

## Original article

# Associated factors for identifying one-year mortality among Thai patients with multiple myeloma: a single-center retrospective study

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**Abstract:**

**Introduction:** An early mortality in multiple myeloma (MM) remains a major concern, especially in resource-limited settings. Data on early mortality in Thailand are limited. **Objectives:** This study aimed to identify factors associated with early mortality and to describe overall survival (OS) and causes of death among patients with newly diagnosed MM (NDMM). **Material and Methods:** This retrospective study included 153 patients with NDMM diagnosed between January 1, 2018, and May 31, 2023, at Maharat Nakhon Ratchasima Hospital. Early mortality was defined as death within 12 months after diagnosis. Clinical and laboratory data were analyzed using univariable and multivariable Cox regression. Causes of death were classified according to a systematic classification of death causes in multiple myeloma. **Results:** Early mortality occurred in 63 patients (41.18%). In multivariable analysis, older age (hazard ratio [HR] 1.07, 95%CI: 1.01-1.16,  $p = 0.034$ ) and  $\beta_2$ -microglobulin ( $\beta_2M$ )  $\geq 5.5$  mg/L (HR 1.32, 95%CI: 1.03-1.67,  $p = 0.026$ ) were independent predictors of early mortality. Patients receiving conventional chemotherapy and those achieving less than partial response were also at increased risk. Most deaths (92.1%) were MM-dependent, of which 58.6% were progression-related and 41.4% were therapy-related. Infections accounted for 50.8% of all deaths. Median OS was 19.97 months. **Conclusion:** Older age and  $\beta_2M \geq 5.5$  mg/L were independent predictors of early death, while conventional chemotherapy and poor treatment response further increased risk. Reducing early mortality requires improved early detection, optimized treatment, expanded access to novel agents and targeted infection-prevention strategies for high-risk patients.

**Keywords :** ● Multiple myeloma ● Early mortality ● Cause of death

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## นิพนธ์ต้นฉบับ

# ปัจจัยที่มีความสัมพันธ์กับการเสียชีวิตภายใน 1 ปีของผู้ป่วยมะเร็งเม็ดเลือดขาวชนิดมัลติโบลมาของไทย: การศึกษาย้อนหลังจากโรงพยาบาลมหาราชานครราชสีมา

ปิยภรณ์ ศิริสันทิติ

สาขาวิชาโลหิตวิทยา ภาควิชาอายุรศาสตร์ โรงพยาบาลมหาราชานครราชสีมา

## บทคัดย่อ

**บทนำ** การเสียชีวิตภายใน 1 ปีหลังการวินิจฉัยของผู้ป่วยมะเร็งเม็ดเลือดขาวชนิดมัลติโบลมาที่ได้รับการวินิจฉัยใหม่ (newly diagnosed multiple myeloma, NDMM) เป็นปัญหาสำคัญ โดยเฉพาะในพื้นที่ที่มีข้อจำกัดด้านทรัพยากร ปัจจุบันข้อมูลในประเทศไทยยังมีจำกัด **วัตถุประสงค์** เพื่อศึกษาปัจจัยที่มีความสัมพันธ์กับการเสียชีวิตภายใน 1 ปีของผู้ป่วย NDMM และระยะเวลาที่รอดชีวิต (overall survival, OS) รวมถึงสาเหตุการเสียชีวิต **วัสดุและวิธีการ** การศึกษาแบบย้อนหลังในผู้ป่วย NDMM จำนวน 153 ราย ที่ได้รับการวินิจฉัยระหว่างวันที่ 1 มกราคม 2561 ถึง 31 พฤษภาคม 2566 ที่โรงพยาบาลมหาราชานครราชสีมา ข้อมูลทางคลินิกและห้องปฏิบัติการถูกวิเคราะห์ด้วย univariable และ multivariable Cox regression และจำแนกสาเหตุการเสียชีวิตตามกรอบแนวคิด a systematic classification of death causes in multiple myeloma **ผลลัพธ์** ผู้ป่วย 63 ราย (41.18%) เสียชีวิตภายใน 1 ปี การวิเคราะห์หลายตัวแปรพบว่า อายุที่มากขึ้น [hazard ratio (HR) 1.07, 95%CI: 1.01-1.16,  $p = 0.034$ ] และค่า  $\beta_2$ -microglobulin ( $\beta_2M$ )  $\geq 5.5$  mg/L (HR 1.32, 95%CI: 1.03-1.67,  $p = 0.026$ ) เป็นปัจจัยที่สัมพันธ์กับการเสียชีวิตภายใน 1 ปี การได้รับเคมีบำบัดแบบดั้งเดิม และการตอบสนองต่อการรักษาน้อยกว่า partial response (PR) เพิ่มความเสี่ยงเสียชีวิตใน 1 ปี การเสียชีวิตส่วนใหญ่ (92.1%) มีเหตุมาจากตัวโรค MM เอง โดยร้อยละ 58.6 เกี่ยวข้องกับการดำเนินโรค และร้อยละ 41.4 เกี่ยวข้องกับผลข้างเคียงจากการรักษา การติดเชื้อเป็นสาเหตุการเสียชีวิตร้อยละ 50.8 ของการเสียชีวิตทั้งหมด ค่ามัธยฐาน OS คือ 19.97 เดือน **สรุป** อายุที่มากขึ้นและค่า  $\beta_2M \geq 5.5$  mg/L เป็นปัจจัยที่สัมพันธ์กับการเสียชีวิตภายใน 1 ปี และการได้รับเคมีบำบัดแบบดั้งเดิม และการตอบสนองน้อยกว่า PR เพิ่มความเสี่ยงต่อการเสียชีวิตภายใน 1 ปี จึงจำเป็นต้องมีการตรวจรักษาอย่างทันท่วงที่ ปรับการรักษาให้เหมาะสม และใช้มาตรการป้องกันการติดเชื้อในผู้ป่วยที่มีความเสี่ยงสูง

**คำสำคัญ :** ● มะเร็งเม็ดเลือดขาวชนิดมัลติโบลมา ● เสียชีวิตภายใน 1 ปี ● สาเหตุการเสียชีวิต

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## Introduction

Multiple myeloma (MM) is the second most prevalent hematological malignancy after lymphoma. In studies from Asia, the incidence has been reported at 0.5-5 per 100,000 population.<sup>1</sup> Over the past two decades, significant advancements in the treatment of newly diagnosed multiple myeloma (NDMM), including autologous stem cell transplant (ASCT) and novel drugs such as proteasome inhibitors (PI), immunomodulatory drugs (IMiD) and monoclonal antibodies, have led to improved treatment responses, longer remission periods and better survival outcomes. However, in Thailand, access to novel drugs remains limited due to their high cost, rendering them unaffordable for many patients.

Only a few studies have reported the incidence of early mortality in MM, and no data are available on predictive factors for early mortality in Thailand. Early mortality, defined as death within one year of diagnosis, has been reported at 8.3-13.8%. Reported predictors include age, Eastern Cooperative Oncology Group performance status, serum albumin, International Staging System (ISS) stage and renal function.<sup>2-4</sup> Understanding the factors contributing to early mortality in MM may help identify high-risk patients and optimize treatment accordingly.

Therefore, this retrospective cohort study was conducted to determine factors associated with death within one year of diagnosis in patients with MM and overall survival (OS) among patients with NDMM at Maharat Nakhon Ratchasima Hospital.

## Material and Methods

### Study population

This retrospective study analyzed the records of 153 patients with NDMM between January 1, 2018 and May 31, 2023, at Maharat Nakhon Ratchasima Hospital. Follow-up continued until November 30, 2024. MM was defined according to the International Myeloma Working Group diagnostic criteria.<sup>5</sup> All patients underwent bone marrow biopsy. Patients with solitary plasmacytoma or smoldering myeloma were excluded.

### Data collection

Data were collected by reviewing medical records. Clinical characteristics, included age, sex, body mass index (BMI), bone marrow transplant status, treatment and response.<sup>6</sup> Laboratory parameters included hemoglobin, serum creatinine, estimated glomerular filtration rate (eGFR), corrected serum calcium, lactate dehydrogenase (LDH), serum albumin,  $\beta_2$ -microglobulin ( $\beta_2$ M), ISS stage,<sup>7</sup> type of abnormal monoclonal protein and serum kappa and lambda light chain levels.

The primary endpoint was the identification of factors associated with early mortality among patients with NDMM. The study was approved by the Institutional Review Board at Maharat Nakhon Ratchasima Hospital.

### Definitions

Early mortality was defined as death from any cause within the first 12 months after diagnosis.<sup>2,3,8</sup> Causes of death were classified according to a systematic classification of death causes in multiple myeloma.<sup>9</sup> They were categorized as MM-dependent, MM-independent, unknown or other. MM-dependent deaths were those directly related to myeloma or its treatment. These were further subdivided into MM progression-related (deaths due to disease activity or direct complications such as infections, renal failure or hypercalcemia) and therapy-related (deaths caused by adverse effects of anti-myeloma therapy, such as treatment-induced infections or organ toxicity). MM-independent deaths were unrelated to myeloma pathology, including cardiovascular events, second primary malignancies, unrelated infections or other comorbidities. Unknown deaths were those with insufficient information to determine the cause. Other deaths included cases that did not clearly fit the above categories or were multifactorial in origin.

### Statistical analysis

Data were summarized as number (proportion), median (interquartile range, IQR) or mean (standard deviation, SD) as appropriate. Hypothesis testing was performed using the chi-square test for categorical variables and the Wilcoxon rank-sum test or t-tests, as appropriate,

for continuous variables. The Kaplan-Meier method was used to assess survival and generate survival curves. Cox proportional hazards regression was applied to fit univariable and multivariable survival models, with results reported as hazard ratios (HRs) and 95% confident interval (CIs). All  $p$ -values were twotailed, and  $p < 0.05$  was considered statistically significant. Variable with  $p < 0.05$  in univariable analysis were included in the multivariable Cox regression model. All analyses were performed using SPSS version 30.

### Results

A total of 153 patients with NDMM diagnosed between January 1, 2018 and May 31, 2023, at Maharat Nakhon Ratchasima Hospital were identified. The median age was 66 (IQR, 60-69 years), and 58.2% were male. According to ISS, 15.7, 39.9 and 44.4% had stages I, II and III, respectively. Treatment of the study included novel agent-based regimens in 41 patients (26.9%), conventional chemotherapy in 91 patients (59.4%) and no treatment due to death before initiation in 21 patients (13.7%). Patient characteristics are shown in Table 1.

#### Features of early mortality

Early mortality occurred in 63 patients (41.18%). Compared with those who survived beyond 12 months, patients with early mortality were older, had lower BMI and did not undergo ASCT. They also showed higher serum creatinine, lower eGFR, higher corrected calcium, elevated serum  $\beta_2$ M levels and more advanced ISS stage. In addition, treatment regimens and response rates differed significantly between the two groups (Table 1).

#### Associated factors of early mortality

In univariable Cox regression analysis, factors significantly associated with early mortality included increasing age (HR 1.07, 95%CI: 1.01-1.12,  $p = 0.012$ ), underweight BMI (HR 1.76, 95%CI: 1.33-2.90,  $p = 0.013$ ), serum creatinine  $> 2$  mg/dL (HR 1.27, 95%CI: 1.14-2.42,  $p = 0.010$ ), corrected calcium  $> 11$  mg/dL (HR 2.05, 95%CI: 1.05-4.02,  $p = 0.036$ ) and  $\beta_2$ M  $\geq 5.5$  mg/L (HR 1.11, 95%CI: 1.05-1.19,  $p = 0.001$ ). In the multivariable

model, only increasing age (HR 1.07, 95%CI: 1.01-1.16,  $p = 0.034$ ) and  $\beta_2$ M  $\geq 5.5$  mg/L (HR 1.32, 95%CI: 1.03 to 1.67,  $p = 0.026$ ) remained independently associated with early mortality. Associations with underweight BMI, serum creatinine and corrected calcium were no longer statistically significant after adjustment. These findings indicate that both older age and elevated  $\beta_2$ M are independent predictors of early mortality in this patient population. Results are summarized in Table 2.

#### Association between treatment type, treatment response and early mortality

Among 132 patients with available treatment data, early mortality occurred in 6 of 41 patients (14.6%) who received novel agent-based regimens, compared with 36 of 91 patients (39.6%) who received conventional chemotherapy. Patients treated with conventional chemotherapy had a significantly higher likelihood of early mortality (OR = 3.31, 95%CI: 1.26-8.70;  $p = 0.012$ ).

In the subgroup of 106 patients with available response assessment, early mortality occurred in 9 of 81 patients (11.1%) who achieved at least a partial response ( $\geq$  PR), compared with 7 of 25 patients (28.0%) who achieved less than partial response ( $<$  PR). A treatment response of  $<$  PR was significantly associated with increased odds of early mortality (OR 3.36, 95%CI: 1.20-9.45;  $p = 0.017$ ).

#### Reasons for early mortality

Overall, 63 patients (41.2%) died within 12 months, including 24 (15.69%) within 2 months. Of these, 21 patients died before receiving induction therapy, accounting for 33.33% of early mortality cases. The median overall survival (OS) was 19.97 months (95%CI: 11.40-28.53). The median follow-up duration was 36.97 months (95%CI: 31.07-42.87). The survival curve is shown in Figure 1.

Among the 63 patients who experienced early mortality, 58 deaths (92.1%) were MM-dependent, 3 (4.8%) were MM-independent, and 2 (3.1%) were of unknown cause. Of the 58 MM-dependent deaths, 34 (58.6%) were progression-related, most commonly due to MM itself ( $n = 20$ , 58.8%), followed by renal disorder ( $n = 6$ , 17.6%),

**Table 1** Baseline clinical and treatment characteristics of patients with multiple myeloma (n = 153)

| Characteristics                                  | Total<br>N = 153<br>n (%) | Early mortality<br>N = 63<br>n (%) | Survivor at 12 months<br>N = 90<br>n (%) | p-value |
|--------------------------------------------------|---------------------------|------------------------------------|------------------------------------------|---------|
| Median age, years (IQR)                          | 66 (60-69)                | 66 (63-71)                         | 64 (58.75-68)                            | 0.011   |
| ≤ 65                                             | 75 (49)                   | 25 (39.7)                          | 50 (55.6)                                | 0.053   |
| > 65                                             | 78 (51)                   | 38 (60.3)                          | 40 (44.4)                                |         |
| Sex                                              |                           |                                    |                                          |         |
| Male                                             | 89 (58.2)                 | 36 (57.1)                          | 53 (58.9)                                | 0.829   |
| female                                           | 64 (41.8)                 | 27 (42.9)                          | 37 (41.1)                                |         |
| BMI, kg/m <sup>2</sup> , mean±SD                 | 21.26±3.83                | 19.88±3.76                         | 21.95±3.7                                | 0.004   |
| ASCT                                             | 9 (5.9)                   | 0 (0)                              | 9 (10)                                   | 0.010   |
| Hemoglobin, g/dL, mean±SD                        | 8.26±2.26                 | 8.17±2.3                           | 8.33±2.25                                | 0.690   |
| Serum creatinine,<br>median (IQR)                | 1.28 (0.91-2.41)          | 1.56 (0.98-3.16)                   | 1.12 (0.87-2)                            |         |
| ≤ 2 mg/dL                                        | 103 (67.3)                | 35 (55.6)                          | 68 (75.6)                                | 0.009   |
| > 2 mg/dL                                        | 50 (32.7)                 | 28 (44.4)                          | 22 (24.4)                                |         |
| eGFR, mL/min/1.73 m <sup>2</sup> , mean±SD       | 52.53±31.49               | 45.26±31.03                        | 57.7±40.00                               | 0.017   |
| Corrected serum calcium                          | 10.22 (9.55-11.95)        | 10.74 (9.56-13.42)                 | 10.1 (9.53-11.2)                         |         |
| ≤ 11 mg/dL                                       | 96 (62.7)                 | 33 (52.4)                          | 63 (70)                                  | 0.035   |
| > 11 mg/dL                                       | 57 (37.3)                 | 30 (47.6)                          | 27 (30)                                  |         |
| LDH, u/L, median (IQR)                           | 222 (155.25-299.25)       | 238 (169-353.25)                   | 219 (148.5-263)                          | 0.224   |
| Serum albumin median (IQR)                       | 2.8 (2.3-3.5)             | 2.8 (2.3-3.5)                      | 2.85 (2.3-3.43)                          |         |
| < 3.5 g/dL                                       | 114 (74.5)                | 46 (73)                            | 68 (75.6)                                | 0.723   |
| ≥ 3.5 g/dL                                       | 39 (25.5)                 | 17 (27)                            | 22 (24.4)                                |         |
| Serum globulin, g/dL, mean±SD                    | 7.18±3.26                 | 6.98±3.05                          | 7.32±3.41                                | 0.510   |
| Serum β <sub>2</sub> -microglobulin median (IQR) | 7.80 (3.33-9.68)          | 6.58 (4.22-14.5)                   | 4.54 (2.9-7.47)                          |         |
| < 3.5 mg/L                                       | 43 (28.1)                 | 11 (17.5)                          | 32 (35.6)                                | 0.021   |
| ≥ 3.5 mg/L                                       | 42 (27.5)                 | 16 (25.4)                          | 26 (28.8)                                |         |
| ≥ 5.5 mg/L                                       | 68 (44.4)                 | 36 (57.1)                          | 32 (35.6)                                |         |
| ISS stage                                        |                           |                                    |                                          |         |
| I                                                | 24 (15.7)                 | 9 (14.3)                           | 15 (16.7)                                | 0.017   |
| II                                               | 61 (39.9)                 | 18 (28.6)                          | 43 (47.8)                                |         |
| III                                              | 68 (44.4)                 | 36 (57.1)                          | 32 (35.5)                                |         |
| Type of heavy chain                              |                           |                                    |                                          |         |
| IgA                                              | 37 (24.2)                 | 13 (20.6)                          | 24 (26.7)                                | 0.846   |
| IgM                                              | 4 (2.6)                   | 2 (3.2)                            | 2 (2.2)                                  |         |
| IgG                                              | 93 (60.8)                 | 39 (62)                            | 54 (60)                                  |         |
| No                                               | 19 (12.4)                 | 9 (14.2)                           | 10 (11.1)                                |         |
| Type of light chain                              |                           |                                    |                                          |         |
| Kappa                                            | 102 (66.7)                | 40 (63.5)                          | 62 (68.9)                                | 0.601   |
| Lambda                                           | 51 (33.3)                 | 23 (36.5)                          | 28 (31.1)                                |         |
| Kappa level, mg/L median (IQR)                   | 137.85 (16.16-1116.86)    | 237.05 (16.47-1715.70)             | 89.09 (14.68-864.63)                     | 0.131   |
| Lambda, mg/L median (IQR)                        | 13.48 (8.26-236.37)       | 15.06 (8.64-415.12)                | 12.45 (6.91-208.74)                      | 0.184   |
| Treatment                                        |                           |                                    |                                          |         |
| Novel agent-based                                | 41 (26.9)                 | 6 (9.6)                            | 35 (39)                                  | < 0.001 |
| CTD                                              | 9 (5.9)                   | 3 (4.8)                            | 6 (6.7)                                  |         |
| BD                                               | 1 (0.7)                   | 0 (0)                              | 1 (1.1)                                  |         |
| BCD                                              | 29 (18.9)                 | 3 (4.8)                            | 26 (29)                                  |         |
| BMP                                              | 1 (0.7)                   | 0 (0)                              | 1 (1.1)                                  |         |
| DaraBTD                                          | 1 (0.7)                   | 0 (0)                              | 1 (1.1)                                  |         |
| Conventional chemotherapy                        | 91 (59.4)                 | 36 (57.1)                          | 55 (61)                                  |         |
| CD                                               | 61 (39.8)                 | 24 (38.1)                          | 37 (41.1)                                |         |
| MP                                               | 7 (4.6)                   | 4 (6.3)                            | 3 (3.3)                                  |         |
| VAD                                              | 21 (13.7)                 | 8 (12.7)                           | 13 (14.4)                                |         |
| DCEP                                             | 2 (1.3)                   | 0 (0)                              | 2 (2.2)                                  |         |
| Died before treatment                            | 21 (13.7)                 | 21 (33.3)                          | 0 (0)                                    |         |

**Table 1** Baseline clinical and treatment characteristics of patients with multiple myeloma (n = 153) (continue)

| Characteristics                   | Total<br>N = 153<br>n (%) | Early mortality<br>N = 63<br>n (%) | Survivor at 12 months<br>N = 90<br>n (%) | p-value |
|-----------------------------------|---------------------------|------------------------------------|------------------------------------------|---------|
| Response                          |                           |                                    |                                          |         |
| < PR                              | 25 (16.4)                 | 7 (11.1)                           | 18 (20)                                  | < 0.001 |
| PD                                | 6 (4)                     | 4 (6.3)                            | 2 (2.2)                                  |         |
| SD                                | 19 (12.4)                 | 3 (4.8)                            | 16 (17.8)                                |         |
| ≥ PR                              | 81 (52.9)                 | 9 (14.3)                           | 72 (80)                                  |         |
| PR                                | 31 (20.3)                 | 6 (9.5)                            | 25 (27.8)                                |         |
| VGPR                              | 12 (7.8)                  | 1 (1.6)                            | 11 (12.2)                                |         |
| CR                                | 17 (11.1)                 | 1 (1.6)                            | 16 (17.8)                                |         |
| sCR                               | 21 (13.7)                 | 1 (1.6)                            | 20 (22.2)                                |         |
| Die before evaluating the disease | 47 (30.7)                 | 47 (74.6)                          | 0 (0)                                    |         |

Abbreviations: ASCT, autologous stem cell transplantation; BCD, bortezomib-cyclophosphamide-dexamethasone; BD, bortezomib-dexamethasone; BMI, body mass index; BMP, bortezomib-melphalan-prednisolone; CD, cyclophosphamide-dexamethasone; CR, complete response; CTD, cyclophosphamide-thalidomide-dexamethasone; DaraBTD, daratumumab-bortezomib-thalidomide-dexamethasone; DCEP, dexamethasone-cyclophosphamide-etoposide-cisplatin; eGFR, estimated glomerular filtration rate; IQR, interquartile range; ISS, international staging system; LDH, lactate dehydrogenase; MP, melphalan-prednisolone; PD, progress disease; PR, partial response; sCR, stringent complete response; SD, standard deviation; VAD, vincristine-adriamycin-dexamethasone; VGPR, very good partial response; sCR, stringent complete response; SD, standard deviation

**Table 2** Univariable and multivariable analysis of factors associated with early mortality (within 12 months) in patients with multiple myeloma

| Predictor                           | Univariable analysis |         | Multivariable analysis |         |
|-------------------------------------|----------------------|---------|------------------------|---------|
|                                     | HR (95%CI)           | p-value | HR (95%CI)             | p-value |
| Age (years)                         | 1.07 (1.01-1.12)     | 0.012   | 1.07 (1.01-1.16)       | 0.034   |
| Sex                                 |                      |         |                        |         |
| Male                                |                      |         |                        |         |
| Female                              | 0.93 (0.49-1.79)     | 0.830   | 0.52 (0.12-2.32)       | 0.393   |
| BMI (kg/m <sup>2</sup> )            |                      |         |                        |         |
| Normal (18.5-24.9)                  |                      |         |                        |         |
| Underweight (< 18.5)                | 1.76 (1.33-2.90)     | 0.013   | 1.74 (0.22-2.54)       | 0.599   |
| Overweight (≥ 25)                   | 1.48 (0.92-2.69)     | 0.074   | 1.12 (0.32-2.13)       | 0.420   |
| Hemoglobin (g/dL)                   | 0.97 (0.84-1.12)     | 0.687   | 0.97 (0.74-1.36)       | 0.784   |
| Serum creatinine (mg/dL)            |                      |         |                        |         |
| ≤ 2 mg/dL                           |                      |         |                        |         |
| > 2 mg/dL                           | 1.27 (1.14-2.42)     | 0.010   | 1.40 (0.62-2.12)       | 0.085   |
| Corrected serum calcium             |                      |         |                        |         |
| ≤ 11 mg/dL                          |                      |         |                        |         |
| > 11 mg/dL                          | 2.05 (1.05-4.02)     | 0.036   | 1.42 (0.57-3.54)       | 0.454   |
| LDH                                 |                      |         |                        |         |
| Normal                              |                      |         |                        |         |
| Elevate                             | 1.42 (0.99-1.94)     | 0.174   | 1.02 (0.54-1.67)       | 0.202   |
| Serum albumin                       |                      |         |                        |         |
| < 3.5 g/dL                          |                      |         |                        |         |
| ≥ 3.5 g/dL                          | 0.88 (0.42-1.83)     | 0.723   | 0.79 (0.26-1.93)       | 0.619   |
| Serum globulin (g/dL)               | 0.97 (0.88-1.07)     | 0.518   | 0.94 (0.78-1.12)       | 0.464   |
| Serum β <sub>2</sub> -microglobulin |                      |         |                        |         |
| < 5.5 mg/L                          |                      |         |                        |         |
| ≥ 5.5 mg/L                          | 1.11 (1.05-1.19)     | 0.001   | 1.32 (1.03-1.67)       | 0.026   |
| ISS stage                           |                      |         |                        |         |
| I                                   |                      |         |                        |         |
| II                                  | 0.63 (0.21-1.89)     | 0.408   | 0.98 (0.40-2.38)       | 0.990   |
| III                                 | 1.89 (0.66-5.42)     | 0.239   | 1.22 (0.52-1.72)       | 0.878   |

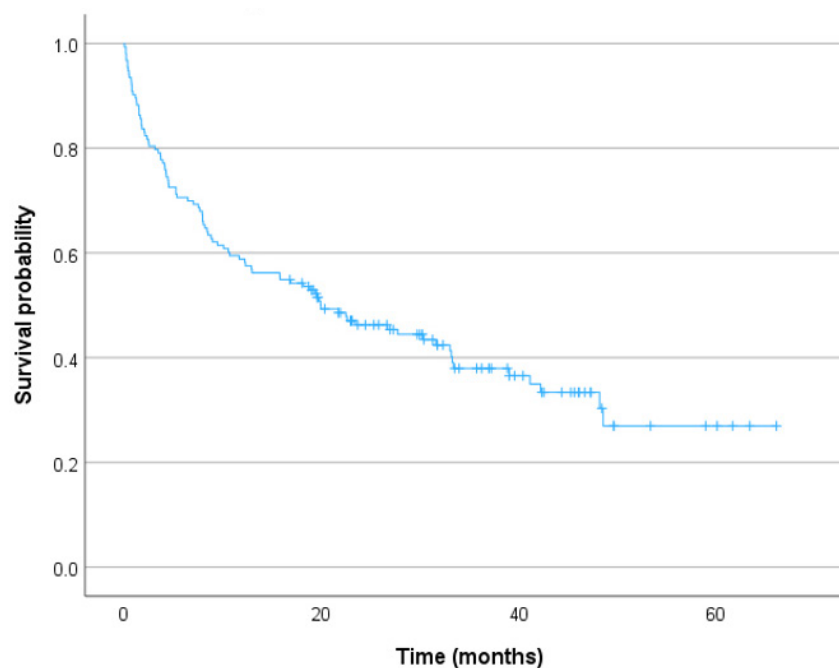
Abbreviations: HR, hazard ratio; others see Table 1

**Table 3** Association between treatment type, treatment response and early mortality in patients with multiple myeloma

| Characteristics              | Early mortality<br>n (%) | Survivor at 12 months<br>N (%) | Total (n) | p-value | OR (95%CI)       |
|------------------------------|--------------------------|--------------------------------|-----------|---------|------------------|
| Treatment type (n = 132)     |                          |                                |           |         |                  |
| ● Novel agents-base          | 6 (14.6)                 | 35 (85.4)                      | 41        | 0.012   | Ref (baseline)   |
| ● Conventional chemotherapy  | 36 (39.6)                | 55 (60.4)                      | 91        |         | 3.31 (1.26-8.70) |
| Treatment response (n = 106) |                          |                                |           |         |                  |
| ● ≥ PR                       | 9 (11.1)                 | 72 (88.9)                      | 81        | 0.017   | Ref (baseline)   |
| ● < PR                       | 7 (28.0)                 | 18 (72.0)                      | 25        |         | 3.36 (1.20-9.45) |

Abbreviations: OR, odds ratio; PR, partial response; Ref, reference group

Note: Of the 153 patients included in the study, 21 patients died before receiving any specific MM cancer treatment, and 26 patients died before treatment response could be evaluated. Treatment response was evaluable in 106 patients

**Figure 1** Kaplan-Meier overall survival (OS)

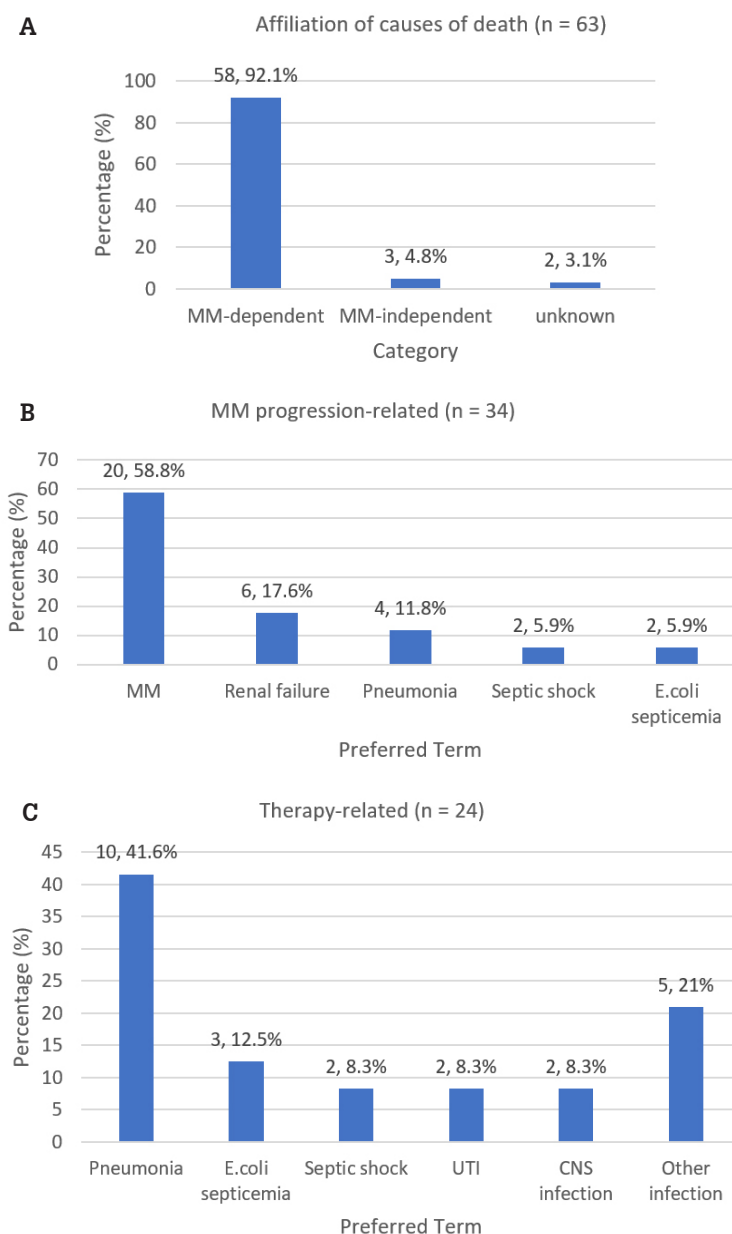
pneumonia (n = 4, 11.8%), septic shock (n = 2, 5.9%) and *Escherichia coli* septicemia (n = 2, 5.9%) (Figure 2A). The remaining 24 MM-dependent deaths, with causes including pneumonia (n = 10, 41.6%), *Escherichia coli* septicemia (n = 3, 12.5%), septic shock (n = 2, 8.3%), urinary tract infections (n = 2, 8.3%), CNS infection (n = 2, 8.3%), disseminate tuberculosis (n = 1, 4.2%), peritonitis (n = 1, 4.2%), *Acinetobacter baumannii* septicemia (n = 1, 4.2%), *Klebsiella pneumoniae* septicemia (n = 1, 4.2%) and COVID-19 infection (n = 1, 4.2%) (Figure 2B).

MM-independent causes of death (n = 3) included congestive heart failure, intraventricular hemorrhage and cerebellar stroke

## Discussion

The introduction of drugs with novel mechanisms of action has transformed the treatment of MM and significantly improved patient outcomes. However, data on early mortality remain limited.

In our study, 63 patients (41.2%) died within 12 months, and the a median OS for the entire cohort was 19.97 months. Only 9 patients (5.9%) underwent ASCT, and all survived beyond 12 months. This ASCT rate is substantially lower than the 20-50% reported in international series. Several factors may explain this finding. First, most patients received conventional chemotherapy and were unable to afford novel agent-based regimens,



CNS, central nervous system; *E.coli*, *Escherichia coli*; UTI, urinary tract infection

**Figure 2** Contributing causes of early deaths A. Categories, B. MM progression-related, C. Therapy-related

resulting in only 32.6% achieving a deep response ( $\geq$  VGPR) sufficient for transplantation eligibility. Second, the absence of stem cell transplant centers in provincial hospitals limits access, requiring referral to tertiary centers. Additional barriers include the lack of available caregivers during the transplantation period and the inability of patients to work for three to six months after ASCT, leading to income loss. Together, these represent significant financial and logistical obstacles, despite coverage of transplantation costs under the national healthcare benefit scheme.

Compared with previous studies, our study showed an early mortality rate three to four times higher, a median overall survival approximately three times shorter and death before first-line treatment five times higher. Previous reports have documented 12-month mortality rates of 8.3-13.8%. McQuilten Z, et al.,<sup>2</sup> with a median (interquartile range in a prospective cohort of 2,377 patients with NDMM enrolled in the Australian and New Zealand Myeloma and Related Diseases Registry (MRDR) between July 2011 and March 2020, reported a median OS of 70 months and 12-month overall mor-

tality of 9.1% ( $n = 216$ ). Among those with a defined primary cause of death, 78% were disease-related, 7% infection-related and 15% due to other causes. Jung SH, et al.,<sup>4</sup> in a retrospective study of 542 patients with NDMM from three hospitals in Korea, reported a median OS of 59.2 months (2010-2014 cohort) and a 12-month mortality of 13.8%. Infection was the leading cause of early mortality (36%), most common septic shock secondary to pneumonia. Similarly, a single-center study from Taipei including 451 patients diagnosed between January 2002 and April 2015 reported early a -6-months early mortality of 12.6%, with pneumonia as the predominant cause of early death.<sup>13</sup> Mohty M, et al.,<sup>14</sup> also reported that 6% of patients died before receiving first-line treatment. Notably, these fatalities were not exclusively due to disease progression; renal failure (46%) and infection (39%) were major contributors.

Additionally, the observed early mortality rate in our cohort was higher than that reported in previous studies. Several factors may have contributed to this discrepancy. Many patients presented with advanced-stage disease or poor performance status at the time of diagnosis, and severe complications such as infection and renal impairment were commonly observed. Another important factor is the limitation in treatment options and infrastructure at our center. As a non-transplant, non-university hospital, we lack access to advanced therapies such as ASCT and novel agents like daratumumab and lenalidomide, which are unavailable due to resource constraints and national reimbursement policies. Consequently, many patients received only conventional therapies, such as cyclophosphamide-dexamethasone, melphalan-prednisolone or vincristine-doxorubicin-dexamethasone regimens. Moreover, structured systems for close post-treatment monitoring were not fully established in our setting, which may have affected the early detection and management of complications.

Early mortality within 12 months occurred more frequently among patients receiving conventional chemotherapy compared with those on novel agent-based regimens (39.6% vs 14.6%; OR = 3.31, 95%CI: 1.26-8.70;

$p = 0.012$ ). Similarly, patients achieving less than PR had a higher rate of early mortality than those with  $\geq$  PR (28.0% vs 11.1%; OR = 3.36, 95%CI: 1.20-9.45;  $p = 0.017$ ). These findings suggest that the use of conventional chemotherapy and suboptimal treatment response ( $< PR$ ) are both associated with a substantially increased risk of early mortality in patients with multiple myeloma. This highlights the potential importance of optimizing treatment regimens and achieving deeper responses to improve survival outcomes.

Furthermore, delays in diagnosis and treatment initiation, as well as socioeconomic barriers—including geographic distance and limited healthcare access in the Thai context—may have further contributed to the higher early mortality rate. These real-world challenges underscore the need for improved early detection strategies and equitable access to effective therapies in resource-limited settings.

Infections represented a major contributor to early mortality, occurring in both MM progression-related and therapy-related categories. Among MM progression-related deaths, 23.6% were due to infectious causes, whereas in therapy-related deaths, infections accounted for 100% of cases. This high burden of infection-related mortality highlights the urgent need for preventive measures, such as targeted antibacterial prophylaxis for high-risk patients at the initiation of therapy. A systematic review and meta-analysis showed that the overall incidence of infection within three months was lower for the antibiotic group compared with the placebo group (18.4% vs 23.4%, RR: 0.79, 95%CI: 0.62-1.00,  $p = 0.05$ ,  $I^2 = 6.5\%$ ). No difference was noted in mortality in the first three months (1.5% vs 3.5%, RR: 0.47, 95%CI: 0.17-1.27,  $p = 0.60$ ,  $I^2 = 28.1\%$ ).<sup>15</sup> By contrast, Vesole, et al.<sup>16</sup> reported that prophylactic antibiotics during the initial two months of NDMM treatment (including trimethoprim-sulfamethoxazole, ciprofloxacin or a placebo) had no significant impact on the incidence of infections (20% vs 23% vs 22%, respectively,  $p = 0.95$ ). In our study, groups at high risk for early mortality included advanced age patients and with high  $\beta_2M$  levels. Accordingly,

antibacterial prophylaxis may be considered for high-risk patients at the commencement of therapy. Addressing strategies aimed at reducing infection-related deaths is imperative. These may include reinforcing patient education on infection prevention and self-care with active caregiver participation, instituting systematic post-treatment follow-up and developing pathways for the early detection and timely treatment of infections.

Similar to our study, previous reports have identified age<sup>2,4</sup> and  $\beta_2$ M<sup>17-19</sup> as factors associated with early mortality. Other reported factors, which were not independent predictors in our study, include male,<sup>13</sup> low BMI,<sup>4</sup> thrombocytopenia,<sup>4</sup> renal failure,<sup>4</sup> low albumin level,<sup>2,13</sup> serum calcium,<sup>13</sup> LDH,<sup>13</sup> plasma cell leukemia,<sup>13</sup> ECOG performance status,<sup>2</sup> cardiac disease<sup>2</sup> and ISS stage.<sup>2</sup>

### Limitation

Our study has several limitations. First, it was a retrospective study with a relatively small sample size. Second, during the period (January 1, 2018, to May 31, 2023), access to expensive drugs was limited due to the national treatment reimbursement policy. In addition, the choice of the first-line therapy was at the discretion of each physician, making it difficult to evaluate the effect of treatment in the development of early mortality without confounding factors or systematic bias. Consequently, the role of treatment in the development of early mortality in patients with MM could not be definitively determined, and further studies are warranted. Third, the interval from diagnosis to initiation of treatment was not collected, which may have affected mortality among patients who died before receiving therapy or before response assessment. Fourth, we did not perform interphase fluorescent in situ hybridization (iFISH) for all patients to assess chromosomal abnormalities. As a result, we were unable to apply recently published recommendations regarding updated prognostic stratification for newly diagnosed MM.<sup>20</sup> Finally, this study was conducted at a single, non-transplant, non-university hospital, which may limit the generalizability of the findings. The patient population may not reflect those

treated at tertiary or academic centers, where access to more advanced therapies and supportive care is more widely available.

### Conclusion

In this real-world cohort of patients with NDMM treated at a non-transplant center in Thailand, the early mortality rate within 12 months was 41.18%, substantially higher than that reported in previous studies. Older age and  $\beta_2$ M levels  $\geq 5.5$  mg/L were independent predictors of early death, while treatment with conventional chemotherapy and suboptimal response ( $< PR$ ) were associated with higher mortality risk. The majority of early deaths were MM-dependent, with infections being the most common cause. These findings highlight the urgent need to improve early detection, optimize treatment strategies, expand access to novel therapies and implement targeted infection prevention measures—particularly among high-risk patients—to reduce early mortality in resource-limited settings.

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