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Immunoglobulin free light chains and interleukin-6 levels in prediction of kidney injury in patients with multiple myeloma

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ABSTRACT

Background: Multiple myeloma (MM) is a disease of B cell population with excessive secretion of immunoglobulins and presence of free light chains (FLCs) that are by products of immunoglobulin synthesis. Free light chains play crucial role in causing renal damage. Interleukine-6 (IL-6) supports the survival and/or expansion of MM cells by stimulating cells as well as by preventing programmed cell death. **Aims and Objectives:** The aim of this study was to evaluate serum and urine free light chains (FLC)measurement and compare with IL-6 levels in patients with different stages of Multiple Myeloma (MM) and control group of subjects and to determine their relevance in acute kidney injury occurrence. **Materials and Methods:** Recruitment of patients with MM (n = 62) made the hematologist that followed clinical Solomon-Durie MM classification. Control group consisted of 20 healthy individuals. **Results:** Patients with MM and renal function injury had significantly higher concentration of urine κ chains compared to control group and group of MM without renal function injury ($p < 0.005$), whereas this difference was not observed when the patients were divided into disease stages groups. Concentration of IL-6 was significantly higher in patients at MM steady stage compared to control group ($p < 0.001$) and significant difference was also detected in patients with MM at relapse stage and control group ($p < 0.0005$). Concentration of IL-6 in MM patients without renal function and with renal function injury was significantly higher compared to control group ($p < 0.001$; $p < 0.0005$ respectively). Statistically significant correlation was determined between sera κ and urine κ chains (rho = 0.437; $p < 0.01$) as well as between urine λ and sera λ chains (rho = 0.505; $p < 0.01$) and between urine κ and urine λ chains (rho = 0.364; $p < 0.01$). **Conclusion:** Results showed that urine κ chains, sera κ chains and IL-6 are constructing a fine tuned net and point to conclusion that FLC and IL-6 are important for an early treatment response detection for patients with potentially reversible renal failure.

Key words: Free light chains; Multiple myeloma; Kidney injury; IL-6

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INTRODUCTION

Multiple myeloma (MM) is a disease of B cell population with excessive secretion of immunoglobulins and is usually present at old age, but may occur in youth. The main characteristics of MM are bone pain, fractures and the presence of immunoglobulin free light chains (FLCs) that are by-products of immunoglobulin synthesis.[1] FLCs can be removed by renal clearance if in small quantities, but not in patients with MM, where clonal proliferation of plasma cells cause thousands times higher quantities of FLCs than normal.[2] These monoclonal FLCs often result in renal pathologies, most importantly cast nephropathy associated with acute kidney injury.[3-6] Free light chains play crucial role in causing renal damage. Since the proximal tubular cells excessive capacity to catabolize light chains, those that are

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not reabsorbed, reach the distal segment of the nephron where they combine with Tamm Horsfall mucoprotein (THP) and precipitate as obstructing casts, which results in leakage of tubular content into interstitium and leads to classic appearance of tubular cast and myeloma kidney.[7]

The plasma cell malignancies and renal disease-associated monoclonal Ig is remarkably broad and encompasses nearly all nephropathologic entities due to highly variable composition of Ig. The diversity of the nephropathologic injury is dictated by the diversity of the abnormal light chains produced by different myeloma clones. The mechanisms underlying the renal disease can be logically separated into those mechanisms resulting from monoclonal Ig and those mechanisms in which other factors predominate, recognizing that, in any particular patient, multiple contributing factors may be observed. The three most common forms of monoclonal Ig-mediated kidney disease are cast nephropathy, monoclonal Ig deposition disease (MIDD), and AL amyloidosis. (The term myeloma kidney refers to cast nephropathy and should not be used to refer to the entire spectrum of renal failure and myeloma).[3]

A complex network of lympho-hematopoietic growth factors and cell surface molecules which establish a fine-tuned communication between stroma cells and lympho-hematopoietic precursors in the bone marrow regulate the proliferation, differentiation and function of lympho-hematopoietic cells. Presence of some of these growth factors which support the survival, proliferation and differentiation of MM cells in the bone marrow (BM) during the different disease stages are the basis of the MM pathogenesis.[8] IL-6 is a cytokine that has pleiotropic effects on hematopoietic cells.[9] It provokes B cells to differentiate into Ig-secreting plasma cells[9-11] and acts as MM growth factor.[11,14] Interleukine-6 (IL-6) supports the survival and/or expansion of MM cells by stimulating cells as well as by preventing programmed cell death.[8]

The aim of this study was to evaluate serum FLC measurement and compare with IL-6 levels in patients with different stages of MM (at presentation, steady stage and relapse stage) and control group of subjects. The study aimed to determine their relevance in acute kidney injury occurrence. The intention was to test their use as possible immunobiological markers in MM. Furthermore, the aim of the study was to determine whether there are correlations between FLCs and IL-6 concentration indicating acute kidney injury in the patients with MM in different stages.

MATERIALS AND METHODS

This study was performed in the Departments of Clinical Immunology, Hematology and Biochemistry at Clinical Center University of Sarajevo. Sixty-two patients with diagnosed MM entered the study as well as 20 healthy individuals, and all were introduced to type of study and signed written content to enter the study. Control group of subjects consisted from 20 apparently healthy volunteers. For all subjects the main inclusion criteria was age >18 years. Patients did not have previous or current malignancy other then MM nor were treated for one, were not drug addicts and did not have any renal function injury caused by other disease.

Recruitment of patients with MM was made by the hematologist that followed clinical Solomon-Durie classification of multiple myeloma, and three groups of patients were formed as: a group at the presentation (n=21), a group withsteadystage (n=21) and a group at relapse stage of the disease (n=20). Steady stage group are patients in post treatment remission. All subjects were age matched. We took blood and urine samples from examined groups of patients and the control group.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

LABORATORY ANALYSIS

Serum and urine samples were stored at -20°C until thawed for this study[14]. Serum κ and λ FLC concentrations were measured by nephelometry on Dade-Behring BN™II Analyzer. All sera were assessed with serum protein electrophoresis (SPE) and FLC immunoassays. Urine of patients was assessed for monoclonal FLCs by immunofixation. ELISA test was performed on Hytec 288 and was used to determine the IL-6 concentrations.

STATISTICAL ANALYSIS

Data were analyzed using SPSS 13.00 for Windows. A p value < 0.05 was considered statistically significant for all comparisons. Receiver operating characteristic (ROC) curve analyses was used to examine the sensitivity and specificity.

RESULTS

In this study, when patients were classified by Solomon-Durie[16] the most frequent were MM IgG kappa CS IIIB

with 17 (27%) patients, follows MM IgG lambda CS IIA and MM IgG kappa CS IA with 13 (21% each); MM IgG kappa CS IIIA with 9 (15%); M IgG kappa CS IIB with 7 (10%) and MM IgG kappa CS IB with 3 (6%).

Then the patients with MM were divided into two groups unrelated to disease stage: group with renal injury (n=35) and group without renal injury (n=27). Group with renal injury included patients with cast nephropathy, and the renal injury was defined by testing sera Cystatin C levels (> 1.53 mg/L) (date not presented). Control group (n=20) had none of individuals with renal injury.

Value of the sera κ chains was significantly higher in a group of MM patients at presentation 7.74 g/L (3.5 g/L - 10.7 g/L) compared to the control group 3g/L (2.23 g/L - 3.4 g/L; p<0.01). Value of the sera κ chains was significantly lower in a group of MM patients at „steady" stage 2.9 g/L (1.23 g/L - 6.16 g/L) compared to the group of MM patients at presentation (p<0.01). There was no statistically significant difference in values of the sera κ chains between relapse group of patients with MM 4.4 g/L (1.32g/L - 6.6 g/L; p=0.53) compared to group MM patients in steady stage 2.9 g/L (1.23 g/L - 6.16 g/L) and at presenting 7.74 g/L (3.5 g/L - 10.7 g/L) (p=0.53 and p=0.095, respectively). Values of urine κ chains at relapse stage of MM were significantly higher compared to control group (p<0.05). Values of urine λ chains at relapse stage, at steady stage and at group of MM patients at presenting were significantly higher compared to control group (p< 0.0005). Values of IL-6 concentration in different stages of MM were significantly higher compared to control. Comparing the IL-6 values at MM relapse stage 5.85 pg/mol (5.25 – 8-25 pg/mol) with control group values 4.95 pg/mol (4.8 – 5.2 pg/mol) (p<0.0005), IL-6 values at steady stage 5.6 pg/mol (5.1 – 6.5 pg/mol) with control group values 4.95 pg/mol (4.8 – 5.2 pg/mol) (p<0.001) and values of IL-6 at presenting group 5.7 pg/mol (4.8 – 7.3 pg/mol) and control group values (p<0.01) (Table 1).

Median sera κ chains value of MM patients with renal injury 6.3 g/L (2.57 g/L - 10.35 g/L) was significantly higher (p<0.05) than those of MM patients without renal injury 3.5 g/L (1.36 g/L - 6.64 g/L). Median sera κ chains value of MM patients with renal injury 6.3 g/L (2.57 g/L - 10.35 g/L) was significantly higher (p<0.01) than that in healthy subjects 3.0 g/L (2.23 g/L - 3.4 g/L). No significant difference (p=NS) in sera κ chains value was observed between MM patients without renal injury and healthy controls.

Concentration of urine κ chains in MM patients that had renal function injury 0.12 g/L (0.024 g/L -0.665 g/L) was statistically much higher (p<0.0005) compared to the concentration of urine κ chains in patients with MM without renal function injury 0.0063 g/L (0.0 g/L -0.015 g/L). Concentration of urine κ chains in MM patients that had renal function injury 0.12 g/L (0.024 g/L -0.665 g/L) was statistically much higher (p<0.0005) compared to the patients in control group 0.01 g/L (in trace). There was no statistical difference (p=NS) between urine κ chain concentrations in MM patients without renal function injury and control group (Table 2).

Urine λ chains were present in the control group in trace, the difference in concentration between disease stages groups and renal function injury occurrence showed no statistical significance, but statistical difference is high between all tested groups compared to control group (p<0.0005).

Concentration of IL-6 in control group was 4.95 pg/ml (4.8 pg/ml - 5.2 pg/ml), compared with concentration of IL-6 at MM patients without renal function injury that was 5.5 pg/ml (5.05 pg/ml - 6.25 pg/ml) significant difference has been detected (p< 0.001). IL-6 concentration in MM patients that had renal function injury was 6.0 pg/ml (5.3 pg/ml - 12.8 pg/ml) and compared with control group 4.95 pg/ml (4.8 pg/ml - 5.2 pg/ml) showed significant difference (p<0.0005), and compared with

Table 1: Comparation of of serum κ chains, serum λ chains, urine κ chains, urine λ chains and IL-6 concentrations between MM patients at different disease stages groups and control group

Variable	Relaps stage group (n=20)	Group at steady stage (n=21)	Group at presenting (n=21)	Control group (n=20)
sK chains (g/L)	4.4 (1.32–6.6)	2.9 (1.23–6.16)	7.74 (3.5–10.7)•+	3.0 (2.23–3.4)
sL chains (g/L)	1.65 (0.95–4.0)	1.66 (0.81–2.56)	1.41 (0.62–3.1)	2.19 (1.56–2.60)
uK chains (g/L)	0.04 (0.007–0.417)•	0.01 (0.0–0.04)	0.04 (0.0–0.19)	0.01 (0.01–0.01)
uL chains (g/L)	0.005 (0.0–0.014)*	0.004 (0.0–0.02)*	0.004 (0.003–0.05)*	0.0
IL-6 (pg/mol)	5.85 (5.25-8.25)*	5.6 (5.1–6.5)#	5.7 (4.8–7.3)•	4.95 (4.8–5.2)

Legend: sK chains – sera kappa; sL – sera lambda; uK – urine kappa; uL – urine lambda
*p< 0.0005 compared to control group
#p<0.001 compared to control group
•p<0.01compared to control group
+p<0.01compared to steady stage
•p<0.05 compared to control group

Table 2: Comparation of serum κ chains, serum λ chains, urine κ chains, urine λ chains and IL-6 concentrations between MM patients with renal function injury, MM patients without renal function injury and control group

Variable	MM with renal function injury (n=27)	MM without renal function injury (n=35)	Control group (n=20)
sK chains (g/L)	6.3 (2.57–10.35)	3.5 (1.36–6.64)$^{\cdot}$	3.0 (2.23–3.4)$^{\blacklozenge}$
sL chains (g/L)	1.41 (0.83-2.4)	1.9 (0.85–3.6)	2.19 (1.56–2.60)
uK chains (g/L)	0.12 (0.024–0.665)	0.0063 (0.0–0.015)*	0.01 (0.01–0.01)*
uL chains (g/L)	0.0059 (0.0035–0.014)	0.00350 (0.0–0.034)	0.0* $^{+}$
IL-6 (pg/mol)	6.0 (5.3-12.8)	5.5 (5.05-6.25)$^{\blacklozenge}$	4.95 (4.8–5.2)*$^{\#}$

Legend: sK chains – sera kappa; sL – sera lambda; uK – urine kappa; uL – urine lambda
*p< 0.0005 compared with MM with renal function injury
$^{\#}$p<0.001 compared to MM without renal function injury
$^{\blacklozenge}$ p<0.01compared to MM with renal function injury
$^{\cdot}$p< 0.05 compared to MM with renal function injury
$^{+}$p<0.0005 compared to MM without renal function injury

Table 3: Correlations between variables

Variables	IL-6 (pg/ml)	sera κ chains (g/L)	sera λ chains (g/L)	urinκ chains (g/L)	urine λ chains (g/L)
IL-6 (pg/ml)					
rho	NS	NS	NS	NS	NS
p<					
sera κ chains (g/L)					
rho	NS	NS	–0.384	0.437	–0.290
p<			0.01	0.01	0.05
sera λ chains (g/L)					
rho	NS	–0.384	NS	NS	0.505
p<		0.01			0.01
urinκ chains (g/L)					
rho	NS	0.437	NS	NS	0.364
p<		0.01			0.01
urine λ chains (g/L)					
rho	NS	–0.290	0.505	0.364	NS
p<		0.05	0.01	0.01	

Legend: sK chains – sera kappa; sL – sera lambda; uK – urine kappa; uL – urine lambda IL-6-interleukin 6; rho-Spearman correlation coefficient; p-probability; NS-not significant

group of patients with MM without renal function injury 5.5 pg/ml (5.05 pg/ml - 6.25 pg/ml) there was also statistically significant difference (p<0.01).

Statistically significant correlation was determined between sera κ and urine κ chains (rho=0.437; p<0.01) as well as between urine λ and sera λ chains (rho=0.505; p<0.01) and between urine κ and urine λ chains (rho=0.364; p<0.01); while the negative statistically significant correlation was present between sera κ and sera λ chains (rho= -0.384; p<0.01) and sera κ and urine λ chains (rho= -0.290; p<0.05) Table 3.

The other correlations among tested variables in patients with multiple myeloma had no statistical significance. Table 3

Test performance of immunoglobulin free light chains and interleukin-6

The test performance (given by the sensitivity/specificity/positive predictive value/negative predictive value/overall accuracy) of urine κ chains, IL-6, sera κ chains, urine λ chains and sera λ chains concentration are shown in Table 4. In summary, the best test performance for discriminating MM patients with renal functional injury from MM patients without renal functional injury was measurement of urine κ chains (74/80/74/80/77) followed by IL-6 (40/97/91/68/72) and sera κ chains (62/60/54/67/61) (Table 4).

The ROC curve for each individual marker in the MM patients with renal functional injury *vs* MM patients without renal functional injury was shown in Figure 1. For differentiation between MM patients with renal functional injury and MM patients without renal functional injuryurine κ chains was the most accurate (AUC 0.780; p<0.0005). IL-6 and sera κ chains had a poor diagnostic accuracy (AUC 0.676; p=0.02 and AUC 0.649; p=0.04), while urine λ chains and sera λ chains showed no statistical significant accuracy (AUC 0.600; p=0.2 and AUC 0.446; p=0.47).

DISCUSSION

The sensitivity of the assay was not unexpected as previous studies have reported greater sensitivity for serum

Table 4: Optimal cut-off, area under the curve with 95% confidence interval (AUC, 95% CI), sensitivity, specificity, positive and negative predictive value, overall accuracy of all studied markers in differencing between MM patients with and without renal injury

Variables	Optimal cut-off	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Predictive value (%)		Overall accuracy (%)
					Positive	Negative	
Urine κ chains (g/L)	≥0.028	0.780 (0.66-0.89)	74	80	74	80	77
IL-6 (pg/ml)	≥7.9	0.676 (0.53-0.82)	40	97	91	68	72
Sera κ chains (g/L)	≥4.66	0.649 (0.51-0.79)	62	60	54	67	61
Urine λ chains (g/L)	-	0.600 (0.46-0.74)	-	-	-	-	-
Sera λ chain s (g/L)	-	0.446 (0.31-0.59)	-	-	-	-	-

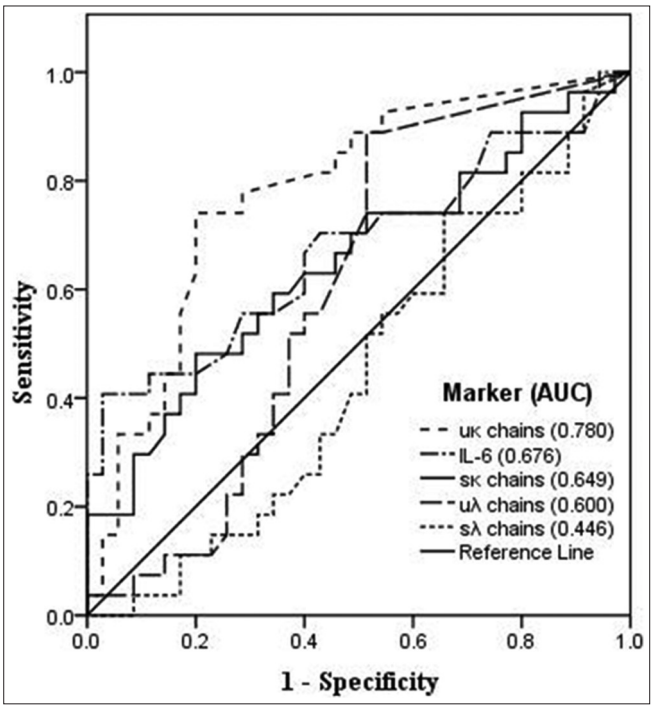

Figure 1: Receiver operating characteristic (ROC) curve of urine κ chains, IL-6, sera κ chains,urine λ chains and sera λ chainslevel for differentiation between MM patient with renal functional injury and MM patients without renal functional injury

versus urine detection of monoclonal FLC in MM.[14] The collection of urine samples, particularly 24 hour collection is frequently problematic[15] but that was not a case in this study. So, we were able to provide correct results from the urine samples of our patients. Patients with MM and renal function injury had significant difference in concentration of urine κ chains related to control group and group of MM without renal function injury ($p<0.005$), whereas this difference was not observed when the patients were divided into disease stages groups (control group, group at presentation, group atsteadystage and relapse group). Hutchinson et al.[14] proposed extension of the reference range for FLC ratio due to reduction of glomerular filtration and renal clearance of all FLCs decreases in patients with renal failure, that results in longer serum half-life's. Animal models showed that irreversible damage has occurred to the nephron within one month of obstruction, by the cast.[16]Myelomas that produce only light chains account for 40%–60% of severe myeloma-associated kidney injury, reflecting the nephrotoxicity of filtered light chain.[4]Kyrtsonin et al.[17] demonstrated that the role of serum FLCs in management of patients with multiple myeloma and renal failure may extend beyond that of a diagnostic tool and management guide to that of an independent indicator of prognosis in the general myeloma population. In a study of Tsakiris et al,[19] other markers that have been implicated in prognosis of MM patients, besides the severity and histology of disease, were age and degree of renal failure at presentation.[19,20] Contrary to that finding was the report of Sharland et al.[21] who did not find any correlation between age, clinical stage, labelling index, and difference in outcome between patients with and without renal failure. In this study the results confirm no correlation between the age, gender or clinical stage (data not shown).

It is in accordance with results recently suggested by Pratt G[22] that FLC measurements are quantitative, correlating with disease activity and an advance in monitoring multiple myeloma light chain only. FLC reflect the disease course producing intact monoclonal immunoglobulin proteins.[4] The most common cause of severe renal failure in MM patients is tubulointerstitial pathology caused by monoclonal immunoglobulin free light chains, which can result in isolated proximal tubule cell cytotoxicity and cast nephropathy (myeloma kidney).[9]

Distribution of IL-6 values between patients with different stages presented the statistical significant difference when control group was compared to MM stages groups ($p=0.001$). Cohen S et al.[23] in their study focused on haemodialysis patients survival and cytokine patterns, where the focus was on the role of increased inflammation in promoting progression of underlying comorbid illnesses that lead to increased mortality among these patients. The presumption that increased levels of pro-inflammatory cytokines are counterbalanced by high levels of anti-inflammatory cytokines of a regulatory immune system was not confirmed when cytokine levels analysed in haemodialysis patients.[24] Contraversy of IL-6 origine, still exists. Some investigators have found IL-6 to be produced

in autocrine manner, by the tumor itself,[8] but stronger evidence supports the notion of a paracrine IL-6 secretion by the tumor microenvironment in the bone marrow.[25]

High serum levels of IL-6 were shown to predict poor prognosis or to reflect an active disease in MM by many studies.[24]The BM of MM patients displayed increased numbers of T cells,[25] and CD40 stimulation induced MM cell migration, which is associated with MM disease progression.[26] CD40 stimulation also triggeres secretion of IL-6 by MM cells, which may mediate an autocrine and/or paracrine mechanism of MM cell proliferation.[27] In addition to CD40L mediated stimulation, MM-specific Th cells could also support autologous MM cells by secreting cytokines.[28]Very recently, has been demonstrated that polyclonally activated allogeneic as well as autologous Th cells stimulated blastogenesis and proliferation of MM cells in a CD40L-dependent manner.[29] Together with the previous reports by others, this suggested that CD40L stimulations presents a key mechanism in Th cell-mediated MM cell support, but cytokines like IL-6 and IL-17 are important components as well.

However, decreases of serum IL-6 receptor levels and IL-6 levels as parameters have been reported to accompany the treatment response in MM.[30] That was not the case in our study, since the IL-6 concentration levels remained insignificantly changed among the patients with MM, but were significantly higher within these groups compared to control group.

Then the correlations between particular variables were tested. Statistically significant positive correlations were determined between sera κ chains and urine κ chains; between sera λ chains and urine λ chains as well as between urine κ chains and urine λ chains (0.01, 0.01 and 0.01 respectively) while negative statistically significant correlation was between sera κ chains and sera λ chains; and sera κ chains and urine λ chains (0.01 and 0.05, respectively).

Receiver operating characteristic (ROC) curves of urine κ chains, IL-6, sera κ chains, urine λ chains and sera λ chains level for differentiation between MM patient with renal functional injury and MM patients without renal functional injury were constructed. The ROC curve has shown that urine κ chains was the most accurate marker, IL-6 and sera κ chains had a modest diagnostic accuracy while urine λ chains and sera λ chains had a poor diagnostic accuracy in distinguishing MM patients with renal functional injury *vs* MM patients without renal functional injury.

So, through different statistic testing, sera κ chains showed as the most valuable marker in predicting occurrence of renal function injury. Results showed that variables as urine κ chains, sera κ chains and IL-6 construct a fine tuned net and are distinguished as good markers for assessment of renal function in MM patients. Correlations between sera κ chains, sera λ chains and urine λ chains can be used for MM assessment. Serum free light chains give an earlier assessment of tumor response to treatment due to their half-life and excretion manner than intact immunoglobulin do. Clinical relevance is an earlier detection of treatment response for patients with potentially reversible renal failure.

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IAM and MRT-Concept and design of the study, reviewed the literature, manuscript preparation and critical revision of the manuscript; **NB, AZ and JH-** Concept, collected data and review of literature and helped in preparing first draft of manuscript; **NA, AZ and OL-** Conceptualized study, literature search, statistically analyzed and interpreted, prepared first draft of manuscript and critical revision of the manuscript; **IAM-** Concept of study, collected data and review of study.

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