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Survival rate of multiple myeloma patients in Indonesia: A retrospective study in multiple myeloma at a single institution

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ABSTRACT

Introduction: To evaluate the response and the correlation between survival and prognostic factors in 32 patients with multiple myeloma.

Method: We recruited 32 patients (18 men and 14 women) with mean age 59 years old who were diagnosed with multiple myeloma that were treated with surgery (n = 21) and without surgery (n = 11). 9 patients underwent hemiarthroplasty, 14 patients underwent open reduction and internal fixation and 4 patients underwent spinal decompression and posterior pedicular instrumentation from January 2012 to December 2017. In this group, there were 6 patients who underwent more than one surgeries. Patients were classified using the International Staging System (ISS) for multiple myeloma by evaluated albumin and β_2-microglobulin level.

Results: The mean follow up period for 32 patients was 30.2 months (range, 3–65 months) with 7 patients in ISS stage I, 22 patients in ISS stage II and 3 patients in ISS stage III. The median survival duration was 28 months (95% CI). We documented the median survival for ISS stage II disease was 29 months, stage III disease 6 months and stage I disease 16 months with the median age of ISS stage I, II, and III disease was 65, 59, 60 years respectively. Survival correlation with ISS stage ($p = 0.009$), the hemoglobin level ($p = 0.772$), and the calcium level ($p = 0.926$).

Conclusions: The survival rate was lower in patients with higher ISS stage for this disease. Survival rate seems to be better among younger patients than in older ones even with lower ISS stage of this disease.

1. Introduction

Multiple myeloma is generally considered an incurable disease that accounts for 10% of all hematological malignancies [1]. It was estimated in 2012 that there were 21,700 new cases and 10,710 deaths due to multiple myeloma in the United States.[1] In the European Union, there were 38,900 new cases and 24,300 deaths due to multiple myeloma in 2012, with only 10% surviving for more than 10 years due to multiple myeloma in 2012, with only 10% of patients currently surviving longer than 10 years [2,3]. Multiple myeloma is slightly more common in men than in women, with the median age of patients at the time of diagnosis is about 65 years [4,5].

Patients with multiple myeloma often present with vague, common symptoms such as back pain, bony pain, fatigue, and anemia. It will have to look for other signs of this disease such as hypercalcemia, impending/pathological fractures, osteopenia, neurological deficit or renal failure.[6] Without early recognition and referrals to oncology specialists, patients are left with a delayed diagnosis and poor symptom control [6].

Diagnosis of multiple myeloma is based on the International Myeloma Working Group guidelines (Table 1). The diagnosis is based on the presence of a monoclonal paraprotein together with marrow plasmacytosis and myeloma-related end-organ damage. These are typically the 'CRAB' (hypercalcemia, renal failure, anemia, or lytic bone lesions) symptoms described, but recurrent bacterial infections (> 2 a year), hyperviscosity symptoms and features of amyloidosis also qualify [7].

Current standards care for first-line treatment of multiple myeloma are evolving rapidly because of the introduction of regimens based on novel agents with unique mechanisms of action: the proteasome inhibitor bortezomib and the immunomodulatory drugs thalidomide and lenalidomide. These regimens are widely used recently, because it offered substantially greater benefit to patients in terms of higher response rates and, more importantly, prolonged response durations and

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Table 1
Diagnostic criteria for multiple myeloma.[7]

Monoclonal gammopathy of uncertain significance	Smouldering myeloma	Multiple Myeloma
Serum monoclonal protein < 30 g/L	Serum monoclonal protein ≥30 g/L	Monoclonal protein in serum and/or urine
Bone marrow clonal plasma cells < 10%	Bone marrow monoclonal plasma cells ≥10%	Bone marrow clonal plasma cells or biopsy proven plasmacytoma
No evidence of other B cell lymphoproliferative disorders	No myelomarelated organ or tissue impairment	Myeloma related organ or tissue impairment
No myeloma related organ or tissue impairment		

survival compared with established standard first-line treatment strategies [8,9].

Determining the prognosis in multiple myeloma requires the knowledge of tumor and host factors. Work on stratifying into different stages started in the 1960s and early 1970s when a number of clinical and laboratory parameters were identified, including hemoglobin level, serum calcium, serum creatinine, and severity of bone lesions [10,11].

In recent years, several population-based epidemiological studies have shown significant improvements in survival rate for myeloma patients in different countries. Nevertheless, access to treatment, health care systems, demographic patterns and patient's management differ between regions and may have an impact on incidence and mortality rates. Therefore, we think it is important to complement this studies from selected patient groups with population-based nation-wide epidemiological data from our center in Indonesia. This study evaluated the response and the correlation between survival and prognostic factors in 32 patients with multiple myeloma. We excluded the patients those lost to follow up in this study. The study has adjusted the following The SCARE 2018 statement: Updating consensus Surgical CAse REport (SCARE) guidelines paper: Agha RA et al. [12].

2. Patients and methods

Records of 18 men and 14 women aged 43 to 79 (mean, 59) years who were diagnosed with multiple myeloma that were treated with surgery (n = 21) and without surgery (n = 11) from January 2012 to December 2017 in our hospital (Table 2). 9 of 21 patients underwent hemiarthroplasty, 14 of 21 patients underwent open reduction and internal fixation (ORIF) and 4 remaining patients underwent spinal decompression and posterior pedicular instrumentation. In this group, there were 6 patients underwent more than one surgeries (hemiarthroplasty, ORIF, spinal decompression posterior pedicular instrumentation). Patients were classified using the International Staging System (ISS) stage for multiple myeloma by evaluated albumin and β_2-microglobulin level.

Table 2
Patient characteristics with multiple myeloma.

Variable	Total
Male, n(%)	18 (56.2%)
Female, n(%)	14 (43.8%)
Age	58.8
Mean Hb	10.37
Hb < 12, n(%)	25 (78.1%)
Hb ≥ 12, n(%)	7 (21.9%)
Mean Ca	8.20
Ca < 8, n(%)	14 (43.8%)
Ca ≥ 8, n(%)	18 (56.3%)
Mean follow up	30.2
Stage by ISS	
I, n(%)	7 (21.9%)
II, n(%)	22 (68.8%)
III, n(%)	3 (9.4%)
Surgery	
Yes, n(%)	21 (65.6%)
No, n(%)	11 (34.4%)
Status	
Dead, n(%)	12 (37.5%)
Alive, n(%)	20 (62.5%)

Hb, Hemoglobin; **Ca,** Calcium.

At the time of diagnosis, all the patients underwent hemoglobin, calcium, ESR, ureum, creatine, albumin, β_2-microglobulin laboratory tests, bone survey and Magnetic Resonance Imaging (MRI) of the affected site. After imaging had been completed, the patient underwent biopsy. Final diagnosis and treatment of all cases were established by clinical, radiological, and histopathological finding in the clinicopathological conference (CPC).

The follow-up period was defined as the length of time elapsed from the date since the patient diagnosed with multiple myeloma until the death or last date of review. Follow up was obtained via the data available from medical records.

Most complications/complaints associated with the disease included pain, impending/pathological fracture, and neurological deficit secondary to a vertebral lesion.

The Kaplan-Meier survival rate was evaluated. The correlation of survival with hemoglobin level, calcium level and ISS stage were analysed using the log rank test. A p value of < 0.05 was considered statistically significant.

This study was registered in research registry with no 4399.

3. Result

The mean follow up period for 32 patients was 30.2 months (range, 3–65 months) with 7 patients in ISS stage I, 22 patients in ISS stage II and 3 patients in ISS stage III. The median survival duration was 28 months (95% confidence interval). In group with stage II we got 16 subjects passed away and 6 subjects still underwent treatment with the 50% chance of death in this group 29 months, stage III we got 3 patients passed away with the 50% chance of death in this group 6 months. Survival correlated with ISS system ($p = 0.009$), the hemoglobin level ($p = 0.772$), and the calcium level ($p = 0.926$).

4. Discussion

Multiple myeloma has a male predominance [13], with median age 54 years (range 39–85) [14]; with the most common presenting symptoms were pain, impending/pathological fracture, anemia, and neurological deficit [6]. It is consistent with our study which showed that 18 male and 14 female with median age was 59 years (range 43–79). A study conducted by Tadjoedin et al. [15] demonstrated that over sixty percent multiple myeloma patients were older than fifty years old, but the gender was approximately equal between male and female.

Symptoms of multiple myeloma were the result of bone marrow infiltration, the development of bone neoplasms, and the effects of the disease's process on the renal system [16]. Kyle RA et al. [5] demonstrated that unexplained backache or bone pain in the long bones, ribs, skull, or pelvis were the most common presenting symptoms. Pathological fractures as a result of diffuse osteopenia or expansile tumours may be the presenting complaint of patients. Vertebral compression fractures were common and could result in spinal cord or nerve root compression [5,16]. Dvorak et al. [6] revelaed that patients with multiple myeloma often present with vague, common symptoms such as

back pain, bony pain, fatigue, and anemia. It was in accordance with our study which demonstrated that the most common symptoms of our patient were pain followed by pathological fracture and neurological deficit.

Study by Rajkumar showed that the diagnosis of multiple myeloma requires the presence of one or more myeloma defining events (MDE) in addition to evidence of either 10% or more clonal plasma cells on bone marrow examination or a biopsy-proven plasmacytoma [17]. MDE consists of established CRAB and more than one focal lesion on MRI. In our study, when multiple myeloma was suspected clinically, patients should be tested for hemoglobin, calcium, ESR, ureum, creatine, albumin, β_2-microglobulin level.

Plain radiographs of the skeleton were also performed to assess the extent of bone disease and MRIs were indicated when symptomatic areas showed no abnormality on routine radiographs, or when there were doubts about the true extent of bone disease on plain radiographs alone. A study by Regelink et al. demonstrated that bone survey gave an equal performance to MRI in order to provide evidence-based diagnostic guidelines in multiple myeloma bone disease indicating that it was a valuable alternative [18].

In our study, thirty percent of patients performed the biopsy. We conducted the biopsy due to doubt in diagnosis. Buss et al. [19] concluded that bone marrow sections and smears biopsy should be examined for suspected multiple myeloma diagnosis, since neither of them could be diagnostic tool alone. Stifter et al. [20], were in accordance with these findings, as each analysis has its limitations, combined methods were applied whenever possible to permit a more thorough approach. At the same time, the presented results gave important information on the association between survival and percentage of plasma cells infiltration in biopsy, which has not been previously perceived [20].

Several biochemical markers have been proposed using other known prognostic factors, including C-reactive protein, albumin, hemoglobin level, calcium level and plasma cell labeling index [9,10]. A study reported that the patients in the good-prognosis group had a hemoglobin greater than or equal to 100 g/l, and no or minimal symptoms [10]. Philip et al. [21] demonstrated that serum albumin and calcium were predictors of survival in patients with multiple myeloma. But, in our study it was revealed that the calcium and hemoglobin level were not correlated with the prognosis of patients with multiple myeloma (Table 3).

Staging of multiple myeloma as initial diagnosis can be assessed by two types of staging system which are Durie Salmon staging system and ISS [11,22]. ISS grading for multiple myeloma is a simple staging system that is based on the serum beta-2 microglobulin (S2βM) and albumin, that gained wide acceptance published in 2005 [11]. In addition, the ISS was demonstrated to be an effective system regardless of the geographic region, age and treatment type [11,23–25]. Greipp et al. [11], in 2005 reported that ISS grading for multiple myeloma proposed as the prognostic factor for this disease. This report corresponded to our analysis indicating that higher stage of the disease tends to correlate with lower survival rate on ISS stage II and III disease as shown in Table 3 and Fig. 1.

In our study, the median survival using ISS grading was lower than the study that was reported by Greipp et al. [11], stage I disease, with a median survival of 62 months and stage III disease, with median survival 29 months. Stage II disease, for patients who did not fulfil the criteria for the other stages, has a median survival of 44 months [11].

Our study demonstrated that the median survival for stage II disease 29 months, stage III disease 6 months and stage I disease 16 months with median age stage I, II, and III disease was 65,59, 60 years respectively. Regarding the survival, we noticed the survival rate on ISS stage II was better than ISS stage I. While the median age in ISS stage II disease was older than stage I. Similar study by Ludwig et al. [26] reported that younger patients in multiple myeloma led to better survival and more favorable features on this disease. Survival was significantly better compared to older patients cohort in life expectancy [27].

Patients with multiple myeloma had improved significantly in the last 15 years with the emergence of thalidomide, bortezomib, and lenalidomide [18]. More recently, carfilzomib, pomalidomide, panobinostat, ixazomib, elotuzumab, and daratumumab have been approved by the Food and Drug Administration (FDA) for the treatment of relapsed multiple myeloma, and promised to improve further outcomes further in Autologous Stem Cell Transplantation (ASCT) [18]. In our study, patients received VAD (vincristine, adriamycine, dexamethason) regimen for six cycles and thalidomide for maintenance therapy. It was similar to the study that was reported by Jacob et al. [14] with result of median survival for the ISS stage I, ISS stage II, and ISS stage III groups was 48 months, 21 and 27 months respectively and it was also lower than our study. If our study was compared to the Western data, where the 5-year survival post-transplant ASCT for ISS I, ISS II, and ISS III was 82%, 62%, and 40%, respectively [28]. It was also in accordance with study by Tajudin et al. [15] that most patients treated with melphalan/prednison or VAD and thalidomide. However, still in a developing country like Indonesia where affordability is a major hurdle for health care, a number of multiple myeloma patients were not able to undergo ASCT even after achieving complete response (CR)/very good partial response post induction.

Multiple myeloma remains an incurable disease and nearly all patients with the disease experienced relapse and eventually succumbed to refractory disease [29]. In our study, we found that all of the patients still with the disease and succumbed with multiple myeloma event after the treatment. It was also in accordance with study by Tajudin et al. [15], that most of the patients with multiple myeloma had partial response to treatment followed by progressive disease [15]. Eventually, the disease became refractory to treatment and the patients succumbs to infection, renal failure or other complications [15].

The trend to higher relative survival rates for myeloma patients in all age groups and the accentuation of improvement for the younger patients with only minimal advantage over time in those aged 75 years and older was similar to other published population-based survival data of myeloma patients [30–33]. In addition to treatment options, long survival of myeloma patients might be related to biological characteristics of tumor cells and/or microenvironment [34–36]. Disease biology is indeed one of the most important determinants of outcome [37,38]. Among patients with similar age, comorbidities, and disease stage, survival can vary widely based on genetic markers of aggressiveness [39,40].

Table 3
Correlation of prognostic factors and survival in multiple myeloma (n = 32).

Variable	Hemoglobin		Calcium		Stage	
	≤12	> 12	≤8	> 8	II	III
Dead, n(%)	11	5	11	9	16	3
Alive, n(%)	3	3	3	9	6	0
p Value	0.772		0.926		0.009	

5. Conclusion

Multiple myeloma remains an incurable disease that the survival rate was lower in patients with higher ISS stage for this disease. Regarding the prognostic impact of age, survival seems to be better among patients younger than in older patients even with lower stage of ISS. Several biochemical markers have been proposed using other known prognostic factors, our study revealed that the calcium and hemoglobin level is not correlated with the prognosis of patients with multiple myeloma.

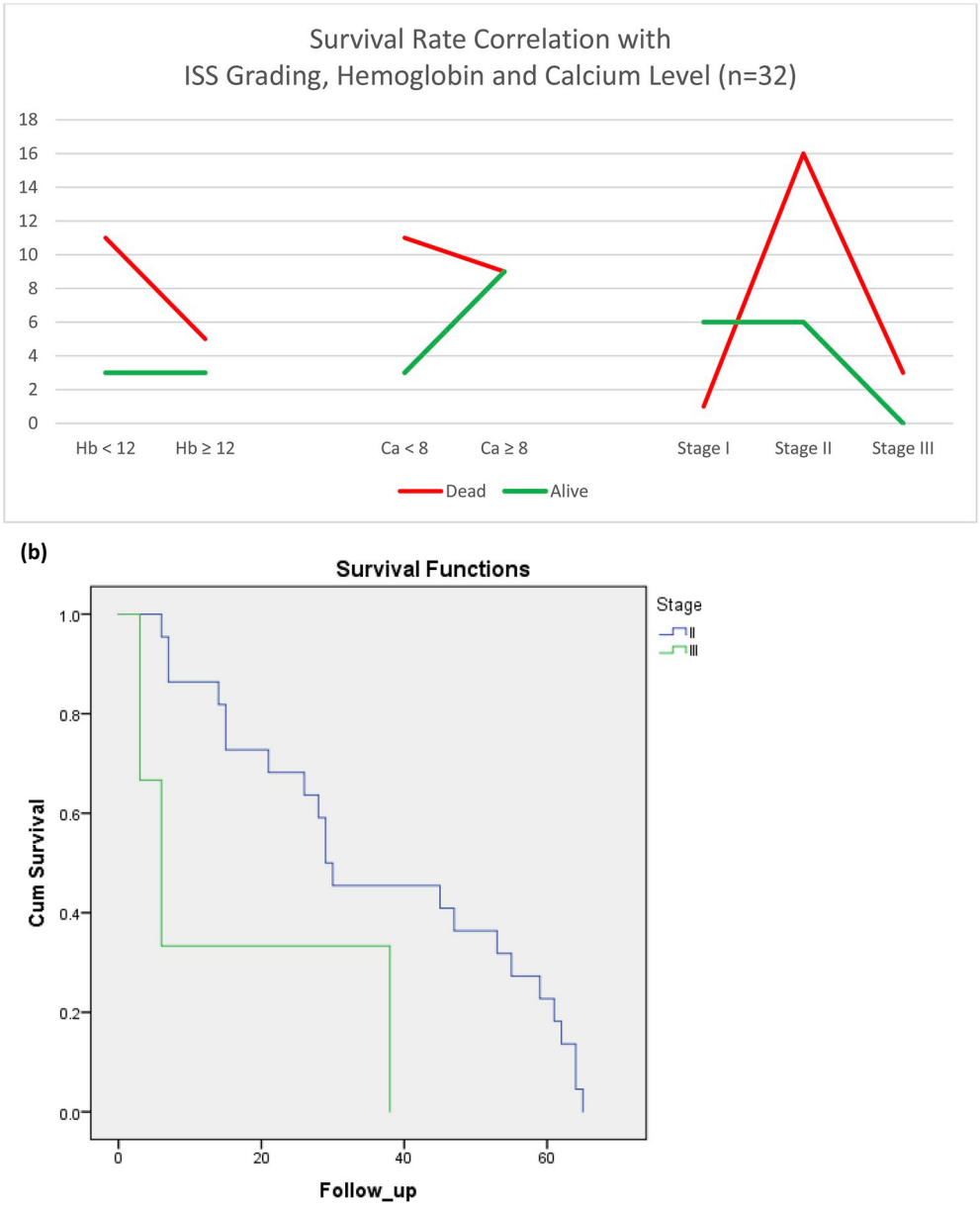

Fig. 1. Kaplan-Meier survival analysis for 32 patients with multiple myeloma showing (a) Survival Rate Correlation with ISS Stage, Hemoglobin and Calcium Level (b) International Staging System (ISS) grading.

Ethical approval

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The authors declare that sponsors had no such involvement.

Author contribution

A contributed to performed the operation, data collection, analysis and interpretation, manuscript drafting, revising, and approval for publishing; AFK contributed to performed the operation, data collection, analysis and interpretation, manuscript drafting, revising, and approval for publishing.

Conflicts of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2019.03.011.

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