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Calculated haemorheological profile and laboratory parameters in new diagnosed multiple myeloma patients: retrospective analysis according to survival

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Abstract

Background: Multiple myeloma is a malignant haematological neoplasm characterised by clonal proliferation of plasma cells, with a complex clinical picture, and a significant impact on patient survival, in which the prognosis evaluation of patients is of great importance.

Objectives: In this single-centre retrospective analysis, performed in a group of newly diagnosed multiple myeloma patients, we examined several clinical and laboratory parameters in order to evaluate their trend according to survival of patients.

Design: We collected data from 190 newly diagnosed multiple myeloma evaluated at the Hematology Division of the 'Paolo Giaccone' University Hospital of Palermo from 1 January 2017 to 30 September 2022. Specifically, we performed our analysis in the entire cohort of patients and also in the specific disease isotype.

Methods: We evaluated simple and low-cost laboratory and haemorheological parameters, the latter obtained in a calculated way. The primary endpoint was to evaluate the trend and the differences of these parameters in the study population, divided into two specific groups, deceased and survivors after a specific observation period of almost 7 years.

Results: In the entire cohort of multiple myeloma patients, we observed a mortality rate of 40%, of whom 36.4% were men and 43.1% were women. Among the patients who died, in comparison with those who survived, it is significantly evident the increase in age, in red cell distribution width (RDW), RDW%/albumin ratio and in the RDW%/haemoglobin ratio; moreover, in the same patients subgroup, we observed a reduction in haematocrit, total serum protein, calculated whole blood viscosity (evaluated according to the de Simone formula), serum albumin, albumin/fibrinogen ratio and in haemoglobin levels.

Conclusion: The obtained data can represent a possible starting point for subsequent targeted analyses, aimed at studying the prognostic value of each individual parameter considered, favouring an increasingly complete and immediate prognostic evaluation of patients.

Keywords: albumin/fibrinogen ratio, calculated blood viscosity, multiple myeloma, RDW/albumin ratio, RDW/haemoglobin ratio, survival

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Introduction

Multiple myeloma (MM) is a malignant disorder of B cells that involves the proliferation of monoclonal plasma cells in the bone marrow and/or extramedullary sites; with a median age at diagnosis of 70 years, it is the second most common haematological malignancy, associated with significant morbidity and mortality by

causing end-organ damage.[1] Typical MM clinical manifestations include anaemia, bone lesions, renal failure, hypercalcaemia and infections. Generally, the prognosis of MM is evaluated performing International Staging System (ISS) and revised ISS (R-ISS) staging systems at the time of diagnosis; however, other important factors play a key role, such as the specific isotype of disease, the tumour burden and some patient-related factors.[2,3]

In the haemorheological literature, what happens to the main haemorheological determinants in plasma cell dyscrasias, and in particular in MM, is well known. We have previously evaluated some haemorheological parameters in a small cohort of MM patients, observing that in MM, as well as in monoclonal gammopathy of undetermined significance (MGUS), the haemorheological profile is referable not only to a condition of extracellular hyperviscosity but also to erythrocyte hyperviscosity.[4–6]

In fact, the diffractometric method used in our laboratory has highlighted that in MM patients the erythrocyte deformability is significantly reduced, although there is no univocal explanation for this finding. This last evaluation was obtained using the diffractometer Rheodyn SSD of Myrenne, that measures the diffraction pattern of a laser beam passing through erythrocytes suspended in a viscous medium and deformed by a force with defined shear stress. To explain it, we referred to the biochemical composition of the erythrocyte membrane in MM patients,[7–10] but more specifically to the marked concentration of phosphatidylserine.[11–15]

The altered distribution of phosphatidylserine can influence the erythrocyte function, also modifying the physiological link between the lipids and proteins on the membrane, with a reduction of the erythrocyte deformability. This latter, like plasma viscosity, only operates in the microcirculatory district, with an important possible role in the organ complications observed in MM.[16,17]

Studying our cohort of newly diagnosed MM patients, time to time we focused on different aspects. Firstly, we evaluated the behaviour of the calculated blood viscosity in relation to the thrombotic risk (expressed according to the IMWG/NCCN guidelines and to the IMEPDE VTE score)[18]; moreover, we analysed the trend of blood viscosity in relation to the ISS and to other prognostic factors, such as albumin, beta-2 microglobulin, bone morrow plasma cell infiltration and red cell distribution width (RDW).[19]

Regarding the RDW parameter, several literature reports, performed on MM patients, conclude that, the increase in this erythrocyte index is associated with the advanced stage of disease, bad response to treatment and poor prognosis, hypothesising therefore an important prognostic role of this parameter in MM setting. Furthermore, in an our previous research, we observe that the RDW, in a cohort of MM patients, is not only increased, but is significantly related to the ISS stages and the main prognostic predictors, such as serum levels of albumin, beta-2 microglobulin, lactate dehydrogenase (LDH), and bone marrow plasma cell infiltration.[20] In addition to the role of the RDW alone, several literature data, in different clinical conditions, they demonstrated the prognostic role of RDW also when associated with other laboratory parameters, such as in the RDW/albumin and RDW/haemoglobin ratio.[21–26] Based on this latest information, in this preliminary study, we retrospectively have examined several laboratory parameters, haemorheological and non-haemorheological, evaluated at the time of diagnosis in a cohort of new diagnosed MM (NDMM) patients, subdivided in two subgroups, deceased and survivors. Our aim is to evaluate the trend of the analysed parameters and any differences between deceased and survivors patients, after a median follow-up of 32 months.

Materials and methods

Population

We performed a single-centre retrospective analysis of patients with NDMM evaluated at the Hematology Division of the 'Paolo Giaccone' University Hospital of Palermo from 1 January 2017 to 30 September 2022. The diagnosis of symptomatic MM was made according to the revised International Myeloma Working Group criteria,[27] on the basis of which the patients were diagnosed with MM, if they had 10% or more bone marrow clonal plasma cells or a biopsy-proven plasmacytoma, serum and/or urinary monoclonal protein (except in non-secretory patients) and the presence of one or more

myeloma defining events (MDEs). MDEs consist of CRAB features (hypercalcaemia, renal failure, anaemia or lytic bone lesions) as well as three specific biomarkers: clonal bone marrow plasma cells ⩾60%, serum free light chain (FLC) ratio ⩾100 (provided involved FLC level is ⩾100 mg/L) and more than one focal lesion on magnetic resonance imaging (MRI).

For patient enrolment, we considered the following inclusion criteria: age ⩾18 years, diagnosis of symptomatic MM according to the above criteria, absence of malignancy in the 6 months prior to enrolment or, at most, diagnosis of in situ neoplasia undergoing treatment with total eradication of the neoplasm. Patients with monoclonal IgM component (since it is more often associated with the diagnosis of lymphoproliferative disease), MGUS, smouldering MM (SMM) and AL amyloidosis at the time of diagnosis were excluded.

As a result, data from 190 patients were collected, and they were staged based on the ISS.[2] At the time of diagnosis, the patients received specific treatment protocols according to specific patients and disease characteristics. We used different drugs including thalidomide (T), lenalidomide (R), dexamethasone (D), bortezomib (V), melphalan (M), daratumumab (Dara), in varying combinations. Specifically, fit NDMM patients, aged <70 years, without comorbidities, they received induction treatment followed by high-dose therapy (HDT) with autologous stem cell transplantation and lenalidomide maintenance. Elderly patients or patients with NDMM, who are 'not' eligible to receive HDT and autologous transplantation, received bortezomib-based or lenalidomide-based regimens.

The baseline demographics information were obtained from the medical records. All the informed consents have been obtained from the patients.

Methods

In this single-centre retrospective study, we evaluated the following data: haematocrit (Ht), obtained using an automated haematology analyser; total plasma proteins, expressed in g/L and evaluated with the colorimetric method; whole blood viscosity (WBV) at 208 s^{-1}, calculated according to the deSimone formula: $(0.12 \times Ht) + 0.17\,(TP - 2.07)$; fibrinogen expressed in g/L and evaluated with the Clauss method; WBV calculated according to Merrill's formula: $[13.5 \times 10^{-6} \times (\text{Fibrinogen})^2 \times (Ht - 6)^3]$; serum albumin (g/L), evaluated with the colorimetric method; albumin (g/L)/fibrinogen (g/L) ratio; RDW, reported as a coefficient of variation (percentage) of red blood cell volume; haemoglobin, expressed in g/L and evaluated with the automated blood count; RDW(%)/albumin (g/L) ratio, and RDW (%)/haemoglobin (g/L)

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 9.5. The data were expressed as medians and interquartile ranges. The median comparison was made with the Mann–Whitney test. The null hypothesis was evaluated for values of $p \leqslant 0.05$.

Results

We evaluated a total of 190 NDMM patients, 102 women and 88 men, with a median age of 69 ± 10 years. Specifically, our study population is represented by 107 patients with IgG MM, 56 patients with IgA MM and 27 patients with a diagnosis of light chain MM (LCMM). The patients characteristics are presented in Table 1.

In this cohort of newly diagnosed MM patents, firstly, we evaluated the medians, interquartile ranges and ranges of all the considered parameters (age, sex, haematocrit, total proteinemia, blood viscosity calculated according to de Simone formula, plasma fibrinogen, blood viscosity calculated according to Merrill formula, serum albumin, albumin/fibrinogen ratio, RDW%, the RDW%/albumin ratio and the RDW%/haemoglobin ratio) at the time of diagnosis (Table 2).

In the entire cohort of MM patients, the percentage of death after 6 years from diagnosis was 40%, of which 36.4% were men and 43.1% women. Among the patients who died, compared to the survivors, we observed the following data: an increased age, RDW% and especially in the RDW%/albumin ratio and RDW%/haemoglobin ratio; we observe instead a decrease in haematocrit, total serum protein, WBV calculated according to the de Simone formula, in serum albumin, albumin/fibrinogen ratio and in haemoglobin

Table 1. Characteristics of patients.

Parameters	Mean/percentage
Sex	
Male	46% (88/190)
Female	54% (102/190)
Age at diagnosis	69 ± 10
ISS stage	
Stage I	22% (41/190)
Stage II	26% (49/190)
Stage III	52% (100/190)
Isotype	
IgA k	15% (28/190)
IgA λ	15% (28/190)
IgG k	37% (71/190)
IgG λ	20% (36/190)
Light chain k	6% (13/190)
Light chain λ	7% (14/190)
LDH U/L (normal range: 50–250)	193 ± 91
Serum calcium mg/dL (normal range: 8.6–10.21)	9.57 ± 1.03
Serum creatinine mg/dL (normal range: 0.51–0.95)	1.55 ± 1.58
Monoclonal component g/L	26.01 ± 20.42
Serum albumin g/L (normal range: 35–52)	35.1 ± 6.39
β2 microglobulin mg/L (normal range: 0.8–2.2)	7.50 ± 7.78
Bone marrow plasma cells (%)	45 ± 26
Haemoglobin g/dL (normal range: 12–16l)	11.11 ± 6.14
Haematocrit % (normal range: 35–48)	32 ± 5.70
MCV fL (normal range: 80–99)	91.83 ± 8.36
RDW-CV% (normal range: 11–15)	15.77 ± 2.68
Treatment	
Patients transplant eligible	81/190 (42.6%)
VTD	66/81
Dara-VTD	15/81
Patients not-transplant eligible	109/190 (57.36%)
Bortezomib-based regimens	42/109
Lenalidomide-based regimens	67/109

ISS, International Staging System; MCV, mean corpuscular volume; RDW-CV%, red cell width distribution-coefficient of variation%; VTD, Bortezomib, Thalidomide and Dexamethasone; Dara-VTD, Daratumumab-Bortezomib, Thalidomide and Dexamethasone.

Table 2. Medians, IQRs and ranges of the erythrocyte and plasma parameters in MM patients.

All MM ($n = 190$)	Median (IQR)	Ranges
Age (years)	71.00 (14.00)	34.00–89.00
Ht %	31.35 (9.05)	21.00–46.70
Plasma proteins (g/L)	78.30 (27.50)	46.40–129.6
cWBV 208 s^{-1} (mPa s)	16.73 (4.25)	10.73–25.35
Fibrinogen (g/L)	3.200 (1.358)	1.090–8.170
cWBV (YSS/dyne cm^2)	0.248 (0.294)	0.012–4.132
Albumin (g/L)	36.70 (10.12)	15.00–48.20
Albumin/fibrinogen	10.88 (5.69)	3.24–28.32
RDW%	15.10 (3.60)	12.10–23.40
Hb (g/dL)	10.30 (2.925)	7.00–16.00
RDW%/albumin	0.423 (0.212)	0.020–1.200
RDW%/Hb	1.449 (0.694)	0.173–2.962

cWBV, calculated whole-blood viscosity; Hb, haemoglobin; Ht, haematocrit; IQR, interquartile range; MM, multiple myeloma; RDW, red blood cells distribution width; YSS, yield shear stress.

Table 3. Medians (IQRs) of the erythrocyte and plasma parameters in all MM patients subdivided into survivors and non-survivors.

MM	All MM ($n = 190$)	Survivors ($n = 114$)	Non-survivors ($n = 76$)
Age (years)	71.00 (14.00)	68.00 (13.25)	75.00 (12.75)***
Males/females	88/102	56/58	32/44
Ht %	31.35 (9.05)	32.70 (10.10)	30.00 (7.07)*
Plasma proteins (g/L)	78.30 (27.50)	80.90 (27.10)	73.45 (24.70)*
cWBV 208 s^{-1} (mPa s)	16.73 (4.25)	17.80 (3.87)	15.92 (3.97)**
Fibrinogen (g/L)	3.200 (1.358)	3.080 (1.385)	3.220 (1.315)
cWBV (YSS/dyne cm^2)	0.248 (0.294)	0.283 (0.294)	0.211 (0.295)
Albumin (g/L)	36.70 (10.12)	37.65 (8.48)	34.35 (9.93)***
Albumin/fibrinogen	10.88 (5.69)	12.05 (5.31)	9.98 (4.59)**
RDW%	15.10 (3.60)	14.60 (2.93)	15.80 (4.05)**
Hb (g/dL)	10.30 (2.925)	11.00 (3.03)	9.90 (2.35)***
RDW%/albumin	0.423 (0.212)	0.390 (0.205)	0.460 (0.242)***
RDW%/Hb	1.449 (0.694)	1.327 (0.672)	1.597 (0.753)***

*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$ versus survivors (Mann–Whitney test).
cWBV, calculated whole-blood viscosity; Hb, haemoglobin; Ht, haematocrit; IQR, interquartile range; MM, multiple myeloma; RDW, red blood cells distribution width; YSS, yield shear stress.

Table 4. Medians (IQRs) of the erythrocyte and plasma parameters in LCMM patients subdivided into survivors and non-survivors.

LCMM	All LCMM ($n = 27$)	Survivors ($n = 15$)	Non-survivors ($n = 12$)
Age (years)	65.00 (18.00)	63.00 (18.00)	67.00 (20.75)
Males/females	14/13	8/7	6/6
Ht %	31.40 (11.70)	37.10 (12.70)	29.15 (10.50)
Plasma proteins (g/L)	64.20 (6.00)	64.40 (4.70)	61.90 (7.93)
cWBV 208 s^{-1} (mPa s)	14.81 (2.40)	14.98 (2.19)	13.84 (1.84)
Fibrinogen (g/L)	3.680 (1.580)	3.650 (1.390)	4.195 (1.822)
cWBV (YSS/dyne cm^2)	0.407 (0.442)	0.503 (0.444)	0.296 (0.346)
Albumin (g/L)	39.90 (5.30)	41.70 (3.80)	37.60 (3.40)*
Albumin/fibrinogen	11.24 (4.428)	11.51 (4.48)	9.24 (4.83)
RDW%	14.40 (3.10)	14.20 (2.20)	14.80 (3.85)
Hb (g/dL)	10.50 (4.10)	11.70 (4.20)	9.75 (2.83)
RDW%/albumin	0.376 (0.108)	0.325 (0.068)	0.407 (0.063)*
RDW%/Hb	1.373 (0.633)	1.248 (0.741)	1.514 (0.763)

*$p < 0.05$ vs survivors (Mann–Whitney test).
cWBV, calculated whole-blood viscosity; Hb, haemoglobin; Ht, haematocrit; IQR, interquartile range; LCMM, light chain multiple myeloma; RDW, red blood cells distribution width; YSS, yield shear stress.

level (Table 3). We have not observed any variations in plasma fibrinogen levels and whole blood viscosity calculated according to Merrill's formula.

In LCMM (Table 4), the death rate is 44.4% (42.8% men and 46.1% women). In this specific disease isotype, despite the small size of the subgroup, the deceased patients presented an increase in age associated with a decrease in haematocrit, haemoglobin, blood viscosity calculated according to the de Simone formula and in albumin/fibrinogen ratio. Moreover, in the deceased patients with LCMM, we particularly observed a decrease in the albumin value and an increase in RDW%/albumin ratio; this latter, although not statistically significant, is also found in the RDW%/haemoglobin ratio. No difference was observed in relation to the total serum proteins, plasma fibrinogen values and blood viscosity calculated according to Merrill's formula.

In the IgA MM (Table 5), the mortality rate was 46.4% (51.5% men and 39.5% women), and in the deceased subgroup, we observed a reduction in total serum protein, blood viscosity calculated according to the de Simone formula, in the albumin/fibrinogen ratio, in the haematocrit, serum albumin and haemoglobin levels, even if these data do not reach a level of statistical significance. Furthermore, we have recorded an increase in age. Although not statistically significant, an increase in RDW% as well as the RDW%/albumin and RDW%/haemoglobin ratio were also observed. There are no differences in plasma fibrinogen values and in calculated blood viscosity according to the Merrill's formula.

In IgG MM (Table 6), the mortality rate was 35.5% (29.5% men and 43.9% women). In this MM isotype, certainly the most numerous within the entire cohort, comparing died and survivor patients, the first significant discriminating parameter appears to be age. No significant changes appear to be recorded for haematocrit, total serum protein, calculated blood viscosity according to de Simone formula, plasma fibrinogen, blood viscosity calculated according to

Table 5. Medians (IQRs) of the erythrocyte and plasma parameters in IgA MM patients subdivided into survivors and non-survivors.

IgA MM	All IgA MM ($n=56$)	Survivors ($n=30$)	Non-survivors ($n=26$)
Age (years)	70.00 (14.75)	66.00 (13.25)	71.00 (15.25)
Males/females	33/23	16/14	17/9
Ht %	30.35 (8.42)	32.85 (9.30)	29.95 (7.85)
Total plasma proteins (g/L)	79.55 (30.47)	87.35 (29.07)	71.60 (26.25)**
cWBV 208 s^{-1} (mPa s)	17.71 (4.63)	18.76 (4.92)	15.86 (4.01)**
Fibrinogen (g/L)	2.870 (1.510)	2.700 (1.482)	3.055 (1.245)
cWBV (YSS/dyne cm^2)	0.208 (0.233)	0.222 (0.265)	0.206 (0.185)
Albumin (g/L)	33.85 (8.37)	34.05 (9.20)	32.75 (10.10)
Albumin/fibrinogen	12.40 (5.667)	13.13 (6.60)	10.06 (5.23)*
RDW%	16.00 (4.40)	15.90 (4.25)	17.00 (6.05)
Hb (g/dL)	9.95 (2.65)	10.70 (3.00)	9.80 (2.10)
RDW%/albumin	0.509 (0.230)	0.485 (0.225)	0.529 (0.268)
RDW%/Hb	1.701 (0.663)	1.448 (0.737)	1.768 (0.735)

*$p < 0.05$. **$p < 0.01$ versus survivors (Mann–Whitney test).
cWBV, calculated whole-blood viscosity; Hb, haemoglobin; Ht, haematocrit; IQR, interquartile range; MM, multiple myeloma; RDW, red blood cells distribution width; YSS, yield shear stress.

Merrill formula and albumin/fibrinogen ratio. Serum albumin, RDW%, haemoglobin value, RDW%/albumin and RDW%/haemoglobin ratio are instead significantly reduced in non-survivors patients. Finally, it is worth underlining that in IgG MM, the mortality rate is lower than the other disease isotypes, and the male patients who die are half as many as female patients.

Discussion

In this preliminary study, the mortality rate in NDMM patients was considered after almost 7 years of clinical observation, in a temporal segment ranging from 1 January 2017 to 31 October 2023. Therefore, for the last enrolled patients it was only possible to evaluate a possible early mortality rate (within 12 months of diagnosis). It is also important to underline that the statistical analysis was carried out both in the whole cohort of patients and in the three different MM isotypes, with all the limitations due to the non-homogeneous numerical distribution of patients in the different disease isotypes.

In the entire cohort of NDMM patients, but also in the three disease isotypes, we observed that the blood viscosity calculated according to Merrill's formula makes no distinction between deceased and surviving patients. Instead, a different and opposite behaviour occurs with the calculated blood viscosity in accordance with the de Simone formula, that show significantly lower values in the deceased patients, especially considering that in these same patients the haematocrit and total serum protein values are lower respect to survivors.

The albumin/fibrinogen ratio distinguishes quite clearly the group of the deceased from those of survivors. In fact, as it is known, this ratio is a marker of the erythrocyte aggregation, and this latter, measured with different methods, is constantly increased in plasma cell dyscrasias.[28,29] Erythrocyte aggregation is a reversible process that affects whole blood viscosity at low shear stress, and it has a key role in particular in areas of blood circulation with low sliding gradients, such as the venous system, in which, especially in MM, thrombotic complications are more frequent.[30–32]

Table 6. Medians (IQRs) of the erythrocyte and plasma parameters in IgG MM patients subdivided into survivors and non-survivors.

IgG MM	All IgG MM ($n = 107$)	Survivors ($n = 69$)	Non-survivors ($n = 38$)
Age (years)	73.00 (12.00)	70.00 (12.00)	77.00 (8.50)***
Males/females	41/66	32/37	9/29
Ht %	31.90 (8.80)	32.70 (9.65)	30.00 (8.92)
Plasma proteins (g/L)	81.90 (25.50)	82.80 (24.95)	80.35 (27.20)
cWBV 208 s^{-1} (mPa s)	17.35 (3.76)	18.19 (3.82)	16.75 (3.86)
Fibrinogen (g/L)	3.200 (1.270)	3.110 (1.300)	3.230 (1.303)
cWBV (YSS/dyne cm^2)	0.255 (0.273)	0.280 (0.239)	0.210 (0.304)
Albumin (g/L)	37.00 (10.20)	37.90 (7.90)	32.70 (9.63)**
Albumin/fibrinogen	10.35 (5.401)	11.11 (5.98)	9.72 (4.02)
RDW%	14.80 (3.10)	14.60 (2.50)	15.75 (4.12)*
Hb (g/dL)	10.30 (3.20)	11.00 (3.05)	9.95 (2.20)*
RDW%/albumin	0.420 (0.210)	0.380 (0.145)	0.460 (0.260)**
RDW%/Hb	1.410 (0.615)	1.282 (0.505)	1.553 (0.732)**

*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$ versus survivors (Mann–Whitney test).
cWBV, calculated whole-blood viscosity; Hb, haemoglobin; Ht, haematocrit; IQR, interquartile range; MM, multiple myeloma; RDW, red blood cells distribution width; YSS, yield shear stress.

In this cohort of patients, as we demonstrated in a previous research,[18] the incidence of thromboembolic events is of 18/190 cases. The increase of albumin/fibrinogen ratio depends above all on the decrease in serum albumin, but also on the behaviour of plasma fibrinogen that tends generally to increase in this haematological neoplasm.[33–35]

Comparing deceased and survivor patients, the age is certainly a parameter markedly discriminating. So far, there are many reports that identify in the age an unfavourable marker of survival in MM.[36–40] In our study population, only 30 patients (15.78%) were under 60 years old, of whom one was under 50 years old, 10 patients were aged between 40 and 50 years and 19 between 51 and 60 years. Respect to disease isotype, the percentage of MM patients under 60 years old was 33.33% in LCMM, 14.28% in IgA MM and 12.4% in IgG MM; in this latter, the mortality rate is lower, but we must underline the different and not uniformly distributed number of patients belonging to each isotype.

Haematocrit and haemoglobin are different in deceased patients compared to survivors, with lower median values in the former group. Present in approximately 70% of patients at diagnosis, the anaemia is in fact a common complication of MM. It is related to multiple pathogenetic causes that include altered balance of the cytokine network, tumour bone infiltration of the bone marrow, altered levels of erythropoietin, blood loss, haemolysis, nutritional defects and changes in erythropoiesis, as result of the same disease and cytotoxic therapy.[41–44] The anaemic condition, in addition to being associated with a poor quality of life, has a negative impact on the cardiovascular system as it tends to aggravate or induce hypoxic or ischaemic complications, representing therefore a negative prognostic factor.[45] In MM, the correlation between anaemic condition and hepcidin, result very interesting[46–49]; in fact, the hepcidin levels are significantly increased in this disease, with a hepatic synthesis mediated by bone morphogenetic protein-2 (BMP-2).[50]

Another parameter with an important prognostic value is the serum albumin. The MM patients with lower levels of albumin (<3.5 g/dL) have highest levels of beta-2 microglobulin, monoclonal component and of the bone marrow plasma cell infiltration.[51] In fact, the ISS and R-ISS, as well as some prognostic nomograms consider serum albumin levels strongly. In our analysis, we observed an important difference in albumin values between deceased and surviving patients, both in the whole cohort of patients and, specifically, in LCMM and in IgG MM.[52,53]

Although highlighted for some decades, the specific cause of reduced levels of albumin in MM patients is uncertain.[54] So far, many reports relate low serum albumin levels to high serum levels of interleukin-6 (IL-6), powerful growth factor the seems to reflect the degree of cell proliferation.[55,56] Serum albumin value correlate negatively with IL-6 levels, which reduce its hepatic synthesis. IL-6 is a multifunctional and pro-inflammatory cytokine that stimulates the maturation and proliferation of B-cells, and its hyperproduction is observed in several B-cell neoplasms, including MM, in which the neoplastic cells have high receptor levels for this cytokine. It is also important to remember that low serum albumin may be related to nutritional status of MM patients.[57] In relation to the serum albumin level in MM, several authors have used the albumin/globulin ratio, both as a predictor of mortality and as a prognostic marker. The authors who used this ratio as a predictor of mortality have observed that the decrease of this ratio is able to predict the lowest survival, at 24 and 36 months from diagnosis.[58] Similarly, other authors who have evaluated the prognostic value of this ratio, observed a greater survival and to a reduced progression rate of disease in patients with an increase in this ratio.[59] Furthermore, it cannot be ruled out that, since MM affects an older population generally, the reduced synthesis of albumin may have other causes, such as lack of appetite, reduced intestinal absorption, muscular hypotrophy and especially malnutrition.[60] Recently, in MM patients, the serum albumin was included in the HALP score along with haemoglobin, lymphocytes and platelets, and thus being simultaneously a marker of both the inflammatory and nutritional status.[61]

Among the several examined parameters, also the RDW distinguishes deceased patients from survivors. The RDW has a role as inflammatory biomarker in several conditions, such as cardiovascular diseases, kidney diseases, chronic pulmonary diseases, critically ill patients but also in several types of cancers and in haematological malignancies, particularly in MM[62–69]; it reflects the heterogeneity of the erythrocyte volume, and it is calculated by dividing the standard deviation of erythrocytes with the mean corpuscular volume of red blood cells. Even if a lot of data are available about the correlation between RDW and some inflammatory markers, such as erythrocyte sedimentation rate and reactive C protein, it is very likely that, in MM, the variation of this erythrocyte index may be due to the high circulating levels of IL-6, TNF-α and hepcidin.[70–72] Interacting with each other, these factors alter the erythropoiesis, and this happens through an alteration of erythrocyte maturation that leads to the increase in RDW. It must be underlined that IL-6 has a specific role in the survival and proliferation of myeloma cells, and therefore it is another marker of a negative prognosis in MM.[73] It should also be noted, that myeloma cells have high levels of reactive oxygen species, associated with low concentration of antioxidant activity, and this circumstance is closely correlated with both increased oncogenic activity and amplified metabolic activity.[74] The cytokine pattern in MM patients is, in fact, altered, with an abnormal balance between the pro-inflammatory and anti-inflammatory pattern and between the proliferative and anti-proliferative pattern.[75,76]

As well as the RDW, the same discriminating power are found to have the RDW%/albumin ratio and the RDW%/haemoglobin ratio. Of these two ratios the most studied, so far, is certainly the one related to the albumin. Up to now, this ratio has been investigated in subjects with aortic aneurysms, in type 2 diabetics with foot ulcers, in heart failure, in acute ischaemic stroke and in acute myocardial infarction.[21–26] In our analysis, the RDW%/albumin ratio discriminates deceased from survived patients, not only in the entire study cohort, but also evaluating the different disease isotypes, particularly in LCMM and in IgG MM. In this regard, it should be remembered that the albumin in LCMM is higher than the other isotypes, and this datum has been also reported by other authors.[77] We have observed the same trend in the RDW%/haemoglobin ratio, in the entire cohort of MM patients and, specifically, in IgG isotype. There is no literature data on these two parameters in MM patients;

however, the RDW%/haemoglobin ratio has been examined in 265 patients with diffuse large B-cell lymphoma showing that its increase reveals a worse prognosis of these patients.[78] The same parameter has also been investigated in 11 retrospective studies, with 2985 neoplastic patients, in those the increment of this ratio was associated with high mortality and disease progression.[79] The reduction of haemoglobin, as an unfavourable prognostic marker, certainly not surprising both in cancer and in MM patients, and in this regard very interesting is the proposal of a 'haematopoietic score', proposed for the outcome of patients with newly diagnosed MM.[80]

Limitation

Limitations of this research include the retrospective nature of the study and the small sample size. Furthermore, after dividing the entire cohort of patients according to disease isotypes, there is no equal distribution in the three identified subgroups, with 27/190 LCMM patients, 56/190 IgA MM patients and 107/190 IgG MM patients. Finally, we acknowledge as a limitation of the study the lack of information regarding the cytogenetic profile of the patients, which could have added further value to our analysis.

Conclusion

From this preliminary study, it emerges that many of the parameters evaluated, acquired at low cost and routinely used (albumin/fibrinogen ratio, RDW%/albumin ration and RDW%/Hb ratio), they are suitable for clearly distinguishing the deceased and survivors of patients with new diagnosis of MM, observed for a period of 6 years, with a median follow-up of 32 months. These findings represent a possible starting point for subsequent analyses aimed at evaluating the prognostic role of the aforementioned parameters in the clinical setting of MM, with the possibility of having new and simple data that allow an increasingly careful evaluation of the patients.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Hospital of Palermo (Report No. 01/2022). Informed consent was obtained from all the enrolled subjects or patient guardians prior to participation.

Consent for publication

As this study used anonymised data and it does not contain images of patients, further informed consent was not required.

Author contributions

Melania Carlisi: Conceptualisation; Data curation; Writing – original draft; Writing – review & editing.

Rosalia Lo Presti: Formal analysis; Validation; Visualisation.

Corinne Spoto: Validation; Visualisation.

Salvatrice Mancuso: Validation; Visualisation.

Sergio Siragusa: Validation; Visualisation.

Gregorio Caimi: Conceptualisation; Methodology; Supervision; Validation; Writing – original draft.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The presented data are available on request from the corresponding author. Correspondence and requests for materials should be addressed to MC.

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