Prognosis of hepatitis B virus reactivation in newly diagnosed multiple myeloma in modern era therapy: a retrospective study

Weiran Lv[1,*], Xiaojin Li[2,*], Jingbo Xu[3], Yun Wang[1], Hanying Huang[1], Fang Hu[1], Yingying Cui[1], Yuanbin Song[1], Lezong Chen[1], Bingyi Wu[1] and Yang Liang[1]

[1] Hematology, Sun Yat-sen University Cancer Center, Guangzhou, China
[2] Hematology, Faculty of Environmental Science and Engineering, Kunming University of Science and Technology, Kunming, China
[3] Hematology, The Fifth Affiliated Hospital, Sun Yat-sen University, Zhuhai, China
* These authors contributed equally to this work.

ABSTRACT

Studies on the prognosis of hepatitis B virus (HBV) reactivation following modern therapies for newly diagnosed MM (NDMM) are lacking. In this retrospective study, we aimed to assess the incidence, risk factors and prognosis of HBV reactivation in NDMM. A total of 33 of 355 patients with NDMM and HBV reactivation were included in this study. Multivariable analysis showed that hepatitis B surface antigen-positivity, hepatitis B core antibody-positivity, bortezomib-containing regimens, autologous stem cell transplantation, and gain of 1q21 were identified as independent risk factors of HBV reactivation in NDMM patients. The NDMM patients with HBV reactivation had poorer 3-year overall survival (OS) and progression-free survival (PFS) than did those without HBV reactivation, as confirmed by multivariate analysis. In conclusion, HBV reactivation in patients with NDMM constitutes a significant complication, correlating with reduced OS and PFS, and emerges as a potential adverse prognostic factor in the contemporary era of treatment.

INTRODUCTION

Infection caused by the hepatitis B virus (HBV), a virus that primarily affects the liver and lymphatic system, poses a significant global health challenge. China harbors a substantial population of individuals who exhibit chronic carriage of HBV, with numbers reaching into the millions (*Guo et al., 2019*). Several extrahepatic malignancies demonstrate associations with HBV infection (*Kwok & Tran, 2016*). Moreover, reactivation of the HBV is a well-documented adverse event commonly observed in individuals with hematologic malignancies undergoing or following cytotoxic drug-based chemotherapy. This reactivation, specifically, refers to an upregulation in the replication of HBV among individuals with latent HBV infection or those who have achieved successful remission from HBV infection (*Wands, Chura & Roll, 1975*). Furthermore, reactivation of the HBV can result in the onset of acute liver inflammation and impairment of hepatic functionality

(*Yeo et al., 2000*; *Hoofnagle, 2019*) and significant complications of tumour chemotherapy and immunosuppressive therapy (*Tsukune, Sasaki & Komatsu, 2019*). In addition, growing evidence has demonstrated that HBV infection can influence the status of the host immune system and alter the response to tumour therapy (*Lin, Chen & Huang, 2017*; *Sallberg & Pasetto, 2020*; *Wang, Zou & Liu, 2016*; *Carretero, Sektioglu & Garbi, 2015*). Cytotoxic agent treatments, monoclonal antibody therapy, and bone marrow transplantation have been proven to be hazardous factors for HBV reactivation (*Yeo et al., 2000*; *Yeo, Chan & Leung, 2009*; *Idilman & Arat, 2011*).

Multiple myeloma (MM) is a malignant condition characterized by clonal proliferation of plasma cells, resulting in the presence of osteolytic lesions, decreased erythrocyte count, impaired renal function, and elevated levels of calcium in the blood (*Tsukune, Sasaki & Komatsu, 2019*). Notably, the occurrence of infection significantly contributes to the development of illness and mortality in patients with MM (*Holmstrom, Gimsing & Abildgaard, 2015*; *Andersen, Klausen & Abildgaard, 2017*), and HBV infection rates are higher in patients with MM than in those without. The increased predisposition to HBV infection in patients with MM is complex and related to multiple factors, such as congenital disease-related defects of the immune system or disease-associated adaptive immune system deficiency (*Pratt, Goodyear & Moss, 2007*; *Brown, Pope & Murray, 2001*). The application of novel treatments, including proteasome inhibitors, immunomodulation intervention, and monoclonal antibodies, has significantly prolonged the overall survival (OS) and progression-free survival (PFS) of patients with MM (*Kumar, Rajkumar & Dispenzieri, 2008*; *Anderson, 2016*). Meanwhile, the utilization of the aforementioned medications has been associated with an increasing prevalence of incidents related to HBV reactivation (*Tsukune, Sasaki & Odajima, 2017*; *Atilla, Yalçıner & Atilla, 2019*; *International Myeloma Working Group, 2003*; *Huang, Li & Zhou, 2012*; *Stasi, Silvestri & Voller, 2017*). Previous studies have shown that the prevalence of HBV reactivation ranging from 2% to 9% among individuals diagnosed with MM (*Tsukune, Sasaki & Komatsu, 2019*; *Tsukune, Sasaki & Odajima, 2017*; *Atilla, Yalçıner & Atilla, 2019*; *Oketani, Ido & Uto, 2012*; *Lee, Lim & Lee, 2015*; *Tsukune, Sasaki & Odajima, 2016*). However, the relationship between MM and HBV reactivation remains incompletely understood, with conflicting evidence regarding its impact on the prognosis of MM patients.

In this retrospective study, we sought to examine the occurrence of HBV reactivation and its related factors among individuals newly diagnosed with multiple myeloma (NDMM), while also evaluating the prognostic significance of HBV reactivation.

METHODS

Patients

We retrospectively enrolled 412 Chinese patients with NDMM between 2015 and 2020 at the Sun Yat-sen University Cancer Center's Department of Hematologic Oncology. None of the patients had received anti-tumor treatment previously. Among these 412 patients with NDMM, 57 cases were excluded due to lack of detection data of HBV. Finally, 355 patients were included in our analysis. The MM diagnosis relied on the criteria established by the International Myeloma Working Group (IMWG). The research has received

approval from the Sun Yat-sen university cancer prevention and control center for ethics committee (ethical approval referenced number: B2023-471-01). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. The utilization of electronic health records was employed for the examination of patients' information.

Patients' characteristics and initial laboratory parameters were documented upon the commencement of chemotherapy (Table S1). The HBV infection-related data included hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb), hepatitis B e-antigen (HBeAg), and hepatitis B e-antibody (HBeAb), and HBV DNA titers. Continuous monitoring of all patients was conducted throughout the study, with the exception of cases where patients could not be traced for follow-up until 31 December 2022 or they had passed away.

Measurements and definitions

HBsAg, HBcAb, HBsAb, HBeAg, and HBeAb were detected by chemiluminescence. Quantitative PCR was utilized to determine the titers of HBV DNA. HBV reactivation was defined as follows: (1) reappearance of HBsAg and loss of HBsAb in patients who were HBsAg-negative and/or HBsAb-positive; (2) increase of HBV DNA level by at least a factor of 10 in HBV DNA levels compared to the initial levels, or an absolute count of HBV DNA reaching 1×10^9 copies/mL In our study, we only analyzed HBV reactivation which occurred before the first progression of NDMM. Overall survival (OS) definition was that time from transplantation to death or date of last follow-up in alive patients. Progression-free survival (PFS) is defined as the time between the NDMM patients received initiation of treatment to disease progression or death from any cause.

Treatment

First-line regimens were as follows (Table 1): cyclophosphamide + thalidomide + dexamethasone (CTD, $N = 19$); bortezomib + adriamycin + dexamethasone (PAD, $N = 140$); ixazomib + lenalidomide + dexamethasone (IRD, $N = 11$); bortezomib + cyclophosphamide + dexamethasone (VCD, $N = 16$); liposomal doxorubicin + vincristine + dexamethasone (DVD, $N = 53$); bortezomib + dexamethasone (VD, $N = 5$); vincristine + doxorubicin + dexamethasone (VAD, $N = 24$); bortezomib + lenalidomide + dexamethasone (VRD, $N = 78$) and bortezomib + thalidomide + dexamethasone (VTD, $N = 9$). A total of 62 patients received autologous stem cell transplantation (ASCT) subsequent to undergoing high-dose chemotherapy. In patients with chronic HBV infection, treatment with entecavir (ETV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide fumarate (TAF), or tenofovir amibufenamide (TMF) for a duration of 48 weeks is recommended. If HBV DNA remains detectable after 48 weeks of therapy (HBV DNA > 20 IU/ml), adjustments can be made to the medication treatment plan, excluding errors related to compliance and detection. Patients currently prescribed ETV should consider transitioning to TDF or TAF, while those on TDF or TAF may consider switching

Table 1 Univariate and Multivariate analysis of the infections in the multiple myeloma patients.

Characteristic	HBV reactivation status		P-value
	Negative *n* (%)	Positive *n* (%)	
A. Univariate analysis			
Number of patients	322	33	
Age, *n* (%)			0.356
<65 years	240 (75%)	27 (82%)	
≥65 years	82 (25%)	6 (18%)	
Sex, *n* (%)			0.631
Male	201 (64%)	22 (67%)	
Female	121 (36%)	11 (33%)	
MM subtype,			0.145
IgG	198 (61%)	14 (43%)	
IgA	77 (24%)	10 (30%)	
Light chain	25 (8%)	5 (15%)	
[a]Others	22 (7%)	4 (12%)	
DS stage			0.969
I	72 (22%)	8 (24%)	
II	79 (25%)	8 (24%)	
III	171 (53%)	17 (52%)	
ISS			0.439
1	89 (28%)	12 (36%)	
2	70 (22%)	8 (24%)	
3	163 (50%)	13 (40%)	
R-ISS			0.185
1	84 (26%)	13 (39%)	
2	195 (61%)	18 (55%)	
3	43 (13%)	2 (6%)	
IMWG risk stratification			0.227
Low risk	77 (24%)	12 (36%)	
Moderate risk	221 (69%)	20 (61%)	
High risk	24 (7%)	1 (3%)	
Number of bone lesions			0.108
None	80 (25%)	3 (9%)	
1	23 (7%)	2 (6%)	
≥2	219 (68%)	28 (85%)	
Plasma cells in bone marrow ≥10%			0.251
<10%	180 (56%)	15 (45%)	
≥10%	142 (44%)	18 (55%)	
EMD			0.240
Yes	29 (9%)	1 (3%)	
No	293 (91%)	32 (97%)	

Table 1 (continued)			
Characteristic	HBV reactivation status		P-value
	Negative n (%)	Positive n (%)	
First-line regimens			0.888
VRD	67 (21%)	11 (33%)	
VTD	7 (2%)	2 (6%)	
VD	5 (1%)	0 (0%)	
VCD	14 (4%)	2 (6%)	
VAD	22 (7%)	2 (6%)	
PAD	125 (39%)	15 (46%)	
IRD	11 (3%)	0 (0%)	
DVD	53 (17%)	0 (0%)	
CTD	18 (6%)	1 (3%)	
[b]Use of bortezomib			0.006
Yes	218 (68%)	30 (91%)	
No	104 (32%)	3 (9%)	
[b]Use of thalidomide			0.369
Yes	92 (29%)	7 (21%)	
No	230 (71%)	26 (79%)	
[b]Use of lenalidomide			0.036
Yes	153 (48%)	22 (67%)	
No	169 (52%)	11 (33%)	
[b]ASCT			0.003
Yes	50 (16%)	[c]12 (36%)	
No	272 (84%)	21 (64%)	
Chromosomal aberrations			
1q21+	48 (15%)	10 (30%)	0.023
13q14−	34 (11%)	1 (3%)	0.167
IGH rearrangements	15 (5%)	1 (3%)	0.668
P53−	19 (6%)	1 (3%)	0.496
[d]HBsAg			<0.0001
Positive	21 (7%)	14 (42%)	
Negative	301 (93%)	19 (58%)	
[d]HBsAb			0.014
Positive	202 (63%)	13 (39%)	
Negative	120 (37%)	20 (61%)	
[d]HBcAb			<0.0001
Positive	157 (49%)	29 (88%)	
Negative	165 (51%)	4 (12%)	
[d]HBeAg			0.012
Positive	3 (1%)	3 (9%)	
Negative	319 (99%)	30 (91%)	

(Continued)

Table 1 (continued)

Characteristic	HBV reactivation status		P-value
	Negative n (%)	Positive n (%)	
[d]HBeAb			0.224
Positive	85 (26%)	12 (36%)	
Negative	237 (74%)	21 (64%)	
Died			0.016
Yes	75 (23%)	14 (42%)	
No	247 (77%)	19 (58%)	
Progression of MM			0.001
Yes	111 (34%)	21 (64%)	
No	211 (66%)	12 (36%)	

Parameter	Multivariate analysis[e]		
	HR	95% confidence interval	P-value
B. Multivariate analysis			
[f]HBsAg	5.584	[2.686–11.606]	<0.0001
[f]HBcAb	4.899	[1.646–14.584]	0.004
[g]Use of bortezomib	4.222	[1.278–13.945]	0.018
[g]ASCT	2.751	[1.330–5.687]	0.006
1q21+	2.752	[1.250–6.055]	0.012

Notes:
[a] Others include IgM, IgD, IgE and non-secretory myeloma.
[b] Before the first progression.
[c] All of these 12 patients developed HBV reactivation after ASCT.
[d] At the initial of the chemotherapy.
[e] Variables significant at $P < 0.05$ in the univariate model were entered in the Cox regression multivariate model.
[f] At the initiation of chemotherapy.
[g] Before the first progression.
MM, multiple myeloma; Ig, immunoglobulin; DS, Durie-Salmon; ISS, International Staging System; R-ISS, Revised-International Staging System; IMWG, International Myeloma Working Group; EMD, extramedullary disease; HBV, hepatitis B virus; ASCT, autologous stem cell transplantation; IGH, human immunoglobulin heavy chains; VRD, bortezomib + lenalidomide + dexamethasone; VTD, bortezomib + thalidomide + dexamethasone; VD, bortezomib + dexamethasone; VCD, bortezomib + cyclophosphamide + dexamethasone; VAD, vincristine + doxorubicin + dexamethasone; PAD, bortezomib + adriamycin + dexamethasone; IRD, ixazomib + lenalidomide + dexamethasone; DVD, liposomal doxorubicin + vincristine + dexamethasone; cyclophosphamide + thalidomide + dexamethasone, CTD; ASCT, autologous stem cell transplantation.

to ETV; alternatively, a combination therapy involving both drugs can be considered. In patients with active HBV infection, treatment with ETV, TDF or TAF is recommended and the most appropriate antiviral regimen were selected according to the patient's specific drug resistance.

Statistical analyses

The results were performed by IBM SPSS Statistics 25.0. The median values, accompanied by their corresponding ranges, were presented to depict the numerical data. The comparison of categorical variables involved the utilization of either Pearson chi-square test or Fisher exact test. The factors influencing HBV reactivation rates were analyzed using a chi-square test in a univariate analysis. Multivariate analysis used Cox regression to

further evaluate the hazard elements. The Kaplan-Meier method was performed to analyze OS. Cumulative incidence was applied to calculate the incidence of HBV reactivation and progression of NDMM using competing risk model, and the death was seen as a risk of competition. The utilization of two-sided P-values was employed. The statistical significance was determined when the *P*-value was less than 0.05. Competitive risk model in R method (R version 4.2.1; *R Core Team, 2022*) was used to analyze the cumulative incidence.

RESULTS

Patients' characteristics

In our study, 355 patients (223 males and 132 females) were enrolled. The age distribution of the confirmed cases ranged from 24 to 85 years, with a median age of 58 years. The duration of follow-up ranged from 0 to 104 months, with a median of 44.0 months. The fundamental attributes of the enrolled patients are summarized in Table S1. Among the patients, 152 showed HbsAg-negativity combined with HBcAb-positivity and all of these individuals were administered entecavir (0.5 mg qd) as a prophylactic measure against HBV reactivation. In addition, 35 patients had confirmed HBV infection at diagnosis of MM characterized by HBsAg-positivity, as indicated by the presence of HBsAg, and all these patients received entecavir (0.5 mg qd) for anti-HBV therapy.

Morbidity and hazard elements of HBV reactivation before the first progression of NDMM

Among the 355 patients enrolled in our analysis, 33 (9.3%) developed HBV reactivation before the first progression of NDMM, with a median HBV reactivation time of 3 months (range, 0–31 months). The characteristics of the 33 patients with HBV reactivation including transaminases and HBV DNA copies were shown in Table S2. The 2- and 5-year overall cumulative incidences of HBV reactivation before the first progression of NDMM were 9.1% (95% confidence interval (CI) [5.96–12.24%]) and 9.9% (95% CI [6.76–13.04%]), respectively. Univariable analysis showed that bortezomib-containing regimens ($P = 0.006$), lenalidomide treatment ($P = 0.036$), ASCT ($P = 0.003$), 1q21+ ($P = 0.023$), HBsAg-positivity ($P < 0.0001$), HBsAb-positivity ($P = 0.014$), HBcAb-positivity ($P < 0.0001$), and HBeAg-positivity ($P = 0.012$) were hazard elements of HBV reactivation before the first progression of NDMM (Table 1A). Multivariable analysis showed that HBsAg-positivity ($P < 0.0001$, hazard ratio [HR] 5.584, 95% CI [2.686–11.606]), HBcAb-positivity ($P = 0.004$, [HR] 4.899, 95% CI [1.646–14.584]), bortezomib-containing regimens ($P = 0.018$, [HR] 4.222, 95% CI [1.278–13.945]), ASCT ($P = 0.006$, [HR] 2.751, 95% CI [1.330–5.687]), and 1q21+ ($P = 0.012$, [HR] 2.572, 95% CI [1.250–6.055]) were identified as independent hazard elements of HBV reactivation (Table 1B).

The occurrence of HBV reactivation during a 2-year period in patients who underwent ASCT (17.7%, 95% CI [8.10–27.30%]) was higher than that in patients who did not undergo ASCT (4.5%, 95% CI [0.21–6.85%]; $P = 0.006$) (Fig. 1A). The 2-year cumulative incidence of HBV reactivation in patients receiving bortezomib-containing regimens
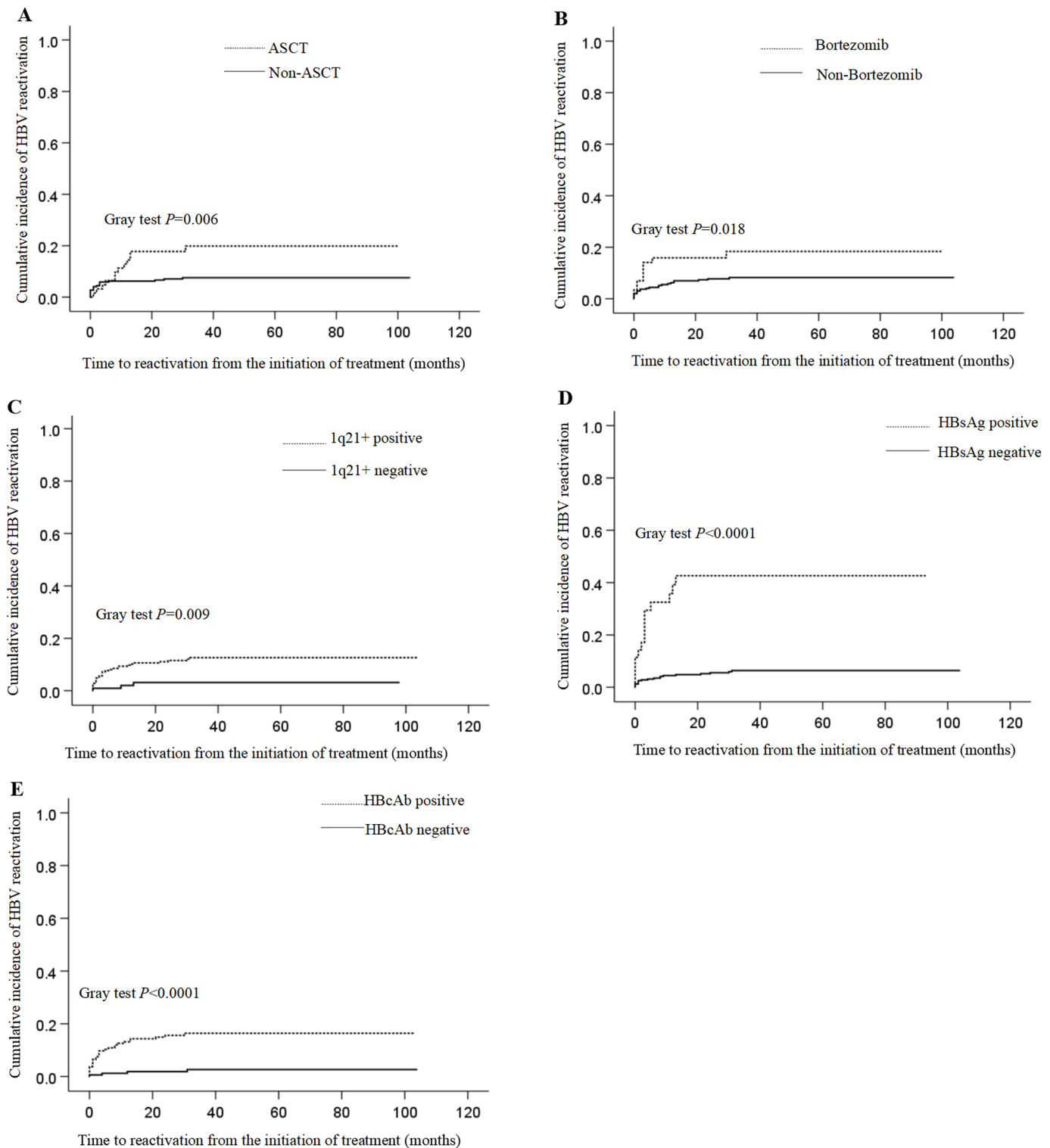
Figure 1 Cumulative incidences of HBV reactivation. (A) Asessment of cumulative incidence of HBV reactivation in NDMM patients according to whether they received ASCT or not; (B) asessment of cumulative incidence of HBV reactivation in NDMM patients according to whether they received bortezomib-containing regimens or not; (C) asessment of cumulative incidence of HBV reactivation in NDMM patients according to whether they had gain of 1q21 or not; (D) asessment of cumulative incidence of HBV reactivation in NDMM patients according to whether they had HBsAg positive or not at initiation of treatment; (E) asessment of cumulative incidence of HBV reactivation in NDMM patients according to whether they had HBcAb positive or not at initiation of treatment.

Full-size 🖼 DOI: 10.7717/peerj.18475/fig-1

(11.8%, 95% CI [7.88–15.72%]) was higher than that in patients not receiving bortezomib-containing regimens (3.1%, 95% CI [0.43–6.63%]; $P = 0.018$) (Fig. 1B). Furthermore, the cumulative incidence of HBV reactivation during a 2-year period in patients with 1q21+ (15.9%, 95% CI: 6.30–25.50%) was higher than that of those without 1q21+ (7.7%, 95% CI [4.56–10.84%]; $P = 0.009$) (Fig. 1C). The 2-year cumulative incidence of HBV reactivation in patients with HBsAg-positivity (42.6%, 95% CI [25.55–59.65%]) was higher than that of those with HBsAg negative (5.5%, 95% CI [2.95–8.05%]; $P < 0.0001$) (Fig. 1D). Finally, the 2-year cumulative incidence of HBV reactivation in patients with HBcAb-positivity (15.6%, 95% CI [10.31%–20.89%]) was higher than that of those with HBcAb-negativity (1.9%, 95% CI [0.26–4.06%]; $P < 0.0001$) (Fig. 1E).

Survival analysis

To analyse the relevance of the clinical parameters of patients with NDMM to their OS and PFS, we assessed multiple clinical data of patients with NDMM in Table 2. Of the 33 patients with HBV reactivation before the first progression of NDMM, 19 (58%) survived, and 14 (42%) died at a median follow-up of 40.0 months (range, 5–94 months) after HBV reactivation. Among these 14 patients, five (36%) died of treatment-related complications, including myocardial infarction (one case), septicaemia (two cases), and severe pneumonia (two cases), while nine (64%) died of complications of MM progression. None of the 33 patients with HBV reactivation developed fulminant hepatitis, and none of them experience MM-related treatment withdrawn. The patients with HBV reactivation had poorer 3-year survival than did those without HBV reactivation (63.1 ± 8.5% *vs* 81.0 ± 2.2%, $P = 0.029$) (Fig. 2A). Furthermore, univariate analysis revealed that International Staging System (ISS), Revised-International Staging System (RISS), IMWG, ASCT, deletion of P53, progression, and HBV reactivation were significant hazard elements for OS (Table 2; $P < 0.05$). Multivariable analysis showed that R-ISS stage, IMWG risk stratification, progression of NDMM, and HBV reactivation were identified as independent hazard elements of OS (Table 3A).

Of the 33 patients with HBV reactivation before the first progression of NDMM, 21 (64%) developed NDMM progression at a median follow-up of 31.0 months (range, 0–83 months). The other 12 (36%) patients were free from disease progression, including two patients who died before primary disease progression. Moreover, the patients with HBV reactivation had poorer 3-year PFS than did those without HBV reactivation (38.4 ± 9.4% *vs.* 67.5 ± 2.8%, $P < 0.0001$) (Fig. 2B). Univariate analysis showed that DS, R-ISS, IMWG, use of thalidomide or lenalidomide, 1q21+, Immunoglobulin Heavy Chain (IGH) rearrangements, deletion of 13q14, deletion of P53, and HBV reactivation were significant hazard elements for PFS (Table 3; $P < 0.05$). Multivariable analysis showed that HBV reactivation, use of lenalidomide, deletion of P53 and 1q21+ were identified as independent hazard elements of PFS (Table 3B).

Considering the therapeutic regimen's impact on survival, patients were categorised into four cohorts: those receiving ASCT, those not receiving ASCT, and those treated with bortezomib-containing regimens, and those without such treatment. Subsequently, we examined the effect of HBV reactivation on OS and PFS. HBV-reactivated patients had a

Table 2 Univariate analysis of survival in patients with multiple myeloma.

Characteristic	Median OS, months	P-value	Median PFS, months	P-value
Age		0.288		0.893
<65 years	46.0		33.0	
≥65 years	39.5		30.0	
Sex, *n* (%)		0.545		0.803
Male	41.0		32.0	
Female	48.5		35.0	
MM subtype,		0.205		0.598
IgG	44.5		35.5	
IgA	44.0		28.0	
Light chain	45.5		32.5	
[a]Others	44.5		31.5	
DS stage		0.308		0.036
I	41.0		33.5	
II	39.0		33.0	
III	46.0		33.0	
ISS		0.001		0.360
1	48.0		33.0	
2	46.5		32.5	
3	43.0		34.0	
R-ISS		<0.0001		0.046
1	48.0		38.0	
2	44.0		33.0	
3	34.0		28.0	
IMWG risk stratification		<0.0001		0.014
Low risk	47.0		36.0	
Moderate risk	44.0		33.0	
High risk	22.0		21.0	
Number of Bone lesions		0.778		0.149
None	49.0		39.0	
1	71.0		35.0	
≥2	41.0		30.0	
Plasma cells in BM ≥ 10%		0.773		0.129
<10%	43.5		34.0	
≥10%	45.0		31.0	
EMD		0.776		0.376
Yes	43.0		30.0	
No	68.0		33.0	
[b]Use of bortezomib		0.130		0.702
Yes	42.0		33.0	
No	61.0		32.0	

Table 2 (continued)

Characteristic	Median OS, months	P-value	Median PFS, months	P-value
[b]Use of thalidomide		0.692		0.006
Yes	67.0		32.0	
No	40.0		33.0	
[b]Use of lenalidomide		0.321		0.019
Yes	39.0		33.0	
No	58.5		32.5	
[b]ASCT		0.028		0.103
Yes	40.0		34.0	
No	45.0		32.0	
Chromosomal aberrations				
1q21+		0.070		0.003
Yes	39.0		21.0	
No	45.0		33.0	
13q14−		0.061		0.015
Yes	45.0		26.0	
No	44.0		33.0	
IGH rearrangements		0.178		0.007
Yes	45.0		29.0	
No	44.0		33.0	
P53-		<0.0001		0.004
Yes	21.5		19.5	
No	45.0		33.0	
HBV reactivation		0.029		<0.0001
Yes	40.0		31.0	
No	45.0		33.0	
Progression of MM		0.001		—
Yes	41.0		—	
No	48.5		—	

Notes:
[a] Others include IgM, IgD, IgE and non-secretory myeloma.
[b] Before the first progression.
MM, multiple myeloma; Ig, immunoglobulin; DS, Durie-Salmon; ISS, International Staging System; R-ISS, Revised-International Staging System; IMWG, International Myeloma Working Group; BM, bone marrow; EMD, extramedullary disease; HBV, hepatitis B virus; ASCT, autologous stem cell transplantation.

significantly shorter OS ($P = 0.012$) and PFS ($P < 0.0001$) than non-HBV-reactivated patients, in the group receiving bortezomib-containing regimens (Figs. 3A, 3C). In contrast, there was no significant difference in either OS or PFS between HBV-reactivated and non-HBV-reactivated patients in the group without bortezomib-containing regimens (Figs. 3B, 3D). HBV-reactivated patients had a significantly shorter OS than did non-HBV-reactivated patients in the group without ASCT ($P = 0.040$). In comparison, there was no statistical significance in the Kaplan–Meier curves between HBV-reactivated patients and non-HBV-reactivated patients in the group with ASCT despite a trend of shorter OS,
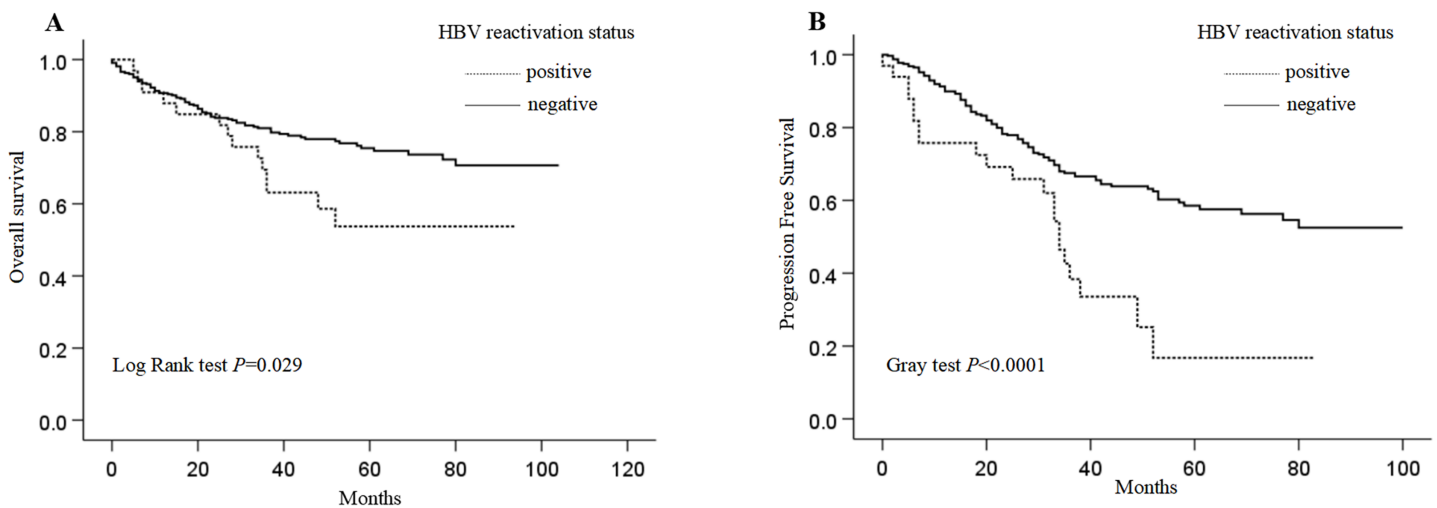
Figure 2 Overall survival (OS) and progression free survival (PFS) of patients with and without HBV reactivation. (A) OS of HBV reactivation or not in patients with NDMM; (B) OS of HBV reactivation or not in patients with NDMM. Full-size 🖾 DOI: 10.7717/peerj.18475/fig-2

Table 3 Multivariate analysis of survival in patients with multiple myeloma.

A. Overall survival

Parameter	Multivariate analysis[a]		
	HR	95% confidence interval	*P-value*
IMWG risk stratification			0.008
Low risk	—	—	—
Moderate risk	1.781	[0.781–4.061]	0.170
High risk	4.356	[1.550–12.236]	0.005
HBV reactivation	2.127	[1.174–3.851]	0.013
Progression of MM	1.622	[1.056–2.490]	0.027
R-ISS			0.041
2	—	—	—
1	1.02	[0.477–2.183]	0.959
3	2.049	[1.171–3.586]	0.012

B. Progression-free survival

Parameter	Multivariate analysis[a]		
	HR	95% confidence interval	*P*-value
HBV reactivation	2.936	[1.812–4.759]	<0.001
[b]Use of lenalidomide	0.542	[0.375–0.783]	0.001
1q21+	2.427	[1.189–4.956]	0.015
P53-	2.256	[1.138–4.472]	0.020

Notes:
[a] Variables significant at $P < 0.05$ in the univariate model were entered in the Cox regression multivariate model.
[b] Before the first progression. ASCT, autologous stem cell transplantation.
IMWG, International Myeloma Working Group; HBV, hepatitis B virus; MM, multiple myeloma; R-ISS, Revised-International Staging System; IGH, Human immunoglobulin heavy chains.
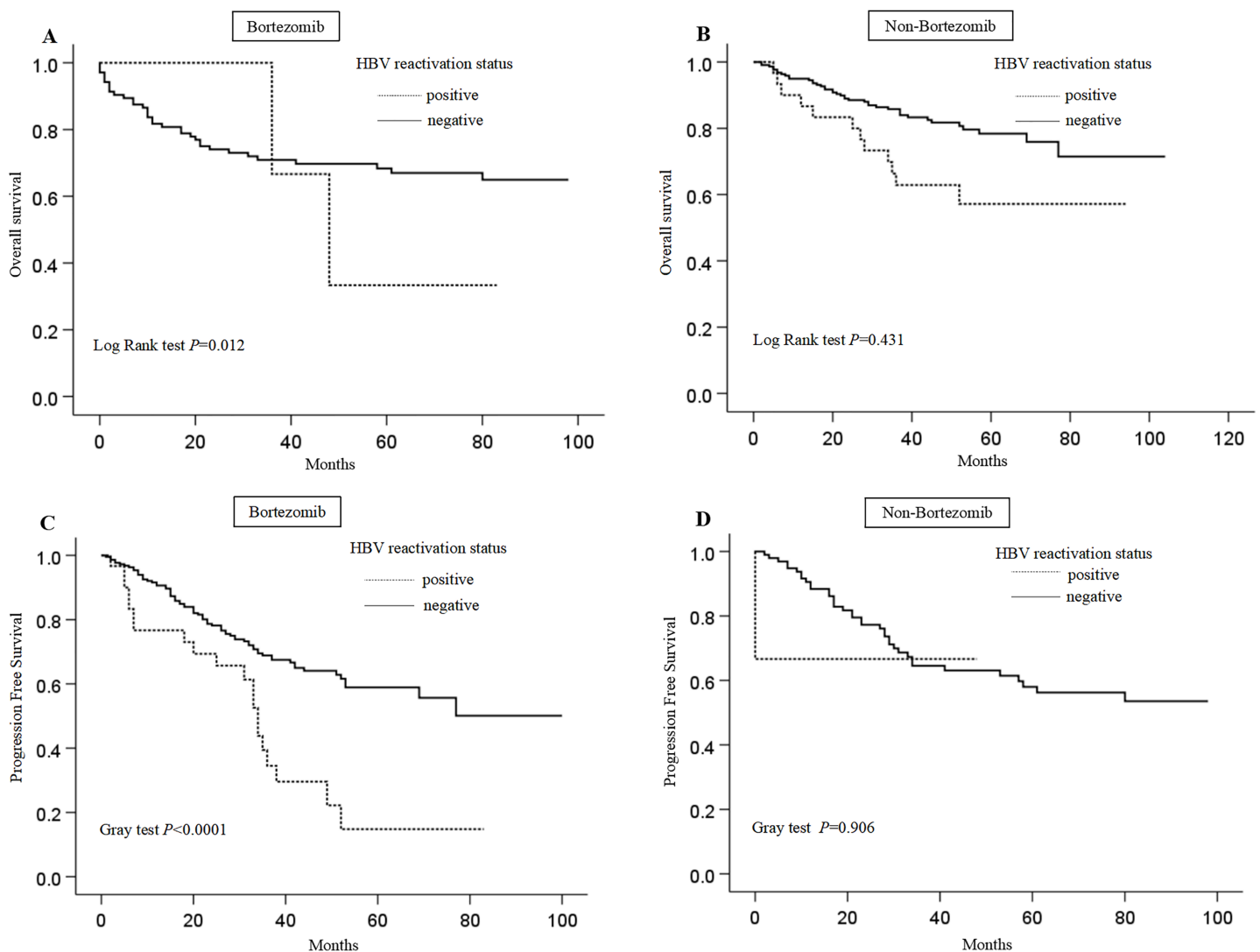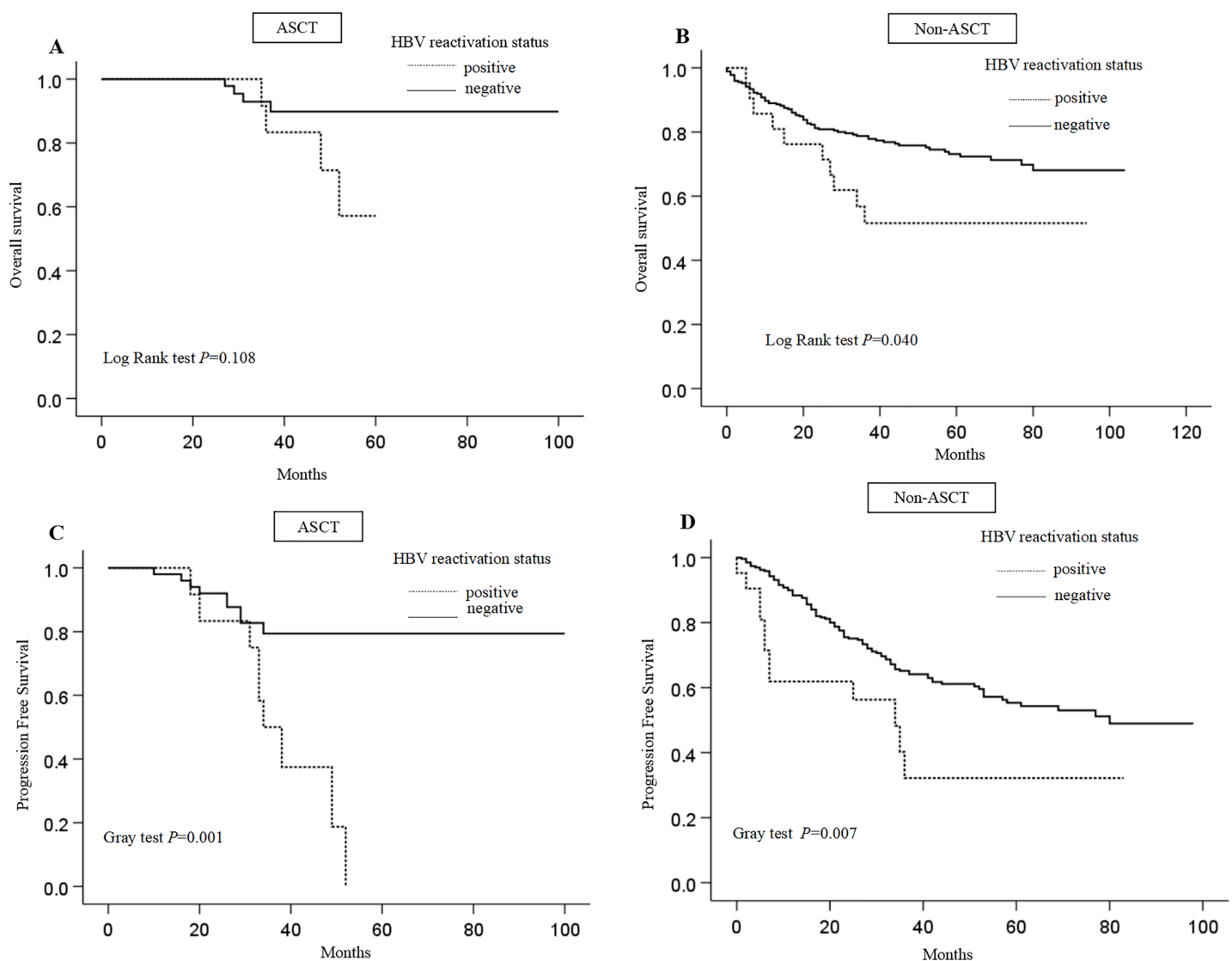
Figure 3 Impact of HBV reactivation on survival of patients with NDMM receiving bortezomib-containing regimens or not. (A) OS of HBV reactivation or not in patients receiving bortezomib-containing regimens; (B) OS of HBV reactivation or not in patients not receiving bortezomib-containing regimens; (C) PSF of HBV reactivation or not in patients receiving bortezomib-containing regimens; (D) PFS of HBV reactivation or not in patients not receiving bortezomib-containing regimens. Full-size 🖻 DOI: 10.7717/peerj.18475/fig-3

which might be because of the insufficient sample size (Figs. 4A, 4C). Finally, HBV-reactivated patients had significantly shorter PFS than non-HBV-reactivated patients in both groups with ($P = 0.001$) and without ASCT ($P = 0.007$) (Figs. 4B, 4D).

DISCUSSION

In this study, we assess the incidence and risk factors for HBV reactivation in NDMM and to further explore the prognosis of patients with HBV reactivation. Our result showed that HBV reactivation in patients with NDMM constitutes a significant complication, correlating with poor OS and PFS.

Our current research showed that the incidence of HBV reactivation was 9.3%, which was consistent with previous studies. The identification of hazard elements associated with

Figure 4 Impact of HBV reactivation on survival of patients with NDMM receiving ASCT or not. (A) OS of HBV reactivation or not in patients receiving ASCT; (B) OS of HBV reactivation or not in patients not receiving ASCT; (C) PSF of HBV reactivation or not in patients receiving ASCT; (D) PFS of HBV reactivation or not in patients not receiving ASCT.   Full-size ☑ DOI: 10.7717/peerj.18475/fig-4

HBV reactivation in patients diagnosed with NDMM remains elusive. Our results showed that HBsAg/HBcAb positivity at the initial stage of chemotherapy, ASCT, bortezomib-containing regimens, and 1q21+ were independent hazard elements for HBV reactivation in patients with NDMM before the first progression. Notably, high-dose chemotherapy with ASCT is widely used to treat MM. However, ASCT is associated with profound deficiencies in the immune system function, and patients undergoing ASCT are susceptible to various infections. Consistent with our results, the potential risk of HBV reactivation associated with ASCT has been demonstrated by multiple studies (*Tsukune, Sasaki & Odajima, 2017*; *Lee, Lim & Lee, 2015*). Bortezomib is a proteasome inhibitor that suppresses T lymphocyte proliferation and decreases the function of natural killer cells as well as that of CD8-positive T cells (*Nucci & Anaissie, 2009*). Previous studies have

suggested that the patients who received bortezomib-containing therapy had a higher incidence rate of HBV reactivation than did those who received conventional chemotherapy (*Li et al., 2015*), which is consistent with our results. Potential risk factors have been reported previously, including HBsAg positivity (*Yeo et al., 2004*) and HBcAb positivity (*Papamichalis, Alexiou & Boulbou, 2012*), which are concordant with our results.

Notably, our study demonstrated that 1q21+ were independent hazard elements for HBV reactivation in patients with NDMM which has not been previously reported. Previous data reported by *Guo et al. (2019)* showed that higher prevalence of 1q21+ in patients with MM who experienced HBV infection, suggesting a potential contribution of HBV infection to the amplification of 1q21, thereby contributing to the progression of MM. Diverging from the aforementioned study, the multivariate analysis in our study proved that 1q21+ was a contributor to HBV reactivation. However, the mechanism underlying the interaction between 1q21 and HBV reactivation requires further investigation.

The effects of HBV infection on the survival of patients with MM are controversial. *Guo et al. (2019)* and *Li et al. (2015)* showed that both the OS and PFS rates of patients with positive HBsAg who received ASCT were significantly lower than those of patients with negative HBsAg. Conversely, *Atilla, Yalçıner & Atilla (2019)* did not detect any advantages in OS or PFS in HBsAg-negative patients. Unlike the above studies, our present data were based on HBV reactivation before the first progression of NDMM rather than on the simple positive status of HBV. Surprisingly, HBV reactivation was shown to be an independent prognostic factor for both OS and PFS in patients with NDMM *via* multivariate prognostic analysis, which has not been reported previously. Considering the therapeutic regimen's impact on outcomes, we conducted an analysis to assess the impact of HBV reactivation on OS and PFS in patients who underwent either bortezomib-containing regimens or ASCT. Notably, among patients receiving either bortezomib-containing regimens or ASCT, the OS and PFS of HBV-reactivated patients were shorter than those of non-HBV-reactivated patients. These results provide further evidence for poor outcomes in patients with HBV reactivation. Patients with HBV infection in an active state, HBV infection in an chronic state, or HBV reactivation received regular administration of antiviral therapy in the current investigation. None of the patients with HBV reactivation developed fulminant hepatitis, and the main cause of death was MM progression. Our multiparameter analysis showed that MM progression was an independent hazard element for OS, while HBV reactivation was an independent hazard element for PFS. Because lymphocytes are the most important target cells of HBV, we speculated that the host immune system might display a set of changes following long-term infection of lymphocytes by HBV, causing refractoriness to pharmacotherapy or evasion of immune response by MM cells and leading to MM progression and shorter OS. However, this hypothesis warrants further investigation. It is crucial to acknowledge that reactivation of HBV can occur at any phase of treatment and requires regular, long-term monitoring of HBV DNA levels. Additionally, a novel approach needs to be established in order to prevent HBV reactivation in MM patients.

There were some limitations in our study. First, this was a retrospective single-centre analysis, wherein the systematic search for HBV reactivation during follow-up was inadequate. Second, 13.8% (57/412) of patients were excluded from the analysis because of a lack of HBV detection data. Therefore, our study might not have accurately determined the incidence of HBV reactivation. Further retrospective multicentre studies are required to validate our results.

In conclusion, our study demonstrated that HBV reactivation in patients with NDMM is not an infrequent complication and is associated with reduced OS and PFS. Bortezomib-containing regimens, ASCT, and 1q21+ were independent hazard elements for HBV reactivation in patients with NDMM. Additional cohort studies are required to confirm these findings.

Clinical practice points

The application of novel treatments of MM, including proteasome inhibitors, immunomodulation intervention, and monoclonal antibodies, has significantly improved the prognosis of MM, but the utilization of the aforementioned medications has been associated with an increasing prevalence of incidents related to HBV reactivation.

Our study provides updated insights into the impact of HBV reactivation on the unfavorable prognosis of NDMM, particularly by significantly diminishing survival rates through its facilitation of disease progression rather than fatal hepatitis, thereby potentially influencing future clinical management and patient care strategies.

ADDITIONAL INFORMATION AND DECLARATIONS

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

- Weiran Lv conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, and approved the final draft.
- Xiaojin Li conceived and designed the experiments, prepared figures and/or tables, and approved the final draft.

- Jingbo Xu conceived and designed the experiments, prepared figures and/or tables, and approved the final draft.
- Yun Wang performed the experiments, prepared figures and/or tables, and approved the final draft.
- Hanying Huang performed the experiments, prepared figures and/or tables, and approved the final draft.
- Fang Hu analyzed the data, prepared figures and/or tables, and approved the final draft.
- Yingying Cui analyzed the data, prepared figures and/or tables, and approved the final draft.
- Yuanbin Song analyzed the data, authored or reviewed drafts of the article, and approved the final draft.
- Lezong Chen analyzed the data, prepared figures and/or tables, and approved the final draft.
- Bingyi Wu performed the experiments, authored or reviewed drafts of the article, and approved the final draft.
- Yang Liang conceived and designed the experiments, performed the experiments, authored or reviewed drafts of the article, and approved the final draft.

Human Ethics

The following information was supplied relating to ethical approvals (*i.e.*, approving body and any reference numbers):

Ethics Committee of Sun Yat-sen University Cancer Center (ethical approval referenced number: B2023-471-01).

Data Availability

The following information was supplied regarding data availability:

The raw measurements are available in the Supplemental Files.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.18475#supplemental-information.

REFERENCES

Andersen KT, Klausen T, Abildgaard T. 2017. Causes of early death in multiple myeloma patients treated with high-dose therapy followed by autologous stem cell transplantation: a study based on the nationwide Danish multiple myeloma registry. *American Journal of Hematology* **92(10)**:E611–E614 DOI 10.1002/ajh.24857.

Anderson KC. 2016. Progress and paradigms in multiple myeloma. *Clinical Cancer Research* **22(22)**:5419–5427 DOI 10.1158/1078-0432.CCR-16-0625.

Atilla PA, Yalçıner M, Atilla D. 2019. Hepatitis B reactivation rate and fate among multiple myeloma patients receiving regimens containing lenalidomide and/or bortezomib. *Turkish Journal of Hematology* **18, 36(4)**:266–273 DOI 10.4274/tjh.galenos.2019.2019.0103.

Brown RD, Pope B, Murray A. 2001. Dendritic cells from patients with myeloma are numerically normal but functionally defective as they fail to up-regulate CD80 (B7-1) expression after

huCD40LT stimulation because of inhibition by transforming growth factor-beta1 and interleukin-10. *Blood* **98(10)**:2992–2998 DOI 10.1182/blood.V98.10.2992.

Carretero R, Sektioglu IM, Garbi N. 2015. Eosinophils orchestrate cancer rejection by normalizing tumor vessels and enhancing infiltration of CD8(+) T cells. *Nature Immunology* **16(6)**:609–617 DOI 10.1038/ni.3159.

Guo D, Xu PP, Guan CY, Xu Y, Yang YG, Xu JY, Zhou RF, Chen B. 2019. Hepatitis B virus infection and 1q21 amplification in multiple myeloma. *Oncology Letters* **18(6)**:6196–6206 DOI 10.3892/ol.2019.10926.

Holmstrom MO, Gimsing P, Abildgaard N. 2015. Causes of early death in multiple myeloma patients who are ineligible for high-dose therapy with hematopoietic stem cell support: astudy based on the nationwide Danish myeloma database. *American Journal of Hematology* **90(4)**:E73-4 DOI 10.1002/ajh.23932.

Hoofnagle JH. 2019. Reactivation of hepatitis B. *Hepatology* **49(5 Suppl)**:S156–S165 DOI 10.1002/hep.22945.

Huang B, Li J, Zhou Z. 2012. High preva-lence of hepatitis B virus infection in multiple myeloma. *Leukemia & Lymphoma* **53(2)**:270–274 DOI 10.3109/10428194.2011.610013.

Idilman R, Arat M. 2011. Evaluation and management of hepatitis B virus infection in hematopoietic stem cell transplantation: before and after transplantation. *Expert Review of Anti-infective Therapy* **9(8)**:641–652 DOI 10.1586/eri.11.79.

International Myeloma Working Group. 2003. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *British Journal of Haematology* **121**:749–757 DOI 10.1046/j.1365-2141.2003.04355.x.

Kumar SK, Rajkumar SV, Dispenzieri A. 2008. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* **111(5)**:2516–2520 DOI 10.1182/blood-2007-10-116129.

Kwok RM, Tran TT. 2016. Hepatitis B and risk of non-hepatocellular carcinoma malignancy. *Clinics in Liver Disease* **20(4)**:693–702 DOI 10.1016/j.cld.2016.06.005.

Lee JY, Lim SH, Lee MY. 2015. Hepatitis B reactivation in multiple myeloma patients with resolved hepatitis B undergoing chemotherapy. *Liver International* **35(11)**:2363–2369 DOI 10.1111/liv.12838.

Li J, Huang B, Li Y, Zheng D, Zhou ZH, Liu JR. 2015. Hepatitis B virus reactivation in patients with multiple myeloma receiving bortezomib-containing regimens followed by autologous stem cell transplant. *Leukemia & Lymphoma* **56(6)**:1710–1717 DOI 10.3109/10428194.2014.941833.

Lin WZ, Chen XH, Huang C. 2017. Increase of programmed death ligand 1 in non-small-cell lung cancers with chronic hepatitis B. *Annals of Oncology* **29**:516–517 DOI 10.1093/annonc/mdx694.

Nucci M, Anaissie E. 2009. Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. *Clinical Infectious Diseases* **49(8)**:1211–1225 DOI 10.1086/605664.

Oketani M, Ido A, Uto H. 2012. Prevention of hepatitis B virus reactivation in patients receiving immunosuppressive therapy or chemotherapy. *Hepatology Research* **42(7)**:627–636 DOI 10.1111/j.1872-034X.2012.00998.x.

Papamichalis P, Alexiou A, Boulbou M. 2012. Reactivation of resolved hepatitis B virus infection after immunosuppression: is it time to adopt pre-emptive therapy. *Clinics and Research in Hepatology and Gastroenterology* **36(1)**:84–93 DOI 10.1016/j.clinre.2011.07.018.

Pratt G, Goodyear O, Moss P. 2007. Immunodeficiency and immunotherapy in multiple myeloma. *British Journal of Haematology* **138(5)**:563–579 DOI 10.1111/j.1365-2141.2007.06705.x.

R Core Team. 2022. *R: a language and environment for statistical computing.* Version 4.2.1. Vienna: R Foundation for Statistical Computing. *Available at* *https://www.r-project.org*.

Sallberg M, Pasetto A. 2020. Liver, tumor and viral hepatitis: key players in the complex balance between tolerance and immune activation. *Frontiers in Immunology* **11**:552 DOI 10.3389/fimmu.2020.00552.

Stasi C, Silvestri C, Voller F. 2017. Emerging trends in epidemiology of hepatitis B virus infection. *Journal of Clinical and Experimental Hepatology* **5(3)**:272–276 DOI 10.1016/j.jceh.2015.06.002.

Tsukune Y, Sasaki M, Komatsu N. 2019. Reactivation of hepatitis B virus in patients with multiple myeloma. *Cancers* **11(11)**:1819 DOI 10.3390/cancers11111819.

Tsukune Y, Sasaki M, Odajima T. 2016. Incidence and clinical background of hepatitis B virus reactivation in multiple myeloma in novel agents' era. *Annals of Hematology* **2016(95)**:1465–1472 DOI 10.1007/s00277-016-2742-7.

Tsukune Y, Sasaki M, Odajima T. 2017. Incidence and risk factors of hepatitis B virus reactivation in patients with multiple myeloma in an era with novel agents: a nationwide retrospective study in Japan. *Blood Cancer Journal* **7(12)**:631 DOI 10.1038/s41408-017-0002-2.

Wands JR, Chura CM, Roll FJ. 1975. Serial studies of hepatitis-associated antigen and antibody in patients receiving antitumor chemotherapy for myeloproliferative and lymphoproliferative disorders. *Gastroenterology* **68(1)**:105–112 DOI 10.1016/S0016-5085(75)80054-0.

Wang DY, Zou LP, Liu XJ. 2016. Chemokine expression profiles of human hepatoma cell lines mediated by hepatitis B virus X protein. *Pathology & Oncology Research* **22(2)**:393–399 DOI 10.1007/s12253-015-0014-9.

Yeo W, Chan TC, Leung NW. 2009. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *Journal of Clinical Oncology* **27(4)**:605–611 DOI 10.1200/JCO.2008.18.0182.

Yeo W, Chan PK, Zhong S, Ho WM, Steinberg JL, Tam JS, Hui P, Leung NW, Zee B, Johnson PJ. 2000. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *Journal of Medical Virology* **62**:299–307 DOI 10.1002/(ISSN)1096-9071.

Yeo W, Zee B, Zhong S, Chan PK, Wong WL, Ho WM, Lam KC, Johnson PJ. 2004. Comprehensive analysis of risk factors associating with hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. *British Journal of Cancer* **90(7)**:1306–1311 DOI 10.1038/sj.bjc.6601699.