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Predictive Role of IGFBP-7 and Activin A in Newly Diagnosis of Multiple Myeloma

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Abstract

Plasma cells tumor or multiple myeloma (MM) is a hematological malignancy and determined the second most common cancer characterized by extensive renal deficiency, lytic lesions of bone, anemia, hypercalcemia and recurrent infections; despite emerging novel approaches and agents, it still incurable. IGFBP-7 is high expressed in liver, kidney, bone and muscle, and the expression level is higher in renal tubules. Activin A is a dimeric glycoprotein, it controls the transcription of downstream target genes; and noncanonical signaling pathways, including as mitogen-activated protein kinase signaling. Aim of the study: Is found the correlation between predictive biomarkers IGFBP-7 and Activin A in newly diagnosed plasma cells tumor. Materials and methods: Cross-sectional study of patients Hospital-Based was conducted from the period extended from May 2020 until August 2021. A total of 58 newly diagnosis MM patients were involved in this study who were subjected to physical examination, standard clinical, radiological, and laboratory investigations and diagnosed by hematologists with MM from both genders. Urine samples were collected to measure the concentrations of IGFBP7 Activin A By ELISA analysis. Results: The mean age of newly diagnosis of patients was (61.69 ± 11.12) years. 80.0 years was the older age and the youngest patient was (34.0) years. Half of them and more were male with (53.4%). According to staging distribution of disease (Stage I, Stage II and Stage III). Stage I represent (37.9%), Stage II represent (27.6%) of patients) and Stage III represent (34.5%) of patients. The mean differences of IGFBP7 (pg/ml) according to stages of MM. There were significant differences between means of IGFBP7 (pg/ml) according to stages of the disease. While, the mean differences of Activin A (ng/ml) according to staging of the disease, there were significant differences between means of Activin A (ng/ml) according to stages of multiple myeloma.

Keywords
Plasma Cell Tumor, MM, Newly diagnosis, Predictive Biomarkers, IGFBP7, Activin A

Multiple myeloma (MM) is a hematological malignancy and determined the second most common cancer characterized by extensive renal deficiency, lytic lesions of bone, anemia, hypercalcemia and recurrent infections; despite emerging novel approaches and agents, it still incurable (1). Multiple myeloma accounts for 1% of all cancers and is the 2nd most common hematologic malignancy after lymphoma with an estimated 24,280 to 30,330 new cases and 12,650 deaths in 2016 (2,3). About 99% of cases are diagnosed in people over age 40 and the median age of patients at diagnosis is approximately 66−70 years.MM is considered extremely rare in people less than 30 years old with a reported frequency of 0.02% to 0.3% and occurs slightly more frequently in men (4), In general, MM is not considered to be a genetic disease, however familial cases, although rare, are reported (5).

IGFBP-7 is high expressed in liver, kidney, bone and muscle, and the expression level is higher in renal tubules. The molecular weight of IGFBP-7 is 29.1 kda; it was initially named IGFBP7 because of its capability to attach IGFs through the N-terminal domain. IGFBP7 has been cloned from numerous kinds of cellular systems (6). The first two major pathways induce epithelial cells to lose their cell-cell adhesion and acquire the cellular identity of the mesenchymal phenotype. Loss of epithelial markers such as the cell adhesion molecule E-cadherin and the gain of Vimentin and other mesenchymal markers are considered hallmarks in the initiation and execution of EMT. (7).

The three pathways may be activated to produce a variety of outcomes, including the production of proteins, cell growth, survival, and anti-apoptosis; IGFBP7 stands for IGF binding protein 7, IGF-1R stands for IGF-1 receptor, IGF-2R stands for IGF-2 receptor, INSR stands for insulin receptor, IRS stands for insulin receptor substrate, MAPK stands for mitogen-activated protein kinase, and PI3K stands for phosphatidylinositol-4,5-bisphosphate 3-kinase; and EMT stands for epithelial-mesenchymal transition (8).

The transforming growth factor (TGF) superfamily includes activin A, which is a member of these family; Activin A is involved in a range of cell-specific activities, such as growth arrest, cell differentiation, proliferation, apoptosis, metabolism, and immunological response (9).

Activin A is a dimeric glycoprotein made up of two A subunits that binds to the activin type II receptors (ActR-IIA and ActR-IIB), which then triggers the activin receptor-like kinase 4 (ALK4) to phosphorylate the SMAD family members 2 and 3 (Smad 2 and 3), Smad 4 translocate to the cell nucleus after binding to this complex, where it controls the transcription of downstream target genes; and noncanonical signaling pathways, including as mitogen-activated protein kinase signaling, have also been linked to activin A (10).

About 20-40% of newly diagnosed multiple myeloma (NDMM) cases are complicated by renal impairment (RI), which is determined as a typical characteristic of MM (11). Cast nephropathy, monoclonal immunoglobulin deposition disease, and light-chain amyloidosis are the three possible causes of the most prevalent kind of RI, or immunoglobulin-mediated RI (12). Other variables, such as hypercalcemia, dehydration, and the use of nephrotoxic drugs, as well as less often occurring conditions including cryoglobulinemic glomerulonephritis, proliferative glomerulonephritis, and myeloma cell infiltration, may also contribute to RI (13).

Up to 80% of patients with multiple myeloma (MM) have osteolytic disease at the time of diagnosis, and up to 90% of patients have it at some point during the course of the disease. This condition can cause devastating skeletal consequences (14). It has been reported that malignant plasma cells cause stromal cells to secrete activin A, which inhibits osteoblast growth both in vitro and in vivo (15).

Materials and Methods

Patients groups

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 in Baghdad Hospital Medical City, Hematology unit – Marjan Teaching Hospital/Hilla and Special Center of Hematology and Oncology /Karbala.

Collection of urine samples

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

Data Assay

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 protein7 (IGFBP7) and the Human Activin A (ACV-A). The ELISA kits were from Biont (china) by using (Bio Tek /USA) ELISA system.

Data Analysis

Statistical analysis was carried out using SPSS version 27. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). ANOVA test was used to compare means among three groups or more. Pearson Chi-Square test was used to find the association between categorical variables. Pearson correlation coefficient was used to find the relationship between two continuous variables. A p-value of ≤ 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

General characterization:

Distribution of patients with multiple myeloma according to the age and gender. Mean age of patients was (61.69 ± 11.12) years. Older patients were (80.0) years and younger patient was (34.0) years. More than half of patients were male (N=31, 53.4%) showed in the table below.

Table (1): Distribution of patients with multiple myeloma according to the general characteristics (N=58)

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

Distribution of patients with multiple myeloma according to stage of disease including (Stage I, Stage II and Stage III). Stage I represent (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.

Table (2) and Figure (1) showed the mean differences of age (years) according to stages of multiple myeloma including (Stage I, Stage II and Stage III). There were no significant differences between means of age (years) according to stages of multiple myeloma.

Table (2): The mean differences of age (years) according to stages of multiple myeloma (N=58)

Study variable	Study groups	N	Mean ± SD	F	P-value
Age (years)	Stage I	22	61.91 ± 10.26	0.688	0.507
	Stage II	16	59.13 ± 11.94		
	Stage III	20	63.50 ± 11.52		
*P value ≤ 0.05 was significant					

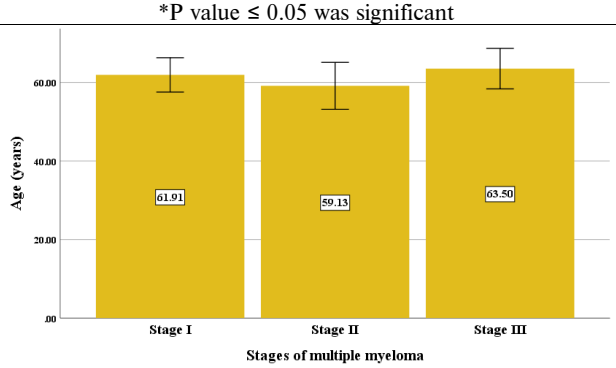

Figure (1): The mean differences of age (years) according to stages of multiple myeloma (P=0.507)

Insulin-like growth factor–binding protein 7 (IGFBP7)

The mean differences of IGFBP7 (pg/ml) according to stages of multiple myeloma including (Stage I, Stage II and Stage III). There were significant differences between means of IGFBP7 (pg/ml) according to stages of multiple myeloma. Listed in the Table(3-4:A&B) and Figure (3-4).

Table (3: A): The mean differences of IGFBP7 (pg/ml) according to stages of multiple myeloma (N=58)

Study variable	Study groups	N	Mean ± SD	F	P-value
IGFBP7 (pg/ml)	Stage I	22	3.30 ± 1.31	5.601	0.006*
	Stage II	16	3.78 ± 1.65		
	Stage III	20	4.70 ± 1.15		
*P value ≤ 0.05 was significant.					

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

Study variable	Study groups		P-value
IGFBP7 (pg/ml)	Stage I	Stage II	0.289
		Stage III	0.002*
	Stage II	Stage III	0.05*

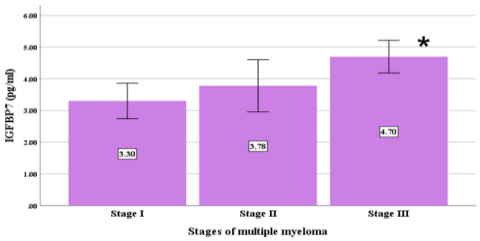

Figure (2): The mean differences of IGFBP7 (pg/ml) according to stages of multiple myeloma (P=0.006*)

Activin A

The mean differences of Activin A (ng/ml) according to stages of multiple myeloma including (Stage I, Stage II and Stage III). There were significant differences between means of Activin A (ng/ml) according to stages of multiple myeloma as shown in the Table (3-6) and Figure (3-6).

Table (4: A): The mean differences of Activin A (ng/ml) according to stages of multiple myeloma (N=58)

Study variable	Study groups	N	Mean ± SD	F	P-value
Activen A (ng/ml)	Stage I	22	3.02 ± 0.90	8.106	0.001*
	Stage II	16	3.95 ± 0.85		
	Stage III	20	3.98 ± 0.85		
*P value ≤ 0.05 was significant.					

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

Study variable	Study groups		P-value
Activin A (ng/ml)	Stage I	Stage II	0.002*
		Stage III	0.001*
	Stage II	Stage III	0.935

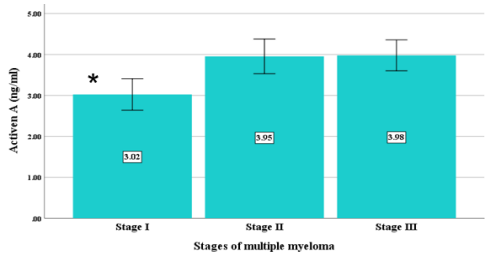

Figure (3): The mean differences of Activen A (ng/ml) according to stages of multiple myeloma (P=0.001*)

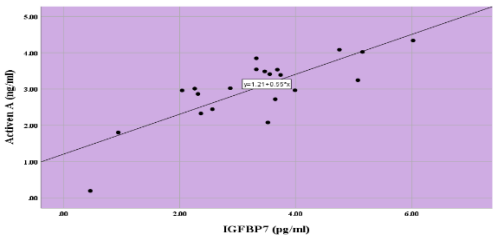

Figure (4): Positive linear Correlation between IGFBP7 (pg/ml) and Activen A (ng/ml) (N=22, r=0.802, P<0.001*)

Discussion

The global incident of MM since 1990, increased 136.10%, and reached to 1,556.88Ч102 cases in 2019; so the overall incidence rate of age-standardized increased from 1.73 in 1900s to 1.92 in 2019 by average of 136.10% annually; multiple myeloma incident cases increased with the age, and those with age over 80 years old had the highest increasing percentage with (229.85%), adults had common cases of MM, especially that older than 75 years old make up the one-third of the patients who diagnosed, also over 30 percent of them were weak (16).

Despite being one of the most fundamental differences between people, it is uncertain how sex affects outcomes in MM; given that men might develop MM more likely compared to women, and according to analysis of all cancers by program of National Cancer Institute's Surveillance Epidemiology and End Results (SEER) which suggested that, possibly worse survival of MM for men than for women (17). On the other hands Derman revealed that, baseline clinical characteristics of MM (age, ISS, status of performance, race, high-risk cytogenetic abnormalities presence and treatment of induction) showed no significant differences there were between males and females (18).

Since the combination of beta-2-microglobulin (β2-MG) and albumin had been recognized with prognostic significance in MM, therefore these two parameters which easily obtainable, were employed subsequently, in the MM staging systems (19). The important prognostic mean used to determine the patient's status and the tumor burden is International Staging System (ISS), and it is not responsible for the natural factors that are crucial in the development of disease and resistance to treatment; the results obtained not related to the previous study, which cleared that, stage I was common in group 40-60 years age, while stage II and stage III were common in age group of 61-80 years, males' gender were predominant in all stages (20). According to ISS there was no differences observed between males and females in patients with MM (21). Study population that done by Mohammed et al., (22) observed that, at younger age women presented in stage I and II more than men, whereas older age of them presented in stage III.

The mean differences of IGFBP7 (pg/ml) according to stages of multiple myeloma including (Stage I, Stage II and Stage III) were included in table (4) and figure (4). And there were significant differences between means of IGFBP7 (pg/ml) according to stages of multiple myeloma.

Woziwodzka et al., (23) told that, to our knowledge, this study is the first one to evaluating the relationship of tubular injury and novel markers with measuring of RI in both healthy and patients with MM at different stages of disease and treatment regimen. Identifying novel markers that reflect developing nephropathology could have high attention, because they could facilitate early diagnosis and might guide choices of treatment; ideally, non-invasive instruments development, specific for distinct lesions of kidney, that in the future could support decisions of treatment and risk stratification (24). Kidney impairment (KI) is common in MM (about one fourth of patients) and poor prognosis can carry, particularly if function of kidney did not recover, serious renal failure is a dangerous condition with a significant risk of early death and is one of the main causes of early mortality, irreversible renal failure is less common but may be present in up to 8% of patients (25).

Similar results were seen, greater IGFBP7 levels are positively connected with malignancies, and soft tissue sarcomas have significantly higher blood levels of IGFBP7 and much higher levels of IGFBP7 in the tissue of subgroups with metastases.; moreover, IGFBP7 may serve as unique tumor marker and encourage anchorage-independent proliferation in malignant cells, furthermore IGFBP7 is positively correlated with adverse clinical characteristics in various types of cancer (26).

The result obtained about the mean differences of Activin A (ng/ml) according to stages of multiple myeloma including (Stage I, Stage II and Stage III). Showed there were significant differences between means of Activin A (ng/ml) according to stages of multiple myeloma as shown in the table (6) and figure (6).

In newly diagnosed MM (NDMM), urinary activin A levels considerably increased, while not in smoldering MM (SMM) and monoclonal gammopathy of undetermined significance (MGUS); in all NDMM patients, the levels of urinary activin A were significantly reduced after initial treatment regardless the regimen of therapy (27). Indeed, these findings support the presence of high circulating activin A in myeloma patients with advanced disease; higher values of activin A in symptomatic would be found in NDMM patients with stage III compared with stage I

and II, also in patients who relapsed after prior responses to therapies compared with symptomatic patients at diagnosis (28).

Given that molecular weight of activin A is (25 kDa), there are at least two potential explanations for the rise in urinary activin A levels in NDMM patients. first one, activin A can theoretically be filtered by glomeruli.; however, similar to other urinary biomarkers, activin A could not be detected in urine of healthy individuals, in the normal kidney glomerulus-filtered activin A might be reabsorbed by the renal tubules by endocytosis; so, the tubular reabsorption dysfunction could lead to the presence of activin A in urine (29). The second explanation is that, tubular damage is associated with serum free light chain (FLC) level, so urinary activin A levels were correlated with serum FLC level, leading to the suggestion that immunoglobulins or light chains may be deposited in the tubular cells, triggering activin A expression; Activin A was detected in tubular cells of the kidneys of MM patients but not in normal (27).

For the first time circulating activin A accelerated in patients with newly diagnosed symptomatic MM and in patients with relapsed disease in contrast, in patients with MGUS and asymptomatic or smoldering myeloma; thus, high levels of circulating activin A correlated with advanced stage of disease at diagnosis (28).

These findings indicate that urinary activin A is a promising biomarker for identifying the presence of tubular damage in patients with MM; to confirm the predictive value of urinary activin A, prospectively observing the renal function of patients with and without elevated urinary activin A level; once its predictive value is confirmed, urinary activin A may assist in decision-making for early intervention prior to RI (27).

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