Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2025.404152.4055 Volume 31, Issue 10 October. 2025
Manuscript ID:ZUMJ-2507-4055
DOI:10.21608/zumj.2025.404152.4055

ORIGINAL ARTICLE

Diagnostic Role of Pituitary Adenylated Cyclase Activating Polypeptide-38 in Multiple Myeloma

Saad El osh[1], Ayman Fathy Arafa[2], Marwa Mohammed Esawy[1], Ahmed Mokhtar[1], Arwa Osama El-Bayaa[1*], Maha Mahmoud Hamed Sakr[1]

[1]Department of Clinical Pathology, Faculty of Human Medicine – Zagazig University, Egypt.
[2] Department of Internal Medicine, Faculty of Medicine, Zagazig University, Egypt

*** Corresponding author:**
Arwa Osama El-Bayaa
Email:
arwaosama3500@gmail.com

Submit Date 20-07-2025
Accept Date 24-08-2025
Modify Date 26-08-2025

ABSTRACT

Background: Multiple myeloma (MM) is a cancerous growth of plasma cells that primarily affects the elderly. It represents 10% of hematological malignancies nowadays. The research reveals that pituitary adenylated cyclase activating polypeptide-38 (PACAP-38) with anti-inflammatory, antioxidant and anti-tumor effects. It influences complex cytokines in bone marrow microenvironment altered by malignant myeloma cells. This study aimed to investigate the variations in PACAP-38 levels in MM cases to explore its clinical significance as a novel biomarker in MM. Methods: A case-control study was conducted, including 38 cases (20 males and 18 females) and 38 controls (22 males and 16 females). The mean age of the cases was 57.16 ± 9.55 years and control was 55±7.33. PACAP-38 levels were measured using the enzyme-linked immunosorbent assay (ELISA) technique. Results: MM patients had a significantly lower PACAP-38 level when compared to the control group at diagnosis (223.97±76.99ng/L and 470.75±149.99, respectively). PACAP-38 levels showed significant positive correlations with hemoglobin, total leukocytes count, platelet count, and albumin. While it showed a negative correlation with creatinine, B2-microglobulin, TP, calcium, LDH, and the percentage of plasma cells. Regarding the international staging system (ISS), 42.1% had ISS I, 42.1% had ISS II, and 15.8% had ISS III. PACAP-38 had a decreasing trend with the progress of the ISS stages. PACAP-38 showed a specificity of 89.47% and a sensitivity of 94.7% for MM prediction. Conclusion: This study indicates that PACAP-38 can be used as a valuable, non-invasive and complementary biomarker in the diagnosis and staging of MM.

Keywords: Diagnostic; Marker; Multiple myeloma; PACAP-38.

INTRODUCTION

Abnormal plasma cells build up in the bone marrow of multiple myeloma (MM), sometimes referred to as plasma cell myeloma, a malignant tumor. This accumulation leads to lytic bone lesions in addition to elevated levels of urinary and serum monoclonal proteins. The interaction between the bone marrow microenvironment and malignant plasma cells facilitates the cells' development, multiplication, metastasis, and resistance to treatment [1].

Multiple myeloma patients must exhibit end organ damage, which includes the following symptoms, in order to be diagnosed: CRAB criteria are characterized by hypercalcemia, renal failure, anemia and lytic bone lesions, examining the percentage of bone marrow plasma cells, the development of, and whether monoclonal proteins are present in the blood or urine [2].

Pituitary adenylated cyclase activating polypeptide (PACAP) is a neuropeptide that has been extensively investigated because of its multifunctional qualities, which have generated

a lot of interest in the biomedical field [3]. PACAP has a structure similar to that of vasoactive intestinal peptide (VIP), contains strong antioxidant and anti-inflammatory properties in a variety of tissues, this neuropeptide is secreted by neurons, immune, endothelial, and endocrine cells. This peptide exists in two physiologically active forms, PACAP-27 and PACAP-38, with PACAP-38 being the predominant form. Our attention is focused on PACAP because of its inhibitory effect on myeloma cells proliferation and renal protective effects for patients with multiple myeloma [4, 5].

PACAP suppresses the development of plasma cells in a manner similar to dexamethasone [6]. The regulation of the production of numerous pro-inflammatory mediators, including IL-6, TNF-α, and MIP-1α, is significantly influenced by PACAP. It also impacts the bone marrow microenvironment's cytokine network [7].

In contrast to the expanding research filed of PACAP in solid tumors and neurologic diseases, the biological and clinical implications of its variations in plasma cell dyscrasias have not been well established. Therefore, we examined PACAP levels in newly diagnosed multiple myeloma (MM) patients to evaluate its potential as a biomarker for diagnosis and staging in MM.

METHODS

A case-control study was conducted between December 2023 and March 2024 at the Hematology Unit, Internal Medicine Department, and the Clinical Pathology Department of Zagazig University Hospitals. The World Medical Association's Helsinki Declaration provided a set of standards for conducting research involving human subjects. This study was approved by the Institutional Review Board of Faculty of Medicine, Zagazig University (IRB# 11124-19-9-2023). All participants signed a written consent for sharing in this study.

Sample size was calculated by assuming that the mean ± SD of PACAP-38 levels in MM patients is (208.4 ± 130 pg/mL) versus (311.7 ± 90 pg/mL) in control group. So, sample size calculated by open EPI was 76 participants (38 MM patients and 38 controls), has an 80% test power and a 95% confidence level.

Patients newly diagnosed with multiple myeloma were enrolled in this study. Matched healthy volunteers also were enrolled. Patients who had received any clinical treatment before sample collection were excluded. Patients with other critical illnesses or cancers, as well as those who declined to take part in the trial, were excluded.

All patients were subjected to the full history taken through an interview, clinical examination, and evaluation for end-organ damage. Patients were categorized into different clinical stages by the International Staging System (ISS) into stage I, stage II, and stage III [8]. Radiological studies were performed, including magnetic resonance imaging (MRI) or plain x-rays to detect osteolytic lesions.

Laboratory investigations, including routine and special investigations, were performed. An automated cell counter, model XN 2000 (Sysmex, Japan), was used to perform a complete blood count (CBC). LDH, calcium, renal function (Blood urea nitrogen (BUN) and creatinine), and liver function (Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), albumin (ALB), total and direct bilirubin.) were evaluated using the Roche/Hitachi Cobas 8000-C702 (Roche, Germany). B2-microglobulin was assessed on Roche/Hitachi Cobas 6000-C502 (Roche, Germany). Protein electrophoresis and immunofixation were assessed by capillary electrophoresis on the Sebia analyzer (Minicap, France). Bone marrow aspirate slides were stained with Leishman stain for morphologic study. Using traditional microscopy, we were able to get a differential cell count of 200. When the bone marrow aspirate smear showed that over 10% of the plasma cells, the morphological examination indicated the presence of a plasma cell neoplasm. Immunophenotyping was done utilizing (FACS CantoII flowcytometer with

Diva software (Becon Dickinson, USA). Cytogenetics examination (karyotyping on peripheral blood and/or FISH on bone marrow aspirate) was utilized to detect deletion of 17p (Cytocell probe, sysmex, Japan).

PACAP-38 was evaluated using the enzyme-linked immunosorbent assay (ELISA) technique. We used Shanghai Sun red Biological Technology Co., Ltd.'s human PACAP-38 ELISA kit (Catalogue number: 201-12-7419), which is made in China. The manufacturer's instructions were followed for performing the ELISA procedures. A Sunrise absorbance reader (Tecan Trading AG, Männedorf, Switzerland) set at 450 nm was used to measure the optical density. Levels of PACAP-38 were displayed in ng/L.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 21.0 (Chicago, IL, USA) was used for data entry and analysis. The Shapiro-Wilk test was used to analyze the distribution of the results. Both tabular data and graphical representations were used to show the results of the current investigation. The standard deviation (SD), range, median, and mean were displayed. When dealing with quantitative independent variables, statistical analysis was conducted using the Mann-Whitney test and the student's t test. Chi-Square was used to analyze the differences between the qualitative data sets. Pearson or Spearman correlation was used to examine the link between the illness features and the indicators under study. The cutoff point selection was aided by the receiver operating characteristic (ROC) curve. When the p value was less than 0.05, the results were deemed significant.

RESULTS

In this study we screened PACAP-38 levels in 38 patients with newly diagnosed Multiple Myeloma and 38 control by ELISA. Their mean age was 57.16 ± 9.55 years for cases and 55±7.326 for controls. About 52.6% of patients were male and 47.4% were female. And 57.9% of the control group was male, and 42.1% were female. Cases had high significant lower hemoglobin level, total leukocytes count, and platelet count than the controls. In bone marrow aspiration, the percentage of plasma cells was 42.89 ± 12.68. In terms of routine laboratory investigations, total protein level was significantly higher in MM cases than controls (p-value=0.001). The level of calcium, creatinine, LDH, and β2 microglobulin were significantly higher in MM cases than controls (p-value =<0.0001, <0.0001, <0.0001, respectively). (Table 1)

Protein electrophoresis was done for MM cases in our study as regards M protein revealed 24 (63.2%) IgG and 14 (36.8%) IgA. They were 30 (78.9%) Kappa and 8 (21.1%) Lambda; however there was not a statistically significant difference between them as regards PACAP-38 level (p= 0.175) (Table 2, Figure1).

In our study 73.7% of myeloma patients had Bence Jones protein in urine, and 42.1 % showed abnormal cytogenetics.

Patients were categorized into different clinical stages by the International Staging System (ISS) into stage I (42.1%), stage II (42.1%), and stage III (15.8%). Also, PACAP-38 level had a significant decreasing trend in progressive MM stages (Table 3), (Figure 2).

This study revealed that there was a significant lower serum levels of PACAP-38 in MM patients in comparison to the controls (223.97 ± 76.99 vs. 470.75 ± 149.99 ng/L) (P=0.0001). (Figure3)

In this study, we observed PACAP-38 is a significant predictor of Multiple Myeloma based on the findings of ROC curve analysis (AUC=0.947, P<0.001) (Figure 4). The distribution of subjects based on PACAP-38 cut off point (<306.89 ng/l). PACAP-38 showed a sensitivity of 94.7%, a specificity of 89.47%, a PPV of 90%, a NPV of 94.4%, and an accuracy of 92.1% for the diagnosis of MM.

There wasn't a significant association between PACAP-38 level and different clinical symptoms. Also, no significant association to Bence Jones protein and abnormal cytogenetics (P=0.7, 0.14 respectively). PACAP-38 levels were significantly positively correlated with albumin, hemoglobin, and TLC levels (r=0.657, 0.0612, 0.559, P=<0.001). However, level of

PACAP-38 was shown to be significantly correlated negatively with total protein (r=-0.564, P=0.001), calcium (r=-0.452, P=0.004), LDH (r=-0.675, p=<0.001), β2-microglobulin (r=-0.680, P=<0.001), and creatinine (r=-0.675, P=<0.001). Furthermore, no statistically significant relationship was found between the levels of PACAP-38 and AST, ALT, and BUN (Table. 4).

In simple regression analysis, our study revealed increased levels of TP, calcium; LDH and B2-microglobulin were significantly associated with high odds of having MM. On the other hand higher levels of PACAP-38 and albumin have significant lower odds of having MM (C.I 95%). (Table 5)

Table 1: Demographic, clinical, and laboratory data of the studied subjects

Parameter	Case group (N.=38)	Controlgroup (N.=38)	Test	P-value
Age (Years)	**57.16±9.558**	**55.00±7.326**	**0.781[a]**	**0.44**
Gender:				
Male	**20 (52.6%)**	**22 (57.9%)**	**0.106 [x2]**	**0.744**
Female	**18 (47.4 %)**	**16 (42.1%)**		
Laboratory tests:				
Hemoglobin (g/dL)	**9.226±1.628**	**12.074±1.253**	**7.258[a]**	**<0.0001***
TLC (x10^{3}cells/µl)	**5.30 [2.1-12]**	**10.0 [5.9-13.2]**	**2.556[b]**	**<0.0001***
Platelets (x10^{3}cells/µl)	**160.0 [50-384]**	**203.0 [159-308]**	**4.235[b]**	**0.0001***
Total bilirubin (mg/dL)	**0.40 [0.2-1.2]**	**0.52 [0.2-1.0]**	**-0.964[b]**	**0.339**
Direct bilirubin (mg/dL)	**0.18 [0.1 - 0.31]**	**0.18 [0.04-0.3]**	**0.453[b]**	**0.665**
TP (g/dL)	**9.51±2.6**	**7.34 ±0.47**	**3.491[a]**	**0.001***
Albumin(g/dL)	**3.11 ±0.63**	**4.25 ±0.45**	**6.357[a]**	**0.0001***
ALT (U/L)	**13.36 ±3.3**	**13.10 ±3.74**	**0.227[a]**	**0.821**
AST (U/L)	**14.5[9.6 -34]**	**15.2 (12.9-23.3)**	**2.088[b]**	**0.067**
BUN (mg/dL)	**55.9 [11.6 -152.9]**	**17.9 (7.4 -27.1)**	**-4.16[b]**	**<0.0001***
Creatinine (mg/dL)	**2.7 [1.2-14.9]**	**0.85 (0.6 -1.1)**	**-5.27[b]**	**<0.0001***
Calcium (mg/dL)	**11.96 ±1.66**	**9.0 ±0.4381**	**-7.51[a]**	**<0.0001***
LDH (U/L)	**343.6 ±67.4**	**111.95±15.62**	**-14.6[a]**	**<0.0001***
β2 Microglobulin (mg/L)	**7.60 [2.9- 16.9]**	**1.20 [0.95-2.3]**	**-5.27[b]**	**<0.0001***
BM plasma cells (%)	**42.89 ± 12.679**	**N/A**	**N/A**	**N/A**
PACAP-38 (ng/L)	**223.97 ± 76.99**	**470.75 ± 149.99**	**6.380[a]**	**0.0001***

Data are presented as No. (%) or median [range] or mean ± SD.

TLC: Total leucocytic count; TP: Total protein; ALT: Alanine transaminase; AST: Aspartate transaminase; BUN: Blood urea nitrogen; LDH: Lactate dehydrogenase. BM: Bone marrow. * Significant

(a): t-test; (b): Mann-Whitney test; (x2): Chi-square test

Table 2: Distribution of the levels of PACAP-38 according to the type of M protein in multiple myeloma patients

parameter	Type of M protein	No	Mean ± SD	t-test	P-value
PACAP-38	**IgG**	**24**	**205.367±68.335**	**1.41**	**0.175**
	IgA	**14**	**255.86±85.70**		

Table 3: The staging of the studied multiple myeloma patients and the Distribution of the levels of PACAP-38 regarding multiple myeloma stages

parameter	Stageof disease	No	Percentage %	Mean ± SD	ANOVA	Comparison of significance	
						P-value	LSD
PACAP-38	Stage I[a]	16	42.1%	282.62±39.37	14.730	<0.0001	a vs b p = 0.007
	Stage II[b]	16	42.1%	208.459±58.34			a vs c p < 0.001
	Stage III[c]	6	15.8%	108.92±37.88			b vs c p = 0.008

Table 4: Correlation of PACAP-38 in relation to laboratory tests

Parameters	PACAP-38	
	R	P
Hemoglobin	0.612 [a]	<0.001*
Total Leucocyte Count	0.559 [b]	<0.001*
BM plasma cells	-0.511[a]	0.025*
Total protein	-0.564[a]	<0.001*
Albumin	0.657[a]	<0.001*
Creatinine	-0.656[b]	<0.001*
Calcium	-0.452[a]	0.004*
LDH	-0.657[a]	<0.001*
β2 Microglobulin	-0.680[b]	<0.001*

(a): Pearson Correlation, (b): Spearman Correlation
LDH: Lactate dehydrogenase. *: Significant

Table 5: Logistic regression analysis for the predictors of multiple myeloma

	B	S.E.	Wald	OR	95% C.I. for OR		P value
					Lower	Upper	
Hb	-2.974	1.128	6.951	0.051	0.006	0.466	0.008*
PLT	-0.008	0.006	1.937	0.992	0.981	1.003	0.164
WBCs	-0.719	0.211	11.661	0.487	0.322	0.736	0.001*
Tbil	-0.046	0.743	0.004	0.955	0.223	4.098	0.951
Dbil	-5.840	4.456	1.717	0.003	0.001	18.069	0.190
TP	1.056	0.483	4.779	2.876	1.115	7.415	0.029*
Alb	-9.491	3.673	6.678	0.120	0.101	0.151	0.010*
ALT	0.022	0.094	0.054	1.022	0.851	1.228	0.816
AST	-0.011	0.048	0.051	0.989	0.900	1.087	0.822
Creatinine	2.070	1.105	3.507	7.926	0.908	69.185	0.061
BUN	0.073	0.043	2.857	1.076	0.988	1.171	0.091
Ca	1.453	0.698	4.328	4.275	1.088	16.800	0.037*
LDH	0.260	0.125	4.376	1.297	1.017	1.656	0.036*
β2-microglobulin	1.032	0.479	4.763	2.786	1.251	4.241	0.0153*
PACAP-38	-0.028	0.010	8.385	0.972	0.954	0.991	0.004*

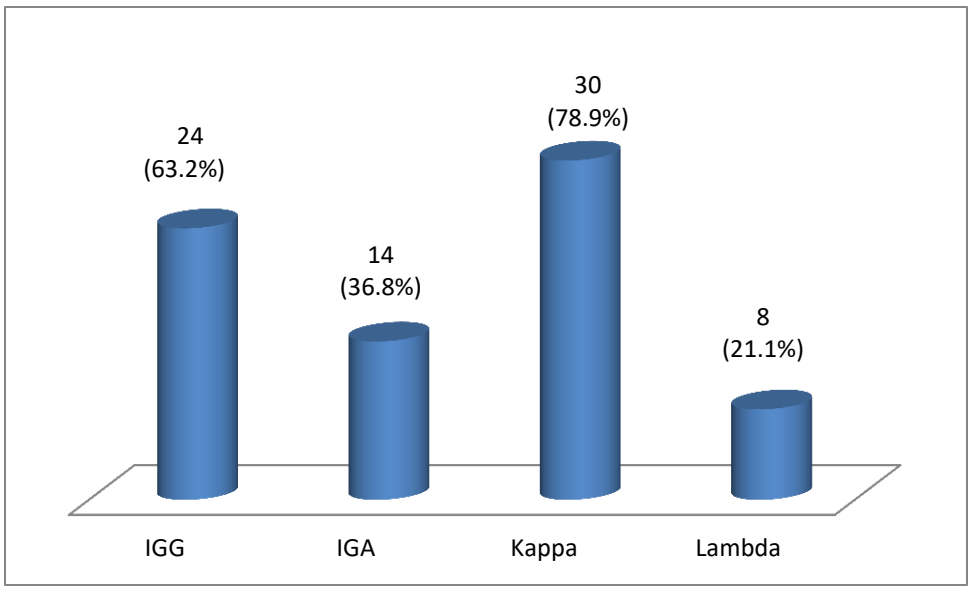

Figure 1: Type of M protein and light chain in multiple myeloma patients.

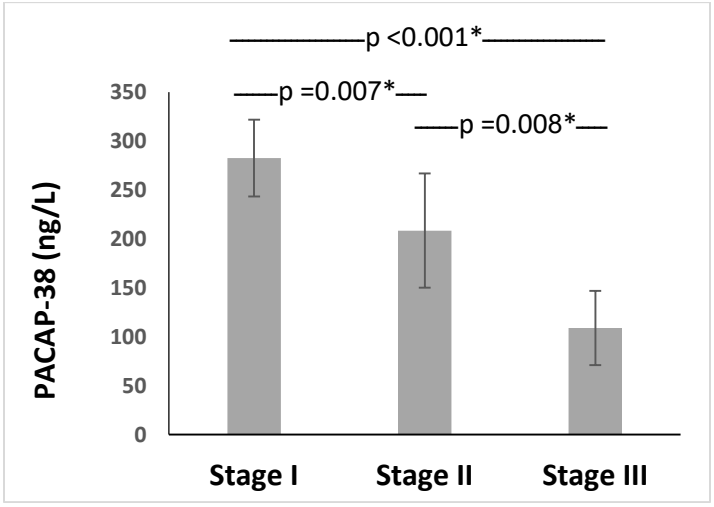

Figure 2: Distribution of the levels of PACAP-38 regarding multiple myeloma stages.

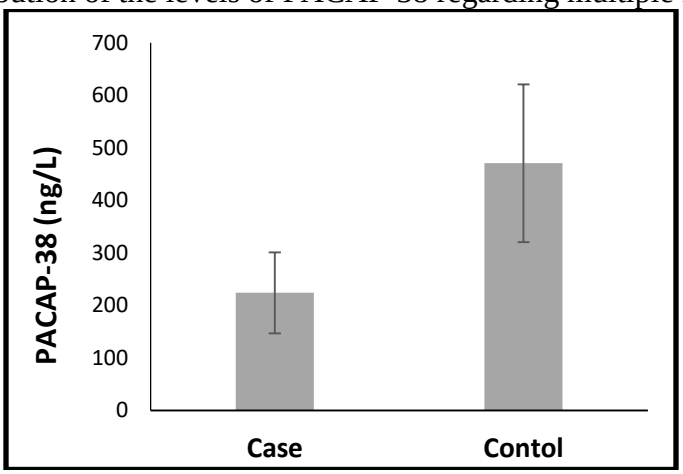

Figure 3: The levels of PACAP-38 in the studied groups.

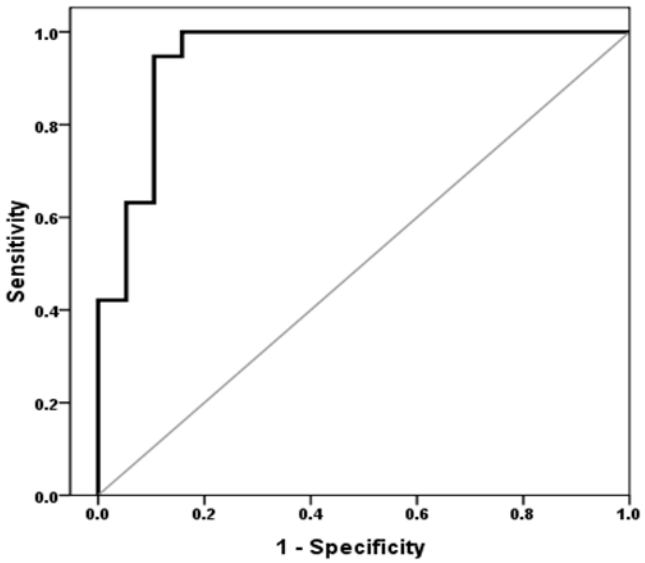

Figure 4: The receiver operating characteristic (ROC) curve of PACAP-38 levels in prediction of multiple myeloma patients against healthy individuals.

DISCUSSION

Multiple myeloma (MM) is a bone marrow tumor that is a malignant neoplasm of B-cells. This illness results in marrow failure and bone lesions. It is typically accompanied by an M protein in the serum and indications of end-organ damage from plasma cell neoplasm. The most prevalent CRAB features of multiple myeloma include renal failure, elevated calcium levels, bone lesions, and anemia [9]. A mix of histological, radiological, and clinical characteristics are used to diagnose MM [10].

PACAP has direct effects on tubule cells (via the PAC1 receptor) and indirect effects (via cytokine-mediated antioxidant function), PACAP-38 has anti-proliferative effects on plasma cells (resulting in a decrease in light chain production), which may help to lessen renal dysfunction associated with MM [11]. The objective of this study was to determine the serum level of PACAP-38 in patients with multiple myeloma and forecast its significance in multiple myeloma diagnosis.

Our investigation of PACAP-38 levels in MM patients provides valuable information about it's potential as a biomarker for diagnosis, disease severity and patients risk stratification.

This study demonstrated that, in terms of demographic information, there was no discernible difference between cases and controls. Pojero et al. [12] discovered that the average age of MM patients was 60 years old, and that the majority of these patients were male, with a male to female ratio of 1.2:1. Similar to our findings, a retrospective cohort study of MM patients with a median age at diagnosis of 67 years and a preponderance of men was reported by Puertas et al. [11].

The most prevalent presenting symptoms were renal, anemia, bone pain, and hypercalcemia. According to Nakaya et al. [13], bone disease was the most frequent presenting factor for multiple myeloma, with anemia, renal failure, and hypercalcemia coming in second and third, respectively.

This study shown that, in comparison to the control group, MM cases had considerably decreased hemoglobin levels, platelets, and TLC. In a similar vein, Mehdi et al. [14] found that the mean hemoglobin, platelet, and TLC values in MM cases decreased significantly. Furthermore, our findings were partially corroborated by Fadilah et al. [15] and Tolba et al. [16], who showed that the only hemoglobin level was significantly lower in MM cases when compared to the control group. Both

myeloma and renal failure can cause anemia, as demonstrated by Nakaya et al. [13]. As a result, anemia can be linked to chronic illness, relative erythropoietin (EPO) shortage brought on by partial renal impairment, and the replacement of BM hematopoietic elements by plasma cells [17].

This study found that whereas total protein, Bence-Jones protein in urine, LDH, serum beta-2-microglobulin, and calcium were higher in the case group, albumin was considerably lower in the case group compared to the control group. This is consistent with the findings of Fadilah et al. [15], who discovered that MM patients had poor prognostic variables like elevated β2-microglobulin and hypoalbuminemia. Our study demonstrated that the levels of calcium and LDH in the patient and control groups differed statistically significantly. In line with Puertas et al.'s findings that patients' serum calcium and B2-microglobulin levels were higher than those of controls [11].

Important indicators of severity during MM include serum albumin, serum LDH, and serum beta2-microglobulin. Furthermore, there is a correlation between high LDH and beta2-microglobulin among these prognostic indicators. Since LDH provides a measure of tumor mass, a rise in LDH over the course of the disease may indicate a relapse, increased tumor mass, or the presence of extra plasmacytomas [18].

Regarding M protein, 63.2% of MM patients in this study had IgG, 36.8% had IgA, 78.9% had kappa, and 21.1% had lambda. These findings are consistent with earlier research by Aita et al. [19], which showed that IgG kappa was more prevalent in MM patients. Nakaya et al. demonstrated that M protein consisted of IgG (69%), and IgA (14%), which is comparable to our findings [13].

According to the International Staging System (ISS), 15.8% of the patients in this study had stage III disease, 42.1% had stage II disease, and 42.1% had stage I cancer. We found that somewhat in line with the findings of Nakaya et al. who found 45% of patients had stage 1, 21% had stage 2, and 34% had stage 3 [13].

Serum PACAP-38 levels in newly diagnosed MM patients were significantly lower than those in the control group, per the results of the current investigation. Tóth et al. found that MM patients had significantly lower endogenous plasma PACAP-38 levels than healthy controls, which is in line with our results [6].

According to reports, PACAP has anticancer properties in MM and affects signaling pathways that are directly linked to MM cell survival and the progression of the disease. Additionally, through the expression of its receptors on MM cells, proximal tubule cells, and bone marrow stromal cells, PACAP has been shown to affect the homeostasis of the bone marrow microenvironment]7]. Similar to Tóth et al. [6], who showed a declining trend between stages, we discovered a substantial drop in PACAP-38 levels in higher ISS stages in this investigation.

The diagnostic utility of PACAP-38 levels in differentiating MM patients from healthy people was also examined in our study. The ROC analysis showed that PACAP-38 had a sensitivity of 94.7% and a specificity of 89.47%, which is an excellent diagnostic performance in MM. This is consistent with the findings of Tóth et al. [6], who said that PACAP-38 had 88% sensitivity and 100% specificity.

The levels of PACAP-38 and various clinical symptoms did not significantly correlate in the current investigation. Tóth et al. [6] discovered no significant correlation between PACAP-38 levels and renal disease associated with MM, whereas lower PACAP38 levels were observed in individuals with hypercalcemia and renal problems. This may result from damage to the renal proximal tubule produced by Myeloma light chain, which PACAP38 successfully prevents by inhibiting the generation of pro-inflammatory cytokines that are triggered by the light chain protein [18].

The percentages of BM plasma cells in the current investigation had a negative correlation with the PACAP-38 level. According to this research, PACAP-38 may be a useful, non-invasive biomarker for diagnosis, prognosis prediction, and therapy response monitoring. The findings of our investigation are in line with those of earlier research [6]. Because PACAP directly prevents the growth of plasma cells and has antitumor effects. Additionally, a number of studies have previously reported that PACAP prevents malignant cells in specific tumors from proliferating and growing [20].

PACAP-38 regulates several signaling pathways via the PAC1 receptor. It alters the bone marrow microenvironment and stops the formation of MM cells that secrete light chains by stopping bone marrow stromal cells from generating pro-inflammatory cytokines like IL-6. This regulation suppresses the p38 MAPK and NF-kB pathways, which are critical to the pathogenesis of MM.

With respect to laboratory data, it was discovered that there was a statistically significant positive link between low levels of PACAP-38 expression and low levels of hemoglobin, total leukocytes count, and albumin. In individuals with multiple myeloma, there was a highly significant negative association between the serum levels of total protein, calcium, LDH, and β2 microglobulin and the PACAP-38 level. A study by Tóth et al. [6] reported a strong negative association between PACAP-38 levels and β2 microglobulin, which is partially in agreement with this. In addition, LDH and PACAP-38 are trending downward. However, there was no discernible correlation between the levels of Hb, PACAP-38, total protein, and serum albumin [6]. Disease burden is correlated with low PACAP levels. Patients with active illness have lower PACAP levels, higher ISS stage, greater tumor markers (LDH, B2M, and BJ protein), and higher bone marrow plasma cell infiltration [21].

MM cells display the short form of the PAC1 receptor, which mediates the activities of PACAP. Among the effects are: Inhibition of proliferation by c-AMP signaling and apoptotic induction (e.g., caspase-9 activation, Bcl-2 regulation), also effects in concert with dexamethasone. MYC, IL-6, TNF-α, and associated pathways (PI3K-mTOR, NF-κB, MAPK) are all altered. These mechanisms help explain PACAP-38 potential as a therapeutic adjunct or predictive biomarker.

Although in Tóth et al. study there was no significant correlation between PACAP and end-organ damage, patients with bone lesions tended to have lower PACAP levels. This may relate to PACAP's inhibitory action on MIP-1α, a critical factor in osteolysis [6].

Limitations:

The Limitations in this study could be the small sample size and the potential treatment-related confounding effects requires validation in larger prospective cohorts.

Conclusion:

In this study, lower PACAP-38 levels in MM patients than control group was detected . This study indicates that PACAP-38 can be used as a valuable, non-invasive and complementary biomarker in the diagnosis and staging of MM.

Recommendations:

Additional investigation is necessary to explore the therapeutic applications of PACAP-38 in MM management.

Conflict of Interest: The authors declare that they have no competing interest.

Financial Disclosures: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Availability of the data: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions: S.E, A.F, M.M.E and A.M contributed to data collection and analysis. M.M.H was responsible for manuscript writing and preparing the article for publication. All authors reviewed and approved the final version

REFERENCE

1- Yan H, Dong M, Liu X, Shen Q, He D, Huang X, et al. Multiple myeloma cell-derived IL-32γ increases the immunosuppressive function of macrophages by

promoting indoleamine 2,3-dioxygenase (IDO) expression. *Cancer Lett.* 2019;446:38–48.
2- Dimopoulos M, Kyle R, Fermand JP, Rajkumar SV, San Miguel J, Chanan-Khan A, et al. Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. *Blood*. 2011;117(18):4701–5.
3- Cardoso JCR, Garcia MG, Power DM. Tracing the origins of the pituitary adenylate-cyclase activating polypeptide (PACAP). *Front Neurosci.* 2020;14:366.
4- Reglodi D, Tamas A, editors. *Pituitary Adenylate Cyclase Activating Polypeptide--PACAP*. Basel: Springer Int Publ; 2016.
5- Reglodi D, Tamas A, Jungling A, Vaczy A, Rivnyak A, Fulop BD, et al. Protective effects of pituitary adenylate cyclase activating polypeptide against neurotoxic agents. *Neurotoxicology*. 2018;66:185–94
6- Tóth T, Alizadeh H, Polgár B, Csalódi R, Reglödi D, Tamás A. Diagnostic and prognostic value of PACAP in multiple myeloma. *Int J Mol Sci.* 2023;24(10):10801.
7- Hou J, Wei R, Qian J, Wang R, Fan Z, Gu C, Yang Y. The impact of bone marrow microenvironment on multiple myeloma (Review). Oncol Rep. 2019 Oct;42(4):1272-82.
8- Cowan AJ, Green DJ, Kwok M, Lee S, Coffey DG, Holmberg LA, et al. Diagnosis and management of multiple myeloma: a review. *JAMA.* 2022;327(5):464–77.
9- Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* 2014;15(12):e538–48.
10- Brawanska-Masluch K, Olchowy C, Mikita G, Wanat M, Swiatko A, Krotlinski M, et al. Diagnostic methods used in detecting myeloma in paleopathological research-A. Heritagr 2025,8,166.
11- Puertas B, González-Calle V, Sobejano-Fuertes E, Jiménez C, Paiva B, García-Sánchez O, et al. Multiple myeloma with t(11;14): impact of novel agents on outcome. *Blood Cancer J.* 2023;13(1):40.
12- Pojero F, Flores-Montero J, Sanoja L, Puig N, Paiva B, Bottcher S, et al. Utility of CD54, CD229, and CD319 for the identification of plasma cells in patients with clonal plasma cell diseases. *Cytometry B Clin Cytom.* 2016;90(1):91–100
13- Nakaya A, Fujita S, Satake A, Nakanishi T, Azuma Y, Tsubokura Y, et al. Impact of CRAB symptoms in survival of patients with symptomatic myeloma in novel agent era. *Hematol Rep.* 2017;9(2):6887.
14- Mehdi WA, Zainulabdeen JA, Mehde AA. Investigation of the antioxidant status in multiple myeloma patients: effects of therapy. *Asian Pac J Cancer Prev.* 2013;14(6):3663–7.
15- Fadilah MS, Sultan HK, Adel El-Gammal MM, Balbaa OA, El-Naggar AA. Prognostic value of B-cell maturation antigen, CD56 expression and neutrophil lymphocyte ratio in patients with multiple myeloma. *Acta Haematol Pol.* 2022;53(6):386–91.
16- Tolba FM, Shabaan HM, Alhanafy AM, Abdelshafy RS, Abdelrahman AN. Study of the role of soluble mannose receptor (sMR/sCD206) in multiple myeloma. *BMFJ*. 2022;39(3):850–7.
17-Liu L, Yu Z, Cheng H, Mao X, Sui W, Deng S& Hao M. Multiple myeloma hinders erythropoiesis and causes anaemia owing to high levels of CCL3 in the bone marrow microenvironment. Scien Rep. 2020; 10(1),20208.
18- Teke HÜ, Başak M, Teke D, Kanbay M. Serum level of lactate dehydrogenase is a useful clinical marker to monitor progressive multiple myeloma diseases: a case report. *Turk J Haematol.* 2014;31(1):84–7.
19- Aita MH, Arantes LC, Aita BC, Silva MR, Oliveira AF, Santos LM, et al. Comparison between immunofixation and electrophoresis for the early detection of relapsed multiple myeloma. *Med Lab.* 2015;51(6):359–68.
20- Georg B, Falktoft B, Fahrenkrug J. PKA, novel PKC isoforms, and ERK is mediating PACAP auto-regulation via PAC1R in human neuroblastoma NB-1 cells. *Neuropeptides.* 2016;60:83–9.
21- de Jong MME, Kellermayer Z, Papazian N, Tahri S, Hofste Op Bruinink D, Hoogenboezem R, et al. The multiple myeloma microenvironment is defined by an inflammatory stromal cell landscape. *Nat Immunol.* 2021;22(6):769–80.

Citation

El osh, S., Arafa, A., Esawy, M., Mokhtar, A., El-Bayaa, A., Sakr, M. Diagnostic Role of Pituitary Adenylated Cyclase Activating Polypeptide-38 in Multiple Myeloma. *Zagazig University Medical Journal*, 2025; (4826-4835): -. doi: 10.21608/zumj.2025.404152.4055