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Impact of CRAB Criteria on The Prognosis of Patients with Multiple Myeloma Compared to Other Prognostic Factors in The Era of Novel Agents

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ABSTRACT

Background: Multiple myeloma can be distinguished from asymptomatic myeloma and monoclonal gammopathy of uncertain significance thanks to CRAB factors. **Objective:** To assess role of CRAB factors in prognosis of cases who had multiple myeloma and being treated with novel therapeutic agents in comparison with non-novel agents.

Patients and Methods: A comparative cross-sectional study was conducted in the Hematology Unit, Internal Medicine Department, in Zagazig University Hospitals on 100 patients with multiple myeloma. We looked at how the existence of CRAB factors affected the survival rates of individuals with symptomatic myeloma who were receiving novel therapies. **Results:** Hb, PLT, albumin were higher in Novel Containing Regimen (NCR) group than Non-Novel Containing Regimen (NNCR) group, while creatinine, Bence Jones protein in urine, serum beta-2-microglobulin and calcium were lower in (NCR) group than (NNCR) group. Bone marrow plasma cells after treatment, lytic lesion, anemia, hypercalcemia and renal insufficiency were lower in (NCR) group than (NNCR) group. About 91% of patients had M protein type IGG and 9% had IGA, the mean bone marrow plasma cells was 24.6 ± 4.3, 21% had abnormal cytogenetics, 25% had high risk FISH, 70% had lytic lesions, 17% had EMD at diagnosis, 29% had anemia (decrease of Hb more than 2 g/dl or to equal or less than 10 g/dl), 17% had hypercalcemia ≥11.5 mg/dl, 16% had renal insufficiency (increase of serum creatinine more than 2 g/dl).

Conclusion: Overall survival and progression-free survival for myeloma patients treated with new medicines; both significantly improved.

Keywords: CRAB, Multiple Myeloma, Novel agents**.**

INTRODUCTION

Multiple myeloma is a clonal neoplastic plasma cell disorder marked by the presence of monoclonal protein in the serum and/or urine and the clonal growth of plasma cells in the bone marrow [(1)]. Multiple myeloma is the second most frequent hematological malignancy, behind non-Hodgkin lymphoma, and is responsible for 20% of all deaths from hematological disorders [(2)]. Diagnosis of multiple myeloma requires the observation of end organ damage, the identification of monoclonal proteins in the blood and/or urine, and the invasion of bone marrow by plasma cells. Bone lesions, renal failure, high calcium levels, and anemia are all signs of end-organ damage [(3)]**.**

Clinical manifestations of multiple myeloma are summarized by the International Myeloma Working Group's CRAB acronym [(4)]. Combining autologous stem cell transplantation with proteasome inhibitors and/or immunomodulatory drugs has been shown to improve patient outcomes [(5)]**.**

Multiple myeloma tumor burden was previously assessed using the International Staging System (ISS), which has inherent limitations because of its dependence on a host factor determinant, specifically serum albumin. Disease-independent variables may have an impact. Multiple myeloma has a new staging method available, called the Revised International Staging System (RISS), which uses cytogenetic abnormalities and lactate dehydrogenase level as a prognostic marker [(6)]**.**

CRAB variables have a crucial role in separating multiple myeloma from smouldering monoclonal gammopathy and monoclonal gammopathy of unclear significance (asymptomatic myeloma). They are important to assess prognosis of the disease and to decide when to start treatment (International Myeloma) [(7)]**.** Osteolytic bone lesions, which occur in 90% of individuals with multiple myeloma, are the disease's defining feature and signal the presence of an active disease that has to be treated [(8)]. Patients with multiple myeloma symptoms who also have bone lesions and hypercalcemia have a poor prognosis [(9)]**.**

The existence of a localised lesion on state-of-the-art imaging, the extent of plasma cell infiltration, and the presence of a serum free light chain were all added by the International Myeloma Working Group (IMWG) as additional criteria for beginning treatment. The effects of anemia on patients' quality of life and likelihood of survival are bad [(10)]**.**

The study aimed to assess role of CRAB factors in prognosis of patients who had multiple myeloma treated with novel therapeutic agents in comparison with non-novel agents.

PATIENTS AND METHODS

A comparative cross-sectional study was conducted in the Hematology Unit, Internal Medicine Department, in Zagazig University Hospitals on 100 patients with multiple myeloma.

As the rate of multiple myeloma patients admitted to Hematology Unit, Internal Medicine Department is 4 per month and 48 per year, so all patients were taken as a comprehensive sample, so the sample size was 100 cases.

Inclusion criteria:

1. Cases which had diagnosed with multiple myeloma.
2. Cases presented with evidence of end organ damage (CRAB factors).

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3. Cases who received novel chemotherapy as bortezomib and/or immunomodulators.

Exclusion criteria:

1. Cases with precursor lesion (MGUS).
2. Cases with smouldering (asymptomatic myeloma).
3. Cases have other causes of anemia, renal impairment and bone lesions.
4. Cases treated with other lines of treatment other than proteosome inhibitors or immunomodulators.

The patients were divided into 2 groups according to line of treatment:

Group 1: Novel Containing Regimen (NCR) e.g., bortezomib, lenalidomide.
Group 2: Non-Novel Containing Regimen (NNCR) e.g., cyclophosphamide, thalidomide.

All patients were subjected to the following:

1) Medical History:

Detailed past and present medical history taking included age, sex, special habits (alcohol, smoking), cause of admission, comorbidities such as hypertension, arrhythmia, diabetes mellitus, and medication (antiplatelets, anticoagulants, NSAIDs, steroids).

2) Investigations:

a) CBC using automated cell counter "Sysmex XS" Sysmex Corporation, Japan) with peripheral blood smear staining with Lishman stain and examination under light microscope.
b) Serum creatinine, creatinine clearance, LFT and LDH, B2 macroglobulin, electrolytes including calcium using autoanalyzer (Cobas Integra 400 plus Roch diagnostics, USA).
c) Bone marrow aspiration, biopsy and IHC. Bone marrow aspirate slides were stained with Lishman stain for morphologic study. Using traditional microscopy, we were able to get a differential cell count of 200. When more than 10% PC was identified in the bone marrow (BM) aspirate smear, the morphological examination indicated the presence of a plasma cell neoplasm.
d) Antibody profiling of bone marrow using a four-color direct immunofluorescence method, BM aspirate samples were analysed immunophenotypically. CD19, CD56, CD138, CD38, CD45, CD20, KAPPA, and LAMBDA were some of the antibody combinations investigated. The antibodies were purchased from BD Biosciences in San Jose, California, USA. FACSDiva software was used for data analysis after multiparameter flow cytometry was conducted on a FACSCantoTM flow cytometer (BD Biosciences). A total of 10,000 events were collected, and the bright CD38+ events were analyzed.
e) FISH for 17pdel, t(4:14), t(14:16).
f) Serum and urine protein electrophoresis and immunofixation.
g) Radiological studies including: Skeletal survey, PET/CT.

Treatment:

All patients were treated with one of the following protocols:

1. VCD (Velcade with dose of 1.3 mg/m^2 per day on days one, four, eight, eleven, cyclophosphamide with dose 300 mg/m^2 per week as well as dexamethasone with dose 40 mg per week).
2. VRD (Velcade with dose of 1.3 mg/m^2 per day, on days one, four, eight, eleven, lenalidomide 25 mg/every other day as well as dexamethasone 40 mg per week).
3. VTD (Velcade with dose of 1.3 mg/m^2 per day on days one, four, eight, eleven, thalidomide 100 mg per day as well as dexamethasone 40 mg per week).
4. CRD (Cyclophosphamide with dose 300 mg/m^2 per week, lenalidomide 25 mg per day as well as dexamethasone 40 mg per week).
5. CTD (Cyclophosphamide with dose of 300 mg/m^2 per week, thalidomide 100 mg/day as well as dexamethasone 40 mg per week).

Response to treatment of the studied patients as:

- Complete response.
- Very good partial response.
- Partial response.
- Stable.
- Refractory.

Overall survival and disease-free survival were assessed among all cases.

Ethical consent:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University. Written informed consent was taken from all participants. The study was conducted according to the Declaration of Helsinki.

Statistical analysis

Statistical Package for the Social Sciences (SPSS), version 20, was used to analyse the collected data. Quantitative data were presented as mean, standard deviation (SD), and range and were compared by independent t-test. Qualitative data were presented as frequency and percentage and were compared by Pearson Chi-Square test. Significant results were considered to exist when the p value was less than 0. 05.

RESULTS

Table (1) shows that the mean age was 64.8 ± 11.6, 64% of patients were male and the most common comorbidities were hypertension (30%) and hypertension and DM (17%).

Table (1): Demographic data and comorbidities of the studied patients

Variables	Patients (N=100)	Range or %
Age (Years)	64.8 ± 11.6	44-84
Gender		
Male	64	64%
Female	36	36%
Comorbidities	67	67%
Type of comorbidities		
Hypertension	30	30%
Hypertension and DM	17	17%
Hypothyroidism	8	8%
IHD	8	8%
Chest allergy	4	4%

Data are presented as mean ± standard deviation or as frequency and percent.

Table (2) shows the staging of patients according to International Staging System (ISS) and Durie-Salmon Staging System (DSS), 50% of patients had disease stage III and 33% of patients had partial response.

Table (2): Stage at time of presentation and response to treatment among the studied patients

Variables	Patients (N=100)
Stage I	29 (29%)
Stage II	21 (21%)
Stage III	50 (50%)
Complete response	28 (28%)
Very good partial response	22 (22%)
Partial response	33 (33%)
Stable	13 (13%)
Refractory	4 (4%)

Table (3) shows the laboratory data of the studied patients.

Table (3): Laboratory data among the studied patients

Variables	Patients (N=100)
Hb (g/dL)	10.1 ± 1.4
PLT (mcL)	242.4 ± 59.1
Serum albumin (g/dl)	3.4 ± 0.21
Creatinine (mg/dl)	1.35 ± 0.32
Bence Jones **protein in urine**	63 (63%)
Serum protein electrophoresis	100 (100%)
Elevated lactate dehydrogenase	21 (21%)
Serum beta-2-microglobulin (mg/l)	4.3 ± 0.95
Calcium (mg/dL)	10.2 ± 1.1

Data are presented as mean ± standard deviation or as frequency and percent

Table (5) shows that bone marrow plasma cells after treatment, lytic lesion, anemia, hypercalcemia and renal insufficiency were lower in Novel Containing Regimen (NCR) group than Non-Novel Containing Regimen (NNCR) group.

Table (5): Clinical data of the studied patients

Variables	Novel Containing Regimen (NCR) (N=54)	Non-Novel Containing Regimen (NNCR) (N=46)	t/X^2	P
Types of M protein **IGG** **IGA**	 49 (90.7%) 5 (9.3%)	 42 (91%) 4 (9%)	0.01	0.92
Bone marrow plasma cells	4.2 ± 0.7	22.2 ± 2.6	48.8	<0.0001*
Abnormal cytogenetics	11 (20.4%)	10 (21.7%)	0.03	0.87
High risk FISH	17 (31%)	8 (17%)	2.6	0.1
Lytic lesions	32 (69.6%)	19 (35%)	3.2	0.073
EMD at diagnosis	9 (16.7%)	8 (17.4%)	0.009	0.92
EMD at follow up	1 (1.9%)	5 (10.9%)	3.5	0.05
Anemia (↓ in hemoglobin ≥2 g/dl or to ≤10 g/dl)	4 (7.4%)	25 (54.3%)	26.5	<0.0001*
Hypercalcemia ≥11.5 mg/dl	4 (7.4%)	13 (28.3%)	7.6	0.006*
Renal insufficiency (↑ serum creatinine ≥2g/dl)	2 (3.7%)	14 (30.4%)	13.2	0.003*

Data are presented as mean ± standard deviation or as frequency and percent, *: Significant

Table (6) shows that response to treatment was better in Novel Containing Regimen (NCR) group than Non-Novel Containing Regimen (NNCR) group.

Table (6): Response to treatment of the studied patients

Variables	Novel Containing Regimen (NCR) (N=54)	Non-Novel Containing Regimen (NNCR) (N=46)	X^2	P
Complete response	28 (52%)	0 (%)		
Very good partial response	22 (41%)	0 (%)		
Partial response	4 (7%)	29 (63%)	85.8	<0.0001*
Stable	0 (0%)	13 (28%)		
Refractory	0 (0%)	4 (9%)		

*: Significant

Table (7) shows that Hb, PLT, and albumin were higher in Novel Containing Regimen (NCR) group than Non-Novel Containing Regimen (NNCR) group, while creatinine, Bence Jones protein in urine, serum beta-2-microglobulin and calcium were lower in Novel Containing Regimen (NCR) group than Non-Novel Containing Regimen (NNCR) group.

Table (7): Comparison of the laboratory data between the studied groups of patients

Variables	Novel Containing Regimen (NCR) (N=54)	Non-novel containing regimen (NNCR) (N=46)	t/X^2	P
Hb (g/dL)	10.8 ± 0.85	9.6 ± 1.6	4.7	<0.0001*
PLT (mcL)	255.2 ± 59.3	223.03 ± 9.4	2.01	0.04*
Serum albumin (g/dl)	3.5 ± 0.23	3.3 ± 0.15	5.1	<0.0001*
Creatinine (mg/dl)	1.13 ± 0.14	1.53 ± 0.17	3.01	0.003*
Bence Jones **protein in urine**	26 (48%)	37 (80%)	11.1	<0.001*
Serum protein electrophoresis	54 (100%)	46 (100%)	0	1
Elevated lactate dehydrogenase	12 (22%)	9 (20%)	0.11	0.75
Serum beta-2-microglobulin (mg/l)	3.8±0.69	4.7 ± 0.97	5.1	<0.0001*
Calcium (mg/dL)	9.2 ± 1.2	10.24 ± 1.07	4.5	<0.0001*

Data are presented as mean ± standard deviation or as frequency and percent, *: Significant

Table (8) shows that number of patients alive and the mean disease-free survival were higher in Novel Containing Regimen (NCR) group than Non-Novel Containing Regimen (NNCR) group.

Table (8): Mortality, and disease-free survival at time of data collection among the studied patients

Variables	Novel Containing Regimen (NCR) (N=54)	Non-novel containing regimen (NNCR) (N=46)	t/X^2	P
Alive **Died**	47 (87.0%) 7 (13.0%)	19 (41.3%) 27 (58.7%)	23.2	<0.0001*
Disease free survival (months)	60 ± 7.8	33.7±5.4	19.2	<0.0001*

Data are presented as mean ± standard deviation or as frequency and percent
*: Significant

DISCUSSION

In the criteria that were established in 2003 by the International Myeloma Working Group, the most common clinical symptoms of multiple myeloma included hypercalcemia, renal failure, anemia, and bone disease, which were grouped together under the abbreviation CRAB. This was done in an effort to make the list easier to understand **(11).**

The staging criteria developed by **Durie and Salmon(4)** make use of all CRAB clinical data. This is due to the fact that the blood levels of calcium, creatinine, and hemoglobin, in addition to the number of bone lesions, are significant in determining the stage of the disease **(12).**

In the context of renal failure, a number of articles suggest that novel drugs have improved renal dysfunction. Despite this, survival rates have not considerably increased as a result of the data presented in these papers. When it comes to the CRAB factors, very little is known about how their relationships to survival actually work **(11)**.

This study showed that the mean age of the patients was 64.8 ± 11.6, ranged from 44 to 84 years, 64% of patients were male and 36% were female. This study showed that there was no significant difference between both groups regarding demographic data.

Nakaya *et al.* (9) examined the presence of CRAB factors on survival in symptomatic myeloma patients treated with novel agents. A total of 113 consecutively diagnosed symptomatic myeloma patients at Kansai Medical University Hospital between 2006 and 2014 were included in this retrospective analysis. Similar to our results, mean age was 72 years old (range: 34-88 years) and 51% were male

This study reported that 67% of patients had comorbidities, the most common comorbidities were hypertension (30%) and hypertension and DM (17%). This study reported that there was significant difference between both groups regarding type of comorbidities while there was no significant difference regarding number of comorbidities.

Similar to our finding, **Nakaya *et al.* (9)** showed that hypercalcemia was the fourth most common presenting factor of multiple myeloma, after anemia (57%) and renal failure (29%) (6 percent). Also Similar to our finding, they showed that stage 1 was present in 45% of patients, stage 2 in 21%, and stage 3 in 34%, as measured by the International Staging System.

In same line of lab results of our study, previous studies as by **Dimopoulos *et al.* (8), Ludwig *et al.* (13), Chanan-Khan *et al.* (14), Roussou *et al.* (15)** and **Dimopoulos *et al.* (16)** revealed that renal dysfunction was improved by treatment with innovative medicines, however whether or not this translates into longer life expectancy for individuals with renal failure is not confirmed.

In agreement with clinical findings of our study, **Puertas *et al.* (17)** showed that greater people in the t (11;14) group had oligosecretory illness (although not substantially more) and more people had non-secretory disease (10.5 vs. 1.6%) compared to the SR group, while fewer people in the t (11;14) group had the IgA subtype (12.6 vs. 24.7%) or the light-chain kappa (51.6 vs. 63.6%). Blood calcium levels were higher in the t(11;14) group (9.97 mg/dL 1.36 vs. 9.62 mg/dL 1.37), and there was a decreased incidence of plasmacytomas (both paraskeletal and extramedullary types) in the t(11;14) group (17.2 vs. 38.6 percent).

Inconsistencies in the interpretation of the number of bone lesions have impeded the implementation of the CRAB criterion and paraprotein level from the original stage system by Durie-Salmon, in addition to other unrelated causes of high serum creatinine and decreased hemoglobin levels **(18)**.

Higher values of 2-microglobulin and lactate dehydrogenase (LDH) are correlated with shorter life and associated with larger tumour load, however renal failure and other comorbidities can contradict the results and limit the usefulness of these biomarkers. High-risk cytogenetics, in addition to 2-microglobulin and LDH, were introduced into the Revised International Staging System (R-ISS) to deal with these concerns **(19).**

Nakaya *et al.* (9) found similar correlations

between the existence of variables and patient outcomes in symptomatic multiple myeloma, corroborating our findings. Survival rates were considerably lower for patients with hypercalcemia and bone disease compared to people with anemia or renal failure.

Puertas *et al.* [17] found after a median follow-up of 80.1 months that 41.1% of patients were still living at the time of the last contact (range, 1.2-273.8 months).

Patients with t (11;14) had a median PFS and OS of 35.3 and 75.8 months, respectively, compared to the overall median of 28.7 months. Age at diagnosis, baseline features, ORR, CR, first-line new drugs, and ASCT all had their univariate relationships with the outcome calculated. A multivariate model was then constructed taking into account the significant factors.

In study performed b**y Puertas *et al.* [17]** failure to achieve complete remission (CR) after induction and 2 microglobulin levels below 5.0 mg/dL. Patients were followed for a median of 80.1 months (range: 1.2-273.8 months), and 239 of them/ (41%) were still alive at the time of the last contact. Patients with t(11;14) had a longer median PFS and OS than those without the translocation, at 35.3 and 75.8 months, respectively, compared to the overall cohort's 28.7 and 72.5 months respectively. Age at diagnosis, baseline features, ORR, CR, first-line new drugs, and ASCT all had their univariate relationships with the outcome calculated. A multivariate model was then constructed taking into account the significant factors.

Puertas *et al.* [17] t(11;14) revealed a trend toward a better response when novel agents were used in first line. Those given novel agents (87.2%) were not significantly different from those given traditional agents (79.5%). The CR rate also did not change noticeably. In contrast, the ORR for the SR group was much higher when using novel drugs (89.8 percent vs. 78.5 percent) than when using traditional therapy. Compared to patients getting standard care, more people who were given new drugs obtained CR.

In the case of the HRCA group, **Puertas *et al.* [17]** found that there were no statistically significant differences in overall response rate (ORR) between patients treated with innovative medicines and those treated with traditional therapy. PFS and OS were 31.1 months and 27.3 months, respectively, for patients in the overall cohort who were treated with new medicines in first line compared to those who received conventional therapy, respectively.

In a study by **Min *et al.* [20]**, sixty-four percent of patients showed signs of worsening disease, and thirty percent had already passed away by the time they conducted their research. From the time of diagnosis, the projected median follow-up for the total cohort was 37.9 months. Overall survival (OS) was at 70.2% after 3 years, while progression-free survival (PFS) was at 42.8%. In terms of overall survival, the median PFS was 32.7 months and the median OS was 66.8 months. Survival results were compared between ASCT recipients who used NA during induction therapy and those who used it during maintenance therapy, providing insight into how much time was saved throughout treatment. Patients who received NAs as maintenance therapy after transplantation fared better in terms of PFS and OS than those who received NAs as induction therapy prior to transplantation.

CONCLUSION

Overall survival and progression-free survival for myeloma patients treated with new medicines both significantly improved.

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REFERENCES

1. **Sridevi H, Rai S, Suresh P *et al.* (2015):** Pancytopenia in multiple myeloma- An enigma: Our experience from tertiary care hospital. J Clin Diagn Res., 9(11): 4-6.
2. **Kumar S, Rajkumar V, Kyle R *et al.* (2017):** Multiple myeloma. Nat Rev Dis Primers, 3: 170-176.
3. **Dimopoulos M, Kyle R, Fermand J *et al.* (2011):** Consensus recommendations for standard investigative workup: Report of the International Myeloma Workshop Consensus Panel 3. Blood, 117(18): 4701–4705.
4. **Durie B, Salmon S (1975):** A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer, 36(3): 842–854.
5. **Kumar S, Flinn I, Richardson P *et al.* (2012):** Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood, 119(19): 4375–4382.
6. **Rajkumar S (2022):** Multiple myeloma: 2022 update on diagnosis, risk-stratification and management. American Journal of Hematology, 97(8): 1086–1107.
7. **International Myeloma Working Group (2003):** Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: A report of the International Myeloma Working Group. British Journal of Haematology, 121(5): 749–757.
8. **Dimopoulos M, Chen C, Spencer A *et al.* (2009):** Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia, 23(11): 2147–2152.
9. **Nakaya A, Fujita S, Satake A *et al.* (2017):** Impact of CRAB symptoms in survival of patients with symptomatic myeloma in novel agent era. Hematology Reports, 9(1):6887. doi: 10.4081/hr.2017.6887.

10. **Kyle R, Gertz M, Witzig T *et al.* (2003).** Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clinic Proceedings, 78(1): 21–33.
11. **Padala S, Barsouk A, Barsouk A *et al.* (2021):** Epidemiology, staging, and management of multiple myeloma. Medical Sciences, 9(1): 3-8.
12. **Wan B, Zhang S, Wang P *et al.* (2023):** Prognostic value of semi-quantitative parameters of 18F-FDG PET/CT in newly diagnosed multiple myeloma patients. Annals of Nuclear Medicine, 37(3): 155-165.
13. **Ludwig H, Adam Z, Hajek R *et al.* (2010):** Light chain-induced acute renal failure can be reversed by bortezomib-doxorubicin-dexamethasone in multiple myeloma: results of a phase II study. J Clin Oncol., 28: 4635-41.
14. **Chanan-Khan A, Kaufman J, Mehta J *et al.* (2007):** Activity and safety of bortezomib in multiple myeloma patients with advanced renal failure: a multicenter retrospective study. Blood, 109: 2604-6.
15. **Roussou M, Kastritis E, Christoulas D *et al.* (2010):** Reversibility of renal failure in newly diagnosed patients with multiple myeloma and the role of novel agents. Leuk Res., 34: 1395-7.
16. **Dimopoulos M, Roussou M, Gkotzamanidou M *et al.* (2013):** The role of novel agents on the reversibility of renal impairment in newly diagnosed symptomatic patients with multiple myeloma. Leukemia, 27: 423-9.
17. **Puertas B, González-Calle V, Sobejano-Fuertes E *et al.* (2023):** Multiple myeloma with t(11;14): impact of novel agents on outcome. Blood Cancer J., 13: 40. doi: 10.1038/s41408-023-00807-9
18. **Wallington-Beddoe C, Mynott R (2021):** Prognostic and predictive biomarker developments in multiple myeloma. J Hematol Oncol., 14(1):151. doi: 10.1186/s13045-021-01162-7.
19. **Palumbo A, Avet-Loiseau H, Oliva S *et al.* (2015):** Revised international staging system for multiple myeloma: A report from International Myeloma Working Group. Journal of Clinical Oncology, 33(26): 2863–2869.
20. **Min C, Lee S, Yahng S *et al.* (2013):** The impact of novel therapeutic agents before and after frontline autologous stem cell transplantation in patients with multiple myeloma. Blood Research, 48: 198-205.