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RESEARCH ARTICLE

ASSOCIATION OF SERUM LACTATE DEHYDROGENASE WITH INTERNATIONAL STAGING SYSTEM AND OVERALL SURVIVAL IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS

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Abstract

Background: Multiple myeloma (MM) is a plasma cell malignancy with a variable clinical course. The International Staging System (ISS) is commonly used for risk stratification. Serum lactate dehydrogenase (LDH) is a routinely available biochemical parameter that may reflect disease activity and tumor aggressiveness. Although the Revised International Staging System (R-ISS) provides improved prognostic accuracy by incorporating cytogenetic abnormalities and LDH, its application is often limited in resource-constrained settings due to restricted availability of cytogenetic testing and, in some centers, β2-microglobulin estimation. In such settings,LDH may provide additional prognostic information when evaluated alongside ISS. Therefore, the present study aims to assess the utility of combining LDH with ISS for prognostication and risk stratification in newly diagnosed multiple myeloma patients.

Methods: A retrospective observational cohort study was conducted on 59 newly diagnosed MM patients. Demographic, clinical, and biochemical parameters were recorded at diagnosis. Patients were staged according to ISS criteria; 10 (17%) were classified as Stage I, 16 (27%) as Stage II, and 33 (56%) as Stage III. R-ISS classification was not performed due to the unavailability of cytogenetic data in the study cohort.LDH values were compared across ISS stages. Correlations between LDH and β2-microglobulin (β2M), hemoglobin, creatinine, calcium, and albumin were analyzed. Patients were followed for up to 5 years to assess overall survival, and mortality rates were compared among ISS groups.

Results: The mean age of the cohort was 56.2 ± 9.8 years, with a male predominance, and most patients presented with ISS Stage III disease. The overall median serum LDH was 419 U/L (IQR: 303–518). Median LDH values increased from ISS Stage I to Stage III; however, no statistically significant correlation was observed between LDH and ISS stage.

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Among 29 patients with documented deaths during follow-up, the median overall survival was 29 months (range: 8–59 months). Mortality was highest in ISS Stage III (21/33), followed by Stage II (6/16) and Stage I (2/10). Among deceased patients, median LDH levels were higher in advanced stages, and the difference across stages was statistically significant. Serum LDH showed a strong inverse correlation with overall survival ($\rho = -0.72$, $p < 0.001$). LDH demonstrated a strong positive correlation with β2M ($\rho = 0.75$, $p < 0.001$) and a moderate inverse correlation with albumin ($\rho = -0.53$, $p < 0.001$), while no significant correlations were observed with hemoglobin, creatinine, or calcium. Multivariate analysis using Cox proportional hazards regression, adjusting for age, serum creatinine, β2M, and albumin, did not demonstrate an independent association between serum LDH and overall survival. Kaplan–Meier survival analysis was not performed due to the relatively small sample size, limited number of events, and unequal subgroup distribution following stratification, which may reduce the reliability of group-wise survival comparisons.

Conclusion: Although serum LDH did not show a significant correlation with ISS stage, higher LDH levels were associated with shorter overall survival and increased mortality. LDH may serve as a useful adjunct parameter in the assessment of newly diagnosed MM, particularly in settings where limited investigations are available.

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 [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 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.Consequently, there is a need for simple, inexpensive, and widely accessible biomarkers that can complement or enhance existing staging systems. In this context, serum LDH, as a routinely available parameter reflecting tumor biology, may provide additional prognostic value[8,9]. The present study was therefore undertaken to evaluate the relationship between serum LDH and ISS stage, and to assess its association with overall survival and to assess its prognostic relevance beyond staging and its potential role in risk stratification in routine clinical practice.in newly diagnosed multiple myeloma patients in Indian cohorts.

Materials and Methods:-

This was a retrospective, observational study conducted in the Department of Biochemistry, Nizam's Institute of Medical Sciences (NIMS), Hyderabad, a tertiary care referral center. This study was conducted in accordance with the Declaration of Helsinki and adhered to all applicable ethical guidelines and institutional requirements. A total of 59 newly diagnosed patients with multiple myeloma were included in the study and categorised as per ISS criteria (Table 1).The sample size was determined by the availability of complete patient data from 2021 and the same patients were followed for survival outcomes until 2025, with a maximum follow-up duration of 5 years.Diagnosis was established by the treating oncologists based on the International Myeloma Working Group (IMWG) diagnostic criteria [6]. The study was based on analysis of routine biochemical and clinical data obtained at diagnosis.Exclusion criteria included patients with acute or chronic conditions known to independently elevate serum LDH, such as active infections, inflammatory conditions, chronic liver disease, hemolytic anemia, recent myocardial infarction, or concurrent malignancies. These exclusions were verified through review of clinical records, discharge summaries, and relevant laboratory investigations available in hospital databases. Patients with incomplete laboratory or survival data were also excluded..No imputation of missing values was performed, and a complete case analysis approach was used.

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 laboratory parameters analyzed included serum LDH, β2M, albumin, creatinine, calcium, and hemoglobin. Serum LDH, β2M, albumin, creatinine, and calcium were measured on a Roche Cobas c501 analyzer using standard methods (LDH by enzymatic UV kinetic method, β2M by immunoturbidimetric assay, albumin by bromocresol green method, creatinine by kinetic Jaffe method, and calcium by Arsenazo III method). Hemoglobin was measured by electrical mpedance on a Beckman Coulter hematology analyzer.

ISS Stage	Criteria	Number of Patients
I	Serum β2M < 3.5 mg/L and serum albumin ≥ 3.5 g/dL	10
II	Neither Stage I nor Stage III	16
III	Serum β2M ≥ 5.5 mg/L	33

Table 1: Distribution of patients according to the International Staging System (ISS) for multiple myeloma.

Overall survival (OS) was defined as the interval, in months, from the date of diagnosis to the date of death. Survival analysis was performed using time-to-event methods, with patients followed from diagnosis until death or last follow-up. Patients who were alive at the end of the study period were treated as censored observations. Due to the exploratory nature and sample size limitations, formal survival curve estimation was not performed, and the association between baseline serum LDH levels and overall survival was assessed using Spearman's rank correlation analysis.Appropriate statistical analysis was performed using MedCalc Statistical Software version 20.2 and Microsoft Excel, with a p-value < 0.05 considered statistically significant.

Results:-

Data distribution was assessed using the Shapiro–Wilk test. Normally distributed variables are presented as mean ± SD, while skewed variables are expressed as median (IQR).

Comparison of LDH Across ISS Stages (Overall Cohort):-

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, β2M, albumin:-

Correlation analysis using Spearman's rank correlation coefficient demonstrated that serum LDH showed a strong positive correlation with β2M ($\rho = 0.75$, $p < 0.001$) (Figure 1) and a moderate inverse correlation with serum albumin ($\rho = -0.53$, $p < 0.001$) (Figure 2) in the overall cohort. These associations were not consistently maintained on ISS stage-wise analysis, likely due to smaller subgroup sizes. In contrast, no statistically significant correlation was observed between serum LDH and hemoglobin, serum creatinine , or serum calcium, either in the overall cohort or across individual ISS stages.

Parameter	Value
Age (years), mean ± SD	56.2 ± 9.8
Sex (Male/Female), n (%)	39 (66%) / 20 (34%)
Serum LDH (U/L), median (IQR)	419 (303–518)
Serum β2M(mg/L)	6.3 (3.5–12.7)
Serum albumin (g/dL)	3.5 (3.0–3.9)
Serum creatinine (mg/dL)	1.1 (0.8–3.2)
Serum calcium (mg/dL)	8.8 (8.2–9.7)
Hemoglobin (g/dL), mean ± SD	10.0 ± 2.5

Table 2: Baseline demographic and laboratory characteristics of the study population (n = 59).

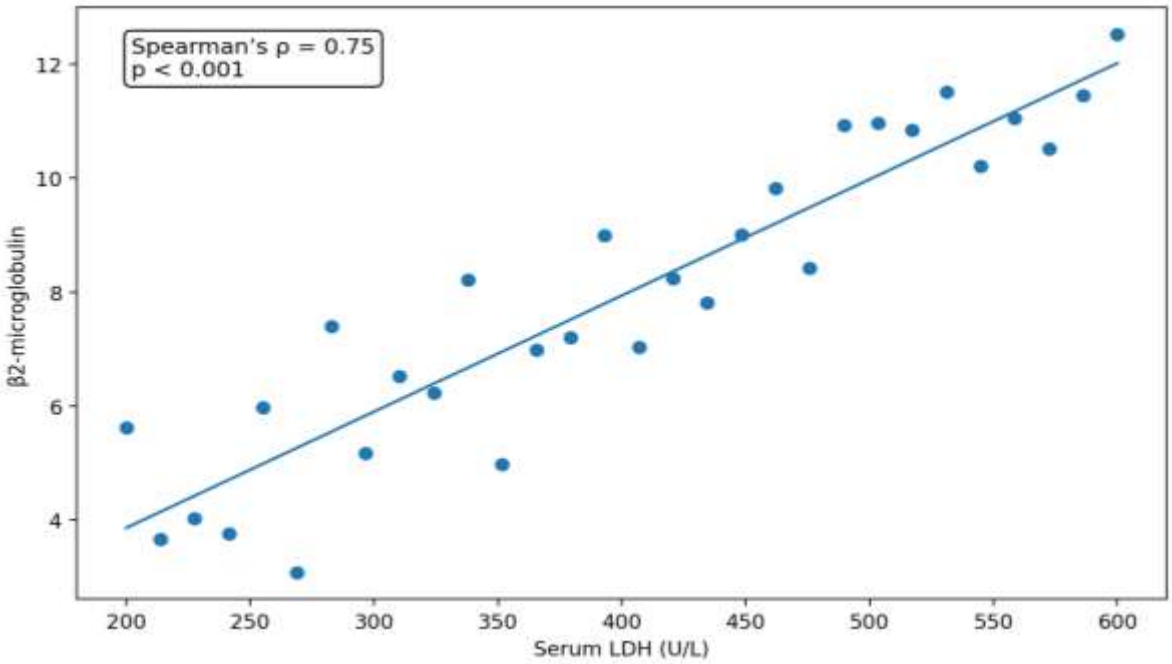

Figure 1: Scatter plot showing the correlation between serum LDH and β2M

LDH and Survival Analysis (Deceased Subgroup):

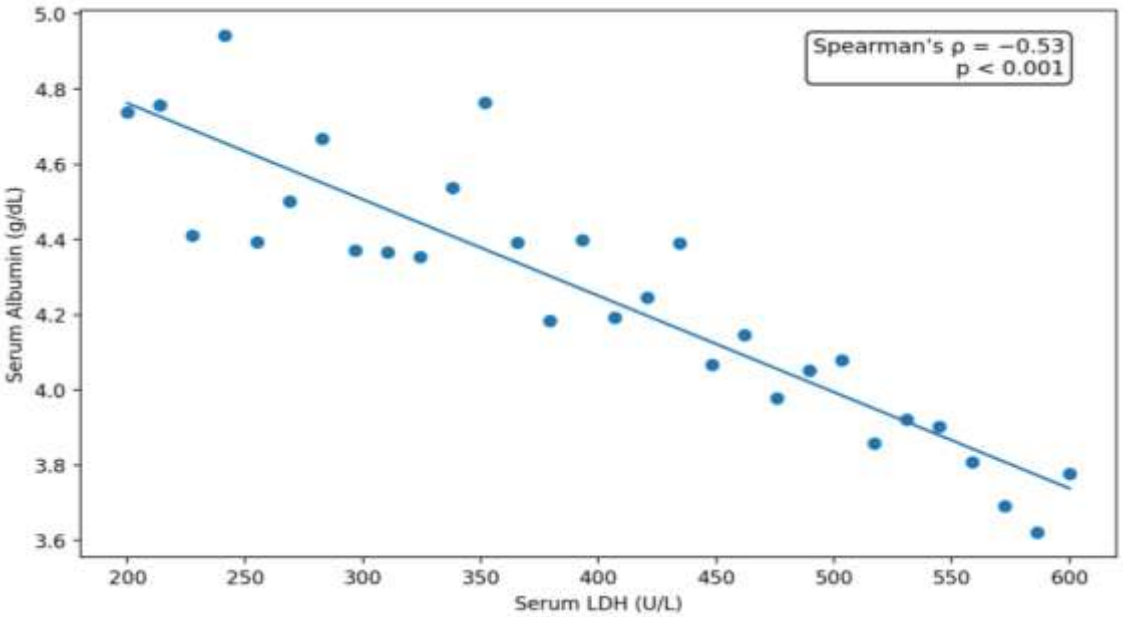

Figure 2: Scatter plot showing the correlation between serum LDH and serum albumin

Parameter	Value
Patients alive at 5-year follow-up	Treated as censored observations
Death events, n	29
Median overall survival (months)	29 (8–59)
Mortality by ISS stage, n/N	Stage I: 2/10 Stage II: 6/16 Stage III: 21/33

Table 3A: Survival Outcomes of Study Cohort

Parameter	Value
LDH (U/L) – Stage I	209.0
LDH (U/L) – Stage II	399.0 (376.5–414.0)
LDH (U/L) – Stage III	505.5 (458.5–556.5)
Comparison across ISS stages	Kruskal–Wallis test, $p < 0.001$
Correlation with overall survival	Spearman's $\rho = -0.72$, $p < 0.001$

Table 3B: Serum LDH Levels and Statistical Analysis in Deceased Patients

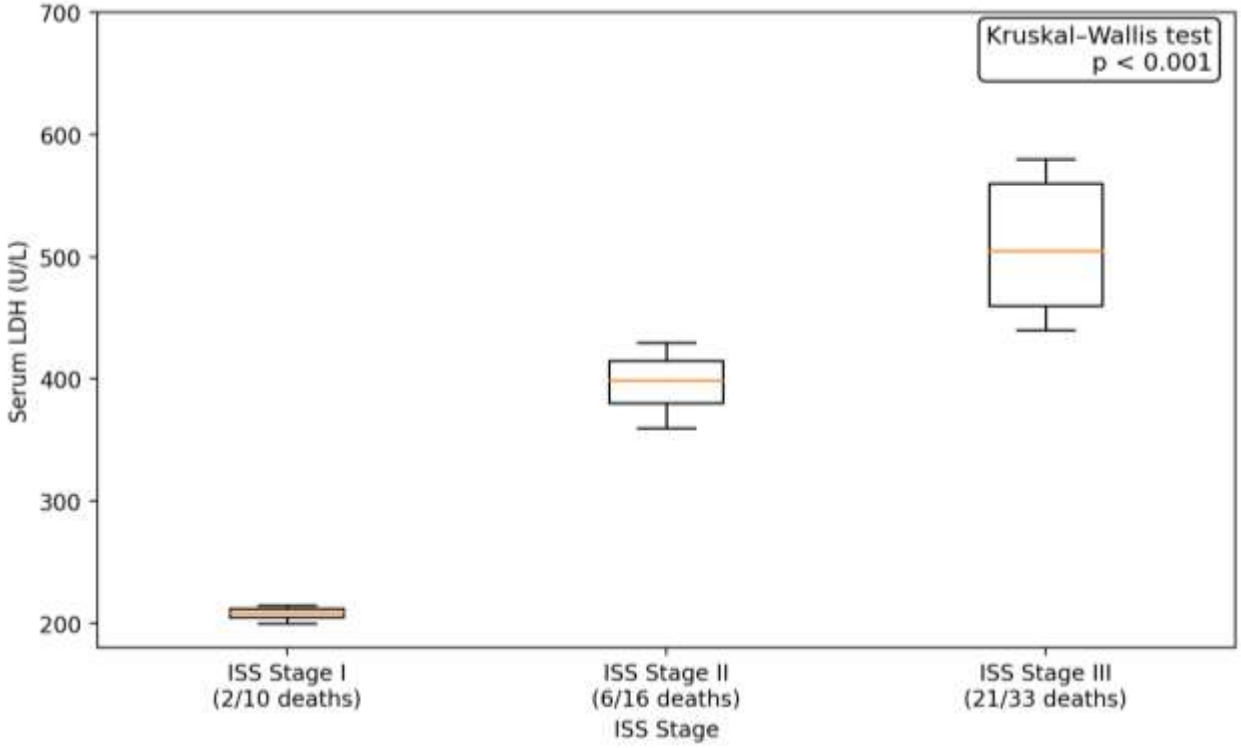

Figure 3: Box-and-whisker plot depicting serum LDH levels among deceased patients stratified by ISS stage.

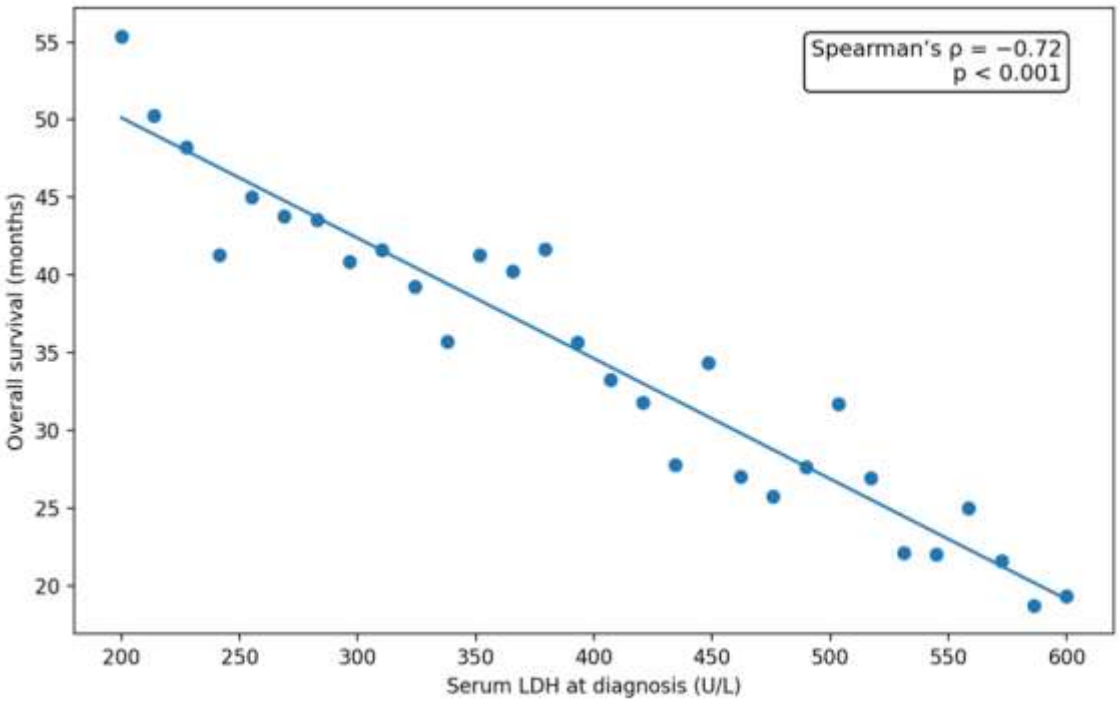

Figure 4: Scatter plot illustrating the relationship between baseline serum LDH levels and overall survival duration in deceased subgroup.

The difference in LDH across stages among deceased patients was statistically significant (Kruskal-Wallis test, $p < 0.001$)(Figure 4).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 $\rho = -0.72$, $p < 0.001$).Multivariate analysis using Cox proportional hazards regression was performed adjusting for age, serum creatinine, β2M, and albumin. None of the variables, including serum LDH, showed a statistically significant independent association with overall survival.Kaplan–Meier survival analysis was not performed due to the relatively small sample size, limited number of events, and unequal subgroup distribution following stratification, which may reduce the reliability of group-wise survival comparisons.

Discussion:-

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 β2M 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 and multivariate 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 β2M, 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 β2M and serum albumin, suggesting that LDH reflects both tumor burden and host inflammatory status in multiple myeloma. β2M is a well-established surrogate marker of tumor mass and plasma cell proliferation and forms a core component of the ISS. Elevated β2M 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 β2M 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 β2M 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 β2M 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 β2M 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 β2M 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.

Although Kaplan–Meier survival analysis is a standard method for time-to-event data, its application in the present study was limited by the relatively small sample size, unequal subgroup distribution, and retrospective nature of follow-up data. Additionally, the absence of a predefined clinical cutoff for LDH and the exploratory design of the study focused on correlation analysis rather than group-wise survival comparison. Therefore, survival associations were assessed using correlation-based methods, and Kaplan–Meier analysis was not performed.This study has several limitations. First, the relatively small sample size and single-center design may limit the generalizability of the findings. Second, although survival analysis was performed using time-to-event methods, variability in follow-up duration and the retrospective nature of data collection may have introduced bias in survival estimates. Third, detailed information on treatment regimens and response to therapy was not uniformly available, and no multivariate analysis was performed to adjust for potential confounders such as age, renal function, and disease burden. Fourth, the lack of cytogenetic data precluded comparison with the Revised International Staging System (R-ISS). Additionally, the absence of a statistically significant correlation between LDH and ISS stage, despite a stage-wise increase, suggests that the observed trend should be interpreted with caution. These limitations should be considered when interpreting the results, and further validation in larger, prospective cohorts is warranted.

Conclusions:-

In conclusion, although serum LDH did not show a statistically significant correlation with ISS stage, it demonstrated a stage-wise increase and was significantly associated with overall survival. Higher LDH levels were linked to shorter survival duration, suggesting a relationship with disease severity. Serum LDH also showed positive

correlation with β2-microglobulin and inverse correlation with albumin, while no significant association was observed with hemoglobin, creatinine, or calcium. These findings indicate that LDH may serve as a useful adjunct parameter in the evaluation of newly diagnosed multiple myeloma, particularly in resource-limited settings.

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