History of Medicine, 2023, 9(1): 2435–2440
DOI: 10.17720/2409-5834.v9.1.2023.315

Predictive Biomarkers of Newly Diagnosed Patients with Plasma Cells Tumor

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Received: 13 January 2023 **Accepted:** 6 April 2023

Citation: Habeeb ZT, Al-Sharifi ZAR, Rahem RM (2023) Predictive Biomarkers of Newly Diagnosed Patients with Plasma Cells Tumor History of Medicine 9(1): 2435–2440. https://doi.org/10.17720/2409-5834.v9.1.2023.315

Abstract

Renal failure refers to the kidneys' inability to carry out their excretory duties, which causes the blood's nitrogenous waste products to be retained; this activity reviews the causes, pathophysiology, presentation, and diagnosis of renal failure and emphasizes the role of the interprofessional team in its management. The generation of monoclonal immunoglobulin by the neoplastic proliferation of plasma cells is the hallmark of the disease known as Plasma Cell Tumor or Multiple Myeloma (MM); pathological fractures, osteolytic lesions, and/or substantial skeletal damage are frequently caused by the proliferation of plasma cells in the bone marrow.Aim of the study: Is found the correlation between predictive biomarkers of newly diagnosed plasma cells tumor.Materials and methods: Patients Hospital-Based cross-sectional study was conducted over sixteen months from May 2020 until August 2021. A total of 58 MM patients were involved in the study who were subjected to physical examination, standard clinical, radiological, and laboratory investigations and diagnosed by hematologists with MM from both genders. Blood samples and urine samples were collected to measure the concentrations of (TIMP2) and Cys-C.Results: Mean age of patients was (61.69 ± 11.12) years. The older patient was (80.0) years and younger patient was (34.0) years. More than half of patients were male (N=31, 53.4%). Stage I represents (N=22, 37.9%) of patients, Stage II represent (N=16, 27.6%) of patients) and Stage III represent (N=20, 34.5%) of patients. There were significant differences between means of TIMP2 (ng/ml) according to stages of multiple myeloma. There were no significant differences between means of Cystatin C (mg/l) according to stages of multiple myeloma.

Keywords

Plasma Cell Tumor, MM, Predictive Biomarkers, TIMP2, Cys-C

Renal failure refers to the kidneys' inability to carry out their excretory duties, which causes the blood's nitrogenous waste products to be retained; this activity reviews the causes, pathophysiology, presentation, and diagnosis of renal failure and emphasizes the role of the interprofessional team in its management; acute and chronic renal failure are the two types of kidney failure, and when a patient requires renal replacement therapy, the condition is known as end-stage renal disease (ESRD) (1). There were five different types of kidney failure; acute kidney failure occurs when acute renal failure occurs and chronic kidney failure develops over time; by other words the types of kidney impairments include acute prerenal kidney failure (2), acute intrinsic kidney failure (3), chronic prerenal kidney failure (4), chronic intrinsic kidney failure (5) and chronic post-renal kidney failure (6).

The generation of monoclonal immunoglobulin by the neoplastic proliferation of plasma cells is the

hallmark of the disease known as Plasma Cell Tumor or Multiple Myeloma (MM); pathological fractures, osteolytic lesions, and/or substantial skeletal damage are frequently caused by the proliferation of plasma cells in the bone marrow (7).

One or more of the clinical manifestations listed fpllowing may raise suspicions for the diagnosis of MM (8); bone pain with lytic lesions found on routine skeletal films or other imaging modalities; an elevated total serum protein concentration and/or the presence of a monoclonal protein in the serum or urine; systemic signs or symptoms suggestive of malignancy, such as unexplained anemia, hypercalcemia, which is either symptomatic or discovered incidentally; acute renal failure with a bland urinalysis; or less frequently, the nephrotic syndrome because of concurrent immunoglobulin light chain (AL) amyloidosis (9,10).

Tissue inhibitor of metalloproteinases2 (TIMP2) is a gene and a corresponding protein, it was cloned by Stetler-Stevenson and his colleagues in 1990 (11). These encoded proteins are the inhibitors of the matrix metalloproteinases (MMP) naturally, a class of peptidases responsible for breaking down the extracellular matrix; the encoded protein plays a distinct role among the TIMP family members in that it has the ability to directly decrease the proliferation of endothelial cells in addition to acting as an inhibitor against metalloproteinases; TIMP2 functions as both an MMP inhibitor and an activator, and as a result, the encoded protein may be essential for the maintenance of tissue homeostasis by inhibiting the proliferation of dormant tissues in response to angiogenic factors and by inhibiting protease activity in tissues undergoing extracellular matrix remodeling (12).

Cystatin C (Cys-C) is a low molecular weight (13-kD) basic protein that all nucleated cells consistently generate; cystatin C was originally identified as a"gamma-trace"protein in the cerebral fluid and urine of renal failure patients in 1961; its amino acid sequence was initially described by Grubb and Löfberg, they observed that patients with advanced renal failure had higher levels of it so Grubb and colleagues first proposed it as a glomerular filtration rate indicator in 1985 (13).

Proximal tubule cells reabsorb and catabolize the filtered Cys-C such that little is typically discharged in the urine; the freely present Cys-C is filtered by the glomerulus and is not secreted, so the measurement of Cys-C cannot be utilized as a traditional urinary excretory marker for GFR, despite the fact that plasma Cys-C levels are used to estimate GFR; instead, Cys-C has been viewed as one of numerous novel biomarkers of kidney damage that are currently available (14).

Materials and Methods

Patients Hospital-Based cross-sectional study was conducted over sixteen months from May 2020 until August 2021. A total 58 MM patients were involved in the study who were subjected to physical examination, standard clinical, radiological, and laboratory investigations and diagnosed by hematologists with MM from both (males=31, females=27) genders (based on the Diagnostic criteria of the IMWG. They were distributed to different Departments of hematology as below: -

Baghdad Hospital Medical City, Hematology unit – Marjan Teaching Hospital, Hilla and Special Center of Hematology and Oncology – Karblaa

Blood sampling

Disposable syringes and needles were used for blood collection. Venous blood samples, about 5 ml were collected from patients in plain tubes without any additives. After allowing the blood to clot at room temperature for about 10-15 minutes, blood samples were centrifuged at 2500 xg for 15 min. Sera were separated, in the bank blood center until transport to the Department of Clinical Biochemistry at College of Medicine in deep frozen until the analysis was started. The sera from patients were used for the measurements of the following parameters serum Human Cystatin C(Cys-C).

Urine sampling

It was performed by giving each subject a suitable disposable container and transferred the urine to the plain tube, the urine samples were centrifuged at x3000, and the clear urine was divided into three parts in sterile Eppendorf's with immediate freezing in the deep freeze at - 20 ° C. The general physical, chemical and microscopic examination of urine was performed on another part of urine specimen to check for the final selection or exclusion of a subject in the study.

The assay principle uses enzyme-linked immune sorbent assay (ELISA) based on the Biotin double antibody sandwich technology to assay the Human Insulin-like

growth factor-binding protein 7 (IGFBP7). Statistical analysis was carried out using SPSS version 18. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as means with their 95% confidence interval (CI). Independent sample t-test was used to compare means between two groups. Pearson's correlation coefficient test has been used to correlate between two continuous variables. A p-value of $\leqslant 0.05$ was considered as significant.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee.

Results

The results we found are summarized in the Tables and Figures below. Distribution of patients with multiple myeloma according to socio-demographic characteristics including (age and gender). Mean age of patients was (61.69 ± 11.12) years. The older patient was (80.0) years and younger patient was (34.0) years. More than half of patients were male (N=31, 53.4%). Table 1.

Table (1): Distribution of patients with multiple myeloma according to socio-demographic characteristics (N=58)

Socio-demographic characteristics		
Age (years)	(61.69 ± 11.12)	(34.0-80.0)
Gender		
Male	31	53.4%
Female	27	46.6%
Total	58	100.0%

The distribution of patients with multiple myeloma according to stage of disease including (Stage I, Stage II and Stage III). Stage I represents (N=22, 37.9%) of patients, Stage II represents (N=16, 27.6%) of patients) and Stage III represent (N=20, 34.5%) of patients. (Figure 1)

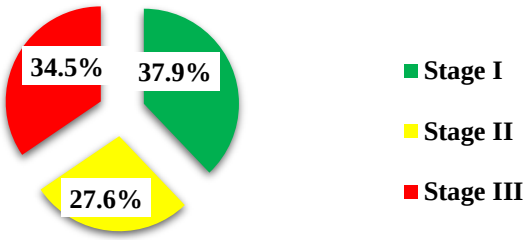

Figure (1): Distribution of patients according to stage of disease (N=58)

In the table 2 and, the association between gender including (male and female) and stages of multiple myeloma including (Stage I, Stage II and Stage III). There was no significant association between gender and stages of multiple myeloma is shown.

Table (2): Association between gender and stages of multiple myeloma

Study variables	Stages of multiple myeloma			Total	P-value
	Stage I	Stage II	Stage III		
Gender					
Male	11 (50.0)	9 (56.3)	11 (55.0)	31 (53.4)	0.916
Female	11 (50.0)	7 (43.7)	9 (45.0)	27 (46.6)	
Total	22 (100.0)	16 (100.0)	20 (100.0)	58 (100.0)	

*P value $\leqslant 0.05$ was significant.

The mean differences of TIMP2 (ng/ml) according to stages of multiple myeloma including (Stage I, Stage II and Stage III). There were

significant differences between means of TIMP2 (ng/ml) according to stages of multiple myeloma are cleared in table and figure 3.

Table (3-A): The mean differences of TIMP2 (ng/ml) according to stages of multiple myeloma (N=58)

Study variable	Study groups	N	Mean ± SD	F	P-value
TIMP2 (ng/ml)	Stage I	22	18.97 ± 9.78	3.586	0.034*
	Stage II	16	25.13 ± 10.08		
	Stage III	20	25.80 ± 7.11		

*P value ⩽ 0.05 was significant.

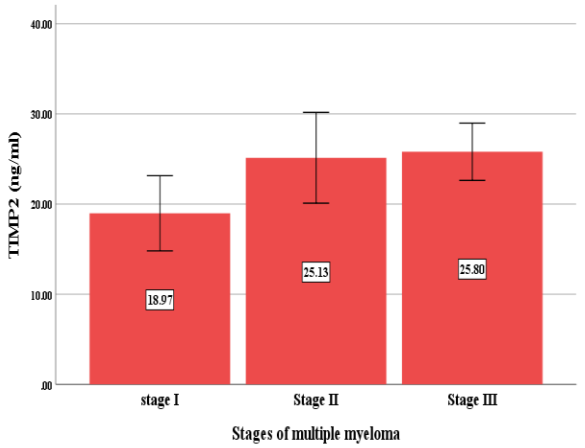

Figure (3): The mean differences of TIMP2 (ng/ml) according to stages of multiple myeloma (P=0.034*)

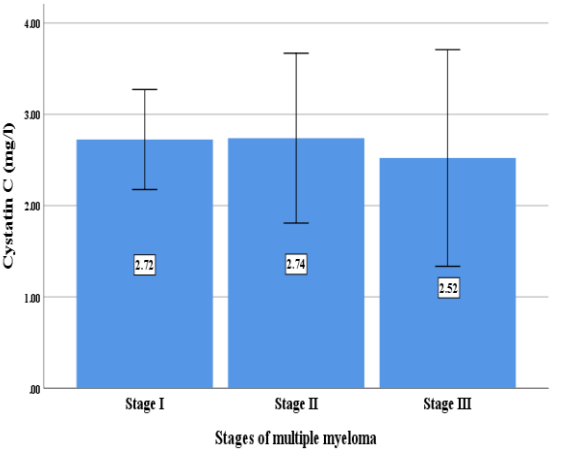

Figure (7): The mean differences of Cystatin C (mg/l) according to stages of multiple myeloma (P=0.931)

Table (3-B): Multiple comparisons (LSD)

Study variable	Study groups		P-value
TIMP2 (ng/ml)	Stage I	Stage II	0.043*
		Stage III	0.018*
	Stage II	Stage III	0.827

In table 4 the mean differences of Cystatin C (mg/l) according to stages of multiple myeloma including (Stage I, Stage II and Stage III). Showed There were no significant differences between means of Cystatin C (mg/l) according to stages of multiple myeloma.

Table (4-A): The mean differences of Cystatin C (mg/l) according to stages of multiple myeloma (N=58)

Study variable	Study groups	N	Mean ± SD	F	P-value
Cystatin C (mg/l)	Stage I	22	2.72 ± 1.29	0.071	0.931
	Stage II	16	2.74 ± 1.86		
	Stage III	20	2.52 ± 2.65		

*P value ⩽ 0.05 was significant.

Table (4-B): Multiple comparisons (LSD)

Study variable	Study groups		P-value
Cystatin C (mg/l)	Stage I	Stage II	0.982
		Stage III	0.745
	Stage II	Stage III	0.748

Discussion

The results obtained were similar to Mathew *et al.* who told, the median age of the patients with MM was 59 years, and their ages ranging from 21- 78 years as well as females make up 24% of them (15). Moreover, the ages of MM cases ranging from 28- 80 years out of 127 patients, and the mean age was at about 58 years; 61.4% of them were males (16). Besides, MM in men is slightly more common than in women (17). The median age about 65 years determined the time of diagnosis of the disease for more patients.

By comparing to females, males among 21 geographic regions among Europe, America and Asia had a higher distribution of rising trend (18). Males may have a heavier load due to a higher prevalence of occupational exposure. (19), smoking and so on (20). Differences in MM stages, kidney function and treatment could not be attributed to the sex-related difference so there were not differences between men and women (21). According to ISS Greipp *et al.,* illustrated that, the distribution of MM in patients was stage I 28%, stage II 33% and stage III 39% (22). While in other study stage I, stage II, and stage III had 35%, 37% and 22% respectively, and missing data at about 5% (23). Besides, Shaikh and his colleagues found 27 patients 33.75% were found to have stage I, 23 patients 28.75% were stage II and 30 patients 37.5% stage III (24).

Research to find renal injury mediators or markers in the unique setting of MM is of high interest, as are novel biomarkers that may help clinicians predict renal injury and the development of chronic kidney disease (25). The strong independent association of TIMP2 levels with neoangiogenesis are prognostic factors in MM (26). The patients with MM presented with higher urinary concentrations IGFBP7 and TIMP2 in significant way (27). Patients with MM who have chronic kidney injury might be investigated for tubular renal impairment using urinary IGFBP7 and TIMP2, which could lead to the early start of treatment that could increase life expectancy and quality of life in those patients (28).

Tissue inhibitor of matrix Metaloproteinase2 (TIMP2) previously demonstrated in MM patients, identified as the primary angiogenesis implicated in MM and other malignancies, and directly connected with disease activity and increased with the disease's development (29).

In patients with MM serum Cys-C maight increased; and according to ISS, stage III had increased amount of Cys-C compared to patients with stage I and II,in other words there was no significant difference between stage I and II patients, in terms of levels of Cys-C serum according to ISS; the analysis revealed that, Cys-C as variables had independent value of prognosis for MM (30).

Patients with newly diagnosis myeloma had lower levels of Cys-C compared to relapsed myeloma patients (31). In contrary Papassotiriou reported that Cyc-C determined a reliable diagnostic biomarker of chronic kidney disease and AKI, and also as a useful biomarker of RI in NDMM patients (32).

Also, serum Cys-C can serve as a useful prognostic marker in MM patients, especially in stage II patients due to they have poor prognoses and are confirmed to benefit from more aggressive therapeutic stratigies; in spite of that, the possibility treatment of myeloma bone disease and nephropathy by regulating the Cys-C expression is still uncertain, and further studies prospectively were needed to clarify the statistical significance of serum Cys-C in MM disease (33).

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