

A STUDY OF THE PROGNOSTIC VALUE OF LACTATE DEHYDROGENASE LEVELS IN MYELODYSPLASTIC SYNDROME

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ABSTRACT

BACKGROUND

Myelodysplastic syndromes are clonal marrow stem cell disorders characterised by ineffective haemopoiesis leading to blood cytopenias. Various prognostic parameters have been used to assess the prognosis of the disease like age, gender, IPSS score, modified IPSS score, serum albumin, Red Cell Distribution Width (RDW), serum ferritin and Lactate Dehydrogenase (LDH).

MATERIALS AND METHODS

The aim of this study was to investigate the relationship of serum lactate dehydrogenase at presentation of patients and the consequent development of complications and death that occurred in the followup period.

RESULTS

For this purpose, we studied 117 consecutive confirmed cases of myelodysplastic syndrome that presented to the Department of Medicine and Haematology in Calicut Government Medical College between July 2009 and June 2013. Serum lactate dehydrogenase levels were taken on diagnosis. All patients were followed up till December 2014. All subsequently developing complications- both outpatient and inpatient along with deaths that occurred were studied.

CONCLUSION

Although, a majority of patients with myelodysplastic syndrome (66.7%) had an LDH levels less than 500 IU/L, the undifferentiated subtype, RAEB-2 subtype and RAEB-1 subtype had a statistically significant high LDH levels probably due to high cell turnover rate. There was a positive correlation between LDH values and the complication rate of patients. A statistically significant correlation was seen between high LDH value and the frequency of death that occurred in the study group.

KEYWORDS

Myelodysplastic Syndrome, Lactate Dehydrogenase.

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BACKGROUND

Myelodysplastic syndromes are clonal marrow stem cell disorders characterised by ineffective haemopoiesis leading to blood cytopenias and by progression to acute myeloid leukaemia in a third of patients. The pathophysiology involves various cytogenetic changes with gene mutations with widespread hypomethylations in the genome. The clinical manifestations result from various combination of cytopenias- anaemias, leucopenias and thrombocytopenias. Diagnosis involves peripheral blood examination and bone marrow examinations showing a variety of changes in the different subtypes of myelodysplastic syndrome ranging from cytopenias to hyperproliferation with dysplasias and variable amount of blast cells. Prognosis depends on the marrow blast percentage, number and extent of cytopenias and

cytogenetic abnormalities. Treatment of patients with lower-risk myelodysplastic syndromes, especially for anaemia, includes growth factors, lenalidomide and transfusions. Treatment of higher-risk patients is with hypomethylating agents and allogeneic stem cell transplantation.

Several attempts have been made to refine IPSS.¹ These refined systems include the WHO Classification-Based Prognostic Scoring System (WPSS), which takes into account WHO classification and requirements for transfusion of red blood cells. The most important is the revised IPSS, which also uses cytogenetic abnormalities, cytopenias and blast count for scoring, but with new thresholds. Revised IPSS uses cytogenetics, bone marrow blast, haemoglobin, platelet count and absolute neutrophil count.¹

Other prognostic indicators used in various studies include clinical factors like age, gender, comorbidities and laboratory variables like haemoglobin levels, serum albumin, red cell distribution width, mean corpuscular volume, serum ferritin and lactate dehydrogenase.^{2,3,4,5,6,7} Multiple studies from the west have shown lactate dehydrogenase levels to correlate well with prognosis of patients.^{3,7,8,9} Studies from India investigating the levels of lactate dehydrogenase levels with prognosis of patients with myelodysplastic syndrome are scanty. The present study is an attempt to study the presenting lactate dehydrogenase level in patients with

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myelodysplastic syndrome with complications and the incidence of death among the patients.

MATERIALS AND METHODS

All clinically and histologically confirmed cases of MDS diagnosed in the Department of Medicine and Haematology, Calicut, Government Medical College, between July 2009 and June 2013 and followed up till December 2014. Clinical history was taken including possible aetiologies and predisposing causes searched. All age groups included except paediatric (<13 years). 117 consecutive cases were studied. Patients were classified by World Health Organisation (WHO) classification and prognosticated. Serum lactate dehydrogenase levels were taken on diagnosis. All patients were followed up till December 2014. All subsequently developing complications- both outpatient and inpatient along with deaths that occurred were studied. If abnormalities in blood count occurred, peripheral smear and bone marrow examinations were repeated. Various clinical parameters was assessed and their relationship to outcome and complications analysed by using Chi-square test to quantitative variables and Mann-Whitney U test to assess distributive variables. The statistical incidence and behaviour of complications in each of the subtypes of MDS was studied using Chi-square test and compared with the existing data.

Exclusion Criteria

Patients lost to follow up, patients whose pathological findings were not clear and patients aged less than 13 years.

OBSERVATIONS AND RESULTS

Patients were divided into two groups- those with presenting LDH less than 500 IU/L and those with LDH greater than 500 IU/L.

78 patients (66.7%) patients had a LDH less than 500 IU/L and 39 patients (33.3%) had an LDH value greater than

500 IU/L. Out of 16 patients with Refractory Anaemia (RA), 1 patient (6.3%) had a high LDH, none of the 5 patients with refractory anaemia with Ringed Sideroblasts (RARS) had a high LDH; 2 patients (10.5%) out of 19 patients with Refractory Cytopenia with Multilineage Dysplasia (RCMD) had a high LDH level. 11 patients (42.3%) out of 26 patients had Refractory Anaemia With Excess Blasts-1 (RAEB-1). 17 patients out of 30 patients (56.7%) who presented with refractory anaemia with excess blasts-2 had a high LDH. 3 patients out of 4 (75%) who had presented with undifferentiated subtype of MDS had a high LDH. 3 patients out of 11 (27.3%) with a diagnosis of CMML/MPD (chronic myelomonocytic leukaemia/myeloproliferative disease) had a high LDH levels. Two patients out of 6 (33.3%) had a diagnosis of hypoplastic MDS with high LDH. The Chi-square value was 0.01, which was significant (Figure 1).

There were 68 cases of complications during the study period. The complications that occurred in descending order of frequency included septicaemia, pneumonia, cellulitis, intracranial bleeding, congestive cardiac failure, abscess formation, malignant pleural effusions, mesenteric artery ischaemia, colitis, aplastic anaemia and recurrent urinary tract infections. Out of 39 patients who had a presenting high LDH levels, 37 patients (94.9%) had developed complications during the subsequent follow up period, while only 31 patients out of 78 patients (39.7%) who had a low LDH levels during presentation had developed complications during the same period. The Chi-square value was 0.00 and was significant (Figure 2).

There were a total of 31 deaths during the period of the study. Out of the 39 patients who had presented with a high LDH level, 20 patients had died during the period of follow up (51.3%) and only 11 patients had died out of 78 patients who had low LDH levels (14.1%). The Chi-square value was 0.00 and was significant (Figure 3).

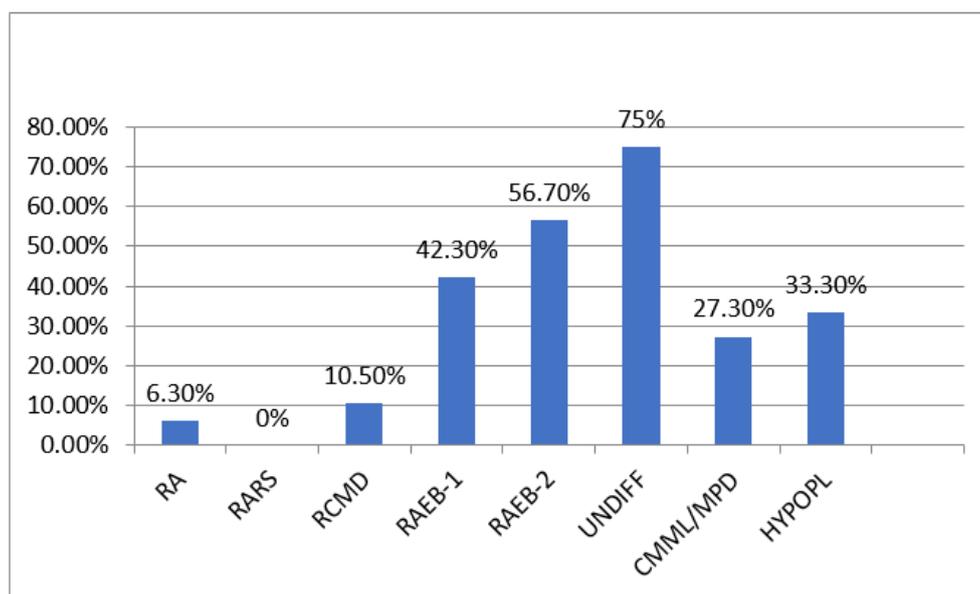


Figure 1. Shows the Proportion of Patients with High LDH in Each Different Subtypes of MDS (Percentage of Patients Having High LDH is Given in Y Axis)

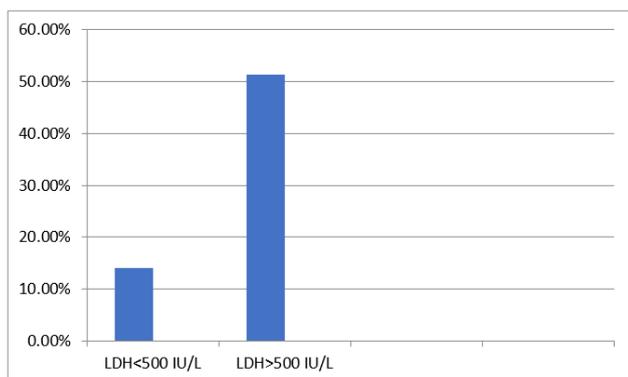


Figure 2. Percentage of Patients with LDH Value Less than 500 IU/L and Greater than 500 IU/L Developing Complications (Percentage of Complications in Y Axis)

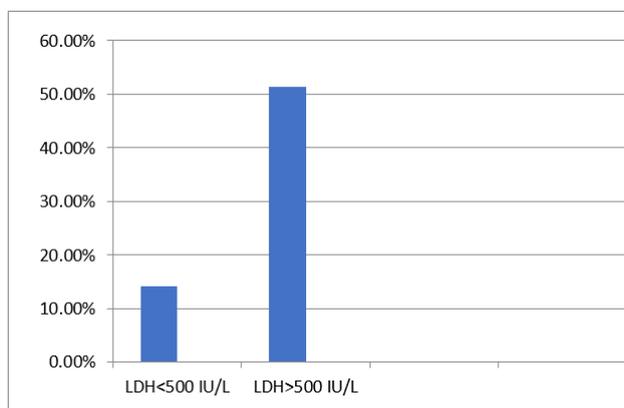


Figure 3. Percentage of Patients with LDH Value Less than 500 IU/L and Greater than 500 IU/L who had Died During the Study (Y Axis shows the Percentage of Patients who had Died)

DISCUSSION

Various studies had shown variable effect of LDH on the overall survival and prognosis of MDS patients. Sotirova T et al had done a retrospective cohort study in 2014, which showed that overall survival in MDS patients did not depend on age, transfusion dependence, haemoglobin level, LDH, and albumin, but instead depended on gender, FAB types, bone marrow blast percentage and serum levels of ferritin.³ Li W.W. in 2012 had found that LDH and B2 microglobulin levels had correlation with progress and prognosis of MDS independently.⁷ Mittelman M in 2010 had shown in a study that so called lower risk patients when they had a high LDH level had accelerated progression of the disease along with other parameters like male sex, old age, low absolute neutrophil count, low platelet count, high blood transfusion requirements, low haemoglobin levels, high ferritin and increased bone marrow fibrosis.⁸

Sotirova et al in a study published in 2014 of data of 108 patients found no association between serum LDH levels and prognosis in MDS.³ Rauw J et al had found positive correlation between serum LDH values and prognosis in MDS patients. Park MJ had also found after studying 149 patients in 2008, positive independent prognostic significance of serum LDH levels and MDS. A study from India by Varma N found wide variation between serum LDH and the different

FAB subtypes of MDS.¹⁰ Wimazal F had concluded in 2001 and 2008 after studying 221 MDS patients that serum LDH levels were very good as a serial followup measurement for studying prognosis of MDS and its probability of turning into acute leukaemia.^{11,9} AulC, Gattermann N et al in 1994 had also found that serum LDH was an important prognostic factor and it definitely had a survival value using the Dusseldorf score.¹²

In the present study, although a majority of patients with myelodysplastic syndrome (66.7%) had an LDH levels less than 500 IU/L, the undifferentiated subtype, RAEB-2 subtype and the RAEB-1 subtype had a statistically significant high LDH levels probably due to high cell turnover rate. So, high serum LDH levels were indirectly related to bad prognostic variants of myelodysplastic syndrome. In the present study, there appears to be positive correlation between LDH values and the complication rate of patients. A high LDH value predicts a poor prognosis in patients with myelodysplastic syndrome. This may be due to the high cell turnover in poor prognosis patients. A statistically significant correlation was seen between high LDH value and the frequency of death that occurred in the patients.

CONCLUSION

The lactate dehydrogenase levels at presentation had a positive correlation with high incidence of both outpatient and inpatient complications that the patients can have in the immediate future and also correlates with high mortality rate of the patient.

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