A Study of the Prognostic Significance of Serum Albumin 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). Multiple studies from the west have shown serum albumin levels at presentation to correlate well with prognosis of patients. Studies from India investigating the levels of serum albumin with prognosis of patients with myelodysplastic syndrome are scanty. The aim of this study was to investigate the relationship of serum albumin levels at presentation of patients and the consequent development of complications and death that occurred in the follow-up period of patients with myelodysplastic syndrome.

METHODS

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 albumin levels were taken on diagnosis. All patients were followed up till December 2014 and subsequently developing complications both outpatient and inpatient) along with deaths that occurred were studied.

RESULTS

Although, only 40.2% of patients with myelodysplastic syndrome had low serum albumin at presentation, the undifferentiated subtype, RAEB-2 subtype and RAEB-1 had a statistically significant low serum albumin levels. Of the 47 patients who had low serum albumin, 33 patients had developed complications during the course of the illness. Of the 70 patients who had normal serum albumin, 35 had developed complications, which was statistically significant.

CONCLUSIONS

A low level of serum albumin (<3.5 mg%) at presentation in cases of myelodysplastic syndrome was statistically associated with poor prognostic subtypes of myelodysplastic syndrome and in turn was associated with high levels of complications and mortality during the course of illness.

KEYWORDS

Myelodysplastic Syndrome, Serum Albumin

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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.[1,2] The clinical manifestations result from various combination of cytopenias- anaemias, leucopenias and thrombo-cytopenias. 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.[1] 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.

Serum albumin forms 50% of serum protein content and provides 75-80% of plasma colloid oncotic pressure. The major trafficking of albumin is through interstitium and lymphatics. Serum albumin transports various substances including bilirubin, fatty acids, metal ions, hormones and exogenous drugs. The normal serum albumin is 3.5 mg% to 4.5 mg%. The total body content of albumin is 300-500 grams. Serum albumin is synthesized from the liver at a rate of 15 grams per day and has a half-life of 21 days. It is degraded at a rate of 4% per day. Serum albumin levels depend on the rate of synthesis, liver cell secretion, distribution in body fluids and level of degradation. In addition, serum albumin is decreased in various acute and chronic inflammatory condition.[2,3] The mechanism postulated for low serum albumin in inflammation is by various cytokines like TNF, IL-6, causing high vascular permeability, high albumin degradation and TNF alpha mediated downregulation of albumin gene transcription.[2]

Decrease in serum albumin in various medical conditions by as low as 10 g/L causes mortality to increase by 137% and morbidity by 89%. The exact mechanism that causes low serum albumin to cause high mortality and morbidity is unknown. Even though the exact cause and effect is unclear, various postulates have been put forward like 1) low nutritional status causing poor prognosis 2) serum albumin can act as an antioxidant and transporter. A low value can interfere in these functions. 3) Serum albumin can act as a negative acute phase protein. That is low serum albumin represents high inflammatory states.[2,3]

Various prognostic indicators used in previous studies in myelodysplastic syndrome 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.[4,5,6,7,8,9] Multiple studies from the west have shown serum albumin levels at presentation to correlate well with prognosis of patients.[4,10,11,12,13] Studies from India investigating the levels of serum albumin with prognosis of patients with myelodysplastic syndrome are scanty. The present study is an attempt to investigate the presenting serum albumin levels to the subtype of myelodysplastic syndrome and the subsequently developing complications.

We wanted to study the relationship between serum albumin level of patients with myelodysplastic syndrome at initial presentation and its correlation with the various subtypes of myelodysplastic syndrome and the subsequent complications that may develop during the course of the illness.

METHODS

All clinically and histologically confirmed cases of MDS (Myelodysplastic syndrome) diagnosed in the Department of Medicine and Haematology, Calicut Govt. Medical College between July 2009 and June 2013 and followed up till December 2014 were studied.

- All age groups included except paediatric (<13 yrs.).
- Patients were classified by World Health Organisation (WHO) classification and prognosticated.
- All clinical features were studied along with it.
- Serum albumin levels were noted at presentation.
- Treatment was instituted depending on low, intermediate and high risk categories
- All complications that developed during the course of the disease was documented.
- Conditions pathologically simulating MDS like malnutrition, vitamin B12 and folic acid deficiency, tuberculosis, alcoholism, drug abuse, toxin exposure, prior chemotherapeutic therapy, prior radiotherapy and HIV infection were ruled out by history and investigations.

All patients were kept under follow up and subsequently developing clinical features with changes in blood count observed. If abnormalities in blood count occurred, repeat peripheral smear and bone marrow examinations were done**.** Serum albumin levels at presentation was documented and its relationship to outcome and complications analysed by using Chi-square test to quantitative variables and Man Whitney U test to assess distributive variables.

Exclusion Criteria

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

RESULTS

117 consecutive cases of Myelodysplastic syndrome were studied. The most common types of MDS according to

frequency were RAEB-2 (30 patients-25.6%), RAEB-1 (26 patients -22.2%), RCMD (19 patients -16.2%), RA (16 patients -13.7%), CMML/MPD (11 patients-9.4%), hypoplastic variety (6 patients -5.1%), RARS (5 patients-4.3%) and undifferentiated (4 patients-3.4%).

70 patients (59.8%) had serum albumin greater than 3.5 mg% while 47 patients (40.2%) had low serum albumin. (<3.5 mg%) at presentation.

The serum albumin was less than 3.5 mg% in 6.3% of RA(Refractory anaemia), 0% of RARS (Refractory anaemia with ringed sideroblasts), 21.1% of RCMD (Refractory cytopenia with multilineage dysplasia), 42.3% of RAEB-1 (Refractory anaemia with excess blasts), 73.3% of RAEB-2, 75% of undifferentiated type, 45.5% of CMML/MPD (chronic myelomonocytic leukemia/ myeloproliferative disorders) and 16.7% of hypoplastic variant. Of this 90% of RAEB-2, 61.5% of RAEB -1, 31.6% of RCMD, 45.5% of CMML, 100% of undifferentiated type had developed complications. The poor prognostic subtypes of MDS namely RAEB-1, RAEB-2 and undifferentiated type had statistically significant association with low albumin levels at presentation.

56 Patients out of 117 (47.8%) developed life threatening complications during the course of the follow up disease. The complications that occurred included septicaemia, pneumonia, cellulitis, intracranial bleed, congestive cardiac failure, abscess, malignant pleural effusion mesenteric artery ischemia, aplastic anaemia, colitis, recurrent urinary tract infection, transformation to acute leukemia and death. 32.5% had developed features of infections including septicaemia, 12% had developed intracranial bleed, 6.8% had developed congestive cardiac failure, 3.4% had developed aplastic anaemia and 1.7% had developed malignant pleural effusion. Septicaemia was found with an increased frequency in RAEB-2 and the undifferentiated subtype. There was a statistically significant increase in the prevalence of intracranial bleed in the undifferentiated subtype and RAEB-2. As expected hypoplastic subtype had a high prevalence of aplastic anaemia during the follow up period.

Of the 47 patients who had low serum albumin, 33 patients had developed complications during the course of the illness, while 14 of them did not. Of the 70 patients who had normal serum albumin, 35 had developed complications while the rest 35 did not. The Chi Square value was 0.02 and was significant.

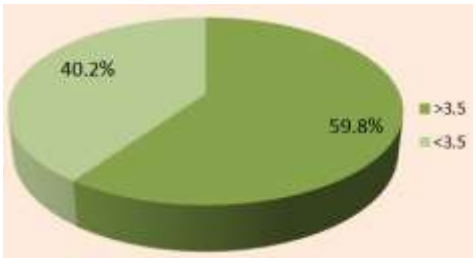

Diagram 1. Pie Diagram Showing the Percentage of Patients Having a Low Serum Albumin (<3.5 mg% to that of Normal Serum Albumin (>3.5 mg%)

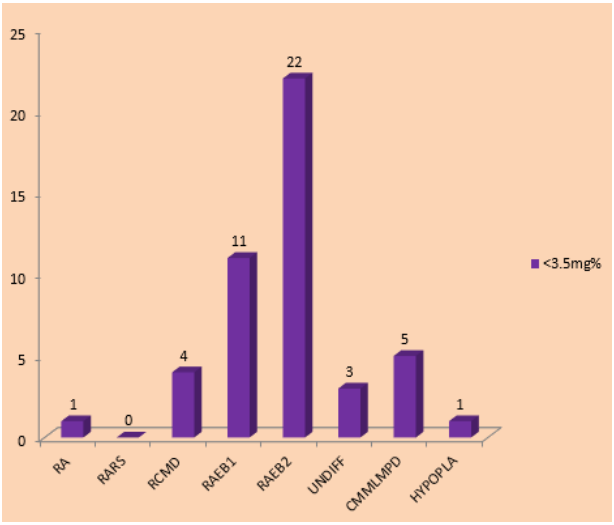

Diagram 2. X Axis Shows the Subtypes of MDS and Y Axis the Number of Patients with Low LDH

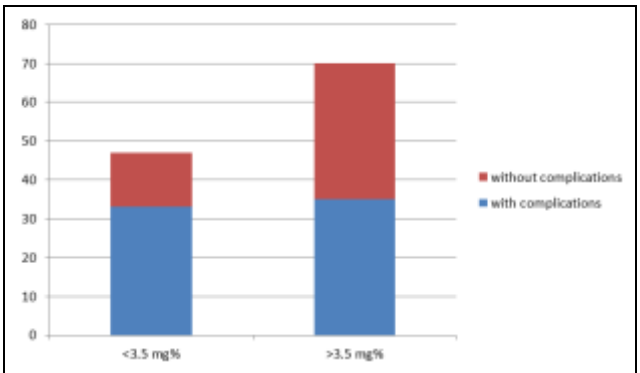

Diagram 3. Number of Patients with and without Complications in Low Albumin and Normal Albumin Groups

Mg%	Frequency	Percentage
>3.5	70	59.8
<3.5	47	40.2
Total	117	100

Table 1. Number of Patients Who Had Low Albumin and Normal Levels at Presentation

DISCUSSION

Serum albumin has long been used as a prognostic marker for various conditions due to its easy availability and its low cost. Jelinge ME has found that hypoalbuminemia is a strong predictor of 30 day mortality in patients admitted in medical ward.[4] Serum albumin levels have been also associated with prognosis of patients admitted in ICU in studies done by McClusky A in 1996.[10] Various solid tumour malignancies also have successfully prognosticated by using serum albumin as in the studies done by Kin SW for head and neck cancers.[11] Snipelisky D and colleagues have found that serum albumin can be used as an independent prognostic indicator for pulmonary artery hypertension.[12]

It has been established as a clear prognostic marker after stem cell transplantations by studies done by Ayuk F and colleagues even before 2011.[13] The study had concluded that low serum albumin levels at the time of diagnosis was associated with poor overall survival. Serum

albumin has also been shown to have prognostic significance in various lymphomas, especially the aggressive variants. Studies done by Gang A.O, Dava S, and Gupta A showed its benefit in Diffuse Large Cell lymphomas. 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, but instead depended on gender, FAB types, bone marrow blast percentage, serum albumin and serum levels of ferritin. In the above study, low serum albumin was described as a 'surrogate biomarker of poor prognoses in MDS even when adjusted for comorbidities. Gerds AT had shown that albumin was still a marker for poor prognosis in MDS. Sevindik OG and colleagues in 2015 had studied overall survival of MDS patients by categorizing them to three groups based on their albumin.[14] They found a significant correlation with serum albumin levels and overall survival in patients. Komrokji RS had also found in 2012 that hypoalbuminemia is an independent prognostic indicator for MDS.[15,16] Various studies of prognostic models in myelodysplastic syndromes have also taken note of the importance of serum albumin in the disease progress and activity.[17,18,19,20,21]

In the present study, a large number of patients (59.8%) had normal serum albumin in the study. Among the subtypes, RAEB-2 and the undifferentiated subtype had a statistically significant low levels of serum albumin and hence more complications. So it appears, in the present study that low serum albumin levels correlated with overall bad prognosis in myelodysplastic syndrome patients. The rate of complications that occurred during the course of the disease was positively correlated with low levels of serum albumin at presentation. The probable mechanisms as already mentioned may involve low nutritional status of the patient in unfavourable subtypes of MDS and consequent high complication rate. The second mechanism may be due to the lack of antioxidant effect of low serum albumin levels. The third mechanism of hypoalbuminemia may be due to high inflammatory states due to high frequency of complications.

CONCLUSIONS

A low level of serum albumin (<3.5 mg%) at presentation in cases of myelodysplastic syndrome was statistically associated with poor prognostic subtypes of Myelodysplastic syndromes. Low serum albumin was also associated with high levels of complications and mortality during the course of illness.

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