GENDER

Most of the western studies had found that there is a slight male predilection for myelodysplastic syndrome\textsuperscript{[28,29,30,31,32,33]} . A study from Hyderabad in Jan 2009 of 30 patients had found equal incidence of males and females\textsuperscript{[34]}. The data suggests no gender preference for the prevalence of myelodysplastic syndrome in this study.

AGE OF PRESENTATION OF MYELODYSPLASTIC SYNDROMES

Myelodysplastic Syndromes occurs most commonly in older adults with a median age at diagnosis in most series of $\geq65$ years and a male predominance. Onset of the disease earlier than age 50 is unusual with the exception of treatment-induced MDS . The risk of developing MDS increases with age\textsuperscript{[28,29,31,32,33,35,36,37,143]}. The observation from this study also indicates that the prevalence of myelodysplastic syndrome increases with advancing age. The apparent low prevalence in greater than 70 years indicates that either prevalence is low in the population who crosses 70 years or it may be due to the low numbers of patients in this group. There was also no statistically significant relationship between age and the different subcategories of myelodysplastic syndromes. From the data from our studies, it seems that our population had onset earlier that western population and most of our patients have onset between 50 and 69 years of age in contrast to western data which showed a significant incidence after 65 years of age . In subdividing different types of MDS all except undifferentiated category show the above pattern and in undifferentiated category, they are equally distributed in all age groups.
INCIDENCE OF MYELODYSPLASTIC SYNDROME IN PATIENTS TAKING ALCOHOL

Studies show varying and contradictory role of alcohol intake in the occurrence of myelodysplastic syndromes\textsuperscript{[43,141]}. According to a cohort study conducted in the United States in 2009 involving 471799 patients, alcohol was not found to be a significant etiologic factor in myelodysplastic syndrome development. Another study in 2008 from the Anderson Cancer Center found no clear evidence for the etiology of alcohol intake, although it found a positive correlation with acute leukemia\textsuperscript{[40]}. A study from China found positive correlation with alcohol intake\textsuperscript{[41]}. Another study from Pittsburg that was published in 2009 had also found no correlation with alcohol intake and MDS\textsuperscript{[42]}. A study done in the university of Texas in 2005 found a protective benefit of consuming alcohol with the incidence of MDS\textsuperscript{[38]}.

\textit{Most of the patients in the study had not consumed alcohol. All the patients who took alcohol were males. No obvious relationship was seen between alcohol consumption and the prevalence of myelodysplastic syndrome. The difficulty in interpreting the data may be due to the low number of patients who had taken alcohol.}

THE RELATIONSHIP OF TOBACCO AS A RISK FACTOR FOR MYELODYSPLASTIC SYNDROME

Data from large cohort study of 471799 patients in the US, done in 2009, implicated smoking a risk factor for myelodysplatic syndrome\textsuperscript{[39]}. Another lifestyle study of MDS done from M.D.Anderson Cancer Center in 2008 also
implicated smoking as a risk factor for MDS\textsuperscript{40}. A study done on a cohort of Chinese patients in 2011 found positive association of smoking with RAEB-1 and RAEB-2 subtypes of myelodysplastic syndrome\textsuperscript{41}. Another study from the United States which appeared in 2010, also showed positive correlation with smoking\textsuperscript{44}. In 2009 another study from Pittsburg also showed positive correlation of smoking to incidence of RA and RARS\textsuperscript{42}.

*The observations from the present study indicated that there is no apparent relationship to the prevalence of myelodysplastic syndrome to the intake of tobacco or its products*

**RELATIONSHIP OF INCIDENCE OF MYELODYSPLASTIC SYNDROME TO EXPOSURE TO FERTILISERS/PESTICIDES**

Myelodysplastic syndrome has been associated with environmental factors (eg, exposure to chemicals, particularly benzene, radiation, tobacco, or chemotherapy drugs)\textsuperscript{39,45,144,137}. A study that came from KEM medical college Mumbai in 2009 found no relation to chemicals or pesticides\textsuperscript{51}. Another study which appeared in the American journal of Epidemiology in 2009 indicted pesticides to myelodysplastic syndrome\textsuperscript{39}. In 2008 the study from M.D.Anderson Cancer center found that pesticides and chemical exposure for 15 years increased the incidence of myelodysplastic syndrome by 10 fold. Ling Gu and colleagues found independent association of benzene, pesticides and herbicides in a population of Chinese patients associated with myelodysplastic syndrome\textsuperscript{54}. Again positive association with benzene was found by Michael Sekeres in 2010 by taking data from 4514 patients\textsuperscript{44}.

*Our data showed that the exposure to fertilizers or pesticides had no obvious relationship to the prevalence of myelodysplastic syndrome.*
RELATIONSHIP OF EXPOSURE TO PRIOR CANCER CHEMOTHERAPY AND ANTITUBERCULUS THERAPY TO THE PREVALENCE OF MDS

M. Sekeres in 2010 found a positive correlation between prior cancer chemotherapy or radiotherapy and the incidence of MDS[44]. Other studies have also shown a positive correlation between prior chemotherapy or radiotherapy or both and the incidence of myelodysplastic syndrome. No major studies appears to have been done probing the relationship of antitubercullos therapy and the prevalence of myelodysplastic syndrome. In our study, only 2 patients had prior exposure to chemotherapy and the association was not significant.

The number of patients in the study who took previous cancer chemotherapy was too low to draw any meaningful conclusions regarding its relationship to myelodysplastic syndrome. No relationship was seen between people who took antitubercullos therapy and the prevalence of myelodysplastic syndrome.

RELATIONSHIP OF EXPOSURE TO AYURVEDIC AND HOMEOPATHIC MEDICATION AND MDS

In the study by Ling Gu in 2011, they showed a positive association between intake of traditional Chinese herbs and the incidence of MDS[41]. No studies have been done correlating the exposure to Ayurvedic and Homeopathic medications to MDS previously. Although many patients had a history of exposure to Ayurvedic drugs, due to the low number of patients, no definite conclusions could be drawn from the data. More studies need to be done in this context.
CORRELATION BETWEEN MDS INCIDENCE AND CHRONIC MENTAL STRESSORS

Although studies of mental stressors in patients after diagnosis of myelodysplastic syndrome are available, no major studies have been undertaken probing the etiological correlates of chronic psychological stressors. A study from France which appeared in Leukemia Research in 2011, found positive correlation between prior mental stressors and development of MDS\textsuperscript{52}.

We had looked into a 3 year retrograde history of chronic mental stresses, lasting greater than at least six months, in the patients as disclosed by the patients/relatives. 48 patients (41\%) had chronic psychological stress interfering in their day to day activities, at least 3 years prior to the diagnosis of the disease.

The data suggests that chronic exposure to psychological stressors had a definite effect on the prevalence of myelodysplastic syndrome, affecting 41\% of the patients. There was no statistical difference between chronic psychological stressors in the different subtypes of myelodysplastic syndrome. Further studies using control population are needed in this area to draw a definite etiological correlation between chronic psychological stressors and the development of myelodysplastic syndromes.
CORRELATION BETWEEN INCIDENCE OF MDS AND DIET - RELATION TO VEGETABLE AND FRUIT INTAKE

The study by Xiaomei Ma and Lim.U in 2009 had found no correlation between vegetable intake and the incidence of myelodysplastic syndrome. The 2008 study from M.D. Anderson center had looked into the role of diet and found to be inconclusive. Otherwise not many studies could be seen exploring the role of diet in the development of MDS. No studies from India examining the etiologic role of Indian diet could be found from the existing literature. A study by Vieira AR et al which is currently appearing in Annals of Oncology in September 2015 says that the current evidence from prospective studies is consistent with a protective role of fruit and vegetables in lung cancer aetiology. Similar effects may occur in myelodysplastic syndrome also. Another study by Liu P et al from China published in August 2015 concludes that diets rich in vegetables and adequate amount of milk reduce the risk of adult leukemia, whereas diets preferring fat, deep-fried, and smoked foods increase the risk in Chinese populations.

This study indicates that a large number of patients (82.9%) had a history of low vegetable intake. This may result in low levels of vitamins and essential nutrients in the patients. This may be causally related epigenetically or it may result in increasing levels of complications the patient may have. There was no significant differences in vegetable consumption and the various subtypes of myelodysplastic syndromes.
Similar was the observation regarding fruit intake also. 90.6% of patients had low consumption of fruits. The observations also showed that a very few percentage of patients (9.4%) had relatively good fruit consumption. This may result in low levels of antioxidants and may be epigenetically related to the initiation of oncogenesis\textsuperscript{[53,138,139]}. Further studies and research are needed in this area to examine the possible relationship between antioxidants in fruits and diet and the prevention of initiation of oncogenesis by epigenetic mechanisms in myelodysplastic syndromes.

**THE CORRELATION OF INCIDENCE OF MDS AND DIET- INTAKE OF FISH, MEAT AND FRIED/FAST FOOD INTAKE**

The study by Ma X. in 2009, which appeared in the American Journal of Epidemiology, had found no correlation between intake of meat, fish or fried foods\textsuperscript{[39]}. Dietary deficiency of folate was found to alter epigenetic alteration and an increase in the incidence of leukemias according Mary Beth Terry, Lissette Delgado et al from Colombia university, New York which appeared in Epigenetics in 2011\textsuperscript{[53]}. Various studies by J H Weisburger, Sugimura T. and others had pointed to various mutagens found in fried food and their role in epigenetically modifying the genome in initiating oncogenesis\textsuperscript{[57,48,138,139]}. Loprieno N et al in 1991 had experimentally caused potentially carcinogenic genetic mutation in bacteria and hamster cells by treating it with cooked meat chemical extracts\textsuperscript{[49]}. Knize MG. had identified several heterocyclic amines in cooked meat, which are known to cause cancer\textsuperscript{[50]}. A study by Liu P et al from China published in August 2015 concludes that diets rich in vegetables and
adequate amount of milk reduce the risk of adult leukemia, whereas diets preferring fat, deep-fried, and smoked foods increase the risk in Chinese populations\textsuperscript{[56,138,140]}.

*The data from the present study suggests that people who took more than three servings of fried fish a week, had a high prevalence of myelodysplastic syndrome. The relation of fish consumption to various subtypes of myelodysplastic syndrome was not statistically significant.*

*The data from the present study showed that a large amount (89.7\%) of patients had consumed meat or meat products in moderate to high amounts. There was no statistical difference in meat consumption among various subtypes of myelodysplastic syndrome. The high consumption of intake of fried meat may result in high intake of various heterocyclic amines and mutagens like 2-amino-3-methylimidazo[4,5-f]quinoline (IQ), which may possibly act epigenetically to initiate oncogenesis. Further studies are needed in this regard\textsuperscript{[46]}.*

**CORRELATION BETWEEN PROXIMITY TO HIGH VOLTAGE ELECTRICITY LINE (110KV) AND PREVALENCE OF MDS**

A study from China in 2007 studied the effects of living close to (100 meters) from high voltage electrical line and the incidence of de novo myelodysplastic syndrome found a positive correlation\textsuperscript{[54]}. Another study from Great Britain in the British journal of Cancer found that there no correlation between blood malignany and living near a high voltage line and concludes that
the apparent correlation was due to changing population\textsuperscript{[57]}. We had 9.4% of people living near a high voltage electric line.

\textit{Even though the relationship between living near a high voltage electricity line and the prevalence of myelodysplastic syndrome was not found to be significant, it may be difficult to interpret due to the very small number of cases in this category.}

**RELATIONSHIP TO FIRST AND SECOND DEGREE RELATIVES DIAGNOSED WITH CANCER**

The study by S.S. Stromm, Y. Guo et al in 2005 had found a significant association of other blood malignancies in first degree relatives of patients with MDS\textsuperscript{[38]}. No relation to first or second degree relatives was found in the study of Mikkael A. Sekeres in the study in 2010\textsuperscript{[44]}. The study had showed a clear relationship between myelodysplastic syndrome prevalence and the prevalence of a first degree relative of the patient having a different cancer. This relationship was not found in second degree relatives of the patients. This may be due to common environmental factors or genetic factors. There was no increased association of first degree relatives and any specific subtype of myelodysplastic syndrome.

**CORRELATION OF MDS PREVALENCE AND PHYSICAL ACTIVITY**

In the study by Xiaomei Ma and colleagues in 2009, they found incidence of MDS had no relation to physical activity\textsuperscript{[39]}. Another study by Edward Giovannucci found that although some cancers such as colon and
stomach cancers clearly showed a relationship\cite{59}. Further studies are needed to link blood malignancies to physical activity.

Patients having ordinary and less than ordinary physical activity included 91 patients (77.8\%) out of 117 patients. This shows that most of the patients had low to ordinary physical activity. Patients who did good physical activity had a low prevalence of myelodysplastic syndrome. There was no difference in association of physical activity with any subtype or subtypes of myelodysplastic syndrome. This observation is suggestive of a possible protective role of exercise in preventing these group of disorders, but further studies are needed in this direction.

ASSOCIATION OF MYELODYSPLASTIC SYNDROMES WITH AUTOIMMUNE DISORDERS.

Previous studies had shown a definite relationship between myelodysplastic syndrome and autoimmune disorders\cite{142}. A study by Amanda Wilson from Boston in 2009 found no evidence of autoimmune phenomenon in 87.9\% of the patients\cite{60}. The incidence was not statistically significant. The inclusion criteria for the onset of autoimmune diseases was 2 years prior to the onset of MDS. The commonest autoimmune disease was psoriasis followed by rheumatoid arthritis. Another study by Neelam Shah from Ahmedabad in 2009 showed 13.33\% of the patients having features of autoimmune phenomenon with the majority having rheumatoid arthritis\cite{61}. Martin stern from Italy had found in 2007 that there was significant association between MDS and autoimmune disorders like autoimmune hemolytic anemias and immune
thrombocytopenic purpura\[63\]. 20% had also developed features of aplastic anemia. Another study by Omwe al Ustwadi et al had found an incidence of 20% of patients with MDS developing autoimmune phenomenon\[62\]. The most common was vasculitic syndromes (40%) followed by seronegative arthritits (27%) and neuropathy(24%). Another study by Saif MV and Hopkins JL had found 10% of MDS patients developing autoimmune phenomenon, with most common having vasculitis followed by arthritis\[63\]. A study by Bouali F et al in 2005 found nearly 40% percent of patients with MDS developing autoimmune phenomenon\[64\]. Thornston Braum in 2013 had found that nearly 30% of the patients had developed autoimmune diseases\[65\]. The most common autoimmune disorders were polyarthritits (60%) followed by vasculitis.

In the present study, there was a significant association between the prevalence of primary myelodysplastic syndrome and the prevalence of all cause autoimmune disorders. (found in 44.44% of patients) followed by arthritis . The most common autoimmune disorder found was autoimmune hemolytic anemias. There was no statistical relationship between autoimmune disorders and any specific subtype of myelodysplastic syndrome. All the autoimmune symptoms developed at least 3 months after the diagnosis of myelodysplasia so as to prevent inclusion of secondary myelodysplastic syndrome due to autoimmune diseases. Even though most studies had shown autoimmune phenomenon associated autoimmune disorders, our study population showed a high frequency of autoimmune phenomenon. Autoimmune hemolytic anemia was also high in our population. It also validates some of the
observations seen clinically that immunosuppressives and immunomodulators show benefit in treating myelodysplastic syndrome.

**CORRELATION BETWEEN THE DIFFERENT PRESENTING SYMPTOMS AND SIGNS OF MYELODYSPLASTIC SYNDROME**

In myelodysplastic syndromes, anemia is the most common cytopenia and can manifest as fatigue, weakness, exercise intolerance, angina, dizziness, cognitive impairment, or an altered sense of well being\[146\]. Less commonly, infection, easy bruising, or bleeding precipitate a hematologic evaluation. Systemic symptoms such as fever and weight loss are uncommon, and generally represent late manifestations of the disease or its attendant complications\[67,68\].

Physical findings in MDS are non-specific. Sixty percent of patients are pale (reflecting anemia), and 26 percent have petechiae and/or purpura (due to thrombocytopenia). Hepatomegaly, splenomegaly, and lymphadenopathy are uncommon. Sweet's syndrome (neutrophilic dermatosis) may be the presenting symptom.

S. Tyagi in 2011 from AIIMS, New Delhi had studied 31 cases had found that fatigue was the most common symptom (48.3%) followed by weight loss (42%) and bleeding (22.6%)\[69\]. Anemia was found in 93.5% of the patients. Hepatosplenomegaly was found in 19.3%.

Fatigue was found in 63.3% of cases by Nilam Shah from Ahmedabad in 2009\[61\]. Weight loss was found in 30% of patients, generalized weakness in 16.6%, bleeding was found in 10%. Splenomegaly was found in 6.6% of
patients; 10% of patients had hepatomegaly; Efficace F, et al in 2015 had found that three most important presenting symptoms of patients with MDS are fatigue (92%), dyspnoea (63%) and pain (55%)\(^{[70]}\).

In our study, fatigue was the most common symptom present in patients with myelodysplastic syndrome followed sequentially by dyspnea on exertion, significant weight loss, fever, syncope and visual symptoms. In respect to individual symptoms, fatigue was the most common symptom in RCMD, dyspnea on exertion in the undifferentiated category, bleeding in the undifferentiated type, weight loss the most common symptom in RA, fever in RAEB-2, edema in the undifferentiated category, bone pain in CMML/CPD, and anorexia in CMML/CPD variant. Out of this, bone pain found in CMML/CPD was only statistically significant.

This study indicates that hepatomegaly or splenomegaly was not significantly seen in myelodysplastic syndrome. Among the subtypes of myelodysplastic syndrome, hepatomegaly was seen most common in the undifferentiated variant and splenomegaly was mostly seen in CMML/CPD.

THE CORRELATION BETWEEN HEMOGLOBIN LEVEL, ESR, TOTAL WBC COUNT AND PLATELET COUNT TO MYELODYSPLASTIC SYNDROME

In the study by S. Tyagi from AIIMS, the mean hemoglobin level was 6 g%\(^{[69]}\). 71% of patients had thrombocytopenia with mean platelet count of 90000/mm\(^3\). In the study by Nilam Shah, hemoglobin less than 10g % was found in 70% of the patients and thrombocytopenia in 53.3% of the patients\(^{[61]}\). The average platelet count was 30000/mm\(^3\). Chen YD had shown that severe
thrombocytopenia had an adverse prognostic significance in patients with myelodysplastic syndrome\(^7\). Otherwise there were not many studies in the correlating on peripheral blood picture and ESR levels in myelodysplastic syndrome.

*In the present study, the hemoglobin levels were low in an overwhelming number of patients (96%). This was comparable to most of the previous studies done\(^1\). Previous studied done from India also showed low hemoglobin levels. Among the subtypes of myelodysplastic syndrome, CMML/CPD had relatively high percentage of patients with hemoglobin greater than 10 gm\%, while hypoplastic variant had very few patients with hemoglobin levels greater than 10 gm\%.*

*A vast majority of patients (89.7\%) in our study had an ESR greater than 50 mm in one hour and within that group more than half of patients (55.6\%) had a significantly high ESR of more than 100 mm in one hour. Of the subtypes of myelodysplastic syndrome, very high ESR- greater than 100 mm in one hour was significantly associated statistically with RAEB-2 subtype and hypoplastic variant. There were not many studies that concentrated on ESR and prognosis of myelodysplastic syndrome. The very high ESR seen in the worse prognostic variants of myelodysplastic syndrome seen in our studies may be due to very low hemoglobin seen in these variants or due to recurrent infections these patients had.*

*Although the total WBC count in the case of myelodysplastic syndromes as a whole was not particularly significant with 48.7\% of patients having total*
WBC counts in the range of 1000-4000 /mcL, a statistically significant number of patients with CMML/CPD had a high total WBC count of greater than 12000/mcL and a significant number of patients with the hypoplastic variant of myelodysplastic syndrome had low total WBC count of less than 4000/mcL. The statistics here was comparable to previous studies which also showed that nearly half the patients had leucopenia.

A vast majority of patients (71.8%) with myelodysplastic syndrome had thrombocytopenia as defined by platelets less than 100000/mcL. Among the subtypes of myelodysplastic syndrome, a statistically significant number of patients with RARS had a normal platelet count (1 lakh to 4 lakh per mcL) and none of the undifferentiated type had platelet had greater than 100000 /mcL. A statistically significant number of patients with hypoplastic subtype and the RAEB-2 subtype had very low platelet count defined by less than 25000/mcL. 9 patients (7.69%) had thrombocytosis. Previous studies from India had also shown thrombocytopenia in nearly half of the study population, even though literature from western countries says that thrombocytopenia was not a major feature of myelodysplastic syndrome. Previous study from China had also shown thrombocytopenia, associated with bad prognosis.[72]

THE DISTRIBUTION OF RED CELL DISTRIBUTION WIDTH IN MYELODYSPLASTIC SYNDROME.

The red cell distribution width (RDW) is often increased reflecting the presence of increased variability in red cell size, also called anisocytosis. In a study by Buckstein R, Jang K et al, from Ontario, age, MCV,LDH and RDW
were independent predictive factors for MDS\cite{73}. Morbidity Rauw J had also had also described age >65 years, MCV, RDW and LDH were independent predictive factor for the diagnosis of MDS and was used as a scoring system for 313 individuals\cite{74}. There were no major studies concentrating on the distribution of presenting RDW of patients with myelodysplastic syndromes.

*In the present study, a large majority of patients (88.9\%) with myelodysplastic syndrome had a high RDW (defined as greater than 15). The distribution of RDW among the subtypes of myelodysplastic syndrome was not statistically significant.*

**THE RELATIONSHIP OF MEAN CORPUSCULAR VOLUME (MCV) TO THE PREVALENCE OF MDS**

Anemia is almost uniformly present and is generally associated with an inappropriately low reticulocyte response. The mean corpuscular volume (MCV) may be macrocytic (\(>100\) femtoliters) microcytic (\(<80\) femtoliters or normal\cite{147}; 80-100 femtoliter). In a study by Buckstein R, Jang K et al, from Ontario, age, high MCV, LDH and RDW were independent predictive factors for MDS\cite{73}. Rauw J had also had also described age >65 years, MCV, RDW and LDH were independent predictive factor for the diagnosis of MDS and was used as a scoring system for 313 individuals\cite{74}. Li WW et al in 2012 from China found prognostic significance for LDH and beta 2 microglobulins but not MCV\cite{75}. Wang H in 2010 found that high MCV had good prognostic prediction and survival\cite{76}.
A majority of patients of myelodysplastic syndrome in this study had a normal MCV. MCV alterations in the various subtypes of myelodysplastic syndrome was not found to be statistically significant, although undifferentiated type and the hypoplastic subtypes showed a high MCV.

THE CORRELATION BETWEEN LACTATE DEHYDROGENASE AND PROGNOSIS IN MYELODYSPLASTIC SYNDROME

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, hemoglobin level, LDH, and albumin, but instead depended on gender, FAB types, bone marrow blast percentage, and serum levels of ferritin\textsuperscript{[57]}. Li W.W. in 2012 had found that LDH and B2 microglobulin levels had correlation with progress and prognosis of MDS independently\textsuperscript{[75]}. MittelmanM 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 1) male sex, 2) old age, 3) low absolute neutrophil count, 4) low platelet count, 5) high blood transfusion requirements, 6) low hemoglobin levels, 7) high ferritin and 8) increased bone marrow fibrosis\textsuperscript{[78]}.

In this study, although a majority of patients with myelodysplastic syndrome (66.7\%) had an LDH levels not highly elevated, 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.

THE DISTRIBUTION OF SERUM ALBUMIN IN THE PATIENTS WITH MYELODYSPLASTIC SYNDROME

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, hemoglobin level, LDH, and albumin, but instead depended on gender, FAB types, bone marrow blast percentage, and serum levels of ferritin\(^{[77]}\). Gerds AT had shown that albumin was still a marker for poor prognosis in MDS\(^{[79]}\). Sevindik OG and colleagues in 2014 had studied overall survival of MDS patients by categorizing them to three groups based on their albumin\(^{[80]}\). 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\(^{[81]}\).

*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 DISTRIBUTION OF VARIOUS SUBTYPES OF MYELODYSPLASTIC SYNDROMES.

The WHO estimated number of patients with different types of MDS are RAEB-1 (40%), RCMD (30%), RA (20%), RARS (3-11%), RAEB (2-7%), Unclassified (unknown) and 5 q- (very rare). In the study by Tyagi S from AIIMS in 2011, the majority of cases were RCMD (48.4%) followed by RAEB-2 (16%), RA (16%) and then RAEB-1, RCMD, unclassified and one case of 5q- type \[69\]. In the study by Nilam Shah from Ahmedabad, the majority type was RA followed by RAEB-2 \[61\]. Another study by Bauduer F et al from France in 1998 had found that the frequency of RA was 31%, RAEB-1 was 24%, RARS was 23%, RAEB-2 was 24%, CMML was 11% and unclassified was 11\% \[82\]. Intragumtornchai T et al had done a retrospective analysis from Thailand in 1998 and the majority of cases had RA and RARS comprising 54.7% of cases, RAEB 23.1%, CMML, 9.4%, RAEB-t -12.8% of cases \[83\].

In the present study, 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%), undifferentiated (4 patients-3.4%).

The most common subtype of myelodysplastic syndrome seen in the present study was RAEB-2 followed by RAEB-1 and the least common was the undifferentiated type. The significance of the result is that in our population we have more frequency of the bad prognostic variant of RAEB-1 and RAEB-2.
than western countries and consequently the frequency of complications during the course of the disease may be high compared to western countries and North Indian states.

THE CORRELATION OF MDS AND ITS TYPES TO THE FREQUENCY OF HOSPITAL ADMISSIONS ANNUALLY

No major study was done previously probing the relation of the type of myelodysplastic syndrome and the frequency of hospitalization.

In the current study, 35% of the myelodysplastic syndrome patients had 4-12 hospital admissions per year, on the average and 58.9% of patients had an average admission rate of less than once per month. A statistically significant high admission rate was found in RAEB-1 and RAEB-2 subtypes. 23% of RAEB-1 patients and 49.9% of RAEB-2 subtype patients had an average hospital admission rate of greater than once per month. The increased number of hospital admissions per year (10-14 times per year) was statistically significant in RAEB-2 subtype and minimum in the RA subtype. The frequency of hospital admissions were proportional to the complications developed by the patient during follow up and also to the cytopenias, the patients developed as the disease progressed. Hence the high frequency of hospital admissions in the RAEB-2 subtype of myelodysplastic syndrome.

THE CORRELATION OF MONTHLY BLOOD AND BLOOD PRODUCT ADMINISTRATION TO MDS AND ITS TYPES

The standard indication of blood transfusion done is when hemoglobin drops below 8 g% in otherwise normal patients and below 10 g% in patients
with coronary heart diseases. In a study in 2006 by Lodovico Bladucci found that frequent blood transfusions cause significant clinical complications such as transfusion reason, infections and iron overload\[84\]. In this study of 50 patients of MDS, 80% had transfusion related complications. Iron chelation was done after 20 transfusions or who reached ferritin levels of 155 mcg/L. Mortality was increased in direct proportion to the frequency of transfusion.

In a study by Scott D. Ramsey, Vox sang in 2012, 94% of the patients had received blood transfusions and 8% had received platelet transfusions\[86\]. The average units of blood or blood products received was 8-22 units per month. The most common types of MDS patients who received blood was MDS-unspecified (44%) followed by 39% of RAEB and 32% of RA. Patients who receive more than 20 units of blood were RA or RAEB, older, and males. There was no clear increasing or decreasing trend with time.

The inverse relation between survival and the need for blood transfusions was also given by Goldberg et al in 2010 and Malcovati L in 2007 and 2005\[88,89\]. Gupta in 1999 from Minneapolis had studied 50 patients of MDS and had found that 82% of the patients required blood/blood product transfusion. The blood products required included 8-88 units of packed RBC, (mean 24), platelets 24-480 units (mean 94).

In the current study, an average of 1-5 units of blood transfusion per month was needed in 49 patients (41.9%). A statistically significant high frequency of blood transfusion was seen in RAEB-2 subtype. The least frequency of blood transfusion need was seen in CMML/MPD subtype of
myelodysplastic syndrome. This may due to the relatively high hemoglobin values seen in the CMML/MPD subtype. Due to the high levels of blast and increasing marrow replacement by blast cells, RAEB-2 had also an increased demand for blood PRBC transfusion.

THE FREQUENCY OF PATIENTS WITH MDS HAVING HIGH SERUM FERRITIN LEVEL

According to Li Y, Serum ferritin was not an independent prognostic factor in patients with MDS[75]. A Study by Remacha AF , Vellegas A, et al in may 2015 had shows that in patients presenting with MDS, 8.7% of the 263 patient had elevated serum ferritin as defined by greater than 1000 mcg/L at diagnosis, they initially had required 2.8 +/- 3.9 PRBC per month[90]: Over the course of the illness, 36.1% of patients had serum ferritin greater than 2500 mcg/L. chelation treated patients had shown better prognosis. Sotirava had also found inverse relationship of serum ferritin and overall survival[77]. Zgang Y had found that 18 out of 35 patients had developed iron overload with high serum ferritin over the course of treatment[91].

In the present study, although only 25.6% of the total number of patients had a high serum ferritin value, (>1000 mcg/L) after 1 year of follow up, .a statistically significant frequency of high serum ferritin was found for RAEB-2 subtype, probably due to frequent blood transfusions needed in this group. The least frequent was found for CMML/MPD and undifferentiated subtype due to less need for transfusion.
RELATIONSHIP OF DIFFERENT COMPLICATIONS TO THE TYPES OF MDS.

Patients with MDS have a high incidence of infections related to neutropenia and granulocyte dysfunction (e.g., impaired chemotaxis and microbial killing) and infection is the principal cause of death in patients with MDS. Bacterial infections predominate, with the skin being the most common site of infection. Fungal infections are not uncommon. Although viral, and mycobacterial infections can occur, they are rare in the absence of concurrent administration of immunosuppressive agents. Infections may also be occult, respond poorly to antibiotics, and resolve slowly. Bleeding in a patient with MDS may be due to thrombocytopenia, other platelet disorders, or disorders of coagulation. Common skin complications include echymosis, various skin infections and sweet’s syndrome.

Titmarch GJ et al in 2014 had found that the most common infections found in patients with MDS were respiratory tract infections like bronchitis, pharyngitis, pneumonia, sinusitis followed by cystitis, cellulitis and gastroenteritis.[97] A metaanalytic study of bleeding as a significant clinical problem in patients with MDS was not found to be true by Escourt LJ et al in 2014.[98]

In the present study, 47.8% of patients had developed one or more life threatening complications during the course of the disease. 32.5% had developed features of infections including septicemia, 12% had developed intracranial bleed, 6.8% had developed congestive cardiac failure, 3.4% had
developed aplastic anemia and 1.7% had developed malignant pleural effusion. Septicemia 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.

THE INCIDENCE OF TRANSFORMATION OF MDS INTO ACUTE LEUKEMIA

Patients with MDS have a variable rate of transformation to acute myeloid leukemia (AML). Indeed, the distinction between MDS and AML is itself arbitrary, as patients with 20 to 30 percent blasts are considered to have MDS by French-American-British (FAB) criteria, but AML by the World Health Organization (WHO) classification.

Marisavljevic D et al in 2014 had found that 28.92% of patients less than 50 years had progressed to acute leukemia and 22.02% of patients greater than 50 years had progressed to acute leukemia [99]. Percentage of blasts in bone marrow correlated with the rate of transformation to acute leukemia. There was a 20% transformation to acute leukemia in a study from Singapore in 1990 of 20 patient of MDS [100]. A study in 1985, by Vallespi T, by the FAB classification found that there was a 40.5% transformation to acute leukemia [101]. In a study from Thailand by Itragumtornachi T et al found that 25% had transformed to acute leukemia [102].

In the present study of all the types of MDS combined, 28 patients (23.9%) out of 117 had transformation to acute leukemia. About 75% of patients in undifferentiated type, 50% of patients in RAEB-2, 25% of RA,
% of RAEB-1 and 5.3% of RCMD had transformed into acute myeloid leukemia, while none of the others did. This was significant for RAEB-2, followed by RA and RAEB-1.

In the present study, 23.9% of patients had transformation to acute leukemia. A statistically significant number of patients with undifferentiated subtype and the RAEB-2 subtype had transformation to acute leukemia. The high transformation in RAEB-2 was expected due to the high levels of blasts seen in the bone marrow and consequent transformation. In the undifferentiated type, the probable reason for increased transformation to leukemia is unknown.

THE INCIDENCE OF DEATH IN MYELODYSPLASTIC SYNDROME

The mortality in the study by Sotirova T et al was 36.1% in 108 patients diagnosed with MDS[77]. Followed up for 3 years Muller Berndorff H et al in 2006 had found that 75% of patients had died in the span of 3 years[149]. In the study by Wei J et al in 2008, in 5 years, 52.38% had died out of 63 patients with MDS[106]. In a study by Jacobs RH et al in 1986, out of 49 patients with MDS, the median 5 year survival for CMML, RAEB and RAEB-T were 25, 21 and 16 months respectively[107].

In the present study, 32 Patients had died (27.4%) during the study period of 4 years. This includes all the various subtypes of MDS. Death occurred in 55.2% of RAEB-2, 33.3% of hypoplastic type, 26.9% of RAEB-1, 25% of undifferentiated, 18.2% of CMML/MPD, 12.5% of RA, 5.3% of RCMD and none of RARS, during the follow up period.
The observation shows that death was more commonly seen in a statistically significant proportion of patients with RAEB-2, hypoplastic type and RAEB-1 subtype. This may be due to increased number of blast cells in RAEB-1 and 2 subtypes and the high mortality due to infection in the hypoplastic variant. The cause of death was the high rate of complications that occurred with RAEB-2, RAEB-1 due to the increased blast burden of these subtypes. The complication and consequent mortality rate of hypoplastic variant was due to the increased frequency of cytopenias and consequent high rate of infections and systemic bleeding.

RELATION BETWEEN TRANSFUSION DEPENDENCE AND ALL CAUSE COMPLICATIONS

In a study from UK in 2014, Arch G. Mainous and Rebecca J Tanner had found that transfusion dependent patients had increased mortality\textsuperscript{103}. Remacha AF in may 2015 had published a paper in which he suggest that who are transfusion dependent without chelation had more organ complications and increased mortality\textsuperscript{104}. In our study, patients who had received an average of 0-1 unit blood transfusion had a complication rate of 39.3%, patients who had received an average of 1-5 unit transfusions per month had a complication rate of 53.1% and patient who received more than 5 units of blood transfusions per month had a complication rate of 77.5%.

The data showed that there was a statistically significant positive correlation between the complication rate of patients and the frequency of blood transfusions. This may be due to the high complication rate seen in
patients with increased cytopenias requiring frequent transfusions. It may also be due to the high iron overload that occurs in these patients and subsequent organ dysfunction.

**RELATION BETWEEN SERUM FERRITIN AND FREQUENCY OF BLOOD TRANSFUSION.**

Ashida T et al from Japan conducted a study published in 2013 which found that after receiving 20 units of more of packed red blood cells and blood had increased the value of ferritin more than 500 ng/ml in 90.8% of patients and more than 1000 ng/ml in 66.2% of patients\[^{108}\]. Delforge M et al in 2011 had conducted a study of 193 patients with MDS which showed the medial serum ferritin was 1550 mcg/L in patients who had received an average of 13.4 units of packed RBC during a 4 month period\[^{109}\]. Makeshova AB et al had found that out of 104 patients with acute leukemia, aplastic anemia and MDS, the average serum ferritin level was 2856 after receiving 20 RBC transfusions \[^{110}\]. Alessandrino EP et al has found that high serum ferritin was associated with increased mortality\[^{113}\]. In the present study, the ferritin value was high (>1000 mcg/l) in 10.7% of patients who received 0-1 units blood transfusions per month, 18.4% in patients who received 1-5 units blood transfusions per month, 45% in patients who had received greater than 5 units per month. All values were taken after one year of transfusions.

*As expected, the value of serum ferritin was found to be high in patients receiving frequent blood transfusions. Since the increased frequency of blood transfusions correlated well with the complications that the patients suffered,*
indirectly the complication levels were high in patients who had a high serum ferritin levels.

RELATIONSHIP BETWEEN FREQUENCY OF BLOOD TRANSFUSIONS AND DEATH IN MDS

Delforge M had found that patients who received more than 20 units of transfusion had serum ferritin greater than 1000 mcg/L and had 70% mortality rate\textsuperscript{111}. Park S had studied 318 patients with MDS having a serum ferritin level greater than 300 ng/ml and found no relationship to survival\textsuperscript{112}. Alessandrono EP et al has found that high serum ferritin was associated with increased mortality\textsuperscript{113}. Currently there are studies both supporting and refuting the role of chelating agents in patients with myelodysplastic syndrome\textsuperscript{144}.

In the present study there was a statistically significant positive correlation between the frequency of blood transfusion and the occurrence of death. This may be due to patients with poor prognosis having an increased demand for blood transfusions or due to increased accumulation of hemosiderin causing organ damages, increased complications and death.

THE CORRELATION BETWEEN PERIPHERAL BLASTS AND COMPLICATIONS OBSERVED

The correlation between bone marrow blasts and prognosis of MDS is well established in literature. The significance of presence of peripheral blasts in MDS was studied by Sabine Knipp et al in 2008 which showed that presence of peripheral blasts had an unfavourable prognosis\textsuperscript{117}. Another study
by G Tricot has also associated initial peripheral blast count with unfavourable prognosis\[118\].

The data in the present study showed that there is a statistically significant correlation between high peripheral blast count and the frequency of complications. The maximum frequency of complication occurred when the peripheral blast count is greater than 10%. Alternatively, when the peripheral blast count is greater than 10% at presentation, a high complication rate is to be expected.

THE CORRELATION BETWEEN LACTATE DEHYDROGENASE (LDH) VALUE AND COMPLICATIONS OBSERVED

Sotirova et al in a study published in 2014 of data of 108 patents found no association between serum LDH levels and prognosis in MDS\[77\]. RaujJ et al had found positive correlation between serum LDH values and prognosis in MDS patients\[124\]. Park MJ had also found after studying 149 patients in 2008, positive independent prognostic significance of serum LDH levels and MDS\[120\]. A study from India by Varma N found wide variation between serum LDH and the different FAB subtypes of MDS\[121\]. Wimazal F had concluded in 2008 after studying 221 MDS patients that serum LDH levels were very good as a serial follow up measurement for studying prognosis of MDS and its probability of turning into acute leukemia\[122\]. Aul C, 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\[123\]. When the LDH value was less than 500 IU/L, the observed complications was 39.7% and if the LDH value was more than 500 IU/L, the complication rate was 94.9%. When the LDH value was less than 500 IU/L, the deaths observed
were 14.3% and when the LDH value was more than 500IU/L the value observed was 51.3%.

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.

THE CORRELATION BETWEEN RED CELL DISTRIBUTION WIDTH (RDW) AND COMPLICATIONS

Rauw J et al had described in 2011 various independent predictive factors for diagnosis of MDS in 313 patients with cytopenias which includes age, LDH, RDW, and MCV\[^{124}\]. Wang H et al had found that patients with high MCV had greater survival benefit in patients with MDS\[^{125}\]. Tenant GB had also concluded the beneficial effect of a high MCV in prognosis of MDS\[^{126}\]. Li L had also concluded the survival benefit of patients having a high MCV\[^{120}\].

Here we had decided to use the variability in corpuscular volume or red cell distribution width (RDW) for prognosticating MDS patients.

Even though it was not statistically significant, the observation showed a positive correlation between complication rate and RDW. The exact cause of this observation is not known, but may be due to the increased dyserythropoiesis and cytopenias seen in poor prognosis subtypes. There was no correlation between RDW and death.
THE CORRELATION BETWEEN ERYTHROCYTE SEDIMENTATION RATE AND COMPLICATION RATE

Schrappe-Bacher M et al in 1990 had suggested a negative correlation between ESR greater than 30 mm in one hour and the prognosis of patients with MDS\textsuperscript{129}. No other major studies has been done linking presenting ESR to prognosis in patients with MDS. Here we have attempted to study any independent prognostic significance to presenting ESR levels and prognosis.

Even though it was not statistically significant, there was a positive correlation between high ESR and the frequency of complications seen. This may be due to low hemoglobin values or concurrent infections that occur in these patients. An ESR value of greater than 100 mm in one hour was associated with a higher frequency of death seen in the patients. This can be due to the high frequency of complications seen in these patients.

RELATIONSHIP BETWEEN HEMOGLOBIN LEVELS AT PRESENTATION AND COMPLICATIONS

Sotirova T et al in a retrospective cohort study of 108 patients in 2014 had concluded that presenting blood hemoglobin levels had no relation to overall survival\textsuperscript{77}. A study from Italy by Malcovat L had concluded that hemoglobin levels less than 9g% in men and 8g% in females were independently related to reduced overall survival, high risk of non leukemic death and cardiac death\textsuperscript{130}. Kao JM et al in 2008 had suggested that hemoglobin levels had additive prognostic significance for overall survival, but not leukemic transformation\textsuperscript{131}. Littlewood T had studied the impact of
anemia on multiple myeloma, leukemias and MDS and had found that anemia had a bad prognostic significance for the patients\textsuperscript{[132]}. Another study by Aul C et al had also found negative prognostic significance for MDS patients the level of hemoglobin\textsuperscript{[133]}. 

\textit{There was a strong correlation between low hemoglobin levels in the patient and the frequency of complications. This may be due to the lower oxygenation and multiple organ dysfunctions or due to low hemoglobin seen in patients with high blast percentage. The study had showed that there is a positive correlation between low hemoglobin levels and the high frequency of death that occurred in these patients. This again may be due to the low hemoglobin levels seen in patients with high blast count and also due to the fact that low hemoglobin levels are seen in patients having high complications.}