Early Mortality Risk in Patients with Multiple Myeloma

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Abstract

Background: advances in treatment has improved greatly survival of multiple myeloma in the last two decades, and this improvement has been endorsed by wider use of novel drugs and tandem autologous stem cell transplantation. however, still there were cases died earlier post diagnosis

Objectives: to study the risk factors of early mortality in patients with multiple myeloma in Kurdistan region of Iraq

Patients and methods: a 176 cases that were diagnosed with symptomatic multiple myeloma between (January 2012 – July 2019) in cancer centers in Kurdistan region of Iraq. a total of 152 were continued within the study through their recorded sheet. their data were analysed to determine what are the main risk factors that have an impact on early mortality among our myeloma patients.

Results: among the total of 152 studied patients nine of them (5.9%) died early. the highest proportion (32.2%) of the sample aged 60-69 years, more than half (57.2%) of the them were male. the majority of the patients (80.9%) have been diagnosed during 2016-2019. the incidence of early death was 8.7% among patients who didn’t take the cytotoxic treatment compared with 1.7% of patients who took that treatment, but the difference was not significant (P = 0.089). the early death rate was significantly high (22.2%) among patients who didn’t take the immunomodulatory drugs, versus 2.4% of patients who took the immunomodulatory drugs (P = 0.001). the incidence of early mortality was 9.6% among patients with lactate dehydrogenase of ≥ 250 U/L compared with 0% among patients with LDH of less than 250 (P = 0.013).

Conclusion: LDH level is a high prediction in finding early mortality among patients with multiple myeloma, and intake of immunomodulatory drugs is highly preventive in early death occurrence.

keywords: Multiple Myeloma, Kurdistan Region of Iraq

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Introduction

Multiple myeloma (MM) is characterized by the proliferation of a single clone of plasma cells that produce a monoclonal protein. The plasma cell proliferation results in extensive skeletal involvement, with osteolytic lesions,
hypercalcemia, anemia and/or soft tissue plasmacytoma. In addition, the excessive production of nephrotoxic monoclonal immunoglobulin can result in renal failure and an increased risk of developing potentially life-threatening infections due to the lack of functional immunoglobulins.\(^1\) MM represents approximately 10% of hematologic malignancy and 1% of all cancers. It is conventionally considered incurable; accounts for 20% of deaths from hematologic malignancy and 2% of all cancer deaths.\(^2\) There is a slight male predominance. The median age of onset is 66 years, and only 2% of patients less than 40 years of age at diagnosis.\(^3\) Geographically, the frequency is very unevenly distributed in the world with the highest incidence in the industrialized regions of Australia, New Zealand, Europe and North America. Incidence and mortality seem to be stable in Asian countries and to increase slowly over the decades among whites in the western countries.\(^4\) In a study done in Iraq in (2000-2004) showed the incidence of MM (0.73\%),\(^5\) lower than that reported in USA (0.76\%).\(^6\) Pneumonia represented as the leading cause of early mortality in myeloma patients, followed by renal failure. And other risk of early mortality in patients with newly diagnosed multiple myeloma compared with non-early mortality myeloma patients is being male, primary plasma cell leukemia, low platelet count, low hemoglobin, low serum albumin, high corrected serum calcium, high serum creatinine, high lactic dehydrogenase, high serum β2-microglobulin, poor performance status, and high international staging system stage.\(^7\) Usual clinical presentation of (MM) includes bone pain, pathologic fractures, weakness, anemia, infection (often pneumococcal), hypercalcemia, spinal cord compression, and renal failure. Patients may also complain of nonspecific constitutional symptoms related to hyper viscosity and hypercalcemia.\(^8\) Once symptoms of multiple myeloma develop, treatment with one or more of the options is recommended for almost all patients.\(^9\) Because multiple myeloma can cause a number of complications, you may also need treatment for those specific conditions like bone pain, renal complications, infections, bone loss, and anemia.\(^10\) The Mayo clinic estimated that the median survival of myeloma patients is 8 years, and improvements have occurred not only during early stages of the disease but also throughout the disease course.\(^11\)

**Aim**

**Aim of the study:** is to analyze the risk factors of early mortality among multiple myeloma patients.

**Patients and Methods**

This retrospective study that was carried out between January 2012 and July 2019 at main cancer centers in Kurdistan region of Iraq (KRI) which includes Nanakaly Hospital in Erbil, Hiwa Hospital in Sulaimaniyah, and Azadi Hospital in Duhok. Among 176 multiple myeloma patients that were diagnosed according to International Myeloma Working Group (IMWG) criteria only 152 were recruited. The exclusion criteria were missing data, Solitary plasmacytoma, and Smoldering myeloma. Data collection was performed by reviewing medical records of the patients that was involved demographic data (age, sex, residency) and laboratory data including hemoglobin, bone marrow examination, serum albumin, corrected serum calcium, serum creatinine, (LDH) and β2-microglobulin (β2M), the performance state of the patients was determined according to the Eastern Cooperative Oncology Group (ECOG) performance score depending on the available
data in the patients files. Clinical stages were determined based on International Staging System (ISS).\(^8\) Cutoff values of serum hemoglobin 10g/dL, calcium 12mg/dL, albumin 3.5g/dL, and \(\beta 2M\) and 5.5mg/mL, were chosen according to Durie–Salmon (DS) and International Staging System (ISS)\(^8\) criteria. Cutoff values of serum creatinine 2mg/dl, and LDH 250 U/L which were correlated with early mortality in previous studies.\(^27\) The diagnosis of primary plasma cell leukemia is based upon the percentage (≥ 20%) and absolute number (≥ \(2 \times 10^9\)/L) of plasma cells in the peripheral blood.\(^12\) Treatment regimens composed of induction treatment and bisphosphonates were collected. In our study, the patients were grouped into 2 diagnosis-year strata: a group from 2012 to 2015 and 2016 to 2019. Our primary endpoint was early mortality, defined as death within 60 days after diagnosis.\(^11,27\) Informed consent was obtained from included patients for accessing their files, and the study was approved by the Ethical Committee of the Kurdistan Board for Medical Specialties.

### Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 22). Categorical variables were presented in the form of frequencies and percentages. Numerical variables were presented in the form of means and standard deviations. Fisher’s exact test was used instead of the Chi square test when the expected count of more than 20% of the cells of the table was less than 5. A p value of \(\leq 0.05\) was considered statistically significant.

### Results

The total number of patients was 152 patients, 9 (5.9%) were early mortality, and 143 (94.1%) were non-early mortality. The highest proportion (32.2%) of the sample aged 60-69 years, and 27.6% aged 50-59 years. No of early mortality was 1 between years 2012-2015 and that’s due to small sample size that is 28 cases, while in 2016-2019 from 115 cases 8 were recorded in early mortality state. More than half (57.2%) of the patients were males as presented in (Table-1). The table shows also that 44.7% of the sample were from Sulaimaniyah center, 40.8% were from Erbil center, and 14.5% were from Duhok. The majority of the patients (80.9%) have been diagnosed during 2016-2019. According to performance state, 61.8% of the patients were of bad performance and according to ISS around half (46.7%) of the patients were of stage II (Table-1).

### Table 1. Basic characteristics of the study sample

| Age (years) | No. | (%)  |
|------------|-----|------|
| < 50       | 27  | (17.8) |
| 50-59      | 42  | (27.6) |
| 60-69      | 49  | (32.2) |
| ≥ 70       | 34  | (22.4) |

| Gender     |     |      |
|------------|-----|------|
| Male       | 87  | (57.2) |
| Female     | 65  | (42.8) |

| Governorate |     |      |
|-------------|-----|------|
| Erbil       | 62  | (40.8) |
| Sulaimaniyah| 68  | (44.7) |
| Duhok       | 22  | (14.5) |

| Date of diagnosis |     |      |
|-------------------|-----|------|
| 2012-2015         | 29  | (19.1) |
| 2016-2019         | 123 | (80.9) |

| ECOG *            |     |      |
|-------------------|-----|------|
| Good performance  | 58  | (38.2) |
| Bad performance   | 94  | (61.8) |

| Stage of disease (ISS)** |     |      |
|--------------------------|-----|------|
| Stage I                  | 41  | (27.0) |
| Stage II                 | 71  | (46.7) |
| Stage III                | 40  | (26.3) |
| Total                    | 152 | (100.0) |

*Eastern Cooperative Oncology Group
**International Staging System

(Table-2), shows that the mean ± SD for the following variables were: Hb (10.00 ± 2.06 g/dl), serum creatinine (1.60 ± 1.55 mg/dl), serum albumin (3.47 ± 0.79 g/dl), \(\beta 2M\) (4.45 ±
2.95 mg/ml), LDH (322.99 ± 182.56 U/l), corrected calcium (10.23 ± 1.53 mg/dl), peripheral plasma cell (1.38 ± 7.47 %), Bone marrow biopsy plasma cell (45.02 ± 20.38 %). The other details are presented in (Table-2).

Table 2. Laboratory characteristics of the studied sample.

|                      | Mean   | (± SD) | SE  | Median | Min.  | Max.   |
|----------------------|--------|--------|-----|--------|-------|--------|
| Hb (g/dl)            | 10.00  | (± 2.06)| 0.17| 10.00  | 4.90  | 16.00  |
| S. creatinine (mg/dl)| 1.60   | (± 1.55)| 0.13| 1.10   | 0.10  | 10.60  |
| S. albumin           | 3.47   | (± 0.79)| 0.06| 3.55   | 0.00  | 5.60   |
| β2M(mg/ml)           | 4.45   | (±2.95)| 0.24| 3.80   | 0.40  | 17.00  |
| LDH (U/l)            | 322.99 | (±182.56)| 14.81| 290.00 | 32.00 | 1055.00|
| Corrected Ca. (mg/dl)| 10.23  | (±1.53)| 0.12| 10.00  | 7.00  | 15.50  |
| Peripheral plasma cell (g/dl) | 1.38 | (±7.47)| 0.61| 0.00   | 0.00  | 70.00  |
| BM biopsy plasma cell % | 45.02 | (±20.38)| 1.65| 44.00  | 3.00  | 95.00  |

That the incidence of early death was 8.7% among patients who didn’t take the cytotoxic treatment compared with 1.7% of patients who took that treatment, but the difference was not significant (p = 0.089). The early death rate was significantly high (22.2%) among patients who didn’t take immunomodulating drugs (IMiDs) compared with 2.4% of patients who took the immunomodulating drugs (Table-3)

Table 3. Incidence of early mortality by cytotoxic drugs and IMiDintake.

|                  | Early mortality | Non-Early Mortality | Total |
|------------------|-----------------|---------------------|-------|
|                  | No.  | %    | No.  | %    | No.  | %    | P  |
| Cytotoxic        |      |      |      |      |      |      |    |
| No               | 8    | 8.7  | 84   | 91.3 | 92   | 100.0|    |
| Yes              | 1    | 1.7  | 59   | 98.3 | 60   | 100.0| 0.089* |
| IMID             |      |      |      |      |      |      |    |
| No               | 6    | 22.2 | 21   | 77.8 | 27   | 100.0|    |
| Yes              | 3    | 2.4  | 122  | 97.6 | 125  | 100.0| 0.001* |
| Total            | 9    | 5.9  | 143  | 94.1 | 152  | 100.0|    |

*By Fisher’s exact test.

It is evident in (Table-4) that there was no significant association between early death with the following variables: age (p = 0.308), gender (p = 0.302), Hb (p = 0.184), serum creatinine (p > 0.999), serum albumin (p = 0.301), β2M (p = 0.052), corrected calcium (p = 0.217), plasma cell (p > 0.999), bone marrow biopsy plasma cell (p = 0.724), ECOG performance state(p = 0.154), ISS clinical staging(p = 0.052), and date of diagnosis (p > 0.999). On the other hand, the table shows that the incidence of early mortality was 9.6% among patients with LDH of ≥ 250 compared with 0% among patients with LDH of less than 250 U/L (p = 0.013).
Table 4. Incidence of early mortality by the studied factors.

|                | Early mortality | Non-early mortality | Total |
|----------------|-----------------|---------------------|-------|
|                | No. (%)         | No. (%)             | No. (%) |
| **Age (years)**|                 |                     |       |
| < 50           | 0 (0.0)         | 27 (100.0)          | 27 (100.0) |
| 50-59          | 2 (4.8)         | 40 (95.2)           | 42 (100.0) |
| 60-69          | 3 (6.1)         | 46 (93.9)           | 49 (100.0) |
| ≥ 70           | 4 (11.8)        | 30 (88.2)           | 34 (100.0) |
| **Gender**     |                 |                     |       |
| Male           | 7 (8.0)         | 80 (92.0)           | 87 (100.0) |
| Female         | 2 (3.1)         | 63 (96.9)           | 65 (100.0) |
| **Hb**         |                 |                     |       |
| < 10           | 7 (8.4)         | 76 (91.6)           | 83 (100.0) |
| ≥ 10           | 2 (2.9)         | 67 (97.1)           | 69 (100.0) |
| **S. creatinine** |               |                     |       |
| < 2            | 7 (5.7)         | 115 (94.3)          | 122 (100.0) |
| ≥ 2            | 2 (6.7)         | 28 (93.3)           | 30 (100.0) |
| **S. albumin** |                 |                     |       |
| < 3.5          | 6 (8.7)         | 63 (91.3)           | 69 (100.0) |
| ≥ 3.5          | 3 (3.6)         | 80 (96.4)           | 83 (100.0) |
| **β2M**        |                 |                     |       |
| < 5.5          | 4 (3.6)         | 107 (96.4)          | 111 (100.0) |
| ≥ 5.5          | 5 (12.8)        | 34 (87.2)           | 39 (100.0) |
| **LDH**        |                 |                     |       |
| < 250          | 0 (0.0)         | 58 (100.0)          | 58 (100.0) |
| ≥ 250          | 9 (9.6)         | 85 (90.4)           | 94 (100.0) |
| **Corrected Calcium** |       |                     |       |
| <12            | 5 (4.3)         | 111 (95.7)          | 116 (100.0) |
| ≥12            | 4 (11.1)        | 32 (88.9)           | 36 (100.0) |
| **Plasma cell**|                 |                     |       |
| Not present    | 9 (6.2)         | 136 (93.8)          | 145 (100.0) |
| Present        | 0 (0.0)         | 7 (100.0)           | 7 (100.0) |
| **BM biopsy plasma cell** |       |                     |       |
| < 60           | 7 (6.6)         | 99 (93.4)           | 106 (100.0) |
| ≥ 60           | 2 (4.3)         | 44 (95.7)           | 46 (100.0) |
| **ECOG**       |                 |                     |       |
| 0-1            | 1 (1.7)         | 57 (98.3)           | 58 (100.0) |
| ≥ 2            | 8 (8.5)         | 86 (91.5)           | 94 (100.0) |
| **ISS Stage**  |                 |                     |       |
| Stage I        | 0 (0.0)         | 41 (100.0)          | 41 (100.0) |
| Stage II       | 4 (5.6)         | 67 (94.4)           | 71 (100.0) |
| Stage III      | 5 (12.5)        | 35 (87.5)           | 40 (100.0) |
| **Date of Diagnosis** |       |                     |       |
| 2012-2015      | 1 (3.4)         | 28 (96.6)           | 29 (100.0) |
| 2016-2019      | 8 (6.5)         | 115 (93.5)          | 123 (100.0) |
| Total          | 9 (5.9)         | 143 (94.1)          | 152 (100.0) |

*By Fisher’s exact test.
The causes of death among 9 patients whom died early were pneumonia in 66.6%, urinary tract infection and septicemia (22.2%) and renal failure in one patient (11.1). (Figure-1)

Discussion
This is the first cohort study to examine the risk factors associated with early mortality in patients newly diagnosed with MM in Kurdistan region Iraq (Erbil, Sulaimaniyah, and Duhok) in which the diagnosis was confirmed by careful evaluation and reviews of all medical records, and complete information on disease description and initial treatment for individual patients was taken. Our study shows the highest proportion (32.2%) of the sample aged 60-69 years, and 27.6% aged 50-59 years which is matched with another study done earlier that was reported the peak incidence of myeloma among 50-70-year age group. However we could not detect any correlation between the age of our patient with early mortality (EM), our finding is corresponded with another two studies, on the other hand our results didn’t matched with these mentioned studies considering the relationship of gender of patient with EM. Regarding the laboratory characteristics of the studied patients our results are in agreement with another study reporting on the connection between EM and the serum level of LDH. Increased LDH, which catalyzes the reversible transformation of pyruvate to lactate in the glycolysis pathway, denotes an aggressive disease and suggests a high proliferation rate and the presence of a tumor mass, in particular extramedullary and extra osseous disease. Several studies in the conventional chemotherapy era of myeloma treatment have
shown that high LDH levels are associated with shorter overall survival.\textsuperscript{16,17} Also in the era of novel therapy, LDH still has its impact on survival. With raising LDH levels, more patients presented with extraosseous soft tissue disease, renal failure, high B2MG levels, hypercalcemia, and a shorter survival time with drug resistance.\textsuperscript{18,19} On the other hand, we could not find a significant correlation between EM and other patients laboratory parameters like Hb, serum creatinine, serum albumin and β2M and serum calcium as well. In our study in spite of having a high incidence of EM (6.7\%) among patients with serum creatinine ≥ 2, but it was not significant (p > 0.999) while Rafael Rios et al. in his study shows that renal failure was significant predictor in patients with early mortality in multiple myeloma.\textsuperscript{20} Low serum albumin in MM is caused mainly by inflammatory cytokines, such as interleukin-6, secreted by the myeloma microenvironment.\textsuperscript{20} It also may reflect that myeloma patients who died early have a high degree of stress caused by severe infection, and impaired kidney and liver function.\textsuperscript{21} However in the current study the incidence of EM was 8.7\% among those with low serum albumin versus 3.6\% among those with patients with serum albumin ≥ 3.5 (p = 0.999) whereas a study by Chen YK et al from Taiwan conclude that serum albumin was a poor prognostic factor and correlated with EM.\textsuperscript{22} Serum and plasma β2M which is emerged as markers for the activation of the cellular immune system, as well as a tumor marker in certain hematologic malignancies including multiple myeloma. \textsuperscript{β2M} has an impact on staging and prognosis of myeloma patient. In the current study there was a high incidence 12.8\% of EM among patients with β2M ≥ 5.5 but it was not significant, whereas Kumar SK, et al. showed elevated β2M has significant role on EM, in his study.\textsuperscript{23} Plasma cell leukemia (PCL), a condition in which malignant plasma cells no longer rely on the bone marrow niche and circulate in the peripheral blood. Our study showed no cases of PCL among EM recorded cases, while Pei Hsu et al. in his study reveals PCL as the main risk factor in EM cases.\textsuperscript{14} Our cohort found that pneumonia was the largest contributors to early death, followed by urinary tract infection and renal failure, this is matched with Cecillie, et al.\textsuperscript{24} when he found out there is a 7-fold increase in infection for patients diagnosed with multiple myeloma than controlled group. In our study there was no correlation between ECOG and ISS disease stage but, Howard Terebelo et al.\textsuperscript{25} in his study found higher ECOG PS, and a high ISS disease stage were associated with a higher likelihood of EM. We analyzed the potential impact of therapies on EM and found that cytotoxic agents were associated with early death, while the clinical use of IMiDs in MM has significantly improved long-term survival and quality of life, and our study shows the early death rate was significantly high (22.2\%) among patients who didn’t take the IMiDs. In conclusion, it is particularly encouraging to note the improved outcomes in the elderly patients, and the decrease in the EM, in agreement with previous study.\textsuperscript{15} Despite advances in supportive care, we found that up to 5.9\% of MM patients died within 60 days after diagnosis. Hsu P, et al. analyzed myeloma patients between 2002 to 2015 and reported a 60-day EM rate of 12.6\%, and another study done by Augustson et al revealed 10\% early mortality.\textsuperscript{26,7} While EM occurred in 22.95\% of patients in Chen et al study 25, this difference and variable results of EM might be due to sample size, different definition of EM, and frequently using novel agents like IMiDs.
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مخاطر الوفاة المبكرة لدى مرضى المايلوما المتعدد

الخلفية: لقد أدى التقدم في العلاج إلى تحسين إبقاء المايلوما المتعددة بشكل كبير في العقدين الماضيين، وقد تم تأكيده هذا التحسن من خلال الاستخدام الواسع للأدوية الجديدة وزرع الخلايا الجذعية الذاتية الترادفية. ومع ذلك، لا تزال هناك حالات توفيت في وقت سابق بعد التشخيص.

الأهداف: دراسة عوامل الخطر للوفيات المبكرة في مرضى المايلوما المتعددة في إقليم كردستان العراق.

المرضى والطريقة: 176 حالة تم تشخيصها بالورم النخاعي المتعدد الأعراض بين (كانون الثاني 2012 - تموز 2019) في مراكز السرطان في إقليم كردستان العراق. استمر ما مجموعه 152 في الدراسة من خلال صياغتهم المسجلة. تم تحديد ما هي عوامل الخطر الرئيسية التي لها تأثير على الوفيات المبكرة بين مرضى المايلوما لدينا.

النتائج: من بين إجمالي 152 مريضاً خضعوا للدراسة، توفي تسعة منهم (5.9%) مبكراً. وكانت أعلى نسبة (32.2%) من أفراد العينة الذين تراوح أعمارهم بين 60-69 سنة وأكثر من النصف (57.2%) من الذكور. تم تشخيص غالبية المرضى (80.9%) خلال 2016-2019. كانت نسبة حدوث الوفاة المبكرة 8.7% بين المرضى الذين لم يتناولوا العلاج السام للخلايا مقارنة بـ1.7% من المرضى الذين تناولوا هذا العلاج، لكن الفرق لم يكن معيناً (P = 0.089). كان معدل الوفيات المبكرة مرتفعًا بشكل ملحوظ (22.2%) في المرضى الذين لم يتناولوا الأدوية المعدلة للمناعة، مقابل 2.4% من المرضى الذين تناولوا الأدوية المعدلة للمناعة (P = 0.001). كان معدل الوفيات المبكرة 9.6% بين المرضى الذين يعانون من نازعة هيدروجين اللاكتات بمقدار 250 وحدة / لتر مقارنة مع 0% بين المرضى الذين يعانون من LDH أقل من 250. 

الخلاصة: مستوى LDH هو تنبؤ عالي في العثور على الوفيات المبكرة بين المرضى الذين يعانون من المايلوما المتعددة، وتناول الأدوية المعدلة للمعانة وقائي للغاية في حدوث الوفاة المبكرة.