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Cardiovascular Co-Morbidity and the Outcome after Myeloablative Hematopoietic Stem Cell Transplantation for Advanced Lymphoma

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Abstract

We evaluated cardiovascular-associated co-morbidities systematically in patients undergoing hematopoietic stem cell transplantation (HCT) for lymphoma. In this study, 101 lymphoma patients (41.3 ± 13.6 years) receiving salvage myeloablative HCT with high-dose conditioning treatments were recruited. Cardiovascular associated factors were reviewed and correlated to outcome after HCT. The mean follow-up period was 1074.8 ± 739.2 days. The Overall Survival (OS) rate was 68.3% and the 3-month survival rate was 89.1%. Multivariate analysis revealed that the independent risk factors for OS were High Sensitivity C-Reactive Protein (HsCRP), Abnormal Regional Wall Motion (ARWM), age, and Eastern Cooperative Oncology Group (ECOG) performance status. Combination of the 4 risk factors significantly increased the predictive value for OS. High HsCRP levels were associated with higher cumulative tumor-related mortality (P=0.045). ARWM was associated with both higher cumulative tumor-related mortality (P=0.01) and non-relapse mortality (P=0.027). In conclusions, ARWM and HsCRP were important predictors for long-term survival in lymphoma patients undergoing HCT.

Keywords: Abnormal regional wall motion; High sensitivity c-reactive Protein; Hematopoietic stem cell transplantation

Introduction

Non-Hodgkin Lymphomas (NHLs) and Hodgkin Disease (HD) are ranked among the top 10 cancer causes of death all over the world [1]. Currently, the treatment option with the highest rate of long term survival in refractory and advanced lymphoma is hematopoietic stem cell transplantation (HCT). The effects of previous cumulative anthracycline doses [2,3] and high-dose cyclophosphamide, especially in patients who receive mediastinal radiation during HCT [4,5], result in a higher risk of cardiovascular complications [3,6]. Lymphoma survivors frequently experience cardiovascular events during long term follow-up [2-8]. Childhood cancer survivor studies have shown that patients with HD commonly develop serious cardiovascular conditions during long term follow-up [2]. The heart is one of the most frequently affected organs in patients who have received allogeneic HCT as treatment for lymphoma or chronic lymphocytic leukemia [9]. Patients with impaired cardiac function show significantly increased treatment-related mortality, which may offset the potential clinical benefit of the transplant [5]. Although several studies have investigated the cardiovascular-associated risk factors after HCT, none of those studies were limited to lymphoma patients who have undergone intensive treatments. In addition, data on the usefulness of eligibility

criteria associated with cardiac function in lymphoma patients who are undergoing HCT are also sparse.

Some important studies have shown that the HCT-specific comorbidity index (HCT-CI), which combines the risk factors derived from different organ systems, can successfully predict Overall Survival (OS) after HCT [4,10]. There are some cardiovascular-associated risk factors such as hyperlipidemia, and Abnormal Regional Wall Motion (ARWM) not involved in the HCT-CI. Several biomarkers with prognostic value in patients with malignancy, such as troponin and High Sensitivity C-Reactive Protein (HSCRP) [11-14], have not been studied specifically in lymphoma patients receiving HCT. It remains unclear if a detailed analysis of cardiovascular-associated risk factors would lead to a more precise prognosis in lymphoma patients receiving HCT.

The aims of the present study were to investigate possible cardiovascular and non cardiovascular-associated risk factors of long term survival after HCT and to study the impact of cardiovascular characteristics, namely ARWM, Hs CRP and troponin levels, on prognosis.

Methods

Patient selection

Patients with lymphoma who received myeloablative HCT (75 autologous, 26 allogeneic) during the period January 2003 to November 2008 at the Taipei Veterans General Hospital were retrospectively analyzed. A total of 101 patients were included in the study (NHLs, n = 86; HD, n = 15). The retrospective review included the assessment of cardiovascular-associated risk factors such as diabetes mellitus, hypertension, and hyperlipidemia. All patients received a comprehensive evaluation of heart function, including resting ejection fraction by first pass and wall motion studies by ^{99m}Tc-pertechnetate before HCT. The comorbidity scores were assigned by the single principal evaluator using the HCT-CI after reviewing the medical records and laboratory values of all patients. Ethical approval was granted by the Institutional Review Board of the Veterans General Hospital, Taipei, Taiwan (VGHIRB No. 201004034IC).

Chemotherapy before stem cell transplantation

First-line chemotherapy comprised R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for patients with Diffuse Large B Cell Lymphoma (DLBCL) and ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) for patients with HD. Second-line regimens included ESHAP (etoposide, prednisone, cytarabine, cisplatin) or ICE (ifosfamide, carboplatin, etoposide), followed by high-dose conditioning chemotherapy and HCT. The use of HCT as salvage treatment was considered in patients who showed an inadequate response to induction chemotherapy or experienced relapse. The dose of stem cells for patients receiving autologous HCT was greater than 2×10^6/kg. In patients who could not obtain a sufficient self-stem cell dose and received allogeneic HCT, HLA typing was performed using the polymerase chain reaction with sequence specific primers. Among the patients who received allogeneic HCT, 23 had sibling donors and 3 had unrelated donors. All patients had 6 completely matched alleles compared with their donors, except for 1 patient who had 1 mismatched allele.

Conditioning regimen for stem cell transplantation

Most patients received conditioning regimens composed of BEAM (carmustine, etoposide, cytarabine, melphalan) or BEAC (carmustine, etoposide, cytarabine, cyclophosphamide). Cy TBI conditioning consisted of 120 mg/kg cyclophosphamide, followed by total body irradiation with 12–13.2 Gy in 3 patients with highly aggressive lymphoma who accepted allogeneic HCT. The immunosuppressive regimen after allogeneic HCT included the following: a dose of 15 mg/m^2 of MTX intravenously administered on day 1 and 10 mg/m^2 on days 3, 6, and 11. The administration of CsA (1.5 mg/kg intravenously or 6.25 mg/kg orally every 12 hours) was started 1 day before marrow infusion and continued until day 50 after HCT. The dose was then decreased by 5% weekly until 6 months after transplantation if the patients were devoid of manifestations of acute or chronic graft versus host disease (GVHD). For patients with GVHD, azathioprine and steroids were added to the treatment regimen until the disease was controlled.

Cardiovascular biomarkers and clinical events

Hs CRP levels were determined using particle-enhanced immunoturbidimetry with latex micro particles sensitized with duck anti-CRP immunoglobulin Y (Good Biotech Corp, Taichung, Taiwan). Troponin I was detected by the ADVIA Centaur cTnI chemiluminescence assay on an ADVIA Centaur Analyzer (Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA). Before HCT, peripheral blood samples were collected from each patient and stored in the blood bank at –80°C until use. Congestive Heart Failure (CHF) was defined in patients who had at least one episode of shortness of breath on minimal exertion or at rest (New York Heart Association [NYHA] functional class III or IV) or paroxysmal nocturnal dyspnea within the month before admission; and in patients with radiographic evidence of cardiomegaly and acute pulmonary edema.

Disease status evaluation

Patients were staged based on the results of computed tomography (CT) scanning and/or Positron Emission Tomography (PET) scanning, and bone marrow biopsy was performed as indicated by physicians. Treatment responses were evaluated using CT in most cases and PET in some cases after 2005. Complete Response (CR), Partial Response (PR), Stationary Disease (SD), and Progressive Disease (PD) were defined according to RECIST criteria [15]. OS was measured from the time of HCT to the date of death from any cause or the last follow-up. Non-Relapse Mortality (NRM) was determined by physicians when the cause of death was independent of lymphoma disease and without recurrence.

Prognostic predictors and survival analysis

All the possible predictive factors were subjected to univariate and Cox proportional hazards regression analysis (adjusted for all univariate factors found to have P value <0.05) to find the independent predictors of survival. The Kaplan-Meier method was used to estimate the OS rate. The survival of patients with different prognostic factors was compared using the log rank test. With the exception of OS and 3-month survival, comparisons of continuous data were performed using the Student's t-test, and The comparisons of categorical data were performed using a Chi-square test with a Yates' correction or Fisher's exact test, such as the relationships among cumulative mortality, Hs CRP, and ARWM. P values less than 0.05 were considered statistically significant. Statistical analyses were performed with the statistical package SPSS for Windows (Version 17.0, SPSS Inc, Chicago, IL).

Results

Baseline characteristics

The characteristics of the 101 patients included in the present

Table 1: Patient and disease characteristics (n = 101).

Characteristics	Data
Age (years)	41.3 ± 13.6
Male (n)	59.4% (60)
Diagnosis	
Hodgkin disease (n)	14.9% (15)
Non- Hodgkin disease (n)	85.1% (86)
Pre-transplantation disease status	
CR (n)	11.9% (12)
PR (n)	47.5% (48)
SD (n)	27.7% (28)
PD (n)	12.9% (13)
Donor type	
Autologous	74.3% (75)
Allogeneic	25.7% (26)
ECOG performance status	
0	61.4% (62)
1	32.7% (33)
2	5.9% (6)
Ann Arbor Stage	
I	3.0% (3)
II	30.7% (31)
III	17.8% (18)
IV	48.5% (49)
HCT-CI	
0	70.3% (71)
1–3	29.7% (30)
Cardiovascular-associated factors	
LVEF (%)	64.6 ± 6.2
ARWM (n)	47.5% (48)
HsCRP (mg/dL)	0.96 ± 2.76
Troponin I (ng/mL)	0.05 ± 0.21
DM (n)	6.9% (7)
Hypertension (n)	6.9% (7)
Hyperlipidemia (n)	3.0% (3)
Radiation therapy (n)	26.6% (27)
Mediastinal	16.8%(17)
Non-mediastinal	9.9%(10)
Hematopoietic stem cell source	
PBSC (n)	99% (100)
BSC (n)	1.0% (1)
Extra-nodular metastasis (n)	33 (32.7%)
LDH (U/L)	558.9 ± 775.1
Anthracycline cumulative dose (mg/m²)	252.1 ± 113.3

CR: Complete Remission; PR: Partial Remission; SD: Stable Disease; PD: Progressive Disease; PBSC: Peripheral Blood Stem Cells; BSC: bone marrow stem cells; HCT-CI: Hematopoietic Cell Transplantation Comorbidity Index; LVEF: Left Ventricular Ejection Fraction; ARWM: Abnormal Regional Wall Motion; DM: Diabetes Mellitus; HsCRP: High Sensitive C-Reactive Protein

study are shown in Table 1. The mean age was 41.3 ± 13.6 years, and the mean follow-up period was 1074.8 ± 739.2 days (range: 14–2392 days). The patients were predominantly male (59.4%). NHLs was the definitive diagnosis in the majority of patients (85.1%). Most patients had Eastern Cooperative Oncology Group (ECOG) performance scores of 0 or 1 and no HCT-CI comorbidities (70.3%). The mean Hs CRP level was 0.96 ± 2.76 mg/dL and the mean troponin I level was 0.05 ± 0.21ng/mL. Seven patients had a left ventricular ejection fraction (LVEF) lower than 45% before HCT. The overall incidence of ARWM was 47.5%. The OS rate was 68.3% and the 3-month survival rate was 89.1%.

Cardiovascular events and non-relapse mortality

Total cardiovascular events in 21 patients with CHF and in 3 patients with major cardiovascular events after HCT were reviewed. As shown in Table 2, there were 3 major cardiovascular events (1 sudden cardiac death with an unknown cause, 1 ventricular tachycardia, 1 myocardial infarction), while the 2nd and 3rd patients were associated with lymphoma progression. The mortality rate was higher among patients with cardiovascular events than among patients without cardiovascular events (57.1% vs. 25.0%, *P*=0.01, data not shown). Non-relapse mortality (NRM) was noted in 14 patients (13.9%). The causes of NRM included sepsis (n=7), fulminant hepatitis (n=3), GVHD (n=1), adult respiratory distress syndrome (n=1), thrombotic thrombocytopenic purpura (n=1), and sudden cardiac death (n=1).

Long term prognostic factors after HCT

Univariate analysis showed that age, disease status, performance status, ARWM, Hs CRP have significantly predictive values (Table 3). After Cox regression analysis with all predictive factors, only ARWM, Hs CRP, age, and ECOG performance status were independent risk factors of long term OS. Kaplan-Meier survival curves for OS were constructed according to the 4 independent risk factors (Figure 1), with cut-off values determined by individual ROC curves (Hs CRP >0.338 mg/dL, sensitivity: 46.9%, specificity: 73.9%, AUC: 0.60; age >43 years, sensitivity: 75.0%, specificity: 62.3%, AUC: 0.68; performance >0, sensitivity: 56.2%, specificity: 69.6%, AUC: 0.65). Combining the prognostic factors to categorize no, one, two, and equal or more than 3 risk factors groups revealed that survival progressively decreased as the number of risk factors increased (Figure 2A). The categorization could also be applied to patients who do not have risk factors traditionally associated with the HCT-CI index (n=71) (Figure 2B).

Relationship among cumulative mortality, Hs CRP and ARWM

The relationships among the cumulative mortalities, Hs CRP levels, and ARWM were further investigated. High Hs CRP levels (>0.338 mg/dL) were associated with higher cumulative tumor-related mortality (*P*=0.045) but not with non-relapse mortality (*P*=0.99). However, ARWM was associated with both tumor-related mortality (*P*=0.01) and non-relapse mortality (*P*=0.027) (Figure 3).

Discussion

The present study is the first to show that ARWM, Hs CRP, age, and ECOG performance are independent predictors of long term OS in patients with lymphoma after HCT. Furthermore, ARWM was associated with both cumulative NRM and tumor-related mortality and HsCRP was specifically associated with cumulative tumor-related mortality.

Long term survivors of allogeneic HCT as well as patients with lymphoma are at increased risk of premature cardiovascular

Table 2: Major cardiovascular events after hematopoietic stem cell transplantation.

Age, years	Sex	Diagnosis	Cardiovascular events	Disease status	Risk factors
58	Male	DLBCL	Myocardial infarction	Disease progression	DM
49	Female	DLBCL	Sudden cardiac death	Stable disease	CKD
55	Female	DLBCL	Ventricular tachycardia	Disease progression	Hyperlipidemia

DLBCL: Diffuse Large B Cell Lymphoma; DM: Diabetes Mellitus; CKD: Chronic Kidney Disease

Table 3: Univariate and multivariate Cox regression analysis of overall survival.

Characteristics	Univariate analysis		Multivariate analysis	
	Harazd ratio (95% CI)	*P*-Value	Harazd ratio (95% CI)	*P*-Value
Non-CV factors				
Age (years)	1.04 (1.01-1.07)	0.006	1.06 (1.02–1.09)	0.002
Sex	1.41 (0.68-2.92)	0.36		
Hodgkin disease	0.51(0.15-1.67)	0.27		
Ann Arbor stage	1.25 (0.85-1.83)	0.26		
Disease status	1.79 (1.19-2.67)	0.005		
HCT score	0.93(0.54-1.60)	0.80		
Donor type	2.01(0.98-4.12)	0.06		
Performance	2.62(1.54-4.46)	<0.001	2.01(1.13–3.59)	0.02
Radiation therapy	0.60 (0.25-2.46)	0.26		
Extranodal metastasis	1.13 (0.55-2.35)	0.74		
LDH	1.00(1.0-1.0)	0.88		
CV factors				
Anthracycline*	0.99 (0.99-1.00)	0.36		
Hypertension	0.39 (0.05-2.88)	0.36		
Hyperlipidemia	1.10(0.15-8.00)	0.93		
DM	1.23(0.37-4.03)	0.74		
LVEF	0.98(0.93-1.04)	0.49		
ARWM	4.80(1.20-11.1)	<0.001	8.02(2.96–21.78)	<0.001
HsCRP	2.10 (1.04-4.17)	0.04	1.27(1.12–1.44)	<0.001
Troponin	0.25(0.02-36.9)	0.59		

CV: Cardiovascular; HCT: Hematopoietic Stem Cell Transplantation; LVEF: Left Ventricular Ejection Fraction; ARWM: Abnormal Regional Wall Motion; HsCRP: High Sensitive C-Reactive Protein; *Cumulative dosage

accidents [2-8]. However, it remains unclear whether these cardiovascular events are associated with differences in survival. Although cardiovascular events occurred frequently after HCT in this study, multivariate Cox regression analysis revealed that those events were not independently associated with OS. This finding could be attributed to the advancement in the treatment of cardiovascular diseases in recent years, especially in cases of heart failure, which has significantly reduced the mortality of patients with cardiovascular complications [18], while most of the mortality is due to tumor progression or infection events. The collinearity between comorbidities and cardiovascular events might also lead to a lack of significance after multivariate analysis.

Screening of all cardiovascular associated risk factors and characteristics showed that ARWM and HsCRP were independently associated with OS. HsCRP, which has been associated with a high risk of coronary artery disease, arrhythmia, and cardiovascular mortality, is considered an important cardiovascular associated risk factor [19,20]. Recently, HsCRP has also been reported to be a predictor of long term mortality in patients with lymphoma after chemotherapy, chronic myeloid leukemia after HCT, or early relapse after chemotherapy [12,13]. Microscopy data from human lymphoma tissues revealed that tumor-associated macrophages, which are associated with inflammatory status, were correlated with a shortened progression-free survival and relapse after autologous HCT [21]. The present study showed that HsCRP was associated with higher cumulative tumor-related mortality but not with NRM. These findings suggest that HsCRP might be the manifestation of inflammatory infiltration in patients with lymphoma, rather than playing a role in the incidence of cardiovascular events. Acute cardiovascular dysfunction induced by acute illness and severe sepsis is associated with increased mortality [22]. In patients undergoing HCT, cardiovascular decomposition induced by either tumor progression or sepsis might contribute to higher mortality rates and be masked by the dominant manifestations of sepsis or tumor progression. Although apparent LVEF dysfunction has been correlated with mortality in patients after HCT [10,23]. However, in patients with normal resting LVEF, cardiovascular reserve in response to stress such as exercise, or sepsis may be a better indicator of mortality. ARWM, which is associated with cardiac dyssynchrony, is an early feature of heart failure in patients with preserved LVEF [24,25], and might be associated with stress-induced cardiac dysfunction [26]. Therefore, ARWM, as an early predictor of subclinical cardiovascular dysfunction, might be exacerbated and

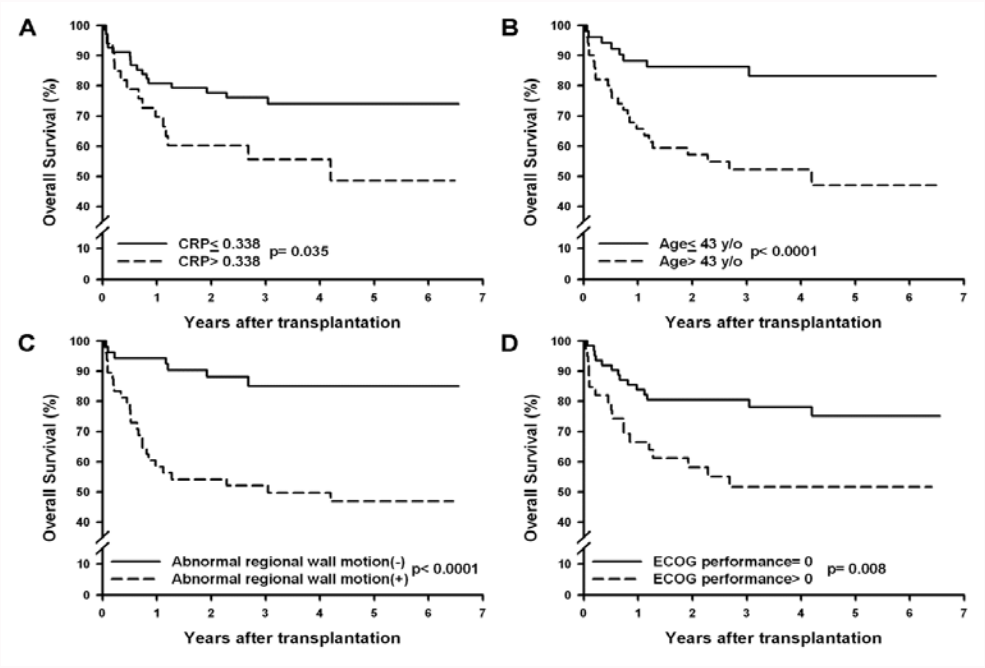

Figure 1: Kaplan-Meier survival curves of 4 independent prognostic factors of overall survival. (A) Lower serum HsCRP level (cut-off value, 0.338 mg/dL; *P*< 0.035), (B) younger age while receiving transplantation (cut-off value, 43 years; *P*< 0.0001), (C) normal regional wall motion (*P*< 0.0001), and (D) ECOG performance=0 (*P*< 0.008) are independent predictors of overall survival.

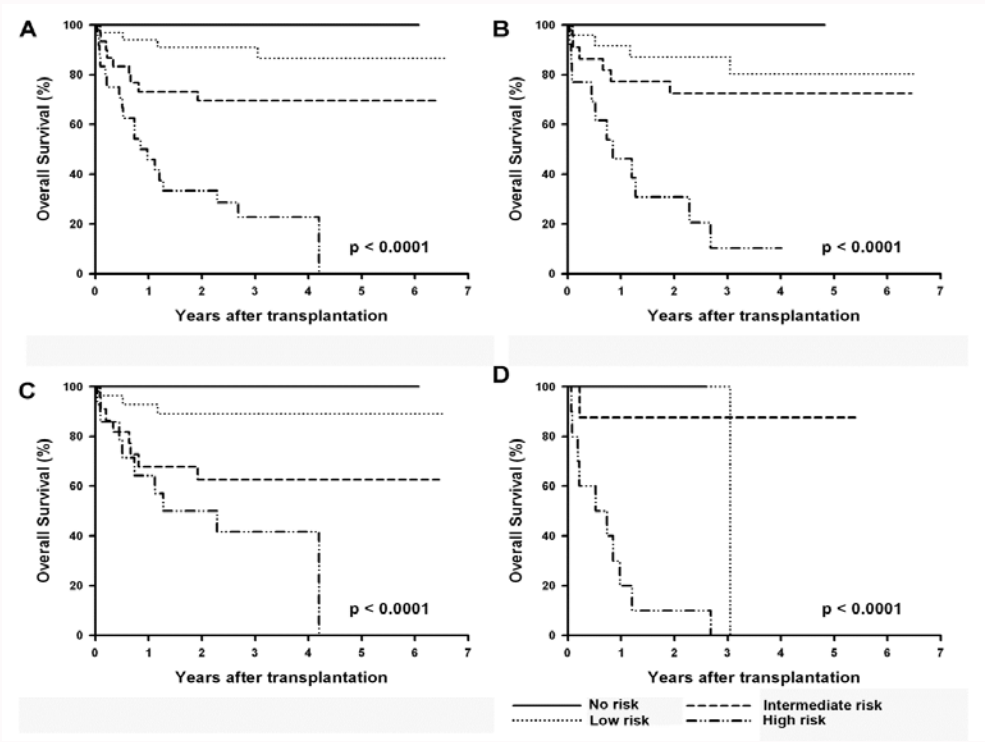

Figure 2: Kaplan-Meier survival curves of the risk groups according to the categorization.
Each of the 4 independent prognostic factors (HsCRP, age, ARWM, and ECOG performance) was viewed as 1 risk factor and then added together. (A) In the whole study population, there were 4 groups of lymphoma patients undergoing stem cell transplantation based on the risk factors=0 (n=13), 1 (n=34), 2 (n=30), equal or more than 3 (n=24). (*P*< 0.0001); (B) in the subgroup without HCT-CI comorbidities, there were still significant survival differences between the 4 risk groups (*P*< 0.0001).

be associated with mortality under stress conditions such as tumor progression or severe infection.

HCT-CI is an important risk assessment score in lymphoma patients receiving HCT [4,27]. In the present study, HCT-CI was not associated with prognosis. Compared to the findings reported by Farina et al., the population in the present study was younger (median age: 43 years vs 53 years), and had lower HCT-CI scores

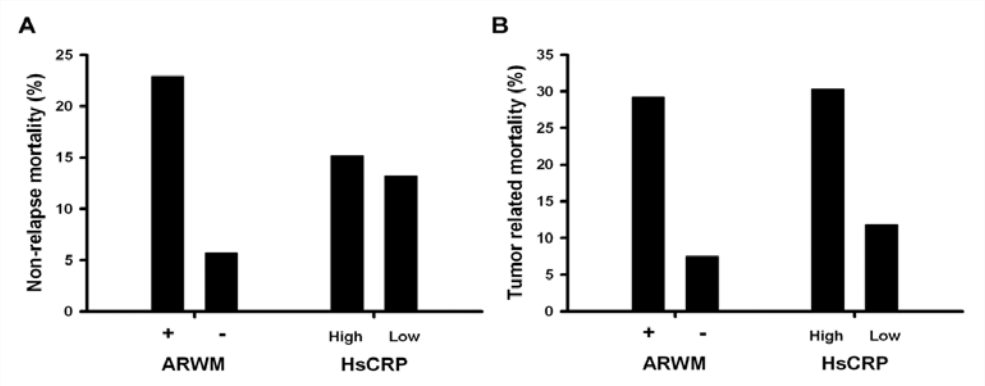

Figure 3: Comparison of tumor related vs. non-relapse mortality between HsCRP and ARWM. (A) The ARWM (+) patients had higher non-relapse mortality rates than the ARWM (−) patients (*P*=0.027), while there were no differences in HsCRP levels (*P*=0.99). (B) Both ARWM (+) and high HsCRP were correlated with higher tumor-related mortality (*P*=0.01 and 0.045, respectively).

(patients with HCT-CI = 0, 70.3% vs. 32% in the study by Farina et al. [4]. Similar differences were found between the present study and the findings reported by Plattel et al. [25] (age, 43 years vs. 52 years; patients with HCT-CI = 0, 70.3% vs. 52%) [27].The younger age and lower HCT-CI scores in the present study population might explain why HCT-CI did not have the same predictive value as in previous studies. The present study introduced new cardiovascular associated risk factors, which might help in the stratification of patients with low HCT-CI scores or those without comorbidities (Figure 2B). There are limitations in this retrospective analysis, including the inevitable selection bias from a single center and small number of studied populations. However, the high-risk group of patients with 3 or more risk factors had a very poor prognosis, which may discourage the use of HCT as treatment for lymphoma in that patient population in the future. A larger scale study is necessary to further validate the present findings. In conclusion, ARWM is a cardiovascular associated factor for long term OS in lymphoma patients after HCT. HsCRP is specifically correlated with tumor-related mortality. Patients with equal or more than 3 independent risk factors may be discouraged for HCT in the future clinical practice.

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