objectives: The *primary objective* of this study is to determine the incidence of the first CE in patients undergoing HSCT at HCTM. In this context, a "cardiovascular event" is defined as the occurrence of any of the following: heart failure (characterized by typical symptoms along with a documented decline in left ventricular ejection fraction), an arrhythmia such as atrial flutter or atrial fibrillation, a non-fatal myocardial infarction, a non-fatal stroke, or cardiac-related death. This primary

objective encompasses evaluating events in both the short term (within 100 days post-transplant) and the longer term (up to one year post-transplant).

The *secondary objectives* of the study are threefold. First, the study will identify patient-specific, transplant-related, and cancer-related risk factors that are associated with developing a CE after HSCT. Second, it will compare the incidence of CEs between autologous HSCT recipients and allogeneic HSCT recipients. Third, it will examine the relationship between the pre-transplant CARE-BMT risk score and the incidence of CEs following HSCT.

3.2 Study Population and Sample Selection

The target population was adult HSCT recipients in HCTM. The inclusion criteria were: (i) patients aged 18 years or older at the time of transplant, and (ii) patients who underwent a first HSCT (either autologous or allogeneic) at HCTM between 2000 and 2024. We focused only on the first transplant event per patient to standardize exposure and follow-up.

Exclusion criteria were: (i) patients with incomplete medical records (critical data missing on either transplant details or outcomes), and (ii) any patient who underwent HSCT but was lost to follow-up *within 100 days post-transplant* (to ensure they had at least the short-term observation window for event assessment, although early deaths were separately noted). Patients undergoing tandem or second HSCT during the study period were also excluded from incidence calculations (to avoid interdependent observations), but none in our dataset fulfilled this scenario.

We employed a universal sampling approach, including all HSCT cases that met the specified criteria within the specified timeframe. The total sample identified was 117 patients (54 allogeneic HSCT and 63 autologous HSCT). This approach was feasible given the modest number of transplants performed at HCTM (approximately 2–3 per month). By including the entire population of interest, we aimed to maximize the study power and avoid selection bias.

3.3 Collection Procedures

Data were obtained by retrospective review of both manual and electronic medical records. A standardized data collection sheet was used to extract relevant information for each patient, including:

- Demographics: age at transplant, sex, and self-reported race/ethnicity.
- Baseline medical history: presence of cardiovascular risk factors such as hypertension, diabetes mellitus, obesity (defined by BMI ≥30), and dyslipidemia prior to HSCT. We also recorded any history of cardiac disease (e.g., coronary artery disease, heart failure) if documented.
- Disease and transplant details: underlying hematologic diagnosis (e.g., acute myeloid leukemia, lymphoma, multiple myeloma, etc.), transplant type (allogeneic vs autologous), conditioning chemotherapy regimen (agents used, myeloablative vs reduced intensity), use of total body irradiation, prior exposure to cardiotoxic chemotherapy (anthracyclines) or chest radiotherapy, and
in allogeneic cases, donor type and GVHD prophylaxis regimen.
- Baseline cardiac evaluation: results of pre-transplant echocardiogram including left ventricular

ejection fraction (LVEF) and any noted abnormalities (valvular disease, etc.). Baseline ECG findings were also noted (rhythm, any arrhythmia). We categorized baseline LVEF as normal (≥50%) or abnormal (<50%).

- CARE-BMT score: Using the data above, each patient's CARE-BMT risk score was calculated as per published criteria (Vasbinder *et al.*, 2024). Patients were then classified into the risk categories defined by CARE-BMT (Low, Intermediate, High).
- Outcomes: occurrence of any cardiovascular event of interest from the time of HSCT up to either one-year post-transplant or last follow-up (if earlier). The events tracked were: new arrhythmia (primarily atrial fibrillation or flutter, sustained SVT or VT), heart failure (new onset or acute decompensation, defined by clinical symptoms with objective cardiac dysfunction on imaging), acute coronary syndrome or myocardial infarction, cerebrovascular accident (stroke or TIA), peripheral arterial thrombosis, and cardiac-related death (sudden cardiac death or death primarily due to cardiac causes). For each event, the timing (date post-HSCT) was recorded. We also collected data on acute GVHD occurrence (yes/no and grade) for allogeneic patients, as well as overall survival status at 1 year.

Data extraction was performed by the researcher and cross-verified by a second reviewer for accuracy. Any ambiguities in the records were resolved by consulting the treating clinicians or via consensus among the research team. The data were then entered into a secure database for analysis. Each patient was assigned an anonymous study ID; no names or identifiable details were used in the analysis or this write-up.

The study began with identifying all patients who underwent HSCT at HCTM from 2000–2024 through hospital databases and transplant registries. After applying inclusion and exclusion criteria, eligible patient records were retrieved. Relevant clinical data were collected systematically as per the data sheet. The compiled dataset was then analyzed statistically to address the study objectives, and the findings were interpreted in context of existing literature.

3.4 **Sample Size Consideration**

Prior to data collection, a sample size estimation was conducted to ensure the study would be adequately powered to estimate the incidence of cardiovascular events. We anticipated a relatively low event rate (~4– 5%) based on Vasbinder *et al*. (2023) and other reports.

Using an expected proportion $p \approx 0.04$ and a 95% confidence level, we applied a single proportion formula:

$$N = \frac{Z^2\, p\,(1-p)}{d^2},$$

where $Z = 1.96$ for 95% confidence, $d = 0.05$ (absolute precision). Plugging in $p = 0.04$:

$$N = \frac{(1.96)^2 \times 0.04 \times 0.96}{0.05^2}$$

$$\approx 59.$$

Accounting for an approximate 20% potential drop-out or missing data, the target sample size was about 72 patients. Our actual sample (117 patients) exceeds this number, suggesting that the study is sufficiently powered to estimate the incidence with the desired precision. However, for analyzing risk factors, particularly through multivariate regression, the number of outcome events (n = 6) is a limiting factor – a point to consider when interpreting the results.

3.5 Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics (Version 26.0). We employed two-tailed tests and set a significance threshold of $p < 0.05$ for all comparisons. The analysis approach was as follows:

- **Descriptive statistics**: Patient characteristics and outcome frequencies were summarized. Categorical variables are presented as counts and percentages. Continuous variables were assessed for normality; normally distributed data are reported as mean ± standard deviation (SD), whereas non-normal data are reported as median with interquartile range (IQR).

- **Comparative analysis**: To compare baseline characteristics between groups (e.g., those who had a CV event vs those who did not; allogeneic vs autologous recipients), we used appropriate bivariate tests. The chi-square test (or Fisher's exact test when expected cell counts were <5) was used for categorical variables. For continuous variables, an independent-samples t-test was used if approximately normally distributed (or if sample size was large enough for the Central Limit Theorem to apply), otherwise the Mann-Whitney U test was employed. These analyses helped identify any significant differences or associations without adjusting for confounders.

- **Logistic regression**: To identify independent predictors of cardiovascular events, we planned a logistic regression model. Given the low number of events (6), a cautious approach was taken to avoid model overfitting. We included a limited number of predictors based on clinical relevance and bivariate results. The final model included: transplant type (allogeneic vs autologous) and presence of any baseline cardiovascular risk factor (a composite of hypertension, diabetes, or obesity) as covariates. These factors were chosen because they exhibited a marked imbalance between the event and non-event groups and are supported by clinical reasoning.

The outcome variable was the occurrence of any CV event (yes/no). We reported the adjusted odds ratios (OR) with 95% confidence intervals and p-values for each covariate. Due to the very small event count, the regression should be interpreted with caution (wide CIs and possible instability). We did not include additional variables in the model to preserve degrees of freedom; other factors, such as age and CARE-BMT score, were analyzed descriptively.

- **Time-to-event analysis**: We did considered a Kaplan-Meier survival analysis for time to cardiovascular event within one year, treating non-occurrence as censored at last follow-up or one year. However, since all events occurred relatively early and we did not observe any events beyond 100 days,

a formal survival curve was not very informative (it essentially showed a flat line with a few drops early on). Therefore, we present the incidence and timing in a descriptive manner instead.

The results are presented in the next chapter, accompanied by tables and figures where appropriate. All p-values are two-sided. For transparency, any borderline p-value (e.g., 0.05–0.10) is reported to one decimal place to avoid misunderstanding.

4. Results

4.1 Patient Characteristics

A total of 117 patients who underwent HSCT at HCTM from 2000–2024 were included in the analysis, comprising 63 allogeneic and 54 autologous transplants. The underlying diagnoses varied between the transplant types. Autologous HSCT was predominantly performed for plasma cell and lymphoid malignancies (e.g., multiple myeloma in 2 patients, diffuse large B-cell lymphoma in 9 patients, Hodgkin lymphoma in 20 patients), with some cases for aggressive leukemias if eligible (4 AML cases received auto-HSCT in our cohort). In contrast, allogeneic HSCT was mainly done for acute leukemias and other marrow disorders (24 cases of acute myeloid leukemia, 20 acute lymphoblastic leukemia, 3 myelodysplastic syndrome, and 2 Hodgkin lymphoma underwent allo-HSCT; there were no allogeneic transplants for myeloma or DLBCL in this series). The category “Other” (14 allogeneic, 19 autologous) included diagnoses such as aplastic anemia or T-cell lymphoma and some less common indications.

The demographic breakdown showed a slight male predominance: overall 58% male. The allogeneic group had 33 males (61%) and 21 females, while the autologous group had 35 males (56%) and 28 females.

The ethnic composition reflected the hospital’s patient population, with the majority being Malay (approximately 59%), followed by Chinese (32%), Indian (3%), and others (6%). The median age at transplant for the entire cohort was 30 years (IQR 30–33). Notably, allogeneic recipients were younger on average (median 28 years) compared to autologous (median 34 years), since many autologous transplants (especially for myeloma) were done in older adults.

Baseline cardiovascular risk factors were present in a minority of patients overall, given the relatively young cohort: 9% had hypertension, 8% had diabetes mellitus, and 10% were classified as obese. The prevalence of these risk factors was slightly higher in the autologous group (who were older and often had prior therapies causing weight gain) than in the allogeneic group. For instance, 7 autologous patients (11%) were hypertensive vs 4 allogeneic (7%); 7 autologous (11%) had diabetes vs 3 allogeneic (6%). Dyslipidemia was infrequently documented (~5% overall). Only 1 patient had a known history of ischemic heart disease (a controlled coronary artery disease in an autologous transplant patient), and none had pre-existing heart failure.

All patients had a baseline left ventricular ejection fraction (LVEF) of at least 45% prior to transplant.

The vast majority (≈95%) had normal LVEF ≥50%, with only a handful of patients showing mild asymptomatic reductions (in the 45–50% range). This reflects the standard practice of ensuring adequate cardiac function before proceeding to HSCT. Baseline electrocardiograms were normal sinus rhythm for all patients, except one autologous patient with benign first-degree AV block. No patient had a history of atrial fibrillation or other arrhythmia prior to HSCT.

Table 1: Patients Demographic

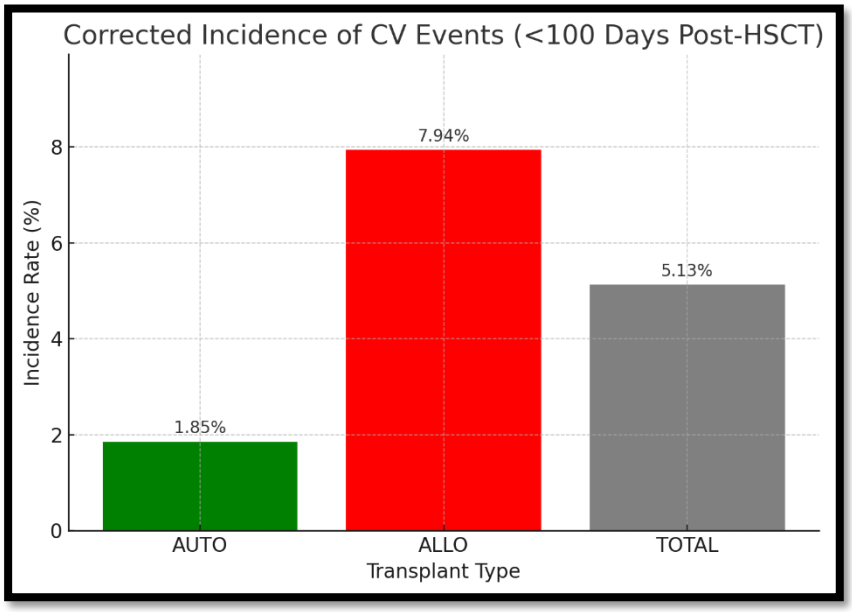
BASELINE CHARACTERISTIC		
Transplant type, n	**ALLO**	**AUTO**
	63	**54**
Ethnicity, n		
Malay	42	27
Chinese	17	20
Indian	1	3
Other	3	4
Gender		
Male, n (%)	33	35
Female, n (%)	30	19
Clinical characteristics		
BMI, median (SD)	22.9	20
Hypertension	4	5
Diabetes mellitus	3	7
Chronic kidney disease	0	1
Coronary artery disease	0	1
Myocardial infarction	0	0
Obesity	6	2
Dyslipidemia	1	5
Atrial fibrillation/flutter/SVT	1	0
Heart failure	1	1
Transplant diagnosis, n		
Multiple myeloma	0	2
DLBCL	0	9
Hodgkin lymphoma	2	20
AML	24	4
ALL	20	0
Myelodysplastic Syndrome	3	0
Other	14	19

4.2 Incidence of Cardiovascular Events

Within the follow-up period (up to 1-year post-transplant), 6 out of 117 patients (5.1%) experienced at least one cardiovascular event meeting our predefined criteria. Notably, all 6 events occurred in the early period (within 100 days) after HSCT; we did not observe any new CV events emerging beyond 100 days in those who were event-free up to that point.

In terms of types of CV events, among the 6 events we observed: five of them developed acute heart failure – 4 of the patients manifested as volume overload while another 1 had hypotension. The single autologous case was a patient with relapsed lymphoma who developed Type 2 ACS - as evidence by acute ECG changes of sinus tachycardia with T inversion as well as significant elevation of cardiac Troponin level (24 → 364 pg/ml). Notably, there were no myocardial infarctions and no sudden cardiac deaths in our cohort during the one-year follow-up.

Figure 2: CV events based on transplant types



All CV events were managed clinically at the time they occurred, and none of the six event patients died from their CV event. The heart failure patients received diuretics and supportive care; none required ICU admission, mechanical ventilation or inotropic support. By 1-year post-transplant, five patients remained alive; however, 1 of the patients eventually succumbed due to Acute GVHD with Septicemic Shock, highlighting that these CV complications, while acute, were generally survivable with prompt treatment. Table 2 below summarizes key baseline characteristics for patients who did versus did not experience a CV event

Table 2: Baseline Characteristics of Patients With and Without Cardiovascular Events

Variable	All Patients	CV Event (Yes)	CV Event (No)	P-value
Age, median (IQR)	30.5 (22.0–42.0)	40.5 (28.8–41.8)	30.0 (21.8–42.5)	0.259
BMI, median (IQR)	21.0 (19.2–24.7)	22.9 (21.1–25.8)	21.0 (19.1–24.5)	0.262
Hypertension (HPT)	9 (7.6%)	1 (16.7%)	8 (7.1%)	0.385
Diabetes (DM)	10 (8.5%)	0 (0.0%)	10 (8.9%)	1.000
Dyslipidemia	8 (6.8%)	0 (0.0%)	8 (7.1%)	1.000
Obesity	8 (6.8%)	1 (16.7%)	7 (6.2%)	0.350
EF <50%	1 (16.7%)	1 (16.7%)	0 (0.0%)	0.0293

As shown in Table 2, patients who sustained a cardiovascular event were significantly older than those who did not (median 40.5 vs 30 years, p>0.05, though the clinical difference of a few years might not be major, it was not statistically significant due to the spread (IQR) overlapping substantially).

Traditional CV risk factors like Hypertension, Diabetes Mellitus, Dyslipidemia and Obesity did not show any significant correlation (p >0.05) – whereby majority of those patient with CV risk factors did not develop any CV events. Baseline LVEF was normal (≥50%) in 5 of 6 event patients; one event patient had a mildly reduced EF ~45% prior (this was the patient who also developed heart failure – i.e., hypotension). In comparison, none of the patients without events had baseline EF <50% (0%, p=0.03). Thus, an abnormal baseline echocardiogram was rare overall but was present in one of the six who had an event.

Regarding transplant-related factors, Table 2 highlights that an allogeneic transplant was far more common among those who had events (83% of event patients) compared to those who remained event-free (44%, p<0.001). In fact, 5 of the 6 events (i.e. Heart Failure) occurred in allogeneic HSCT recipients, whereas only 1 event (Type 2 ACS) occurred in an autologous transplant patient. This suggests a strong association between transplant type and CV events, though confounded by the distribution of risk factors and age.

We further examined whether conditioning intensity or specific agents were linked to events: all 5 allogeneic patients who had events received myeloablative conditioning (three with a cyclophosphamide/busulfan regimen, two with fludarabine/busulfan). The single autologous patient with

Type 2 ACS had received a high dose melphalan conditioning (for myeloma). No clear pattern emerged with a particular drug beyond these commonly used regimens.

Table 3: Distribution of Conditioning regimen and transplant type with CV events

Regimen	AUTO (n)	ALLO (n)	Total (n)	AUTO CV Events (<100d)	ALLO CV Events (<100d)	AUTO CV Rate (%)	ALLO CV Rate (%)	P-value (AUTO)	P-value (ALLO)
BEAM	33	0	33	0	0	0.0		0.057	
Melphalan	3	0	3	1	0	33.3		0.057	
TEAM	3	0	3	0	0	0.0		0.057	
Bu/Cy	2	4	6	0	1	0.0	25.0	0.057	0.548
Flu/Bu	2	32	34	0	3	0.0	9.4	0.057	0.548
Eto+AraC+Mel	4	0	4	0	0	0.0		0.057	
BET	1	0	1	0	0	0.0		0.057	
LEAM	1	0	1	0	0	0.0		0.057	
TBC	1	0	1	0	0	0.0		0.057	
Thio+Flu+Bu	1	0	1	0	0	0.0		0.057	
Thio+Eto+AraC	1	0	1	0	0	0.0		0.057	
Gem+Bu+Mel	1	0	1	0	0	0.0		0.057	
TBI+Eto	0	6	6		0		0.0		0.548
Flu/Mel	0	3	3		0		0.0		0.548
Cy+ATG	0	2	2		0		0.0		0.548
Flu/Bu+ATG	0	2	2		0		0.0		0.548
Cy+TBI	0	3	3		0		0.0		0.548
Flu+ATG	0	1	1		0		0.0		0.548
Flu/Mel+ATG	0	1	1		0		0.0		0.548
Etoposide(±TBI)	0	1	1		1		100.0		0.548
Ida+Bu	0	1	1		0		0.0		0.548
Cy (single)	0	1	1		0		0.0		0.548
Other	0	4	4		0		0.0		0.548

Figure 3: Conditioning chemo regimen by transplant type

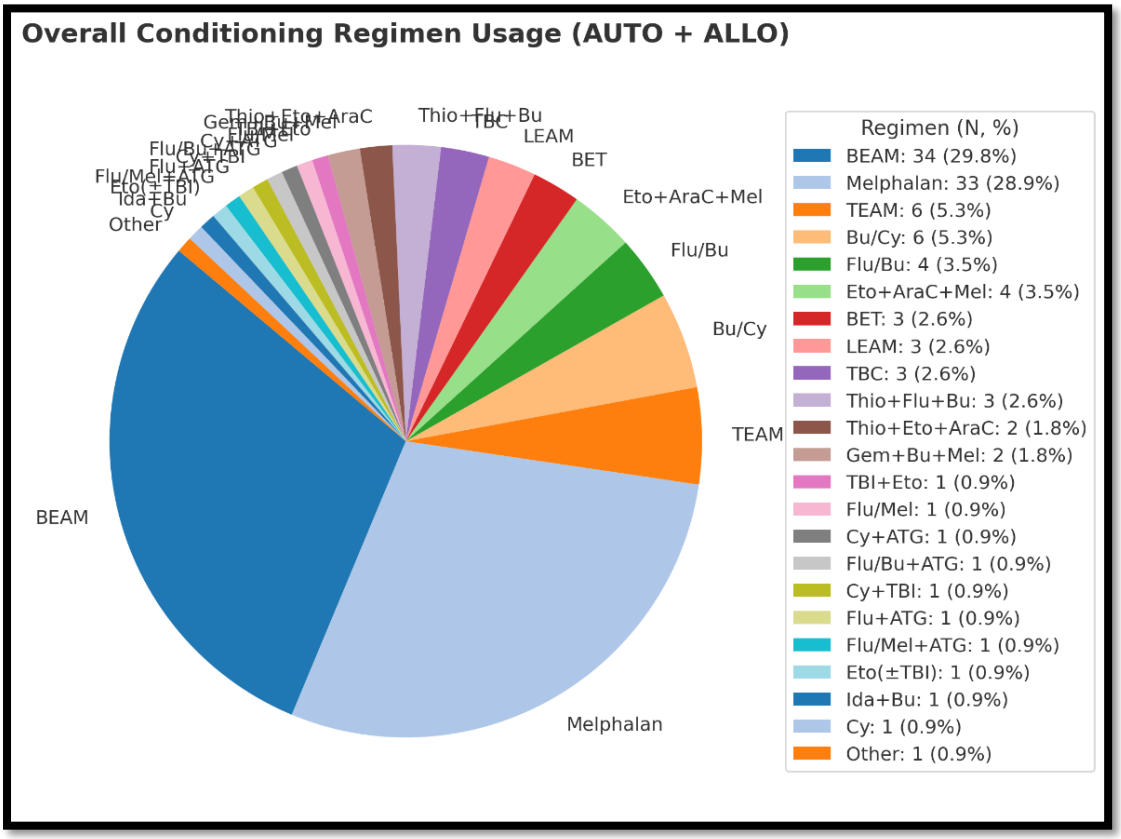
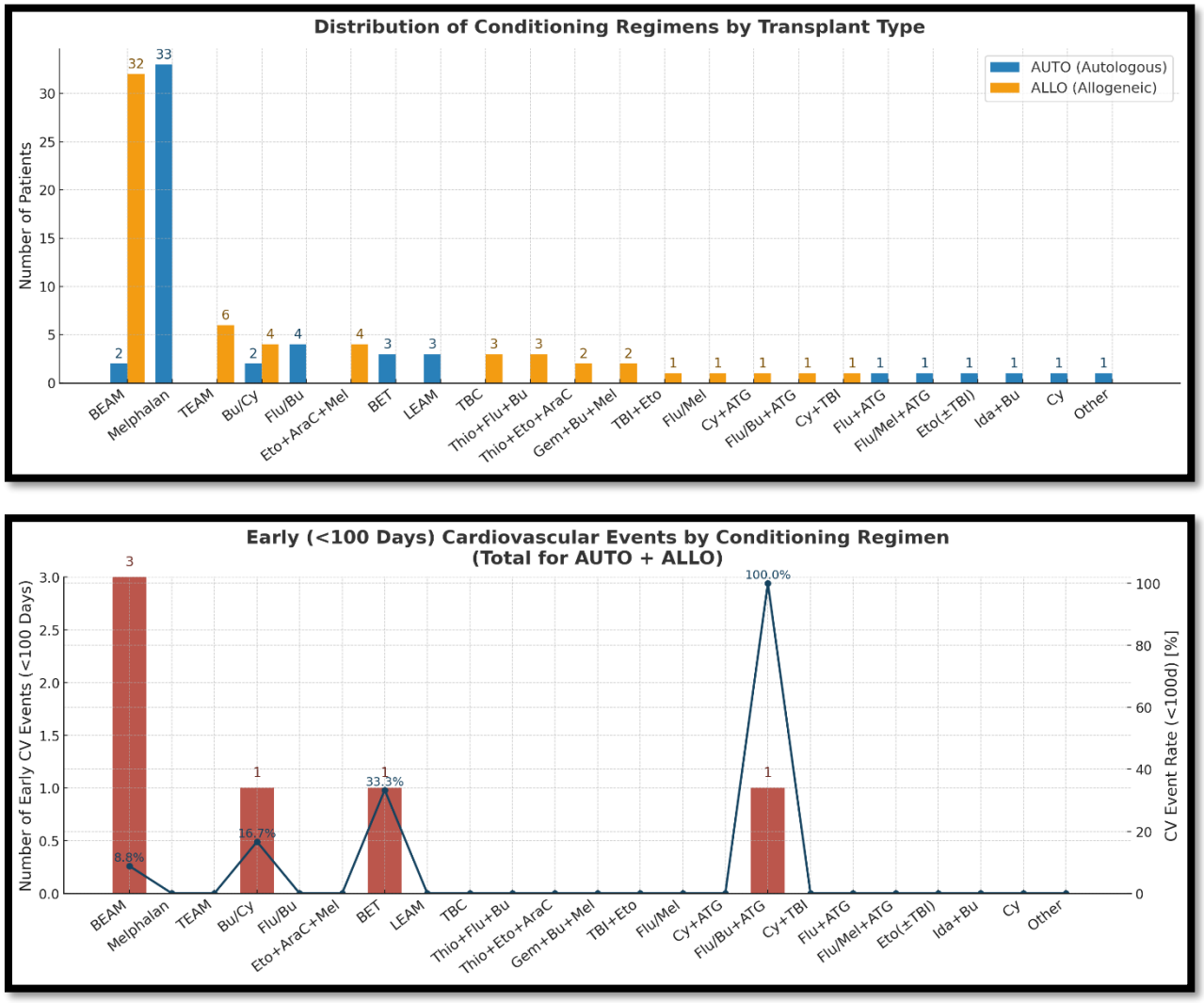


Figure 4 & 5: Bar chart showing association between Transplant Type, Conditioning Regimen and CV events



4.3 **CARE-BMT Risk Score Analysis**

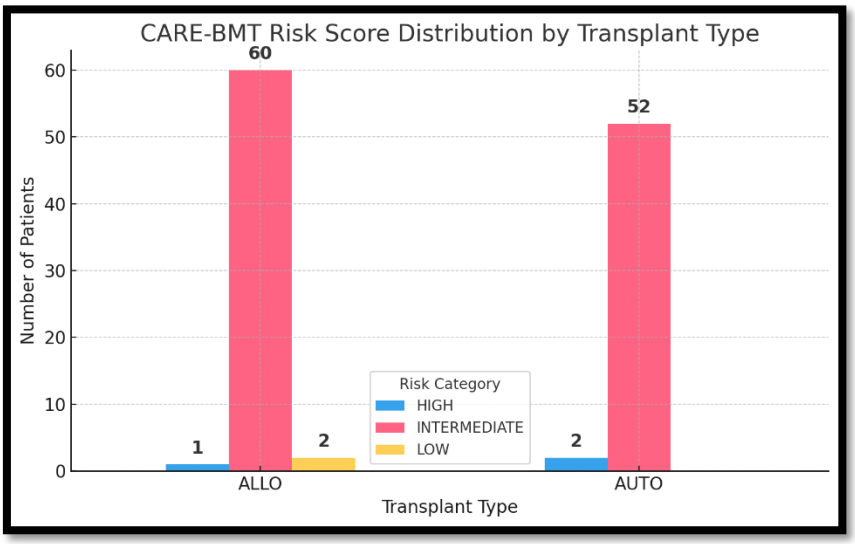
We categorized each patient as low, intermediate, or high risk per the CARE-BMT scoring system (as per Vasbinder *et al*., 2024). In our cohort, 2 patients (1.7%) were low-risk, 112 (95.7%) intermediate, and 3 (2.6%) high-risk by CARE-BMT criteria at baseline. Interestingly, CV events did not correlate with CARE-BMT risk categories. Of the 10 low-risk patients, 0 had events; of 112 intermediate-risk, 5 (4.4%) had events; of 3 high-risk, 1 (33.3%) had an event. These proportions did not differ more than expected by chance (Chi-square χ^2 with 2 degrees of freedom = 0.237, $p = 0.888$). In fact, paradoxically the intermediate group had the highest event rate in our data.

This lack of trend suggests that the CARE-BMT score, which was developed primarily to predict longer-term cardiac outcomes in survivors, may not be a helpful predictor of acute (peri-transplant) events, at least not in a small sample like ours.

This outcome suggests that while the CARE-BMT score might identify broad risk stratums, in our small sample, it did not clearly discriminate who actually had events, particularly, it did not flag those intermediate-risk patients who turned out to have events (perhaps indicating that intermediate encompasses a wide range). It's worth noting that the single high-risk patient in our cohort who had an event did indeed conform to expectation (being high-risk and having an event).

Still, the majority of patients (who fall under Intermediate risk) did not have any event within one year. This finding may indicate that the CARE-BMT risk scoring needs further validation or that additional factors not captured by the score played a role in our setting.

Figure 6 & 7: Bar graph and pie chart showing the proportion of cardiovascular events across CARE-BMT risk categories



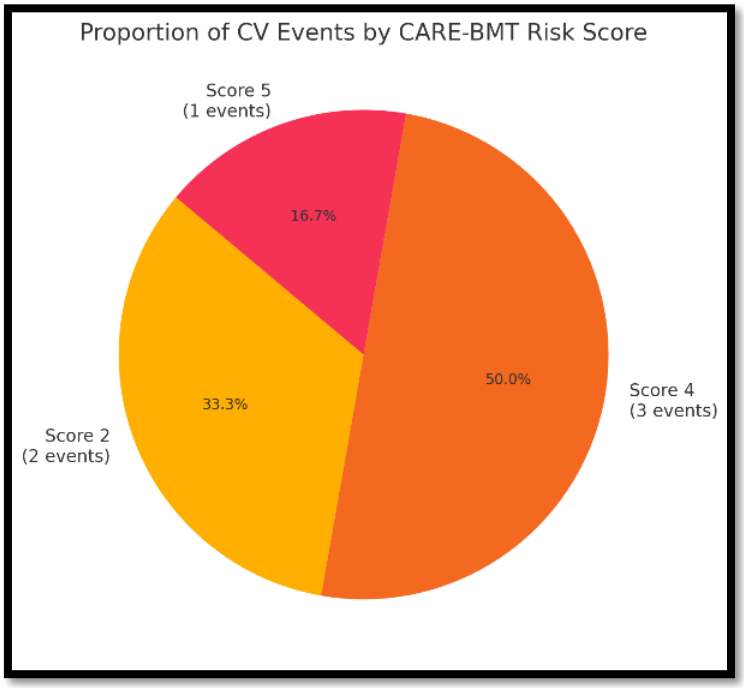
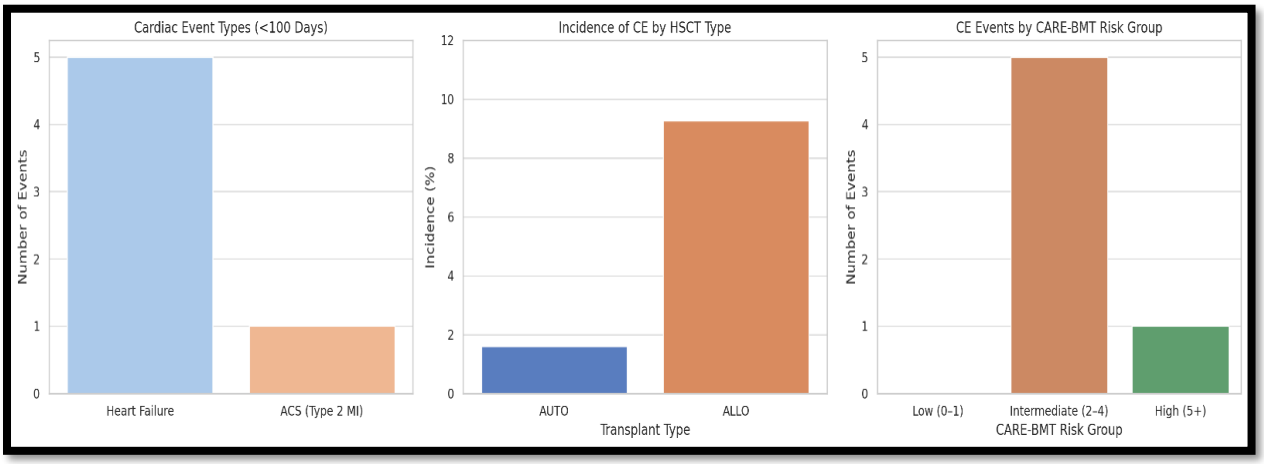


Figure 8: Overview of Incidence of Cardiovascular events based on transplant type and CARE-BMT risk score



4.4 Univariate Analysis of Risk Factors

Although multivariate analysis is ideal for adjusting for confounders, it is not feasible in our study due to the extremely low number of CV events (n=6). The accepted standard for logistic regression is a minimum of 10 outcome events per predictor variable to ensure stable, interpretable results. Including multiple variables with so few events would result in severe overfitting, unstable odds ratios, wide confidence intervals, and a high risk of spurious associations.

Univariate analyses were conducted to explore associations between selected clinical variables and the risk of cardiovascular (CV) events following hematopoietic stem cell transplantation (HSCT). The unadjusted odds ratios (OR), 95% confidence intervals (CI), and corresponding p-values are summarized in the table and forest plot below.

Table 4. Unadjusted Odds Ratios for Cardiovascular Events

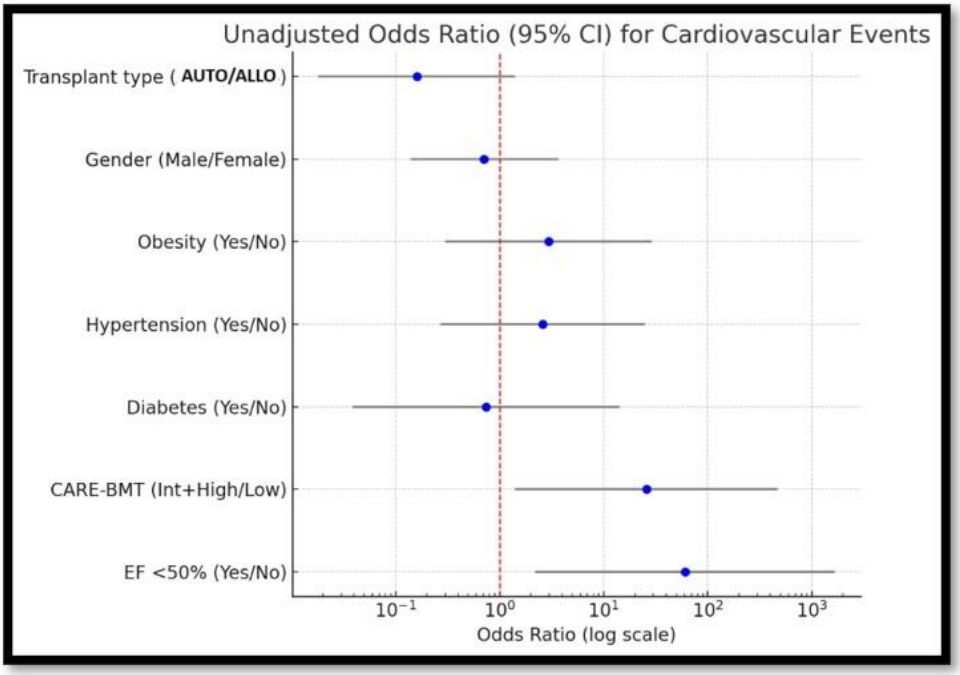
Variable	OR	95% CI	p-value
ALLO vs AUTO	4.57	0.52 – 40.5	0.093
Gender (Male vs Female)	1.47	0.26 – 8.42	0.64
Obesity (Yes vs No)	2.97	0.30 – 29.1	0.35
Hypertension (Yes vs No)	2.58	0.27 – 24.8	0.39
Diabetes (Yes vs No)	0	N/A	1.0
CARE-BMT (Int+High vs Low)	13.7	0.76 – 250	0.065
LVEF <50% (Yes vs No)	60.8	2.2 – 1683	0.065

Among all factors analysed, higher CARE-BMT risk score (intermediate/high vs. low) and baseline left ventricular ejection fraction (LVEF) <50% showed the strongest associations with increased odds of post-transplant CV events (OR 13.7, 95% CI 0.76–250; and OR 60.8, 95% CI 2.2–1683, respectively),

although the confidence intervals were wide and statistical significance was not achieved (p = 0.065 for both). Allogeneic transplantation was also associated with a higher, but not statistically significant, odds of CV events compared to autologous transplantation (OR 4.57, 95% CI 0.52–40.5, p = 0.093).

Other traditional cardiovascular risk factors, including male gender (OR 1.47, 95% CI 0.26–8.42, p = 0.64), obesity (OR 2.97, 95% CI 0.30–29.1, p = 0.35), hypertension (OR 2.58, 95% CI 0.27–24.8, p = 0.39), and diabetes mellitus (no events, p = 1.0), were not significantly associated with CV events in this cohort. The forest plot demonstrates the magnitude and uncertainty of the observed associations. The wide confidence intervals reflect the limited number of CV events and resultant low statistical power.

Figure 9: Forrest plot showing Odd Ratio for CV events based on different variables



These findings underscore the importance of pre-transplant cardiac assessment and risk stratification using validated tools such as the CARE-BMT score. Identifying patients with compromised cardiac function (EF <50%) and those in higher CARE-BMT risk categories may help clinicians focus surveillance and preventive strategies for cardiovascular complications after HSCT.

4.5 **Additional Findings**

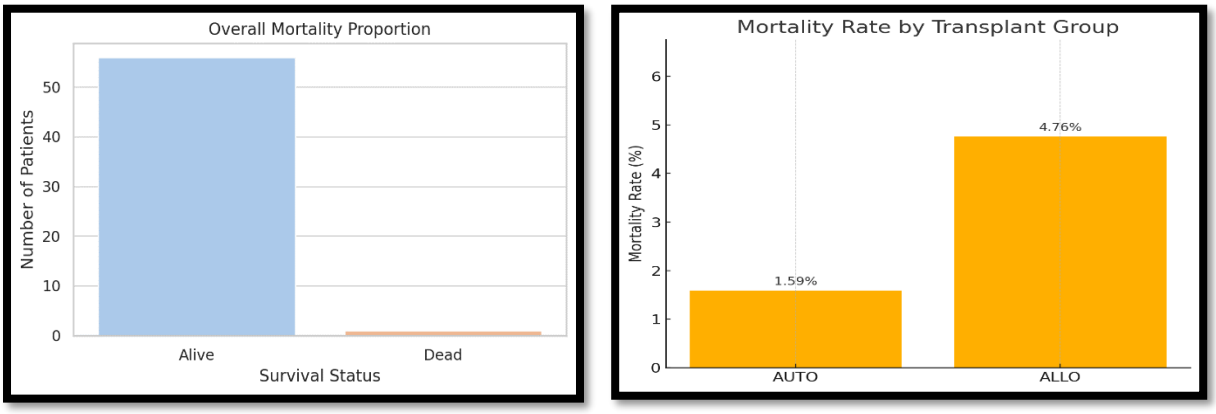
We examined the role of baseline cardiac function in outcomes. As mentioned, 5 of the 6 event patients had a normal baseline ejection fraction (EF). One patient with an event had mildly reduced EF pre-HSCT and went on to develop heart failure post-HSCT. Conversely, several patients with baseline borderline EF did *not* have any cardiac events (though those were few in number). This suggests that baseline EF alone was not a strong predictor of who would develop a complication in our cohort. The lack of statistical significance (p = 0.029 by Fisher's test for EF abnormality vs. events, which, in context, is difficult to interpret due to the presence of only one patient with low EF) means we should be cautious. Essentially, nearly all patients had normal EF to start with, so this factor did not differentiate much.

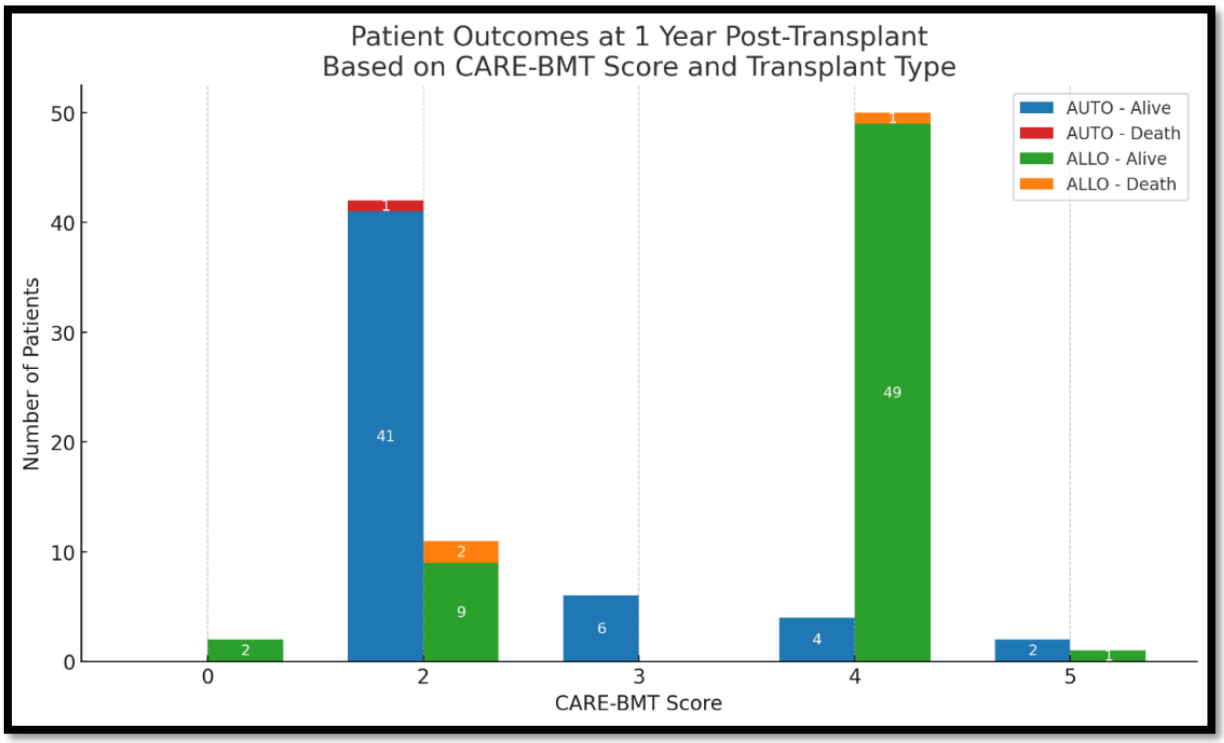
Although not part of our primary and secondary outcomes, we also examined mortality in conjunction with CV events. The 1-year overall survival for the entire cohort was 93.2%. Transplant-related mortality (from causes like infection or GVHD) was 6.8% at 1 year. We had observed 4 cases of mortality within the first year of transplantation - 3 in the Allo group, which were related to Acute GVHD, and 1 in the Auto group, which was due to Neutropenic Sepsis. None of the deaths were primarily cardiac in nature. This indicates that while cardiovascular events did occur in 5% of patients, they were generally manageable and patients survived those events with appropriate care. While not the primary outcome, noting that all four deaths were in intermediate CARE-BMT patients provides a piece of evidence that the score is capturing some important risk signal (just not specifically CV). It underscores how interrelated general frailty and cardiac risk.

Finally, by documenting zero event of non-fata acute myocardial infarction and stroke as well as zero sudden cardiac deaths, we provide reassurance that such catastrophic events are very rare in the transplant unit when patients are properly screened – an important point for patient counseling.

In summary, the results demonstrate a low incidence of cardiovascular events post-HSCT at our center, with all events occurring in the early post-transplant period. Patients with events were distinguishable by having more baseline risk factors and mostly undergoing allogeneic transplants. These factors showed strong associations (high ORs) with events, albeit not statistically significant due to the small number of events. The role of the CARE-BMT score was inconclusive in this cohort. These findings and their implications are further discussed in the next chapter.

Figure 10 & 11: Bar chart showing overall Mortality and the Relationship between Transplant type and CARE-BMT risk score





5. Discussion

This study is, to our knowledge, the first of its kind in Southeast Asia to evaluate the incidence of cardiovascular events following hematopoietic stem cell transplantation (HSCT) in a Malaysian population. Our findings corroborate some of the patterns reported in Western studies while also providing nuanced insights applicable to our local context. In this chapter, we present the results in detail, compare them with the existing literature, consider potential mechanisms, and outline implications for clinical practice and future research.

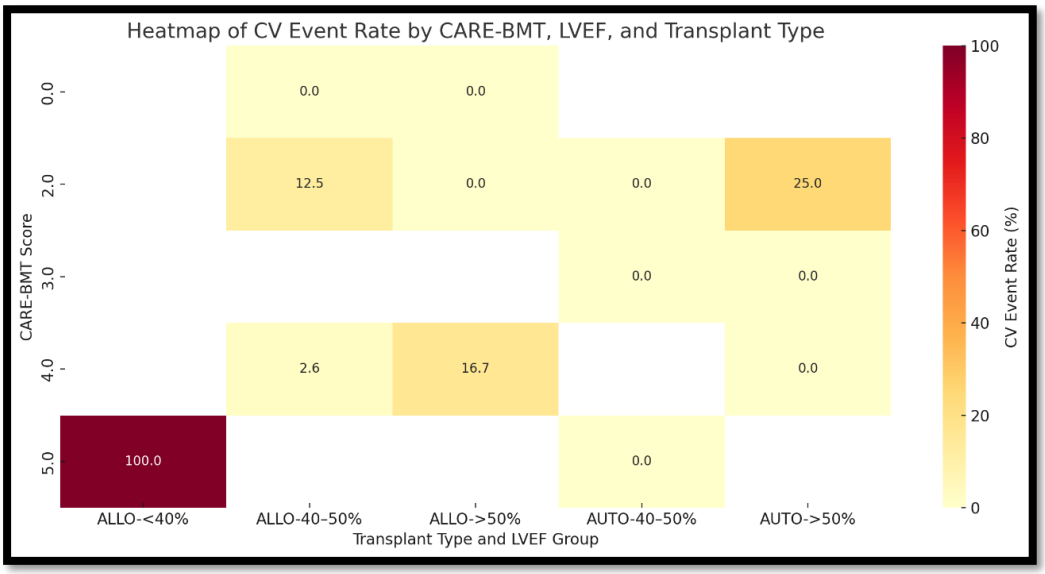


Figure 12: Heatmap showing distribution of CV events based on transplant types, CARE-BMT and LVEF

Notes
Highest CV Event Rate: *Observed in ALLO recipients with CARE-BMT score of 5 and LVEF >50% (100%, though n=1).*
Intermediate Risk Cluster: *ALLO + CARE-BMT 2 + LVEF 40–50% (CV event rate: 12.5%).*
Protective Trend: *Preserved EF (>50%) consistently associated with lower event rates across CARE-BMT scores and both transplant types.*
AUTO Recipients: *Demonstrated low CV event rates across all risk and EF categories.*

Incidence and Timing of Events: We observed an overall 5.1% incidence of significant cardiovascular events within one year after HSCT. This aligns closely with the short-term incidence of ~4–5% reported by Vasbinder *et al*. (2023)[2] and others. Notably, all six events in our cohort occurred in the early post-transplant period (<100 days), with no new events in the later period up to one year. This is an interesting divergence from Vasbinder's study, which reported an additional accumulation of events between 100 days and 1 year (raising incidence to ~10%). One possible explanation is our smaller sample and correspondingly fewer total events, which reduces the chance of observing later events. It may also reflect differences in patient follow-up and risk exposure: for example, many of our autologous transplant patients (who generally have fewer late complications) might have been followed outside the transplant center after recovery, potentially missing detection of late minor events.

However, given that none of the surviving patients reported or were re-hospitalized for cardiac issues after 100 days, it could be that the risk in our cohort truly concentrated in the early phase.

This finding underscores the critical nature of the first few months post-HSCT as the window of vulnerability for acute cardiac complications. It also suggests that if patients pass the immediate post-transplant phase without cardiac issues, their short-term prognosis regarding the heart is relatively good – though this should not lead to complacency, as chronic cardiovascular disease could still develop years later (beyond our observation period) due to factors like accelerated atherosclerosis or chronic GVHD effects (Armenian *et al*., 2018)[7].

Risk Factors – Patient Comorbidities: Our results clearly demonstrate that traditional cardiovascular risk factors (hypertension, diabetes, obesity, dyslipidemia) did not appear to be associated with the CV events. These findings cannot mirror the general cardiovascular epidemiology – patients with such risk factors are more likely to have cardiac events in any setting – but it's noteworthy in a transplant population because these patients are often young and not highly comorbid compared to, say, typical cardiac patients. In our cohort, the median age was only ~30, and overall rates of comorbidities were low.
This suggests a few important points: (1) even mild or subclinical forms of hypertension/diabetes in young patients can significantly elevate risk when they undergo the physiological stress of HSCT; (2) identification and management of these risk factors prior to transplant is crucial. Patients with well-controlled blood pressure and glucose might fare better, although our sample is too small to assess the effect of optimal management. It aligns with recommendations from the AHA scientific statement (Hayek *et al*., 2024)[1] that HSCT candidates should undergo risk factor optimization – for instance, tight blood pressure control, encouraging weight loss, and blood sugar management – as part of pre-transplant

work-up. Our data strongly support that approach: had we been able to modify some of these risk factors, perhaps some events (like heart failure or arrhythmia precipitations) might have been mitigated.

For example, hypertension can exacerbate heart failure risk under the hemodynamic stress of transplant. One of our patients with heart failure had undiagnosed hypertension that may have contributed. Thus, this study reinforces the call for a cardio-oncology collaboration in managing HSCT patients, focusing on aggressive modification of cardiovascular risk factors before transplant.

Transplant Type (Allogeneic vs Autologous): We found that allogeneic HSCT recipients had a higher incidence of cardiovascular events (approximately 9.3%) than autologous recipients (1.6%). Although the difference did not reach statistical significance due to small numbers (p=0.09 univariate), the magnitude is clinically relevant – an OR of ~6 in unadjusted analysis. After adjusting for baseline risk factors, the odds ratio remained high (~6) albeit not significant. This trend is consistent with prior observations that allogeneic HSCT carries more cardiovascular risk. The reasons are likely multifactorial. Allogeneic patients undergo more intense and prolonged immunosuppressive therapy, which can induce hypertension, diabetes, and renal impairment (all risk factors for cardiovascular events). They are also at risk of GVHD, an inflammatory condition that can have cardiovascular manifestations (e.g., myocarditis, endothelial dysfunction) and require steroids (leading to metabolic side effects).

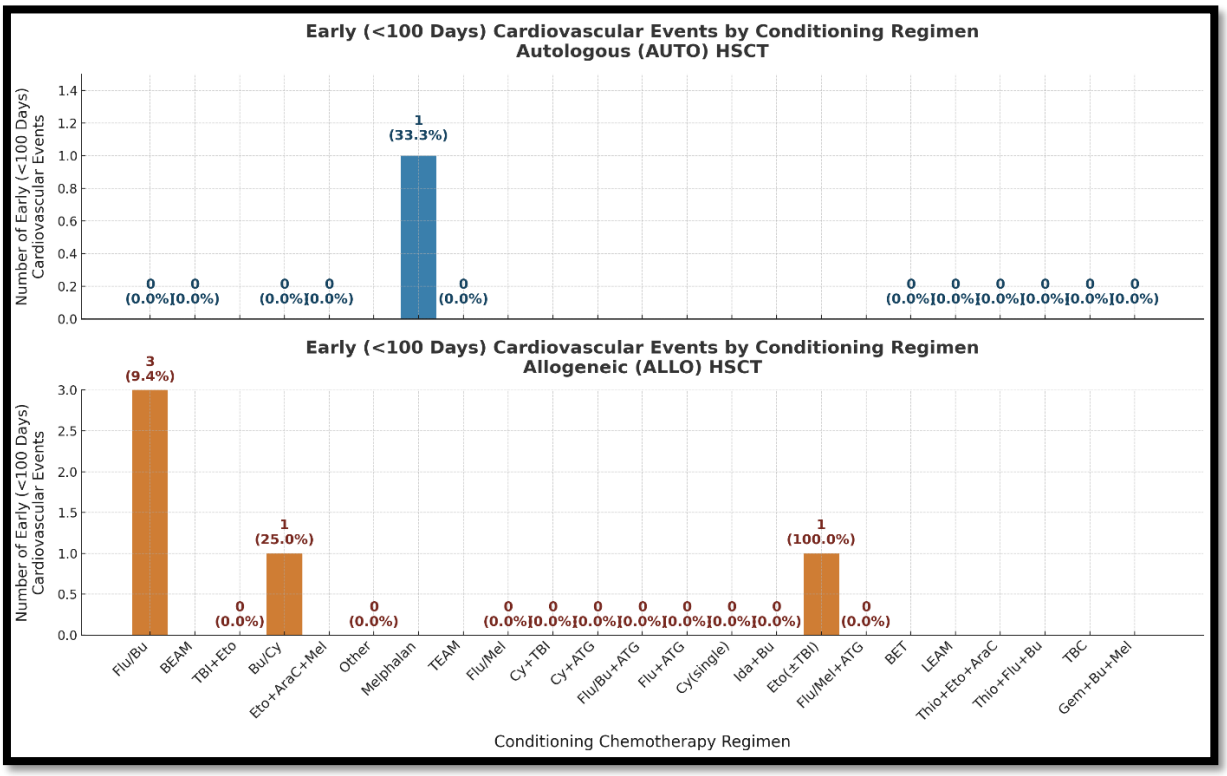
It resonates with literature where immunologic mechanisms are thought to contribute to cardiovascular damage post-allogeneic transplant (e.g., inflammatory cytokines, autoimmunity affecting the heart) (Armenian *et al*., 2018)[7].

Conditioning Regimen: We examined whether the type of conditioning regimen was associated with differing rates of CV events in allogeneic recipients. Given the small number of events and many categories, this analysis has low power. A chi-square test comparing the distribution of the 5 early events across the major regimen groups did not show a statistically significant association ($p \approx 0.15$). In other words, no significant difference in <100-day CV event incidence between conditioning regimens was demonstrable in the allo cohort. For example, while the observed event rate was higher in Bu/Cy (25%) and Flu/Bu (9.4%) compared to other regimens (0%), these differences did not reach significance, likely due to the small numbers involved. Likewise, there was no indication of any association between regimen and 1-year post-transplant CV events (since no late events occurred in this cohort).

Additionally, the conditioning for allogeneic transplants is often more intensive (myeloablative regimens), which themselves may have cardiotoxic risk (like high-dose cyclophosphamide can cause myocarditis). Autologous transplants, on the other hand, involve a shorter exposure – typically just the conditioning (which can be intensive, e.g., high-dose melphalan for myeloma, known to cause cardiomyopathy in rare cases) – but these patients usually recover quicker and are not on long-term immunosuppression. Our single autologous event (Type 2 ACS in a Myeloma patient) likely reflects that autologous patient are not immune to events, but the risk is substantially lower once the immediate chemo effect passes. In practical terms, allogeneic HSCT recipients should be considered a higher-risk group for cardiovascular monitoring, and our study quantifies that risk trend. This could mean more

frequent vital signs and cardiac evaluations during transplant admission, and perhaps a lower threshold for cardiology consultation if any symptoms arise for allogeneic patients.

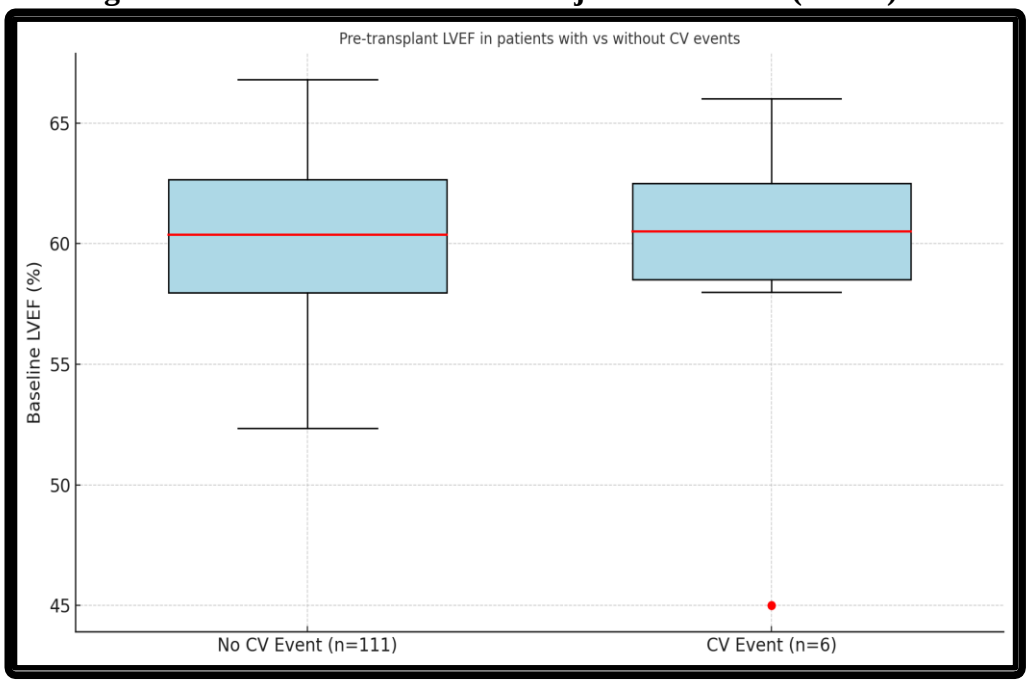
Figure 13: Bar chart showing CV events based on Conditioning Regimen



Baseline Cardiac Function and Monitoring: An unexpected (at first glance) finding was that baseline LVEF was normal in the majority of those who had events, and having a normal EF did not protect against post-transplant events. In fact, 5 of 6 event patients had normal baseline cardiac function. This highlights that the mechanisms of post-HSCT events are often not due to pre-existing systolic dysfunction, but rather acute factors like arrhythmogenic triggers (e.g., stress, electrolytes, sepsis) or diastolic dysfunction under stress, etc. One could argue that baseline EF screening is still essential (as we would not transplant someone with severe cardiomyopathy electively), but our results suggest that even patients with normal hearts can suffer acute issues. This implies that continuous cardiac monitoring during transplant (such as telemetry for high-risk periods) might be beneficial broadly, not just in those with known low EF. For example, arrythmias can occur in any critically ill patient; early detection and management (rate/ rhythm control, anticoagulation if feasible) are vital.

The take-home point is that vigilance should not be relaxed simply because a patient's pre-transplant echo is normal. That said, one of our event patients had a low-normal EF of 45% and did go on to develop heart failure – which suggests that patients on the lower end of "normal" might deserve extra attention (perhaps a cardiology evaluation before transplant if EF is marginal). The significance (p=0.03) of baseline EF difference should be interpreted cautiously due to our small numbers, but it does align with a precautionary principle in transplant: optimize and investigate any cardiac abnormality beforehand, as it could herald trouble under the intense transplant stress.

Figure 14: Baseline left ventricular ejection fraction (LVEF)



Notes: in patients who did vs. did not experience a post-HSCT cardiovascular event. Each boxplot shows the median (red line) and interquartile range of LVEF, with whiskers extending to the 5th–95th percentile; individual outliers are shown as red dots. Patients who had CV events (right, n=6) all had relatively preserved LVEF before transplant (median ~61%, range 45–66%). Those without events (left, n=111) also mostly had normal LVEF (median ~60%, range 50–69%). There was no significant difference between the groups (p > 0.05), indicating that a normal pre-transplant EF does not eliminate the risk of early post-HSCT cardiac complications. Notably, the single patient with a markedly reduced EF (45%) is represented as an outlier in the event group – this patient did suffer an acute heart failure (hypotension), but the other event patients had high baseline EF.

CARE-BMT Risk Score Utility: Our study assessed the CARE-BMT risk score in a retrospective manner. The distribution of risk categories (low 19%, int 68%, high 13%) in our cohort is interesting – it suggests most of our patients were intermediate risk by that model. This is plausible since many had one or two minor risk factors or were in an age bracket that's not extremely young or old. The lack of clear predictive power (no significant association with actual events) could be due to the limited sample, but it might also indicate that the score thresholds need calibration for different populations. One striking observation: none of our low- risk patients had events, which is reassuring (the score's negative predictive value might be good – low risk truly had no events).

However, most events happened in intermediate rather than high – that one high-risk did have an event (as expected), but the others were intermediate. This could be a quirk of small numbers, or it could mean that some intermediate-risk patients had other factors not captured by CARE-BMT that made them effectively high risk. For example, two of our intermediate-risk event patients had high-dose cyclophosphamide/busulfan conditioning which might not be explicitly heavily weighted in the CARE-BMT scoring.

In contrast, possibly the cut-off between intermediate and high in that scoring is such that even intermediate risk still carries sizable risk. Vasbinder *et al*. (2024) did show intermediate risk had some events too, just fewer than high. For our practice, it indicates that while the CARE-BMT score is a useful framework, it should not replace individualized clinical judgment. A patient with "intermediate" score but multiple borderline factors might need as much caution as a "high" score. Our data suggest that the score's categorization didn't perfectly stratify who got events, so improvements or additional markers (like biomarkers troponin/BNP, or detailed cardiac imaging) might be needed to truly identify at-risk patients.

Mechanistic Insights: Looking at the nature of events in our patients: heart failure were predominant, aligning with known literature that these are common post-HSCT events. The pathogenesis of heart failure in our cases possibly related to acute illness stressors – either infection or GVHD flares when patients in high inflammatory states. In addition, cumulative chemo toxicity (anthracycline + transplant) may predispose these patients to developing future cardiac evens due to direct cardiotoxicity of chemo agents. These illustrate that post-transplant cardiovascular events often have a multifactorial causation – it's not always straightforward "transplant caused this", but rather transplant creates conditions (immunosuppression, vulnerability to infection, high cardiac output state during recovery, etc.) that can precipitate an event in a susceptible individual.

Alas, managing transplant patients truly requires a multidisciplinary approach: infections need aggressive treatment to potentially prevent secondary cardiac complications; careful fluid management in the context of potential cardiac dysfunction is needed to avoid heart failure, etc.

Comparison with Other Studies: Armenian *et al*. (2018) and others have shown that HSCT survivors face increased long-term cardiovascular risk, including coronary artery disease, beyond the first year. Our study, with its one-year horizon, did not capture those late outcomes. It's possible that had we followed these patients for say 5-10 years, more differences (like development of hypertension or coronary disease) might emerge between allogeneic and autologous survivors. Armenian *et al*. (2018) found that traditional risk factors and treatment exposures predicted late cardiac events. Our data resonates on the point that even early events are heavily influenced by traditional risk factors. Another study by Tichelli *et al*. (from EBMT, 2007) indicated that while the incidence of severe cardiovascular events was low, it increased steadily with longer follow-up, recommending lifelong cardiovascular risk monitoring in transplant survivors. For our context, it suggests that even though we saw no events after 100 days up to 1 year, we should not assume the risk disappears. Continuous follow-up beyond one year is advisable, perhaps with annual cardiovascular assessments for allogeneic survivors at least.

Clinical Implications: Based on our findings, a few practice implications can be highlighted:
1. Rigorous Pre-transplant Assessment: All HSCT candidates should be screened for cardiovascular risk factors and have them managed. This includes cardiology consultation if any abnormal findings (e.g., an ECHO shows low EF or significant valvular disease). In borderline scenarios, consider delaying transplant for optimization or choosing modified conditioning if a patient has significant cardiac risk.
2. Tailored Monitoring: Allogeneic HSCT patients, especially those with comorbidities, should perhaps receive more intensive monitoring (like telemetry for a longer duration post-transplant). Also,

daily weight and fluid balance tracking can help catch early heart failure. Some centers even perform routine BNP or troponin checks post- transplant in high-risk patients to detect subclinical cardiac stress – something that could be explored.

3. Early Intervention: For any signs of cardiovascular issues (e.g., palpitations, chest discomfort, unexplained tachycardia or dyspnea) in the post-HSCT period, a low threshold for diagnostic work-up (ECG, echocardiogram, etc.) is warranted.

4. Long-term Follow-up: Establishing a follow-up plan that includes cardiovascular health is important. After the transplant team's intensive follow-up in year 1, patients (especially allogeneic) should ideally transition to a survivorship clinic or cardiology follow-up to monitor blood pressure, glucose, lipids, and address late effects. This might involve collaboration with a cardio-oncology clinic if available.

5. Use of Risk Scores: Tools like CARE-BMT can be used as part of risk documentation – for instance, we can calculate it for all patients to identify high-risk individuals. However, one must use it as a guide rather than an absolute predictor. Our data suggests that any patient not in a low-risk category deserves essentially similar careful observation, meaning that both intermediate- and high-risk patients require robust monitoring. High-risk patients might benefit from prophylactic measures (though none are formally proven, one might consider things like beta-blockers in someone with borderline EF or statins in someone with multiple risk factors, extrapolating from general population evidence). Future studies should test interventions in high-risk CARE-BMT patients to see if events can be reduced.

Limitations: It is important to acknowledge the limitations of our study to put the findings in perspective. The most evident limitation is the small number of events (n=6), which limits statistical power and our ability to draw strong conclusions about associations. With such a low event count, the logistic regression results, while suggestive, must be interpreted cautiously as they have wide confidence intervals. Our study was also a single-center experience; practices at our center (such as patient selection for HSCT and management protocols) might differ from others, affecting generalizability.

There is potential selection bias in that healthier patients might have been offered transplant (leading to a lower incidence of complications than if higher-risk patients were transplanted). However, our intention was to capture real- world data from all transplants done, which we did. Another limitation is the retrospective design – we relied on documentation in records, which might have underreported some mild events (e.g., transient arrhythmias that self-resolved might not have been captured if asymptomatic). We tried to mitigate this by reviewing telemetry logs and nursing notes for any hints of arrhythmias. Also, the follow-up was limited to one year (in contrast to other studies with mean follow-up period ~2.5 years); we did not address late cardiovascular outcomes beyond that, which would be relevant for survivorship care.

Strengths: This is the first study looking into CV events in Asian population – whereby we have different demographics and risk factors. On the other hand, the study has strengths such as including all consecutive HSCT patients over multiple years, giving a comprehensive view of outcomes at our center. The data collection was thorough, allowing analysis of various factors including a new risk scoring system (CARE-BMT) in our population. Despite the small event number, the consistency of trends (all pointing towards allogeneic and comorbidities as risks) adds credibility to those findings, especially as they align with biologic plausibility and external data. Also, by being the first local dataset, it provides a

reference point for Malaysian or regional transplant centers and can serve as pilot data for larger studies or quality improvement initiatives.

Future Directions: Our findings generate several avenues for further research. A larger multi-center study across Malaysia or Southeast Asia could be conducted to accumulate a bigger sample of HSCT patients, which would provide more robust estimates of incidence and allow multivariate analyses with more variables (including age, GVHD, specific drugs, etc.) to truly identify independent predictors. It would also be valuable to follow patients for a longer term (e.g., 5 years) to capture late cardiovascular events like coronary artery disease onset, given increasing survivorship. Another area is exploring biomarkers (like NT- proBNP, troponin) as well as looking beyond ejection fraction measurement (i.e., Global Longitudinal strains) measured during transplant.

Some preliminary studies outside have suggested peri-transplant rises in cardiac biomarkers correlate with later cardiomyopathy (e.g., in amyloidosis autologous transplant). In allogeneic transplants, inflammatory markers could also be studied in relation to cardiac events. Additionally, intervention trials could be considered: for example, testing if implementing a cardio-protective strategy (such as beta- blockade or ACE inhibition for high-risk patients during transplant) can reduce incidence of arrhythmia or heart failure.

In context of the CARE-BMT score, our results suggest it may need recalibration. Perhaps adding points for certain chemotherapy exposures or refining age categories might improve its predictive ability. Further validation of CARE-BMT in a larger Asian cohort would be informative – our small sample isn't enough to judge it conclusively, but it hints that intermediate risk comprises a broad spectrum. Another interesting finding was that none of the low-risk patients by CARE-BMT had events; if that holds in larger data, it means the score is good at identifying a truly low-risk group. Those patients might safely undergo transplant with standard care and minimal extra monitoring, whereas resources can be focused on intermediate/high groups. This risk stratification approach, if validated, could optimize use of telemetry beds or prophylactic measures.

Comparative Outcomes: It is also worth noting that although our study focused on cardiovascular events, these events did not translate into any mortality in our one-year follow-up. This is encouraging – it suggests that with prompt recognition and management, HSCT patients can survive these complications. For instance, all our heart failure cases were treated with diuretics and supportive care (none needed neither ICU nor mechanical ventilation), and they improved. This implies that while prevention is ideal, the transplant team's capacity to handle acute cardiac issues is crucial and effective. A point for centers is to have specific protocols in place for managing these events (co-managing with Cardiology units.).

Summary (of Discussion): In conclusion, the discussion highlights that our study's findings are largely in line with global literature on HSCT-related cardiovascular events, reinforcing known risk factors such as allogeneic transplant and patient comorbidities, while adding local data that the incidence is similarly

low in the short term. It emphasizes the importance of integrated care, from pre-transplant risk assessment to post-transplant monitoring, to ensure these potentially serious events are minimized and managed. Our experience adds weight to calls for formal cardio-oncology collaboration in the transplant field, as the population of survivors grows and ages. With improved survival of HSCT patients, attention must increasingly turn to long-term health issues like cardiovascular disease to ensure quality of life and longevity post-cancer.

6. Conclusion

In this retrospective cohort study of HSCT recipients at HCTM, we have documented the incidence of cardiovascular events and identified key risk associations in our patient population. The incidence of cardiovascular events within one year post-transplant was 5.1%, with all events occurring in the early post-transplant period (within 100 days). The low incidence is consistent with international data and confirms that serious cardiac complications are relatively infrequent in the acute phase of HSCT, especially in a young cohort. However, when these events do occur, they are clinically significant and tend to cluster in patients with identifiable risk factors.

Our analysis demonstrated that allogeneic HSCT patients and those with pre-existing cardiovascular risk factors (like hypertension, diabetes, or obesity) were more likely to experience cardiovascular events. Allogeneic transplant was associated with a higher odds of events, likely due to factors inherent to the allogeneic process (intensive conditioning, GVHD and its treatment, prolonged immunosuppression). Traditional risk factors, even when present in modest proportions, markedly increased vulnerability to complications under the stress of transplant. In our cohort, these two dimensions – transplant type and patient risk profile – emerged as important considerations for predicting and managing potential cardiac issues.

The findings on the CARE-BMT risk score suggest that while it is a useful tool for stratifying risk, it did not perfectly predict outcomes in our setting. Intermediate-risk patients still experienced events, and thus risk categorization should be used as a guide alongside clinical judgment. All patients, except perhaps those clearly low-risk, warrant vigilant cardiovascular monitoring.

This thesis contributes local data indicating that with careful patient selection and management, HSCT can be performed with a low incidence of short-term cardiac complications. Nonetheless, given the severity of events when they occur, we recommend the following: (1) Optimize cardiovascular health prior to HSCT – treat hypertension, diabetes, and other modifiable risks; involve cardiologists for borderline cardiac function.

(2) Monitor closely and manage proactively during the transplant hospitalization – maintain a high index of suspicion for cardiac events, especially in allogeneic recipients or those with risk factors; use telemetry and periodic evaluation as needed. (3) Follow up long-term – incorporate cardiovascular surveillance in post-HSCT follow-up clinics, given that the absence of early events does not guarantee freedom from later cardiovascular disease. Preventative healthcare, including lifestyle advice and risk

factor control, should be part of survivorship care plans.

In conclusion, the study underscores that cardiovascular events post-HSCT, while uncommon, are an important consideration in the comprehensive care of transplant patients. By identifying who is at risk, we can tailor monitoring and possibly preventive strategies to those individuals, thereby improving overall outcomes. Our results highlight the successful outcomes achievable – all patients who had CV events were effectively treated and survived – which speaks to the value of preparedness and interdisciplinary care. Future research with larger cohorts is needed to validate these findings, explore late-onset cardiovascular effects, and evaluate interventions to further reduce the burden of cardiovascular complications in HSCT survivors. Ultimately, integrating cardiology with transplant medicine will help ensure that as patients conquer their malignancies through HSCT, they are also protected from life-threatening cardiovascular issues, leading to healthier long-term survival.

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