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The influence of kidney function parameters in different phases of multiple myeloma

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Abstract

Background: Patients with multiple myeloma are characterized by increased production of light chains of immunoglobulins and thus increase in the concentration of proximal nephron tubule lumen that leads to renal injury.

Methods: This cross-sectional study involved 62 patients with MM. They were characterized in three different stage groups of the disease using Salmon-Durie classification and by International Staging System (ISS). Blood samples were drawn to measure concentration of Cystatin C, Immunoglobulins, Free light chains (FLC), C-reactive protein (CRP), polyclonal chains, while urine is collected to measure creatinine level. ELISA and nephelometry were employed to determine those concentrations. Statistical analyzes were performed by SPSS 16. System.

Results: In patients without renal injury and with renal injury differ among the phases. Significant difference was observed between the mean values of CRP, creatinine, serum kappa chains and the ratio of serum kappa and λ chains ($p < 0.05$) while in the „steady" phase, difference was observed between the mean values of Cystatin C levels and creatinine.

In ISS stage 1, the mean serum Cystatin C level in patients without renal injury and with renal impairment statistically differ as well as serum creatinine, CRP and serum κ chains levels in ISS stage 2. In ISS stage 3, no statistically significant difference was observed between the mean values of the examined parameters and renal injury.

Conclusion: This confirms that beside serum Cystatin C, serum creatinine level, serum CRP level and serum κ chains' level were early signs of kidney impairment as well.

Keywords: Multiple myeloma; Kidney injury; Cystatin C; Free light chains; CRP; Creatinine

1. Introduction

Renal injury occurs as one of the most common causes of morbidity and mortality in patients with Multiple Myeloma MM [1,2].

Our study examined the significance of the elevated values of the creatinine clearance, serum creatinine, Cystatin C, CRP, serum κ light chains, serum λ light chains, the ratio between serum κ and λ light chains and serum polyclonal light chains on the renal function injury in patients with Multiple Myeloma in different phases of illness according to two different disease phases classification: Salmon-Durie and International Staging System of Multiple Myeloma.

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2. Material and methods

2.1. Subjects

62 patients with multiple myeloma (MM) entered the study. Patients with multiple myeloma were divided into 3 groups based on the stage of the disease; 21 patients with MM at presentation, 21 patients with MM in "steady" phase of disease and 20 patients with MM in relapse.

2.2. Methods

Peripheral blood, i.e. serum collected from patients by venipuncture process, was used as a starting sample. Creatinine and CRP concentrations were determined using ARCHITEKTc Systems, Abbott Diagnostics. The method is based on the fact that a strong base like NaOH reacts with creatinine to form a red chromophore. The degree of increase in absorption at 510 nm as a consequence of the formation of this chromophore is directly proportional to the concentration of creatinine in the sample and was measured at a wavelength of 510 nm.

Based on the collected 24 h of urine and a certain concentration of creatinine within the urine, glomerular filtration of the kidneys and creatinine clearance were calculated with specific formulas.

ELISA test is an enzyme-linked immunosorbent assay that determines the presence and amount of antigen or antibody in the presence of enzymes as an indicator, and because it can detect very low concentrations of the target, substance is considered one of the most commonly used and powerful laboratory techniques. Immunological tests use a specific antibody or immunoglobulin to detect antigen. Monoclonal antibodies react with one specific, and polyclonal with several different epitopes on the antigen molecule. This test served to determine the concentration of Cystatin C as one of the important parameters used in the assessment of renal function.

Nephelometry is a modification of photo-optical end-point detection in which 90-degree or forward-angle light scatter, rather than optical density, is measured. A light-emitting diode produces incident light at approximately 600 nm, and a photodetector detects variations in light scatter at 90 degrees (side scatter) and 180 degrees (forward-angle scatter) used for measuring intact immunoglobulins, immunoglobulin light chains, immunoglobulin heavy–light chain pairs, and many other proteins in body fluids. Nephelometry is a modification of the basic precipitin reaction that relies upon light scattering by soluble immune complexes in solution.

Statistical analysis of data were done using computer SPSS - Statistical package for social sciences - programs, version 13.0. Statistical analysis Mean, standard deviation, frequency and percentage were used to describe the data. Distribution of the studied variables was evaluated by Kolmogorov-Smirnov test and Chi-square test was used to compare the qualitative variables between the groups and t-test Independent test and Fisher exact test were used for quantitative variables. For variables that did not follow the normal distribution we applied Mann-Whitney's test .To examine significance of differences in variables between more than two groups of patients, we used the ANOVA test, after that we used the post-hoc test (Tuckey test) to test the variables between two specific groups of patients. To examine the variables between groups of subjects at different stages of the disease that did not follow the normal distribution, we used the Kruskal-Wallis test, followed by the Mann-Whitney test to test the variables between the two groups of patients. The evaluation of categorical variables was performed by Chi square test, i.e. Fisher's test. $P < 0.05$ was considered statistically significant.

3. Results

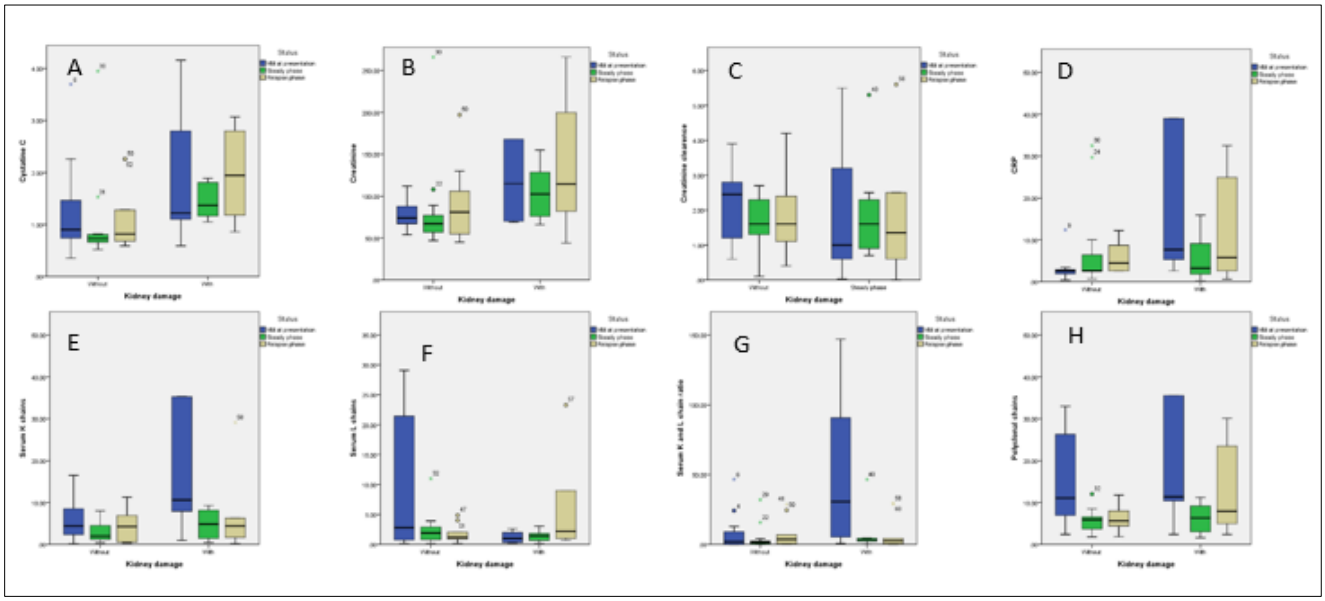
When we applied Salmon-Durie Multiple Myeloma classification and renal injury, the relations and significance between parameters were analyzed by Kolmogorov-Smirnov test which showed that the parameters as age and creatinine clearance follow the rules of normal distribution, and the parameters creatinine, Cystatin C, CRP, serum kappa chains, serum λ chains, the ratio of serum kappa and λ chains as well as polyclonal chains do not follow the rules of normal distribution.

Age and creatinine clearance that had normal distribution were further analyzed using Student's t-test. The mean age of patients without renal impairment was 61.94 years, and with renal impairment 62.81 years ($p = 0.781$; not presented). The average age of patients by disease stages also did not reach statistical significance.

The mean value of creatinine clearance in patients without renal impairment was 2.12 mmol/d and with renal impairment 1.90 mmol/d (p =0.637). The average value of creatinine clearance by disease stages also did not reach statistical significance.

For parameters that do not follow the rules of normal distribution, further analyze was done by Mann-Whitney test (Figure 1)

The mean level of serum λ chains in patients without renal injury was 18.49 g/l, and in patients with renal injury 2.80 g/l (p = 0.469). The mean value of Cystatin C levels in patients without renal injury was 1.11 mg/l, and with renal injury 2.11 mg/l (p<0.001). The mean value of creatinine levels in patients without renal injury was 83.42 mmol/dl, and with renal injury 167.14 mmol/dl (p=0.001). The mean CRP level in patients without renal injury was 6.96 mg/l and with renal injury 22.80 mg/l (p=0.052). The mean value of serum kappa chain levels in patients without renal injury was 4.45 g/l, and with renal injury 30.36 g/l (p <0.05). The mean value of polyclonal chain levels in patients without renal injury was 22.95 g/l, and with renal injury 33.16 g/l (p = 0.212).



A – creatinine and renal injury I (77.75 mmol/dl – 239.44 mmol/dl; p<0.05); II (83.61 mmol/dl – 104.37 mmol/dl; p<0.05); III (90.00 mmol/dl – 152.30 mmol/dl; p=0.165); **B** – creatinine clearance and renal injury I (2.18 ml/s – 1.99 ml/s; p=0.788); II (1.68 ml/s – 1.95 ml/s; p=0.596); III (1.85 ml/s – 2.37 ml/s; p=0.616); **C** – Cystatin C and renal injury I (1.25 mg/l – 2.10 mg/l; p=0.19); II (1.00 mg/l – 1.79 mg/l; p=0.003); III (1.10 mg/l – 2.36 mg/l; p<0.05); **D** – CRP and renal injury I (3.08 mg/l– 35.18 mg/l; p=0.003); II (5.56 mg/l – 7.63 mg/l; p=0.860); III (10.75 mg/l – 25.45 mg/l; p=0.684); **E** – serum κ chains and renal injury I (5.83 g/l – 51.58 g/l; p=0.05); II (3.04 g/l – 4.84 g/l; p=0.301); III (4.64 g/l – 31.67 g/l; p=0.853); **F** – serum λ chains and renal injury I (1.22 g/l – 49.73 g/l; p=0.148); II (1.39 g/l – 2.50 g/l; p=0.414) III (1.79 g/l – 5.35 g/l; p=0.218); **G** – serum κ/λ ratio and renal injury I (8.22 – 52.17; p<0.05); II (4.85 – 8.38; p=0.121); III (7.49 – 7.57; p=0.912); **H** – polyclonal chains and renal injury I (52.08 – 55.56; p=0.702); II (5.54 – 6.23; p=0.750); III (6.44 – 37.02; p=0.143).

Figure 1 Analyzed parameters through Salmon-Durie classification of Multiple Myeloma disease phases

In the initial phase, in patients without renal injury and with renal injury, a statistically significant difference was observed between the mean values of CRP (3.08 mg/l and 35.18 mg/l; p=0.003), creatinine (77.75 mmol/dl and 239.44 mmol/dl; p <0.05), serum kappa chains (5.83 g/l and 51.58 g/l; p <0.05) and the ratio of serum kappa and λ chains (8.22 g/land 52.17 g/l; p <0.05).

In a „steady“phase, in patients without renal injury and with renal injury, a statistically significant difference was observed between the mean values of Cystatin C levels (1.00 mg/l and 1.79 mg/l; p = 0.003) and creatinine (83.61 mmol/dl and 104.37 mmol/dl; p <0.05).

In relapse phase, no statistically significant difference was observed between the mean values of the examined parameters and renal injury except for Cystatin C (1.10 mg/l and 2.36 mg/l; p<0.05)

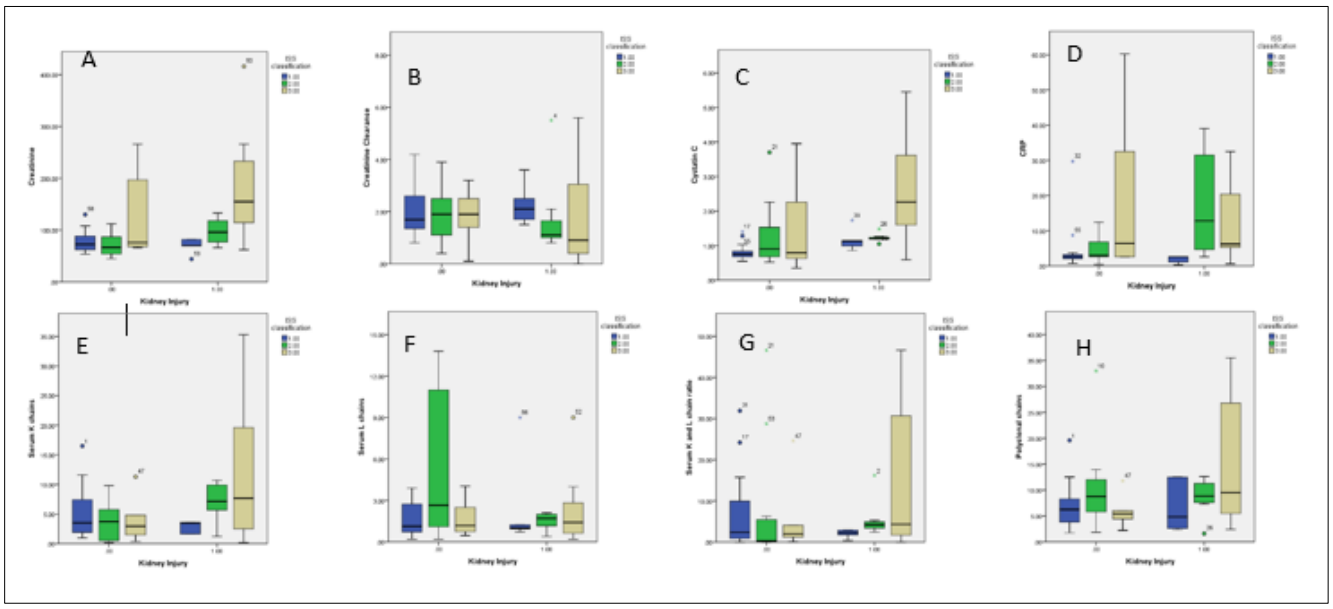
When applied International Staging System for MM and renal injury, the relations and significance between parameters were analyzed by Kolmogorov-Smirnov test which showed that the parameters as age and creatinine clearance follow

the rules of normal distribution, and the parameters creatinine, Cystatin C, CRP, serum kappa chains, serum λ chains, the ratio of serum kappa and λ chains as well as polyclonal chains did not follow the rules of normal distribution.

In ISS stage 1, the mean serum Cystatin C level in patients without renal injury was 0.82 and with renal impairment 1.17 ($p<0.05$).

In ISS stage 2, the mean serum creatinine level in patients without renal injury was 72.36 mmol/dl and with renal impairment 97.86 mmol/dl ($p<0.05$); mean serum CRP level in patients without renal injury was 4.88 mg/l and with renal impairment 35.39 mg/l ($p<0.05$) and mean serum κ chains' level in patients without renal injury was 3.69 g/l and with renal impairment 7.18 g/l ($p<0.05$).

In ISS stage 3, no statistically significant difference was observed between the mean values of the examined parameters and renal injury.



A – Creatinine and renal injury I (77.13 mmol/dl– 69.6 mmol/dl; p=0.660); II (72.36 mmol/dl – 97.86 mmol/dl; p=0.038); III (134.6 mmol/dl – 232 mmol/dl; p=0.306). B – Creatinine clearance and renal injury I (1.98 ml/s – 2.28 ml/s; p=0.540); II (1.84 ml/s – 1.81 ml/s; p=0.961); III (1.82 ml/s – 2.21 ml/s; p=0.766). C – Cystatin C and renal injury I (0.82 mg/l – 1.17 mg/l; p=0.011); II (1.29 mg/l – 1.23 mg/l; p=0.322); III (1.6 mg/l – 2.84 mg/l; p=0.142). D – C reactive protein and renal injury I (4.45 mg/l – 1.83 mg/l; p=0.130); II (4.88 mg/l – 35.39 mg/l; p=0.025); III (20.86 mg/l – 23.92 mg/l; p=0.933). E – Serum K chains and renal injury I (5.22 g/l – 31.08 g/l; p=0.905); II (3.69 g/l – 7.18 g/l; p=0.025); III (4.19 g/l – 40.94 g/l; p=0.306). F – Serum L chains and renal injury I (21.16 g/l – 2.58 g/l; p=0.905); II (21.42 g/l – 1.5 g/l; p=0.287); III (1.78 g/l – 3.48 g/l; p=1.00). G – Polyclonal chains and renal injury I (26.38 g/l – 33.66 g/l; p=0.905); II (25.1 g/l – 8.68 g/l; p=0.971); III (5.97 g/l – 44.43 g/l; p=0.142). H – Serum K and L chain ratio and renal injury I (6.9 g/l – 30.46 g/l; p=0.968); II (6.8 g/l – 5.66 g/l; p=0.197); III (6.39 g/l – 27.97 g/l; p=0.230).

Figure 2 Analysed parameters through International Staging System classification of Multiple Myeloma phases

4. Discussion

Almost all patients with ISS stage III and patients with advanced lytic bone disease had elevated values of Cystatin C, while patients with relapsed disease had higher values of Cystatin C even compared to newly diagnosed patients [3]. The same results are in our study in ISS classification (p=0.001) but not in SD classification (p=0.734) (Figure 1C and Figure 2C).

C reactive protein is one of the important factors in the detection of inflammatory processes in the body in general, and is therefore considered a highly sensitive biomarker for inflammation. Although a nonspecific factor for MM, serum CRP levels represent a new and powerful prognostic factor in MM because its determination is fast, simple, reliable, and inexpensive [4]. The FLCs are a valuable and well-established tool to reflect MM-related kidney disease. We noticed statistically significant difference in concentration of serum κ chains and renal injury in Salmon Durie at presentation and ISS classification II (Figure 1EI and Figure 2EII).

Du et al. report as imperative to combine R-ISS and sFLC prognostic factors as modified R-ISS to better stratify patients who are likely to experience rapid progression or relapse [5].

Mead et al. [6] in their research of serial samples from Intact Immunoglobulin MM patients (IIMM) noticed that reduction in the glomerular filtration rate (as evidenced by rising serum creatinine and cystatin C concentrations) resulted in elevations of both FLC, without alteration of the κ/λ ratio.

Kumar et al. [7], used the sum of the kappa and λ FLC (ΣFLC) to examine the impact of polyclonal elevation of serum free light chains. The polyclonal elevation in the immunoglobulin free light chain pointed toward a general activation of plasma cells or other lymphoid cells that may precede the development of the monoclonal plasma cell population. It strengthened the argument in favor of chronic antigenic stimulation, infectious or otherwise, as a possible initial trigger for the establishment of the MGUS clone. They hypothesized that the first step in the pathogenesis of MGUS is a polyclonal expansion of plasma cells in response to antigenic stimulation that manifests as higher levels of free serum kappa and λ FLCs. As they have previously described, the MGUS clone once established is at the risk of acquiring additional cytogenetic abnormalities, which results in a long-term persistent risk of progression to MM or related malignancy.

From a population standpoint, the identification of biomarkers for development of monoclonal gammopathies can have potential clinical applications in the long term. There is clear evidence suggesting the early intervention in MM at the asymptomatic SMM phase may provide an opportunity to alter the natural history of the disease in a positive way. This is likely to lead to more screening approaches and identification of monoclonal gammopathies in the population, especially in high-risk populations. However, more importantly, the finding that polyclonal elevations precede the development of MGUS provides clues to etiologic factors [8].

In our study, we examined the values of creatinine clearance, serum creatinine, Cystatin C, CRP, serum free light chains and κ/λ ratio in three stages of the disease in patients with MM, regarding renal injury.

Although our creatinine clearance concentration study did not prove to be a statistically significant prognostic factor for multiple myeloma (Figure 1 and Figure 2), a study conducted by Yun et al. aimed at comparing the prognostic value of β2-microglobulin levels with creatinine clearance concentration value showed that creatinine clearance could be a more important prognostic factor than β2-microglobulin levels in patients with multiple myeloma and suggested that creatinine clearance concentration be re-classified as one of the significant biomarkers of this disease [9].

In a study conducted by Terpos et al. [10], a variation in serum Cystatin C concentration was observed with respect to the disease phase. Thus, patients in ISS phase III had an elevated median Cystatin C compared to phase I ($p < 0.0001$), as well as patients in phase II ($p < 0.001$), while there was no statistically significant difference between ISS phases I and II; we got the same results (Graph 2C). Specifically, in ISS phase III, only 6% of patients had a Cystatin C concentration that was within the reference values, compared with 66% of phase I patients and 50% of phase II patients who showed normal Cystatin C values. In contrast, normal serum creatinine levels were observed in a large number of patients in ISS phase I (94%) and ISS phase II (88%), as well as 50% of patients in ISS phase III disease [3].

However, in a study by Nückel et al. [11], it was shown that 24 patients (35%) had elevated serum Cystatin C values at diagnosis, while only 13 of those 24 (54%) also had elevated serum creatinine levels. Median serum Cystatin C levels increased significantly with higher ISS phases. All patients in ISS phase III had abnormal serum cystatin C levels, while 13% of patients in ISS phase I and 60% of patients in ISS phase II had serum Cystatin C levels above the reference values. On the other hand, almost all patients in ISS phase I were presented with normal creatinine levels. In contrast, five of 24 patients in ISS phase II and 8 of 11 patients in ISS phase III had elevated serum creatinine levels [11].

In a study conducted by Li et al. [12], it was shown that the level of CRP in patients with ISS phase III was statistically significantly different from ISS phase I ($p < 0.05$) and ISS phase II ($p < 0.005$), respectively. The concentration of CRP in multiple myeloma patients was statistically significantly higher than in the control group of subjects ($p < 0.05$).

In a study conducted by Bataille et al. [4], serum CRP levels were above the upper limit in 60 of 162 subjects with multiple myeloma at diagnosis, which was shown to be statistically significant ($p < 0.05$). In addition, low values of serum CRP were observed in MM during the steady phase, and high values again in the relapse phase.

A study conducted by Waikar and Bonventre observed a significant and previously unrecognized significance of the definition of AKI that uses a percentage increase in serum creatinine above baseline [13]. Namely, in patients with chronic renal impairment (high initial serum creatinine concentration), any percentage decrease in creatinine clearance led to a slower increase in serum creatinine concentration compared to patients without chronic renal impairment. This leads to a different classification of acute renal impairment depending on initial renal function despite an identical percentage decrease in creatinine clearance. Although the percentage increase in serum creatinine concentration after

acute renal impairment in a stable state does not depend on the basic renal function, i.e. 50% decrease in creatinine clearance will lead to a 100% increase in serum creatinine concentration regardless of baseline [13].

5. Conclusion

The incidence of renal impairment in multiple myeloma varies from study to study. This is primarily caused by the different definition of renal impairment in each study. Serum creatinine is often used to define renal impairment, and study by Dimopoulos et al. [14] reported that 21% of newly diagnosed patients with multiple myeloma showed renal failure, compared with their study from 2014 [14]. Approximately 30% of patients with impaired renal function in „at presentation"phase of disease were observed by Park and associates. In our study, impaired renal function was diagnosed in 42.9% of patients at this stage of the disease. Beside Cystatin C, well known parameter for kidney function, serum creatinine level, serum CRP level serum κ chains' level were early signs of kidney impairment.

Compliance with ethical standards

Acknowledgments

The authors would like to thank all subjects who participated the study

Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of ethical approval

The study was approved by Clinical Centre University of Sarajevo.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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