RESEARCH ARTICLE

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The Relationship between Changes in Serum Element Concentrations and Pathological Condition and Disease Status in Japanese Multiple Myeloma Patients: A Pilot Study and Literature Review

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Abstract

Background: Multiple myeloma (MM) is a rare cancer, and information on its pathological condition and serum element levels is lacking. In this pilot study, we examined serum element concentrations in Japanese patients with MM by a comprehensive multi-element analysis. **Methods:** This is a case-control study of 12 Japanese patients diagnosed with MM at the Nagoya City University Hospital between 2008 and 2013. Blood samples were taken, at the initial diagnosis and at relapse. The serum concentrations of 12 elements were analyzed by inductively coupled plasma mass spectrometry and compared between MM patients and non-MM volunteers. We also analyzed the correlation between serum element concentrations and laboratory values related to disease status and tumor volume of MM. **Results:** We found that serum chromium (Cr), copper (Cu), molybdenum (Mo), and barium (Ba) concentrations were significantly increased in MM patients. Ba was significantly increased in MM patients, suggesting an association with bone lesions. There was no consistent trend between these elements and existing indices related to MM tumor volume and disease status. **Conclusions:** Although this is a pilot study, serum Cr, Cu, Mo, and Ba concentrations were found to be significantly elevated in MM patients. Further studies with large sample sizes are needed, since the changes in serum concentrations of these elements may reflect the pathological condition of MM.

Keywords: Multiple myeloma- serum- elements- pathological condition- bone

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Introduction

Multiple myeloma (MM) is a rare hematological cancer, accounting for approximately 1% of all cancers (Kazandjian 2016; Siegel et al., 2020). MM is characterized by the monoclonal proliferation of plasma cells with abnormal hematopoiesis, increased immunoglobulins called M-proteins, hypercalcemia, decreased renal function, anemia, and bone lesions. Bone lesions cause pain and decrease quality of life and have a negative impact on life expectancy (Zhang and Zhuang, 2022).

Trace elements in the body are well-balanced and play an important role in maintaining normal life functions (Wada, 2004; Nishito and Kambe, 2018; Mehri, 2020). Serum element concentrations have been shown to change in patients with leukemia and lymphoma (Stevens et al., 2011; Azarm et al., 2013; Shen et al., 2023). It has been reported that patients with acute leukemia have higher serum copper (Cu) concentrations and lower serum zinc (Zn) concentrations than healthy individuals, and the serum Cu concentration and Cu to Zn ratio (Cu/Zn ratio) are associated with survival in patients with acute leukemia (Demir et al., 2011; Li et al., 2023). Similarly, decreased serum Zn concentration and increased Cu

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concentration and Cu/Zn ratio have been reported in MM patients (Khadem-Ansari et al., 2018). It has also been reported that abnormal iron (Fe) metabolism is involved in anemia in MM (VanderWall et al., 2013), that serum Fe concentration affects the therapeutic efficacy of bortezomib (Campanella et al., 2013; Camiolo et al., 2020), and that there is a correlation between selenium (Se) levels and the risk of developing MM (Yuan et al., 2022). However, no studies have analyzed multiple element concentrations simultaneously in MM patients. Additionally, although MM is likely to relapse after remission, changes in serum element concentrations between initial diagnosis (newly diagnosed: ND) and relapse (relapsed and/or refractory: RR) in the same patient are not clear.

Therefore, as a pilot study, we aimed to investigate changes in serum element concentrations in Japanese MM patients by multi-element exhaustive analysis and to compare the levels in MM patients and those in non-MM volunteers. We also compared serum element concentrations of the same MM patients at diagnosis and relapse.

Materials and Methods

This study was approved by the Ethics Committee of Nagoya City University Graduate School of Medical Sciences (60-00-1118) and the Epidemiological Ethics Review Committee of the Aichi Prefectural Institute of Public Health (18E-07). Informed consent was obtained from all study participants in accordance with the Helsinki Declaration.

Study participants

The study was designed as a case-control study. We included 12 Japanese patients (5 men and 7 women) diagnosed with MM between 2008 and 2013 at the Nagoya City University Hospital. Patients who underwent blood transfusion prior to blood collection were excluded. Samples were collected from the same patients at diagnosis and at relapse. The control group included 9 volunteers (5 men and 4 women). Controls were recruited from non-MM volunteers of similar age and sex as the patients in the MM group, and those with hepatic or renal disease that could affect serum element concentrations were excluded. The administration of medication in the control group was confirmed through interviews with participants.

For each MM patient, information on age, sex, disease type, stage according to the Durie-Salmon Staging System (Durie and Salmon, 1975) and the International Staging System for MM (Greipp et al., 2005), common myeloma-related cytogenetic abnormalities, various laboratory values, dietary intake status, bone lesions based on computed tomography (CT) or magnetic resonance imaging (MRI), and medications was obtained from medical records. We also analyzed the correlation between serum element concentrations and laboratory values related to disease status and tumor volume. The control group did not include any patient treated at the study site. Hence, there were no laboratory data available for this study.

Measurement of serum element concentrations and their relation to MM

To examine the relationship between the development of MM and serum element concentrations, we compared the differences in serum concentrations of each element between the control and MM groups. We targeted 12 elements (chromium [Cr], manganese [Mn], Fe, Cu, Zn, arsenic [As], Se, rubidium [Rb], strontium [Sr], molybdenum [Mo], antimony [Sb], and barium [Ba]). Preliminary tests confirmed that these elements had good measurement accuracy.

In all study participants, blood was collected before breakfast at fasting status. In all MM patients, blood samples were taken during hospitalization, and they were put on a hospital diet of a certain caloric and nutritional composition. After blood collection, serum was separated, and stored frozen until element concentrations were determined. The Insepack®II-D (Kyokuto Pharmaceutical Industrial, Tokyo, Japan) blood collection tube was used for the control and MM groups. Since the specimens were stored, their element concentrations were compared in a preliminary experiment with those of specimens collected using BD Vacutainer® (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) blood collection tubes, which are blood collection tubes for testing trace elements, to confirm that there was no elution of the target elements. The samples were diluted (1 + 99) in nitric acid and filtered through a 0.45-μm membrane filter if insoluble material was present. Element concentrations were measured using inductively coupled plasma mass spectrometry (ICP-MS; 7800, Agilent Technologies, Santa Clara, CA, USA). The reagents used were nitric acid 1.38 (Kanto Chemical, Tokyo, Japan) and ICP-MS mixing standard XSTC-622 (SPEX CertiPrep, Metuchen, NJ, USA).

Statistical analysis

For samples with element concentrations below the lower limit of quantification (0.20 μg/L), half the lower limit of quantification, 0.10 μg/L, was used for statistical processing. Steel's method was used to compare controls and MM patients (at diagnosis and relapse), and the Wilcoxon signed-rank test was used to compare MM patients at diagnosis and at relapse (the ND and RR groups, respectively). Correlation coefficients were determined using Spearman's correlation coefficient. Differences were considered significant at $P < 0.05$. Statistical analyses were performed using the SPSS software package (version 17.0, SPSS Inc., Chicago, IL, USA) and EZR (version 1.54, Saitama Medical Center, Jichi Medical University, Saitama, Japan) (Kanda, 2013).

Results

Patient information

The baseline characteristics of the study participants are presented in Table 1. The mean age of the control group was 66.6 ± 14.7 years, and the mean ages of the MM patients at diagnosis and relapse were 64.0 ± 10.3 years and 65.8 ± 10.1 years, respectively. Based on the radiologist's evaluation by CT or MRI, bone lesions were found in 10 of 12 MM patients at diagnosis. Two patients

Table 1. Patient Clinical Characteristics

	Mean ± S.D. or No. (%)		
	Control (n = 9)	MM patients (n = 12)	
		ND	RR
Age, years	66.6 ± 14.7	64.0 ± 10.3	65.8 ± 10.1
Sex			
Male	5 (55.6)	5 (41.7)	
Female	4 (44.4)	7 (58.3)	
MM disease type			
IgA		3 (25.0)	
IgG		5 (41.7)	
BJP		4 (33.3)	
Durie-Salmon Staging System stage (At initial diagnosis)			
Stage II		1 (8.3)	
Stage III		7 (58.3)	
Not listed		4 (33.3)	
International Staging System stage (At initial diagnosis)			
Stage I		2 (16.7)	
Stage II		3 (25.0)	
Stage III		5 (41.7)	
Not listed		2 (16.7)	
Common myeloma-related cytogenetic abnormalities			
t(11;14)		3 (25.0)	
t(4;14)		3 (25.0)	
t(14;16)		2 (16.7)	
No cytogenetic abnormalities		4 (33.3)	
Bone lesions (At initial diagnosis)			
Presence		10 (83.3)	
Absence		2 (16.7)	
Treatment history for MM until relapse			
1 regimen (MPB or BD)		4 (33.3)	
2 regimens (MP and LD)		1 (8.3)	
Auto-SCT		7 (58.3)	
Days from start of initial treatment to relapse		660 ± 247	
Concomitant medications at the time of blood collection (duplicate)			
Antihypertensive	6 (66.7)	4 (33.3)	6 (50.0)
Antihyperlipidemic	5 (18.5)	1 (8.3)	3 (25.0)
Antiosteoporosis	1 (11.1)	2 (16.7)	3 (25.0)
	(Raloxifene +Alfacalcidol)	(Alfacalcidol +Risedronate, or Elcatonin)	(Alendronate, or Zoledronate)
Normal hydration (≤1500mL/day) [a)]	0 (0)	2 (16.7)	1 (8.3)
Others [b)]	5 (18.5)	10 (83.3)	11 (91.7)

BD, bortezomib + dexamethasone; BJP, Bence Jones protein; IgA, immunoglobulin A; IgG, immunoglobulin G; LD, lenalidomide; MM, multiple myeloma; MP, melphalan + predonisolone; MPB, melphalan + prednisolone + bortezomib; ND, newly diagnosed; RR: relapsed and/or refractory; SCT, stem-cell transplantation; S.D, standard deviation. a), Contains only Na and K and no Ca; b), Specific medications including the following: adrenocortical hormone, analgesic, anti-allergic, antianginal, antibiotics, antidiabetic, antigout, anti-platelet, antiulcer, diabetic neuropathy, insomnia and anxiety, laxative.

had no obvious bone lesions at diagnosis or relapse. There were no grade 3 cases of decreased dietary intake (limitation of self-care activities of daily living) (National Cancer Institute, 2017).

Table 2 shows the median and range of the laboratory values of the ND and RR groups. Laboratory values for calcium (Ca) were defined as albumin-adjusted Ca values. Laboratory Ca values, hemoglobin (Hb) levels, and the free light chain (FLC) ratio were significantly different between the ND and RR groups, but there was no

Table 2. Laboratory Values in MM Patients

	Median (Min-Max)		
	ND (n = 12)	RR (n = 12)	P-value
Calcium (mg/dL)	10.1 (9.5–14.0)	9.6 (8.5–10.7)	0.031*
Serum creatinine (mg/dL)	0.8 (0.3–3.0)	0.8 (0.5–2.1)	0.240
Blood urea nitrogen (mg/dL)	13 (9–46)	16 (8–35)	0.476
Blood urea nitrogen/serum creatinine ratio	18 (10-42)	18 (10-32)	0.875
Uric acid (mg/dL)	6.5 (2.9–10.2)	4.9 (3.0–6.7)	0.139
Estimated glomerular filtration rate (mL/min/1.73 m^2)	68.1 (15.6–163.0)	66.8 (19.5–101.1)	0.937
Hemoglobin (g/dL)	9.6 (7.8–12.6)	11.8 (8.2–14.3)	0.041*
β2 microglobulin (μg/mL)	5.3†††† (1.8–12.9)	3.7 †††(2.2–8.4)	0.208
Total protein (g/dL)	8.4 (6.0–12.5)	7.6 (5.7–9.5)	0.060
Albumin (g/dL)	3.7 (2.2–4.2)	3.9 (3.4–4.5)	0.059
Lactate dehydrogenase (U/L)	191 (78–473)	181 (136–260)	0.937
Free light chain ratio	81.3† (1.5-2154.5)	51.5† (8.5-1000)	0.043*
Urine protein (mg/day)	903†† (24-10074)	1358† (127-4987)	0.893
Ratio of plasma cells in bone marrow (%)	31.4††† (3.0–89.2)	20.4††† (1.0–97.8)	> 0.999

MM, multiple myeloma; ND, newly diagnosed; RR, relapsed and/or refractory; †, n = 7; ††, n = 8; †††, n = 9; ††††, n = 10; * P < 0.05 ND vs. RR indicating a statistically significant difference.

difference between the two groups in the other laboratory values.

Changes in serum elemental concentrations

The serum concentrations of each element in the control and MM groups are shown in Table 3. Significant differences between the control and MM groups were observed for Cr, Cu, Mo, and Ba. The changes in concentration of each element in the ND and RR groups were analyzed, but no elements had significantly different serum levels. However, although the value was not significant for Cu, there was a tendency for it to be higher in the RR group than in the ND group (P = 0.060). The Cu/Zn ratio is shown in Table 3. There was no significant difference between the control and MM groups.

Correlation between serum element concentrations and various laboratory values

Figure 1 shows the correlations between serum Cr, Cu, Mo, and Ba concentrations and laboratory values related to disease state and tumor volume in patients with MM. Although the ND and RR groups consisted of the same patients, they were treated as separate cases because of the different tumor statuses, and the correlation was analyzed as though there were 24 patients. Due to lack of data, β2-microglobulin (β2MG) was analyzed in 19 patients, the FLC ratio in14, urine protein (UP) in 15, and the ratio of plasma cells in bone marrow in 18.

Table 3. Serum Element Concentrations in Controls and Multiple Myeloma (MM) Patients

	Median (Min-Max)			P-value		
	Control (n = 9)	MM patients (n = 12)				
		ND	RR	Control vs. ND	Control vs. RR	ND vs. RR
Cr (μg/L)	0.54 (0.47-0.67)	0.81 (<0.20-0.92)	0.66 (<0.20-1.11)	0.042*	0.198	0.695
Mn (μg/L)	0.63 (0.52-0.94)	0.54 (0.46-1.14)	0.58 (0.39-1.09)	0.344	0.686	0.875
Fe (mg/L)	1.09 (0.72-1.79)	0.92 (0.68-1.69)	0.88 (0.54-1.44)	0.406	0.326	0.754
Cu (mg/L)	0.91 (0.81-1.36)	0.91 (0.63-1.61)	1.09 (0.95-2.15)	0.966	0.035*	0.060
Zn (mg/L)	0.77 (0.55-0.84)	0.71 (0.36-1.27)	0.76 (0.63-1.12)	0.940	0.784	0.209
As (μg/L)	4.87 (0.84-7.23)	4.81 (2.06-13.72)	6.23 (1.00-16.25)	0.590	0.471	>0.999
Se (mg/L)	0.15 (0.10-0.20)	0.13 (0.11-0.24)	0.16 (0.11-0.21)	0.200	0.908	0.209
Rb (mg/L)	0.16 (0.12-0.23)	0.17 (0.11-0.19)	0.17 (0.09-0.23)	0.737	0.689	0.814
Sr (μg/L)	33.07 (22.66-60.56)	29.83 (21.30-49.34)	28.37 (20.58-57.84)	0.542	0.784	0.480
Mo (μg/L)	<0.20 (<0.20-1.36)	1.18 (<0.20-6.14)	0.98 (<0.20-2.95)	0.029*	0.014*	0.657
Sb (μg/L)	3.51 (1.87-3.74)	2.38 (1.75-4.20)	2.66 (2.03-4.88)	0.163	0.784	0.530
Ba (μg/L)	1.12 (0.45-1.60)	1.58 (1.00-2.65)	2.18 (1.24-2.69)	0.016*	0.002**	0.209
Cu/Zn	1.31 (1.07-1.67)	1.36 (0.70-2.67)	1.58 (0.95-2.80)	0.966	0.405	0.433

MM, multiple myeloma; ND, newly diagnosed; RR, relapsed and/or refractory; * P < 0.05, ** P < 0.01 vs. control, statistically significant difference. Steel's method was used to compare the controls and MM groups. Wilcoxon signed-rank test was used to compare the ND and RR groups

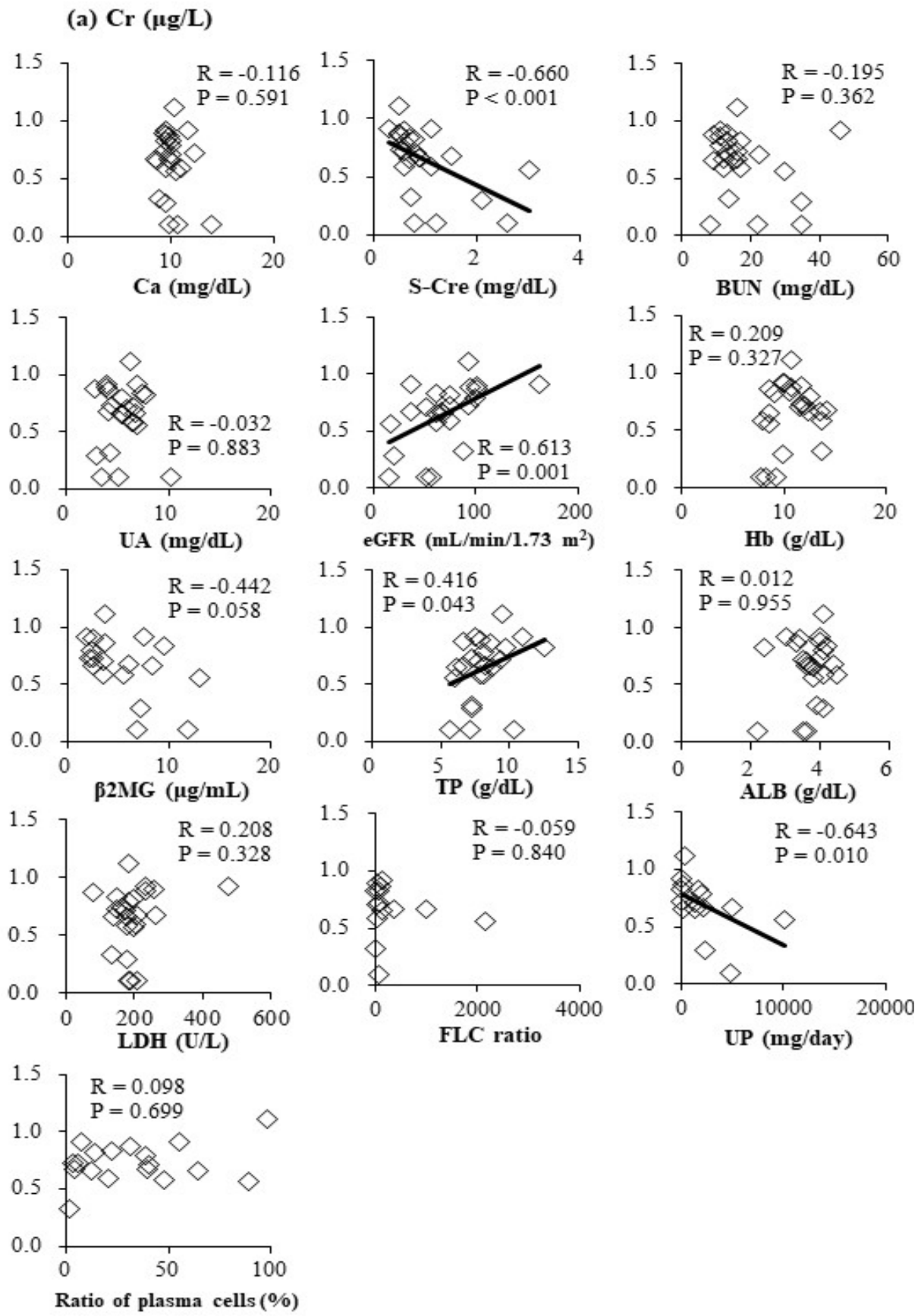
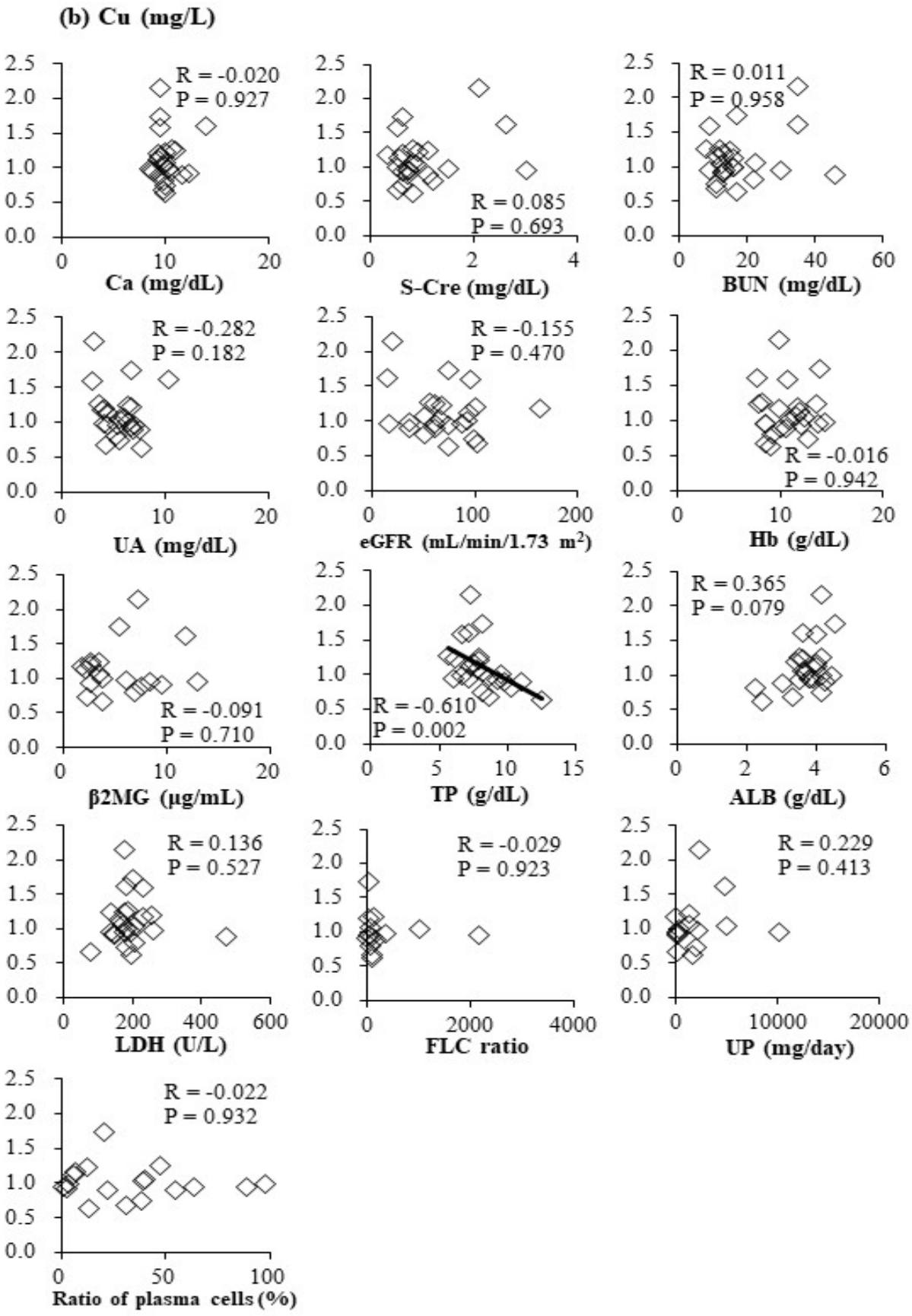


Figure 1. Correlation Plots between Cr, Cu, Mo, and Ba Serum Concentrations and Various Laboratory Values. Each plot shows the correlation between serum (a) Cr, (b) Mo, (c) Cu, and (d) Ba concentrations and various laboratory values in 12 patients with newly diagnosed (ND) and relapsed and/or refractory (RR) multiple myeloma (MM). Correlation coefficients were calculated using the Spearman's correlation coefficient. ALB, albumin; β2MG, β2 microglobulin; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; FLC, free light chain; Hb, hemoglobin; LDH, lactate dehydrogenase; S-Cre, serum creatinine; TP, total protein; UA, uric acid; UP, urine protein



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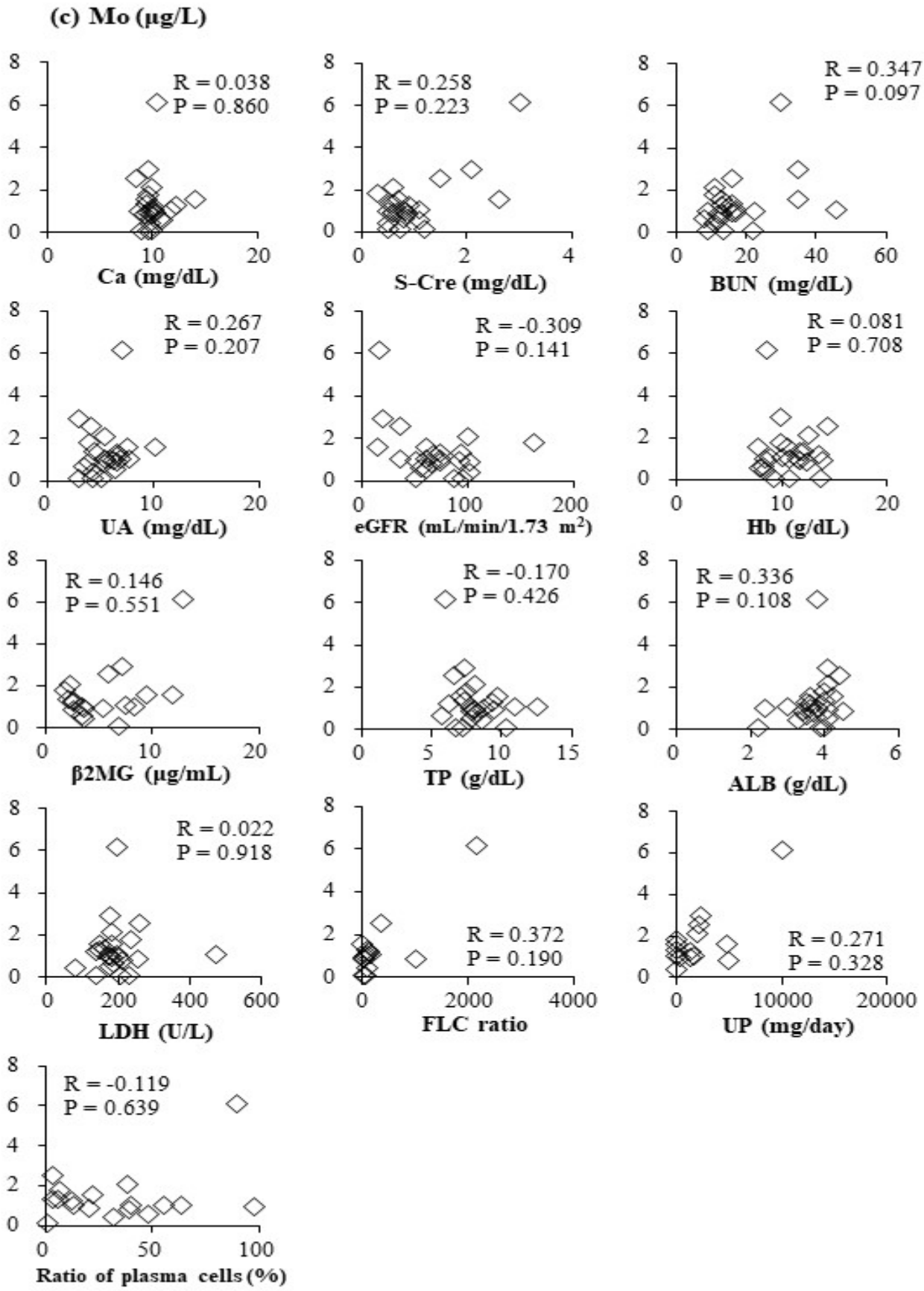

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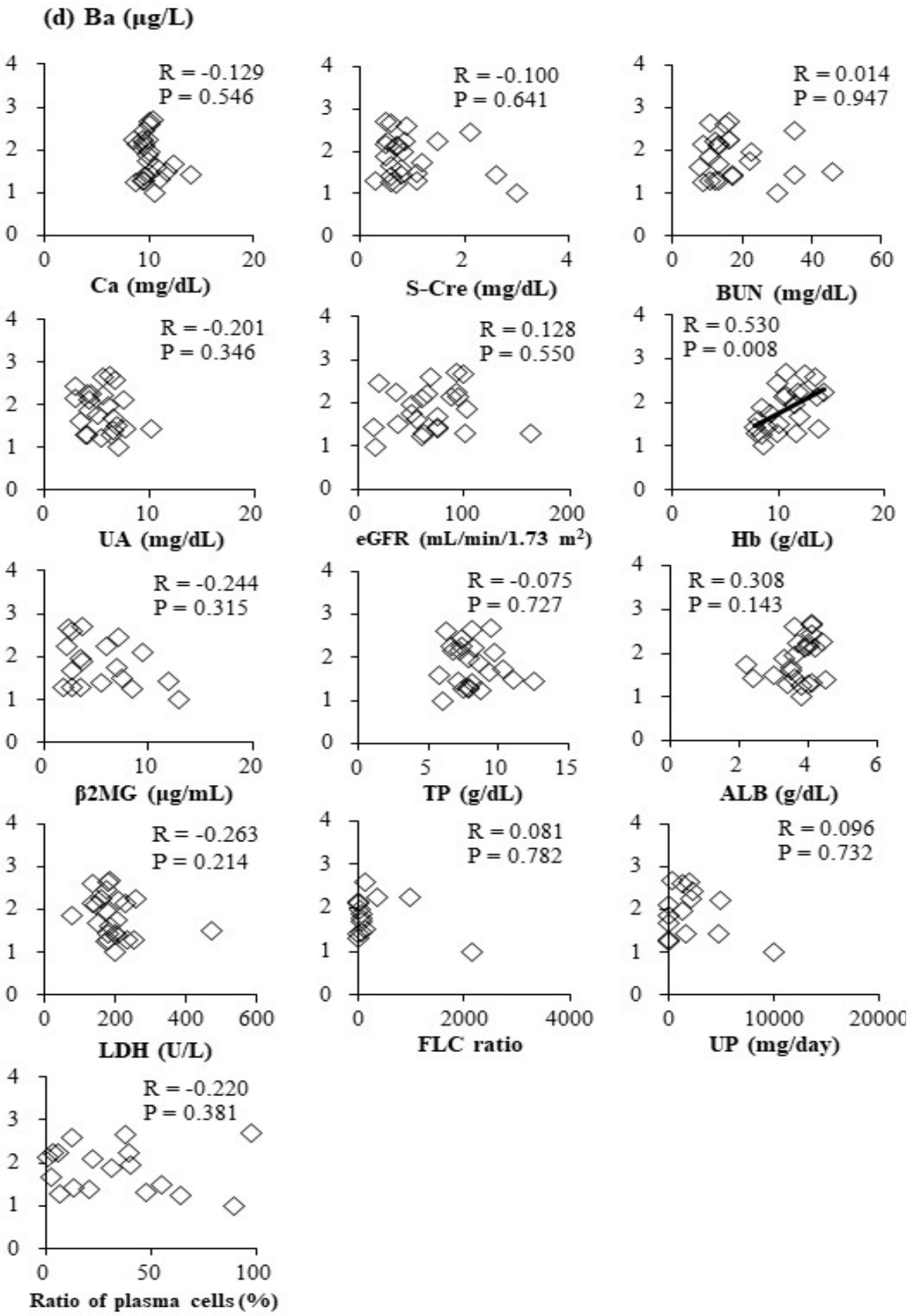

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Cr was negatively correlated with serum creatinine and UP levels ($P < 0.001$ and $P < 0.05$, respectively) and positively correlated with the estimated glomerular filtration rate and total protein (TP) levels ($P < 0.01$ and $P < 0.05$, respectively). Cu was negatively correlated with the TP level ($P < 0.01$). There were no significant correlations between Mo concentration and any laboratory values. Ba concentration was positively correlated with Hb level ($P < 0.01$).

Discussion

The present study is the first to comprehensively measure element concentrations in MM patients and investigate their relationship with pathological conditions. Moreover, it is rare to be able to analyze specimens from the same patient at both diagnosis and relapse, which makes this study unique and significant. The results showed that serum Cr, Cu, Mo, and Ba concentrations were significantly increased in MM patients compared to non-MM volunteers. Changes in serum concentrations of these elements may reflect the pathological condition of MM.

Ba is taken up from the plasma by the bone, and about 90% of the body's Ba is contained in the bone (World Health Organization, 1990; Kovrlija et al., 2021). Most MM patients show generalized osteopenia and osteolytic lesions during the course of the disease, and approximately 60% of MM patients develop pathological fractures (Melton et al., 2005; Silbermann and Roodman, 2013; Hiasa et al., 2021). In our study, 10 of the 12 patients in the MM group had bone lesions at diagnosis. Therefore, our results suggest that the concentration of Ba in MM may be a marker for the pathological condition, particularly reflecting bone lesions of MM. In this study, the association between the presence or absence or number and size of bone lesions and Ba concentration could not be evaluated because most of the patients in the MM group already had bone lesions at the time of diagnosis. Consequently, there may have been no significant difference in Ba concentration between the ND and RR groups. There were two patients who did not have clear bone lesions throughout the course of their disease and had Ba concentrations of 1.44 μg/L and 1.87 μg/L at diagnosis and 1.28 μg/L and 2.24 μg/L at relapse, respectively, which were not lower than those of patients with bone lesions. Another two patients had bone lesions at diagnosis but no obvious bone lesions at relapse. In one patient, the Ba increased from diagnosis to relapse (from 1.74 μg/L to 2.13 μg/L), whereas in the other, the Ba concentration decreased (from 2.15 μg/L to 1.60 μg/L). Although there was no consistent trend in the ND and RR groups, the serum Ba concentration was significantly higher in the MM group than in the control group. These results suggest that higher serum Ba concentrations may be related to bone lesions that were not detected by CT or MRI; however, a larger sample size is needed to confirm this. Nevertheless, being able to determine the exact time to start treatment based on the serum Ba concentration would be extremely beneficial.

Ba, like Ca, is an alkaline earth element. Ca is a major component of the bone. In the present case, two patients at diagnosis and three at relapse received bisphosphonates or elcatonin, and serum Ca concentrations were decreased by the drugs. Hypercalcemia is a major manifestation of MM that is often treated by medication as, it causes clinical symptoms that affect quality of life, such as nausea, vomiting, and anorexia. It is speculated that the administration of such medications is one of the reasons why laboratory Ca values were lower in the RR group than in the ND group. The mechanism by which Ba accumulates in the bone remains unclear. It has been reported that Ba^{2+} has a larger ionic radius than Ca^{2+} and is more likely to be eliminated during the recrystallization process of hydroxyapatite (Bligh and Taylor, 1963). Therefore, Ba is likely deposited in the bone by another mechanism. It is possible that Ba is adsorbed on the bone surface in the form of colloidal particles by reaction with phosphate groups (Bligh and Taylor, 1963; Kovrlija et al., 2021). This difference in distribution in the bone may be why we observed a difference in the serum Ba concentration, but not in the Ca concentration, between the control and MM groups.

Cu is an essential element and is involved in a variety of physiological actions as a cofactor for many enzymes, including oxidoreductases (Tsang et al., 2021). It has been shown that Cu is involved in tumor initiation, growth, and metastasis (Cheng et al., 2022). A study from Iran reported increased serum Cu concentrations and decreased serum Zn concentrations in patients with stage I MM (Khadem-Ansari et al., 2018). Cu and Zn are part of the active site of superoxide dismutase (SOD) (Banks and Andersen, 2019). Khadem-Ansari et al. (2018) also reported a decrease in Cu/Zn SOD activity in patients with stage I MM. In our study, no significant changes in Zn concentration or the Cu/Zn ratio were observed in patients with MM, but an increase in Cu concentration was observed. Cu concentrations were higher in the RR group than in the ND group, but this was not significant. This trend suggests that Cu can be useful as a marker for relapse. It is not clear why no change in Zn concentration was observed in our study. One of the factors may be that our study included patients with various stages of disease. Future studies should examine larger cohorts.

Cr has been reported to be carcinogenic (Kawanishi et al., 1986; Nickens et al., 2010; Balali-Mood et al., 2021). In occupationally exposed individuals, an increased risk of developing various malignancies has been reported (Hara et al., 2010; Deng et al., 2019). In the present study, no patients had information on exposure to high concentrations of Cr. No previous studies have examined the mechanism by which increased Cr is associated with MM; changes in Cr concentration may be due to MM symptoms or changes in the general condition.

Mo is an essential element in humans and is present in the active sites of enzymes such as xanthine oxidase, sulfite oxidase, and aldehyde oxidase (Komada et al., 1990; Forrer et al., 2001). The reason for the elevated Mo concentration in MM patients in this study was not clear, and no prior reports have examined this, but this, increase in Mo may reflect changes in pathological condition and systemic status in MM.

This study had several limitations. It was a small pilot study of 12 patients with MM, and a larger prospective observational study that includes presence and extent of bone lesions and high and low tumor volume would be needed to investigate the roles of changes in serum element concentrations in the pathogenesis of MM, especially in accurately assessing the association between Ba and bone lesions. In addition, for the control group, a large group of individuals without MM should be established for which detailed information, including laboratory values, can be collected. The relationship between the pathological condition of MM and trace elements may be further clarified by examining patients with various stages of MM, such as the remission stage after primary treatment for MM. However, no previous studies examining this relationship exist, and this study may provide an opportunity to examine this relationship.

In conclusion, we found that serum Cr, Cu, Mo, and Ba concentrations were significantly increased in MM patients compared to non-MM volunteers, suggesting a relationship between the pathological condition of MM and elemental concentrations. Future studies with large sample sizes are needed to investigate this trend.

Author Contribution Statement

Y.Y., M.K., Y.H., Y.T., M.R., H.K., and K.K. were involved in the conception and design of the study. Y.Y. and M.K. obtained the data. M.K and Y.T. were involved in participant recruitment. Y.Y. drafted the manuscript. M.K., Y.H., Y.T., A.S., T.K., Y.F., M.R., H.K., S.I. and K.K. revised the manuscript. All authors read the manuscript and approved the final version.

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This study did not rely on any external sources of funding.

Student Thesis

Not applicable

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethics approval

This study was approved by the Ethics Committee of Nagoya City University Graduate School of Medical Sciences (60-00-1118) and the Epidemiological Ethics Review Committee of the Aichi Prefectural Institute of Public Health (18E-07). Informed consent was obtained from all study participants in accordance with the Helsinki Declaration.

Availability of data

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

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