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A Population-Based Study on Myelodysplastic Syndromes in the Lazio Region (Italy), Medical Miscoding and 11-Year Mortality Follow-Up: the Gruppo Romano-Laziale Mielodisplasie Experience of Retrospective Multicentric Registry

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Abstract. Data on Myelodysplastic Syndromes (MDS) are difficult to collect by cancer registries because of the lack of reporting and the use of different classifications of the disease. In the Lazio Region, data from patients with a confirmed diagnosis of MDS, treated by a hematology center, have been collected since 2002 by the Gruppo Romano-Laziale Mielodisplasie (GROM-L) registry, the second MDS registry existing in Italy.

This study aimed at evaluating MDS medical miscoding during hospitalizations, and patients' survival. For these purposes, we selected 644 MDS patients enrolled in the GROM-L registry. This cohort was linked with two regional health information systems: the Hospital Information System (HIS) and the Mortality Information System (MIS) in the 2002-2012 period.

Of the 442 patients who were hospitalized at least once during the study period, 92% had up to 12 hospitalizations. 28.5% of patients had no hospitalization episodes scored like MDS, code 238.7 of the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). The rate of death during a median follow-up of 46 months (range 0.9-130) was 45.5%. Acute myeloid leukemia (AML) was the first cause of mortality, interestingly a relevant portion of deaths is due to cerebro-cardiovascular events and second tumors.

This study highlights that MDS diagnosis and treatment, which require considerable healthcare resources, tend to be under-documented in the HIS archive. Thus we need to improve the HIS to better identify information on MDS hospitalizations and outcome. Moreover, we underline the importance of comorbidity in MDS patients' survival.

Keywords: Myelodysplastic syndromes; Epidemiology; Medical miscoding.

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Introduction. Myelodysplastic syndromes (MDS) are characterized by hematopoietic impairment associated with peripheral blood (PB) cytopenias, leading to serious morbidity, and an increased risk of leukemic transformation.[1]

In the general population, MDS occurs in 3-5 per 100,000 people/year. However, in individuals aged over 70 years, the incidence constantly increases up to 40-60 /100,000.[2,3] Survival of MDS patients is poor,[4] with 2-4 years reported median overall survival (OS).[1,5,6] Factors known to impact survival include age, the number of blasts, cytogenetic profile, cytopenias, transfusion requirements and disease type, according to 2008 WHO classification.[7] Some of these parameters have been used to develop MDS prognostic indexes: the International Prognostic Scoring System (IPSS),[8] the Revised International Prognostic Scoring System (R-IPSS)[9] and the WHO-adapted Prognostic Scoring System (WPSS).[10] The introduction of new treatments in the last decade, including hypomethylating and immunomodulating agents, improved supportive care measures and the more frequent use of allogeneic stem cell transplantation (HSCT) are changing the natural history of these diseases.[11]

Results on MDS from population-based studies are rare, and these data are under-reported by cancer registries. Underreporting is likely a result of inadequate infrastructure of reporting to cancer registries or by under diagnosis of MDS (i.e. no bone marrow examination performed to confirm the MDS diagnosis).

The reasons why an extensive epidemiological analysis has not been conducted are:

i) the use of the code International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) does not specify MDS subtypes,[12] and a complete international classification of diseases for oncology ICD-O-3 is not usually adopted in Italian medical claim databases;
ii) the inaccuracy of case reporting because diagnosis and management are performed by different medical service.

In the last decades, in several countries, many registries have been created as the "Surveillance and epidemiological and End Results" (SEER) from the National cancer Institute,[5] the "Dusseldorf registry" started in 1986,[6] the "Netherlands Cancer Registry", established in 1989[2,13] or the "Victorian Cancer Registry",[14] which provided a basis for epidemiological and clinical studies in MDS.

The incidence of MDS in Italy is not well documented because large population-based studies are scarce, since oofficial statistics on morbidity and mortality is not available on a national basis, but derives from some regional cancer surveys and hospital-based registries.

The only registry active in Italy was the Piedmont one[15] created in 1999, which started as a regional database, and has been recently expanded to other regions, in the FISM (Federazione Italiana Sindromi Mielodisplastiche), but does not include the whole Italian territory.

In the last decades, information from large administrative datasets, like hospital or drug registries, has been widely used to describe the epidemiological impact of chronic diseases through standardized methodologies.[16-20] In the case of MDS epidemiological figures from population-based studies using linked health information systems are lacking[13] and no study exists in Italy to test the quality of claims data in this field.

Based on the experience of international epidemiological surveillance, the Gruppo Romano-Laziale Mielodisplasie (GROM-L) gathered in 2009 to encourage the cooperation between the hematological departments in the area, to promote the harmonization of clinical and diagnostic pathways in MDS.

It has been built a registry and patients with a confirmed diagnosis of MDS are enlisted in the GROM-L registry by a hematologic center of the

Lazio Region, and the database is regularly updated.

The study reported here had two main aims:

1) to evaluate MDS-miscoding in medical claims, through the analysis of the concordance between the diagnosis of the MDS patients enrolled in the GROM-L registry, considered as gold-standard, and the diagnosis reported by the physician in-charge in the claims recorded during the hospitalization episodes in any regional hospital, following the MDS diagnosis;
2) to conduct an 11-year mortality follow-up of the MDS cohort enrolled in the registry using data from the Lazio region mortality registry.

Patients and Methods.

Data sources.

a) Clinical dataset: the GROM-L registry

Our study enrolled patients diagnosed with MDS in 12 Hematology Centers in the Lazio Region, between 2002 and 2010. Individual data were collected in a homogeneous electronic platform. About 40% of patients were enrolled because of hematologic counseling in a ward different from 'hematology,' 20% accessed through the emergency room and 40% due to an outpatient visit required by their physician. After diagnosis, 45% MDS patients were monitored through the outpatient clinic, while the remaining patients were followed in day-hospital since they received transfusions or other treatments. In addition, some outpatients needed to access the emergency room for severe anemia and were admitted to internal medicine wards. The information on MDS type according to 2008 WHO classification was available for each patient.

b) Healthcare Information Systems

The following Lazio region healthcare databases were used:

- The Hospital Information System (HIS) database for every hospitalization in any hospital of region Lazio, containing information on patients' personal data, diagnose of discharge, and the procedure performed, encoded according to the ICD-9-CM.

- The regional Mortality Information System (MIS) database, including information on demographic characteristics, as well as date, place, and cause of death (codified by ICD-9-CM codes).

Data available in the regional Healthcare Information Systems are routinely collected for administrative purposes. The Department of Epidemiology of the Lazio Regional Health Service is authorized to manage these databases within the rules of the National Privacy Policy. Linkage among different information systems is possible using an Anonymous Unique Patient Code (AUPC) for every citizen enrolled in the regional healthcare service.

Standardized procedures of deterministic record linkage are applied to connect the archives, to build the clinical history of patients for the evaluation of epidemiological studies.[1-5] The high quality of individual data is the basic requirement for epidemiological studies, based on the Healthcare Information Systems.

Statistical analysis. A retrospective cohort study was conducted. Only patients with a valid AUPC were linked to the Healthcare Information Systems.

About the first aim of the study (to evaluate MDS-miscoding in medical claims), the HIS for the years 2002-2012 was linked to the MDS cohort. The ICD-9-CM code used to identify MDS is 238.7 (neoplasm of uncertain behavior of other lymphatic and hematopoietic tissues). Only patients who had at least 1 hospitalization between the date of MDS diagnosis by the Hematology Center and the end of 2012 were considered. We calculated the proportion of patients where the 238.7 ICD-9-CM code or sub-classification, were reported at least once in any principal or secondary diagnosis. In patients who had a concordant MDS diagnosis, specific ICD-9-CM code recorded for MDS in HIS claims were explored. Specific ICD-9-CM code registered in the principal diagnosis in HIS claims were examined for patients who did not have a concordant MDS diagnosis.

About the second aim of the study (to conduct a mortality follow-up), the MIS for the years 2002-2012 was linked to the MDS cohort. Mortality follow-up started on the day of the MDS diagnosis until 31 December 2012, or the date of death if it occurred before. Thus, potentially, each patient had a minimum of 2 years and a maximum of 11 years observation time. The main causes of death were examined.

Time to death was examined using the Kaplan-Meier curve, stratified by MDS subtype, according to 2008 WHO classification. These curves show the cumulative probability of surviving during a given follow-up time (expressed in months). End

Table 1. Patient characteristics according to the Lazio Hematology center where the diagnosis was made.

Hematology center N	N	Mean age at MDS diagnosis	% women	WHO 2008 classification						
				RARS	5q-	MDS-U	RA	RAEB I	RAEB II	RCMD
1	32	71.63	59.38	2	3	1	10	7	4	5
2	67	73.40	62.69	1	8	0	35	5	1	17
3	27	71.56	29.63	3	0	0	9	3	7	5
4	104	68.96	34.62	3	1	0	17	21	13	49
5	125	68.38	44.8	18	5	13	27	18	28	16
6	31	71.00	45.16	0	0	6	19	1	5	0
7	37	65.95	56.76	0	1	0	21	5	4	6
8	43	59.91	32.56	1	3	0	14	5	9	11
9	82	66.37	46.34	0	2	7	40	15	5	13
10	48	78.46	45.83	3	2	0	23	9	3	8
11	38	76.08	47.37	1	1	1	21	5	0	9
12	10	73.00	50.00	0	1	0	4	0	0	5
TOTAL	**644**	**69.73**	**45.50**	**32**	**27**	**28**	**240**	**94**	**79**	**144**

RA = Refractory anemia; RARS = Refractory anemia with ring sideroblasts; RCMD = Refractory cytopenia with multilineage dysplasia; RAEB I = Refractory anemia with excess blasts type I; RAEB II = Refractory anemia with excess blasts type II; MDS-U = MDS unclassifiable; 5q- = MDS with isolated del(5q). Hematology centers: (1) Az. Osp. San Giovanni-Addolorata, Rome; (2) Sant'Andrea "Sapienza" University, Rome: (3) Az. Osp. San Camillo-Forlanini, Rome; (4) "Sapienza" University, Rome; (5) Università Cattolica del Sacro Cuore, Rome; (6) Campus Biomedico University, Rome; (7) Regina Elena National Cancer Institute, Rome; (8) Az. Osp. Sant'Eugenio, Rome; (9) Tor Vergata University, Rome; (10) Az. Osp. Sandro Pertini, Rome; (11) Ospedale Nuovo Regina Margherita, Rome; (12) Az. Osp. Belcolle, Viterbo.

of the study period (31 December 2012) was considered a reason for censoring. Censored patients do not contribute to the denominator for the succeeding proportion of deaths. The Log-Rank test was used to compare the full curves of each group to evaluate if the seven survival curves are statistically significantly different.

Finally, we analyzed the proportion of patients alive stratified by year of diagnosis at one year follow up and at five years follow up, therefore for the second aim we restricted our analysis to patients diagnosed from 2002 to 2007. The Log-Rank test was performed.

Results.

Patients' characteristics. We enrolled 644 patients with MDS, diagnosed at 12 Hematology Centers of the Lazio Region during the period 2002-2010. **Table 1** reports patient characteristics according to the Hematology Center where the diagnosis was made. Mean patients' age was 69.7 years, and 45.5% were female. According to the 2008 WHO classification, there were 5% RARS, 4.2% 5q- syndromes, 4.3% MDS-U, 37.3% RA, 14.6% RAEB I, 12.2% RAEB II and 22.4% RCMD.

MDS miscoding in HIS medical claims. The analysis of *MDS miscoding in HIS medical* claims and the *Mortality follow-up* was limited to 556 patients with a valid AUPC.

The data of patients with a correct AUPC enrolled by the GROM-L registry per year had to be linked with administrative databases. Patients who were hospitalized at least once during the period 2002-2012 are reported in **Table 2**. Of the 442 patients, 92% had a maximum of 12 hospitalizations for any cause.

According to the cause of hospitalization reported in the principal and secondary diagnoses, the 442 patients have been divided into 2 groups:

Table 2. Frequency of patients who were enrolled by the GROM-L registry, with a correct anonymous patient code, who had at least 1 hospitalization episode during the period 2002-2012. (Numbers refers to the year of diagnosis).

Year Of Diagnoses	Patients enrolled from GROM registry	Patients with a valid anonymous ID	Patients with at least 1 hospitalization between MDS diagnoses and 31/12/12
2002	29	23	22
2003	39	31	23
2004	44	35	31
2005	65	58	49
2006	67	60	40
2007	99	86	66
2008	106	95	80
2009	115	96	76
2010	80	72	55
TOTAL	644	556	442

Table 3. Distribution of the sub-diagnostic codes for 238.7 in 180 patients during various hospital admissions.

Myelodysplastic Syndrome Diagnosis	ICD9-CM code	Patients who had the same ICD9-CM code in all hospitalizations during the study period	
		N	%
Essential thrombocythemia	238.71	1	0.56
Low grade myelodysplastic syndrome lesions	238.72	27	15.00
High grade myelodysplastic syndrome lesions	238.73	18	10.00
Myelodysplastic syndrome with 5q deletion	238.74	3	1.67
Myelodysplastic syndrome, unspecified	238.75	40	22.22
Myelofibrosis with myeloid metaplasia	238.76	0	0.00
Other lymphatic and hematopoietic tissues	238.79	3	1.67
Other lymphatic and hematopoietic tissues	238.7	88	48.89
	Total	**180**	**100**

1) 316 patients (71.5%) who had at least 1 hospitalization with the 238.7 ICD-9-CM code in any principal or secondary diagnosis.
2) 126 patients (28.5%), who had no hospitalization with the 238.7 ICD-9-CM code in any primary or secondary diagnosis.

Patients in group 1 were hospitalized 1107 times during the study period. Of the 316 patients, 180 had the same diagnosis code 238.7 for all hospital admissions. **Table 3** shows the distribution of code 238.7 for these 180 patients. Half of the cases had the diagnosis "MDS unspecified" (ICD-9 code 238.75). The remaining 136 patients had mixed diagnosis within the class 238.7 for the various hospital admission.

Of the 126 patients in group 2, 66 patients had at least one hospitalization with a primary hematologic diagnosis (ICD-9-CM codes 280-289:

Table 4. Distribution of the principal diagnostic codes for the 203 hospitalization in 60 patients who had no hospitalization episodes with the ICD9-CM code 238.7 or another hematologic code.

PRINCIPAL DIAGNOSES	ICD9-CM CODES	N	%
MALIGNANT NEOPLASM OF LYMPHATIC AND HEMATOPOIETIC TISSUE	200-208	19	31.7
ACUTE MYELOID LEUKEMIA	205.0	18	30.0
CHRONIC MYELOID LEUKEMIA	205.1	21	35.0
OTHER MALIGNANT NEOPLASM	140-199	7	11.7
DISEASES OF THE CIRCULATORY SYSTEM	390-459	16	26.7
DIABETES MELLITUS	250	28	46.7
DISEASES OF THE RESPIRATORY SYSTEM	460-519	6	10.0
DISEASES OF THE DIGESTIVE SYSTEM	520-579	15	25.0
DISEASES OF THE GENITOURINARY SYSTEM	580-629	8	13.3
INFECTIOUS AND PARASITIC DISEASES	001-139	2	3.3
DISEASES OF THE MUSCULOSKELETAL SYSTEM AND CONNECTIVE TISSUE	710-739	7	11.7
PATHOLOGIC FRACTURE	733.1	2	3.3
TRAUMATISM	800-959	4	6.7
CHEMOTHERAPY	V58.1	6	10.0
TRANSFUSIONS	V58.2	1	1.7

diseases of the blood and blood-forming organs). For the remaining 60 patients, the distribution of the main diagnosis during their 203 hospitalization episodes is reported in **Table 4**. For these patients, the sum is not 60 because each patient could have been hospitalized more than once.

Mortality follow-up. The median observation time for the 556 MDS patients with evaluable survival data was 46 months (range: 0.9 - 130 months). During the follow-up, 253 deaths (45.5% patients) occurred. Of whom, 158 (62.5%) were men. **Figure 1A** shows the OS curve expressed as months for the whole 2002-2012 period.

The frequency distribution of survived and deceased patients along the whole follow up period stratified by type of MDS are reported in **Table 5**. **Figure 1B** illustrates the survival curve stratified by MDS type according to 2008 WHO classification. The median survival of specific MDS subpopulations was: 5q- syndromes: 110 months, MDS-U: not reached, RA: 102 months, RCMD: 93 months, RARS: 80 months, RAEB I: 37 months, RAEB II: 24 months. At the end of the follow up 58.9%, 62.5% and 57.1% of patients with RCMD, RA and RARS were alive. Survival was 36% and 34% for patients with RAEB I and

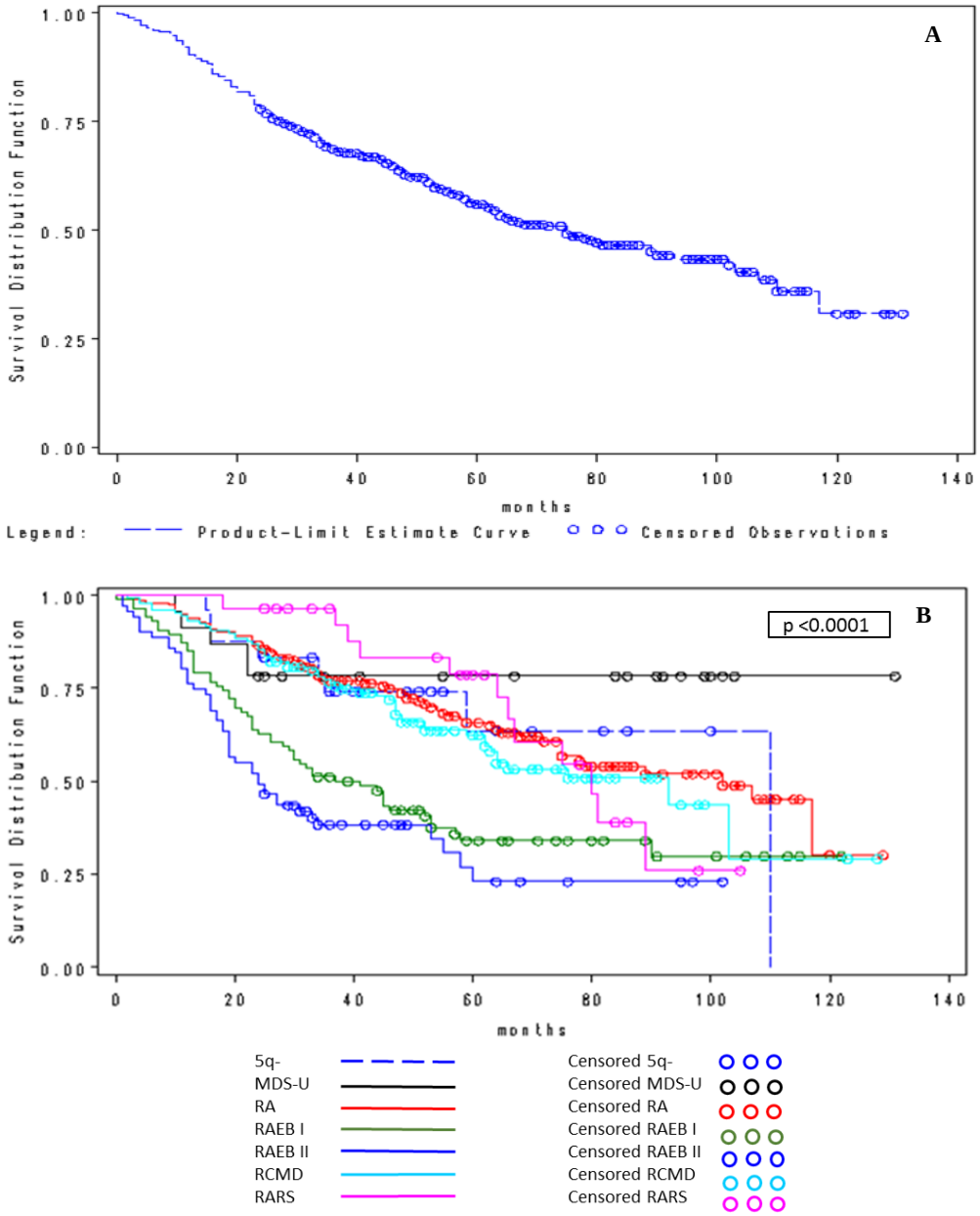


Figure 1. Survival. **A.** Overall survival. **B.** Overall survival stratified by the type of MDS: In low-risk MDS, survival of RCMD and RARS are coincident until month 47 of follow-up, later-on the RCMD curve slightly fell. Survival of RA patients, compared to RCMD and RARS, shows a lower death rate before month 80 and higher afterwards. This might be influenced by the fact that RARS patients are fewer (N=28) than RCMD (N=129) and RA patients (N=195). In the high-risk group, death rates for RAEB II are higher at the beginning: 59% of RAEB II patients died by month 33 conversely to 49% of RAEB I patients.

Table 5. Distribution of deceased/survived patients by type of diagnosis.

MDS DIAGNOSES	MDS patients	Patiens died		Patients survived	
		N	%	N	%
5q-	24	8	33.33	16	66.67
MDS-U	23	5	21.74	18	78.26
RA	195	73	37.44	122	62.56
RAEB I	86	55	63.95	31	36.05
RAEB II	71	47	66.20	24	33.80
RCMD	129	53	41.09	76	58.91
RARS	28	12	42.86	16	57.14
TOTAL	**556**	**253**	**45.50**	**303**	**54.50**

RAEB II (**Table 5**). Patients with a 5q- syndrome or an MDS-U had the best survival probability (67% and 78%, respectively). The last observed death in MDS-U patients occurred at 22 months, while it occurred at 112 months in 5q-patients. The Log-Rank test confirmed a statistically significant difference among the patient sub-groups (p-value <0.0001).

The distribution of patients alive at last follow-up, stratified by year of diagnosis at one year and five years are reported in **Table 6**, no significant differences in survival according to the time of diagnosis were observed.

Figure 2 shows the five-year survival curve according to the year of MDS diagnosis, no significant differences were observed among the six curves (Log-Rank test=0.593).

The distribution of the most frequent causes of death, according to ICD-9-CM coding, is described in **Table 7**. The number of fatalities from acute leukemia accounts for 41% in high-risk MDS and 21% in low-risk MDS, respectively. Interestingly, a relevant portion of death causes is represented by cerebro-cardiovascular events and second tumors. The most frequent cause of mortality was "acute myeloid leukemia" (ICD-9-CM code 2050) which accounts for 23% causes of death (data not shown), "other lymphatic and hematopoietic tissues" (ICD-9-CM code 238.7) was the second cause of death, while 12% of deaths were due to other hematologic diseases.

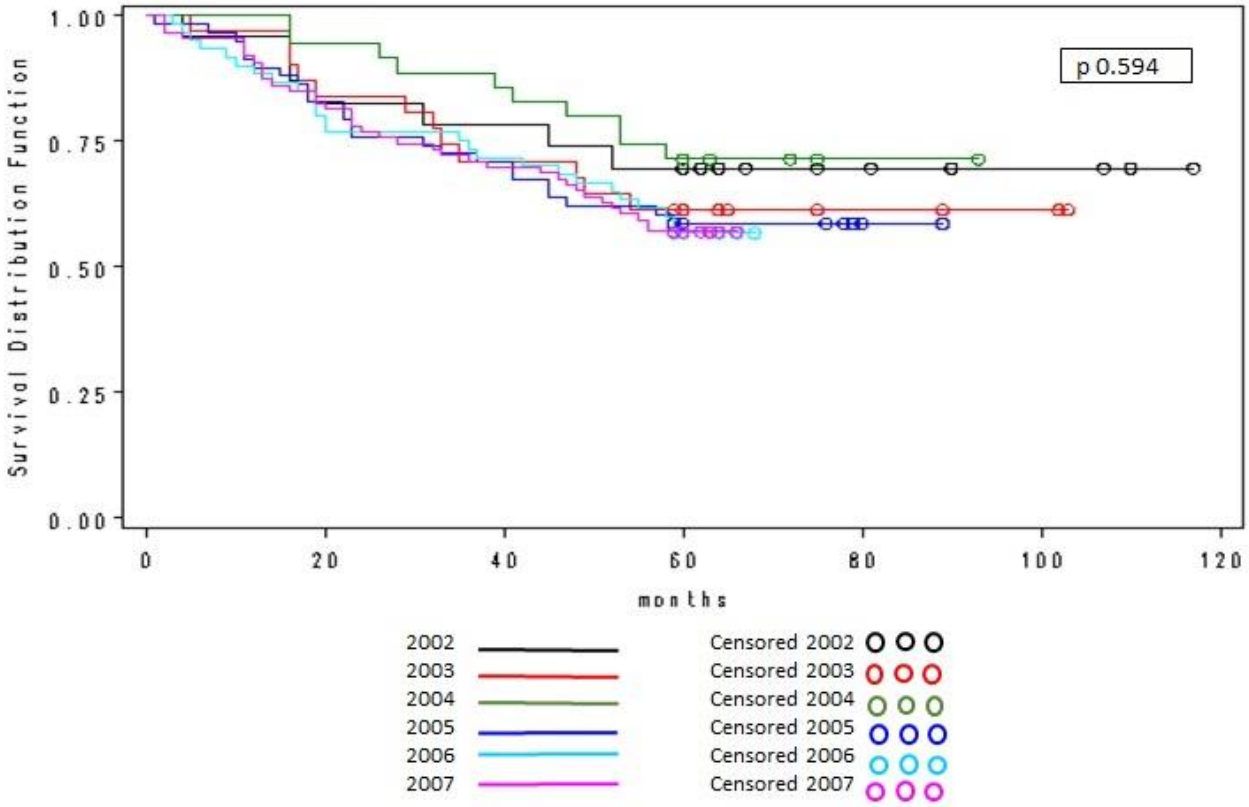
Discussion. Here, we report the first regional Lazio study on diagnosis, sub-classification, and survival of MDS patients. MDS patients are often difficult to recognize, and diagnostic difficulties might affect reporting frequency.[13,21,22] Our results confirm these issues in the Lazio Region.[2,23-25] MDS are hematologic diseases whose identification and classification criteria have undergone major changes in recent years. Although it is difficult to recognize by the clinicians, awareness on this disease among hematologists has increased in the last years. In particular, the GROM-L registry required that diagnoses reported in the present study were accurate and homogeneously assessed by all participating hematologic centers.

Among the 644 patients enrolled, we could evaluate only those who had a valid AUPC and a hospitalization episode (regularly or day hospital regimen) in the period from the date of diagnosis to December 31, 2012 (up to 11 years). Discrepancies between the GROM-L registry and administrative databases are due to incorrect reporting of the personal data, leading to an invalid AUPC. Thus, health care information was retrieved for 442 patients only (64.6%). In 71.5%

Table 6. Distribution of patients alive stratified by year of diagnosis at one year follow up and at five years follow up.

		Patients survived after ONE year of follow-up		Patients survived after FIVE year of follow-up	
Year of MDS diagnosis	N	N	%	N	%
2002	23	22	95.7	16	69.6
2003	31	30	96.8	19	61.3
2004	35	35	100.0	25	71.4
2005	58	53	91.4	34	58.6
2006	60	54	90.0	34	56.7
2007	86	78	90.7	49	57.0
Total	***293***	***272***		***177***	***60.4***
2008	95	89	93.7		
2009	96	84	87.5		
2010	72	64	88.9		
TOTAL	**556**	509	91.5		

Figure 2. Survival stratified by year of MDS diagnosis – 5 year follow-up.



No significant differences in survival according to time of diagnosis are observed.

Table 7. Distribution of the causes of death (ICD-9-CM coding) stratified by MDS subtype.

Cause of death	ICD-9-CM code	RAEB I and II		Other MDS diagnoses		Total	
		N	%	N	%	N	%
Acute Leukemia	2040, 2050, 2070, 2080	42	41	32	21	74	29
MDS (neoplasm of uncertain behavior of other lymphatic and hematopoietic tissues)	2387	22	22	33	22	55	22
cardio-cerebrovascular disease (including diabetes)	2500, 2502, 2506, 4029, 4100, 4140, 4149, 4148, 4241, 4254, 4280, 4291, 4293, 4299, 4321, 4360, 4371, 4379, 5184, 5570, 5715, 8521, 9960	13	13	30	20	43	17
Other hematologic diseases	2019, 2028, 2029, 2058, 2059, 2069, 2089, 2849, 2850, 2898, 2041, 2051	16	16	15	10	31	12
Tumours (other than hematologic)	1519, 1533, 1536, 1539, 1551, 1560, 1579, 1590, 1629, 1749, 1850, 1890, 2307	4	4	20	13	24	9
OTHER CHRONIC DISEASES (lung, intestine, liver, bone etc...) plus unknown	381, 384, 2858, 2859, 2890, 2892, 4912, 5698, 5712, 5761, 5850, 7425, 7999, 8210	4	4	19	13	23	9
Infections	4210, 4850, 5580	1	1	2	1	3	1
TOTAL		102	100	151	100	253	100

of these patients, the code 238.7 (Myelodysplastic Syndrome) was recorded at least once in one of the hospital admissions. As in previous studies,[26] a high proportion of non-specific MDS codes was

reported. In the remaining 28.5% of patients, the primary diagnosis was hematologic in more than half of hospital admissions.

Our observation confirms that survival of patients with MDS is poor. The OS curve (**Figure 1A**) is similar to other large analysis,[1,6] although different study cohorts are not comparable, as observed in the recent report of Della Porta et al.,[27] mainly due to different proportion of high risk patients and variable median age. The Kaplan-Meier curve stratified by MDS subtype according to 2008 WHO classification (**Figure 1B**), is similar to other studies of the same type,[28] with shorter survival for patients with RAEB I or RAEB II. Survival was similar in low-risk MDS (RCMD, RA, and RARS), and it reached a plateau in high-risk MDS (RAEB I and RAEB II), similar to other registries.[1,6] Patients with a 5q- syndrome survived the longest, followed by MDS-U patients, although numbers are low (24 and 23 patients, respectively). This is due to the favorable cytogenetic category and probably to the recently introduced lenalidomide treatment.

These results confirm data from a smaller patient group (380 patients) previously analyzed by our group,[29] which was used to validate the IPSS-R, compared to IPSS and WPSS.

MDS patients' therapy has improved over the past decades after the introduction of new treatment strategies. We performed a survival analysis stratified by year of diagnosis to investigate a possible survival gain over time, as assessed by existing literature,[30,31] but no significant differences in survival were seen at one year and five years follow up. These results could be due to the low proportion of patients eligible for new treatment strategies (high risk MDS and 5q- syndrome).

During the follow up almost half of the patients died. 29% of deaths are ascribable to acute leukemia (**Table 7**), in particular, acute myeloid leukemia (2050 ICD-9-CM code) is the first cause of death; indeed it represents a natural evolution of the disease.[32] The second cause of death is MDS (2387 ICD-9-CM code), but 12% of deaths are due to other hematologic diseases, this could indicate mis-classification also in the causes of death.

An important focus of our "real life" observation is the impact of comorbidity on survival, which induced physicians to choose the comorbidity code, instead of the MDS code, as the first diagnosis in the hospital report. Furthermore, we observed that mortality causes in low-risk MDS patients' include not only hematologic diseases but also cerebro-cardiovascular events and second tumors. In particular, 20% of low risk patients died of cerebro-cardiovascular events and 13% of second tumors. This finding draws attention to comorbidity assessments to increase patients' survival and quality of life. Our observation is in line with most recent reports on the negative prognostic value of comorbidity not only *per se* but also in the context of the different therapeutic strategies, which may increase the risk of complications.[27,33,34]

All these results can be interpreted in several ways including: 1) inappropriate use of existing ICD-9-CM codes; 2) misclassification with other blood disorders; 3) evolution of the disease over time (which justifies the use of codes specific for different hematological diseases).

Moreover, it is important to stress the limitations of ICD-9-CM classification currently utilized in the HIS, as well as of the more recent ICD-10-CM. In fact, the MDS subtypes are identifiable only by evolving complex algorithms, based on various criteria including symptoms, laboratory tests and molecular genetic investigations that will further change with the application of 2016 WHO classification.[35]

This study highlights for the first time in the Lazio Region that diagnosis and treatment of MDS, which require a considerable use of healthcare resources, tend to be under-documented in the HIS archive, due to difficulties in recognition and coding. We need instruments to improve the HIS, increasing sensitivity and specificity in order to capture information on MDS hospitalizations and outcome.

The strength of our study is the existence of an updated and verified MDS regional registry. One limit is the possible incomplete link between the GROM-L registry and the administrative databases, which drives to the absence of a valid AUPC with a consequent loss of patients in the examined cohort.

The registry could be a useful investigational tool to perform continued surveillance of MDS, effective to monitor potential misdiagnosis and underreporting of these conditions and to collect clinical and epidemiological data for future prevention and treatment strategies.

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