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Research Paper

Overall survival in myelodysplastic syndromes: a cohort study

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ABSTRACT:- Factors like age, gender, FAB subtypes, cytopenias, proportion of bone marrow (BM) blasts, comorbidities, transfusion dependence, albumins, lactate dehydrogenase (LDH), karyotype abnormalities and molecular biomarkers can refine the prediction of prognosis in MDS. The aim of this study was to evaluate factors that influence overall survival (OS) in MDS.

We conducted retrospective cohort study of 184patients (98 male, 86 female) with MDS who presented to the University Clinic of Hematology, Skopje, Macedonia, from January 2011 to October 2014. The differences in OS between male and female were not significant (p = .08368). The mean age at diagnosis was 66,5 years. Differences in OS among FAB subtypes were significant (p = .00117). OS inversely correlated with BM blast percentage (p = .00054). Hemoglobin, platelets and absolute neutrophil count (ANC) did not influence OS - p=0.107161, (p= .79288) and (p= .94860), respectfully. Ferritin (p = .63575), LDH and transfusion (p= .48247) did not influence OS. Albumins and comorbidities influenced OS (p= .01137 and p= .00184, respectfully). We can conclude that FAB subtypes, BM blast percentage, albumins and comorbidities had an influence on OS, while age, gender, hemoglobin, platelet count, ANC, transfusion dependence and LDH had no impact on OS.

Keywords:- Myelodys plastic syndromes, overall survival, prognostic factors

I. INTRODUCTION

Myelodysplastic syndromes (MDS) comprise a group of clonal hematopoietic stem-cell disorders characterized by ineffective hematopoiesis and peripheral cytopenias. [1]They are regarded as a spectrum of diseases with distinct underlying biology (characterized by chromosomal abnormalities) and different prognosis. Disease characteristics and outcome are defined by FAB classification that segregates MDS by the degree of progression from relatively benign conditions with no excess of blasts (RA/RARS), excess of blasts (RAEB) excess of blasts in transformation to leukemia (RAEB-t) and WHO classification which includes cytogenetic abnormalities. Prognosis is defined by IPSS and R-IPSS score, which combine bone marrow (BM) blast cell count, peripheral cytopenias and cytogenetics to identify very poor, poor, intermediate, good and very good prognosis. [2]

Myelodysplastic syndromes (MDS) are clonal hematopoietic disorders with heterogeneous clinical presentation, laboratory findings and life expectancies ranging from a few months to several years.[3]

Overall survival (OS) and leukemia free survival (LFS) are important both for the patients and their physicians alike. Patients are interested how much time they have left, and if survive how long they can live without disease. Doctors want to know what modality treatment to choose depending on the patients characteristics. Accurate prediction of a patient's prognosis is useful to define the risk posed by the disease. It is of great importance to know the impact of some prognostic factors on OS and LFS. Some of them are already included in IPSS and R-IPSS - BM blast cell count, peripheral cytopenias and cytogenetics. There are a lot of studies trying to define other prognostic factors that can influence prognosis and later to be included as parameters refining the prognostic scores: age[4,5,6,7,8],gender [4,7,8], FAB subtypes [9], degree of anemia and RBC transfusion dependence [10,11], ferritin [12,13,14,15,16], LDH [17], albumins [18], mutations [19,20,21] and co-morbidities. [1]

Diagnosis requires BM examination and cytogenetic studies, and lately molecular studies. The consensual minimum criterion for diagnosis is the presence of erythroid, granulocyte or megakaryocyte dysplasia in 10% or more of informative cells. [22]

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The incidence of MDS increases with age (median about 70 years) [4,5,6,7,23]. Age had a significant effect on OS of the MDS population analyzed as a whole and stratified by subgroups - the older the age, the worse the prognosis. During the analysis on the subgroups, the effect of age was statistically relevant within RA and RARS patients, whereas it was not significant within and RAEB subgroup. [23]

The impact of gender on OS was observed in several studies. The overall incidence of MDS is slightly higher in males than in females (1.5 - 2 to 1). Male patients had worse prognosis.[4,7]

FAB subtypescan worsen the prognosis in MDS in terms of OS, with differences among subtypes. Refractory anemia had the best and RAEB-T the worst prognosis. [9]

BM blast count showed a significant predictive value on OS in MDS patients. [23]More than 5% blasts in BM are considered as a bad prognostic factor for OS and leukemic transformation. [24,25]

According to the multivariate analysis peripheral cytopenias did not reach a statistical significance on OS in MDS patients. [23] The occurrence of anemia (hemoglobin < 100 g/l) or thrombocytopenia (platelets < 100/μL) was significantly associated with a higher risk for OS. A lower absolute neutrophil count (< 1.8 × 109/L) did not significantly affect OS. [7]

Red blood cell (RBC) transfusions are a commonly used therapy to treat symptomatic anemia that affects most patients with MDS. Transfusion dependence is defined by the MDS International Study Group (2000) as requiring transfusion of at least one RBC at 8 weeks for 4 months. [9] Transfusion-dependent patients had shorter survival rate than those who received less than 18 units of blood over a period of 36 months. [26]
Serum ferritinlevel ≥500 μg/l at diagnosis was a strong independent predictor of survival. Serum ferritin was significantly correlated with OS in Chinese patients. [12]

Lactate dehydrogenase (LDH) is a parameter that should be recognized as a prognostic factor in MDS. [17] One German study pointed out the correlation between LDH level and OS. [21]

Serum albumin is an independent prognostic factor that influences OS in patients with MDS. Hypoalbuminemia is a marker for shorter OS in MDS. [18]

Recurrent chromosomal abnormalities have been identified in 40–70% of the 'de novo' MDS and 95% of secondary MDS. These chromosomal aberrations include 5q-, 7q-/-7, +8, 20q-, 12p-, abnormalities in 17p, 11q23 and chromosome 3. (28) Favorable prognostic markers according to IPSS include: a normal karyotype, 5q- as an isolated anomaly, 20q- as an isolated anomaly and -Y chromosome. Karyotype findings associated with poor prognosis include complex karyotype and abnormalities of chromosome 7. Other cytogenetic abnormalities confer an intermediate prognosis. [27,28]Abnormal karyotype correlates with poor prognosis and shorter OS. [19,29] According to the multivariate analysis, cytogenetics showed a significant predictive value on OS**.** [8]

Somatic mutations are identified in more than 70% of patients with MDS, including more of the patients with normal karyotype. These mutations are major predictors of the clinical phenotype, and could also be predictors of prognosis. [19,20,21]

The incidence of MDS increases with the age, so does the prevalence of co-morbidities. About 50% of MDS patients have one or more co-morbidities.These patients suffer from co-morbidities such as heart failure, diabetes, infections, disorders of the thyroid gland and liver, shortening their survival. [12,13,14,15,16] Congestive heart disease, hypertension, lung diseases, diabetes, liver failure, bleeding and solid tumors are cited as the most often reasons for non-leukemic dead.[1] Co-morbidities are significant and independent predictors in MDS.[1] Congestive heart disease and chronic obstructive lung disease are associated with shorter OS, while diabetes and cerebro-vascular diseases do not change prognosis in MDS.[1] The median OS in MDS is 2.5 years. [6]The median survival rates according to IPSS are estimated at 8, 5.3, 2.2, and 0.9 years, respectfully. [21,30]

The aim of this study was to assess the influence of the some prognostic factors in myelodysplastic syndromes (age, gender, FAB subtypes, BM blast percentage, cytopenias, transfusion dependence, serum levels of ferritin, lactate dehydrogenase and albumin, comorbidities and specific karyotype abnormalities) on OS in myelodysplastic syndromes.

II. PATIENTS AND METHODS

We conducted a retrospective cohort study that included 184 adultpatients with MDS who presented to the University Clinic of Hematology, Ss Cyril and Methodius University, Skopje, Macedonia from January 2011 to October 2014. Observation time was 46 months. In addition to demographic data, we collected information on each patient's date of presentation and date of death or time of last follow-up. FAB classification, treatment and outcome (survival and leukemic transformation) were also obtained. This study was approved by the Ethical Board of the University.

Patients were evaluated for clinical and hematologic features at diagnosis and leukemic transformation. Diagnosis was made upon dysplastic changes in peripheral blood smear and bone marrow aspirate. Confirmation analysis included bone marrow aspirate, cytochemical, histochemical and cytochemical stain

(medullar iron) and karyotype analysis in some cases. We evaluated some parameters that could influence OS: age, gender, cytopenias, BM blast percentage, RBC transfusion dependence, serum levels of hemoglobin, ferritin, LDH and albumin as well as specific karyotype abnormalities. Chromosomal analysis was performed only in 5 patients using BM aspirate, according to laboratory procedures. IPSS was not calculated in the vast majority of patients, because we could not perform cytogenetic analysis in most patients. Most patients (pts) received supportive care: transfusion of RBC and platelets, red cell and granulocyte growth factors (25 pts), vitamins, corticosteroids, iron chelatation therapy (7 pts), some received chemotherapy (15 pts), one patient was treated with azacytidine and few patients underwent allogeneic transplantation (3 pts). OS was estimated in months including the period from the date of presentation to the time of death / time of last visit. Leukemic transformation was noticed in 10 (5.4%) patients. Mortality was 32.6% (58 pts). Infectious and hemorrhagic complications as well as BM failure were considered causes of MDS-related deaths.

III. RESULTS

A total of 184 adultpatients were included in the study. OS was 13.1 months (SD 10.9).(Fig.1)
In thiscohort study group 98 patients (53.3%) were male and86 patients (46.7%) female. Male to female ratio was 1,14 to 1. Women had better OS than men - 12.6 months (SD 10.9) versus 13.6 months (SD 10.9). Differences in OS considering sex were not statistically significant (p = .08368). (Fig. 2) Surviving at 46 months was 77.9% for male and 75.2% for female patients.

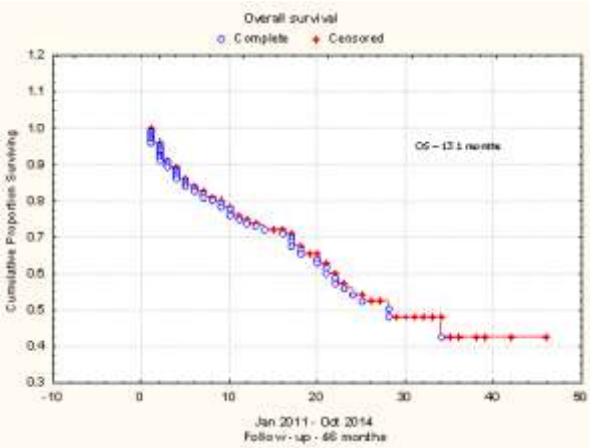

Figure1.Overall survival in the cohort group

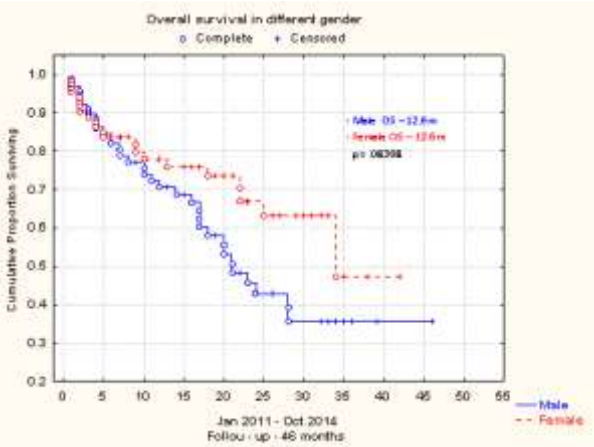

Figure 2. Overall survival in different gender

Median age at presentation was 66,5 years (range 17 to 89 years) (SD 14,5). Median OS depending on age was 13,2 months (SD 10.92), and the correlation it was not statistically significant(p= .31867).When patients were divided in five groups: first ≤ 50 years (28 patients) with OS 15.7 months, second 51-60 years (17 patients) with OS 12.8 months, third 61-70 years (44 patients) with OS 13.7 months, forth 71-80 years (67 patients) with OS 13.2 months and the fifth >80 years (28 patients) with OS 10.8 months, but the differences in OS among groups were not statistically significant (p = .31521). (Fig. 3) When patients were divided in two groups, OS in the first group ≤ 65 years was 14.2 months (SD 9.86) and in the second group >65 years was 12.7 months (SD 11.72), showing no statistically significant differences between them (p = .12402). Surviving at 46 months in the first group was 72.61% and in the second 82.61%. (Fig. 4)

According to the FAB classificationpatients were classified as follows: 123 patients as having refractory anemia (RA)- 67%, 3 patients with RA with ringed sideroblasts (RARS) - 2%, 34 patients with RA with excess of blasts (RAEB) - 18%, 9 patients with RAEB in transformation (RAEB-T) - 5%, and 11 as having chronic myelomonocytic leukemia (CMML) - 6% and 4 patients with secondary MDS (MDSs) – 2%. (Table1)

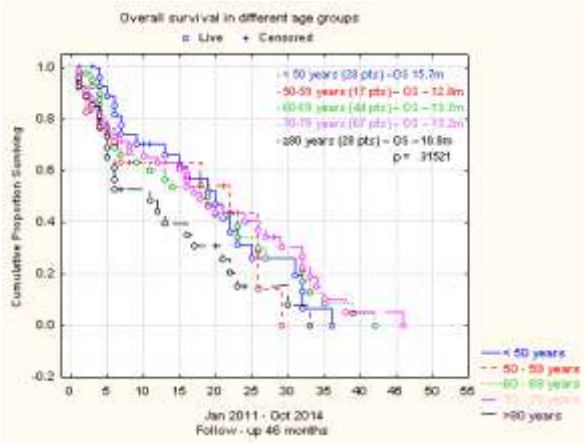

Figure 3. Survival in different age groups

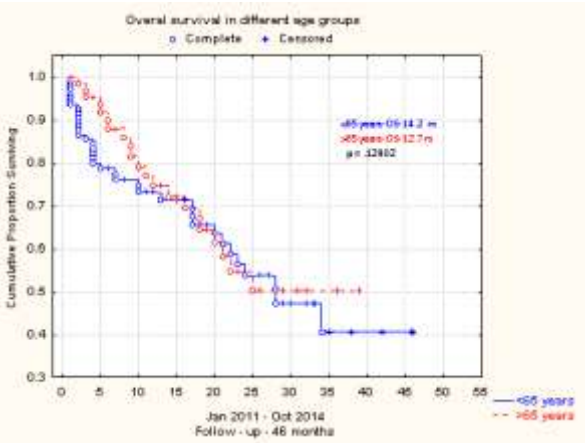

Figure 4. Survival in two age groups

Table 1. Distribution of patients according to the FAB classification

FAB subtypes	No cases	%
RA	123	67%
RARS	3	2%
RAEB	34	18%
RAEB-T	9	5%
CMML	11	6%
MDS sec.	4	2%

OS in patients with RA was 14.7 months, with RARS 12.0 months, with RAEB 8.4 months, with RAEB-T 6.3 months, with CMML 15.4 months and with MDSs 15.7 months. The difference in OS among different groups were statistically significant (p = .00117). (Fig. 5)

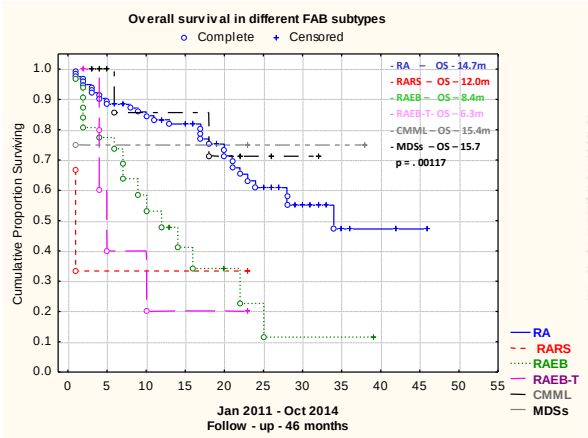

Figure 5. Survival according to FAB subtypes

Figure 6. Survival according to BM blast %

Mean BM blast percentage was 6.9% (SD 7.4). Percentage of BM blasts strongly correlated with OS (p= 0.002637). Mean OS in the group with < 5% blasts was 15.2 months, in the group with blasts 5-10% - 9.47months, with blasts 11-20% - 7.7 months and in the group with 21-30% blasts – 7.3 months. The differences among groups were statistically significant (p = .00054).(Fig. 6)

Anemia is the main clinical manifestation in myelodysplastic syndromes. Mean hemoglobin (Hb) level in our cohort was 86.2 g/L (SD 24.65) (range 40-150 g/L). Hb had no impact on OS (13.1 months) (p=0.107161). The patients were divided in three categories according to the severity of anemia: severe anemia (Hb<80 g/L), moderate anemia (Hb 80-100 g/L) and patients with Hb>100 g/L. OS was highest in patients with Hb>100 g/L -15.4 months, in patients with Hb 80-100 g/L was 12.6 months and patients with Hb<100g/L– 13.0 months, the differences being not statistically significant (p = .49899). (Fig. 7)

Mean platelet count was 126.2×10(9) /L(range 3-629). Platelets had no impact on OS (13.3 months) (p= .79288). The patients were divided in two groups: first group with platelet count <100×10(9) /L with OS –

11.8 months (SD 10.1) and second group with platelet count >100×10(9) /L with OS – 15.6 months (SD 11.4). (Fig. 8)

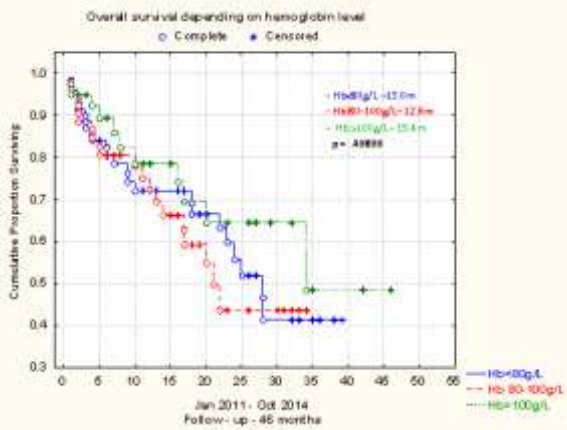

Figure 7. Survival according to hemoglobin

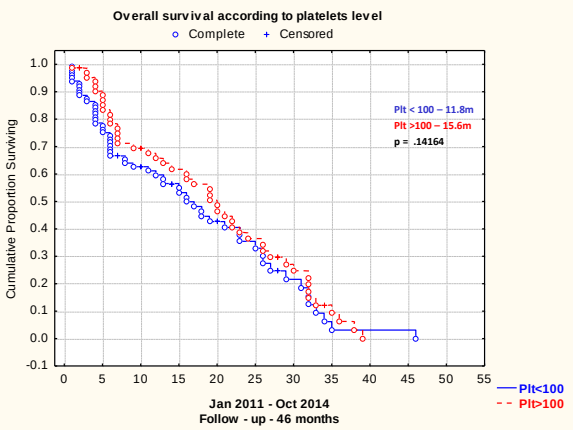

Figure 8. Survival according to platelets count

Absolute neutrophil count (ANC) had no impact on OS (p= .94860). Mean ANC was 4314×10(9) /L (SD 1608) (range 200 – 197000×10(9) /L). Patients were divided in three groups according to the ANC: first group with ANC < 500×10(9) /L with OS – 11.5 months (SD 9.71), second 500-1000×10(9) /L with OS – 12.6 months (SD 11.20) and third >1000×10(9) /L with OS – 13.9 months (SD 11.20). (Fig. 9)

Mean level of serum ferritin in our group was 760.2µg/L (SD 848.84) (range 10.0-3940.0). Serum ferritin had no impact on OS – 11.2 months (p = .63575). Also, groups with ferritin <500 µg/L (OS – 10.8 months, SD 10.35) and >500µg /L (OS - 11.6 months, SD 11.02) had no significant differences in OS (p = .62147). (Fig. 10)

Figure 9.Survival according to ANC

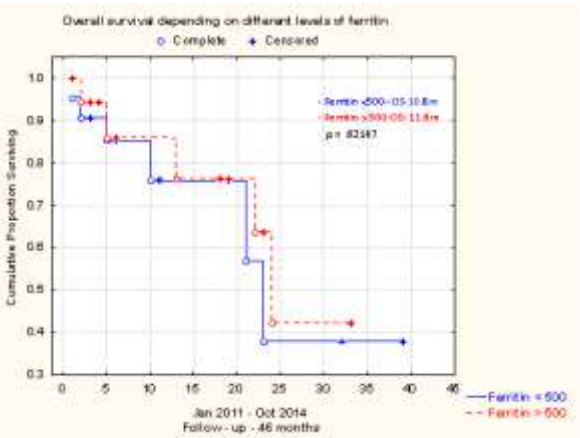

Figure 10. Survival according to ferritin levels

Transfusion dependence is defined by the MDS International Group (2000) study as requiring transfusion of at least one packed red blood cells (RBC) at 8 weeks for 4 months. (13) Mean RBC units was 11.2 units (SD 12.08) (range 0-87). OS depending on transfusion as a whole was 13,6 months, being not statistically significant (p= .48247). OS in the group without RBC units was 12.5 months (SD 10.99), in the group that received ≤ 18 RBC units was OS 12.1 months (SD 10.87) and the group that received >18 RBC units was OS 20.7 months (SD 9.02). Mean transfused RBC units in this cohort were 13,2RBC(St.dev.-16,8). Transfusion dependent patients with >18 doses RBC had shorter survival than patients who required ≤ 18 doses RBC, being not statistically significant (p = .35192). (Fig. 11)

Mean albuminlevel in the study group was 39.7 g/L (SD 3.79) (range 21-49). Albumins had statistically significant influence on OS – 13.1 months (p= .01137). Also, there was statistical significance in OS (p = .00312) among the three groups with different levels of albumins: first group with albumins <35 g/L had OS – 7.8 months (SD 9.02), second group with albumins 35-40g/L had OS – 13.9 months (SD 11.44) and the third group with albumins >40 g/L had OS – 12.1 months (SD 11.31). (Fig. 12)

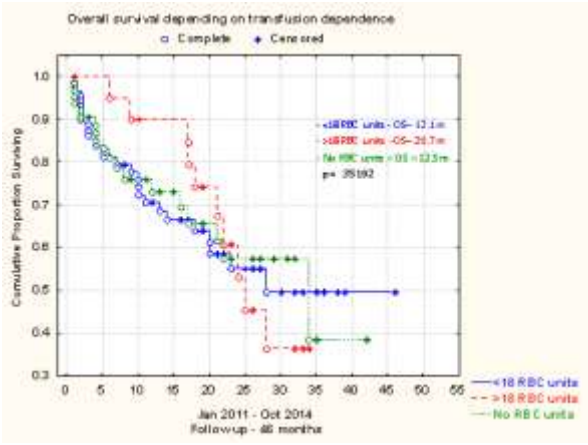

Figure 11.Survival according to RBC units

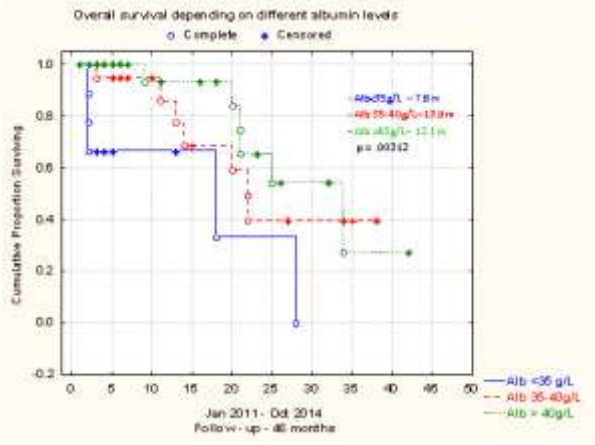

Figure 12. Survival according to albumin levels

Mean serum level of LDH was 786.2IU/L (SD 856.1) (range 217-5790). There was no statistical significance in OS (p = .07807) between the two groups with different LDH: first group with LDH<423IU/L had OS 15.6months (SD 12.63) and the second group with LDH>423IU/L had OS 11.4 months (SD 8.97). (Fig. 13)

Co morbidities had an impact on OS – 13.2 months (SD 11.04) and it was statistically significant (p= .00184). Also, there were differences in OS in the two groups: first group with no comorbidities had OS – 13.7 months (SD 10.82) and the second group with comorbidities had OS 10.9 months (SD 11.75) and it was statistically significant (p = .03085). (Fig. 14)

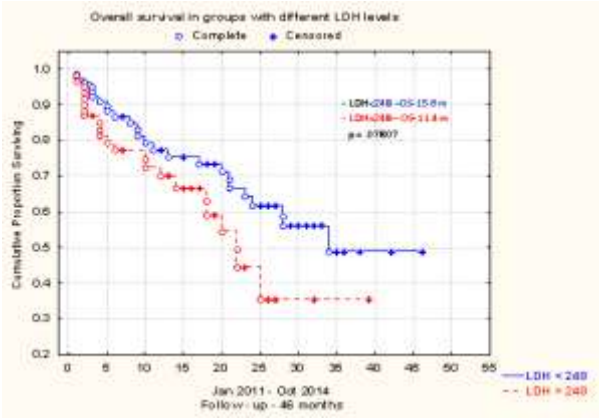

Figure 13. Survival according to LDH levels

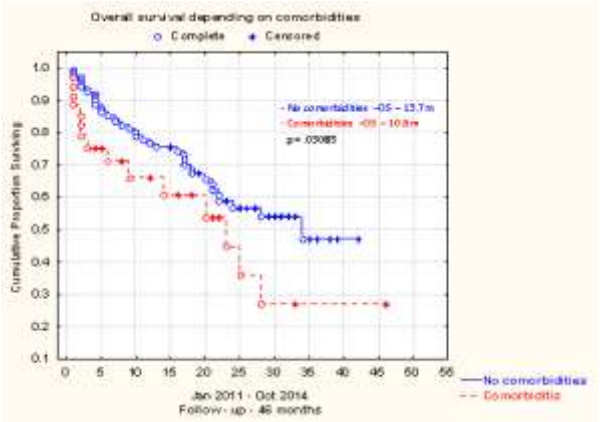

Figure 14. Survival with/without co morbidities

The influence of joint effect of multiple variables (factors such as age, sex, FAB subtypes, BM blast percentage, hemoglobin, platelets, ANC, RBC transfusion, ferritin, albumin, LDH and comorbidities) on OS is shown on Fig.16. The association of multiple factors as independent variables on OS as a dependent variable is statistically significant (p= .00063).

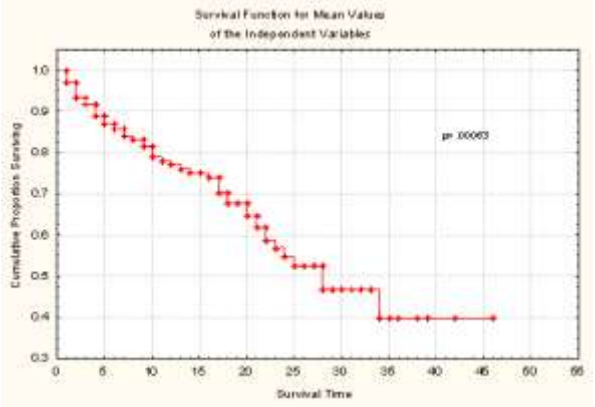

Figure 16. OS as a function of all independent variables

We were unable to perform cytogenetic analysis in all patients. From those 6 patients who underwent cytogenetic tests, 3 had normal karyotype, one patient had +8, one inv16 and one with t(3;3)(q21;q26). We could not show survival curves due to the small number of patients in whom cytogenetic analyses were performed.
Leukemic transformation was noted in 10 (9,3%) patients. Mortality was 36,1%.

IV. STATISTICAL ANALYSIS

Descriptive statistics of the study population, including means (with corresponding standard deviations), medians (with corresponding ranges), and proportions, together with 95% CIs were computed. Differences among variables were evaluated by the Chi-square test. The determinations of correlations between different variables was based on the Pearson correlation coefficient in all cases where the variables had a normal distribution, and a certain correlation was considered statistically significant if $p < 0.05$. Overall survival was defined as the time interval between diagnosis date and death date. Patients who were alive were censored at the last follow-up date. OS was calculated in months from day of presentation until death as a result of any cause. Observations were censored for patients last known to be alive. The probabilities of OS were estimated using the method of Kaplan and Meier. Cox proportional hazards regression models were used to assess the association between prognostic factors and OS.The statistical analyses were carried out using statistical package SPSS version 8.0.

V. CONCLUSION

Our results considering age (66,5 years) correspond with those in the literature.[8]Considering gender, men had worse OS than women, corresponding with the data in the literature. [4,7]Age in this group did not affect OS neither as a whole nor stratified by subgroups, similar with some studies. [23] FAB subtypes had a significant effect on OS. Considering subtypes, the worst results were observed in RAEB-T, than in RAEB, RARS, RA and CMML subtype, similar with those in the literature. [9] OS correlated inversely with BM blast percentage, showed also in other studies. [24, 25] Hemoglobin as a whole and stratified into subgroups did not show any impact on OS.We could not demonstrate an impact of platelet count on OS. Also, prognostic significance of ANC was not demonstrated in our cohort. Serum ferritin level ≥500 μg/l at diagnosis was a strong independent predictor of survival [12], although it was not the case in our cohort. Transfusion dependence is an independent prognostic factor for bad prognosis [15], although in our study group the impact on OS was not significant. LDH is a factor sited as having predictive value [17],although we could not prove that. Albumin is an independent prognostic factor in MDS patients. [8] Also in our study group it had significant prognostic impact on OS, and levels <35g/L were associated with poor survival. Comorbidities had strong impact on OS in our study group. Patients without comorbidities had better OS, which corresponds with data from the literature. [1] Cardiac diseases were the most frequent comorbidities. Cytogenetics in other studies showed a significant predictive value on OS[23] and patients were accordingly stratified in groups with different IPSS score. [19,25,29] Only 6 patients were analyzed for cytogenetic abnormalities, three of them with good prognosis, two of them (+8 and inv16) with intermediate prognosis, and one - t(3;3) with poor prognosis.
We can conclude that FAB subtypes, BM blast percentage, albumins and comorbidities had an influence on OS, while age, gender, hemoglobin, platelet count, ANC, transfusion dependence and LDH had no impact on OS.
Limitations in our study include retrospective analysis, insufficient data on cytogenetic analysis and impossibility to stratify patients according to IPSS score, lack of data on ferritin and LDH, that probably reflected on the results making them different than those cited in the literature.

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