# Association of Serum Lactate Dehydrogenase with International Staging System and Overall Survival in Newly Diagnosed Multiple Myeloma


## Abstract

**Background:** Multiple myeloma (MM) is a plasma cell malignancy with a highly variable prognosis. The International Staging System (ISS) is widely used for risk stratification; however, serum lactate dehydrogenase (LDH) is increasingly recognized as a marker of tumor burden and aggressive disease biology. Although the Revised International Staging System (R-ISS), which incorporates cytogenetics and LDH, provides superior prognostic discrimination, cytogenetic facilities and even β2-microglobulin estimation are not universally available in many resource-limited settings. In this context, LDH, being inexpensive and widely accessible, may offer additional prognostic value when evaluated alongside ISS.

**Objective:** To investigate the association between serum LDH levels and ISS staging in newly diagnosed MM patients and to explore the utility of LDH as a surrogate prognostic marker in resource-limited settings.

**Methods:** A cross-sectional study was conducted on 59 newly diagnosed MM patients. Demographic, clinical, and biochemical parameters including serum LDH were recorded at diagnosis. Patients were staged according to ISS criteria,of the 59 newly diagnosed multiple myeloma patients, 10 (17%) were classified as ISS Stage I, 16 (27%) as Stage II, and 33 (56%) as Stage III.LDH values were compared across ISS stages. Correlations between LDH and hemoglobin, creatinine, and calcium were analyzed.Patients were followed for up to 5 years from diagnosis to assess overall survival, and mortality rates were compared amongst ISS groups using appropriate statistical tests.

**Results:**The mean age of the study cohort was 56.2 ± 9.8 years, with a male predominance, and the majority of patients presented with ISS Stage III disease. Serum lactate dehydrogenase (LDH) showed a non-normal distribution, with an overall median of 419 U/L (IQR: 303–518). A stage-wise increase in median LDH levels was observed from ISS Stage I to Stage III; however, no statistically significant correlation was demonstrated between LDH and ISS stage. Among 29 patients with documented death events after 5 year follow up the median overall survival was 29 months (range: 8–59 months).Mortality was highest in ISS Stage III patients (21/33), compared to Stage II (6/16) and Stage I (2/10).Median serum LDH levels increased with advancing ISS stage. Median (IQR) LDH was 209.0 U/L in Stage I, 399.0 (376.5–414.0) U/L in Stage II, and 505.5 (458.5–556.5) U/L in Stage III. The difference in LDH across stages among deceased patients was statistically significant (Kruskal–Wallis test, $p < 0.001$).Serum LDH showed a strong inverse correlation with overall survival (Spearman's $\rho = -0.72$, $p < 0.001$). Correlation analysis using Spearman's rank correlation coefficient demonstrated that, in the overall cohort, serum LDH showed a strong positive correlation with β2-microglobulin ($\rho = 0.75$, $p < 0.001$) and a moderate inverse correlation with serum albumin ($\rho = -0.53$, $p < 0.001$). However, these associations were not consistently

maintained on stage-wise analysis across individual ISS stages, likely due to smaller subgroup sizes. No statistically significant correlations were observed between serum LDH and hemoglobin ($\rho \approx -0.03$, $p > 0.05$), serum creatinine ($\rho \approx 0.13$, $p > 0.05$), or serum calcium ($\rho \approx -0.22$, $p > 0.05$), either in the overall cohort or on ISS stage-wise analysis.

**Conclusion:** Although serum LDH did not show a significant correlation with ISS stage, its stage-wise increase and strong inverse association with overall survival support its role as an indicator of disease aggressiveness. LDH may serve as a useful, inexpensive adjunct prognostic marker in newly diagnosed MM, particularly in resource-limited settings.

**Keywords:** Multiple myeloma; Lactate dehydrogenase; International Staging System; Prognosis

## Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by clonal proliferation of plasma cells in the bone marrow, overproduction of monoclonal immunoglobulins (M-protein), and associated end-organ damage such as renal dysfunction, bone lesions, anemia, and hypercalcemia, commonly summarized by the CRAB criteria [1]. MM accounts for approximately 10% of all hematological malignancies and about 1% of all cancers worldwide [2].In India, multiple myeloma contributes to a significant mortality burden, with approximately 5,900 deaths annually, reflecting late presentation and limited access to advanced therapies in many regions.[3]

The clinical course of MM is highly heterogeneous. Some patients present with indolent disease and survive for more than a decade, whereas others develop aggressive, treatment-refractory disease with survival measured in months. Common complications include recurrent infections, skeletal fractures, renal impairment secondary to light-chain deposition, hyperviscosity syndrome, and neurological manifestations [4]. Prognosis depends on both tumor burden, such as the extent of plasma cell proliferation, paraprotein levels, and organ damage, and tumor biology, which includes genetic and molecular characteristics of malignant plasma cells [1]. Consequently, reliable staging and risk-stratification systems are essential for therapeutic decision-making, prognostication, and comparison of outcomes across clinical trials.

The first widely accepted staging system was the Durie–Salmon system introduced in 1975, which classified patients into stages I–III based on hemoglobin concentration, serum calcium, M-protein levels, skeletal lesions, and serum creatinine [5]. Although clinically useful, this system relied heavily on skeletal surveys, which often underestimated bone disease, and failed to capture biological heterogeneity.

The International Staging System (ISS), developed by the International Myeloma Working Group in 2005, represented a major advancement by incorporating two simple and reproducible biochemical markers: serum β2-microglobulin (β2M) and serum albumin . β2M reflects tumor mass and renal function, while albumin reflects host

nutritional and inflammatory status. Patients are categorized as ISS stage I (β2M < 3.5 mg/L and albumin ≥ 3.5 g/dL), stage II (intermediate), or stage III (β2M ≥ 5.5 mg/L). Due to its simplicity and prognostic value, ISS rapidly became the global standard [6]. However, ISS does not account for cytogenetic abnormalities or tumor proliferative activity, both of which significantly influence prognosis [6].

To overcome these limitations, the Revised International Staging System (R-ISS) was introduced in 2015, incorporating high-risk cytogenetic abnormalities detected by fluorescence in situ hybridization (del(17p), t(4;14), t(14;16)) and serum lactate dehydrogenase (LDH) in addition to ISS [6]. R-ISS provides superior prognostic discrimination, categorizing patients into R-ISS I (ISS I with standard-risk cytogenetics and normal LDH), R-ISS II (intermediate risk), and R-ISS III (ISS III with high-risk cytogenetics or elevated LDH). This system has been validated internationally and is now recommended for routine risk stratification [6].

LDH is a key glycolytic enzyme catalyzing the conversion of pyruvate to lactate. Elevated LDH reflects increased cellular turnover, tissue damage, and hypoxia. In MM, raised LDH levels mirror aggressive tumor biology, including enhanced proliferation and hypoxic adaptation, commonly referred to as the Warburg effect [7]. Several studies have identified LDH as an independent predictor of poor overall survival and progression-free survival [8,9]. High LDH levels are also associated with plasma cell leukemia, extramedullary disease, and relapsed or refractory MM [10].

Despite its advantages, R-ISS requires cytogenetic testing, which is not universally available, particularly in resource-limited settings. Even β2M estimation may be constrained by cost and laboratory infrastructure in many centers. In contrast, LDH testing is inexpensive, widely available, and routinely performed in most clinical laboratories [2]. This makes LDH an attractive surrogate or adjunct biomarker where advanced diagnostic facilities are lacking.

Given these challenges, there is growing interest in evaluating ISS in combination with LDH as a feasible alternative to R-ISS in the absence of cytogenetic data. Correlating LDH with ISS may help identify high-risk patients who might otherwise be misclassified. Furthermore, in settings where β2M estimation is unavailable, LDH alone may provide meaningful prognostic insight comparable to ISS [8,9].

The present study investigates the relationship between serum lactate dehydrogenase and International Staging System staging in newly diagnosed multiple myeloma patients, with the hypothesis that LDH correlates with advancing ISS stage and may serve as a cost-effective prognostic adjunct in Indian cohorts where access to cytogenetic testing is limited. In addition, the study evaluates the association between baseline LDH levels and overall survival to assess its prognostic relevance beyond staging and its potential role in risk stratification in routine clinical practice.

## Materials and Methods

### Study Design and Setting

This was a cross-sectional, observational study conducted in the Department of Biochemistry, Nizam's Institute of Medical Sciences (NIMS), Hyderabad, a tertiary care referral center. Newly diagnosed multiple myeloma patients were identified and recruited from the Department of Medical Oncology, NIMS. The study was based on analysis of routine biochemical and clinical data obtained at diagnosis.

The study protocol was followed the Institutional Ethics Committee,as the study involved retrospective analysis of routinely generated laboratory data, patient confidentiality was maintained and no personal identifiers were used.

### Study Population

A total of 59 newly diagnosed patients with multiple myeloma were included in the study. Diagnosis was established by the treating oncologists based on the International Myeloma Working Group (IMWG) diagnostic criteria[6].Only newly diagnosed cases were included, and all laboratory investigations were performed prior to initiation of definitive therapy.

### Inclusion and Exclusion Criteria

Inclusion criteria were newly diagnosed multiple myeloma patients evaluated at the Department of Medical Oncology, NIMS, with complete baseline biochemical data available at diagnosis.

Exclusion criteria included patients with acute or chronic conditions known to independently elevate serum lactate dehydrogenase (LDH), such as active infections, inflammatory conditions, chronic liver disease, hemolytic anemia, recent myocardial infarction, or concurrent malignancies. Patients with incomplete laboratory or survival data were also excluded.

### Data Collection

Demographic details including age and sex were recorded from hospital records. Clinical information such as date of diagnosis, ISS stage, and survival status was obtained from oncology case files and hospital databases.

Baseline biochemical parameters analyzed included serum LDH, β2-microglobulin, albumin, creatinine, calcium, and hemoglobin. All values were obtained as part of routine diagnostic evaluation and retrieved from the laboratory information system of the Department of Biochemistry, NIMS.

### Laboratory Analysis

All biochemical analytes were measured on a clinical chemistry analyzer (Roche Diagnostics Cobas c501). Serum lactate dehydrogenase (LDH) was estimated by the UV kinetic enzymatic method based on the IFCC reference procedure. Serum β2-microglobulin was measured using a particle-enhanced immunoturbidimetric assay. Serum albumin was analyzed by the bromocresol green (BCG) dye-binding method, serum creatinine by an enzymatic method traceable to IDMS reference standards, and serum calcium by a colorimetric Arsenazo III method. Hemoglobin estimation was performed on an automated hematology analyzer using theelectrical impedance method(Beckman Coulter). All assays were carried out according to the manufacturers' instructions as part of routine laboratory testing.

## Staging

Patients were staged according to the International Staging System (ISS) based on serum β2-microglobulin and serum albumin values (Table1). [6] Cytogenetic analysis was not included, as the primary objective was to evaluate the role of LDH in relation to ISS staging in a setting where cytogenetic facilities may not be readily available.

| ISS Stage | Criteria |
|---|---|
| **ISS Stage I** | Serum β2-microglobulin < 3.5 mg/L **and** serum albumin ≥ 3.5 g/dL |
| **ISS Stage II** | Neither Stage I nor Stage III |
| **ISS Stage III** | Serum β2-microglobulin ≥ 5.5 mg/L |

*Table 1.International staging system (ISS)*

## Survival Analysis

Overall survival (OS) was defined as the interval, in months, from the date of diagnosis to the date of death. Patients who were alive at the time of analysis were treated as censored observations. Survival data were obtained from medical oncology records and follow-up information available in hospital databases.

## Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics. Age was expressed as mean ± standard deviation due to approximate normal distribution, while serum LDH values were summarized using median and interquartile range (IQR) owing to their non-normal, right-skewed distribution.The association between serum LDH levels and ISS stage in the overall cohort was assessed using Spearman's rank correlation coefficient.

Survival analysis was performed descriptively using overall survival duration.The association between serum LDH and overall survival duration was assessed using Spearman's rank correlation coefficient, given the non-normal distribution of both variables. Comparison of LDH across the non-survivors subgroup was performed using the Kruskal–Wallis test, an appropriate non-parametric method for skewed data and unequal group sizes. Correlation between serum LDH and hemoglobin, creatinine, and calcium was assessed using Spearman's rank correlation coefficient.A p-value $< 0.05$ was considered statistically significant.

## Results

The mean age of the study population was 56.2 ± 9.8 years, and there was a male predominance (66%).The overall median LDH level in the study cohort was 419 U/L, with an IQR of 303–518 U/L.Median serum β2-microglobulin was 6.3 mg/L (IQR: 3.5–12.7), while serum albumin had a median of 3.5 g/dL (IQR: 3.0–3.9). Renal function assessment showed a median serum creatinine of 1.1 mg/dL (IQR: 0.8–3.2). Serum calcium levels had a median of 8.8 mg/dL (IQR: 8.2–9.7), with corrected calcium values used where appropriate. Hemoglobin concentration showed a mean value of 10.0 ± 2.5 g/dL, reflecting the presence of anemia in a substantial proportion of patients.

### Comparison of LDH Across ISS Stages

Serum LDH values were then analyzed according to ISS stage. Patients classified as ISS Stage I had a median LDH of 229 U/L (IQR: 209–286). In ISS Stage II, the median LDH increased to 334.5 U/L (IQR: 286–403). The highest LDH levels were observed in ISS Stage III, with a median of 518.5 U/L (IQR: 456–571).Median LDH levels demonstrated a progressive increase with advancing ISS stage.Following this stage-wise comparison, correlation analysis was performed to assess the association between serum LDH and ISS stage. Correlation analysis did not demonstrate a statistically significant association between LDH and ISS stage.

### Correlation of LDH with Hemoglobin, Creatinine,Calcium, β2-microglobulin, albumin

Correlation of serum LDH with hemoglobin, creatinine, calcium, β2-microglobulin, and albumin was performed to evaluate whether LDH elevation reflected aggressive disease biology and tumor burden or was influenced by secondary factors such as anemia, renal dysfunction, or metabolic complications. β2-microglobulin and albumin were specifically included due to their established prognostic role in ISS staging, while hemoglobin,

creatinine, and calcium were analyzed to assess potential confounding effects of CRAB features.

Correlation analysis using Spearman's rank correlation coefficient demonstrated that, in the overall cohort, serum LDH showed a strong positive correlation with β2-microglobulin ($\rho = 0.75$, $p < 0.001$) and a moderate inverse correlation with serum albumin ($\rho = -0.53$, $p < 0.001$). However, these associations were not consistently maintained on stage-wise analysis across individual ISS stages, likely due to smaller subgroup sizes. No statistically significant correlations were observed between serum LDH and hemoglobin ($\rho \approx -0.03$, $p > 0.05$), serum creatinine ($\rho \approx 0.13$, $p > 0.05$), or serum calcium ($\rho \approx -0.22$, $p > 0.05$), either in the overall cohort or on ISS stage-wise analysis.

### Overall Survival Analysis

Patients who were alive after 5 year follow up were treated as censored observations. Among 29 patients with documented death events after 5 year follow up the median overall survival was 29 months (range: 8–59 months).Mortality was highest in ISS Stage III patients (21/33), compared to Stage II (6/16) and Stage I (2/10).Median serum LDH levels increased with advancing ISS stage.Median (IQR) LDH was 209.0 U/L in Stage I, 399.0 (376.5–414.0) U/L in Stage II, and 505.5 (458.5–556.5) U/L in Stage III.The difference in LDH across stages among deceased patients was statistically significant (Kruskal–Wallis test, $p < 0.001$)Following survival estimation, correlation analysis was performed to assess the relationship between baseline serum LDH levels and overall survival. Serum LDH demonstrated a strong inverse correlation with overall survival. Higher LDH values at diagnosis were associated with shorter survival duration. The correlation between LDH and overall survival was statistically significant (Spearman's $\rho = -0.72$, $p < 0.001$).

## Discussion

LDH is a cytosolic enzyme involved in anaerobic glycolysis and is released into circulation during increased cellular turnover, hypoxia, and tissue injury. In malignancies, elevated LDH reflects enhanced tumor proliferation and altered metabolic pathways, commonly described as the Warburg effect. [11]In MM, multiple studies have demonstrated that elevated LDH is associated with aggressive disease features and inferior outcomes. Dimopoulos et al. showed that patients with elevated LDH at diagnosis had significantly shorter overall survival and progression-free survival, independent of ISS stage[10].Similarly, Wu et al. reported that LDH retained prognostic significance even after adjustment for ISS and treatment-related variables, supporting its role as an independent adverse prognostic marker[7]. Avet-Loiseau et al. further demonstrated that elevated LDH frequently coexisted with high-risk cytogenetic abnormalities such as del(17p) and t(4;14), suggesting that LDH reflects underlying aggressive molecular biology.[8]

The relationship between LDH and ISS stage has been inconsistently reported in the literature. Some studies have shown higher LDH levels in advanced ISS stages, while

others have found LDH to be prognostically independent of ISS. Greipp et al. noted that although LDH tended to be elevated in advanced disease, it did not consistently correlate with ISS stage, indicating that LDH and ISS measure different biological dimensions of MM. ISS is primarily driven by serum β2-microglobulin and albumin, reflecting tumor burden, renal function, and host inflammatory status, whereas LDH reflects tumor proliferation, hypoxia, and metabolic stress.[4]

In the present study, serum LDH demonstrated a clear stage-wise increase across ISS stages, with progressively higher median LDH values observed from ISS Stage I to Stage III. This finding is biologically plausible and consistent with several previous studies reporting higher LDH levels in patients with advanced disease. However, despite this observed gradient, correlation analysis did not demonstrate a statistically significant association between LDH and ISS stage. This suggests that while LDH levels tend to rise with increasing disease severity, they do not show a direct linear relationship with ISS staging.

Several factors may explain this finding. First, ISS is heavily influenced by β2-microglobulin, which is affected not only by tumor burden but also by renal function. As a result, patients with similar tumor biology may be classified into different ISS stages based on renal impairment. In contrast, LDH reflects intrinsic tumor proliferation and metabolic activity, which may vary widely within the same ISS stage. Second, the relatively small sample size and uneven distribution of patients across ISS stages may have limited the statistical power to detect a significant correlation. Nonetheless, the consistent stage-wise increase in LDH supports a biological association that may not be fully captured by correlation analysis alone.

In our study,  correlation with β2-microglobulin and serum albumin, suggesting that LDH reflects both tumor burden and host inflammatory status in multiple myeloma. β2-microglobulin is a well-established surrogate marker of tumor mass and plasma cell proliferation and forms a core component of the International Staging System (ISS). Elevated β2-microglobulin levels arise from increased tumor cell turnover as well as reduced renal clearance, both of which are features of advanced and aggressive disease. The observed positive correlation between LDH and β2-microglobulin in our cohort supports the concept that LDH elevation parallels high cellular turnover and aggressive disease biology, rather than being a nonspecific biochemical abnormality. Similar associations between LDH and β2-microglobulin have been reported in previous studies, where LDH was shown to identify biologically high-risk disease even within the same ISS stage.[4]

An important component of the present study was the evaluation of correlations between LDH and hemoglobin, creatinine, calcium.Anemia, renal dysfunction, and hypercalcemia are common manifestations of MM and are closely related to disease burden and end-organ damage. Elevated LDH could theoretically result from hemolysis, renal impairment, or metabolic disturbances rather than reflecting tumor biology. In this study, LDH showed no significant correlation with hemoglobin, creatinine, or calcium levels.

Similar observations have been reported by Wu et al., who demonstrated that LDH retained prognostic significance independent of anemia and renal dysfunction. The absence of significant correlations in the present study suggests that LDH elevation reflects intrinsic tumor aggressiveness rather than secondary effects of end-organ damage.

Nearly half of the cohort (29/59 patients) experienced death during the 5-year follow-up period, while 30 patients remained alive, highlighting the substantial mortality burden of multiple myeloma. Patients who died were predominantly classified as ISS Stage III, whereas survivors were more frequently distributed across ISS Stages I and II, underscoring the prognostic relevance of ISS staging. Importantly, serum LDH levels were markedly higher among patients who died compared to those who survived, and LDH levels increased progressively with advancing ISS stage among non-survivors. This observation suggests that elevated LDH identifies a subset of patients with biologically aggressive disease, characterized by high tumor cell turnover, metabolic reprogramming, and rapid disease progression.In contrast, patients who remained alive during follow-up generally had lower LDH levels and earlier ISS stages, suggesting a lower tumor burden, less aggressive disease biology, and better response to therapy. These findings are consistent with prior studies demonstrating that elevated LDH is associated with poor overall survival independent of traditional staging systems and forms a key component of the Revised International Staging System (R-ISS).

Overall survival analysis in this cohort revealed a median survival of 29 months among patients with documented death events. This survival duration is shorter than that reported in large Western clinical trials but is comparable to several real-world Indian studies. Differences in survival outcomes may be attributed to delayed diagnosis, higher disease burden at presentation, limited access to novel therapeutic agents, and variations in treatment strategies. These factors are well documented in resource-limited settings and highlight the importance of simple prognostic markers applicable to routine clinical practice.[12]

Furthermore, the strong inverse correlation observed between LDH and overall survival duration in this study supports the role of LDH as a dynamic prognostic marker, rather than merely a reflection of disease stage. While ISS captures tumor burden and host factors through β2-microglobulin and albumin, LDH provides additional insight into tumor aggressiveness and proliferative activity, explaining why patients with high LDH experienced higher mortality even within the same stage. These findings reinforce the clinical value of LDH in identifying high-risk patients, particularly in resource-limited settings where cytogenetic testing may not be routinely available.

The findings of this study have important clinical implications, particularly in resource-limited settings. While R-ISS is the current standard for risk stratification, it requires cytogenetic testing that may not be universally available. Even β2-microglobulin estimation may be constrained by cost and laboratory infrastructure. In contrast, LDH testing is inexpensive, widely available, and routinely performed in most clinical laboratories. Although LDH did not show a statistically significant correlation with ISS

stage, its strong association with overall survival suggests that it provides independent prognostic information.

Therefore, LDH should be viewed as a valuable adjunct rather than a substitute for ISS. Combining LDH with ISS may improve risk stratification in settings where cytogenetic data are unavailable, and in centers lacking β2-microglobulin testing, LDH alone may still provide meaningful prognostic insight. The present study supports the continued evaluation and utilization of LDH as a practical prognostic marker in real-world clinical settings.

## Conclusion:

In conclusion, this study demonstrates that serum LDH is a clinically meaningful prognostic marker in multiple myeloma. Although LDH did not show a statistically significant correlation with ISS stage, it displayed a clear stage-wise increase and a strong inverse association with overall survival, identifying patients with aggressive disease biology and poor outcomes. LDH correlated positively with β2-microglobulin and inversely with albumin, supporting its role as a marker of tumor burden and inflammatory disease activity, while remaining independent of anemia, renal dysfunction, and hypercalcemia. The higher LDH levels and predominance of ISS Stage III among deceased patients further underscore its prognostic relevance. Given its low cost, wide availability, and strong association with survival, LDH serves as a valuable adjunct to ISS for risk stratification, particularly in resource-limited settings where cytogenetic testing may not be routinely accessible.

**Acknowledgements:**

The authors would like to express their sincere gratitude to the **Department of Biochemistry, Nizam's Institute of Medical Sciences (NIMS), Hyderabad**, for providing the laboratory facilities and access to patient data necessary for the conduct of this study. We also acknowledge the support of the institute in facilitating clinical collaboration and record retrieval, which made this research possible.

**Conflict of Interest:**

The authors declare that there are no conflicts of interest related to this study. No financial or non-financial competing interests exist that could have influenced the outcomes of this research.

**Funding:**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**References:**

*1)Rajkumar SV et al. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95(5):548–67.*

*2)Kyle RA et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78(1):21–33.*

*3)Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.*

*4)Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Blade J, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412-20.*

*5)Durie BG et al. A clinical staging system for multiple myeloma: Correlation of measured myeloma cell mass with presenting clinical features, response, and survival. Cancer. 1975;36(3):842–54.*

*6)Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. Revised International Staging System for Multiple Myeloma: A report from the International Myeloma Working Group. J Clin Oncol. 2015;33(26):2863-9.*

*7)Wu P, Davies FE, Boyd K, Thomas K, Dines S, Saso RM, et al. Prognostic role of serum lactate dehydrogenase in multiple myeloma. Clin Lymphoma Myeloma Leuk. 2015;15(3):213-9.*

*8)Avet-Loiseau H, Leleu X, Roussel M, Moreau P, Guerin-Charbonnel C, Caillot D, et al. Prognostic significance of high LDH in multiple myeloma. Leukemia. 2010;24(3):622-8.*

*9)Rasche L, Kortüm KM, Pantesco V, Caprio C, Rios R, Preuss B, et al. Features of extramedullary myeloma: Independent prognostic significance in relapsed/refractory multiple myeloma. Blood. 2012;120(5):1005-14.*

*10)Dimopoulos M, Kyle R, Fermand JP, Rajkumar SV, San Miguel J, Chanan-Khan A, et al. Prognostic factors for multiple myeloma in the era of novel agents: A report from the International Myeloma Workshop Consensus Panel 3. Blood. 2011;117(9):4696-700.*

*11)Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: The metabolic requirements of cell proliferation. Science. 2009;324(5930):1029-33.*

*12) Shah V, Chawla S, Gopal R, et al. Real-world outcomes of multiple myeloma from a tertiary cancer center in India. Indian J Hematol Blood Transfus. 2018;34(4):663–70.*