Original Article

Correlation between initial alkaline phosphatase levels and overall survival in newly diagnosed multiple myeloma patients

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Background: Alkaline phosphatase (ALP) reflects changes in the condition of multiple myeloma (MM) patients to some extent. However, the relationship of ALP in MM remains uncertain. Our study aimed to determine the association between initial ALP levels and overall survival in newly diagnosed MM patients.

Methods: Clinical data from 202 newly diagnosed MM patients at Beijing Chaoyang Hospital between 2012 and 2016 were collected. Baseline characteristics, disease progression staging, serum markers, and patient survival data were recorded. The cut-off value for ALP was calculated based on patient survival data, and patients were divided into groups. Differences in patients' 3- and 5-year survival rates, liver function, bone disease and other indicators among different groups were compared. Independent risk factors influencing newly diagnosed MM patients were identified using COX regression analysis.

Results: Patients were categorized into three groups based on ALP cut-off points: Group 1 (ALP <70 U/L), Group 2 (ALP 70 to <120 U/L), and Group 3 (ALP ≥120 U/L). Significant differences were observed in lactate dehydrogenase, serum calcium, white blood cell count, hemoglobin, and liver function indicators (including alanine aminotransferase, aspartate aminotransferase, albumin, and γ-glutamyl transferase) among different ALP groups (P<0.05). ALP levels varied significantly among patients with different bone disease grades (P<0.05). Median survival times for Groups 1, 2, and 3 were 25, 52, and 31 months, respectively. Group 2 exhibited significantly higher 3-year survival compared to the other two groups (P=0.006), while no significant difference was observed in 5-year survival among the three groups (P=0.51). Age, International Staging System staging, aspartate aminotransferase, β2-microglobulin, ALP grading, and severe bone disease were identified as independent factors influencing survival in newly diagnosed patients (P<0.05).

Conclusions: ALP levels are correlated with the prognosis of MM patients, and an ALP range of 70 to <120 U/L reflects a better survival expectation.

Keywords: Multiple myeloma (MM); alkaline phosphatase (ALP); survival analysis; liver function; skeletal related event

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Introduction

Multiple myeloma (MM) is the second most common hematological malignancy, accounting for approximately 14% of all hematological malignancies (1). Despite significant improvements in patient survival with the continuous advancement of chemotherapy drugs and treatment regimens (2), there is considerable variation in prognosis, with overall survival (OS) ranging from a few months to over 10 years (3). Therefore, identifying reliable prognostic factors is of crucial significance.

Alkaline phosphatase (ALP) is produced by various cells from different tissues (4). Based on the tissue expression sites, it can be classified into four isozymes: placental ALP, intestinal ALP, liver/bone/kidney ALP, and germ cell ALP. Placental, intestinal, and germ cell ALPs generally exhibit stable activity in most cases. The liver/bone/kidney ALP form is heat-labile isozyme, abundant in hepatic, skeletal, and renal tissue (5). When patients experience liver and bone diseases, their ALP levels will deviate from the normal range, and change with the progression of the disease (6).

In some cases of MM, systemic amyloidosis can occur, leading to the functional impairment of certain organs. Liver involvement is most commonly observed (7), often manifesting as hepatomegaly or an elevated ALP. Bone destruction is a prevalent feature of MM, of which the disease inhibits bone formation, promotes bone resorption, and causes changes in bone remodeling. During the process of the disease an estimated 80% of patients may develop skeletal-related event (SRE). SREs, including bone pain and spinal cord compression, may necessitate the use of radiation therapy or surgery. Liver disease may lead to noticeable fatigue, affecting appetite and digestion, while bone disease might cause some pain, limiting mobility. Thus, health issues concerning the liver and bones not only passively impact quality of life but may even subtly affect OS.

Compared to other serum markers, ALP can provide a relatively sensitive and comprehensive reflection of the progression of bone and liver diseases in patients, and it is more acceptable than invasive procedures. Currently, it has been widely used to monitor liver or bone metastasis in patients with various types of cancer, and it has even been used to predict the survival outcomes of some patients (8). The value of ALP in diagnosing and predicting the prognosis of MM is gradually being recognized. ALP levels can reflect the residual quantity of myeloma cells to some extent. Generally, elevated ALP levels in the early stages of treatment are associated with better therapeutic outcomes (9). They are indicative of good treatment responses to bortezomib (10), bisphosphonates (11), daratumumab (12), proteasome inhibitors (13), and chimeric antigen receptor T cells (14). However, until now, there has been no exact study showing the prognostic value of ALP in newly diagnosed MM. The aim of our study is to determine connection between OS and the initial level of ALP in MM. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-330/rc).

Highlight box

Key findings

- The clinical characteristics and prognostic factors of newly diagnosed multiple myeloma (MM) patients were analyzed, and the cut-off value of alkaline phosphatase (ALP) was calculated based on patient survival data. Subsequently, the grouping of ALP for assessing the prognosis of MM patients was established and validated.

What is known and what is new?

- ALP can reflect the progression of bone and liver diseases in MM patients and serve as an indicator for evaluating treatment efficacy post-MM treatment.
- The grouping of ALP was developed and validated to predict the overall survival of newly diagnosed MM patients.

What is the implication, and what should change now?

- ALP grouping can assist clinicians in assessing patient prognosis and implementing personalized treatment.
- Future research should further refine the grouping and focus more on mechanistic studies.

Methods

Study design

Clinical data from 202 patients with newly diagnosed MM were collected at Beijing Chaoyang Hospital, between 2012 and 2016.

Inclusion criteria: (I) the diagnosis of MM was based on the International Myeloma Working Group (IMWG) diagnostic criteria (15); (II) patients who had not received chemotherapy drugs before coming to the Beijing Chaoyang Hospital.

Exclusion criteria: (I) patients with other diseases unrelated to MM that cause an increase in ALP levels in the serum; (II) patients aged ≤18 years; (III) those unable to accept continued follow-up visits and lacking some of the

primary indexes required for the analysis were also excluded from the study.

OS was calculated from the time of diagnosis to the date of death from any cause or until the last follow-up, conducted on April 1, 2019. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Human Research Ethics Committee of Beijing Chaoyang Hospital approved this study, including access to the patient data used in this research (No. 2018-ke-259). The conducted study contains a retrospective analysis of medical records of our hospital database. Beijing Chaoyang Hospital Human Research Ethics Committee classifies this as a retrospective audit and, as such, consent for publication is not required.

Data collection

Patients' general information and disease status were collected through the hospital's medical records. Additional information about patients before they undergo systemic treatment, including ALP, albumin (ALB), β2-microglobulin (β2-MG), serum calcium (Ca), creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (γ-GT), lactate dehydrogenase (LDH), haemoglobin (Hb), platelet (Plt) and white blood cell (WBC), liver color doppler ultrasound and skeletal disease stage, was gathered. Bone lesions were detected by using magnetic resonance imaging at the time of diagnosis and they were divided into degrees from 0 to 2 (0—no bone involvement, 1—less than or equal to 3 bone lesions, 2—more than 3 bone lesions or fracture or vertebral collapse) (10). Follow-up with patients was conducted through telephone communication, recording the patients' survival status and the occurrence of any complications.

Statistical methods

IBM SPSS 26.0 (Armonk, NY, USA) was used for data analysis. The Kolmogorov Smirnov Test was used to assess the normality of the quantitative data. Kaplan-Meier was employed to determine the median survival period of patients. Receiver operating characteristic (ROC) analysis of patients' status at the median survival time was conducted to obtain the cut-off value for ALP and patients were grouped accordingly based on this cut-off value. The Kruskal-Wallis test was separately employed to assess differences in various indicators among different ALP groups and among patients with different bone disease grades. Kaplan-Meier analysis was used to determine the median survival time of patients in different ALP groups, and survival curves were plotted. The Tarone-Ware test was then employed to examine survival differences among the groups. Spearman correlation analysis was conducted to assess the correlations between variables, with a significance level set at $P<0.05$. Single-factor COX regression analysis was utilized to screen potential risk factors influencing patient survival. Unordered multicategorical variables were transformed into dummy variables, and variables with $P<0.1$ were further included in a multivariable COX regression analysis to identify independent factors affecting the OS of newly diagnosed MM patients ($P<0.05$). The ISS stages and ALP groups were converted into dichotomous categorical variables, and their predictive abilities for the 3- and 5-year survival outcomes of patients were compared by calculating the area under the curve (AUC).

Results

General information

According to the inclusion and exclusion criteria, and based on the principle of having a sample size at least 10 times the number of influencing factors collected, a total of 202 patients were included (*Table 1*). The median follow-up time for patients was 39 months. The average age of the patients was 61.06±10.92 years (max 85 years, min 33 years). Among them, 111 were male (55%) and 91 were female (45%). The group with bone disease grade 0 (no bone disease) consisted of 40 patients (19.8%), the group with bone disease grade 1 (3 lesions or fewer) consisted of 55 patients (27.2%), and the group with bone disease grade 2 (3 or more bone lesions or fractures) consisted of 107 patients (53.0%). There were 87 cases (43.1%) of patients with severe bone disease, including bone pain, pathological fractures, and spinal cord compression (3). Isotype type frequency in the population, consisting of 29.7% IgG κ, 17.3% IgG λ, 8.9% IgA κ, 10.9% IgA λ, 1.0% IgD κ, 8.9% IgD λ, 8.4% κ, 11.9% λ, 2.5% non-secretory, 0.5% double M protein. A total of 172 patients (85.1%) were treated with bortezomib.

The estimated median survival time for patients in this group was 37 months (*Figure 1*). Based on the 3-year survival data after MM diagnosis, the Youden index was calculated to determine the cut-off values for ALP, corresponding to the maximum (positive value) and minimum (negative value) Youden index, which were 66.5 and 126.5 U/L, respectively. Considering the median ALP value of 91 U/L

Table 1 General information

Variables	Total	ALP				Multiple myeloma bone disease stage			
		<70 U/L	70 to <120 U/L	≥120 U/L	P value	Grade 0	Grade 1	Grade 2	P value
Gender					0.76				0.12
Male	111 (55.0)	29 (55.8)	52 (52.5)	30 (58.8)		17 (42.5)	35 (63.6)	59 (55.1)	
Female	91 (45.0)	23 (44.2)	47 (47.5)	21 (41.2)		23 (57.5)	20 (36.4)	48 (44.9)	
Age, years	61.06±10.92	60.94±10.63	60.91±11.35	61.47±10.57	0.92	60.85±10.47	62.95±10.66	60.23±11.23	0.29
ISS stage					0.20				0.11
I	26 (12.9)	3 (5.8)	18 (18.2)	5 (9.8)		7 (17.5)	8 (14.5)	11 (10.3)	
II	86 (42.6)	23 (44.2)	41 (41.4)	22 (43.1)		20 (50.0)	24 (43.6)	42 (39.3)	
III	90 (44.6)	26 (50)	40 (40.4)	24 (47.1)		13 (32.5)	23 (41.8)	54 (50.5)	
DS stage					0.13				0.14
I	9 (4.5)	1 (1.9)	8 (8.1)	0 (1.5)		4 (10.0)	2 (3.6)	3 (2.8)	
II A	15 (7.4)	2 (3.8)	10 (10.1)	3 (5.9)		6 (15.0)	4 (7.3)	5 (4.7)	
II B	4 (2.0)	0	3 (3.0)	1 (2.0)		0	2 (3.6)	2 (1.9)	
III A	131 (64.9)	39 (75.0)	58 (58.6)	34 (66.7)		22 (55.0)	38 (69.1)	71 (66.4)	
III B	43 (21.3)	10 (19.2)	20 (20.2)	13 (25.5)		8 (20.0)	9 (16.4)	26 (24.3)	
β2-MG, mg/L	8.75±11.35	8.50±10.18	8.12±10.95	10.30±13.28	0.41	7.35±11.64	10.51±13.22	8.36±10.12	0.47
LDH, U/L	170.46±92.21	154.65±69.57	170.21±103.08	188.08±88.94	0.01*	153.82±76.17	168.65±104.13	177.81±91.36	0.27
Cr, μmol/L	163.02±185.30	159.76±176.14	167.29±191.59	157.93±185.65	0.97	175.59±198.99	156.45±164.29	162.40±192.64	0.93
Ca, mmol/L	2.21±0.32	2.27±0.34	2.24±0.33	2.10±0.28	0.001*	2.19±0.30	2.14±0.24	2.26±0.36	0.25
WBC, 10^9/L	5.53±2.47	4.89±2.05	5.48±2.39	6.29±2.84	0.009*	6.40±2.82	5.38±2.48	5.29±2.29	0.10
Hb, g/L	93.83±23.98	85.91±22.48	96.85±22.56	96.09±26.69	0.04*	101.23±20.98	90.58±25.00	92.46±24.11	0.10
Plt, 10^9/L	182.21±85.45	159.13±70.29	191.15±89.17	188.80±89.53	0.09	212.00±89.15	174.38±77.79	176.17±86.15	0.03*
ALB, g/L	28.72±8.67	24.34±9.65	30.85±7.01	29.11±9.05	<0.001*	30.29±8.50	26.77±9.18	29.09±8.39	0.13
ALT, U/L	21.33±15.83	19.50±12.91	20.04±13.65	25.71±21.12	0.02*	19.75±15.14	21.18±20.80	22.06±13.05	0.09
AST, U/L	23.96±13.31	22.83±10.49	21.62±9.71	29.65±19.24	0.01*	22.68±12.49	24.40±18.02	24.29±10.62	0.34
γ-GT, U/L	43.72±50.41	27.25±18.61	36.54±38.22	74.29±75.10	<0.001*	29.33±16.57	37.22±30.30	52.82±64.16	0.14
ALP, U/L	102.32±48.24	58.08±8.35	92.06±15.06	167.35±47.76	–	110.05±57.11	106.68±47.82	87.45±38.91	0.006*

The data were expressed as mean ± standard deviation or n (%). *, P<0.05. Group 1, ALP <70 U/L; Group 2, ALP 70 to <120 U/L; Group 3, ALP ≥120 U/L. ALP, alkaline phosphatase; ISS, International Staging System; DS, Durie-Salmon; β2-MG, β2-microglobulin; LDH, lactate dehydrogenase; Cr, creatinine; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, γ-glutamyl transferase; WBC, white blood cell.

and the interquartile range of 69–120 U/L, the patients were grouped as follows: Group 1 (ALP <70 U/L) consisted of 52 patients (25.7%), Group 2 (ALP 70 to <120 U/L, close to the median values of healthy people) consisted of 99 patients (49.0%), and Group 3 (ALP ≥120 U/L) consisted of 51 patients (25.2%).

Patients in different ALP groups exhibited statistically significant differences in LDH, Ca, WBC, Hb, and liver function indicators (ALT, AST, ALB, and γ-GT) with a significance level of P<0.05. Statistical analysis showed that the median age and proportion of gender of three groups did not show significant differences. The mean values of AST, ALT, and γ-GT were significantly higher in Group 3 compared to Group 1 and Group 2. Patients with different bone disease grades showed statistically significant differences in Plt and ALP levels (P<0.05).

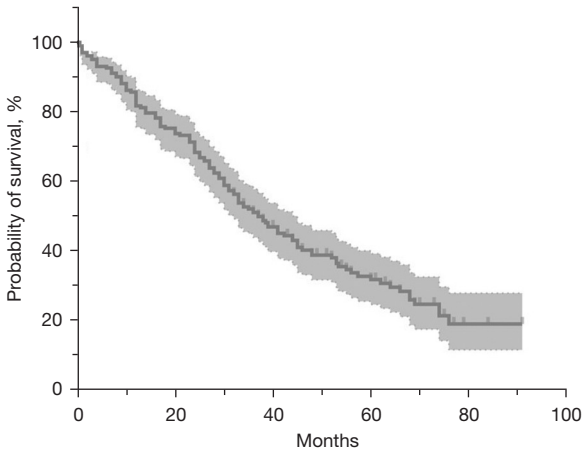

Figure 1 Kaplan-Meier survival curves.

Table 2 Causes of patient death

Classification	N [%]
Infection	107 [80]
Organ failures	35 [26]
Paraplegia	7 [5]
Thrombus	4 [3]
Plasma cell leukemia	4 [3]

Table 3 Comparison of survival

Survival	ALP			P value
	<70 U/L	70 to <120 U/L	≥120 U/L	
3-year survival, %	32.7	58.6	41.2	0.006*
5-year survival, %	17.3	19.2	11.8	0.51

*, P<0.05. ALP, alkaline phosphatase.

Survival analysis

During the follow-up period, 134 patients (66.3%) died. For the 134 patients who had passed away, 107 (80%) patients died of severe infection including pneumonia and urinary tract infection even septic shock, 35 (26%) patients died of worsening renal failure or multiorgan failure. The other reasons of death were paraplegia (7, 5%), thrombus (4, 3%) and plasma cell leukemia (4, 3%). Notably, 23 (17.2%) cases died both with infection and organ failure (*Table 2*).

The 3-year survival rate in Group 2 was significantly longer compared with the other two groups (32.7%, 58.6%, 41.2%; P=0.006). Regarding the 5-year survival rates, there was no apparently difference among the three groups (17.3%, 19.2%, 11.8%; P=0.51) (*Table 3*).

Plotting the survival curves for patients in different groups (*Figure 2*), the median survival times were 25 months for patients in Group 1, 52 months for patients in Group 2, and 31 months for patients in Group 3. Tarone-Ware test revealed statistically significant differences in survival times among the three groups (P=0.004). Specifically, there were significant differences in survival between Groups 2 and 1, as well as Groups 3 and 2 (with P values of 0.003 and 0.01, respectively). However, no significant difference was observed in the survival between patients in Group 1 and Group 3 (P=0.69).

Factors influencing the OS

Spearman correlation analysis revealed significant positive correlations: ALT with AST (r=0.561, P<0.001), DS stage with ISS stage (r=0.596, P<0.001), and severe bone disease with bone disease grade (r=0.456, P<0.001). To avoid collinearity, variables with significant correlations were excluded. Age, Isotype, ISS stage, AST, γ-GT, β2-MG, LDH, ALB, Cr, Ca, WBC, Hb, Plt, ALP grouping, presence of severe bone disease, and use of bortezomib were included in the single-factor COX regression analysis. Dummy variables were set for ALP grouping, with patients in Group 2 serving as the reference.

Age, ISS stage, AST, γ-GT, β2-MG, LDH, Cr, Hb, Plt, ALP grade, and presence of severe bone disease were identified as potential influencing factors for the survival time of MM patients after initial diagnosis (P<0.1, *Table 4*). Dummy variable analysis for ALP grouping suggested that compared to Group 2, Group 1 and Group 3 had a higher risk of death. With other variables held constant, the risk of death for patients in ALP Group 1 was 1.779 times that of Group 2, and for patients in Group 3, the risk of death was 1.604 times that of Group 2.

Incorporating the aforementioned potential influencing factors into a multivariable COX regression model (*Table 5*), it was determined that age, ISS stage, AST, β2-MG, ALP grade, and the presence of severe bone disease were independent factors significantly impacting the survival time of newly diagnosed MM patients (P<0.05).

The ISS stages and ALP groups were converted into two binary categories (ISS stages 1 and 2 grouped together, and

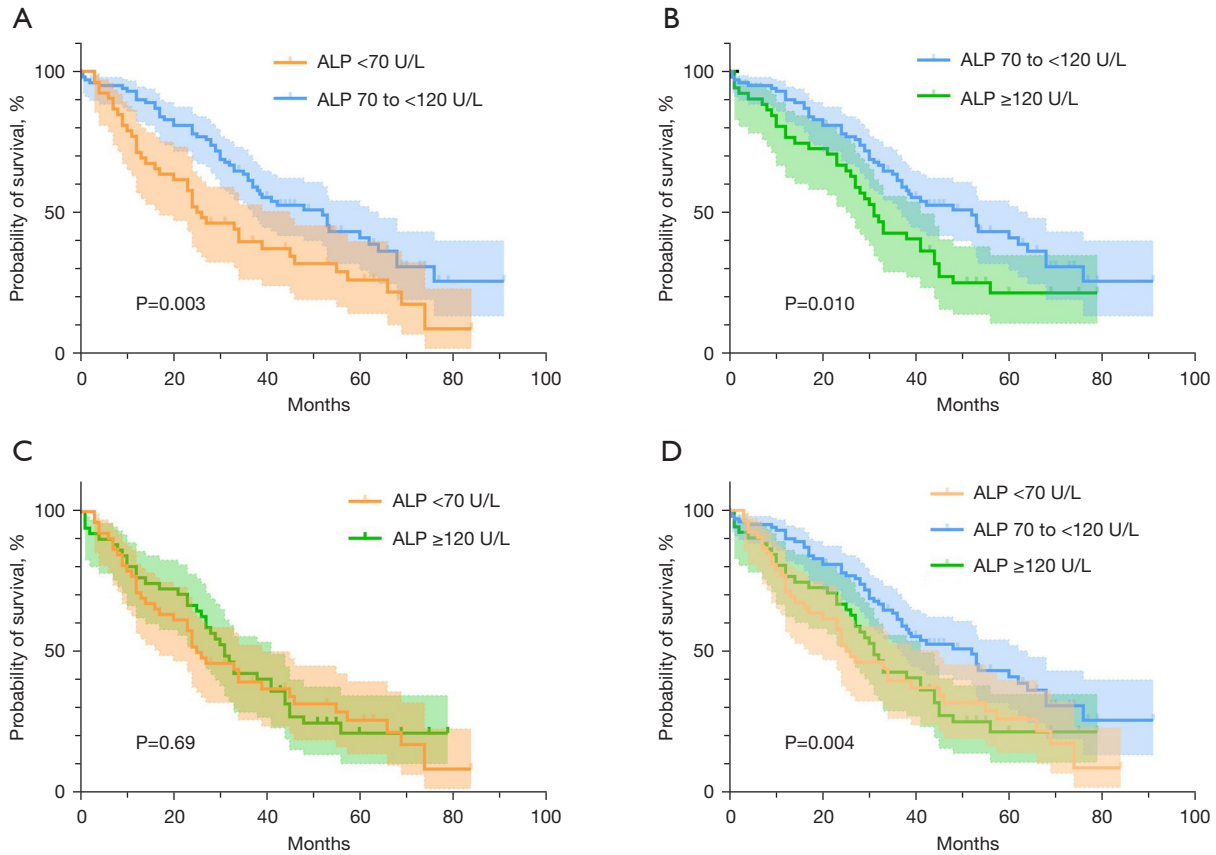

Figure 2 Survival curves. (A) Group 1 *vs.* Group 2; (B) Group 2 *vs.* Group 3; (C) Group 1 *vs.* Group 3; (D) overall comparison. Group 1, ALP <70 U/L; Group 2, ALP 70 to <120 U/L; Group 3, ALP ≥120 U/L. ALP, alkaline phosphatase.

stage 3 as a separate group; ALP Groups 1 and 3 grouped together, while Group 2 remains a distinct category). The AUC for predicting the 3-year survival rate using ISS stages was 0.627 (P=0.002, 95% CI: 0.296–0.450). When assessing the 3-year survival rate based on ALP values, the AUC was 0.600 (P=0.01, 95% CI: 0.521–0.678). In the evaluation of the 5-year survival outcomes, the AUC for ISS stages was 0.573 (P=0.18, 95% CI: 0.323–0.530), while the AUC for ALP was 0.539 (P=0.48, 95% CI: 0.432–0.646).

Discussion

The expression of liver/bone/kidney ALP is the most extensive and fluctuates with changes in the disease, serving as a marker for predicting disease progression (16). Ninety-five percent of ALP activity comes from liver cells and osteoblasts (17). Therefore, by assessing total ALP, doctors can obtain important information about certain diseases. Currently, ALP has been widely used in the diagnosis, prognosis, or reactive assessment during drug therapy for various diseases (18). It is particularly significant in the prognosis and treatment assessment of patients with prostate cancer, breast cancer, liver cancer, and osteosarcoma (19). In addition, the values of ALP for MM patients exhibit a wider range than in healthy individuals (20). This suggests that during different stages of MM development, there may be significant variations in ALP levels, indicating the potential of ALP in assessing the prognosis of MM.

This study categorized newly diagnosed MM patients based on the determined cut-off values into three groups: ALP <70 U/L (Group 1), ALP 70 to <120 U/L (Group 2), and ALP ≥120 U/L (Group 3). COX regression results indicated a significant overall difference in prognosis among patients in different groups, with 3-year survival rates for Groups 1, 2, and 3 being 32.7%, 58.6%, and 41.2%, respectively (P=0.006). However, intriguingly, the 5-year survival rates for the three groups of patients were 17.3%, 19.2%, and 11.8%, respectively (P=0.51), showing no

Table 4 Univariate COX regression analysis

Characteristic	P value	HR	95% CI
Age	0.05*	1.016	1.000–1.033
Isotype	0.61	1.017	0.954–1.085
ISS stage	0.000*	1.726	1.322–2.252
AST	0.04*	1.014	1.000–1.027
γ-GT	0.004*	1.005	1.001–1.008
β2-MG	0.002*	1.024	1.009–1.039
LDH	0.03*	1.002	1.000–1.003
ALB	0.36	0.992	0.974–1.010
Cr	<0.001*	1.001	1.001–1.002
Ca	0.84	0.946	0.562–1.594
WBC	0.83	0.992	0.921–1.068
Hb	0.02*	0.991	0.983–0.998
Plt	0.08*	0.998	0.996–1.000
ALP grade	0.010*		
ALP <70 U/L	0.006*	1.779	1.184–2.672
ALP ≥120 U/L	0.03*	1.604	1.062–2.422
Severe bone disease	<0.001*	1.933	1.366–2.736
Bortezomib	0.84	1.047	0.670–1.636

*, P<0.1. HR, hazard ratio; CI, confidence interval; ISS, international staging system; AST, aspartate aminotransferase; β2-MG, β2-microglobulin; LDH, lactate dehydrogenase; ALB, albumin; Ca, serum calcium; Cr, creatinine; WBC, white blood cell; Hb, haemoglobin; Plt, platelet; ALP, alkaline phosphatase.

Table 5 Multivariate COX regression

Characteristic	P value	HR	95% CI
Age	0.005*	1.026	1.008–1.045
ISS stage	0.003*	1.596	1.174–2.168
AST	0.004*	1.023	1.007–1.038
β2-MG	0.03*	1.019	1.002–1.036
ALP grade	0.03*		
ALP <70 U/L	0.007*	1.793	1.171–2.745
ALP ≥120 U/L	0.25	1.323	0.823–2.127
Severe bone disease	0.000*	2.040	1.410–2.952

*, P<0.05. HR, hazard ratio; CI, confidence interval; ISS, international staging system; AST, aspartate aminotransferase; β2-MG, β2-microglobulin; ALP, alkaline phosphatase.

significant difference. Despite significant advancements in treatment strategies and outcomes for MM patients over the past decade, with more effective and less toxic therapies gradually emerging and being applied in clinical practice, MM remains an incurable disease. This may contribute to the lack of differences in the 5-year survival rates among patients. Kaplan-Meier survival curves indicated a median survival time of 25 months for patients in Group 1, 52 months for patients in Group 2, and 31 months for patients in Group 3. It is evident that both ALP <70 U/L and ALP ≥120 U/L are associated with poorer survival outcomes. In different groupings, there were significant differences in patients' white blood cell counts, hemoglobin, liver function, and calcium levels. Additionally, ALP levels vary significantly across different grades of bone disease. Therefore, the differences in prognosis among patients grouped by ALP levels may be linked to the condition of liver and bone involvement.

Elevated ALP reflects osteoblastic changes, while low ALP indicates inhibition of osteoblasts (21). SRE results from the interaction between MM cells and bone cells (including osteocytes, osteoblasts, and osteoclasts) (22). Osteocytes produce soluble factors such as receptor activator of NF-κB (RANK, also known as TNFRSF11A) ligand (RANKL, also known as TNFSF11), sclerostin, and Dickkopf-1, promoting osteoclast activity and impairing osteoblast maturation, leading to bone loss and elevated blood calcium levels (23). Suppressed osteoblast activity is mainly mediated by the inhibition of the Wnt and β-catenin pathway (24), resulting in reduced calcium deposition (25). As shown in *Table 1*, patients with involvement of more than three bone sites exhibited significantly lower ALP levels compared to the other two groups, with higher blood calcium levels, consistent with previous findings (26). Multifactorial COX regression analysis indicated that severe bone involvement was an independent risk factor affecting patient survival. SRE serves as a marker for the progression of MM, increasing the disease burden on the survival and quality of life of MM patients. It also elevates complications, particularly the risk of infections (26). Pulmonary infections were the most common cause of death in this group of patients. Studies have shown that MM patients with SRE have a 20–40% increased risk of death (27), with a shortened survival period of 2–3 years (28). The results above suggested that patients with ALP <70 U/L had a significantly increased risk of developing

bone disease, leading to a corresponding reduction in survival.

Patients with ALP ≥120 U/L showed significantly elevated liver enzyme levels compared to other groups, suggesting possible liver dysfunction due to amyloid protein deposition or plasma cell infiltration in hepatic tissue (29). Disease progression can lead to liver failure, ultimately shortening patient lifespan (30). Furthermore, as many chemotherapy drugs are metabolized in the liver, liver disease may limit treatment options and reduce therapeutic efficacy, posing challenges for long-term survival (31). Research by Souvannavong and colleagues further indicates that elevated ALP is associated with cell proliferation, differentiation, and immunoglobulin secretion (32), indicating its correlation with tumor progression. These factors imply that ALP ≥120 U/L may indicate the onset of liver dysfunction and disease progression, resulting in a poorer prognosis for patients.

The ISS stage is a widely employed staging system for MM, with stage 3 often indicating a poorer prognosis (33). Elevated β2-MG levels, a factor in ISS staging, correlate with high tumor burden and renal impairment in MM (34). The accuracy of these associations is further validated in this study. COX analysis revealed age was a risk factor influencing OS. Elderly patients often have poor fitness and more comorbidities, reducing prognosis. In patients aged 50–80 years in North America, Europe, and Japan, progression-free survival decreases by 0.7–1.0 years for every 10-year age increase (35). The light chains of myeloma proteins are nephrotoxic, damaging the kidneys (36). About 20–30% of MM patients have elevated creatinine at diagnosis, risking renal failure and increased mortality (37). Anemia, present in 50% of MM cases at diagnosis, is linked to myeloma cell infiltration and MM progression (38,39). Elevated LDH signals indicate high tumor burden and invasive growth in MM, often associated with extramedullary plasmacytomas (40). Cr, Hb, and LDH, validated in this study, are potential factors influencing the survival period of newly diagnosed MM patients.

There are some limitations in this study. Firstly, it is a retrospective study with a relatively long-time span of research, and some treatment regimens may have been updated over time. Patients enrolled at different time points may have received different treatment plans, introducing some confounding factors. Secondly, the patients included in this study were all diagnosed and treated at a single center in China, limiting the generalizability of the study. Finally, the article did not perform a differential statistical analysis and testing for ALP isoenzymes, opting to use total ALP as the assessment indicator. While this approach enhances efficiency, reduces costs, and simplifies the work, it is essential to conduct further determination of ALP isoenzymes to validate the conclusions.

Conclusions

Low ALP levels are associated with bone damage in MM patients, while elevated ALP levels may indicate liver involvement, both of which adversely impact the OS of MM patients. Patients with ALP levels in the range of 70 to <120 U/L, which is similar to the ALP levels in the healthy population, are more likely to have a good prognosis. ALP can serve as a predictor for the prognosis of newly diagnosed MM patients. However, due to limitations in diagnostic methods for complications such as bone disease and liver damage, some aspects of the investigation require further refinement. We will continue this work to explore the value of ALP in MM patients, aiming to contribute to the diagnosis, treatment, and prognosis assessment for MM patients.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-330/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Human Research Ethics Committee of Beijing Chaoyang Hospital approved this study, including access to the patient data used in this research (No. 2018-ke-259). The conducted study is a retrospective analysis of medical records of our hospital database. Beijing Chaoyang Hospital Human Research Ethics Committee classifies this as a retrospective audit and, as such, consent for publication is not required.

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