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ORIGINAL RESEARCH

Serum Free Light Chain Profiles and Their Association with CRAB Features in Newly Diagnosed Multiple Myeloma Patients

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Abstract

Introduction: Multiple myeloma (MM) is a hematological malignancy characterized by the clonal proliferation of plasma cells in the bone marrow, resulting in end-organ damage manifested as hypercalcemia, renal impairment, anemia, and bone lesions (CRAB criteria). This study aimed to evaluate the pattern of serum free light chain (FLC) elevation, determine the distribution of kappa and lambda light chains, and investigate the association between the kappa/lambda (κ/λ) ratio and CRAB features in newly diagnosed MM patients. **Materials and Methods:** A retrospective observational study was conducted on 115 newly diagnosed multiple myeloma patients. Clinical and laboratory data, including serum free light chain levels, κ/λ ratio, serum calcium, creatinine clearance, hemoglobin concentration, and radiological evidence of bone lesions, were retrieved from medical records. Correlations between the κ/λ ratio and CRAB parameters were assessed using Pearson's correlation coefficient, while categorical variables were analyzed using the Chi-square test. A P value <0.05 was considered statistically significant. **Results:** A significant weak negative correlation was observed between the κ/λ ratio and hemoglobin level ($r = –0.199$, $P = 0.033$), indicating that higher κ/λ ratios were associated with lower hemoglobin concentrations. No statistically significant correlations were found between the κ/λ ratio and creatinine clearance ($r = –0.081$, $P = 0.391$), serum calcium levels, or the presence of bone lesions. Among the study population, females constituted 53.0% of patients, while males accounted for 47.0%. **Conclusion:** The serum κ/λ ratio showed a significant association with anemia but not with the other CRAB parameters in newly diagnosed multiple myeloma patients. These findings suggest that the κ/λ ratio may have clinical value as an indicator of disease burden, although larger prospective studies are required to validate its prognostic significance.

Keywords: Multiple myeloma- free light chains- kappa/lambda ratio- CRAB criteria- anemia

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Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by the clonal proliferation of abnormal plasma cells within the bone marrow and the production of monoclonal immunoglobulins or free immunoglobulin light chains. It accounts for approximately 10% of all hematological malignancies and remains an important cause of cancer-related morbidity and mortality worldwide [1]. In most patients, malignant plasma cells secrete monoclonal immunoglobulin (M protein) that can be detected in serum and/or urine, whereas approximately 15–20% produce only monoclonal free light chains (FLCs), a condition referred to as light chain multiple myeloma (LCMM) [2].

The excessive production of monoclonal proteins contributes directly to end-organ damage through several pathogenic mechanisms. Free light chains may accumulate in the kidneys as Bence Jones proteins, leading to renal impairment and, in severe cases, renal failure [3]. In addition, interactions between malignant plasma cells and the bone marrow microenvironment stimulate osteoclast activity through receptor activator of nuclear factor-kappa B ligand (RANKL), resulting in osteolytic bone lesions, skeletal pain, pathological fractures, and hypercalcemia [4]. The principal clinical manifestations of MM are summarized by the CRAB criteria, which include hypercalcemia (C), renal impairment (R),

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anemia (A), and bone lesions (B). The disease is also characterized by considerable genetic heterogeneity, including chromosomal abnormalities and recurrent gene mutations, which contribute to disease progression and therapeutic resistance [5].

Advances in diagnostic criteria have enabled earlier identification of patients at high risk of disease progression. In 2014, the International Myeloma Working Group (IMWG) updated the diagnostic criteria for MM by incorporating validated biomarkers in addition to the traditional CRAB features. These include an involved/uninvolved serum free light chain ratio of ≥100 (provided the involved free light chain concentration is ≥100 mg/L), more than one focal lesion (≥5 mm) detected by magnetic resonance imaging (MRI), and ≥60% clonal plasma cells in the bone marrow. Furthermore, computed tomography (CT) and positron emission tomography-computed tomography (PET-CT) are now accepted imaging modalities for detecting myeloma-related bone disease, facilitating earlier diagnosis and treatment before irreversible organ damage develops [2].

The incidence of MM varies considerably across different populations. In the United States, approximately 30,280 new cases were diagnosed in 2017, representing about 1.8% of all newly diagnosed cancers [6]. While incidence rates are generally comparable across Europe, substantially lower rates have been reported in many Asian countries. In India, the reported incidence is approximately 1.0 per 100,000 population, compared with the global incidence of approximately 4.1 per 100,000. Nevertheless, recent epidemiological studies have suggested a gradual increase in MM incidence in metropolitan regions of India, highlighting the growing clinical burden of this disease [7].

The diagnosis and monitoring of MM require a combination of laboratory, radiological, and pathological investigations. Routine evaluation includes complete blood count, renal and liver function tests, serum calcium, lactate dehydrogenase, serum protein electrophoresis (SPE), immunofixation electrophoresis (IFE), serum free light chain assay, urine Bence Jones protein analysis, bone marrow examination, and appropriate imaging studies. Among these investigations, the serum free light chain assay has become an essential diagnostic and prognostic tool, particularly in patients with light chain myeloma or those without measurable M protein by serum electrophoresis [4].

The serum FLC assay quantitatively measures free κ and free λ light chains and determines clonality using the κ/λ ratio. The normal reference ranges are 3.3–19.4 mg/L for free κ, 5.7–26.3 mg/L for free λ, and 0.26–1.65 for the κ/λ ratio. An abnormal κ/λ ratio indicates monoclonal plasma cell proliferation and has been associated with disease burden, prognosis, and treatment response [8]. However, limited data are available regarding the relationship between serum free light chain abnormalities and individual CRAB manifestations among Indian patients with newly diagnosed MM.

Therefore, the present study aimed to evaluate the pattern of serum free light chain elevation, determine the distribution of κ and λ light chain abnormalities, and investigate the association between the κ/λ ratio and CRAB features in newly diagnosed multiple myeloma patients.

Materials and Methods

Study Design and Participants

This retrospective observational study was conducted at the Division of Biochemistry, Department of Clinical Laboratory Services and Translational Research, Malabar Cancer Centre, Thalassery, Kerala, India. The study protocol was approved by the Institutional Review Board (IRB) of Malabar Cancer Centre (IRB approval number should be provided by the authors). Owing to the retrospective nature of the study, patient data were retrieved from the institutional cancer registry and electronic medical records.

A total of 141 medical records of patients diagnosed with multiple myeloma between September 2021 and March 2022 were initially screened. After excluding cases with incomplete clinical or laboratory information, 115 newly diagnosed multiple myeloma patients with complete datasets were included in the final analysis. Demographic characteristics, including age, sex, body weight, laboratory findings, and radiological evidence of bone lesions, were extracted for analysis.

Laboratory Measurements

Hemoglobin concentration was measured using the Beckman Coulter LH780 automated hematology analyzer based on the electrical impedance principle. Serum biochemical parameters, including calcium and creatinine, were analyzed using the Vitros® 5600 Integrated Dry Chemistry System (Ortho Clinical Diagnostics, USA) according to the manufacturer's instructions.

Creatinine clearance was estimated using the Cockcroft–Gault equation:

Creatinine Clearance=(140−Age)×Weight (kg)72×Serum Creatinine (mg/dL)\text{Creatinine Clearance}=\frac{(140-\text{Age}) \times \text{Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}} Creatinine Clearance=72×Serum Creatinine (mg/dL)(140−Age)×Weight (kg)

The calculated value was multiplied by 0.85 for female patients.

Serum free kappa (κ) and lambda (λ) light chains were quantified using the Freelite® Human Kappa and Lambda Free Light Chain Assay (The Binding Site Group Ltd., Birmingham, UK) on an automated analyzer according to the manufacturer's recommendations. The κ/λ free light chain ratio was subsequently calculated for each patient.

Outcome Measures

The primary objective of the study was to evaluate the distribution of serum free light chain abnormalities and investigate the association between the κ/λ ratio and CRAB features, including anemia, hypercalcemia,

renal impairment, and bone lesions, in newly diagnosed multiple myeloma patients.

Statistical Analysis

Statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range), depending on data distribution, whereas categorical variables are expressed as frequencies and percentages.

Associations between categorical variables were evaluated using the Chi-square test or Fisher's exact test, as appropriate. Pearson's correlation coefficient was used to assess the relationship between the κ/λ ratio and continuous clinical variables, including hemoglobin concentration, serum calcium level, and creatinine clearance. All statistical tests were two-tailed, and a P value <0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 115 newly diagnosed multiple myeloma patients were included in the analysis. The mean age of the study population was 62 years (range, 34–86 years). The cohort comprised 61 females (53.0%) and 54 males (47.0%). Most patients were older adults, reflecting the higher incidence of multiple myeloma in the elderly population. The baseline demographic and clinical characteristics are summarized in Table 1.

Distribution of Free Light Chain Type According to CRAB Features

The distribution of κ and λ light chain involvement according to the CRAB criteria is presented in Figure 1 and Table 2. No statistically significant differences were observed between κ and λ light chain predominance with respect to any of the CRAB manifestations.

Anemia was present in 46% of patients with κ light chain predominance and 40.5% of those with λ light chain predominance (P = 0.571). Renal impairment, assessed by reduced creatinine clearance, was observed in 23% and 32% of κ and λ groups, respectively (P = 0.286). Bone lesions were detected in 51% of κ cases and 38% of λ cases (P = 0.140). Hypercalcemia was observed in 4% of κ cases and 5% of λ cases (P = 0.656).

Table 1. Baseline Age Characteristics of Newly Diagnosed Multiple Myeloma Patients (n = 115)

Variable	n	Minimum	Maximum	Mean ± SD
Age (years)	115	34	86	62.03 ± 10.56

Table 2. Clinical Characteristics of Newly Diagnosed Multiple Myeloma Patients (n = 115)

Clinical characteristic	Value
Involved light chain	Kappa: 78 (67.8%)
	Lambda: 37 (32.2%)
Anaemia (Hb <10 g/dL)	51 (44.3%)
Renal dysfunction (Creatinine clearance <40 mL/min)	30 (26.1%)
Bone lytic lesions	60 (52.2%)
Hypercalcaemia (Serum calcium >11 mg/dL)	5 (4.3%)

Association Between κ/λ Ratio and CRAB Criteria

Serum Calcium

Pearson correlation analysis demonstrated no significant association between the κ/λ ratio and serum calcium levels (r = –0.102, P = 0.279) (Figure 2A).

Hemoglobin

A weak but statistically significant negative correlation was observed between the κ/λ ratio and hemoglobin concentration (r = –0.199, P = 0.033), indicating that higher κ/λ ratios were associated with lower hemoglobin levels (Figure 2B).

Creatinine Clearance

No statistically significant correlation was identified between the κ/λ ratio and creatinine clearance (r = –0.081, P = 0.391) (Figure 2C).

Bone Lesions

The association between the κ/λ ratio and the presence of bone lesions was assessed using the Chi-square test. No statistically significant association was found (P = 0.795).

A summary of the associations between the κ/λ ratio

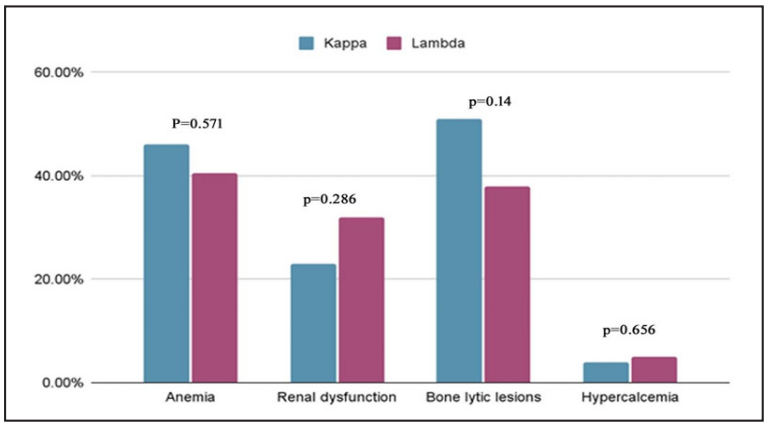

Figure 1. Distribution of CRAB Criteria According to Involved Free Light Chain Type (κ vs λ).

and the CRAB parameters is presented in Table 3.

Discussion

Multiple myeloma is a plasma cell malignancy characterized by monoclonal immunoglobulin production and progressive end-organ damage. The serum free light chain (FLC) assay has become an important diagnostic and prognostic tool because it reflects clonal plasma cell activity and has been incorporated into the International Myeloma Working Group (IMWG) diagnostic criteria. In the present study, we evaluated the distribution of serum free light chain abnormalities and examined the association between the κ/λ ratio and CRAB manifestations in newly diagnosed multiple myeloma patients from an Indian tertiary cancer center.

All patients included in this study demonstrated an abnormal κ/λ ratio, confirming the diagnostic utility of serum free light chain analysis in newly diagnosed multiple myeloma. Although several international studies have established the value of the serum FLC assay, data from the Indian population remain relatively limited. Bora et al. [9] reported regional differences in the incidence of multiple myeloma across India, suggesting that environmental and lifestyle factors may contribute to disease distribution. Similarly, Cowan et al. [10] demonstrated a global increase in the incidence of multiple myeloma, particularly among older adults, reflecting population aging and improved diagnostic practices.

The mean age of the study population was 62 years, which is consistent with previous reports indicating that multiple myeloma predominantly affects older individuals. Previous studies have reported median ages at diagnosis ranging from approximately 66 to 72 years. Although our cohort included a slightly higher proportion of female patients, this finding differs from most epidemiological

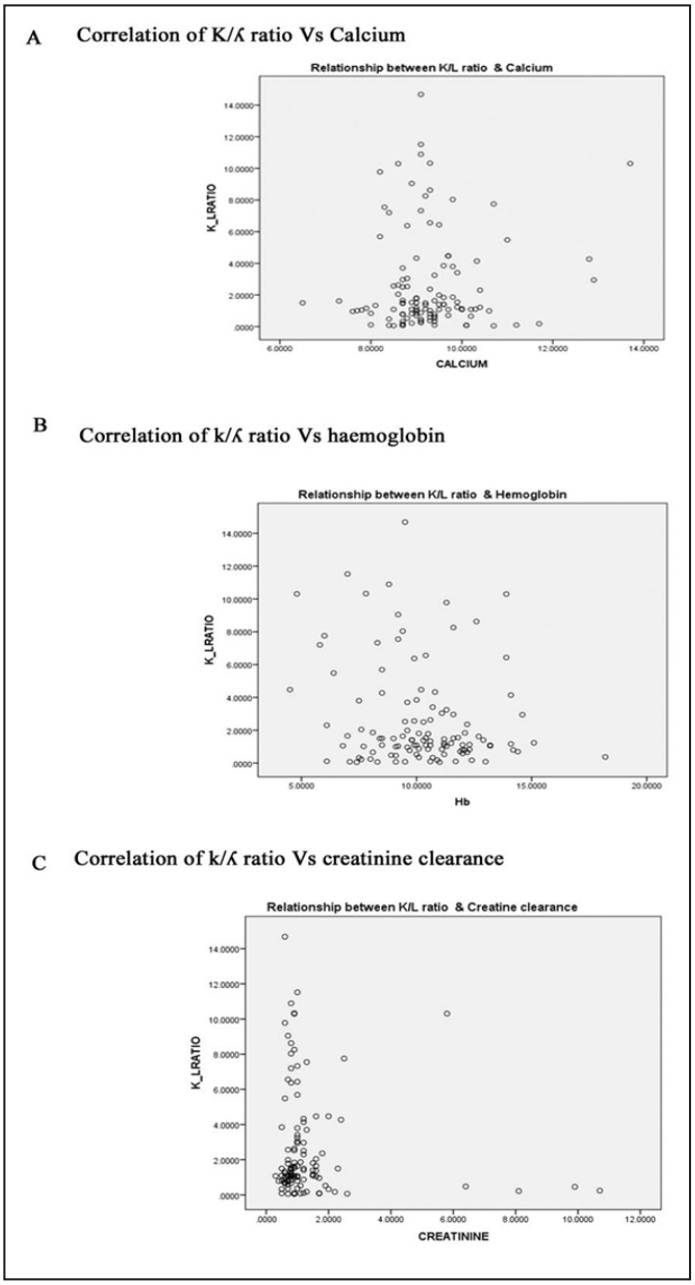

Figure 2. Correlation between the Serum κ/λ Free Light Chain Ratio and CRAB Parameters

Table 3. Correlation between the Serum κ/λ Ratio and CRAB Criteria

Variable	Statistical test	Correlation coefficient (r)	P value
Haemoglobin	Pearson correlation	- 0.199	0.033*
Creatinine clearance	Pearson correlation	- 0.081	0.391
Serum calcium	Pearson correlation	- 0.102	0.279
Bone lytic lesions	Chi-square test	—	0.795

*P < 0.05 indicates statistical significance; κ/λ = kappa/lambda free light chain ratio.

studies, which generally report a male predominance. Given the relatively small sample size and single-center design, this difference should be interpreted cautiously and may not reflect the true sex distribution of the disease.

The present study investigated the relationship between the κ/λ ratio and the CRAB features of multiple myeloma. Among the evaluated parameters, only hemoglobin concentration demonstrated a statistically significant association with the κ/λ ratio. Specifically, higher κ/λ ratios were associated with lower hemoglobin levels, suggesting that increasing monoclonal light chain production may reflect greater bone marrow infiltration and impaired erythropoiesis. This observation is consistent with previous findings reported by Dingli et al. [11] who also demonstrated an association between serum free light chain abnormalities and disease burden.

In contrast, no statistically significant associations were observed between the κ/λ ratio and serum calcium concentration, creatinine clearance, or the presence of bone lesions. These findings suggest that although the serum free light chain ratio reflects clonal plasma cell proliferation, it may not reliably predict the severity of individual CRAB manifestations at the time of diagnosis. Renal dysfunction, hypercalcemia, and skeletal involvement are multifactorial complications influenced by several biological and clinical factors beyond monoclonal light chain production alone.

The absence of significant correlations for most CRAB parameters may also be related to the modest sample size, heterogeneity of disease stage, and the retrospective nature of the study. Larger multicenter studies incorporating molecular characteristics, disease stage, and treatment outcomes are warranted to further clarify the prognostic significance of serum free light chain abnormalities in newly diagnosed multiple myeloma.

Overall, our findings support the continued use of the serum free light chain assay as an important component of the diagnostic evaluation of multiple myeloma. However, the κ/λ ratio alone should not be considered a surrogate marker for all CRAB features and should be interpreted alongside established clinical, laboratory, and radiological parameters.

In conclusion, this study provides valuable insights into the clinical profile of newly diagnosed multiple myeloma patients and the relationship between the serum free light chain (κ/λ) ratio and CRAB criteria. A statistically significant negative correlation was observed between the κ/λ ratio and haemoglobin levels, suggesting that a higher κ/λ ratio may be associated with greater disease-related anaemia. In contrast, no significant associations were identified between the κ/λ ratio and serum calcium levels, creatinine clearance, or the presence of bone lesions. Although a slightly higher proportion of female patients was observed in this cohort, this finding is likely related to the limited sample size and should be interpreted with caution. Overall, the findings support the clinical value of serum free light chain assessment as an adjunctive biomarker in the initial evaluation of multiple myeloma. Larger prospective multicentre studies are warranted to validate these findings and further clarify the relationship between free light chain abnormalities and disease manifestations.

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Conflict of Interest

The authors declare that they have no competing interests.

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