Prognostic and biological characteristics associated with multiple myeloma presenting only with anemia

Multiple myeloma (MM) is a hematologic malignancy caused by an abnormal proliferation of monoclonal plasma cells.[1] MM is characterized by highly heterogeneous prognoses.[2] The main tools that are used for estimation of prognosis are the International Staging System (ISS), the Revised ISS (R-ISS), and the Durie-Salomon staging system (DSS).[3-5] Studies have shown that age, comorbidities, cognitive and physical condition,[6] as well as specific serum cytokine level[7] can be used to predict the prognosis of newly diagnosed patients.

Multiple myeloma treatment is based on combining proteasome inhibitors, immunomodulatory drugs, dexamethasone, high-dose chemotherapy plus autologous stem-cell transplantation,[8] monoclonal antibodies, novel immunotherapies such as chimeric antigen receptor T cells, antibody drug conjugate monoclonal antibodies targeting B-cell maturation antigen, and bispecific antibodies into MM therapy.[9-11] Management of newly diagnosed MM patients largely depends on their ability to tolerate aggressive treatments.

Multiple myeloma presents with a wide range of symptoms and signs.[12] Lytic bone lesion is the most common CRAB criterion (calcemia, renal dysfunction, anemia, bone pain) and is detected in 80% of new patients, compared to 75% for anemia, 20% for elevated serum creatinine, and 15% for hypercalcemia.[13]

A retrospective multi-center study that investigated MM patients presenting with anemia only (without any other CRAB symptoms)[14] suggested that these patients had a less favorable prognosis due to a higher percentage of monoclonal plasma cells in the bone marrow, a lower response rate to therapy, and a shorter overall survival (OS).

Our research aims to assess the unique characters of anemia-only MM patients and explore their OS and progression-free-survival (PFS) in comparison to other MM patients.

In this retrospective cohort study, data were extracted from the Soroka University Medical Center (SUMC) database and the Israeli Ministry of Health data network (Southern region). Data from both databases were combined prior to researchers' access using patients' ID before anonymization to avoid double inclusion. The study was approved by SUMC Helsinki ethics commission (SOR-0158-22).

The study population included adult patients who were diagnosed with MM (as defined by ICD-9 code 203 or ICD-10 code C90) between January 1st 2005 and December 31st 2020. Patients with IgM paraprotein were excluded due to the high association with Waldenstrom disease.

Follow-up started at the date of MM diagnosis and ended at the earliest date of death or December 19th 2022 (date of data extraction). Data on socio-demographic and clinical characteristics, laboratory test closest to diagnosis, treatment received, and date of death were collected for each patient.

Overall survival was defined as the time from MM diagnosis to death. PFS was defined as the time from the date of starting first-line therapy to the date of switching to second-line therapy or, for patients who did not receive a second-line of treatment, to the date of death.

The anemia-only group included patients who presented with anemia at diagnosis (hemoglobin <12 g/dL for males, <10 g/dL for females) but who did not exhibit any other CRAB symptoms, independently of expressing SLIM CRAB criteria. The no-anemia group included patients who did not present with anemia. The not-only-anemia group comprised patients who presented with anemia along with at least one additional CRAB symptom.

Data were summarized by absolute numbers and percentages for categorical variables, and means with standard deviations for continuous variables. Groups were compared by *t* tests or analysis of variance for normally distributed continuous variables, Wilcoxon rank-sum test or Kruskal-Wallis test for continuous variables with non-normal distribution, and χ^2 test or Fisher test for categorical variables.

Survival curves were estimated using the Kaplan-Meier method and compared by log-rank test. Hazard ratios (HR) were calculated by Cox proportional hazard regression. Multivariate models were used to assess factors associated with survival and to obtain adjusted HR. Analysis was performed using the R statistical software (version 2024).[15]

In total, 1,232 patients were diagnosed with MM during the study period. A total of 995 patients were enrolled in the study after the exclusion of 7 patients with unknown age, 21 patients with IgM paraprotein-type disease, and 209 patients for whom it had not been determined whether they exhibited lytic bone lesions. Patients were divided into two groups: the anemia-only (N=31) and the not-only-anemia group (N=964) (*Online Supplementary Figure S1*).

The anemia-only group showed a higher average age at diagnosis (75±10 years *vs*. 68±13 years, *P*<0.001), a higher percentage of males (71% *vs*. 42%, *P*=0.002), a higher prevalence of chronic diseases (*P*=0.002), and a higher prevalence of laboratory features associated with poor prognosis: thrombocytopenia (39% *vs*. 15%, *P*<0.001), hyperglobulinemia (74% *vs*. 54%, *P*=0.026), hypoalbuminemia (74% *vs*. 31%, *P*<0.001), and a higher presence of β_2 microglobulin >5.4 mg/L (45% *vs*. 28%, *P*=0.008). The anemia-only group also exhibited a higher percentage of

Table 1. Patient characteristics by anemia only groups.

Characteristic	Other MM patients, N=964	Anemia only N=31	*P*	Overall N=995[1]
Sociodemographic				
Age in years at diagnosis, mean ± SD (N)	68 ± 13 (964)	75 ± 10 (31)	<0.001[2*]	68 ± 13 (995)
Age in years >71, N (%)[a]	417/964 (43)	24/31 (77)	<0.001[3*]	441/995 (44)
Male sex, N (%)	410/964 (43)	22/31 (71)	0.002[3*]	432/995 (43)
Year of diagnosis, N (%)[b]			0.7[3]	
<2009	259/964 (27)	10/31 (32)		269/995 (27)
2009-2015	367/964 (38)	12/31 (39)		379/995 (38)
>2015	338/964 (35)	9/31 (29)		347/995 (35)
Clinic Social Score, N (%)			0.55	
Low	426/816 (52)	16/25 (64)		442/841 (53)
Intermediate	264/816 (32)	6/25 (24)		270/841 (32)
High	126/816 (15)	3/25 (12)		129/841 (15)
Missing	148 (15)	6 (19)		154 (15)
Hematology and chemistry, N (%)				
Anemia[b]	289/964 (30)	31/31 (100)	<0.001[3*]	320/995 (32)
Hypercalcemia[c]	110/956 (12)	0/31 (0)	0.040[5*]	110/987 (11)
Renal failure[d]	158/962 (16)	0/31 (0)	0.010[5*]	158/993 (16)
Thrombocytopenia[e]	149/964 (15)	12/31 (39)	<0.001[3*]	161/995 (16)
Hypoalbuminemia[f]	291/952 (31)	23/31 (74)	<0.001[3*]	314/983 (32)
Missing	12 (1)	0		12 (1)
β2 microglobulin			0.008[5*]	
<3.5 mg/L	259/474 (55)	5/22 (23)		264/496 (53)
3.5-5.4 mg/L	84/474 (18)	7/22 (32)		91/496 (18)
>5.4 mg/L	131/474 (28)	10/22 (45)		141/496 (28)
Missing	490 (51)	9 (29)		499 (50)
ISS, N (%)			0.003[5*]	
Stage 1	203/474 (43)	2/22 (9.1)		205/496 (41)
Stage 2	142/474 (30)	10/22 (45)		152/496 (31)
Stage 3	129/474 (27)	10/22 (45)		139/496 (28)
Missing	490 (51)	9 (29)		499 (50)
Hyperglobulinemia[g]	510/944 (54)	23/31 (74)	0.0263*	533/975 (55)
Missing	20 (2)	0		20 (2)
LDH >333 U/L	610/908 (67)	20/31 (65)	0.83	630/939 (67)
Missing	56 (6)	0		56 (6)
Treatment lines, N (%)				
First-line treatment			0.051[5]	
VD	130/964 (13)	1/31 (3.2)		131/995 (13)
VCD	52/964 (5.4)	2/31 (6.5)		54/995 (5.4)
VMP	98/964 (10)	9/31 (29)		107/995 (11)
VRD	31/964 (3.2)	0/31 (0)		31/995 (3.1)
VTD	41/964 (4.3)	0/31 (0)		41/995 (4.1)
Other treatments	6/964 (0.6)	0/31 (0)		6/995 (0.6)
Unknown MM treatment	606/964 (63)	19/31 (61)		625/995 (63)
Missing	127	5		132
ASCT, N (%)	131/718 (18)	2/31 (6.5)	0.15[5]	133/749 (18)
Missing	246 (26)	0		246 (25)
Comorbidity				
Diabetes, N (%)	158/964 (16)	10/31 (32)	0.020[3*]	168/995 (17)
Chronic diseases, N (%)			0.002[5*]	
No chronic diseases	546/964 (57)	9/31 (29)		555/995 (56)
1 chronic disease	103/964 (11)	9/31 (29)		112/995 (11)
>2 chronic diseases	315/964 (33)	13/31 (42)		328/995 (33)

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Characteristic	Other MM patients, N=964	Anemia only N=31	*P*	Overall N=995[1]
Smoking,N (%)	185/647 (29)	6/18 (33)	0.7[3]	191/665 (29)
Missing, N (%)	317 (33)	13 (42)		330 (33)
BMI, N (%)			0.7[5*]	
<18.5	20/546 (3.7)	1/18 (5.6)		21/564 (3.7)
18.5-25	219/546 (40)	7/18 (39)		226/564 (40)
>25	307/546 (56)	10/18 (56)		317/564 (56)
Missing	418 (43)	13 (42)		431 (43)
Serologic				
Free Kappa, N (%)			0.043[5*]	
<3.3 mg/mL	313/617 (51)	7/23 (30)		320/640 (50)
3.3-19.4 mg/mL	171/617 (28)	6/23 (26)		177/640 (28)
>19.4 mg/mL	133/617 (22)	10/23 (43)		143/640 (22)
Missing	347 (36)	8 (26)		355 (37)
Free lambda third, N (%)			0.7[5]	
<5.7 mg/mL	470/618 (76)	18/23 (78)		488/641 (76)
5.7-26.3 mg/mL	62/618 (10)	3/23 (13)		65/641 (10)
>26.3 mg/mL	86/618 (14)	2/23 (8.7)		88/641 (14)
Missing	346 (36)	8 (26)		354 (37)
Outcomes				
Tracking time, median (IQR) [N]	115 (63-173), [964]	125 (76-183), [31]	0.4[4]	115 (64-174), [995]
Death event, N (%)	565/964 (59)	24/31 (77)	0.036[3*]	589/995 (59)
Progression, N (%)	320/358 (89)	20/20 (100)	0.2[5]	340/378 (90)
Progression-free survival, median (IQR) [N]	29(10-118), [358]	16 (6-87), [20]	0.3[4]	28 (10-118), [378]
Missing, N (%)	606 (63)	11 (35)		617 (62)

[1]Mean ± standard deviation (SD) (N); N (%). [2]Welch two-sample *t* test. [3]Pearsons χ^2 test. [4]Wilcoxon rank sum test. [5]Fisher exact test. ASCT: autologous stem cell transplantation; BMI: body mass index; IQR: interquartile range; ISS: International Staging System; LDH: lactate dehydrogenase; MM: multiple myeloma; VCD: bortezomib-cyclophosphamide-dexamethasone; VD: bortezomib-dexamethasone; VMP: bortezomib-melphalan-prednisone; VRD: bortezomib-lenalidomide-dexamethasone; VTD: bortezomib-thalidomide-dexamethasone. [a]Median age of diagnosis of whole cohort is 71 years. [b]Hemoglobin <12 g/dL for males, and <10 g/dL for females. [c]Calcium >10.5 mg/dL. [d]Creatinine >2 mg/dL. [e]Serum thrombocytes <150 mcL. [f]Serum albumin <3.5 g/dL. [g]Serum globulin >3.5 g/dL. [*]Statistical significance.

death during the study period (77% *vs*. 59%, *P*=0.036). No differences were observed in the incidence of disease progression (Table 1).

Overall median survival time for the entire cohort was 68 months (interquartile range [IQR]: 60-78). Kaplan-Meier analysis shows that survival among both the anemia-only group (21 months, IQR: 12-56) and the not-only-anemia group (32 months, IQR: 22-40) is lower compared to the no-anemia group (107 months, IQR: 89-127, *P*<0.001) (Figure 1).

In comprehensive OS multivariate Cox regression analysis, anemia-only patients displayed a HR of 1.91 (95% CI: 1.19, 3.07, *P*=0.007), and not-only-anemia patients showed a HR of 1.69 (95% CI: 1.31, 2.18, *P*<0.001), compared to no-anemia patients, with no difference in HR between anemia-only to not-only-anemia (Table 2). Additional variables found to affect OS included advanced age, hypercalcemia, renal failure, thrombocytopenia, hypoalbuminemia, lactate dehydrogenase (LDH) >333 U/L, and patients with multiple chronic diseases.

Overall median PFS for the entire cohort was 25 months (IQR: 20-30). Kaplan-Meier analysis shows that median PFS among both anemia-only (16 months, IQR: 7-198) and no-anemia patients (18 months, IQR: 13-26) is lower compared to no-anemia patients (41 months, IQR: 25-81, *P*=0.019) (*Online Supplementary Figure S2*). Comprehensive PFS multivariate COX regression showed a protective effect from disease progression of not-only-anemia (HR=0.74, 95% CI: 0.58, 0.94, *P*=0.013) in comparison to the no-anemia group; there was no difference in effect between the anemia-only and the no-anemia groups (*Online Supplementary Table S1*). Additional variables found to affect PFS include hypercalcemia, hyperglobulinemia, and the year of diagnosis - patients diagnosed after 2009 showed higher risk for disease progression. The presence of comorbidities was found to have a protective effect on PFS (HR=0.73, 95% CI: 0.57, 0.93, *P*=0.01).

The anemia-only group was characterized by older age and comorbidity, possibly indicative of delayed diagnosis due to less pronounced symptoms or symptoms masked by those of other diseases. Late diagnosis can suggest a potential explanation for the association between anemia-only patients to poor prognosis biomarkers such as hypoalbuminemia, high levels of serum β_2 microglobulin, thrombocytopenia, and hyperglobulinemia, which indicate those patients diagnosed at advanced stage of the disease.

Shargai *et al.*[14] indicated a trend of shorter OS among anemia-only MM patients compared to other MM patients. The current study establishes this trend. Notably, the survival analysis of anemia-based groups suggests that the effect of anemia on OS is attributable to the presence of anemia itself, rather than to its presentation with or without additional symptoms.

The negative impact of presenting CRAB symptoms, particularly anemia, on the OS observed in our research is consistent with previous research[11] and with the DSS.[5] It refers to presenting CRAB symptoms as a risk factor for the poor prognosis of MM without specifying specific combinations of symptom presentation. Anemia in MM, associated with the infiltration of myeloma cells into bone marrow,[16] can provide an explanation for the effect of anemia on prognosis.

Consistent with the suggestion of Shargai *et al.*,[14] the current research shows the tendency toward shorter PFS for anemia-only MM patients. No difference in PFS was observed between the anemia-only group and the no-anemia group.

The association between advanced year of diagnosis and increased risk of disease progression can be explained by the availability of new therapies that has led to more frequent changes in treatment lines; another possible explanation is the tendency in later years of adopting a more detailed recording of data.

The unexpected results of the PFS analyses can be elucidated in a several ways. The retrospective data collection limits our ability to determine the exact cause for changes in treatment; this limitation may have introduced unforeseen biases into the PFS results analysis. Additionally, our database lacks information about MM treatments. Diagnosis with MM is an indication for starting treatment; reasons for not giving treatment can be because of a very grim prognosis, patient unwillingness to receive treatment, or limited access to treatment, particularly among rural populations in the southern region of Israel. These situations do not explain such a lack of information, the result of which is that it is difficult to draw conclusions about PFS. To address this, the progression analyses were conducted exclusively on the subset of patients for whom data on anti-myeloma treatment were available and we verified the information on the anemia-only group regarding receiving treatment by manually double-checking the patients' files. This ensured that conclusions regarding progression were drawn only from patients with complete treatment information and enabled an effective analysis of the data.

The unusual finding of comorbidities as a protective factor from disease progression can be explained by the possibility that patients with significant comorbidities were less likely to receive or have documented anti-myeloma treatment, which may have influenced the recording of disease progression in the data.

The main limitation of this study is that anemia-only MM patients are relatively rare. In a previous study, these patients made up only 1.9% of all MM patients, and a low number of cases can make it difficult to have significant results. To cope with this limitation, we extracted data

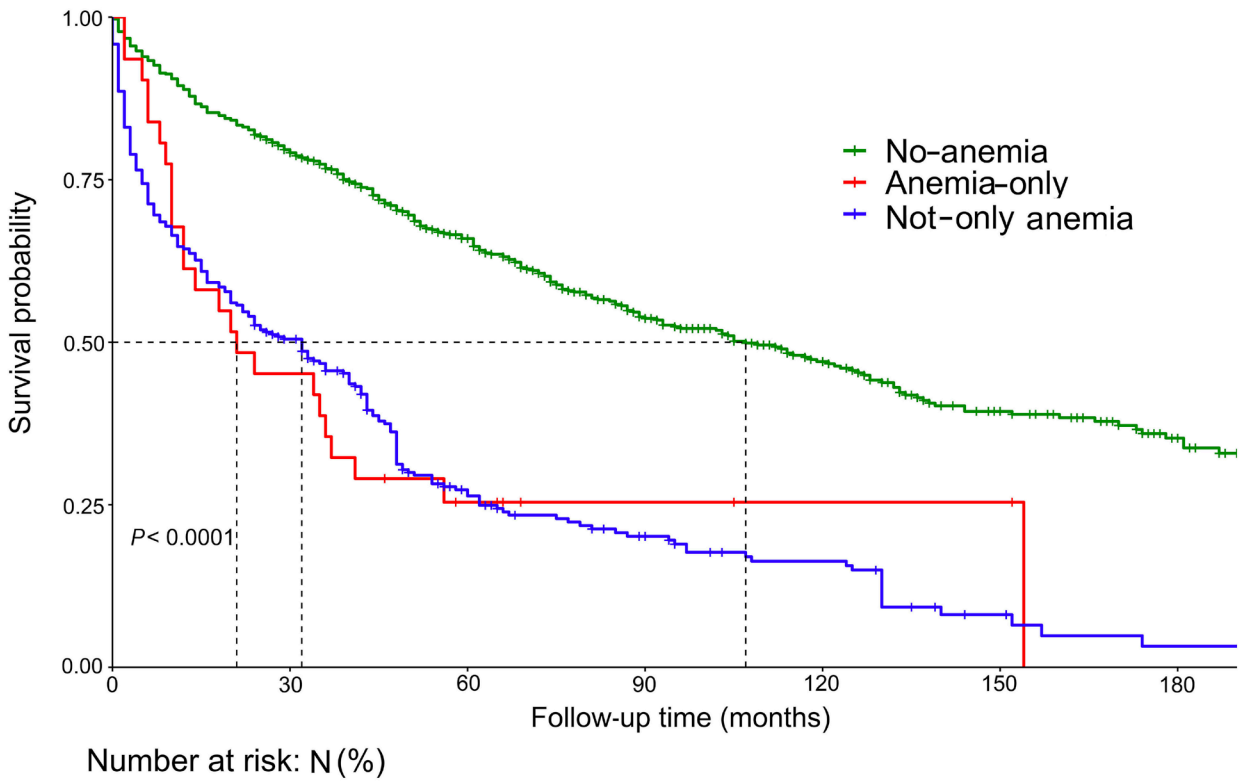

Figure 1. Kaplan Meier survival curve by anemia groups. Comparison of overall survival of patients presenting with no anemia (no-anemia; green), patients presenting with only anemia (anemia-only; red), and patients presenting with anemia and at least one other CRAB symptom (not-only anemia; blue).

Table 2. Overall survival multivariate Cox proportional hazard regression.

Variable	HR	95% CI	*P*
Anemia groups			
No-anemia	-	-	-
Anemia-only	1.91	1.19-3.07	0.007*
Not-only-anemia	1.69	1.31-2.18	<0.001*
Age >71 years	2.67	2.17-3.28	<0.001*
Hypercalcemia	1.72	1.30-2.28	<0.001*
Renal failure	1.54	1.18-2.01	0.002*
Thrombocytopenia	1.47	1.15-1.86	0.002*
Hypoalbuminemia	1.82	1.47-2.25	<0.001
LDH >333 U/L	1.29	1.05-1.58	0.015*
Comorbidity			
No chronic diseases	-	-	-
1 chronic disease	1.22	0.91-1.63	0.2
≥2 chronic diseases	1.71	1.39-2.11	<0.001*
First-line treatment			
VD	-	-	-
VCD	0.56	0.37-0.87	0.009*
VMP	0.93	0.67-1.28	0.7
VRD	0.78	0.42-1.45	0.4
VTD	1.15	0.74-1.78	0.5
Other treatments	1.01	0.40-2.52	>0.9
Unknown MM treatment	0.54	0.40-0.71	<0.001*
AIC	5,435	-	-

AIC: Akaike information criterion; CI: Confidence Interval; HR: Hazard Ratio; LDH: lactate dehydrogenase; MM: multiple myeloma; VCD: bortezomib-cyclophosphamide-dexamethasone; VD: bortezomib-dexamethasone; VMP: bortezomib-melphalan-prednisone; VRD: bortezomib-lenalidomide-dexamethasone; VTD: bortezomib-thalidomide-dexamethasone. *Statistical significance.

from two sources in order to obtain as large a sample size as possible. Furthermore, according to the sample size calculation, we could provide a reliable conclusion with our estimated sample size.

Although it is difficult to differentiate between MM and smoldering myeloma due to the ICD coding overlap, we assumed that most patients included in the study had MM based on the presentation of CRAB symptoms.

This study suggests that the poor prognosis of anemia-only MM patients is linked to the unfavorable clinical features characterizing these patients. The association between anemia-only MM to poor clinical features can be explained by late diagnosis due to indolent disease. In terms of PFS, the effect of anemia-only on PFS seems to be negative compared to not-only-anemia MM.

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Disclosures

No conflicts of interest to disclose.

Contributions

GS performed research and data analysis, and wrote the manuscript. OR supervised the study, and guided the planning and execution of research with respect to the clinical aspects. AR-B supervised and

guided the planning of the research and data analysis.

Data-sharing statement

Data are available from the corresponding author upon reasonable request. Protocols can be shared for non-commercial use. De-identified data will be provided to protect confidentiality, with requests reviewed for ethical compliance. Availability is subject to legal and ethical regulations.

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