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ORIGINAL ARTICLE

Pretransplant serum beta-2 microglobulin level is a potential novel prognostic marker of overall survival after allogeneic hematopoietic cell transplantation – a retrospective observational study

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SUMMARY

Although elevated serum beta-2 microglobulin (BMG) has been reported as a poor prognostic marker for various hematological malignancies, no study has assessed its prognostic significance in allogenec hematopoietic cell transplantation (allo-HCT). Therefore, we conducted this retrospective observational study in 227 consecutive patients with available pretransplant serum BMG levels between April 2010 and September 2017 at our institute. We also collected and retrospectively analyzed various pretransplant variables likely related to transplant outcomes. Multivariable analysis, including major prognostic variables, such as the disease risk index and the hematopoietic cell transplant-comorbidity index, showed a significant association between higher serum BMG levels and poorer overall survival (OS) in all three adjusted models [hazard ratio (HR) per its standard deviation (SD) (SD = 1.094): 1.67 (1.35–2.03; $P < 0.001$), HR per SD: 1.46 (1.14–1.86; $P = 0.002$), HR per SD: 2.03 (1.62–2.55; $P < 0.001$)], respectively, due to the significant association between higher serum BMG levels and relapse/progression [HR 1.52 (1.20–1.94; $P < 0.001$)] instead of nonrelapse mortality [HR 1.06 (0.70–1.60; $P = 0.780$)]. Moreover, DRI and serum BMG had statistically significantly higher c-statistic estimates for OS compared with DRI alone (c-index 0.74 and 0.68, respectively; $P < 0.001$). In conclusion, pretransplant serum BMG level may serve as a useful prognostic marker and help clinical decision in allo-HCT.

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Key words
beta-2 microglobulin, allogeneic hematopoietic cell transplantation, pretransplant prognostic marker, overall survival, relapse/progression

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Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) is a curative treatment for hematologic malignancies. The advances in conditioning regimens, graft-versus-host disease (GVHD) prophylaxis, and supportive care have improved the outcome of allo-HCT [1]; however, further improvement is desirable for recurrence and nonrelapse mortality (NRM). In addition to age, performance status, conditioning regimen intensity, and donor source, comorbidities and disease status have often been used for estimating the risk of mortality after allo-HCT. Hematopoietic cell transplantation-comorbidity index (HCT-CI) provides a valid and reliable scoring of pretransplant comorbidities to predict NRM and overall survival (OS) [2]. Disease risk index (DRI) uses available information on the type of disease and disease status to divide patients into four risk groups with different OS and progression-free survival depending on the differences in the relapse risk [3]. Both prognostic models are useful; however, these effective models still have room for improvement. In recent years, several serum markers, such as ferritin and albumin, have been reported as additional useful prognostic markers [4,5].

Beta-2 microglobulin (BMG) is a component of major histocompatibility complex class I molecules in all nucleated cells. Serum BMG levels are reflective of the renal function [6] and inflammatory conditions [7,8]. Several studies have reported elevated serum BMG level as a poor prognostic factor, which may reflect tumor burden for several hematological malignancies at diagnosis and autologous HCT (auto-HCT) [9–17]. However, no study has assessed the prognostic significance of pretransplant serum BMG levels for allo-HCT.

In the present study, we evaluated the prognostic role of pretransplant serum BMG levels in patients with hematologic malignancies undergoing allo-HCT.

Materials and methods

Patients and data collection

We undertook this single-center retrospective observational study in patients with hematological malignancy that received their first allo-HCT at our institute from April 2010 to September 2017. We analyzed patients who had serum BMG examination within 1 month from the start of conditioning regimen. We evaluated our cohort using HCT-CI and DRI, which were confirmed as prognostic prediction models in accordance with previous reports [2,3]. Additionally, we collected other clinical and laboratory data at transplant that served as prognostic factors, including patients' age [18], performance status [19], tumor and inflammatory biomarkers, such as ferritin [20], albumin [21], and C-reactive protein [22], within a month before the start of the conditioning regimen for allo-HCT. Furthermore, we collected the serum data of creatinine and the estimated glomerular filtration rate evaluated for patients' renal function analysis at transplant that could be associated with serum BMG [6]. All serum BMG measurements were performed by immunonephelometry, using two kinds of systems (7600 Clinical Analyzer: Hitachi High-Technologies, Japan from April 2010 to December 2010. JCA-BM Bio Majesty: Japan Electron Optics Laboratory, Japan from January 2011 to January 2016.). We confirmed the correlation formula of serum BMG measured by the former method and the latter method when changing the system ($Y = 1.051X - 0.004$; X: serum BMG by the former method, Y: serum BMG by the latter method). We analyzed all the data using the serum BMG level corrected as described above. We defined myeloablative or reduced-intensity conditioning in accordance with a previous research [23]. An HLA-A, B, C, and DRB1 8/8 allele matched-related donor was defined as a "matched-related donor;" any other related donor was defined as "mismatched-related donor;" an HLA-A, B, C, and DRB1 8/8 allele matched-unrelated donor was defined as a "matched-unrelated donor;" any other unrelated donor was defined as "mismatched-unrelated donor;" cord blood was dealt with a separate donor category. Acute and chronic GVHD were diagnosed and graded in accordance with classic criteria [24,25]. This study was approved by the local institutional review board and conducted as per the Declaration of Helsinki.

Statistical analysis

Serum BMG values of each disease or disease category were compared using Mann–Whitney U test and Kruskal–Wallis test. Cox regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CI) in the univariate and multivariable analyses. The variables analyzed were age, sex, disease, HCT-CI, performance status, DRI, conditioning regimen intensity, donor source, cytomegalovirus serostatus, and pretransplant serum BMG level. We used Firth's correction for monotone likelihood in the low DRI risk group for OS. Multivariable analyses were conducted to assess

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the independence of the serum BMG level from all of the variables, which had been previously reported as prognostic factors for OS, relapse/progression (Rel/Prog), and NRM, respectively. A P-value <0.050 was considered statistically significant. The Kaplan–Meier method was used for calculating OS. Gray's test was used to estimate the cumulative incidence of Rel/Prog or NRM and acute/chronic GVHD. Rel/Prog and NRM were considered competing events. Competing risks for acute or chronic GVHD were defined as death from all-cause. The Fine–Gray proportional hazard regression model was used for the univariate and multivariable analyses with competing risks. The Spearman's correlation coefficient was employed to estimate the correlation between serum BMG and other factors, which were continuous variables. Jonckheere–Terpstra trend test was used to estimate the correlation between serum BMG and both DRI and HCT-CI. We assessed the two models using c-statistics on the basis of time to event, using the total follow-up period to compare the predictive accuracy of DRI or HCT-CI, which have been previously reported as important prognostic models in allo-HCT [3,18] with BMG-added models. Standard errors for the c-statistics were evaluated by applying a bootstrap procedure using 1000 bootstrap samples to check the reproducibility. The standard errors for the difference in c-statistics between the above two models were compared with the bootstrap samples and used to compute a z-score and a p-value for the difference, as in two previous studies [2,18]. All statistical analyses were conducted using EZR version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [26] and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria), using packages coxphf, survival, rms, and boot.

Results

Patient characteristics

We enrolled 227 consecutive transplant cases between April 2010 and September 2017 that received first allo-HCT at our institute and underwent pretransplant serum BMG measurement. The patients' characteristics at transplant are shown in Table 1. The median CD34+ counts (range) for the patients who received peripheral blood stem cell transplantation and cord blood cell transplantation were 4.38×10^6 (1.91–31.4) and 0.75×10^6 (0.37–3.09)/kg patient's body weight, respectively. The median total nucleated cell count (range) for the patients who received bone marrow transplantation and cord blood cell transplantation was 2.58×10^8 (range, 0.39–5.30) and 2.8×10^7 (range, 1.73–23.5)/kg patient's body weight, respectively. The median serum BMG levels concerning patients with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), malignant lymphoma (ML), adult T-cell leukemia/lymphoma (ATLL), and myeloproliferative neoplasm (MPN) were 1.9 mg/dl (range, 0.9–7.9), 1.9 mg/dl (range, 1.1–5.6), 2.1 mg/dl (range, 1.0–5.4), 2.4 mg/dl (range, 1.0–6.3), 2.0 mg/dl (range, 1.4–8.4), and 1.9 mg/dl (range, 1.0–3.4), respectively, and there was no significant difference between each disease ($P = 0.131$). We divided each disease into lymphoid ($n = 81$) and myeloid group ($n = 146$) and found no significant difference in serum BMG level between the two groups ($P = 0.176$). The lymphoid group included ALL, ML, and ATLL, while the myeloid group comprised AML, MDS, and MPN. During the follow-up period, 87 patients died (38%). The incidence rates concerning transplant outcomes and causes of death are shown in Tables 2 and 3, respectively.

Univariate analysis of prognostic factor for transplant outcomes

We assessed the relationship between transplant outcomes and prognostic classification in our cohort with DRI and HCT-CI (Fig. 1). These results were similar to those previously reported, confirming the reproducibility and external validity of these prognostic models. Furthermore, we also evaluated whether other factors including serum BMG were associated with OS, Rel/Prog, NRM, acute GVHD, and chronic GVHD. In the univariate analysis, patient age, DRI, HCT-CI, performance status, donor source, conditioning regimen intensity, cytomegalovirus serostatus, serum albumin level, serum ferritin level, and serum C-reactive protein level, as well as serum BMG were significantly associated with OS (Table 4). Moreover, serum BMG level showed a significant association with both Rel/Prog and NRM (Table 5). The serum level of BMG showed no significant association with grade 2–4 acute GVHD (HR: 1.09, 95% CI: 0.86–1.40, $P = 0.430$), grade 3–4 acute GVHD (HR: 1.05, 95% CI: 0.78–1.42, $P = 0.714$), extensive chronic GVHD (HR: 0.86, 95% CI: 0.56–1.30, $P = 0.500$), and overall chronic GVHD (HR: 0.82, 95% CI: 0.57–1.20, $P = 0.352$).

Subgroup analysis

Our findings differed from those of Costa-Lima et al. [28], who reported an association between the

Table 1. Patients' characteristics (n = 227).

Characteristics	No.	%
Age, median (range), year	47 (17–68)	
Sex		
Male	132	58.1
Female	95	41.9
Disease		
AML	102	44.9
ALL	35	15.4
MDS	35	15.4
ML	28	12.3
ATLL	18	7.9
MPN	9	4.0
Disease risk index		
Low	13	5.7
Intermediate	115	50.7
High	75	33.0
Very high	24	10.6
HCT-CI		
0	112	49.3
1,2	71	31.3
≥3	44	19.4
PS		
0	129	56.8
1	92	40.5
2	3	1.3
3	2	0.9
4	1	0.4
Donor source		
MRD	43	18.9
MMRD	65	28.6
MUD	56	24.7
MMUD	10	4.4
CB	53	23.3
Conditioning regimen		
MAC	140	61.7
RIC	87	38.3
CMV serostatus		
Recipient-donor	24	10.6
Other	203	89.4
BMG, median (5–95% percentile), mg/l	2.0 (1.2–4.3)	
Albumin, median (5–95% percentile), g/dl	3.9 (3.0–4.6)	
Ferritin, median (5–95% percentile), ng/ml	1346 (116–5898)	
CRP, median (5–95% percentile), mg/l	0.28 (0.02–4.45)	
Creatinine, median (5–95% percentile), mg/dl	0.65 (0.44–1.04)	
eGFR, median (5–95% percentile), ml/min/1.73 m^2	90.5 (54.7–156.9)	

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; ATLL, adult T-cell leukemia/lymphoma; BMG, beta-2 microglobulin; CB, cord blood; CMV, cytomegalovirus; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HCT-CI, hematopoietic cell transplantation-comorbidity index; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; ML, malignant lymphoma; MMRD, mismatch-related donor; MMUD, mismatch-unrelated donor; MPN, myeloproliferative neoplasm; MRD, match-related donor; MUD, match-unrelated donor; PS, performance status; RIC, reduced-intensity conditioning.

pretransplant serum BMG level and the risk of grade 2–4 acute GVHD. We considered that the differences in the influence of serum BMG on acute GVHD between our study and Costa-Lima et al.'s study could be attributed to differences in terms of patient background. In Costa-Lima et al.'s study, the cohort comprised only patients with lower disease risk and matched-related donors and matched-unrelated donors, whereas our cohort comprised patients with varying disease risk and more varied donors including HLA-mismatched donors. We considered that, as a result, these differences led to differing incidences in disease Rel/Prog and GVHD, and that the influences of BMG on OS and GVHD might change. Therefore, we limited the patients to those who were in complete remission at transplant, as well as those with matched-related donor and matched-unrelated donor allo-HCT (n = 58), similar to the patient backgrounds in Costa-Lima et al.'s study, and we conducted additional analyses. Consequently, no significant association was observed between serum BMG and OS (HR: 1.07, 95% CI: 0.41–2.80, P = 0.886), Rel/Prog (HR: 0.43, 95% CI: 0.16–1.11, P = 0.081), NRM (HR: 3.07, 95% CI: 0.90–10.5, P = 0.073), grade 2–4 acute GVHD (HR: 0.90, 95% CI: 0.49–1.66, P = 0.740), extensive chronic GVHD (HR: 1.08, 95% CI: 0.53–2.42, P = 0.750), and overall chronic GVHD (HR: 1.13, 95% CI: 0.43–2.75, P = 0.870). However, the serum BMG level was significantly associated with grade 3–4 acute GVHD (HR: 2.86, 95% CI: 1.31–6.25, P = 0.008; Tables S1 and S2).

Additionally, we analyzed the effect of serum BMG only in AML. Serum BMG levels showed a significant

Table 2. The frequencies of transplant outcomes* (n = 227).

Outcomes*	%	95% CI
Overall survival at 2 years	60.1	52.8–66.6
The cumulative incidence of relapse/progression at 2 years	33.4	26.9–40.0
Nonrelapse mortality at 2 years	12.3	8.20–17.3
The cumulative incidence of grade 2–4 acute GVHD at 100 days	48.0	41.3–54.4
The cumulative incidence of grade 3–4 acute GVHD at 100 days	17.7	13.0–23.0
The cumulative incidence of overall chronic GVHD within 2 years	23.8	17.4–30.8
The cumulative incidence of extensive chronic GVHD within 2 years	18.6	12.7–25.4

CI, confidence interval; GVHD, graft-versus-host disease.

*The median follow-up period of survivors (n = 140) was 1078 days (range, 22–2648 days).

Table 3. Causes of death (n = 87).

Causes of death	No.	%
Relapse/Progression	58	66.7
Acute GVHD	13	14.9
Chronic GVHD	4	4.60
Infection	4	4.60
Interstitial pneumonia	2	2.30
Secondary malignancy	1	1.15
Engraft failure	1	1.15
Sinusoidal obstruction syndrome	1	1.15
Thrombotic microangiopathy	1	1.15
Heart failure	1	1.15
Alveolar hemorrhage	1	1.15

GVHD, graft-versus-host disease.

association with OS (HR: 1.92, 95% CI: 1.44–2.56, $P < 0.001$) and Rel/Prog (HR: 2.00, 95% CI: 1.57–2.55, $P < 0.001$), but not with NRM (HR: 1.18, 95% CI: 0.68–2.06, $P = 0.550$; Table S3).

Multivariable analysis of prognostic factors for transplant outcomes

Multivariable analyses were conducted to assess the independence of serum BMG level in relation to all the variables previously reported as prognostic factors for OS. Moreover, we performed multivariable analyses by selecting each of the variables reported as prognostic factors for Rel/Prog [3,21,22] and NRM [2,19–22]. Age and sex were mandatorily added to the multivariable analyses. We first applied and validated three multivariable models to evaluate the effect of serum BMG on OS to meet the requirements of the one-in-ten rule to avoid overfitting (Table 5). Higher serum BMG level was significantly associated with poorer OS in all three adjusted models. We assessed the effect of serum BMG on Rel/Prog and NRM and found a significant association between serum BMG and Rel/Prog but not NRM (Table 6).

Correlations between serum BMG and other factors

In general, serum BMG level is associated with disease status, age [27], renal function [6], and inflammatory condition [7,8], all of which influence the outcome of allo-HCT. Therefore, we analyzed the correlation between BMG and other factors, such as age, ferritin, albumin, C-reactive protein, creatinine, and estimated glomerular filtration rate to evaluate the strength of association. In Spearman's rank correlation test, a significantly weak correlation was observed with all these factors (Table 7). We also evaluated the correlation between serum BMG and prognostic models, such as DRI comprising four groups (low, intermediate, high, and very high groups) and HCT-CI consisting of three groups (0, 1–2, and 3 or more than three points groups), using the Jonckheere–Terpstra test. Higher serum BMG at transplant showed a significant correlation with poorer group of HCT-CI ($P = 0.003$) and a trend of correlation with higher risk group of DRI ($P = 0.060$; data not shown).

Prognostic significance of BMG-added models for OS through computing the c-statistic

Disease risk index is one of the most common prognostic prediction models for OS in allo-HCT. As shown in Fig. 1, OS was significantly stratified with DRI. Therefore, we compared the capabilities of DRI versus the composite model, consisting of DRI and serum BMG to assess the prognostic significance of serum BMG for OS. DRI and serum BMG had statistically significantly higher c-statistic estimates for OS compared with DRI

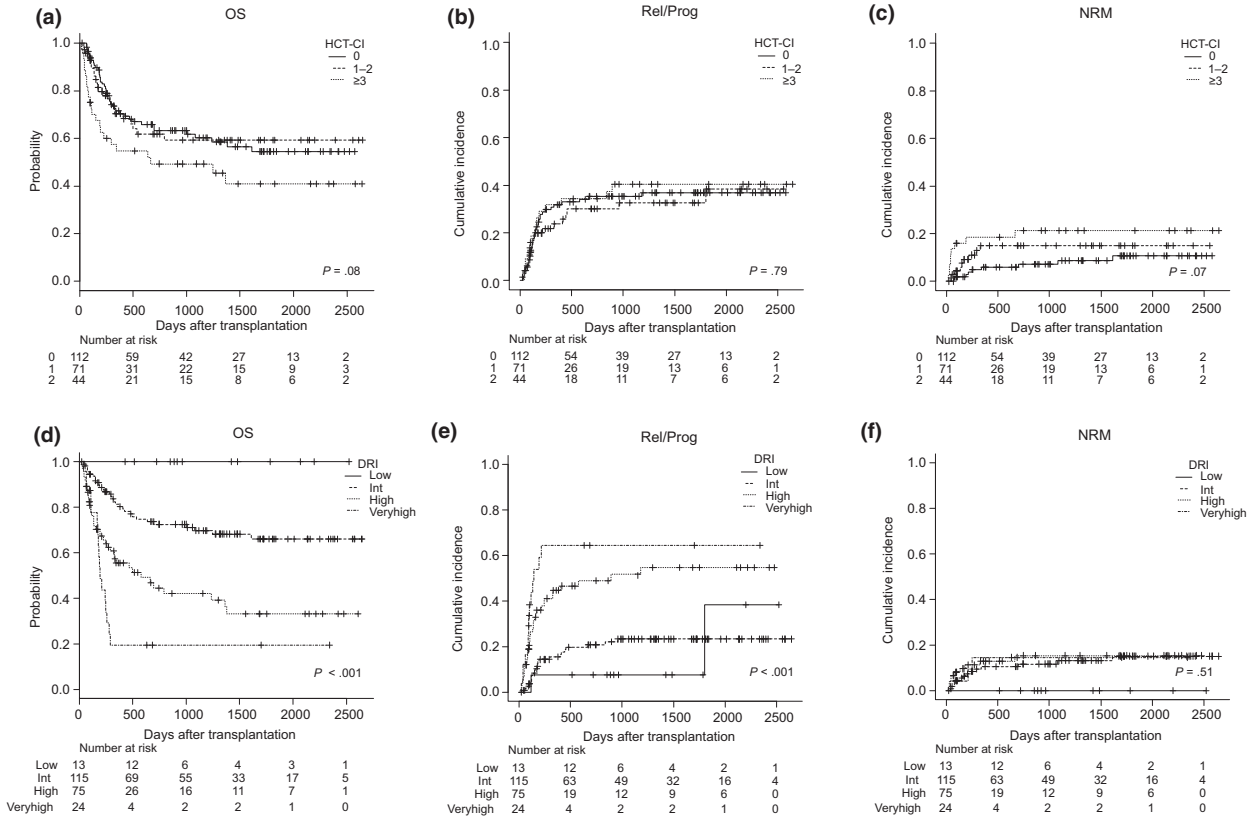

Figure 1 OS, Rel/Prog, and NRM after allo-HCT were stratified with HCT-CI (a–c) and DRI (d–f).

alone (c-index 0.74 and 0.68, respectively; $P < 0.001$). Moreover, HCT-CI and serum BMG had statistically significantly higher c-statistic estimates for OS compared with HCT-CI alone (c-index 0.66 and 0.55, respectively; $P < 0.001$).

Discussion

In the present study, we found that high serum BMG level at allo-HCT was significantly associated with poor OS, mainly caused by the increase in the incidence of Rel/Prog even after adjustment for other several prognostic factors, including HCT-CI and DRI.

The prognosis of allo-HCT mainly relies on Rel/Prog and NRM. As a prognostic prediction of allo-HCT, DRI focusing on patients' disease status [3] and HCT-CI focusing on patients' health status [2] are representative models that are widely used. Recent studies have reported that the inclusion of several clinical and laboratory parameters such as ferritin and albumin to DRI and HCT-CI could refine their discriminative powers for transplant outcomes [4,5]. The usefulness of serum BMG for the prognosis of various hematological malignancies at diagnosis [10–17] and high-dose chemotherapy with auto-HCT for malignant lymphoma [9] has been reported. In allo-HCT, only one report has described the association between high serum BMG level at transplant and incidence of grade 2–4 acute GVHD [28]. This study did not show the significance of BMG for other transplant outcomes. As per our search, this study is the first report indicating the significance of BMG for OS after allo-HCT.

Serum BMG level is a component of major histocompatibility complex class I molecules in all nucleated cells. Therefore, the proliferation of all types of tumors leads to elevated serum BMG levels. Major histocompatibility complex class I is strongly expressed in lymphocytes and BMG plays an important role in stabilizing its three-dimensional structure. Some inflammatory conditions activating lymphocytes lead to the production of high level of serum BMG [29]. In addition, serum BMG is filtered by the glomerulus and is almost reabsorbed by the proximal tubules. Therefore, serum BMG is known as a renal function-biomarker in the clinical setting [6]. Shinkai et al reported serum BMG as a more useful marker than cystatin C or C-reactive protein for

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Table 4. Univariate analyses of OS, Rel/Prog, and NRM.

	OS			Rel/Prog			NRM		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age per SD (year)	1.57	1.23–2.01	**<0.001**	1.12	0.86–1.45	0.400	1.63	0.96–2.74	0.069
Sex, male	1.35	0.87–2.07	0.181	1.10	0.69–1.74	0.670	2.18	0.92–5.19	0.076
Disease, myeloid	0.85	0.55–1.30	0.443	0.96	0.61–1.55	0.870	0.54	0.25–1.13	0.100
Disease risk index									
Low	0.11	0.00–0.77	**0.020**	0.67	0.17–2.70	0.570	NE		
Intermediate	1.00	Ref		1.00	Ref		1.00	Ref	
High	2.71	1.70–4.37	**<0.001**	3.11	1.85–5.21	**<0.001**	1.19	0.53–2.67	0.670
Very high	4.91	2.65–8.83	**<0.001**	4.76	2.39–9.51	**<0.001**	1.07	0.31–3.69	0.900
HCT-CI									
0	1.00	Ref		1.00	Ref		1.00	Ref	
1–2	1.00	0.60–1.67	0.996	0.88	0.52–1.52	0.650	1.77	0.72–4.35	0.220
≥3	1.71	1.03–2.85	**0.039**	1.11	0.62–1.98	0.730	2.88	1.14–7.29	**0.025**
PS									
0–1	1.00	Ref		1.00	Ref		1.00	Ref	
2–4	2.69	1.09–6.64	**0.032**	0.90	0.24–3.29	0.870	5.59	1.66–18.9	**0.006**
Donor source									
MRD	1.00	Ref		1.00	Ref		1.00	Ref	
MMRD	3.28	1.55–6.93	**0.002**	1.57	0.82–3.00	0.170	1.76	0.44–7.06	0.380
MUD	2.05	0.95–4.44	0.067	0.92	0.45–1.86	0.810	2.17	0.60–8.20	0.250
MMUD	0.94	0.20–4.36	0.940	0.56	0.13–2.45	0.440	1.44	0.20–14.2	0.750
CB	2.76	1.28–5.98	**0.010**	1.05	0.52–2.13	0.890	2.53	0.67–9.50	0.170
Conditioning regimen									
MAC	1.00	Ref		1.00	Ref		1.00	Ref	
RIC	1.92	1.25–2.94	**0.003**	1.27	0.79–2.03	0.310	1.82	0.85–3.85	0.120
CMV serostatus									
Recipient-donor	1.00	Ref		1.00	Ref		1.00	Ref	
Others	3.43	1.08–10.9	**0.036**	1.58	0.66–3.78	0.310	2.90	0.39–21.4	0.300
BMG per SD	1.83	1.49–2.26	**<0.001**	1.62	1.28–2.06	**<0.001**	1.42	1.08–1.86	**0.012**
Alb per SD	0.60	0.48–0.74	**<0.001**	0.85	0.66–1.08	0.180	0.56	0.39–0.81	**0.002**
Ferritin per SD	1.38	1.22–1.56	**<0.001**	0.97	0.84–1.13	0.700	1.34	1.24–1.44	**<0.001**
CRP per SD	1.23	1.09–1.40	**0.001**	1.25	1.10–1.41	**<0.001**	1.18	0.95–1.47	0.140
Cre per SD	0.97	0.80–1.18	0.786	0.81	0.62–1.04	0.097	1.19	0.97–1.46	0.096
eGFR per SD	1.08	0.88–1.33	0.442	1.22	1.01–1.50	**0.045**	0.88	0.58–1.30	0.520

Alb, albumin; BMG, beta-2 microglobulin; CB, cord blood; CI, confidence interval; CMV, cytomegalovirus; Cre, creatinine; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate, SDs for age, BMG, Alb, ferritin, CRP, Cre, and eGFR were 13.04, 1.094, 0.489, 5195, 2.824, 0.266, and 31.84, respectively; HCT-CI, hematopoietic cell transplantation-comorbidity index; HR, hazard ratio; MAC, myeloablative conditioning; MMRD, mismatch-related donor; MMUD, mismatch-unrelated donor; MRD, match-related donor; MUD, match-unrelated donor; NE, not estimable; NRM, nonrelapse mortality; OS, overall survival; PS, performance status; Ref, reference; Rel/Prog, relapse/progression; RIC, reduced-intensity conditioning; SD, standard deviation.

Disease (myeloid) indicates acute myeloid leukemia, myelodysplastic syndrome, chronic myeloid leukemia, myeloproliferative neoplasms. Disease (lymphoid) indicates acute lymphoid leukemia/lymphoblastic lymphoma, malignant lymphomas, adult T-cell leukemia/lymphoma.

Statistically significant values (P <0.050) are marked with bold font.

risk stratification of total mortality in the elderly population, as serum BMG level could reflect potential inflammatory and renal dysfunctions [30]. As a result, serum BMG level at transplant is probably reflective of tumor burden, inflammatory condition, and renal function, which were reported as the prognostic factors for allo-HCT [21,31–36]. In the present study, serum BMG level showed a strong relation to Rel/Prog rather than NRM, and a weak correlation between serum BMG level and several inflammatory markers and renal function markers was reported. Thus, serum BMG could be mainly affected by the disease status at allo-HCT. The significant influence of inflammatory markers such as ferritin, albumin, and C-reactive protein on the

Table 5. Multivariable analyses for overall survival.

	HR (95% CI)	*P*-value
Model 1		
BMG, per SD	1.67 (1.35–2.03)	**<0.001**
DRI low	0.11(0.00–0.77)	**0.019**
Intermediate	Ref	
High	2.56 (1.60–4.17)	**<0.001**
Very high	5.36 (2.82–9.93)	**<0.001**
HCT-CI 0	Ref	
1–2	1.35 (0.79–2.24)	0.267
≥3	1.77 (1.04–3.03)	**0.046**
Model 2		
BMG, per SD	1.46 (1.14–1.86)	**0.002**
Ferritin per SD	1.32 (1.09–1.76)	**0.004**
Albumin per SD	0.83 (0.64–1.07)	0.150
CRP per SD	1.39 (1.09–1.76)	**0.008**
Age per SD (year)	1.55 (1.18–2.02)	**0.001**
Sex, male	1.31 (0.83–2.08)	0.250
PS, 0–1	0.46 (0.08–2.54)	0.370
Disease, myeloid	0.79 (0.50–1.24)	0.300
Model 3		
BMG, per SD	2.03 (1.62–2.55)	**<0.001**
Conditioning, RIC	1.81 (1.08–3.04)	**0.025**
CMV status	2.46 (0.77–7.90)	0.130
Donor source MRD	Ref	
MMRD	2.19 (0.99–4.88)	0.054
MUD	2.14 (0.98–4.69)	0.056
MMUD	0.75 (0.16–3.53)	0.720
CB	2.84 (1.31–6.15)	**0.008**
eGFR per SD	1.23 (1.00–1.51)	0.053

BMG, beta-2 microglobulin; CB, cord blood; CI, confidence interval; CMV, cytomegalovirus; CRP, C-reactive protein; DRI, disease risk index; eGFR, estimated glomerular filtration rate, SDs for age, BMG, Alb, ferritin, CRP, and eGFR were 13.04, 1.094, 0.489, 5195, 2.824, and 31.84, respectively; HCT-CI, hematopoietic cell transplantation-comorbidity index; HR, hazard ratio; MMRD, mismatch-related donor; MMUD, mismatch-unrelated donor; MRD, match-related donor; MUD, match-unrelated donor; NE, not estimable; PS, performance status; Ref, reference; RIC, reduced-intensity conditioning; SD, standard deviation.

Statistically significant values (P <0.050) are marked with bold font.

prognosis of allo-HCT has been previously reported [20–22]. Our study showed the weak correlation between serum BMG and these inflammatory markers. Concerning why no strong relation between BMG, ferritin, and albumin was found, we consider that serum BMG, ferritin, and albumin levels not only reflected the inflammatory status but also the patients' status in relation to other conditions, for example, serum BMG is associated with the disease status and renal dysfunction, ferritin is associated with iron overload, and albumin is associated with nutritional status. Serum BMG, ferritin, and albumin appear to be varying composite biomarkers providing various types of information apart from inflammatory status. Costa-Lima et al. [28] had reported the association between pretransplant serum BMG level and risk of grade 2–4 acute GVHD that was independent of HCT-CI. These authors discussed that pretransplant serum BMG level could reflect the subclinical inflammatory status and lead to the risk of acute GVHD. Patient's inflammatory conditions, including their disease and nondisease statuses, may also influence BMG level.

Unlike the study by Costa-Lima et al, our result showed no significant correlation between high serum BMG and high incidence of acute GVHD. This discrepancy may be attributed to the difference of the transplant conditions, including donor source and disease status. Their study included only HLA-identical related and HLA-matched unrelated donor, and benign diseases such as anaplastic anemia, although the disease status was not clearly reported. Our cohort contained a broader range of disease risk and donors, including HLA-mismatched donors. A broader range of disease risk might increase the degree of importance of the disease status in terms of the BMG level and enhance the relationship between BMG and Rel/Prog, whereas a broader range of donors might result in an increased degree of importance for various donors in the development of GVHD and weaken the relationship between BMG and GVHD. In fact, in our additional analysis of limited patients with complete remission status at transplant and matched-related donor or matched-unrelated donor (n = 58) that were relatively similar to Costa-Lima et al.'s study cohort, high BMG showed a significant association with the development of grade 3–4 acute GVHD. The high diversity in disease status in the present study may enable to detect the influence of BMG on Rel/Prog and OS instead of acute GVHD as a result that serum BMG level depended on patients' disease condition rather than inflammatory conditions.

The present study has several limitations. We examined very few populations at a single institution without any validation cohort. As this is a retrospective analysis, the existence of possible bias should be taken into consideration. In conclusion, in future clinical decision of allo-HCT, it may be useful to include serum BMG as a pretransplant prognostic marker, which is easy and inexpensive to measure with biochemical tests. The reproducibility of our result should be verified in a larger cohort.

Table 6. Multivariable analyses of Rel/Prog and NRM.

	Rel/Prog			NRM		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age per SD (year)	0.95	0.73–1.24	0.720	1.51	0.86–2.66	0.150
Sex, male	1.02	0.64–1.63	0.930	2.22	0.88–5.62	0.092
Disease risk index						
Low	0.69	0.16–2.91	0.620			
Intermediate	1.00	Ref				
High	2.82	1.65–4.83	**<0.001**			
Very high	4.51	2.29–8.90	**<0.001**			
HCT-CI						
0				1.00	Ref	
1–2				1.78	0.68–4.66	0.240
≥3				2.29	0.87–6.02	0.095
PS						
0–1				1.00	Ref	
2–4				2.72	0.42–17.6	0.290
BMG per SD	1.52	1.20–1.94	**<0.001**	1.06	0.70–1.60	0.780
Alb per SD				0.68	0.46–1.01	0.058
Ferritin per SD				1.10	0.92–1.31	0.290
CRP per SD	1.12	0.96–1.31	0.160	1.00	0.71–1.41	1.000

Alb, albumin; BMG, beta-2 microglobulin; CI, confidence interval; CRP, C-reactive protein, SDs for age, BMG, Alb, ferritin, and CRP were 13.04, 1.094, 0.489, 5195, and 2.824, respectively; HCT-CI, hematopoietic cell transplantation-comorbidity index; HR, hazard ratio; NRM, nonrelapse mortality; PS, performance status; Ref, reference; Rel/Prog, relapse/progression; SD, standard deviation.

Statistically significant values (P <0.050) are marked with bold font.

Table 7. Correlation between serum BMG and other important factors influencing BMG.

	BMG	Ferritin	Albumin	CRP	Creatinine	eGFR	Age
BMG	1	0.212	−0.250	0.307	0.333	−0.396	0.272
Ferritin		1	−0.344	0.376	−0.052	0.078	0.034
Albumin			1	−0.423	0.005	0.097	-0.176
CRP				1	−0.010	0.007	0.060
Creatinine					1	−0.804	0.178
eGFR						1	−0.454
Age							1

BMG, beta-2 microglobulin; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

Authorship

NH and TN: designed the study, collected the data, analyzed the data and wrote the manuscript. MN, MH and HN: designed the study and reviewed the manuscript. YH, HO, SN, MN, YN, and HK: interpreted the data and reviewed the manuscript. AH and MN: refined the data. All authors approved this final manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Univariate analyses of OS, Rel/Prog, and NRM in patients with complete remission at transplant as well as those with MRD and MUD allo-HCT (n = 58).

Table S2. Univariate analyses of acute and chronic GVHD in patients with complete remission at transplant, as well as those with MRD and MUD allo-HCT (n = 58).

Table S3. Univariate analyses of OS, Rel/Prog, and NRM in patients with acute myelogenous leukemia (n = 112).

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