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Characteristics and Outcomes of Patients with Myelodysplastic Syndrome: First Report from Upper Egypt

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ABSTRACT

Background and Objectives: Myelodysplastic syndromes (MDS) are a group of myeloid neoplasms with significant clinical heterogeneity and variable overall survival (OS). This was the first study that aimed to assess characteristics and outcomes of MDS patients at Upper Egypt.

Patients and Methods: Seventy six MDS patients were prospectively enrolled in the study; they were recruited in the period Jan. 2017 – Jan. 2019. Data were collected at enrollment and after 3-months to assess overall response rate (ORR).

Results: Patients' median age at diagnosis was 44.5 years, 50% of them were in age range 18-45 years. Female predominance 46 (60.5%) was obvious with M:F ratio 1:1.5. Rural residency and exposure to fertilizers were reported in 62% and 15.8%, respectively. Eastern co-operative group (ECOG) performance status of most patients was good and only 40% have co-morbid diseases. Hematologically, anemia was normocytic normochromic in 40 (52.6%) and BM hypercellular in 43 (56.6%). ORR and complete remission (CR) were reported in 55% and 1.3%, respectively. Median OS was 13 and the longest 168 months, without significant gender differences.

Conclusion: Compared with other studies, this study showed a younger age and female predominance of MDS at Upper Egypt. It reports normocytosis, rather than macrocytosis, to be the salient feature of MDS in our region. Moreover, the study concludes lower ORR and CR of our patients and the hematologic improvement at level of erythrocyte is the most achievable therapeutic response. Finally, the study concludes that MDS could be an indolent disease with long OS up to 14-years.

Key Words: *Myelodysplastic syndrome – Upper Egypt – Survival.*

INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid neoplasms characterized by peripheral cytopenias, bone marrow (BM) failure, morphologic dysplasia in one or more hematopoietic lineage, and genetic instability with an increased risk to transform to acute myeloid leukemia (AML) **[1-4]**. The disease progression of MDS is multistep with a series of genetic events that reduce the ability of the proliferating clone to differentiate and mature. Hematopoiesis is ineffective, due to premature apoptosis, with the apparent paradox of peripheral cytopenia in one or more cell lines associated with hypercellular BM. The risk of transformation to acute myeloid leukemia (AML) is variable and the clinical outcome is greatly heterogeneous. Therefore, MDS constitutes a complex hematological problem that gives rise to difficulties in diagnosis and therapeutic decision-making **[5-7]**.

The incidence of MDS has appeared to be increasing. The apparent rise was presumed to reflect improvements in recognition and criteria for the diagnosis **[8]**. MDS can be classified as primary (de novo) or secondary. Eighty% of patients with MDS do not have an obvious cause as being secondary to aggressive treatment of other cancers with exposure to radiation, alkylating agents, or topoisomerase II inhibitors. It also occurs in heavily pretreated patients who underwent autologous bone marrow transplants. In certain patients, MDS is an indolent disorder; serious cytopenias occur in other patients and

in the remainder of cases, the disease follows an aggressive course and transforms into secondary AML **[9,10]**.

The standard care for patients with MDS and decreased blood counts is constantly evolving. Supportive therapy is the main component of care. The therapeutic strategy for MDS is based on the revised International Prognostic Scoring System (IPSS-R) score, patient's age, co-morbidities, patient's expectations and personal goals. The more toxic and aggressive forms of therapy, such as stem cell transplantation and aggressive chemotherapy, are reserved for fit and young patients with high-risk disease. The hypomethylating agent azacytidine has been shown to improve survival compared with either supportive or aggressive therapy **[11-13]**.

Numerous researchers reported differences in incidence of MDS, disease presentation, progression and outcome, among different countries and regions **[14-16]**. Upper Egypt is a region in South Egypt and far away from Mediterranean basin. It has different demographic characteristics regarding gender (male to female ratio), age (life expectancy), occupation, level of education, ethnicity, income, geographical location, social class, and various other aspects of the population which differ from lower Egypt. These differences affect risk factors and characteristics of many diseases particularly hematological diseases. To our knowledge, this is the first study of MDS in Upper Egypt. The study aimed to explore demographic and clinical characteristics, hematologic, morphologic, and BM features of patients with MDS residing in Upper Egypt. Moreover, the study assessed ORR to various treatment modalities, OS, PFS and clinical outcomes in those patients. The overall study objectives were to provide a full scenario of MDS in Upper Egypt territory; thus could help hematologists, oncologists and clinical pathologists when dealing with those patients.

PATIENTS AND METHODS

Study design, patients and settings:

This prospective longitudinal study was conducted at the Clinical Hematology Unit of the Internal Medicine Department and the Hematology Laboratory at Assiut University Hospital and the Medical Oncology Department, South Egypt Cancer Institute, in the period from Jan. 2017 to Jan. 2019. The study included MDS patients who were attending/admitted in those departments during the study period. Both newly diagnosed patients and follow-up patients were recruited. Patients' data were collected at enrollment in the study and after 8-12 weeks follow-up to assess patients' response to treatment.

Methods:

Patients' demographic and clinical data were collected through medical history taking and clinical examination.

Diagnosis of MDS patients:

MDS was diagnosed, in the study patients by clinical suspicion in those presented with manifestations of cytopenias of one or more of the affected myeloid lineage cells. Next diagnosis was proved with laboratory investigations as following:

- Complete blood count shows refractory cytopenia (s) in one or more lineage.
- Morphological examination of blood smear, bone marrow aspirate and biopsy for dysplasia in one or more lineage; the dysplasia is considered significant if ≥10% in the erythroid precursors and granulocytes, ≥10% dysplastic megakaryocytes based on evaluation of at least 30 megakaryocytes on smears or sections.
- Dyserythropoiesis: Megaloblastoid changes, cytoblasmic vacuolization and Periodic Acid Schiff (PAS) positivity, internuclear bridging, karyorrhexis, multinuclarity and/or nuclear budding.
- Dysgranulopoiesis: Nuclear hpolobation (pseudo Pelger Huet), hypersegementation and/ or hypogranulation.
- Megakaryocytic dysplasia: Micromegakaryocytes, hpolobated or non-lobated nuclei or widely separated nuclei.
- BM aspirate and/or biopsy provides definitive diagnosis where evidence of dyserythropoiesis, dysmyelopoiesis or dysplastic megakaryocytes could be present.
- Cytogenetic studies: Normal cytogenetics do not exclude MDS.

Morphological classification of MDS was done by counting the blast cells in a 500 cell differential of all nucleated cells in a bone marrow aspirate, or a 200 cells in PB. MDS subtypes were categorized according to the 2016 World Health Organization (WHO) criteria **[17]**.

Treatment and Response criteria:

- Treatment varied from symptomatic therapy for cytopenias, especially transfusions and hematopoietic growth factors, immunosuppressive therapy (IST), chemotherapy, to hypomethylating agents (Decitabine).
- Patients were investigated during their regular follow-up visits, every 2-4 weeks, at the outpatient clinic with clinical examination and peripheral hemogram.
- Response to treatment was assessed after 8-12 weeks and response criteria were based on recommendations of an international working group (IWG 2006) **[18]**.
- OS and PFS were estimated from the time of disease diagnosis till death or disease progression, respectively.

Statistical analysis:

Numerical data were expressed as mean ± SD, median and range, whereas categorical variables were presented as percentages. Kaplan-Meier survival analysis was used to calculate survival outcomes. All analyses were done using SPSS statistical package V. 20 (IBM; corporation, New York, USA). Graph pad Prism V.5 was used for creation of figures.

RESULTS

Socio-demographic and clinical characteristics of MDS patients included in the study (Table 1):

The study included 76 MDS patients who were admitted to our Institutions in the period from Jan. 2017 to Jan. 2019. Female predominance was apparent among the study patients where females represented 46 (60.5%) compared with 30 (39.5%) for males and a 1:1.5 male to female ratio. The median age at diagnosis of our MDS patients was 44.5 years, and the majority of them (50%) were diagnosed at an age range of 18-45 years. MDS was diagnosed in those older than 60-years in one fifth only of the study patients. Housewife, unemployment and farming were the most common occupational status in the study patients, 55.3%, 17.1% and 15.8% in order. Residency in Urban areas was reported in only 36.8% of the study patients Nearly one fifth of MDS patients were smokers and exposure to fertilizers was reported in 15.8%.

Table (1): Demographic characteristics of patients with myelodysplastic syndrome included in the study (n=76).

Variable	Results
Demographics:	
Age (years):	
- Mean± SD	45.80±16.4
- Median (range)	44.5 (18-80)
Age groups [n (%)]:	
- 18-45	38 (50%)
- 46-60	23 (30.3%)
- 61-80	15 (19.7%)
Gender:	
- Males	30 (39.5%)
- Females	46 (60.5%)
Urban area	28 (36.8%)
Occupation:	
- Farmer	12 (15.8%)
- Housewife	42 (55.3%)
- Employed	7 (9.2%)
- Student	2 (2.6%)
- Unemployed	13 (17.1%)
Environmental exposure:	
- Alcohol	2 (2.6%)
- Smoking	15 (19.7%)
- Fertilizers	12 (15.8%)
- Insecticides	5 (6.6%)
- Familial	0 (0%)
- t-MDS	0 (0)
- Hair dyes	1 (1.3%)

N.B.: SD: Standard deviation.
t-MDS: Therapy related MDS.

Fig. (1) Illustrates the distribution of the study patients over 8-Governorates of Upper Egypt including Assiut, Sohag, El Menia, Qena, Luxor, Aswan, Al Wady El Jadeed and Red Sea. The highest prevalence was at Assiut followed by Sohag 53.9% and 21.1% respectively.

Clinically the ECOG PS was grade 0 in 57.6% of the study MDS cases. Anemic manifestations followed by fever were the predominant presenting complaints, 29 (38.2%) and 19 (25%) respectively. However, pallor and purpura were the predominant physical signs 22 (28.9%) and 18 (23.7%) respectively (Table 2). Comorbid illnesses were detected in 40.8%, and secondary MDS in 22.4% of cases.

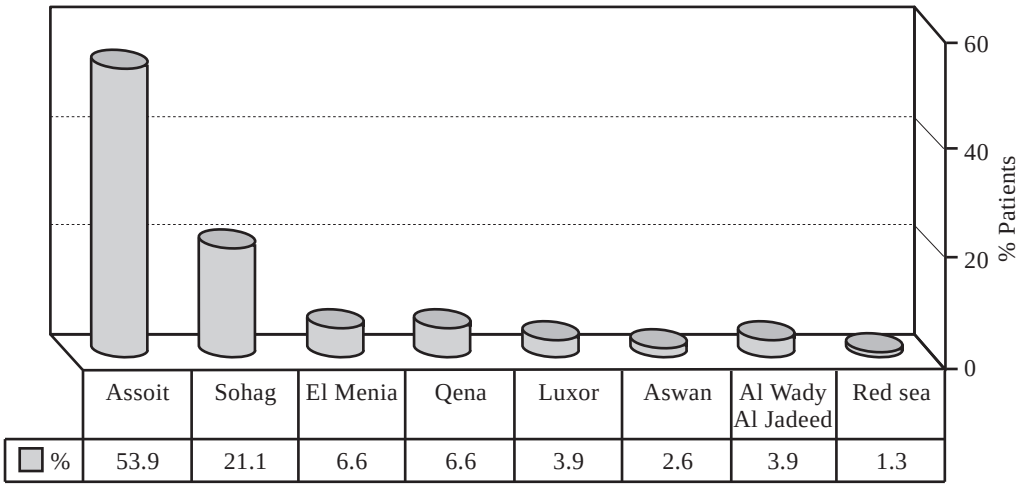

Fig. (1): Distribution of 76 myelodysplastic syndrome patients over 8-Governorates of Upper Egypt in the period from Jan. 2017 to Jan. 2019.

Table (2): Clinical characteristics of 76 myelodysplastic syndrome patients.

Variable	No. (%)
Clinical characteristics:	
ECOG PS:	
- Grade 0	44 (57.9%)
- Grade 1	22 (28.9%)
- Grade 2	9 (11.8%)
- Grade 3	1 (1.3%)
Symptoms:	
- Symptoms of anemia	29 (38.2%)
- Fever	19 (25%)
- Anemia and fever	17 (22.4%)
- Anemia and bleeding	11 (14.5%)
Signs:	
- Pallor	22 (28.9%)
- Purpura	18 (23.7%)
- Pallor and fever	17 (22.4%)
- Fever	8 (10.5%)
- Pallor, purpura and fever	5 (6.6%)
Co-morbidity:	
- Present	31 (40.8%)
- Absent	45 (59.2%)
Clinical MDS subtype:	
- De novo	59 (77.6%)
- Secondary	17 (22.4%)

ECOG PS: Eastern Co-operative Group performance status.

Hematologic, morphologic, bone marrow features and subtypes of MDS in the study patients:

Table (3) shows the hematological profile of patients with MDS included in the study at their first presentation. Table (4) reveals morphologic and bone marrow features of MDS patients included in the study, at diagnosis. Normocytic normochromic anemia was predominant among cases 40 (52.6%) while macrocytosis was detected in only 13.2% of cases. BM cellularity was hyper-cellular in 43 (56.6%), Hypocellular in 20 (26.3%), normocellular in 8 (11.3%) and heterogeneous cellularity in 4 (5.3%) of cases. Different MDS subtypes in the study patients are shown in Fig. (2), half (50%) of cases were MDS with multilineage dysplasia.

Treatment modalities, response to treatment and clinical outcome of the study patients (Table 5):

Various treatment plans were applied according to patients' age, performance status, treatment availability and financial issues. Supportive treatment was the mainstay of therapy in most patients 37 (48.7%) followed by immunosuppressive therapy and growth factors in 27 (35.5%). Hematologic improvement at the level of erythrocyte was the most noticeable treatment response in 24 (31.6%) of the study patients. CR and marrow CR were observed in one patient only (1.3%), each. Progression to AML occurred in 12 (15.8%) cases, and 5.3% died during the period of the study.

Survival studies of MDS patients included in the study:

Figs. (3,4) show OS and PFS survival curves of MDS patients included in the study. Patient's median PFS and OS were 12 and 13 months respectively. The longest OS was 14-years. Remarkably, there was no gender effect on OS (log Rank=0.34, p=0.55) or PFS (log Rank= 1.15, p=0.28).

Table (3): Hematological profile of 76 patients with myelodysplastic syndrome.

Statistics	TLCx10^9/L	Neut. x10^9/L	Hb g/dl	Plts.x10^9/L	Retics. %	Blast %	MCV fl	MCHC g/dl
Mean	5.20	2.45	6.19	175.08	1.65	1.46	86.21	31.61
SE	.50	.27	.25	23.54	.231	.368	1.06	.231
Median	3.15	1.45	6.00	98.50	.80	.00	85.50	32.00
SD	4.43	2.41	2.25	205.28	2.02	3.206	9.29	2.019
Minimum	1.1	.01	2.5	6	.10	0	64.00	23.00
Maximum	20.0	9.10	14.0	833	9.00	15	108.00	36.00

N.B.: SE: Standard error, SD: Standard deviation, TLC: Total leucocytic count, Neut.: Neutrophil, Retics.: Reticulocytes, Hb: Hemoglobin, Plts.: Paltelets, MCV: Mean corpuscular volume, MCHC: Mean corpuscular hemoglobin concentration.

Table (4): Erythrocyte morphology and bone marrow (B.M.) cellularity of patients with myelodysplastic syndrome included in the study.

Variable	Frequency	Percent	Cumulative Percent
Erythrocyte morphology:			
- Normocytic normochromic	40	52.6	52.6
- Normocytic hypochromic	12	15.8	68.4
- Macrocytic normochromic	10	13.2	81.6
- Microcytic hypochromic	13	17.1	98.7
- Microcytic normochromic	1	1.3	100.0
B.M. cellularity:			
- Hypercellular	43	56.6	56.6
- Hypocellular	20	26.3	82.9
- Normocellular	9	11.8	94.7
- Heterogenous cellularity	4	5.3	100.0

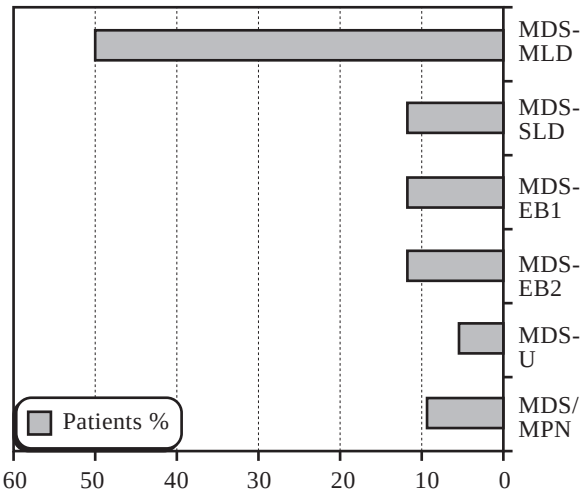

Fig. (2): Types of myelodysplastic syndrome (MDS) in the study patients.

N.B.: MDS-MLD: MDS with multilineage dysplasia, MDS-SLD: MDS with single lineage dysplasia, MDS-EB1: MDS with excess blast1, MDS-EB2: MDS with excess blast2, MDS-U: MDS-unclassifiable, MDS/MPN: MDS Myeloproliferative Neoplasm overlap.

Table (5): Treatment modalities, treatment responses and outcome of 76 myelodysplastic syndrome patients.

Treatment modalities:			
Decitabine & GF	5	6.6	6.6
Supportive treatment	37	48.7	55.3
IST & GF	27	35.5	90.8
IST and thrompoietin mimetics	7	9.2	100.0
Treatment response:			
CR	1	1.3	1.3
PR	6	7.9	9.2
HI-E	24	31.6	40.8
HI-N	1	1.3	42.1
HI-p	8	10.5	52.6
SD	15	19.7	72.4
Failure	8	10.5	82.9
Marrow CR	1	1.3	84.2
Disease progression	12	15.8	100.0
Outcome:			
Living	53	69.7	69.7
Died	4	5.3	75.0
Progression to AML	12	15.8	90.8
Discharge on request	1	1.3	92.1
Stopped follow-up	6	7.9	100.0
Total	76	100.0	

IST: Immunosuppressive therapy; GF: Growth factors; CR: Complete remission; PR: Partial remission;
HI-E, HI-N and HI-P: Hematologic improvement erythrocyte, neutrophil and platelet; SD: Stable disease; AML: Acute myeloid leukemia

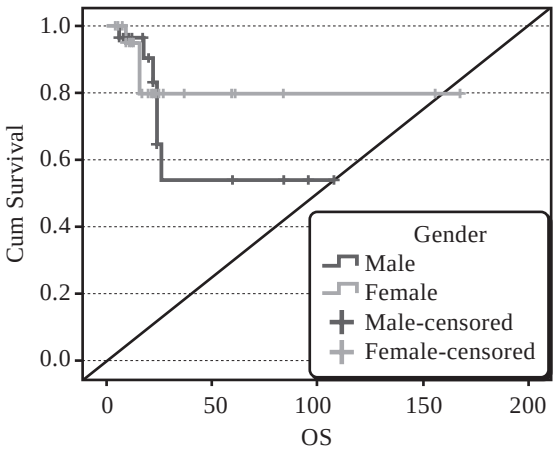

Fig. (3): Overall survival (OS) of 76 myelodysplastic syndrome (MDS) patients included in the study; Log Rank (Mantel-Cox) = 0.35, *p*=0.55.

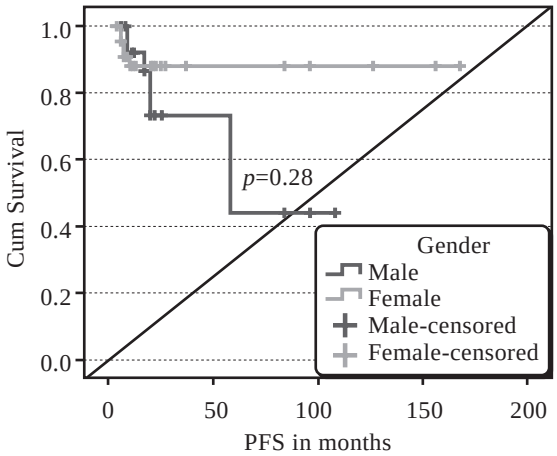

Fig. (4): Progression free survival (PFS) of 76 myelodysplastic syndrome (MDS) patients included in the study; Log Rank (Mantel-Cox) = 1.15, *p*=0.28.

DISCUSSION

In the last few years, our knowledge about MDS diagnosis and treatment improved. Patients with MDS have various medical problems that affect their quality and duration of life **[19]**. However, research about MDS whether primary or secondary is rare in our region. Here we prospectively analyzed 76 MDS cases aiming to investigate their disease characteristics and outcomes. Cases were collected among those admitted at our Institutions in the period from Jan. 2017 to Jan. 2019, over 8-different Governorates of Upper Egypt, of which the higher prevalence was at Assiut, the largest medical Governorate in Upper Egypt.

It is universally agreed that MDS is a disease of elderly subjects with frequent incidence of other co-morbid conditions, however it may occur in persons of any age including children **[16]**. This was not the case in the current study where the median age at diagnosis was 44.5 years and half of cases were diagnosed in the age group 18-45 years. In one study, the annual incidence per 100,000 was estimated to be 0.5, 5.3, 15, 49, and 89 for individuals <50, 50 to 59, 60 to 69, 70 to 79, and ≥80 years of age, respectively **[14]**. Based on the November 2018 SEER data submission, posted to the SEER web site, April 2019, only 4-7% of all MDS cases were below 50 years **[20]**. Both studies are not consistent with our results. Nevertheless, similar to our results, a retrospective Egyptian study of 69 MDS patients that was conducted at the Clinical Hematology Unit Of Cairo University in the period from 2007 to 2010, in which the median age at diagnosis was 55 years **[21]**. The younger age of our patients compared to other Eastern and Western countries could be explained by socio demographic differences as shorter life span or could denote ethnic differences in incidence of MDS.

It is widely agreed that, there is a male predominance in most categories of MDS, with the exception of MDS with isolated del (5q) which is more common in females **[22]**. Based on SEER data from 2001-2003, the incidence rate was significantly higher in men than in women (4.5 vs 2.7 per 100,000 population) **[15]**. This is not the case of our study as the proportion of MDS was higher among females 60.5% compared with that of males 39.5%. Moreover, urbanization was detected in only 36.8% of patients, this may explain, to some extent the increased contact with chemical substances in rural areas. Again, our findings of female predominance and rural residence were albeit consistent with the previously mentioned Egyptian study **[21]**. The female predominance in our patients could be also explained with higher exposure to environmental hazards as most of them were housewives living in rural areas **[23]**.

Clinically, most of our patients have good ECOG-PS and lower incidence of co-morbid conditions compared to other studies; this may be due to the younger age of our patients. Nevertheless, consistent with others the vast majority of them have primary MDS **[24]**. Furthermore, exposure to chemical fertilizers and insecticides were the most important risk factors for secondary MDS; t-MDS was not reported in this study.

Anemia is the most common cytopenias occurring with MDS, and this was the case in our study. Anemia in MDS is generally associated with an inappropriately low reticulocyte response and the red blood cells are usually normocytic or macrocytic, but some patients may have hypochromic microcytic red cells; ovalomacrocytosis is the most common morphologic abnormality **[25,26]**. Normocytic normochromic anemia was predominant among our cases 52.6%. Why most of our patients have normocytic normochromic anemia? This could be explained by the concomitant iron deficiency, the most prevalent nutritional deficiency in our region **[27]**.

MDS-MLD accounts for approximately 30 percent of all cases of MDS **[10]**. In our series, it accounted for half of the patients. This may denote late presentation of our patients, where patients start to complain in advanced stages of the disease.

MDS is usually associated with a normo- or hypercellular bone marrow (BM) whereas 10-20% of cases present with hypocelluar BM **[28]**. This was concordant with our findings in this study where BM was hypercellular in 56.6%, normocellular in 11.3% and hypocellular in 26.3% of cases.

The mainstay of treatment for MDS aims to deal with symptoms and potential morbidity associated with the disease **[29,30]**. Supportive treatment was the mainstay in most of our patients, immunosuppressive therapy and growth factors applied in one third of cases. Therapy that is more intensive was applied in a smaller portion of our patients due to profound cytopenias, availability and financial issues **[31,32]**. Hematologic improvement at the level of erythrocyte was the most noticeable treatment results among our patients, as packed red blood cells transfusion and hematopoietic growth factors were the most accessible treatment lines used. ORR (55%) and CR were lower in our study compared with other studies **[29-32]**. This could be due to shorter follow-up, 3-months, in our study, besides profound cytopenias at presentation in our patients.

OS is extremely variable in MDS ranging from few months to almost a decade with significant clinical heterogeneity and various treatment options. Gender is considered an important predictive factor for survival in MDS patients but is not stated until now as a prognostic factor in the scoring system **[33]**. In a study analyzed 897 MDS patients, further demonstrated gender as a potential prognostic factor **[34]**. Our patients' median PFS and OS was 12 and 13 moths respectively without significant overall survival difference based on gender, this may be due to small sample size of our study with predominance of female gender. Evolution to AML occurs in approximately 10% and 70% of lower- and higher-risk (HR) patients respectively **[35]**. This was albeit consistent with our findings where progression to AML occurred in 12 (15.8%) of our cases.

In Conclusion, this is the first study that assessed characteristics and outcomes of MDS at Upper Egypt. It assessed various aspects of the disease including, demographic, clinical, hematologic and bone marrow features. MDS subtypes, treatment responses, OS, PFS and clinical outcomes. Although it is widely accepted that MDS is a disease of elderly males with co-morbid conditions, poor general health and shorter OS than females. This study concluded obvious differences in disease description in our region, compared to other studies as following:

- Younger age at presentation, female predominance.
- Rural residency.
- No link of disease to previous treatment (therapy related MDS).
- Lower incidence of co-morbid conditions.
- Normocytosis was the hallmark of erythrocyte morphology in our patients.
- MDS-MLD was the commonest MDS subtypes in our region.
- Lower ORR and poor outcome.
- The disease was indolent in some patients with long OS up to 14-years.

These socio-demographic differences in MDS incidence among different regions may be attributed to ethnic differences and late presentation in our patients. Furthermore, these different ORR and outcome results may be due to lack of accessibility of advanced therapeutic options in our patients.

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