*Journal of BUON* **15:** 547-555, 2010


*ORIGINAL ARTICLE*

# Demo-geographical data of myelodysplastic syndrome based on a large sample of patients from a Romanian Hematological Center

R. Gologan

*Center of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, Bucharest, Romania*

## Summary

***Purpose:*** *To present some retrospective data on the epidemiology of myelodysplastic syndrome (MDS) in Romania, in a large but well-defined territory and over a long period of time, as reflected by a large single-hospital based Registry.*

***Methods:*** *The registration forms provided by the MDS Foundation were filled in with the data of the new adult primary MDS patients admitted in the Hematological Department of Fundeni Clinical Institute, Bucharest, during 1985-2004 and classified according to French-American-British (FAB) criteria.*

***Results:*** *The study comprised 306 patients accrued from a delimited geo-administrative zone, 137 (45%) from Bucharest and 169 (55%) from the rest of the region. The results revealed male predominance, obvious increase of the crude and ≥ 60 years age group specific incidence temporal trend, nonnegligible proportion of the < 50 years age group, similar distribution and temporal trend of both rural/urban areas and gender in all included counties, and no geographical and familial clustering.*

***Conclusions:*** *The increase of the MDS incidence in Romania appears not to be related to the ageing of the population but rather to: 1) the increasing addressability to health care of the elderly; 2) the greater awareness of the physicians on MDS; 3) the expansion of the hematological laboratories network; 4) the increasing number of hematologists and oncologists. The methodology used in this work, using a comprehensive analysis of the standard population, can allow a better comparison of the different MDS Registries of an European or regional network and of the data of the same Registry from different time intervals.*

**Key words:** demo-geographical data, descriptive epidemiology, myelodysplastic syndrome, Romania

## Introduction

Due to difficulties of diagnosis, classification and case recording, the epidemiological features of MDS are still poorly defined. A number of Cancer Registries, mostly from Western countries, have published data on the regional occurrence of MDS, suggesting that MDS is much more common than previously thought and has an increasing incidence trend during the past 20 years, particularly in the elderly [1-3]. However, some studies suggested that many factors such as regional variations, ageing of the population, the increasing performances in the laboratory diagnosis, the degree of awareness in this group of diseases among both the physicians and the patients, differences in classification and in the invasiveness and the complexity of the diagnostic methods are factors which could influence the epidemiological parameters [4-8]. Even with differences in diagnosis and registration, MDS is more and more diagnosed worldwide and therefore population-based studies are still necessary endeavors [9], stimulated also by the appearance of new effective drugs during the past years [10-12].

The aim of this study was to present some detailed demo-geographical characteristics of MDS based on the informations available in the Registry of the Hematological Department, Fundeni Clinical Institute, Bucharest, the most important center of clinical and laboratory hematology in Romania. The general epidemiological data and comparison with other MDS Western and Eastern Registries were reported in a previous paper [13].

*Correspondence to:* Radu Gologan, MD, PhD. Center of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, 258 Fundeni Road, sector 2, Bucharest, Romania. Tel/fax: +40 213180423, E-mail: mds.fundeni@yahoo.com

Received 09-09-2009; Accepted 18-10-2009

## Methods

The registration form provided by the MDS Foundation was filled in with the data of the new adult MDS patients admitted during 1985-2004. For completion, the existing data in the medical records from the archive of the department were used. The FAB classification of MDS was used as it was stipulated by the registration form, but the category "unclassified" was extended in this study for practical reasons, including-besides the cases with isolated neutropenia or thrombocytopenia - also those belonging to hypoplastic, fibrotic and mixed myelodysplastic/myeloproliferative entities. The cases with features or overt MDS secondary either to other disorders or to oncologic therapy were excluded. The diagnosis of MDS was based on well-accepted minimal diagnostic and FAB classification criteria [14]. The cytological examination of smears of peripheral blood and bone marrow was performed in a centralized manner. The morphological features of MDS in more than 10% of cells, the percentage of blasts and of the ringed sideroblasts (Perls stain), as well as the blood cell counts with differential, constituted the main reference points for diagnosis and classification. The histopathological examination of the bone marrow was used everytime when the cytology was inconclusive or for excluding other diseases. Cytogenetic investigation was performed sporadically and therefore no such data were included in this study.

The cohort of 306 patients comprised in this study originated in the geographic-development region South-Muntenia which includes also Bucharest, joined with the surrounding county Ilfov (IF), this zone being denoted B-IF. Besides B-IF, in this region there are 7 adjacent counties: Arges (AG), Calarasi (CL), Dambovita (DB), Giurgiu (GR), Ialomita (IL), Prahova (PH), and Teleorman (TR). Also, 2 close counties, Buzau (BZ) and Olt (OT), belonging to the South-East and South-West region respectively, and providing at least 10 patients each (selected criterion for inclusion), were added. The different administrative subunits had various degrees of environmental pollution by chemical residues of plants, petroleum fields and processing, agrochemicals and mining, and different quality of roads. Also, they differed by the presence of a clinical hematologist, besides a general oncologist in the county hospital (existing only in PH, AG and IL in that time).

The distribution of incidence by age and sex groups, rural and urban dwelling and frequency of FAB subtypes was comparatively analyzed in the different administrative subunits. The specific-adjusted incidence was computed for groups of ≥60 and 16-59 years of age, sex and rural/urban location of the patients, using the specific adult standard population from the whole area and from the different administrative territories. According to the Romanian health system, the limit between pediatric and adult age of patients is 16 years.

### *Statistical analyses*

The setting of the data and their statistical and graphic analysis were performed by means of Excel (Microsoft) and the Primer of Biostatistics Soft [15]. The tests of relative risk for comparing two proportions and the test for coincidence of two regression lines to compare the slopes of the temporal trends were used, respectively. The significance threshold was 0.05. The demographic data of the standard population were obtained from the official information of the Romanian Institute of Statistics.

The temporal trend of the incidence was determined by two methods, namely by statistical comparison of the incidence in the first and the second decade of the whole investigated interval, and by statistical comparison of the slopes of the temporal trend of the incidence. Because the results were comparable, the second method was used in this study due to its practical advantages (automatic and graphic facilities for computing and illustration, the standard error determination and easiness of the statistical comparison).

## Results

### *Overall demo-geographical distribution*

The existing geographic-development regions of Romania and the public hospital units with clinical hematology facilities are presented in Figure 1A. At the beginning of the study there were only 2 hematological departments in Bucharest and around 10 in the rest of the country. Presently, there are 20 units with hospitalized hematological patients in the county-towns and 6 in Bucharest. No private physicians' offices or medical centers existed that time.

The selected 306 patients analyzed in this study represented the greatest part (73%) of the patients from our MDS Registry. They were recruited from a well-delineated geographic-administrative area, corresponding to the region South-Muntenia and two adjacent counties (Figure 1B). As shown in Table 1, the average standard population in the delineated zone was 5,560,566 inhabitants, 1/3 of the population (1,940,710 inhabitants) originating in B-IF and 2/3 (3,619,856 inhabitants) in the rest of the territory. Referring to the MDS patients, B-IF supplied 137 (45%) and the rest of the ar-

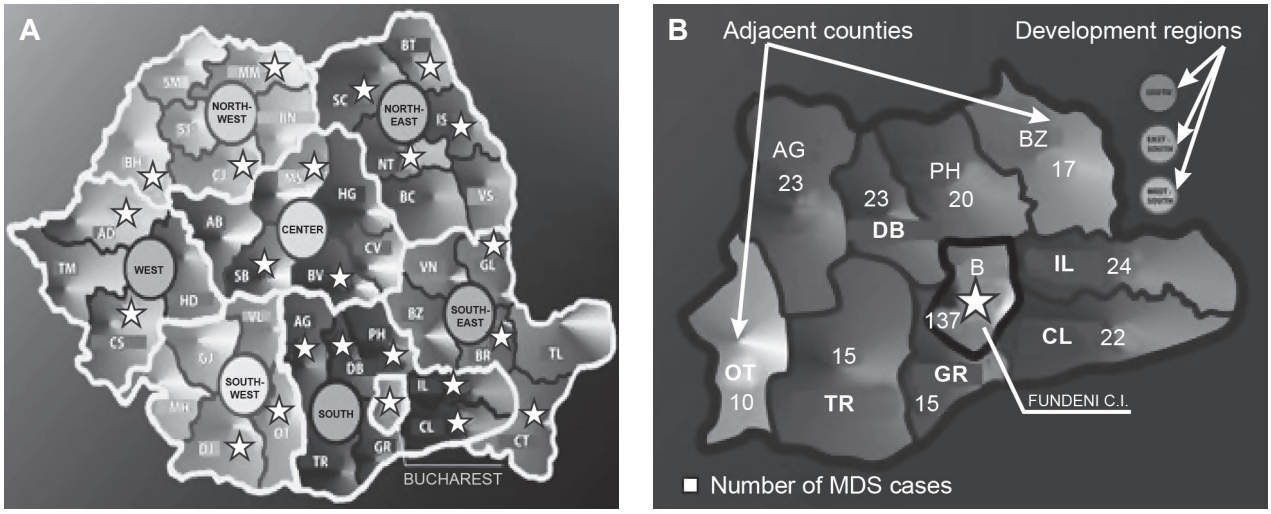


**Figure 1.** Map of Romania. **A:** The geographic-development regions and the county hospitals with clinical hematology departments (marked by white stars). **B:** The South-Muntenia region (marked by a darker greyish shade) and two adjacent counties OT and BZ. For abbreviations of the counties see text.

**Table 1.** The overall demo-geographical distribution of MDS cases in the whole area and in its administrative territorial subunits[a]

| *Administrative subunits* | *Adult standard population[b] (inhabitants)* | *MDS cases n (%)* | *Crude incidence[c]* | *Slope values of the trend of the crude incidences* |
|---|---|---|---|---|
| B-IF | 1,940,710 | 137 (45) | 0.35 | 0.033 ± 0.006 |
| AG | 541,342 | 23 (7.5) | 0.21 | 0.012 ± 0.006 |
| BZ | 379,260 | 17 (5.5) | 0.30 | 0.032 ± 0.011 |
| CL | 290,060 | 22 (7.2) | 0.38 | 0.042 ± 0.017 |
| DB | 441,196 | 23 (7.5) | 0.26 | 0.020 ± 0.007 |
| GR | 241,622 | 15 (4.9) | 0.31 | 0.032 ± 0.014 |
| IL | 243,503 | 24 (7.8) | 0.49 | 0.070 ± 0.009 |
| OT | 412,634 | 10 (3.2) | 0.12 | 0.013 ± 0.006 |
| PH | 702,545 | 20 (6.5) | 0.14 | 0.012 ± 0.005 |
| TR | 367,694 | 15 (4.9) | 0.20 | 0.026 ± 0.006 |
| WA | 5,560,566 | 306 (100) | 0.27 | 0.029 ± 0.004 |

[a]Significantly discrepant values are underlined, [b]Average values in the period 1990-2004, [c]Average annual incidence in the period 1985-2004, WA: whole area, MDS: myelodysplastic syndrome. For abbreviations of the counties see text

ea 169 (55%). The distribution of the MDS cases in the counties was the following: AG 23 (7.5%), 17 (15%), 22 (7.2%), 23 (7.5%), GR 15 (4.9%), IL (7.8%), OT (3.2%), PH (6.5%), TR 15 (4.9%).

The crude incidence in the whole area during the analyzed period of time was 0.27 cases/100,000 inhabitants, the greatest incidence being found in the county IL (0.49) (relative risk 1.791, 95% confidence interval 1.182-2.713, p=0.008). The incidence of the MDS cases increased during the analyzed period in the whole area and in all the administrative subunits as indicated by the positive values of the slopes, which express the temporal trend of the MDS incidence. They varied between 0.012 in AG and PH to 0.07 in IL (Table 1), and are illustrated by the ascending linear curve of the temporal trend of the overall MDS cohort in all administrative areas (Figure 2A). The increasing trend was significantly higher (p=0.0001) in the county IL (slope value=0.07±0.009; Table 1). The dynamics of the increase was not continuous over the analyzed period and not similar in the different administrative territorial subunits.

The increase of the incidence was also visible when it was assessed by comparing its values from the first and the second part (10 years each) of the analyzed period of time. A highly significant difference (p=0.0001) between the two decades for the whole area was found. The increase of the incidence measured by this method was not significant for the counties AG, OT and PH, for which the slopes of the trend determined by the first method were very small.

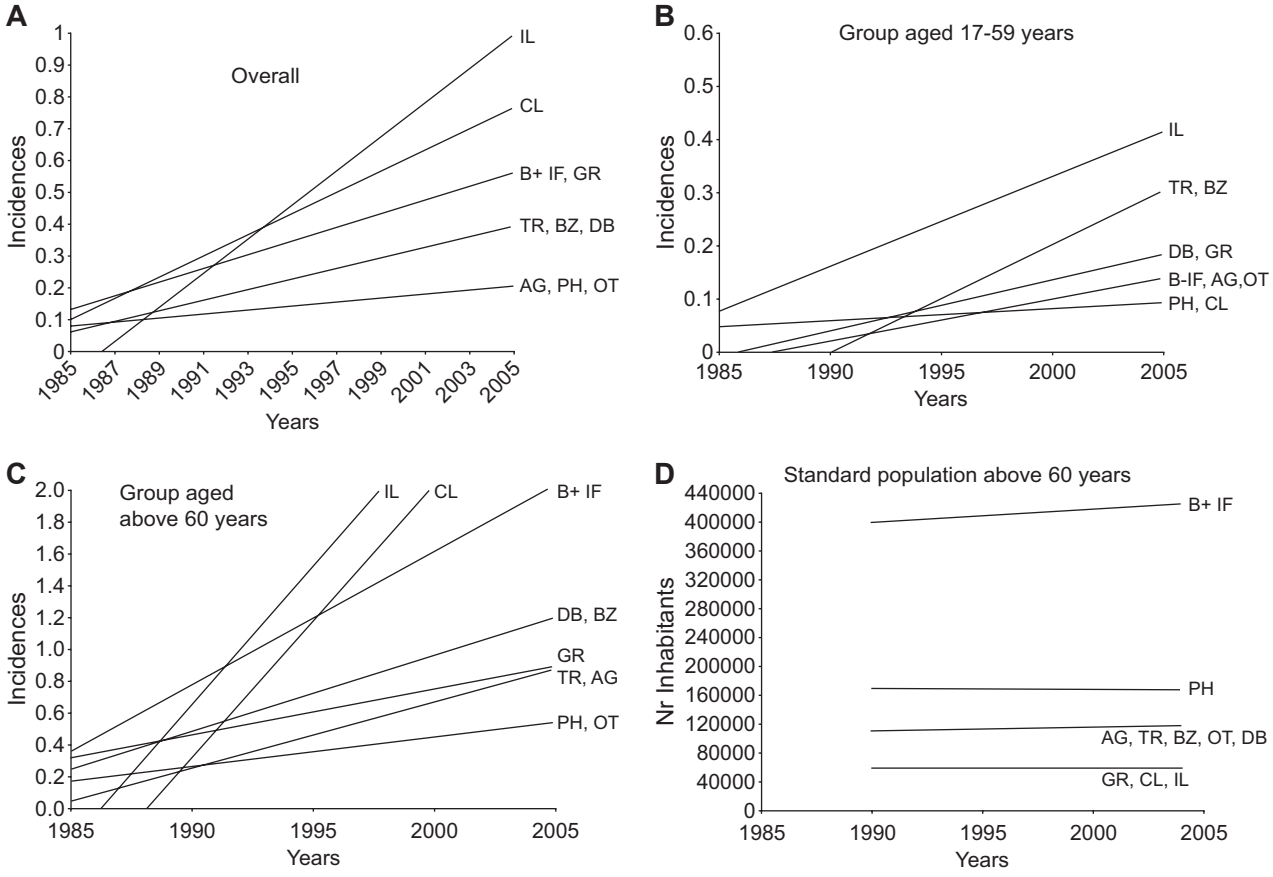


**Figure 2. A:** The trends of overall, **B:** 17-59 years age group, **C:** ≥ 60 years age group MDS incidence, and **D:** the "ageing" of the standard population in different administrative subunits. For abbreviations of the counties see text.

*Demo-geographical distribution depending on age and gender*

Distribution by age showed that 72% of the patients were ≥60 years old. On the other hand, a non-negligible proportion of the patients < 50 years (14% in the whole area) was registered (Table 2). Ascending temporal trends of the age-adjusted incidence of the groups > 60 and 16-59 years old were registered in all the administrative subunits as illustrated in Figure 2C and 2B, respectively. Also, the values of the slope of the trend of age group-adjusted incidence were greater in

**Table 2.** The demo-geographical distribution of MDS cases by groups of age over 60 and 16-59 years

| *Area subunits* | *Proportion of over 60 years SP and MDS cases (%)* | | *Proportion of cases 16-50 years (%)* | *Comparison of age-adjusted incidence of the groups over 60 and 16-59 years* | | | *Comparison of the slope values of the trend of age-adjusted incidences* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *SP* | *MDS* | | *over 60* | *16-59* | *p-value* | *over 60* | *16-59* | *p-value* |
| B-IF | 19 | 79 | 13 | 1.30 | 0.09 | 0.0001 | 0.126 | 0.006 | 0.0001 |
| AG | 23 | 60 | 12.5 | 0.61 | 0.10 | 0.0001 | 0.037 | 0.006 | 0.3 |
| BZ | 28 | 53 | 23.5 | 0.41 | 0.14 | 0.05 | 0.059 | 0.025 | 0.2 |
| CL | 25 | 84 | 8.6 | 1.30 | 0.09 | 0.0001 | 0.153 | 0.001 | 0.04 |
| DB | 24 | 65 | 17.3 | 0.73 | 0.11 | 0.0001 | 0.084 | 0.012 | 0.04 |
| GR | 30 | 73 | 13.3 | 0.76 | 0.11 | 0.0001 | 0.057 | 0.012 | 0.2 |
| IL | 25 | 62 | 16 | 1.22 | 0.24 | 0.0001 | 0.205 | 0.026 | 0.0001 |
| OT | 26 | 60 | 0 | 0.28 | 0.06 | 0.03 | 0.023 | 0.010 | 0.5 |
| PH | 24 | 60 | 25 | 0.36 | 0.07 | 0.0001 | 0.023 | 0.005 | 0.4 |
| TR | 29 | 65 | 5.8 | 0.42 | 0.09 | 0.009 | 0.045 | 0.019 | 0.2 |
| WA | 23 | 72 | 14 | 1.2 | 0.16 | 0.0001 | 0.117 | 0.016 | 0.0001 |

SP: standard population, WA: whole area, MDS: myelodysplastic syndrome. For abbreviations of the counties see text

**Table 3.** The demo-geographical distribution of MDS cases depending on gender[a]

| *Administrative subunits* | *Sex-adjusted incidence* | | | *Slope values of the trend of sex-adjusted incidence* | |
|---|---|---|---|---|---|
| | *Male* | *Female* | *M/F* | *Male* | *Female* |
| B-IF | 0.40 | 0.30 | 1.3 | 0.036 | 0.022 |
| AG | 0.26 | 0.16 | 1.6 | 0.017 | 0.010 |
| BZ | 0.19 | 0.25 | 0.8 | 0.025 | 0.028 |
| CL | 0.42 | 0.33 | 1.3 | 0.035 | 0.035 |
| DB | 0.30 | 0.22 | 1.4 | 0.022 | 0.013 |
| GR | 0.34 | 0.28 | 1.2 | 0.012 | 0.037 |
| IL | 0.60 | 0.40 | 1.5 | 0.077 | 0.041 |
| OT | 0.20 | 0.04 | 5.0 | 0.015 | 0.001 |
| PH | 0.12 | 0.16 | 0.7 | 0.009 | 0.010 |
| TR | 0.36 | 0.05 | 7.2 | 0.038 | 0.009 |
| WA | 0.32 | 0.23 | 1.4 | 0.027 | 0.021 |

[a]Significantly discrepant values are underlined, WA: whole area. All p-values non significant. For abbreviations of the counties see text

the ≥ 60 than in the 16-59 age group, the difference being significant in all administrative subunits and in the whole area (p=0.0001; Table 2). An overall significant difference (p=0.001) between the percentage of the ≥ 60 years age group of the standard population and of MDS cases in all local areas was found. The trend of the incidence in the group ≥ 60 years was not in correlation with the trend of the standard population of the same age group, the last one being much slower or even decreasing (Figure 2D).

A more detailed analysis of the ≥ 60 years age group was performed. In the standard population of 5,560,566 inhabitants, the ≥ 60 years age group constituted 23% (range 19-30% in different administrative subunits). In this category, the groups aged 60-69 and over 70 years represented 50% each, with almost similar distribution in B-IF and the counties.

The MDS patients ≥ 60 years represented 72% from all cases in the whole area (range 53 - 84% in different administrative subunits), being almost equally distributed in B-IF and in the territory outside it. In this category, the group 60-69 years represented 52% (37% in B-IF and 63% in the counties), the group 70-79 years 40% (71% in B-IF and 29% in the counties) and the group >80 years 8% (70% in B-IF and 30% in the counties). Concerning the distribution of these age groups in and outside B-IF, a predominance of the 60-69 years age group in the counties (63%) vs. a predominance (70%) of the age groups 70-79 and >80 years and a significant higher specific incidence of the group > 70 years in B-IF were noticed (2.0 vs. 0.54). Also, only in B-IF the increase of the temporal trend of the >70 years age group was significantly higher compared with the 60-69 years group. No analysis of the ≥80 years age group was performed due to missing precise data on the specific standard population and to the small number of the MDS cases in this group.

The male (M)/female (F) average ratio in the standard population was 0.95. Concerning MDS patients, the M/F ratio in the whole region was 1.3. A predominance of males was found in all the geographic-administrative subunits, except the BZ county (Table 3), indicating a higher increase of the number of new cases in males during the analyzed period. However, the slope values of the temporal increase of the male-specific incidence were not significantly different (all p-values >0.05) from those of the females (Table 3).

*Demo-geographical distribution depending on rural (R)/ urban (U) location*

R or U location of the standard population in the analyzed area (B-IF excluded), indicated a R predominance in all counties except PH where the R/U ratio was 0.9 vs. 1.4 in the whole area (Table 4). As for the MDS patients, a greater than one R/U ratio of specific incidence was found only in the OT (1.5), CL (1.4), IL and GR (1.3) counties, R/U being 0.9 in the whole area (Table 4). Therefore, no R predominance of MDS could be proved in our cohort, despite an evident R predominance of the standard population in the analyzed territory. Also, no difference between the slope values of the temporal trend of the incidence in R vs. U location could be noticed (all p-values >0.05; Table 4). No geographical or familial clustering in U or R areas was found.

*Demo-geographical distribution depending on FAB subtype*

The distribution of the FAB subtypes was not significantly different in the administrative subunits, except a higher frequency of RA in the DB county, of RAEB in TR and of CMML in IL (Table 5). The "zigzag" dynamics, generally characterizing the temporal distribution of the MDS cases from this cohort, and an increasing temporal trend of all FAB subtypes was observed (Figure 3A). The slope value of the number of new cases with RA was 0.5526±0.11, being significantly higher than the slopes of those with unclassified type (slope value 0.2782±0.05), RARS (slope value 0.2±0.08), RAEB-T (slope value 0.1496±0.05), and CMML (slope value 0.1038±0.03), but nonsignificantly higher than those with RAEB (slope value 0.3233±0.08). A nonsignificant higher temporal trend of the low-risk vs. high-risk MDS cases was noticed, the slope values being 0.750±0.164 and 0.472±0.094, respectively (Figure 3B).

**Table 4.** The rural (R) vs. urban (U) incidence of MDS patients

| *Area subunits* | *Rural (R)* | | *Urban (U)* | | *R/U ratio of standard population* | *R/U ratio of MDS incidence* | *Slope values of the trend of rural and urban incidence* | |
|---|---|---|---|---|---|---|---|---|
| | *Standard population* | *MDS specific incidence* | *Standard population* | *MDS specific incidence* | | | *R* | *U* |
| AG | 284,916 | 0.20 | 256,426 | 0.20 | 1.1 | 1.0 | 0.011 | 0.012 |
| BZ | 221,235 | 0.18 | 158,025 | 0.28 | 1.4 | 0.6 | 0.026 | 0.048 |
| CL | 174,036 | 0.43 | 116,024 | 0.30 | 1.5 | 1.4 | 0.066 | 0.030 |
| DB | 307,501 | 0.24 | 133,695 | 0.27 | 2.3 | 0.8 | 0.022 | 0.043 |
| GR | 166,116 | 0.33 | 75,506 | 0.26 | 2.2 | 1.3 | 0.038 | 0.023 |
| IL | 146,102 | 0.54 | 97,401 | 0.41 | 1.5 | 1.3 | 0.088 | 0.047 |
| OT | 247,581 | 0.14 | 165,053 | 0.09 | 1.5 | 1.5 | 0.015 | 0.011 |
| PH | 332,785 | 0.04 | 369,760 | 0.23 | 0.9 | 0.2 | 0.007 | 0.015 |
| TR | 240,903 | 0.19 | 126,791 | 0.24 | 1.9 | 0.8 | 0.030 | 0.020 |
| WA | 2,121,175 | 0.23 | 1,498,681 | 0.24 | 1.4 | 0.9 | 0.029 | 0.025 |

WA: whole area. All p-values non significant. For abbreviations of the counties see text

**Table 5.** The demo-geographical distribution of MDS cases depending on FAB subtypes[a]

| *Administrative subunits* | *FAB subtypes (%)* | | | | | |
|---|---|---|---|---|---|---|
| | *RA* | *RARS* | *RAEB* | *RAEB-T* | *CMML* | *UNCLAS* |
| B-IF | 30 | 21 | 19 | 14 | 3 | 13 |
| AG | 35 | 4 | 22 | 9 | 4 | 26 |
| BZ | 29 | 0 | 18 | 6 | 6 | 41 |
| CL | 45 | 23 | 9 | 5 | 9 | 9 |
| DB | 53 | 13 | 4 | 4 | 0 | 26 |
| GR | 20 | 7 | 40 | 7 | 0 | 26 |
| IL | 25 | 4 | 25 | 17 | 17 | 12 |
| OT | 20 | 20 | 40 | 20 | 0 | 0 |
| PH | 20 | 15 | 35 | 10 | 10 | 10 |
| TR | 27 | 0 | 73 | 0 | 0 | 12 |
| Average | 30.4 | 10.7 | 28.5 | 8.6 | 4.9 | 16.3 |
| SD | 11.1 | 8.8 | 19.7 | 6.2 | 5.6 | 13.1 |
| WA | 31 | 14 | 24 | 11 | 5 | 15 |

[a]Significantly discrepant values are underlined, SD: standard deviation, WA: whole area. For abbreviations of the counties see text

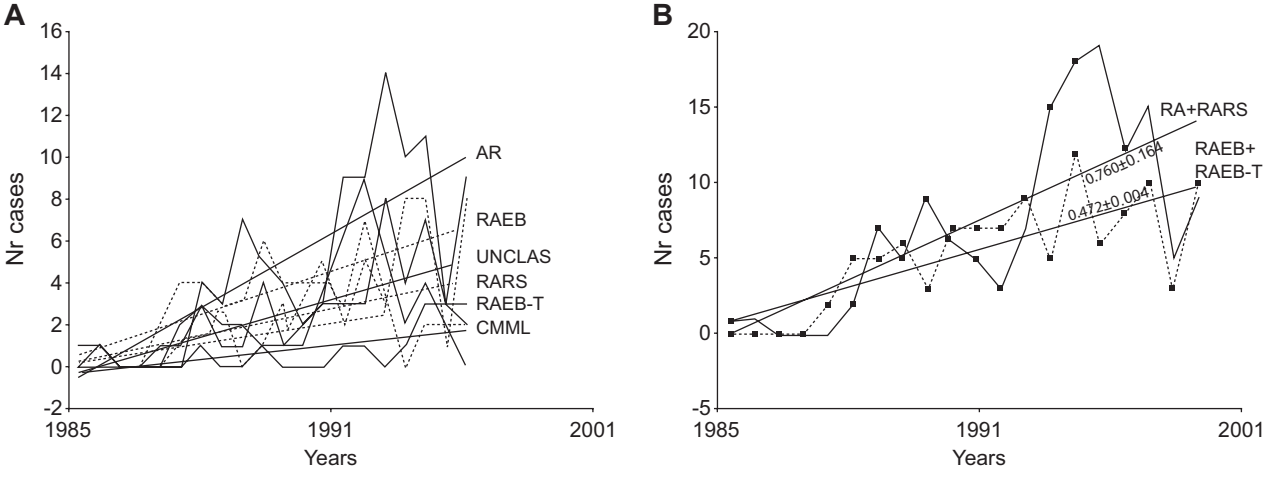


**Figure 3.** The dynamics and trends of the FAB subtypes (**A**) and of low and high-risk MDS (**B**).

## Discussion

The present study is comparable to several other Western studies [5-8,16-20] emphasizing the incidence and other epidemiological characteristics of MDS based on intervals long enough to assess the dynamics of these parameters in a well-established area. For the first time in Romania and in Central and Eastern Europe, a descriptive demo-geographical analysis in a whole well-delineated region and in its territorial-administrative subunits, with a comparison of the temporal trends of the different parameters, was performed.

Some findings of this study are in accordance with those mentioned by others, i.e. that men are more likely to be diagnosed with MDS than women and that MDS predominates in the ≥60 years age group, its incidence being increasing significantly with age. In the present study, a marked temporal increase but with important temporal and interdistrict variations of the crude and age-adjusted incidence, particularly in the elderly, was found. A still unexplained difference between various administrative subunits was also signaled by a recent epidemiological study in USA [16], where MDS rates ranged from 1.5/100,000 in North Carolina to 5.6/100,000 in Detroit. This finding is similar to the significantly higher incidence and trend of MDS in one of the counties (IL) in the present study, which deserves further investigation.

The percentage of the different MDS subtypes was close to those specified by the classical FAB findings, except CMML which was much lower. The unclassified subgroup, which included 15% of all MDS cases from our cohort, will be separately analyzed elsewhere.

Some peculiar epidemiological aspects were, however, revealed by this study and will be discussed below.

*Low incidence of MDS*

In Romania, as in other countries, MDS appears to be a more frequent group of disorders than it was considered in the past. However, in the present study, the crude incidence of MDS was almost 10 times lower than that reported in Western studies, despite the marked increase of the number of new cases during the emphasized interval. As an example, the data of the MDS Registry from Düsseldorf (Germany) indicated a crude median annual incidence of ~ 4/100,000, which was stable during the last 10 years [5,6]. A marked increase of the crude and age-adjusted incidence was found only during the first 15 years of the follow-up, these findings being explained by the improvement in the diagnosis of MDS and by the increasing proportion of the elderly in these countries.

The low incidence of MDS found in the present study could be firstly due to the low representation (5.7%) of the patients ≥80 years, which is in accordance with the very small proportion of the over 80 standard population in Romania. This was in contrast with the proportions of ≥80 years MDS cases of 26, 38 and 37.3% reported in Germany [5], Great Britain [18], and USA [16], respectively. This factor is important having in mind that MDS affects mostly the oldest people as it is emphasized by the reported 5-fold increase of the incidence of MDS in patients aged 80 and older, as compared with those aged 60 to 69 years [9].

Secondly, the chance of old MDS patients to be examined by a hematologist is rather poor in Romania, being much poorer in the rest of the area than in B-IF. This could explain the higher incidence and higher slope of the temporal trend of the MDS patients over 70 years in B-IF observed in this study. Therefore, although the addressability to a specialized health care center of patients from any age group and their level of health education, as well as the physicians' level of information on MDS could be appreciated as increasing in Romania during the past 10 years of the study, the so-called "old MDS" category remained unfavored. Also, the expanding - over time - network of hematological laboratories, facilitating the detection of the non-severe anemic patients, as well as the increasing number of the hematologists and oncologists have to be considered.

The MDS incidence was low in this study, probably because not all the MDS patients were diagnosed and registered in this department. Other two smaller hematological units in Bucharest recruited MDS patients from the same area in this interval. However, even if the number of cases would be doubled by adding these cases, the real crude incidence would remain inferior to that reported in Western studies.

As Romania was a developing country, some demographical findings concerning the overall standard population and MDS cases could be explained by the poorer socio-economic conditions during the analyzed interval. Thus, the temporal dynamics of the MDS incidence in our study appears to be comparable to that reported for the situation existing 30 years ago in Germany and Spain [6,21]. In these countries, in the first decade of the follow-up, the average age at diagnosis was lower by more than 10 years and the incidence of MDS was a little more than 1/100,000. In the USA, in 1995 there were approximately 1,500 new cases each year, while a more recent estimate indicated as many as 15,000 new cases each year [22].

Other factors, such as the quality of diagnosis, could not be incriminated in this study because the level of performance of the laboratory of hematocytol-

ogy was the same during the whole analyzed period of time. Since only cases diagnosed and registered in this department were included in the study, misdiagnosis and underreporting of MDS cases mentioned in other studies [15] cannot be incriminated here.

The improvement of some of the factors mentioned above would probably allow the increase of the number of the registered new MDS adult patients.

*Increasing elderly-specific incidence not related to the ageing of the population*

In the present study, a more than 4-fold higher frequency in the elderly (age-adjusted incidence 1.2/100,000 in the whole area) was found. Despite the lower addressability to health care of the elderly outlined above, the temporal trend of the incidence of this age group increased continuously and, in contrast with the situation in other Western countries [4-6], the rise was not correlated with the ageing of the standard population. The annual average rate of the rise of the over 60 years age group of the standard population was only 0.5% during the past 15 years, while the rate of the annual average rise of the new MDS cases of the similar group of age was 6.6%. Also, the percentage of the elders with MDS was 3-fold higher than the percentage of the standard population of the similar age group in the whole area, and the rising temporal trends of the MDS elderly-adjusted incidence appeared much higher than that of the standard population of the same age group. The overall and ≥60 years-adjusted MDS incidence increased continuously, even during the past 5 years, with no correlation with the ageing of the population, which showed a very slight rise. Taking into account the increased susceptibility of the ≥60 years age group to MDS revealed by this study, a real increase of the incidence of MDS can not be excluded in Romania.

*No apparent influence of the external factors*

With respect to the environmental, occupational, and habitual factors (household habits, traditional practices) no geographical clustering of MDS cases was found. The nature and the degree of environmental pollution varied in different districts: petroleum extraction and processing (PH, BZ), chemical plants (CL, TR), mining (DB), metallurgy (CL), agrochemicals (IL, CL), but no difference in the frequency of MDS in different districts, except IL, and no rural or urban predominance were found. Despite the well-documented more recent data supporting the association between the increased risk of male MDS and occupational exposures to solvents - benzene included - and agrochemicals (pesticides, herbicides or fertilizers) [23], the results are still considered inconclusive. Because in Romania females were involved in many industrial and agricultural activities and because the temporal trends of the males and females MDS cases were very close and sometimes parallel but with slightly higher slopes for males, we suppose that more the increased inborn susceptibility of males than the occupational exposure would explain the MDS male predominance.

No geographical clustering in the analyzed area was found in this study, supporting the general opinion that this is not considered yet a common finding in MDS, even if it was reported recently in USA [24].

The methods of descriptive epidemiological analysis used in this study, including a comprehensive analysis of the standard population, could facilitate a better comparison of the different MDS Registries and of the different study intervals of the same Registry, being useful for the cooperation within the frame of MDS European and international networks.

The results of this study indicate the existence of some regional particularities of the epidemiology of MDS in Europe. Further epidemiological studies are necessary for the assessment of the exact influence of various factors on the incidence of MDS and its trend, using also the study of East/West population migrations in Romania and/or Europe, the standard population and MDS cases in different ethnic groups and the comparison with the surrounding countries from Eastern Europe.

## Acknowledgements

This work was supported by the Romanian Ministry of Education and Research (Contract of Research CEEX-III, Nr 119/2006) and was accepted to the 9th International Symposium on Myelodysplastic Syndrome, Florence, Italy, 16-19.05.2009 (abstr #PO009).

The author would like to thank Professors Ulrich Germing, David Bowen and John M. Bennett for useful discussions, the staff of the Center of Hematology and Bone Marrow Transplantation for their cooperation, and Daniela Georgescu, MD, for the contribution in the setting-up of the material.

## References

1. Mufti GJ. Pathobiology, classification and diagnosis of myelodysplastic syndrome. Best Pract Res Clin Hematol 2004; 17: 543-557.
2. Hamblin TJ. Epidemiology of Myelodysplastic Syndromes. In: Bennett JM (Ed): The myelodysplastic syndromes. Pathobiology and clinical management". Marcel Dekker, NY, 2002, pp 15-27.

3. Reizenstein P, Dabrowski L. Increasing prevalence of the myelodysplastic syndrome. An international Delphi study. Anticancer Res 1991; 11: 1069-1070.
4. Aul C, Germing U, Gattermann N, Minning H. Increasing incidence of myelodysplastic syndromes: real or fictitious? Leuk Res 1998; 22: 93-100.
5. Germing U, Strupp C,. Kündgen A et al. No increase in age-specific incidence of myelodysplastic syndromes. Haematologica 2004; 89: 905-910.
6. Aul C, Giagounidis A, Germing U. Epidemiological features of myelodysplastic syndromes: results from regional cancer surveys and hospital-based statistics. Int J Hematol 2001; 73: 405-410.
7. Maynadie M, Verret C, Moskovtchenko P et al. Epidemiological characteristics of myelodysplastic syndromes in a well-defined French population. Br J Cancer 1996; 74: 288- 290.
8. Radlund A, Thiede T, Hansen S, Carlsson M, Engquist L. Incidence of myelodysplastic syndromes in a Swedish population. Eur J Haematol 1995; 54: 153-156.
9. Strom SS, Vélez-Bravo V, Estey EH. Epidemiology of myelodysplastic syndromes. Semin Hematol 2008; 45: 8-13.
10. Emerging treatment options for adult MDS: a clinical perspective. MDS Foundation Public, 2007.
11. Meletis J, Terpos E. Transplantation strategies for the management of patients with myelodysplastic syndromes. J BUON 2009; 14: 551-564.
12. Grudeva-Popova J. New options in the treatment of myelodysplastic syndrome. J BUON 2005; 10: 35-42.
13. Gologan R, Georgescu D, Tatic A, Radulescu I, Vasilache D. Epidemiological data from the registry of patients with myelodysplastic syndrome in a single hospital center of Romania. Leuk Res 2009; 33: 1551-1561.
14. Steensma DP, Bennett JM. The myelodysplastic syndromes: diagnosis and treatment. In: Tefferi A, Rajkumar SV, Kantarjian HM (Eds): Neoplastic hematology, diagnosis and treatment. Mayo Clinic Proceed, 2006, p 30.
15. Glantz AS (Ed). Primer of Biostatistics (6th Edn). McGraw-Hill, NY, USA, 2005.
16. Rollison DE, Howlader N, Smith MT et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs. Blood 2008; 112: 45-52.
17. Aul C, Gattermann N, Schneider W. Age-related incidence and other epidemiological aspects of myelodysplastic syndromes. Br J Haematol 1992; 82: 358-367.
18. Williamson PJ, Kriger AR, Reynolds PJ, Hamblin TJ, Oscier DG. Establishing the incidence of myelodysplastic syndrome. Br J Haematol 1994; 87: 743-745.
19. Giralt M, Franco-Garcia E, Girlado P et al. Incidence rates of MDS in a Northern-Spanish area. Leuk Res 1999; 23 (Suppl 1): S158 (abstr).
20. Fryzek JP, Kuhen CM, Kaye JA. MDS incidence and mortality in UK general practice research database. Proceedings of the 9th International Symposium on Myelodysplastic Syndrome, Florence (Italy) 16-19.05.2007, (abstr # P005).
21. Sanchez Fayos J, Outeirino Perez JJ, Prieto E et al. Evolutive epidemiologic profile of myelodysplastic syndromes (1959-1993). Comparative study with acute myeloid leukemia and aplastic pancytopenias. Sangre (Barc) 1994; 39: 441-448.
22. Ma X, Does M, Raza A, Mayne ST. Myelodysplastic syndromes. Incidence and survival in the United States. Cancer 2007; 109: 1536-1542.
23. Strom SS, Gu Y, Gruschkus SK, Pierce SA, Estey EH. Risk factors of myelodysplastic syndromes: a case-control study. Leukemia 2005; 19: 1912-1918.
24. Ma X, Selvin S, Raza A, Foti K, Mayne S. Clustering in the incidence of myelodysplastic syndromes. Leuk Res 2007; 31: 1683-1686.