The combination of serum calcium levels, neutrophil-to-lymphocyte ratio and platelet count in the prognosis of multiple myeloma: A retrospective cohort study and review of the literature

MINH PHUONG VU[1,2], VIET TRUNG HAN[2], PHUONG THAO PHAM[1] and HOANG VU[2]

[1]Department of Hematology, Hanoi Medical University; [2]Clinical Department, Center of Hematology and Blood Transfusion, Bach Mai Hospital, Hanoi, Vietnam

Received April 20, 2022; Accepted July 11, 2022

DOI: 10.3892/wasj.2022.165

Abstract. The prognosis of multiple myeloma (MM) can be determined by the serum calcium levels, the neutrophil-to-lymphocyte ratio (NLR) and the platelet count (PLT). The objective of the present study was to determine the influence of the combined prognostic index (CPI), which included the aforementioned three indices (serum calcium levels, NLR and PLT), on the survival rates of patients with MM. A total of 111 patients newly diagnosed with MM undergoing treatment were analyzed. The prognostic values for the survival times were determined at the time of pre-treatment. The patients with high serum calcium levels (2.665 mmol/l), a high NLR (2.245) and a low PLT (<150x10^9/l) received a score of 1. Based on the scores obtained, the CPI was formed, in which the patients were grouped into a low-risk group (0-1 points), an intermediate-risk group (2 points) and a high-risk group (3 points). Univariate analysis demonstrated significant differences between the three CPI groups (P<0.001). Multivariate analysis indicated that the CPI was an independent prognostic factor for overall survival [intermediate-risk group: Hazard ratio (HR), 3.244; 95% confidence interval (CI), 1.213-8.679; high-risk group: HR, 4.290; 95% CI, 2.180-8.443; P<0.001]. This level of significance was also observed in the subgroups, which were divided according to the percentage of bone marrow plasma cells (≥30 or <30%) and age (≥65 or <65 years). On the whole, the present study demonstrates that the CPI determined by the high serum calcium levels, high NLR and low PLT may be used as an independent prognostic indicator for patients with MM.

Correspondence to: Dr Minh Phuong Vu, Department of Hematology, Hanoi Medical University, 1 Ton That Tung Street, Dong Da, Hanoi, Vietnam
E-mail: vuminhphuong@yahoo.com

Key words: serum calcium level, platelet, neutrophil-to-lymphocyte ratio, prognosis, multiple myeloma

Introduction

Multiple myeloma (MM) is a B-cell neoplasm characterized by the clonal proliferation of plasma cells that develops due to the presence of genetic changes and the interaction of plasma cells with the bone marrow microenvironment (1). The improvement in the overall survival (OS) and progression-free survival (PFS) rates of patients with MM due to the application of specific immunomodulators and proteasome inhibitors has been based on risk stratification (2,3). Chromosomal abnormalities, including t(4;14), t(14;16), t(14;20), amp1q21 and del 17p have been shown to be associated with a poor prognosis. the revised international staging system (R-ISS) is based on a combination of cytogenetic aberrations detected by fluorescence *in situ* hybridization (FISH), ISS (international staging system, a combination of albumin and β2-microglobulin) and lactate dehydrogenase (LDH). R-ISS is accepted as the prognostic scoring system for patients with MM. However, patients with MM have highly variable prognoses and a meticulous evaluation of their prognosis is required for optimal treatment strategies to be administered (2,3).

Afram *et al* (4) indicated that the performance status may be useful in determining the prognosis of patients. Cai *et al* (5) suggested that a high albumin-to-globulin ratio was associated with an improved survival time (5). Qian *et al* (6) and Chen *et al* (7) indicated that a high percentage of abnormal plasma cells in the bone marrow were highly associated with a poor prognosis. Qian *et al* (6) also demonstrated that a high serum calcium level was a poor prognostic factor for OS.

Several studies have examined the expression levels of certain inflammatory factors and have suggested that these factors (8-10) exerted adverse effects on the survival rate of patients with MM. These inflammatory factors include the platelet count (PLT), the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), the monocyte-to-lymphocyte ratio (MLR) and C-reactive protein (CRP) levels. Previous studies, such as those of Zhang *et al* (8), Liu *et al* (9), Kim *et al* (10), Szudy-Szczyrek *et al* (11) and Zuo *et al* (12) suggested that a high NLR was an adverse prognostic factor. However, no consensus has yet been reached on the cut-off value used for the diagnosis of MM. Recently,

Gui *et al* (13) and Solmaz *et al* (14) identified that a high PLR was a significant factor for a poor survival time.

Several studies have investigated the combination of several prognostic indicators to provide a system equivalent to the ISS or R-ISS. Kim *et al* (10) identified that the multiple prognostic index (MPI) value included NLR, PLT and CRP for patients with MM. Liu *et al* (9) identified application of IPSI (inflammatory prognostic score index), which included the following parameters: NLR, platelet count and red blood cell distribution width (RDW).

Since 2005, ISS (with albumin and β2-microglobulin) has been applied for the prognosis of patients with symptomatic MM from 17 institutions (15). It is a simple and easy-to-use prognostic indicator; however, it was developed prior to the use of the new regimen. In August 2015, the International Myeloma Working Group (IMWG) published the R-ISS. It is a system that was established by the development of additional biomarkers in MM, including ISS, LDH and cytogenetic analysis. R-ISS was developed based on clinical and laboratory data following the evaluation of chromosomal abnormalities by FISH [high-risk includes the following markers: t(4;14), t(14;16) and del 17 p, standard-risk without these chromosomal abnormalities] from patients with a new diagnosis of MM who were treated with new drugs (immunomodulatory agents or proteasome inhibitors) (16). Therefore, it is suitable for the prognosis of patients treated with new drugs. However, this indicator requires technical expertise, has a high cost and requires a long period of analysis. Therefore, it is necessary to propose tools that are simple, cost- and time-effective and suitable for a new regimen.

To facilitate the stratification of the risk of patients with MM using the simple factors, the present study was conducted to determine the influence of the combined prognostic index (CPI), which included the serum calcium levels, the NLR and the PLT, on the survival rates of patients with MM.

Patients and methods

Patients. From January, 2015 to April, 2019, 111 patients with *de novo* MM, according to the criteria of IMWG 2014, were enrolled in the present study at the Center of Hematology and Blood Transfusion, Bach Mai Hospital, Hanoi, Vietnam (17). The study protocol was approved by the Ethical Committee in Hanoi Medical University (no. 187). Patient consent was waived by the committee as the present study was a retrospective observational study.

Screening tests. Prior to treatment, all patients were evaluated by the Eastern Cooperative Oncology Group performance status (PS) (18). The percentage of bone marrow plasma cells, the hemoglobin levels, the NLR, PLT, as well as the serum albumin, β2-microglobulin and calcium levels were assessed to evaluate the pre-chemotherapy patient status and the prognostic risk.

Treatment. All patients were treated with chemotherapy including the following regimens: The MPT protocol, which included melphalan-prednisone-thalidomide for patients ≥65 years of age, the VCD protocol, which included bortezomib-cyclophosphamide-dexamethasone or the VTD protocol, which included bortezomib-thalidomide-dexamethasone for patients <65 years of age.

Table I. Characteristics of the patients included in the present study.

Characteristic	No. of patients (n=111)	Percentage
Sex		
Male	55	49.5
Female	56	50.5
ISS stage		
I	10	9
II	27	24.3
III	74	66.3
Age, years (mean, 60; min, 32; max, 84)		
<65 years	80	72.1
≥65 years	31	27.9

Definitions. The stage classification was defined according to the ISS (16). The response to the remission induction therapy was evaluated according to the IMWG 2016 response criteria (19).

Statistical analysis. The following prognostic factors were subjected to univariate analysis: PS, the percentage of bone marrow plasma cells, hemoglobin levels, ISS stage, platelet count, NLR and serum calcium levels. The optimal cut-off value of PS (score 2) was determined as described in study by Kim *et al* (10). The optimal cut-off value of a high percentage of bone marrow plasma cells (30%) and a low hemoglobin level (<100 g/l) were determined according to the study of Qian *et al* (6). The optimal cut-off value for low PLT (<150x10^9/l) was determined according to the study of Kim *et al* (10). The present study carefully considered and selected a PLT cut-off value of 150x10^9/l instead of 100x10^9/l according to the study of Jung *et al* (20). However, a higher level of alert is required when assessing patient prognosis. The receiver operating characteristic curve was performed separately for the determination of the NLR and the serum calcium levels to obtain a predictive value for OS. The cut-off value of NLR was 2.245, whereas the cut-off value of the serum calcium levels was 2.665 mmol/l. OS was calculated using the Kaplan-Meier method. Univariate analysis of prognostic factors for OS was performed using the log-rank test with the following variables: PS (score 2), high percentage of bone marrow plasma cells (30%), low hemoglobin levels (<100 g/l), high NLR (2.245), low PLT (<150x10^9/l), high serum calcium levels (2.665 mmol/l), and stage ISS. P<0.05 was considered to indicate a statistically significant difference. The variables that indicated statistically significant differences in the univariate analysis were included as prognostic factors in the multivariate analysis. Multivariate analysis of prognostic factors for OS was performed using the Cox proportional hazards method. Statistical analysis was performed using SPSS 25 software. P<0.05 was considered to indicate a statistically significant difference.

Table II. Laboratory indices of the patients included in the study.

Characteristic	Minimum	Maximum	Mean	Standard deviation
Hemoglobin (g/l)	39.00	136.00	87.5721	21.93982
WBC (x10^9/l)	1.47	59.93	7.8307	6.11695
Platelet (x10^9/l)	37.00	626.00	213.8559	92.44338
NLR	.54	19.53	2.6394	2.37388
Urea (mmol/l)	2.50	32.70	10.5464	6.78404
Creatinine (mmol/l)	43.00	1,073.00	196.3036	196.81591
AST (U/l)	12.00	143.00	30.0800	18.95692
ALT (U/l)	6.00	228.00	28.1109	29.51206
Albumin (g/l)	17.30	51.00	32.3649	7.33865
LDH (U/l)	89.00	756.00	201.4048	114.21689
B2M (μg/ml)	1.70	91.80	11.7759	13.54150
Ferritin (ng/ml)	46.40	7,180.00	892.9460	928.97367
Calcium (mmol/l)	1.09	3.94	2.3539	.44654
Bone marrow count (x10^9/l)	5.56	258.58	58.0596	54.77775
Plasma cells in bone marrow (%)	2.00	86.00	27.8018	19.52798

WBC, white blood cell count; NLR, neutrophil-to-lymphocyte ratio; AST, aspartate aminotransferase; ALT, alanine transaminase; LDH, lactate dehydrogenase; B2M, β2-microglobulin.

Table III. Prognostic factors included in the survival analysis.

	Univariate analysis		Multivariate analysis		
Factor	OS (months)	P-value (log-rank test)	HR	95% CI	P-value (Cox analysis)
Performance status					
0-1	45.948	0.004			
≥2	32.615				
Bone marrow plasma cells (%)					
<30	40.529	0.004	1		0.047
≥30	31.815		1.951	1.010-3.766	
NLR					
<2.245	41.344	0.015	1		0.042
≥2.245	31.296		2.001	1.025-3.905	
Platelet count (x10^9/l)					
≥150	39.834	0.025	1		0.025
<150	29.698		2.105	1.096-4.046	
Calcium levels (mmol/l)					
<2.665	40.492	0.001	1		0.015
≥2.665	26.241		2.173	1.166-4.050	
ISS					
ISS1	50.400	0.002			
ISS2	40.885				
ISS3	33.524				

OS, overall survival; NLR, neutrophil-to-lymphocyte ratio; ISS, international staging system; HR, hazard ratio; 95% CI, 95% confidence interval.

Results

Clinical data. At diagnosis, 111 patients were included in the present study, of whom 55 were males (M:F ratio, 0.98). The characteristics of the patients are presented in Tables I and II.

Prognostic factors of survival. Univariate analysis was performed to assess the OS. The data indicated that a PS

Table IV. CPI used in the survival analysis.

	Univariate analysis		Multivariate analysis		
Factor	OS (months)	P-value (log-rank test)	HR	95% CI	P-value (Cox analysis)
CPI					
Low-risk	49.048	<0.001	1		<0.001
Intermediate-risk	34.009		3.244	1.213-8.679	
High-risk	24.960		4.290	2.180-8.443	
Bone marrow plasma cells (%)					
<30	40.529	0.004	1		0.009
≥30	31.815		2.270	1.228-4.196	

CPI, combined prognostic index; HR, hazard ratio; 95% CI, 95% confidence interval.

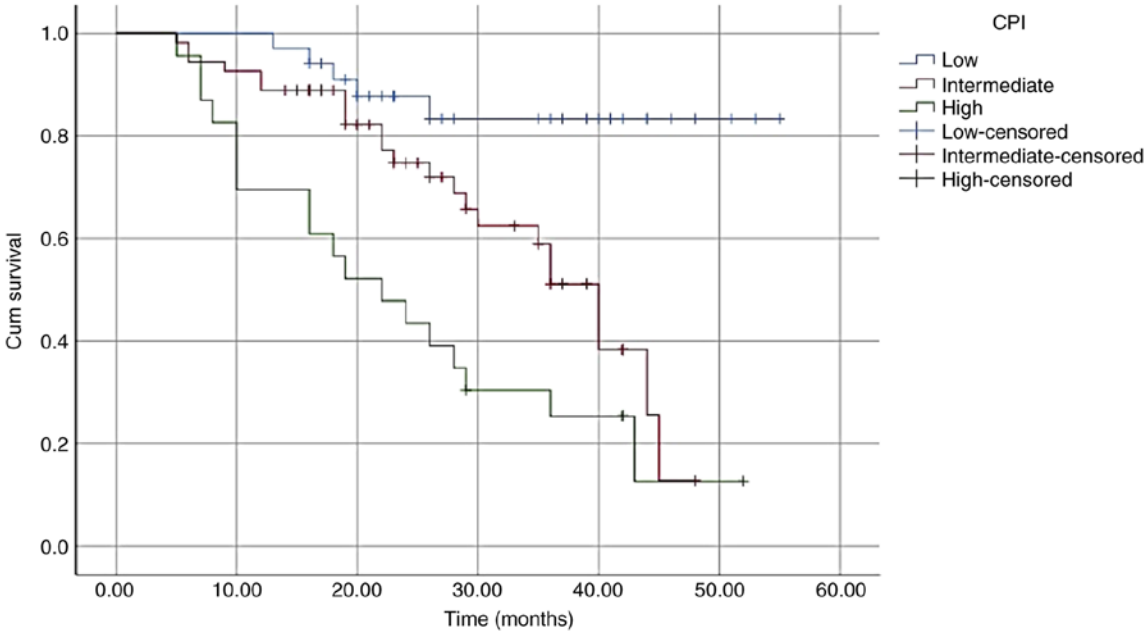

Figure 1. Patient overall survival curve according to the CPI. CPI, combined prognostic index (which included the serum calcium levels, the neutrophil-to-lymphocyte ratio and the platelet count).

≥2 (P=0.004), a high percentage of bone marrow plasma cells (P=0.004), a high NLR (P=0.015), a low platelet count (P=0.025), high serum calcium levels (P=0.001) and the stage of ISS (P=0.002) were prognostic factors, which were significantly associated with a poor prognosis (Table III). Multivariate analysis for OS indicated that a high percentage of bone marrow plasma cells (P=0.047), a high NLR (P=0.042), a low PLT (P=0.025) and high serum calcium levels (P=0.015) were independent and significant prognostic factors for the survival of the patients with MM (Table III).

Establishment of CPI. Multivariate analysis demonstrated that high serum calcium levels (2.665 mmol/l), high NLR (2.245) and low platelet count (<150x10^9/l) were independent and significant adverse prognostic factors and were included in the CPI. The criteria for scoring of the CPI were based on the presence of each risk factor. The patients with high calcium levels (2.665 mmol/l), a high NLR (2.245) and a low PLT (<150x10^9/l) demonstrated a score of 1. Based on the scores obtained, the CPI was formed, in which the patients were grouped into a low-risk group (0-1 points), an intermediate-risk group (2 points) and a high-risk group (3 points). Although the results of the multivariate analysis indicated that the high percentage of the bone marrow plasma cells was an independent and significant prognostic factor for patient OS, this parameter was not included in the plasma cell index of the CPI, since the objective of the present study was to provide a simple and easy-to-use index that could be applied in the peripheral blood samples of the patients.

Role of CPI in survival analysis. Univariate analysis demonstrated that significant associations were noted between the three CPI groups (P<0.001; Table IV and Fig. 1). Multivariate analysis suggested that the CPI was an independent prognostic

Table V. OS determined according to the CPI in the groups of plasma cell percentage and age.

Factor	CPI	OS (months)	P-value
Plasma cell count, <30%	Low	51.429	0.001
	Intermediate	34.785	
	High	31.757	
Plasma cell count, ≥30%	Low	38.662	<0.001
	Intermediate	33.797	
	High	17.545	
Age <65 years	Low	46.912	0.001
	Intermediate	35.119	
	High	25.867	
Age ≥65 years	Low	48.667	<0.001
	Intermediate	29.427	
	High	5.000	

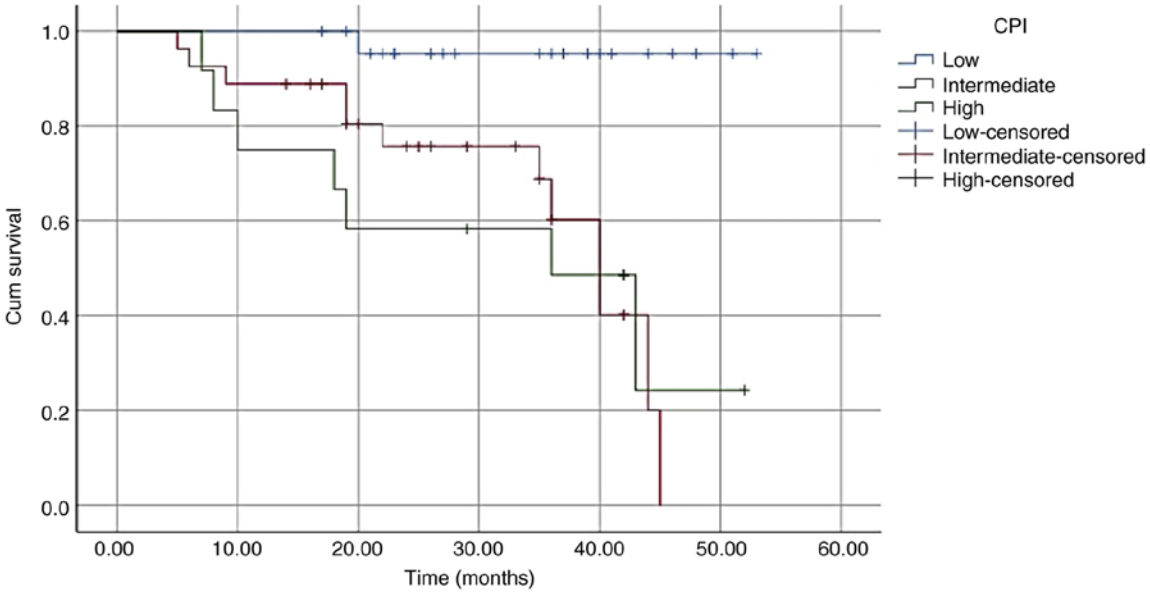

Figure 2. Patient overall survival curve according to the CPI in the group with bone marrow plasma cell counts <30%. CPI, combined prognostic index (which included the serum calcium levels, the neutrophil-to-lymphocyte ratio and the platelet count).

factor for OS [intermediate-risk group: Hazard ratio (HR), 3.244; 95% confidence interval (CI), 1.213-8.679; high-risk group: HR, 4.290; 95% CI, 2.180-8.443; P<0.001; Table IV]. This level of significance was also observed in the subgroups that were divided according to age (≥ or <65 years) and to the percentage of bone marrow plasma cells (≥ or <30%; Table V, Figs. 2-5).

Discussion

Hypercalcemia is noted in several cancer types, inflammatory conditions and specific diseases, which are usually caused by increased bone resorption due to increased osteoclast activity (21). During the development of MM, the increased osteoclastic bone resorption is caused by cytokines (receptor activator of the nuclear factor-κB ligand, macrophage inflammatory protein-1α and tumor necrosis factors) that are oversecreted by myeloma or other types of cells in the bone marrow microenvironment (22). Secondly, patients with MM often have impaired renal function and increased renal tubular calcium reabsorption. Therefore, this causes an elevation in serum calcium levels (22).

Several studies have focused on the prognostic value of the serum calcium levels in patients with MM. Zagouri *et al* (23) suggested that hypercalcemia was related to a two-fold increase in the risk of early mortality. Similarly, Cheng *et al* (24) indicated a statistically significant difference in the mortality rate between the groups of patients with serum calcium levels > or <2.44 mmol/l. Qian *et al* (6) suggested that a high serum calcium level of 2.75 mmol/l was a poor prognostic factor for OS. The present study demonstrated that a high serum calcium level of 2.665 mmol/l was also an independent adverse prognostic factor for OS.

Recent studies have investigated the application of various inflammatory factors as prognostic indices in patients with

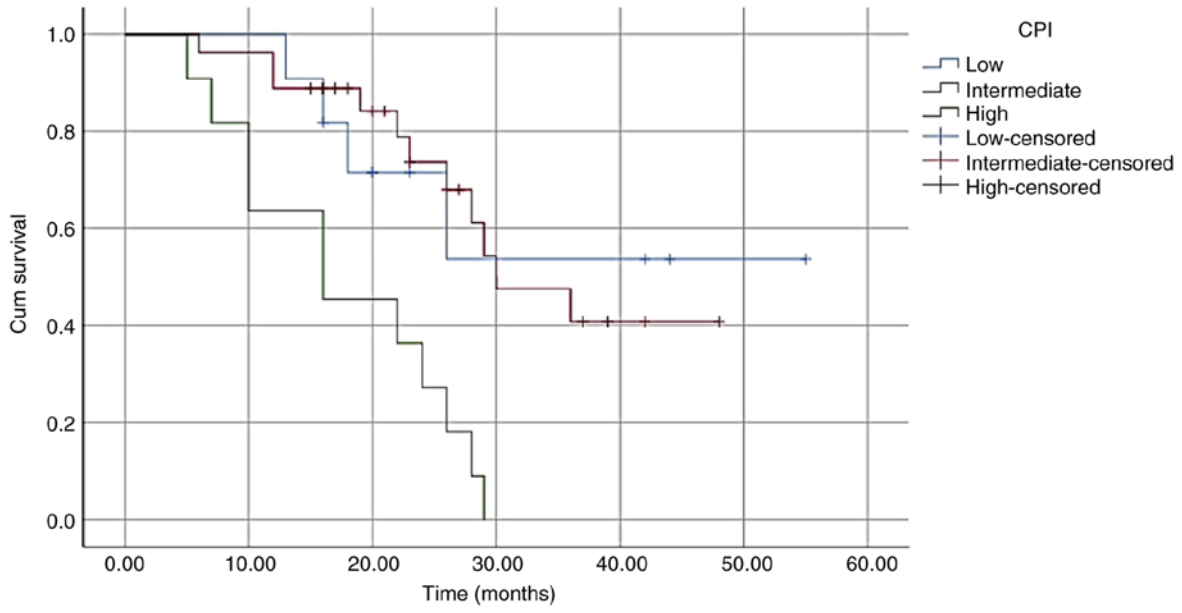

Figure 3. Patient overall survival curve according to the CPI in the group with bone marrow plasma cell counts ≥30%. CPI, combined prognostic index (which included the serum calcium levels, the neutrophil-to-lymphocyte ratio and the platelet count).

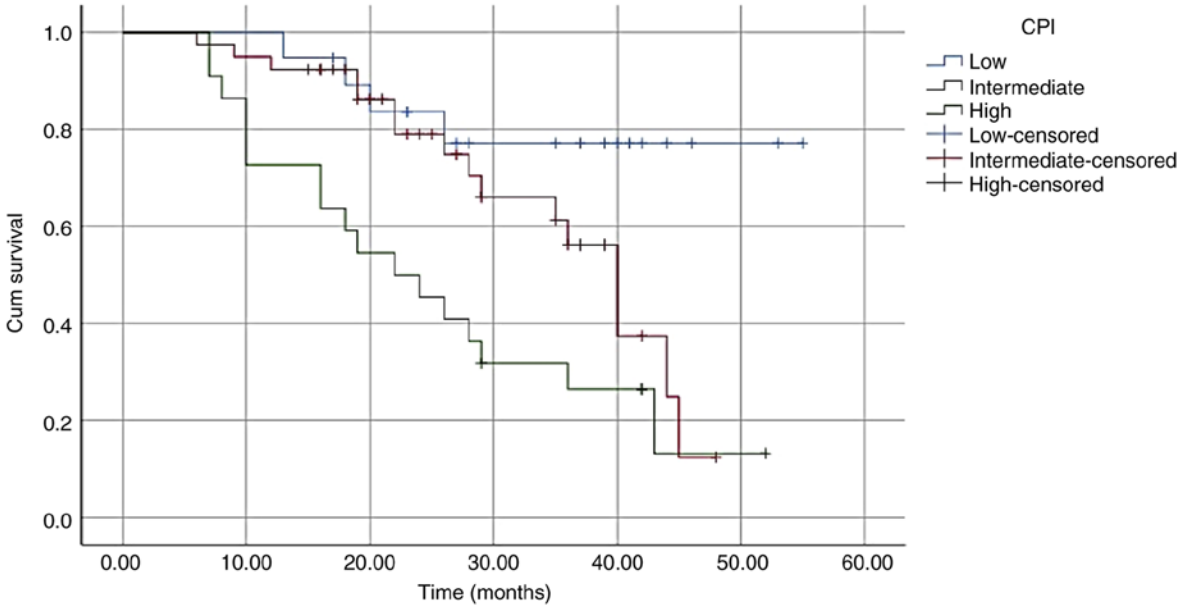

Figure 4. Patient overall survival curve according to the CPI in the group with an age <65 years. CPI, combined prognostic index (which included the serum calcium levels, the neutrophil-to-lymphocyte ratio and the platelet count).

MM. Inflammatory factors have a substantial impact on the tumor microenvironment and in tumor progression; therefore, they are related to the prognosis of patients with malignant diseases (25). Inflammation-related indices derived from peripheral blood cells, including NLR, PLR and MLR, are considered prognostic biomarkers (8).

The majority of the studies have agreed on the prognostic value of NLR. Zhang *et al* (8), Liu *et al* (9), Kim *et al* (10), Szudy-Szczyrek *et al* (11) and Zuo *et al* (12) suggested that a high NLR was an adverse prognostic factor; however, no consensus was reported on its cut-off value (8-12). These cut-off values ranged from 2 to 3.1 (9-12). The data of the present study indicated that a high NLR (2.245) was an independent prognostic factor for a poor survival rate of patients with MM.

Platelets are an important factor involved in the development of inflammation. Multiple inflammatory elements are present in platelets, which can activate innate immune cells and stimulate the endothelium. Platelets interact with leukocytes and support their interaction with the vessel wall, which enables their migration to the tissues (26). In various cancer types, platelets protect metastatic cancer cells from surveillance by natural killer (NK) cells. They also reduce the beneficial effects of immunotherapy (27). Therefore, the role of platelets in the prognosis of MM is very complex. An increase

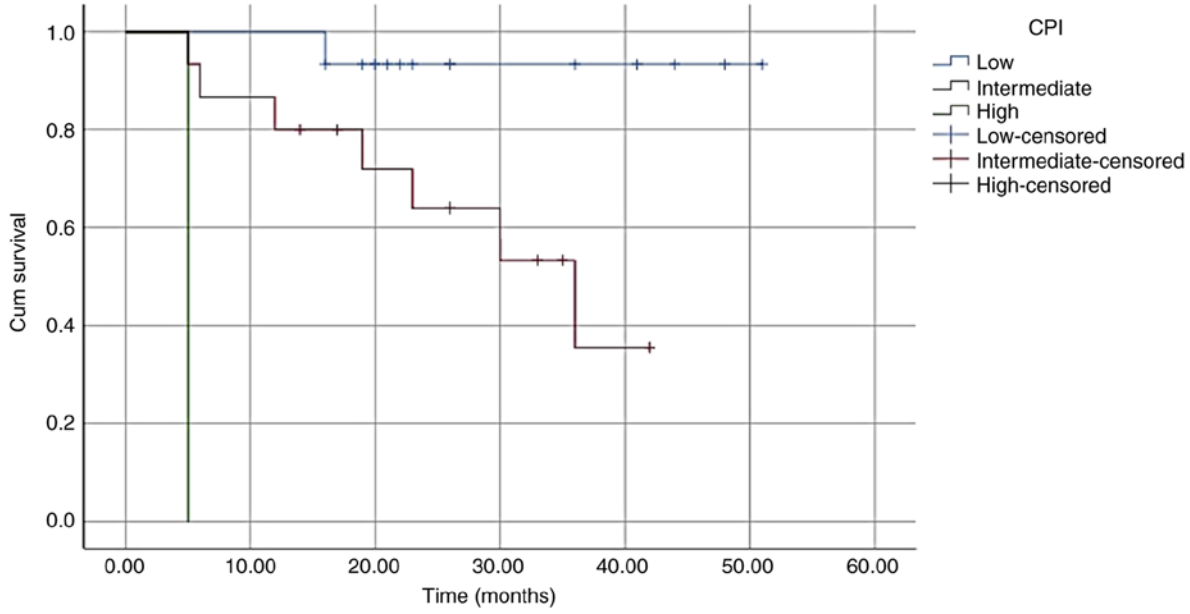

Figure 5. Patient overall survival curve according to the CPI in the group with an age ≥65 years. CPI, combined prognostic index (which included the serum calcium levels, the neutrophil-to-lymphocyte ratio and the platelet count).

or decrease in platelet levels has been considered to be a poor prognostic factor for MM. Previous studies by Liu *et al* (9) and Kim *et al* (10) have demonstrated that a low platelet count (<150x10^9/l) is a poor prognostic factor in MM. The current study also indicated similar results. In contrast to these findings, Jung *et al* (20) considered a value below 100x10^9/l to be used as a prognostic factor for MM. However, a higher level of alert is required when assessing patient prognosis. A recent study by Mellors *et al* (28) indicated that following two cycles of chemotherapy treatment with novel agents, patients with MM and thrombocytopenia (<150x10^9/l) exhibited worse OS and PFS survival rates than those of patients who maintained a platelet count ≥150x10^9/l.

The combination of the prognostic factors can be used to establish an accurate prognostic system. This has been a challenge for several studies that have investigated MM (9,10,15,16). In addition to the successful prognostic systems that have been recognized for several years, such as the ISS or the R-ISS, novel valuable systems are currently investigated, notably those that exhibit potential applications with novel treatment regimens.

Kim *et al* (10) demonstrated that the MPI value included the following parameters: NLR, platelet count and CRP for patients with MM. The MPI applies to conventional chemotherapy, as well as to novel agents (10). Liu *et al* (9) identified the value of IPSI including the following parameters: NLR, PLT and RDW. IPSI supports the use of ISS by further dividing the subgroups at each disease stage (9). The present study focused on providing a prognostic scale (CPI) that combines simple pathological factors. Serum calcium levels may be an indicator of the tumor growth. The NLR is an inflammatory marker that affects the tumor microenvironment and tumor progression. Platelets protect cancer cells from NK cells and may reverse the effects of immunotherapy. These indices are easy to evaluate and not expensive. Furthermore, the CPI was also applicable to all subgroups of patients regardless of the percentage of bone marrow plasma cells (≥30 or <30%) and the age (≥65 or <65 years).

The present study exhibits certain limitations. Firstly, it was not performed on a group of patients who had received autologous stem cell transplantation. Secondly, this was merely an initial research study and additional studies with a larger number of patients who will be treated with novel drugs need to be conducted in the future.

In conclusion, the present study demonstrates that the CPI, which comprises high serum calcium levels, a high NLR and a low PLT, can be used as an independent prognostic factor for patients with MM. The combination of the prognostic factors can be used to establish an accurate prognostic system. As it is the result of a combination of factors, it is more predictive than using each factor individually. Moreover, the usage is also very simple and convenient.

Acknowledgements

The authors would like to thank Dr Duc Anh Nguyen, from the Hanoi Obstetrics and Gynecology Hospital, Hanoi, Vietnam, for his efforts in supporting the research. The present study was carried out at the Center of Hematology and Blood Transfusion, Bach Mai Hospital, Hanoi, Vietnam.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MPV conceived the study. MPV and VTH designed the study. VTH, PTP and HV were involved in data collection and processing. MPV, VTH, PTP and HV were involved in data analysis and interpretation, as well as in the literature search. MPV was involved in the writing of the manuscript. MPV and VTH confirm the authenticity of the all raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Ethical Committee in Hanoi Medical University (no. 187). Patient consent was waived by the committee as the present study was a retrospective observational study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that have no competing interests.

References

1. Fairfield H, Falank C, Avery L and Reagan MR: Multiple myeloma in the marrow: Pathogenesis and treatments. Ann N Y Acad Sci 1364: 32-51, 2016.
2. Wallington-Beddoe CT and Mynott RL: Prognostic and predictive biomarker developments in multiple myeloma. J Hematol Oncol 14: 151, 2021.
3. Bustoros M, Mouhieddine TH, Detappe A and Ghobrial IM: Established and novel prognostic biomarkers in multiple myeloma. Am Soc Clin Oncol Educ Book 37: 548-560, 2017.
4. Afram G, Gran C, Borg Bruchfeld J, Wagner AK, Hussein A, Alici E and Nahi H: Impact of performance status on overall survival in patients with relapsed and/or refractory multiple myeloma: Real-life outcomes of daratumumab treatment. Eur J Haematol 105: 196-202, 2020.
5. Cai Y, Zhao Y, Dai Q, Xu M, Xu X and Xia W: Prognostic value of the albumin-globulin ratio and albumin-globulin score in patients with multiple myeloma. J Int Med Res 49: 300060521997736, 2021.
6. Qian J, Jin J, Luo H, Jin C, Wang L, Qian W and Meng H: Analysis of clinical characteristics and prognostic factors of multiple myeloma: A retrospective single-center study of 787 cases. Hematology 22: 472-476, 2017.
7. Chen R, Zhang X, Gao C, Luan C, Wang Y and Chen B: Treatment and prognostic factors for survival in newly diagnosed multiple myeloma patients with bortezomib and dexamethasone regimen: A single Chinese center retrospective study. Cancer Manag Res 9: 373-380, 2017.
8. Zhang X, Duan J, Wen Z, Xiong H, Chen X, Liu Y, Liao K and Huang C: Are the derived indexes of peripheral whole blood cell counts (NLR, PLR, LMR/MLR) clinically significant prognostic biomarkers in multiple myeloma? A systematic review and meta-analysis. Front Oncol 11: 766672, 2021.
9. Liu S, Shi J, Guo H, Xu F, Wei M, Sun K and Chen Y: Prognostic significance of the inflammatory index-based scoring system in patients preliminarily diagnosed with multiple myeloma in the bortezomib-based chemotherapy era. Cancer Manag Res 11: 9409-9420, 2019.
10. Kim DS, Yu ES, Kang KW, Lee SR, Park Y, Sung HJ, Choi CW and Kim BS: Myeloma prognostic index at diagnosis might be a prognostic marker in patients newly diagnosed with multiple myeloma. Korean J Intern Med 32: 711-721, 2017.
11. Szudy-Szczyrek A, Mlak R, Mielnik M, Szczyrek M, Nowaczyńska A, Homa-Mlak I, Zmorzyński S, Kuśmierczuk K, Sompor J, Filip A, *et al*: Prognostic value of pretreatment neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in multiple myeloma patients treated with thalidomide-based regimen. Ann Hematol 99: 2881-2891, 2020.
12. Zuo H, Zhai L, Liu X, Gao H and Xu P: Prognostic significance of neutrophil-lymphocyte ratio in multiple myeloma patients. Transl Cancer Res 7: 88-96, 2018.
13. Gui L, Wang F, Shi J and Chen B: The significance of inflammatory markers in the prognosis of newly diagnosed multiple myeloma patients. Blood 136 (Suppl 1): S15, 2020.
14. Solmaz S, Uzun O, Acar C, Sevindik OG, Piskin O, Ozsan HG, Demirkan F, Undar B, Alacacioglu A, Ozcan MA and Alacacioglu I: Is the platelet-to-lymphocyte ratio a new prognostic marker in multiple myeloma? J Lab Physicians 10: 363-369, 2018.
15. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J, Boccadoro M, Child JA, Avet-Loiseau H, Kyle RA, *et al*: International staging system for multiple myeloma. J Clin Oncol 23: 3412-3420, 2005.
16. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, Richardson P, Caltagirone S, Lahuerta JJ, Facon T, *et al*: Revised international staging system for multiple myeloma: A report from international myeloma working group. J Clin Oncol 33: 2863-2869, 2015.
17. Rajkumar SV: Multiple myeloma: 2016 Update on diagnosis, risk-stratification, and management. Am J Hematol 91: 719-734, 2016.
18. Azam F, Latif MF, Farooq A, Tirmazy SH, AlShahrani S, Bashir S and Bukhari N: Performance status assessment by using ECOG (eastern cooperative oncology group) score for cancer patients by oncology healthcare professionals. Case Rep Oncol 12: 728-736, 2019.
19. Garderet L, D'Souza A, Jacobs P, van Biezen A, Schönland S, Kroeger N, Morris C and Hari P: Response assessment in myeloma: Practical manual on consistent reporting in an era of dramatic therapeutic advances. Biol Blood Marrow Transplant 23: 1193-1202, 2017.
20. Jung SH, Cho MS, Kim HK, Kim SJ, Kim K, Cheong JW, Kim SJ, Kim JS, Ahn JS, Kim YK, *et al*: Risk factors associated with early mortality in patients with multiple myeloma who were treated upfront with a novel agents containing regimen. BMC Cancer 16: 613, 2016.
21. Deftos LJ: Hypercalcemia in malignant and inflammatory diseases. Endocrinol Metab Clin North Am 31: 141-158, 2002.
22. Oyajobi BO: Multiple myeloma/hypercalcemia. Arthritis Res Ther 9 (Suppl 1): S4, 2007.
23. Zagouri F, Kastritis E, Zomas A, Terpos E, Katodritou E, Symeonidis A, Delimpasi S, Pouli A, Vassilakopoulos TP, Michalis E, *et al*: Hypercalcemia remains an adverse prognostic factor for newly diagnosed multiple myeloma patients in the era of novel antimyeloma therapies. Eur J Haematol 99: 409-414, 2017.
24. Cheng J, Zhang W, Zhao Y, Li X, Lv R, Li H and Chen J: Association of serum calcium levels with renal impairment and all-cause death in Chinese patients with newly diagnosed multiple myeloma: A cross-sectional, longitudinal study. Nutr Metab (Lond) 18: 19, 2021.
25. Greten FR and Grivennikov SI: Inflammation and cancer: Triggers, mechanisms and consequences. Immunity 51: 27-41, 2019.
26. Arman M, Payne H, Ponomaryov T and Brill A: Role of Platelets in Inflammation. Intechopen, 2015. https://www.intechopen.com/chapters/48530.
27. Karachaliou N, Pilotto S, Bria E and Rosell R: Platelets and their role in cancer evolution and immune system. Transl Lung Cancer Res 4: 713-720, 2015.
28. Mellors P, Binder M, Buadi FK, Lacy MQ, Gertz MA, Dispenzieri A, Hayman SR, Kapoor P, Gonsalves WI, Hwa Y, *et al*: Development of thrombocytopenia and survival outcomes in newly diagnosed multiple myeloma. Blood 132 (Suppl 1): S1902, 2018.