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Evaluation of serum cystatin C levels in multiple myeloma: diagnostic significance and clinical implications

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Abstract

Cystatin C (CysC) levels in patients with multiple myeloma (MM) have been linked to tumour load and outcomes' prediction. This study aimed at assessing the diagnostic utility of CysC in distinguishing MM patients from controls and advanced stages of MM. In total, 98 MM patients and 57 healthy controls participated in this cross-sectional case-control study. Demographic, clinical, and biochemical data were assessed. The study groups exhibited significantly diverse measures of urea, creatinine, CysC, β_2-microglobulin, and lactate dehydrogenase activity. β_2-Microglobulin was found to be a reliable predictor for both the MM staging and its diagnosis, but CysC was found to only possess a partial capacity of predicting advanced MM stages. Our results highlight the significance of taking into account many biomarkers in the therapy of MM, so as to achieve effective clinical evaluation. More research is required in order to clarify the CysC implication in the prognosis and management of MM.

KEYWORDS
multiple myeloma, LDH, β_2-microglobulin, staging, cystatin C

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1. INTRODUCTION

Multiple myeloma (MM) is characterized by a clonal plasma cell proliferation and is frequently complicated by renal insufficiency, which predicts an unfavourable prognosis [1]. Serum cystatin C (CystC) is considered as an accurate marker of the glomerular filtration rate and renal impairment [2]. Serum CystC levels, especially in patients with International Staging System "stage II" MM, have been linked to tumour load in MM and are predictive of patient outcomes [3], and tumour burden [4]. Nonetheless, there is still much to learn about the prognostic value of CystC in MM. This study aimed at assessing the CystC diagnostic utility in distinguishing MM patients from controls, and at comparing its levels between MM patients of different tumour stages.

2. PATIENTS AND METHODS

There were 155 participants in this case-control study, which was carried out in 2022 at the Babylon Main Hospital's Haematology Department. Ninety-eight patients with MM (49 men and 49 women) were chosen, and 57 healthy people served as the controls. Specific criteria, such as the presence of monoclonal proteins in the serum or the urine, osteolytic lesions in the bone, cytological examination of the bone marrow aspirate revealing at least 10% plasmacytes, and additional diagnostic tests (like complete blood counts, plasma protein electrophoresis, and renal function assessment) were used in order to establish the diagnosis of MM.

Our study included were 40 newly-diagnosed MM patients (15 on stage III and 25 on stage II) and 58 patients (35 on stage III and 23 stage II) undergoing first-line treatment with lenalidomide or bortezomib. Expert haematologists validated the diagnosis of MM by accepted protocols. The patient group was matched with healthy controls.

Patient demographics and medical histories were taken from hospital records and were among the data collected. Biochemical tests were conducted on blood samples at the hospital and at the College labs so as to measure creatinine, urea, β_2-microglobulin (β_2-M), CystC, and lactate dehydrogenase (LDH) levels.

All individuals provided written consent, and ethical approval was obtained. The SPSS and JASP software were used for statistical analysis.

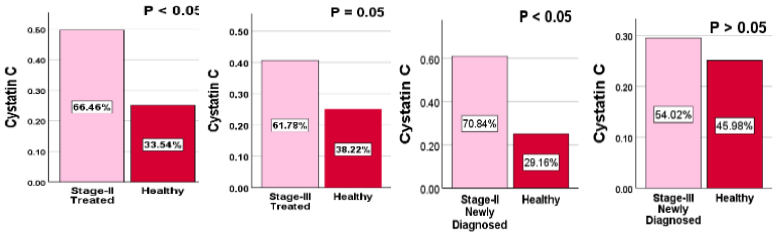

Figure 1-A

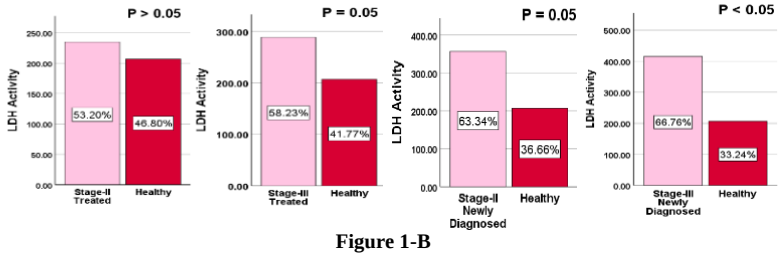

Figure 1-B

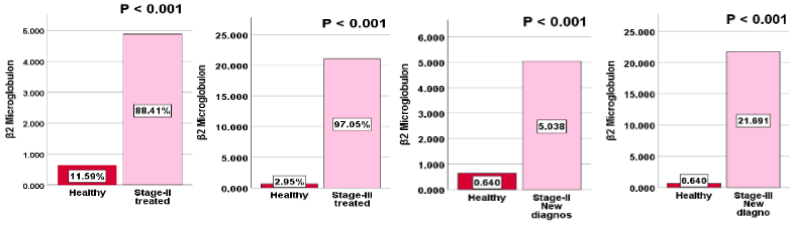

Figure 1-C

Figure 1. Multiple comparisons of the cystatin C levels (**A**), LDH activity (**B**), and β_2-microglobulin levels (**C**) among patients with different stages of multiple myeloma as compared with a healthy group.

3. RESULTS

Our study revealed no significant differences in age, body mass index, and sex distribution between MM patients and healthy controls. However, significant variations were noted in LDH activity,

β_2-M levels, CystC levels, creatinine levels, urea levels, and the prevalence of diabetes and hypertension. Age differences between sexes were significant, with men having a higher mean age. However, there were no significant differences in biomarker levels between men and women.

The β_2-M levels demonstrated excellent predictive ability (AUC=0.859) for differentiating MM patients from healthy controls, followed by LDH activity (AUC=0.817) and CystC levels (AUC=0.662). For differentiating between stage III and stage II MM cases, the β_2-M levels exhibited the perfect predictive ability (AUC=1.000). Moreover, β_2-M levels and LDH activity showed statistically significant variations when assessed as means between groups, thereby suggesting their significant role in discriminating between MM patients and controls. However, CystC levels did not exhibit significant differences in terms of group means (Figure 1).

4. DISCUSSION

The results of our investigation shed light on the potential diagnostic and prognostic value of several biomarkers in patients with MM. We understand more about the difficulties in managing and diagnosing MM by comparing MM patients with healthy controls, and by assessing the effectiveness of biomarkers in detecting different MM stages.

β_2-M confirms its long-standing function as a prognostic marker in the disease by revealing itself to be a reliable predictor in separating MM patients from healthy controls [5]. Meanwhile, CystC has little predictive capacity, indicating its limited utility in the MM analysis. Moreover, β_2-M exhibits effectiveness in differentiating various MM stages, underscoring its significance in predicting the disease progression. Nevertheless, LDH demonstrates a moderate predictive ability in identifying stage III MM, while CystC performs poorly in discriminating between MM stages. However, other researchers have found that the LDH is a biomarker of poor prognosis not only at diagnosis, but also at the first-relapse of MM patients [6].

Elevated CystC levels have been linked to higher levels of creatinine, LDH, and β_2-M according to recent studies [3], which is not different from what this study has found. In MM, higher CystC levels are linked to a considerably shorter progression-free survival and overall survival. Serum CystC serves as sensitive biomarker that successfully separates stage II survival characteristics, although it is not a stand-alone prognostic factor [7].

In MM, LDH emerges as a crucial prognostic factor. Poor prognosis, lower overall survival, progression-free survival, and aggressive disease are associated with elevated LDH activity at diagnosis [8]. LDH activity can be used to track the course of an illness and inform clinical decisions.

In individuals with MM, elevated levels of β_2-M are suggestive of a significant tumour load and are associated with either disease regression or progression after treatment. Elevations of β_2-M levels before therapy are linked to a less favourable outcome, rendering it a significant independent prognostic factor [9]. Similarly, studies have suggested that LDH could be used to monitor disease activity and directly shape clinical decision-making when combined with other indicators such as β_2-M and monoclonal immunoglobulin [10].

The LDH protein is a predictor of a poor outcome for MM patients, both at the onset and during their first episode of relapse [6]. Serum LDH levels have also been shown in several studies to be a helpful clinical measure for monitoring the progression of MM illnesses [8]. Furthermore, although elevated readings of LDH are uncommon at the beginning of MM, they frequently increase dramatically as the illness progresses. Compared to patients with normal LDH levels, those with higher concentrations have a shorter median life expectancy.

Finally, LDH and β_2-M are significant markers for the diagnosis, staging, and prediction of MM. These findings demonstrate how important it is to employ integrative diagnostic research in order to improve our approaches to the management of MM. Moreover, additional studies are required in order to fully appreciate the potential of β_2-M as a therapeutic target for MM, particularly when considering the application of antibody therapy in managing the symptoms of this type of cancer.

5. CONCLUSION

The current study exposes substantial variations in markers between MM patients and healthy subjects. β_2-M was found to be a robust predictor for both tumour staging and diagnosis, thereby contrasting the partial predictive capacity of CystC for later MM stages. This stresses β_2-M's significance as a reliable diagnostic and predictive marker in MM. Furthermore, the study shows links among variables, mainly connecting LDH activity with creatinine and urea levels.

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CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

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