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# Role of BMI and age in predicting pathologic vertebral fractures in newly diagnosed multiple myeloma patients: A retrospective cohort study

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## Abstract

Vertebral fractures affect approximately 30% of myeloma patients and lead to a poor impact on survival and life quality. In general, age and body mass index (BMI) are reported to have an important role in vertebral fractures. However, the triangle relationship among age, BMI, and vertebral fractures is still unclear in newly diagnosed multiple myeloma (NDMM) patients.

This study recruited consecutive 394 patients with NDMM at Taipei Veterans General Hospital between January 1, 2005 and December 31, 2015. Risk factors for vertebral fractures in NDMM patients were collected and analyzed. The survival curves were demonstrated using Kaplan-Meier estimate. In total, 301 (76.4%) NDMM patients were enrolled in the cohort. In the median follow-up period of 18.0 months, the median survival duration in those with vertebral fractures ≥ 2 was shorter than those with vertebral fracture < 2 (59.3 vs 28.6 months; $P = 0.017$). In multivariate Poisson regression, BMI < 18.5 kg/m$^2$ declared increased vertebral fractures compared with BMI ≥ 24.0 kg/m$^2$ (adjusted RR, 2.79; 95% CI, 1.44–5.43). In multivariable logistic regression, BMI < 18.5 kg/m$^2$ was an independent risk factor for vertebral fractures ≥ 2 compared with BMI ≥ 24.0 kg/m$^2$ (adjusted OR, 6.05; 95% CI, 2.43–15.08). Among age stratifications, patients with both old age and low BMI were at a greater risk suffering from increased vertebral fractures, especially in patients > 75 years and BMI < 18.5 kg/m$^2$ (adjusted RR, 12.22; 95% CI, 3.02–49.40). This is the first study that demonstrated that age had a significant impact on vertebral fractures in NDMM patients with low BMI. Elder patients with low BMI should consider to routinely receive spinal radiographic examinations and regular follow-up.

**KEYWORDS**

age, BMI, multiple myeloma, survival, vertebral fracture

**Abbreviations:** ALKP, alkaline phosphatase; BMI, body mass index; CI, confidence interval; CT, computed tomography; DS, Durie-Salmon; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; LDH, lactate dehydrogenase; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; MRI, magnetic resonance imaging; NDMM, newly diagnosed multiple myeloma; OR, odds ratio; RR, risk ratio; β2M, β2-microglobulin

Yi-Lun Chen and Yao-Chung Liu contributed equally to this work.

  

## 1 | INTRODUCTION

Multiple myeloma (MM) accounts for 13% of hematological cancers.[1] Patients who suffered from MM usually present with bone lesions, anemia, renal impairment, and hypercalcemia. Approximately 80% of patients were diagnosed myeloma with osteolytic bone lesions.[1] Involvement of bone in MM occurred much more frequently than solid tumors, including breast and prostate cancer.[2] On top of that, MM patients have the highest probability of fractures, and those fractures lead to increased mortality.[3,4] There have been several literatures suggesting that low body mass index (BMI) is a potential predictor for increased osteoporotic fractures in general population[5,6] and skeletal fractures both in breast and prostate cancer.[7,8] Low BMI is associated with loss of muscle strength which leads to increased vertebral fractures in patients with osteoporosis.[9,10] However, the relationship and survival between BMI and vertebral fracture risks in MM are less characterized in the literatures. Regarding the influence of quality of life and survival, it is important to identify the potential risk factors for vertebral fractures in MM patients. The goal of the study is to inform risk stratification and follow-up decisions. To investigate this issue, we thus designed the study.

## 2 | PATIENTS AND METHODS

### 2.1 | Patient population

This retrospective study conducted consecutive patients with newly diagnosed MM (NDMM) at Taipei Veterans General Hospital between January 1, 2005 and December 31, 2015. Individuals with solitary plasmacytoma, smoldering myeloma, and monoclonal gammopathy of undetermined significance (MGUS) were not included in this cohort. All patients were followed until either loss of follow-up, death, or June 2016. The study has been approved by Taipei Veterans General Hospital's Institutional Review Board (No. 2014-12-001AC).

Data were reviewed in a retrospective manner. Clinical characteristics including sex, age, BMI, Eastern Cooperative Oncology Group (ECOG) performing status, laboratory data, Durie-Salmon (DS) stage, and radiographic data were collected at the initial presentation of MM. Laboratory data included plasma cells percentage in bone marrow, hemoglobin level, platelet counts, serum albumin, corrected serum calcium, serum creatinine, lactate dehydrogenase (LDH), serum β2-microglobulin (β2M), and alkaline phosphatase (ALKP). Furthermore, all patients were divided into 3 subgroups, which were underweight (BMI < 18.5 kg/m$^2$), normal-weight (BMI = 18.5–23.9 kg/m$^2$), and overweight (BMI ≥ 24 kg/m$^2$), according to recommendations for Taiwanese adults from the Ministry of Health and Welfare of the Republic of China.[11]

### 2.2 | Radiographic reviews

A computed tomography (CT) scan, magnetic resonance imaging (MRI), or plain film radiography of spine was performed in NDMM patients, who suffered from low back pain or any radiculopathy and myelopathy symptoms. Patients were excluded if they did not have spinal images of either CT scan, MRI, or plain film radiography. Compression fractures were diagnosed according to the semiquantitative technique proposed by Genant HK, *et al* in 1993.[12] Any loss of vertebral height greater or equal to 20% is defined as compression fracture. No visible loss of vertebral height or loss of height less than 20% is defined as "no compression fracture". The degrees of the loss of the vertebral height were measured on the computer display and performed by the board certified radiologists in our hospital.

### 2.3 | Statistical analysis

The characteristics of NDMM patients in this cohort are shown as the total number (*n*) and proportion (%). Categorical variables were compared between vertebral fractures ≥2 group and vertebral fracture <2 group by Pearson chi-square test. Poisson regression was used to estimate risk ratio (RR) for the numbers of vertebral fractures at diagnosis with the logarithm of the follow-up times as the offset term and was adjusted for overdispersion. In addition, we used Poisson regression to analyze the impact of BMI on vertebral fractures among the different age subgroups based on a meta-analysis, which suggested advancing age was associated with a significant increase in gradient risk per unit of BMI for any fracture.[6] In the age stratification subgroup analysis, age was not adjusted as a confounding factor, but as an effect modifier. Overall survival was evaluated using the time from MM diagnosis until June 2016, death, dropout, or loss to follow-up. The survival curves were demonstrated in both groups, with and without multiple fractures more than or equal to 2 at presentation, using Kaplan-Meier estimate and tested with log-rank test. Odds ratio (OR) and 95% CI were estimated by logistic regression to determine the risk factors associated with multiple vertebral fractures according to the result in survival analysis. All statistics were performed using the SAS 9.3 software (SAS Institute Inc., Cary, NC) or SPSS statistical software version 20.0 for Windows (SPSS, Inc., Chicago, Illinois). Independent variables with $P < 0.1$ in the univariate model were included in the multivariable analysis. All statistical significances were set at $P < 0.05$.

## 3 | RESULTS

### 3.1 | Clinical characteristics of the study population

From January 1, 2005 to December 31, 2015, a total of 394 with NDMM were identified in Taipei Veteran General Hospital. Patients without any spinal images at diagnosis (n =88) or without BMI data at diagnosis (n = 5) were excluded. Finally, 301 (76.4%) patients were enrolled in the final cohort, categorized as 108 patients with vertebral fractures ≥2 group and 193 patients with vertebral fracture <2 group (Figure 1). The median age of the cohort was 70 years interquartile range (IQR, 59–79 years), and 61.5% of patients were male. Patients whose BMI < 18.5 kg/m$^2$, BMI 18.5–23.9 kg/m$^2$, and BMI ≥ 24 kg/m$^2$ were 12%, 46.2%, and 41.9%, respectively. In addition, using the DS stage system, 30.2% of patients were stage I, 22.9% were stage II, and 46.8% were stage III. The median plasma cells in bone marrow were 65% (IQR, 30–85%). Patients with vertebral fractures ≥2 had lower hemoglobin, lower albumin, higher corrected serum calcium, more plasma cells in bone marrow, and poor ECOG, as compared with patients with vertebral fracture <2 group (Table 1).

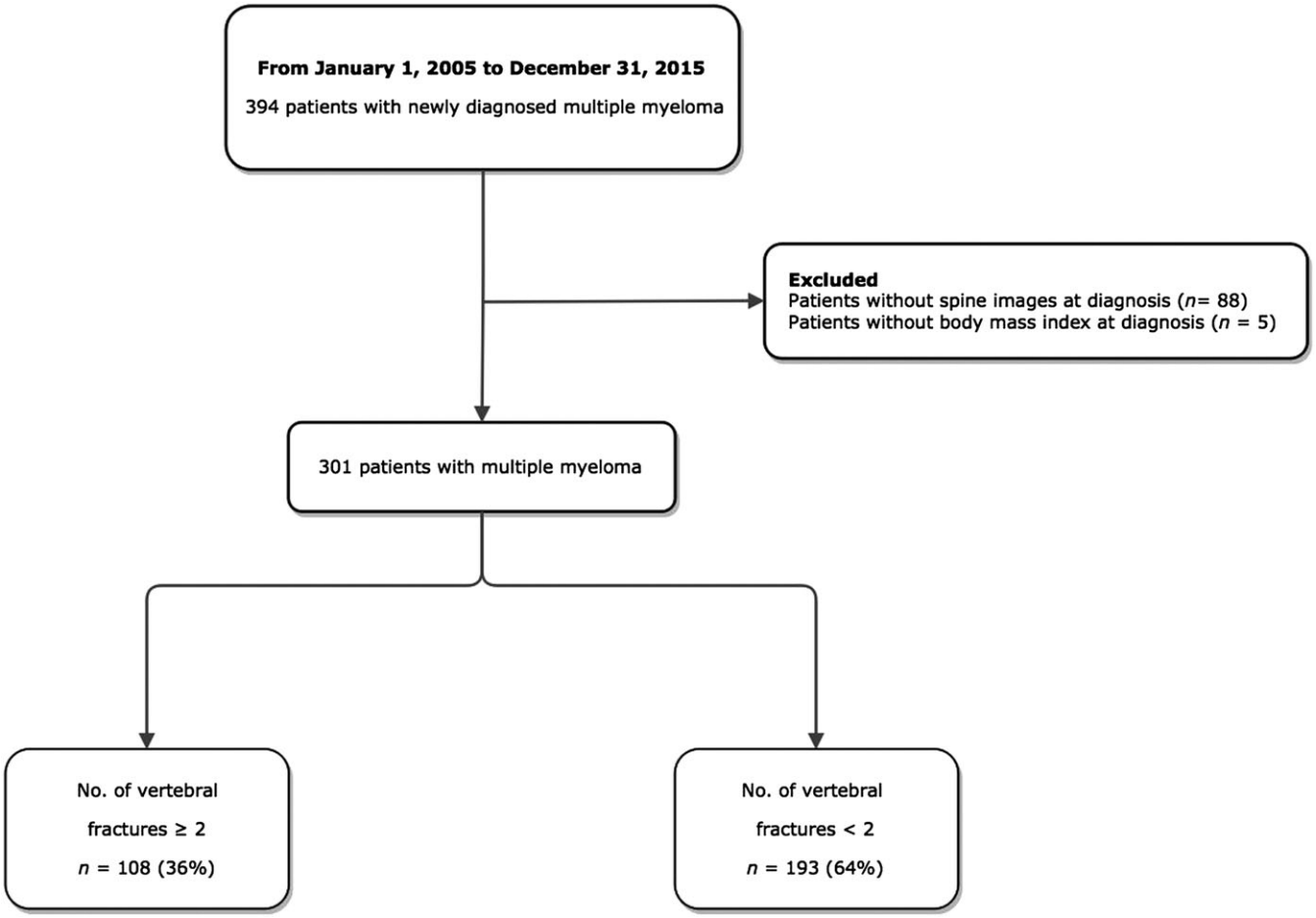


**FIGURE 1** Patient selection

### 3.2 | Baseline characteristics associated with increased vertebral fractures

In the univariate Poisson regression, BMI categories (BMI < 18.5 kg/m$^2$ and BMI 18.5–23.9 kg/m$^2$ compared with BMI ≥ 24.0 kg/m$^2$), serum albumin <3.5 g/dL, corrected serum calcium ≥12 mg/dL, serum creatinine ≥2 mg/dL, LDH ≥ 250 U/L, ALKP ≥100 U/L, ECOG ≥2, and DS stage were associated with increased vertebral fractures ($P$ < 0.1). After the multivariate Poisson regression, 7 independent variables remained significant, which were BMI < 18.5 kg/m$^2$ compared with BMI ≥ 24.0 kg/m$^2$ (adjusted RR, 2.79; 95% CI, 1.44–5.43), BMI 18.5–23.9 kg/m$^2$ compared with BMI ≥ 24.0 kg/m$^2$ (adjusted RR, 2.55; 95% CI, 1.42–4.58), LDH ≥ 250 U/L (adjusted RR, 1.93; 95% CI, 1.12–3.31), ALKP ≥100 U/L (adjusted RR, 1.95; 95% CI, 1.15–3.31), ECOG ≥2 (adjusted RR, 2.13; 95% CI, 1.29–3.53), and DS stage II (adjusted RR, 2.11; 95% CI, 1.03–4.36) and III (adjusted RR, 2.37; 95% CI, 1.25–4.48) compared with stage I (Table 2).

### 3.3 | The effect of age on relative risk of increased vertebral fractures

In the cohort, the lower BMI, either in patients with BMI <18.5 kg/m$^2$ (adjusted RR, 2.79; $P$ = 0.002) or with BMI 18.5–23.9 kg/m$^2$ (adjusted RR, 2.55; $P$ = 0.002), had increased quantities of vertebral fractures, as compared with patients with BMI ≥ 24 kg/m$^2$ in the multivariate analysis. In addition, we analyzed the impact of BMI on vertebral fractures among the different age intervals between age 60 and 75. In the multivariate Poisson regression, the impact of age became more prominent in older patients whose BMI < 18.5 kg/m$^2$ as compared with patients with BMI ≥ 24 kg/m$^2$, the adjusted RR increased from 3.03 ($P$ = 0.088) in age ≤ 60 group, 5.28 ($P$ = 0.013) in age between 60 and 75 group, to 12.22 ($P$ < 0.001) in age > 75 group (Table 3). As the result, there was a positive correlation between age and quantities of vertebral fractures in patients with lower BMI.

### 3.4 | Multiple vertebral fractures and poor survival

In the median follow-up period of 18.0 months, 125 patients (42%) had died. The median survival time in patients with multiple vertebral fractures were 28.6 months, which was shorter than patients without (median survival time, 59.3 months, $P$ = 0.017) (Figure 2).

Risk factors of multiple vertebral fractures (vertebral fractures ≥2).

In the univariate logistic regression, BMI categories, plasma cells of bone marrow ≥60%, hemoglobin <10.0 g/dL, serum albumin <3.5 g/dL, corrected serum calcium ≥12 mg/dL, ALKP ≥100 U/L, ECOG ≥2, and DS stage were associated with multiple vertebral fractures at presentation. After the multivariate logistic regression, 3 independent variables remained significant, which were BMI < 18.5 kg/m$^2$ (adjusted OR, 6.05; 95% CI, 2.43–15.08), plasma cells in bone marrow ≥60% (adjusted OR, 2.19; 95% CI, 1.18–4.10), and ALKP ≥100 U/L (adjusted OR, 1.94; 95% CI, 1.03–3.65) (Table 4).

**TABLE 1** Baseline patient characteristics of multiple myeloma patients

| Characteristics | Total[a] *n* = 301 *n* (%) | No. of Vertebral Fractures ≥2 *n* = 108 (36%) *n* (%) | No. of Vertebral Fractures <2 *n* = 193 (64%) *n* (%) | *P* Value |
|---|---|---|---|---|
| Median age, years (IQR) | 70 (59–79) | 70 (58–80) | 70 (59–78) | |
| ≥70 | 157 (52.2) | 57 (52.8) | 100 (51.8) | 0.872 |
| <70 | 144 (47.8) | 51 (47.2) | 93 (48.2) | |
| Sex | | | | |
| Male | 185 (61.5) | 67 (62.0) | 118 (61.1) | 0.878 |
| Female | 116 (38.5) | 41 (38.0) | 75 (38.9) | |
| Laboratory data | | | | |
| Plasma cells in BM | | | | |
| Median (IQR) | 65.0 (30.0–85.0) | 70.0 (50.0–85.0) | 57.5 (25.0–80.0) | |
| ≥60% | 169 (56.9) | 73 (69.5) | 96 (50.0) | 0.001 |
| <60% | 128 (43.1) | 32 (30.5) | 96 (50.0) | |
| Hemoglobin | | | | |
| Median (IQR) | 9.3 (8.2–11.0) | 9.2 (8.2–10.1) | 9.6 (8.3–11.4) | |
| ≥10.0 g/dL | 114 (37.9) | 32 (29.6) | 82 (42.5) | 0.027 |
| <10.0 g/dL | 187 (62.1) | 76 (70.4) | 111 (57.5) | |
| Platelet | | | | |
| Median (IQR) | 172 000 (109 000–233 000) | 161 000 (108 500–218 000) | 178 000 (112 000–240 000) | |
| ≥150 000/μ | 178 (59.1) | 61 (56.5) | 117 (60.6) | 0.483 |
| <150 000/μ | 123 (40.9) | 47 (43.5) | 76 (39.4) | |
| Serum albumin | | | | |
| Median (IQR) | 3.3 (2.8–3.8) | 3.1 (2.5–3.6) | 3.4 (2.9–3.8) | |
| <3.5 g/dL | 175 (58.7) | 74 (68.5) | 101 (53.2) | 0.010 |
| ≥3.5 g/dL | 123 (41.3) | 34 (31.5) | 89 (46.8) | |
| Corrected serum calcium | | | | |
| Median (IQR) | 9.5 (9.0–10.5) | 9.7 (9.1–11.4) | 9.4 (8.9–10.2) | |
| ≥12 mg/dL | 34 (11.5) | 20 (18.5) | 14 (7.4) | 0.004 |
| <12 mg/dL | 263 (88.6) | 88 (81.5) | 175 (92.6) | |
| Serum creatinine | | | | |
| Median (IQR) | 1.2 (0.8–2.2) | 1.3 (0.9–2.8) | 1.2 (0.8–2.1) | |
| <2 mg/dL | 211 (70.3) | 71 (65.7) | 140 (72.9) | 0.192 |
| ≥2 mg/dL | 89 (29.7) | 37 (34.3) | 52 (27.1) | |
| Lactate dehydrogenase | | | | |
| Median (IQR) | 196.0 (148.5–272.0) | 190.0 (150.5–273.0) | 197.0 (147.5–269.5) | |
| ≥250 U/L | 86 (29.5) | 30 (28.9) | 56 (29.8) | 0.866 |
| <250 U/L | 206 (70.6) | 74 (71.2) | 132 (70.2) | |
| Serum β2-microglobulin | | | | |
| Median (IQR) | 5296.0 (3152.0–10500.0) | 5539.0 (3931.0–12096.0) | 4850.0 (2801.0–9709.0) | |
| <5500 mg/L | 142 (50.9) | 48 (47.5) | 94 (52.8) | 0.396 |
| ≥5500 mg/L | 137 (49.1) | 53 (52.5) | 84 (47.2) | |
| Alkaline phosphatase | | | | |
| Median (IQR) | 75.5 (58.0–99.0) | 78.0 (61.0–109.0) | 72.0 (56.0–95.0) | |
| ≥100 U/L | 64 (24.2) | 30 (30.9) | 34 (20.4) | 0.053 |
| <100 U/L | 200 (75.8) | 67 (69.1) | 133 (79.6) | |
| ECOG | | | | |
| 0–1 | 165 (54.8) | 51 (47.2) | 114 (59.1) | 0.048 |
| ≥2 | 136 (45.2) | 57 (52.8) | 79 (40.9) | |

(Continues)

**TABLE 1** (Continued)

| Characteristics | Total[a] *n* = 301 *n* (%) | No. of Vertebral Fractures ≥2 *n* = 108 (36%) *n* (%) | No. of Vertebral Fractures <2 *n* = 193 (64%) *n* (%) | *P* Value |
|---|---|---|---|---|
| Durie-Salmon stage | | | | |
| I | 91 (30.2) | 19 (17.6) | 72 (37.3) | 0.001 |
| II | 69 (22.9) | 27 (25.0) | 42 (21.8) | |
| III | 141 (46.8) | 62 (57.4) | 79 (40.9) | |
| Body mass index | | | | |
| <18.5 kg/m$^2$ | 36 (12.0) | 25 (23.2) | 11 (5.7) | < 0.001 |
| 18.5–24.0 kg/m$^2$ | 139 (46.2) | 52 (48.2) | 87 (45.1) | |
| ≥24.0 kg/m$^2$ | 126 (41.9) | 31 (28.7) | 95 (49.2) | |

Abbreviations: BM, bone marrow; ECOG, the Eastern Cooperative Oncology Group performance status; IQR, interquartile range.

[a]Including some missing values.

**TABLE 2** Univariate and multivariate analysis of factors associated with vertebral fractures in patients with multiple myeloma (Poisson regression)

| | Univariate Analysis | | Multivariate Analysis[a] | |
|---|---|---|---|---|
| **Predictive Variables** | **RR (95% CI)** | ***P* Value** | **RR (95% CI)** | ***P* Value** |
| Body mass index, kg/m$^2$ | | | | |
| <18.5 | 4.20 (2.26–7.81) | <0.001 | 2.79 (1.44–5.43) | 0.002 |
| 18.5–24.0 | 2.16 (1.27–3.67) | 0.005 | 2.55 (1.42–4.58) | 0.002 |
| ≥24.0 | Reference | | Reference | |
| Sex (male) | 1.00 (0.63–1.59) | 0.996 | | |
| Laboratory data | | | | |
| Plasma cells in BM ≥ 60% | 1.50 (0.92–2.45) | 0.104 | | |
| Hemoglobin <10.0 g/dL | 1.47 (0.91–2.39) | 0.119 | | |
| Platelet <150 000/μ | 1.45 (0.92–2.29) | 0.113 | | |
| Serum albumin <3.5 g/dL | 1.91 (1.19–3.07) | 0.008 | 1.57 (0.93–2.64) | 0.090 |
| Corrected serum calcium ≥12 mg/dL | 3.33 (1.89–5.89) | <0.001 | | |
| Serum creatinine ≥2 mg/dL | 1.62 (1.01–2.60) | 0.045 | 0.93 (0.56–1.52) | 0.766 |
| Lactate dehydrogenase ≥250 U/L | 2.10 (1.28–3.43) | 0.003 | 1.93 (1.12–3.31) | 0.018 |
| Serum β2-microglobulin ≥5500 mg/L | 1.41 (0.88–2.27) | 0.155 | | |
| Alkaline phosphatase ≥100 U/L | 1.88 (1.12–3.17) | 0.017 | 1.95 (1.15–3.31) | 0.013 |
| ECOG ≥2 | 2.52 (1.60–3.97) | <0.001 | 2.13 (1.29–3.53) | 0.003 |
| Durie-Salmon stage | | | | |
| I | Reference | | Reference | |
| II | 1.88 (0.95–3.73) | 0.071 | 2.11 (1.03–4.36) | 0.042 |
| III | 2.83 (1.54–5.20) | <0.001 | 2.37 (1.25–4.48) | 0.008 |

Abbreviations: CI, confidence interval; ECOG, the Eastern Cooperative Oncology Group performance status; RR, risk ratio.

[a]All factors with $P < 0.1$ in univariate analysis were entered in a multivariate Poisson regression model.

## 4 | DISCUSSION

According to previous reports, in the general population, individuals with lower BMI experienced fractures more frequently than those with higher BMI.[6] Vertebral fractures are common in MM patients affecting approximately 30% of patients.[13] However, the relationship between BMI and fractures in MM patients at diagnosis is rarely described. In addition, the associated risk factors or survival in MM patients with vertebral fracture(s) are also unclear.

In a meta-analysis based on 12 prospective studies including almost 60 000 participants worldwide, Laet *et al* suggested that the lower the BMI, the greater the fracture risk for all kinds of fractures in the general population.[6] When compared with a BMI of 25 kg/m$^2$, a BMI of 20 kg/m$^2$ was associated with an obvious increase in RR for osteoporotic or hip fractures. With a decreasing BMI, an increased risk of fractures was also noted. According to another article described by Miller *et al*, they proposed to characterize the clinical and radiologic features of these fractures and to identify independent predictors of fracture burden and severity in MM patients.[14] This article documented that additional 1 vertebral fracture was associated with 10 unit decreased in BMI. Lower BMI, lower albumin, higher paraprotein, higher light chains, and higher creatinine predicted a greater number of fractures at presentation of MM.

Based on these literatures, we further investigated how BMI impacted the risk of vertebral fractures in patients with NDMM. In our study, in the multivariate Poisson analysis, increased number of

**TABLE 3** Age-subgroup analysis (Poisson regression)

| Predictive Variables | Univariate Analysis | | Multivariate Analysis[a] | |
|---|---|---|---|---|
| | RR (95% CI) | *P* Value | RR (95% CI) | *P* Value |
| Total | | | | |
| BMI < 18.5 | 4.20 (2.26–7.81) | < 0.001 | 2.79 (1.44–5.43) | 0.002 |
| 18.5 ≤ BMI < 24.0 | 2.16 (1.27–3.67) | 0.005 | 2.55 (1.42–4.58) | 0.002 |
| BMI ≥ 24.0 | Reference | | Reference | |
| Age ≤ 60 (*n* = 91) | | | | |
| BMI < 18.5 | 2.11 (0.61–7.31) | 0.238 | 3.03 (0.85–10.81) | 0.088 |
| 18.5 ≤ BMI < 24.0 | 2.64 (1.06–6.54) | 0.036 | 3.34 (1.15–9.70) | 0.027 |
| BMI ≥ 24.0 | Reference | | Reference | |
| Age 60–75 (*n* = 109) | | | | |
| BMI < 18.5 | 3.55 (1.42–8.89) | 0.007 | 5.28 (1.42–19.62) | 0.013 |
| 18.5 ≤ BMI < 24.0 | 1.10 (0.47–2.54) | 0.829 | 1.24 (0.46–3.35) | 0.667 |
| BMI ≥ 24.0 | Reference | | Reference | |
| Age > 75 (*n* = 101) | | | | |
| BMI < 18.5 | 11.29 (3.58–35.57) | < 0.001 | 12.22 (3.02–49.40) | < 0.001 |
| 18.5 ≤ BMI < 24.0 | 3.23 (1.13–9.21) | 0.029 | 7.29 (2.18–24.33) | 0.001 |
| BMI ≥ 24.0 | Reference | | Reference | |

Abbreviations: CI, confidence interval; ECOG, the Eastern Cooperative Oncology Group performance status; RR, risk ratio.

[a]All factors with *P* < 0.1 in univariate analysis were entered in a multivariate Poisson regression.

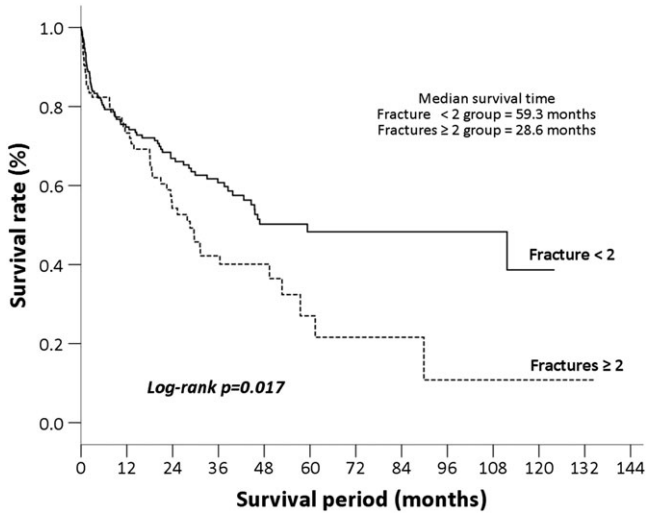


**FIGURE 2** Multiple vertebral fractures and poor survival

vertebral fractures in NDMM was significantly associated with BMI < 18.5 kg/m$^2$ and 18.5–23.9 kg/m$^2$. The relative risks were 2.79 (*P* = 0.002) and 2.55 (*P* = 0.002), respectively. The results implied that lower BMI predicted a greater risk of vertebral fractures. In addition, this is the first study that demonstrated that age had a profound impact on vertebral fractures in NDMM patients with low BMI. In our subgroup analysis, we stratified patients into 3 groups, age under 60, age between 60 and 75, and age over 75, to see in patients with lower BMI, how age affected the relative risk of vertebral fracture. Cut-off values were set at 60 and 75 years according to a Taiwanese epidemiology study of MM.[15] Tzeng *et al* conducted the study including 3970 patients with NDMM between 1997 and 2009 from National Health Insurance Research Database in Taiwan. The majority of patients with NDMM (45.2%) were diagnosed between 60 and 75 years. The rest patients diagnosed at age under 60 years and over 75 years were 27.6% and 27.2%, respectively. The result of our subgroup analysis showed that in patients with BMI < 18.5 kg/m$^2$, the relative risks for age ≤ 60, age 60 to 75, and age > 75 were 3.03 (*P* = 0.088), 5.28 (*P* = 0.013), 12.22 (*P* < 0.001), respectively. In a nutshell, in patients with lower BMI, the relative risks of vertebral fractures increased with age.

Low BMI has been described as a risk factor for fractures both in breast and prostate cancer.[7,8] Patients with advancing age were also at higher risk suffering from fractures in breast cancer.[8] These risk factors have also been identified in NDMM patients in our study, but there is no definite mechanism to explain the relationship between age and BMI in vertebral fractures in NDMM. However, loss of muscle strength, which becomes more evident in aging process, is responsible for vertebral fractures in patients with osteoporosis.[9] Low BMI and increased age are associated with sarcopenia in both sexes.[10] In addition, sarcopenia has been recognized as a significant predictor for osteoporotic vertebral fractures[16]and multiple vertebral fractures in women.[17]

The relationship between the number of vertebral fractures and mortality has been well established.[18,19] Several literatures have documented that increased number of vertebral fractures has been associated with higher mortality in the general population.[20-22] Similar outcome was also observed in our study. The median survival time for myeloma patients with ≥2 vertebral fractures at presentation was 28.6 months, which was much shorter than patients with 1 or without vertebral fracture (59.3 months, *P* = 0.017). Hence, the predictors for multiple fractures were worth to be further identified in NDMM patients. Thus, we performed a multivariate logistic regression which revealed that BMI < 18.5 kg/m$^2$ was a significant independent predictor for multiple vertebral fractures.

Myeloma disease severity is related to performance status, serum albumin, serum calcium, serum creatinine, β2M level, bone marrow plasma cell percentage, and LDH level.[23] Furthermore, predictors such

**TABLE 4** Univariate and multivariate analysis of factors associated with vertebral fractures in patients with multiple myeloma (Logistic regression)

| | Univariate Analysis | | Multivariate Analysis[a] | |
|---|---|---|---|---|
| **Predictive Variables** | **OR (95% CI)** | ***P* Value** | **OR (95% CI)** | ***P* Value** |
| Body mass index, kg/m$^2$ | | | | |
| <18.5 | 6.97 (3.08–15.76) | <0.001 | 6.05 (2.43–15.08) | <0.001 |
| 18.5–24.0 | 1.83 (1.08–3.12) | 0.026 | 1.80 (0.99–3.28) | 0.054 |
| ≥24.0 | Reference | | | |
| Sex (male) | 1.04 (0.64–1.69) | 0.878 | | |
| Laboratory data | | | | |
| Plasma cells in BM ≥ 60% | 2.28 (1.38–3.77) | 0.001 | 2.19 (1.18–4.10) | 0.014 |
| Hemoglobin <10.0 g/dL | 1.75 (1.06–2.90) | 0.028 | | |
| Platelet <150 000/μ | 1.19 (0.74–1.91) | 0.484 | | |
| Serum albumin <3.5 g/dL | 1.92 (1.17–3.15) | 0.010 | 1.57 (0.87–2.85) | 0.138 |
| Corrected serum calcium ≥12 mg/dL | 2.84 (1.37–5.89) | 0.005 | | |
| Serum creatinine ≥2 mg/dL | 1.40 (0.84–2.33) | 0.192 | | |
| Lactate dehydrogenase ≥250 U/L | 0.96 (0.56–1.62) | 0.866 | | |
| Serum β2-microglobulin ≥5500 mg/L | 1.24 (0.76–2.02) | 0.396 | | |
| Alkaline phosphatase ≥100 U/L | 1.75 (0.99–3.10) | 0.055 | 1.94 (1.03–3.65) | 0.040 |
| ECOG ≥2 | 1.61 (1.00–2.59) | 0.048 | 1.09 (0.62–1.91) | 0.770 |
| Durie-Salmon stage | | | | |
| I | Reference | | Reference | |
| II | 2.44 (1.21–4.90) | 0.013 | 1.75 (0.76–4.03) | 0.188 |
| III | 2.97 (1.62–5.45) | <0.001 | 1.58 (0.76–3.32) | 0.224 |

Abbreviations: CI, confidence interval; ECOG, the Eastern Cooperative Oncology Group performance status; OR, odds ratio.

[a]All factors with $P < 0.1$ in univariate analysis were entered in a multivariate logistic regression model.

as low serum albumin, high serum calcium, and LDH help us identify potential patients for early mortality.[24] As for our study, we confirmed that LDH ≥ 250 U/L, ALKP ≥100 U/L, ECOG ≥2, DS stage II, and DS stage III were significant predictors for increased vertebral fractures, whereas plasma cells in bone marrow ≥60% and ALKP ≥100 U/L served as predictors for multiple vertebral fractures at presentation in NDMM patients. Some of these independent variables are considered as indicators for disease severity mentioned earlier. As myeloma itself is already a malignancy with prominent bone involvement, greater number of vertebral fractures may be related to heavier disease burden. This may explain why patients with multiple vertebral fractures are at higher risk of mortality.

Apart from our findings, several other studies have identified predictors for fractures in MM.[14,25-27] Miller *et al* suggested that a greater number of vertebral fractures in NDMM was associated with decreased BMI, decreased albumin, increased M-protein, increased light chains, and increased creatinine at presentation.[14] Three studies below revealed factors for future vertebral fracture risks. An earlier study proposed that corticosteroid use, serum calcium levels, and chemotherapy were predictors for future fractures after the diagnosis of MM.[25] Another study in Belgium showed that the number of bone marrow lesions under initial MRI, serum calcium levels, and cumulative prednisolone use were prognostic factors for future fracture risks.[26] Recently, a retrospective study conducted by Xiao *et al* reported that a higher risk of future vertebral fractures was related to osteopenia or osteoporosis, increased serum light chain, and elevated serum calcium level.[27]

There are several limitations in our study. The major limitation in our study was that radiographic measurements were not routinely performed in every NDMM patient. Only patients with low back pain or other neurologic symptoms received the radiographic examinations. Thus, approximately 23% of patients were excluded in our cohort, causing potential selection bias. Second, this study was based on the experience of a single tertiary teaching hospital, and the cohort was not representative of the general population. In light of the actual age distribution of NDMM patients, we stratified patients into 3 different age subgroups according to a large Taiwanese NDMM epidemiology study including 3970 patients with NDMM.[15] Third, BMI may not truly reflect the body compositions. In our hypothesis, muscle wasting may be responsible for vertebral fractures. Hence, a more precise measurement should be applied in the future study. For example, the third lumbar vertebral muscle area measured under CT or MRI could be considered as standard landmark for estimating body muscle mass.[28-30] Lastly, due to the nature of retrospective study, the causation cannot be determined. After adjusting potential confounding factors, the identified predictors for vertebral fractures remained consistent, suggesting the independence of these risk factors. However, a further prospective study with asymptomatic patients included should eliminate the limitations, offering more robust conclusion.

## 5 | CONCLUSION

This is the first study that demonstrated that age had a profound impact on vertebral fractures in NDMM patients with low BMI. Additionally, BMI < 18.5 kg/m$^2$, 18.5 to 23.9 kg/m$^2$, LDH ≥ 250 U/L, ALKP ≥100 U/L, ECOG ≥2, and DS stage II and III were predictors for

increased number of vertebral fractures in NDMM. BMI < 18.5 kg/m$^2$, plasma cells in bone marrow ≥60%, and ALKP ≥100 U/L were predictors for multiple vertebral fractures at presentation. Higher mortality was significantly associated with multiple fractures. In conclusion, NDMM patients at high risk of vertebral fractures should consider to routinely receive spinal radiographic examinations and regular follow-up.

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### CONFLICT OF INTEREST

The authors declare no competing interests.

## AUTHOR'S CONTRIBUTIONS

C. J. L. was responsible for the accuracy of analysis and the integrity of the cohort. Y. C. L. and Y. L. C. contributed equally and are the first authors. Y. C. L., Y. L. C., and C. J. L. designed the study. C. H. W. interpreted the radiographic images. C. J. L. and C. M. Y. performed the statistical analysis. Y. C. L., Y. L. C., and C. J. L. interpreted the results. Y. C. L., Y. L. C., and C. H. W. drafted the manuscript. H. I. C., G. Y. L., Y. T. L., P. H., T. W. L., J. P. G., L. T. H., T. J. C., and J. H. L. made critical revisions to the manuscript for important intellectual content. J. P. G., L. T. H., T. J. C., and J. H.L. provided administrative, technical, and material support. C. J. L. was the study supervisor. C. J. L. is guarantor and accepts responsibility for the integrity of the work. All authors approved the final version for submission.

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