Income, education and their impact on treatments and survival in patients with myelodysplastic syndromes

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Abstract

Objectives: To assess whether socioeconomic indices such as income and educational level can explain part of the variation in survival among patients with myelodysplastic syndromes, and further to assess whether these factors influence care and treatment decisions.

Methods: Population-based cohort study on 2945 Swedish patients diagnosed between 2009 and 2018 and included in the Swedish MDS Register. Relative mortality was assessed by Cox regression, whereas treatment differences were assessed by Poisson regression. Regarding mortality, patients were also compared to a matched comparison group from the general population.

Results: Mortality was 50% higher among patients in the lowest income category compared to the highest and 40% higher in patients with mandatory school education only compared to those with college or university education. Treatment with hypomethylating agents and allogeneic stem cell transplantation, as well as investigation with cytogenetic diagnostics were also linked to income and education. The findings were not explained by differences in risk class or comorbidity at the time of diagnosis.

Conclusions: Income and education are linked to survival among patients with myelodysplastic syndromes. Socioeconomic status also seems to influence treatment intensity as patients with less income and education receive hypomethylating agents and transplants.

Keywords
cohort studies, epidemiology, mortality, myelodysplastic syndromes, socioeconomic factors

Novelty statement: Myelodysplastic syndromes are diseases associated with high risk of death, but the course of disease varies substantially between patients.

In our study, we demonstrate that patients with high education or high income have better prognosis and are more actively treated, even in a uniform health care system with low direct costs for patients.

The study indicates that removal of underlying risk factors or increased health care support to less privileged MDS patients could improve prognosis in this group.
### INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal haematopoietic stem cell disorders, characterised by cytopenias, expansion of myeloid cell lines with impaired maturation and risk of transformation to acute myeloid leukaemia.\(^1\) The yearly incidence of MDS is reported to be approximately 3-5 per 100 000 inhabitants.\(^2,3\) MDS is a disease with high mortality, with a 5-year overall survival of 21%-30%.\(^5,6\) However, the prognosis varies for individual patients and the International Prognostic Scoring System, IPSS,\(^7\) and its revision IPSS-R\(^8\) are useful and powerful tools in determining prognosis in MDS. Treatment options for higher-risk MDS are limited and the only potentially curative treatment is allogeneic stem cell transplantation (SCT). However, since MDS primarily affects the ageing population with a median age of 75 years at diagnosis,\(^9\) only a limited number of patients can be offered SCT due to high age and comorbidities. Hypomethylating agents (HMA) are disease-modifying treatments shown to improve survival in high-risk MDS and also used as a bridge to SCT.\(^10\)

Whether the course of MDS is affected by socioeconomic factors is still under debate. A study based on SEER data from the United States found higher mortality in MDS patients from low- or medium-income areas compared to high-income areas.\(^11\) However, smaller studies from Minnesota,\(^12\) Maryland,\(^13\) Ontario\(^14\) and Scotland,\(^15\) have failed to replicate this finding, and authors have suggested that the reported differences in the larger US study could derive from unequal access to primary care.

In this population-based study of 2945 Swedish MDS patients, we aim to assess the impact of income, educational level and family characteristics on survival. We further evaluate whether socioeconomic factors may influence probability among MDS patients to be treated with HMA or with allogeneic SCT in a country where the population has general access to a tax-financed health care.

### METHODS

#### 2.1 Data sources

Our cohort consisted of all patients in the Swedish MDS Register with a diagnosis of any variant of MDS, excluding patients with myelodysplastic/myeloproliferative neoplasm (MDS/MPN), between January 2009, when the register was initiated, and December 2018. Two patients had no registered income or education and were excluded. In all, the cohort included 2945 patients.

The Swedish MDS Register aims at including all adult Swedish patients with MDS, with diagnostic, prognostic and clinical data from time of diagnosis. From 2012 and onwards, follow-up data at 1 year and every third year after diagnosis is recorded. Compared to the Swedish Cancer Register, to which reporting is mandatory for clinicians and pathologists, the coverage was 97% for the years 2009-2015.\(^16\) In our data, we had access to 1-year follow-up for 1562 patients (53%), 3-year follow-up for 523 patients (18%) and 6-year follow-up for 26 patients (1%). The Swedish MDS register is described in detail elsewhere.\(^7\) Use of HMA was retrieved from the MDS register, and a patient was considered treated if treatment with azacitidine or decitabine was reported at diagnosis or any of the follow-up reports. Patients with a history of treatment with irradiation or chemotherapy prior to the diagnosis of MDS according to the MDS register were considered to have therapy-related MDS. In the register, all patients are classified according to WHO 2008 or 2016. For our analyses and for the presentation all patients were reclassified according to WHO 2016.\(^17\) MDS with ring sideroblasts were grouped together and not divided according to single- or multi-lineage dysplasia.

Since all residents in Sweden are assigned a unique national registration number at birth or immigration, linkage of several nationwide registers is possible. To assess the burden of comorbidity at the time of MDS diagnosis, we used data from the National Patient Register, which holds records of ICD (International Classification of Diseases) coded hospital discharge diagnoses. The National Patient Register was also used to detect SCT not recorded in the Swedish MDS Register. The National Patient Register covers all Swedish in-patient care from 1987 and onwards. Since 2001, diagnoses from specialised out-patient care are also recorded.\(^18\) Comorbidity was estimated using the Charlson comorbidity index,\(^19\) including all relevant diagnoses from the register during 10 years preceding MDS diagnosis. As the Charlson comorbidity index was originally not intended for register-based research, we used the adjusted version suggested by the Royal College of Surgeons,\(^20\) which in a recent evaluation has been recommended.\(^21\)

Socioeconomic characteristics were obtained from the integrated database for labour market research (LISA),\(^22\) with data available from 1990 onwards on educational background, income, sick leave and several other socioeconomic indicators for all Swedish citizens 16 years of age and older. The LISA database is a compilation of data from several registers at Statistics Sweden and other authorities. Data on disposable income include not only taxable income (such as salary, dividends, capital gain, interests, pensions), but also all types of governmental benefits (health insurance, child support, study allowances and likewise). Since tax-deductible losses in the capital market, from property sales, or from interests are also included, income can in extreme cases be negative. To avoid undue impact of outliers, both personal and family incomes were divided into quintiles. Data on education were collapsed from the original classification into three categories; primary (mandatory) school only (≤9 years), at least some college or university (≥13 years), or anything between these two (10-12 years).

As socioeconomic indices are known to affect mortality in the normal population, five population comparators for each MDS case were randomly chosen from the Swedish Total Population Register among those with the same sex, birth year and county of residence. One comparator subject was later excluded due to missing data, leaving 14 724 matched comparators. Both patients and comparators were followed for death or permanent emigration in the Swedish Total Population Register until November 20th 2019.
2.2 | Statistical analysis

Analyses of relative mortality were performed with Cox proportional hazards models, yielding hazard ratios (HR) with 95% confidence intervals (95% CI) as measures of relative risk of death. Potential interactions (such as differences in associations between cases and population comparator subjects) were analysed by stratified analyses and formally tested by adding interaction terms to the proportional hazards model. Survival plots were designed using the Kaplan-Meier method. The probabilities of obtaining cytogenetic diagnostics, receiving HMA treatment or undergoing SCT were assessed by Poisson regression using PROC GENMOD in SAS. All P-values were two-sided and a value below .05 was considered statistically significant. All analyses were performed with SAS University Edition statistical software (SAS Inc).

2.3 | Ethical considerations

The study was approved by the Ethics Committee of Uppsala University (2014/176). Record linkages were performed at Statistics Sweden and the National Board of Health and Welfare. All data were de-identified before analysis.

3 | RESULTS

In our cohort, the median age at MDS diagnosis was 76 years, range 16-97 years. At diagnosis, 71% of the patients were above age 70. There was a clear male predominance, with 59% male and 41% female patients. Follow-up for survival ranged between 0 and 10 years, with a median follow-up of 1.9 years. Median survival was 2.3 years.

Age and comorbidity at time of diagnosis increased mortality, while calendar year of diagnosis had no impact on survival. Female patients had slightly better survival compared to males, transfusion-dependent patients and patients with therapy-related MDS had worse survival, and as expected the prognostic scoring systems IPSS and IPSS-R were both closely linked to survival (Table 1). Living in a region with or without a university hospital had no impact on prognosis (data available on request).

Both income and education were correlated to survival (Figure 1), and these associations remained after adjustment for baseline factors (age, sex, MDS subclass, Charlson comorbidity index and IPSS-R) (Table 2). Following adjustment, the mortality was 50% higher in the lowest income quintiles compared to the highest (HR 1.5; 95% CI 1.3-1.8) and 40% higher among patients with only mandatory school compared to those with college or university education (HR 1.4; 95% CI 1.2-1.6). Mortality was also higher among patients living in a single-person household. Meanwhile, similar associations were also present among population comparators. The association between mortality and income was slightly stronger in cases than in comparators, whereas associations to education were slightly stronger in comparators than in cases.

| TABLE 1 | Baseline clinical parameters in 2945 MDS patients and their impact on all-cause mortality |
|-----------------|------------------------|------------------------|
| **Age at diagnosis, y** | n (%) (total n = 2945) | Hazard ratio (95% confidence interval) |
| <75 | 1371 (47%) | 1 (ref) |
| ≥75 | 1574 (53%) | 1.7 (1.6-1.9) |
| **Year of diagnosis** | Hazard ratio (95% confidence interval) |
| 2009-2012 | 1132 (38%) | 1 (ref) |
| 2013-2015 | 952 (32%) | 1.0 (0.9-1.1) |
| 2016-2018 | 861 (29%) | 1.0 (0.9-1.1) |
| **Sex** | Hazard ratio (95% confidence interval) |
| Male | 1744 (59%) | 1 (ref) |
| Female | 1201 (41%) | 0.9 (0.8-0.9) |
| **MDS subtype** | n (%) | Hazard ratio (95% confidence interval) |
| MDS-SLD | 225 (8%) | 1 (ref) |
| MDS-MLD | 908 (31%) | 1.1 (0.9-1.3) |
| MDS-RS | 308 (11%) | 0.6 (0.5-0.8) |
| MDS-EB1 | 462 (16%) | 2.1 (1.8-2.6) |
| MDS-EB2 | 527 (18%) | 2.4 (2.0-2.9) |
| MDS with isolated 5q- | 116 (4%) | 0.8 (0.6-1.1) |
| MDS-U | 353 (12%) | 1.4 (1.1-1.7) |
| **IPSS** | Hazard ratio (95% confidence interval) |
| Low | 808 (34%) | 1 (ref) |
| Intermediate-1 | 832 (35%) | 1.7 (1.5-1.9) |
| Intermediate-2 | 539 (22%) | 3.6 (3.1-4.1) |
| High | 222 (9%) | 5.0 (4.2-5.9) |
| **IPSS-R** | Hazard ratio (95% confidence interval) |
| Very low | 424 (19%) | 1 (ref) |
| Low | 664 (30%) | 1.6 (1.4-2.0) |
| Intermediate | 418 (19%) | 2.9 (2.4-3.5) |
| High | 355 (16%) | 4.8 (3.9-5.8) |
| Very high | 345 (16%) | 7.8 (6.5-9.5) |
| **Erythrocyte transfusion dependent at diagnosis** | Hazard ratio (95% confidence interval) |
| No | 2490 (85%) | 1 (ref) |
| Yes | 455 (15%) | 1.5 (1.4-1.7) |
| **Charlson comorbidity index** | Hazard ratio (95% confidence interval) |
| 0 | 1449 (49%) | 1 (ref) |
| 1 | 482 (16%) | 1.5 (1.3-1.7) |
| 2 | 501 (17%) | 1.6 (1.4-1.8) |
| 3 | 240 (8%) | 1.8 (1.5-2.1) |
| 4 | 109 (4%) | 2.4 (1.9-3.0) |
| 5 | 54 (2%) | 2.5 (1.9-3.3) |
| ≥6 | 110 (4%) | 2.4 (2.0-3.0) |

Abbreviations: EB, excess blasts; MLD, Multi lineage dysplasia; RS, Ring sideroblasts; SLD, Single lineage dysplasia; U, Unclassified.

Missing data on 46 cases for subtype, 544 cases for IPSS, 739 cases for IPSS-R, and 9 cases for transfusion dependency.
Transfusion dependency at diagnosis was associated with worse survival, but also with income and education. Among patients in the highest personal income quintile, 36% were transfusion dependent at diagnosis compared to 46%-52% among lower-income quintiles, possibly indicating lead time bias (Table 3).

Overall, 23% of patients (663/2945) were reported to have received HMA treatment upfront or in follow-up reports. The probability of receiving HMA treatment was 40% lower in the lowest personal income quintile compared to the highest (relative risk 0.6, 95% CI 0.5-0.8) and 20% lower among patients with only mandatory school compared to those with the highest education (relative risk 0.8, 95% CI 0.7-1.0) (Table 4). Neither sex, nor living in a single-person household, had an impact on the chance of receiving HMA treatment.

Among the 1371 patients younger than 75 years at diagnosis, 242 patients (18%) had a record of SCT either in the MDS register or in the Patient register. Independently of age, transfusion dependency, comorbidities and prognostic indices at diagnosis, income and education were both associated with probability of undergoing SCT (relative risk in lowest income categories compared to highest 0.3, 95% CI 0.2-0.5) (Table 5).

Most patients were evaluated with cytogenetic diagnostics at diagnosis. Among the 20% who were not, patients tended to have lower income and education, also after adjustment for age, subtype, transfusion dependency and comorbidity index (Table S1). The probability of not having cytogenetic diagnostics in the lowest household income category compared to the highest was 2.1 (95% CI 1.5-2.9), and in the lowest education category compared to the highest 1.4 (95% CI 1.2-1.8).
In this large, population-based study, we demonstrate that Swedish MDS patients with lower income or shorter education have shorter survival. They are further less likely to be investigated with cytogenetic diagnostics, and less likely to receive treatment with hypomethylating agents, or an allogeneic SCT—the only existing curative treatment for MDS today.

The findings on mortality are in line with the previous reported SEER data from the United States. On a similar topic, three American studies on SCT have also found associations between survival among transplanted MDS patients and income. While it could be speculated that the differences in the American studies derive from differences in health insurance policies, our study was performed in a country where nearly all specialised care and medications are publically funded with minimal cost to the individual patient, and healthcare on equal conditions for the entire population is mandated by law. Sweden is also a country with free schools and higher education, and relatively small variance in income. Although income redistribution has declined during the recent decades, Sweden remains one of the world’s most economically equal countries.

As mentioned in the background section, four studies from various regions of North America and Europe have failed to demonstrate survival differences in MDS patients based on socioeconomic factors. As socioeconomic differences depend on the population studied, the discrepancy between their and our results could be correct. However, the four previous studies were substantially smaller, with analyses on socioeconomic factors on cohorts ranging from 159 to 399 patients. They might thus have been underpowered to detect differences demonstrated in our material, encompassing approximately ten times as many patients as each of the previous studies. Moreover, three of the studies had not access to individual data on income or education, but used median incomes based on residential area.

Data on socioeconomic factors in relation to treatment choices in MDS are scarce. In a study from the Dana-Farber institute in

### TABLE 2  Mortality in MDS patients and in age- and sex-matched comparators in relation to personal and socioeconomic data

| Household income quintile | n (%) | MDS patients | Comparators |
|--------------------------|-------|--------------|-------------|
| 1 (more affluent)        | 567 (19%) | 1 (ref) | 1 (ref) |
| 2                        | 624 (21%) | 1.2 (1.1-1.4) | 1.2 (1.0-1.5) |
| 3                        | 549 (19%) | 1.4 (1.2-1.6) | 1.4 (1.2-1.7) |
| 4                        | 631 (22%) | 1.6 (1.3-1.8) | 1.5 (1.2-1.8) |
| 5 (less affluent)        | 551 (19%) | 1.6 (1.4-1.9) | 1.5 (1.3-1.8) |

| Personal income quintile | n (%) | MDS patients | Comparators |
|--------------------------|-------|--------------|-------------|
| 1 (more affluent)        | 579 (20%) | 1 (ref) | 1 (ref) |
| 2                        | 608 (21%) | 1.3 (1.1-1.5) | 1.3 (1.1-1.5) |
| 3                        | 586 (20%) | 1.4 (1.2-1.7) | 1.4 (1.2-1.7) |
| 4                        | 592 (20%) | 1.6 (1.3-1.8) | 1.5 (1.2-1.7) |
| 5 (less affluent)        | 557 (19%) | 1.4 (1.2-1.7) | 1.5 (1.3-1.8) |

| Educational level (y in school) | n (%) | MDS patients | Comparators |
|---------------------------------|-------|--------------|-------------|
| ≥13 y                           | 689 (24%) | 1 (ref) | 1 (ref) |
| 10-12 y                         | 1170 (40%) | 1.3 (1.2-1.5) | 1.3 (1.1-1.4) |
| ≤9 y                            | 1046 (36%) | 1.4 (1.2-1.6) | 1.4 (1.2-1.6) |

| Living alone | n (%) | MDS patients | Comparators |
|--------------|-------|--------------|-------------|
| No           | 1650 (56%) | 1 (ref) | 1 (ref) |
| Yes          | 1295 (44%) | 1.1 (1.1-1.3) | 1.1 (1.0-1.2) |

**Abbreviations:** HR, Hazard ratio, CI, Confidence interval. comorbidty index.

1Adjusted for age at diagnosis, sex, MDS WHO subclass, IPSS-R risk class, transfusion dependency, and Charlson

2Adjusted for age and Charlson comorbidity index.

3Missing data for income on 23 cases and 65 controls and for education on 40 cases and 244 controls.

### 4 | DISCUSSION

In this large, population-based study, we demonstrate that Swedish MDS patients with lower income or shorter education have shorter survival. They are further less likely to be investigated with cytogenetic diagnostics, and less likely to receive treatment with hypomethylating agents, or an allogeneic SCT—the only existing curative treatment for MDS today.

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| TABLE 3  | Baseline clinical parameters in MDS patients in relation to income quintile |
|----------|--------------------------------------------------------------------------------|

| Personal disposable income quintile | 1 (highest) | 2 | 3 | 4 | 5 (lowest) | P |
|-----------------------------------|-------------|---|---|---|-------------|---|
| **Age at diagnosis, y**           |             |   |   |   |             |   |
| <75                               | 420 (73%)   | 317 (52%) | 216 (37%) | 205 (35%) | 196 (35%) | <.0001 |
| ≥75                               | 159 (27%)   | 291 (48%) | 370 (63%) | 387 (65%) | 361 (65%) |           |
| **Year of diagnosis**             |             |   |   |   |             |   |
| 2009-2012                         | 155 (27%)   | 203 (33%) | 216 (37%) | 269 (45%) | 275 (49%) | <.0001 |
| 2013-2015                         | 197 (34%)   | 202 (33%) | 178 (30%) | 195 (33%) | 174 (31%) |           |
| 2016-2018                         | 227 (39%)   | 203 (33%) | 192 (33%) | 128 (22%) | 108 (19%) |           |
| **Sex**                           |             |   |   |   |             |   |
| Male                              | 430 (74%)   | 435 (72%) | 368 (63%) | 302 (51%) | 194 (35%) | <.0001 |
| Female                            | 149 (26%)   | 173 (28%) | 218 (37%) | 290 (49%) | 363 (65%) |           |
| **MDS subtype**                   |             |   |   |   |             |   |
| MDS-SLD                           | 36 (7%)     | 40 (7%)  | 39 (7%)  | 40 (7%)  | 54 (10%)  | .3       |
| MDS-MLD                           | 183 (35%)   | 193 (34%) | 161 (30%) | 171 (30%) | 147 (27%) |           |
| MDS-RS                            | 50 (10%)    | 58 (10%)  | 64 (12%)  | 68 (12%)  | 56 (10%)  |           |
| MDS-EB1                           | 86 (16%)    | 98 (17%)  | 92 (17%)  | 87 (15%)  | 76 (14%)  |           |
| MDS-EB2                           | 100 (19%)   | 100 (17%) | 97 (18%)  | 105 (19%) | 93 (17%)  |           |
| MDS with isolated 5q-             | 16 (3%)     | 24 (4%)   | 17 (3%)   | 22 (4%)   | 28 (5%)   |           |
| MDS-U                             | 54 (10%)    | 63 (11%)  | 69 (13%)  | 70 (12%)  | 81 (15%)  |           |
| **Therapy-related MDS**           |             |   |   |   |             |   |
| Yes                               | 86 (15%)    | 96 (16%)  | 93 (16%)  | 94 (16%)  | 83 (15%)  | 1.0      |
| No                                | 493 (85%)   | 512 (84%) | 493 (84%) | 498 (84%) | 474 (85%) |           |
| **IPSS**                          |             |   |   |   |             |   |
| Low                               | 181 (34%)   | 183 (35%) | 157 (34%) | 141 (31%) | 143 (35%) | .4       |
| Int-1                             | 184 (35%)   | 189 (36%) | 151 (33%) | 157 (34%) | 144 (35%) |           |
| Int-2                             | 123 (23%)   | 117 (22%) | 108 (24%) | 102 (22%) | 84 (20%)  |           |
| High                              | 41 (8%)     | 37 (7%)   | 41 (9%)   | 57 (12%)  | 42 (10%)  |           |
| **IPSS-R**                        |             |   |   |   |             |   |
| Very low                          | 95 (19%)    | 103 (21%) | 86 (21%)  | 65 (16%)  | 73 (19%)  | .1       |
| Low                               | 160 (32%)   | 143 (30%) | 108 (26%) | 124 (30%) | 126 (34%) |           |
| Intermediate                      | 101 (20%)   | 95 (20%)  | 85 (20%)  | 80 (19%)  | 56 (15%)  |           |
| High                              | 69 (14%)    | 79 (23%)  | 73 (17%)  | 70 (17%)  | 57 (15%)  |           |
| Very high                         | 71 (14%)    | 61 (13%)  | 66 (16%)  | 78 (19%)  | 64 (17%)  |           |
| **Erythrocyte transfusion dependent at diagnosis** |       |   |   |   |             |   |
| Yes                               | 209 (36%)   | 277 (46%) | 272 (46%) | 306 (52%) | 268 (48%) | <.0001   |
| No                                | 367 (64%)   | 330 (54%) | 314 (54%) | 282 (48%) | 288 (52%) |           |
| **Charlson comorbidity index**    |             |   |   |   |             |   |
| 0                                 | 347 (60%)   | 312 (51%) | 264 (45%) | 244 (41%) | 267 (48%) | <.0001   |
| 1                                 | 78 (13%)    | 91 (15%)  | 92 (16%)  | 117 (20%) | 101 (18%) |           |
| 2                                 | 90 (16%)    | 107 (18%) | 110 (19%) | 103 (17%) | 88 (16%)  |           |
| 3                                 | 33 (6%)     | 49 (8%)   | 62 (11%)  | 53 (9%)   | 41 (7%)   |           |
| 4                                 | 13 (2%)     | 17 (3%)   | 22 (4%)   | 31 (5%)   | 26 (5%)   |           |
| 5                                 | 6 (1%)      | 5 (1%)    | 13 (2%)   | 17 (3%)   | 13 (2%)   |           |
| ≥6                                | 12 (2%)     | 27 (4%)   | 23 (4%)   | 27 (5%)   | 21 (4%)   |           |

Abbreviations: EB, Excess blasts; MLD, Multi lineage dysplasia; RS, Ring sideroblasts; SLD, Single lineage dysplasia; U, Unclassified.
Boston, household income has been linked to quality of care in MDS, measured as probability of iron status assessment before initiation of erythropoiesis-stimulating agent therapy. In line with our findings, a case-control study from Minnesota also found that MDS patients undergoing SCT had higher incomes and educational level than non-SCT MDS patients, although the associations in their study did not remain significant after adjustment for comorbidities.

When interpreting our results regarding treatment choices, it must be kept in mind that we were missing a proportion of data from follow-up reports, especially regarding HMA treatment. According to the latest report from the Swedish MDS register, 37% of patients are estimated to be treated with HMA during the first year following diagnosis, whereas we only found records of HMA treatment in 23% of the patients in our study. However, this non-differential misclassification based on the fact that the register did not include follow-up in the first years and reporting has been slow for some patients in the recent years, could not explain our associations, but would rather introduce a bias towards null.

If poorer and less educated MDS patients have higher mortality, is it then due to differences in MDS prognosis, comorbidities or lifestyle factors or does it simply come down to the fact that more affluent persons always have better chances in life? Indeed, our population-based comparators also had survival differences based on income and education in the same magnitude as the cases, as has been repeatedly demonstrated in other populations.

That said, the correlation between income and mortality in our MDS patients is not due to higher background mortality in poorer patients. MDS is a lethal disease, and the 2-year mortality was 47% in our patients compared to 9% in our population comparators. Hence, the background mortality has limited impact on the survival among our patients. Furthermore, in a previous study on chronic myeloid leukaemia, we found similar associations between socioeconomic factors and survival, but these associations

| TABLE 4 Relative probability of receiving treatment with hypomethylating agents among MDS patients in relationship to socioeconomic data |
| --- |
| | HMA treated (%) (total n = 2945) | Probability ratio (95% confidence interval) |
| | | Age adjusted | Fully adjusted† |
| Sex | | | |
| Male | 401/1744 (23%) | 1 (ref) | 1 (ref) |
| Female | 262/1201 (22%) | 1.0 (0.8-1.1) | 1.0 (0.9-1.1) |
| Household income quintile | | | |
| 1 (more affluent) | 162/567 (29%) | 1 (ref) | 1 (ref) |
| 2 | 155/624 (25%) | 1.0 (0.8-1.2) | 1.0 (0.8-1.2) |
| 3 | 126/549 (23%) | 1.0 (0.8-1.2) | 0.9 (0.7-1.1) |
| 4 | 124/631 (20%) | 0.9 (0.7-1.1) | 0.8 (0.7-1.0) |
| 5 (less affluent) | 91/551 (17%) | 0.7 (0.6-0.9) | 0.7 (0.5-0.8) |
| Trend | | 0.9, P = .004 | 0.9, P < .0001 |
| Personal income quintile | | | |
| 1 (more affluent) | 167/579 (29%) | 1 (ref) | 1 (ref) |
| 2 | 152/608 (25%) | 1.0 (0.8-1.2) | 0.9 (0.8-1.1) |
| 3 | 129/586 (22%) | 1.0 (0.8-1.2) | 0.9 (0.7-1.1) |
| 4 | 121/592 (20%) | 0.9 (0.7-1.1) | 0.8 (0.7-1.0) |
| 5 (less affluent) | 89/557 (16%) | 0.7 (0.5-0.8) | 0.6 (0.5-0.8) |
| Trend | | 0.9, P = .0006 | 0.9, P < .0001 |
| Educational level (y in school) | | | |
| ≥13 y | 164/689 (24%) | 1 (ref) | 1 (ref) |
| 10-12 y | 293/1170 (25%) | 1.1 (0.9-1.3) | 1.0 (0.8-1.1) |
| ≤9 y | 195/1046 (19%) | 0.9 (0.7-1.1) | 0.8 (0.7-1.0) |
| Trend | | 0.9, P = .2 | 0.9, P = .01 |
| Living alone | | | |
| No | 399/1650 (24%) | 1 (ref) | 1 (ref) |
| Yes | 264/1295 (20%) | 0.9 (0.8-1.1) | 0.9 (0.8-1.0) |
| | | P = .3 | P = 0.2 |

†Adjusted for age at diagnosis, MDS subclass, IPSS-R risk class, transfusion dependency, and Charlson comorbidity index.
could entirely be explained by differences in age, sex and comorbidity index. In the present data, the associations remain in spite of such adjustments, leading us to believe that there is a true relationship.

Lead time bias arises in studies of mortality when some patients are diagnosed later during the natural course of disease than others. In such cases, the shorter life span stems from later diagnosis rather than earlier death. It has recently been argued that the perceived better prognosis in MDS patients diagnosed early is due to lead time bias rather than a true gain from early detection. In our data, we have indications of lead time bias, as a lower percentage of the high-income patients presented with erythrocyte transfusion dependency. However, adjustments for transfusion dependency and IPSS/IPSS-R risk class should at least in part control this bias (with a reservation for the fact that risk class more often were missing in the patients from lower socioeconomic categories), and such adjustments did not alter our results. Moreover, lead time bias cannot explain the estimated differences in treatment and diagnostic procedures. If anything, an early diagnosis before severe symptoms arise would supposedly decrease the use of HMA or SCT.

Due to the relatively short follow-up, our results may be less accurate for the small proportion of long-term surviving patients. Median follow-up was only 1.9 years, although this to a large degree is due to a median survival of only 2.3 years. Nevertheless, no patient was followed for more than 10 years, and longer follow-up could possibly have decreased differences in mortality.

Another limitation of our study is that global measures of performance status, such as the Clinical Frailty Scale or the WHO/ECOG scale were missing from our data. The Clinical Frailty Scale has been shown to predict mortality in MDS better than, and independent of, Charlson comorbidity index. Accordingly, we cannot argue that the differences in treatment choice between patients from different socioeconomic strata must be based on poor judgement or prejudice.

### Table 5
Relative probability of receiving an allogeneic stem cell transplant (SCT) among MDS patients below 75 y of age at diagnosis in relation to socioeconomic data

|                     | SCT (%) (total n = 1371) | Probability ratio (95% confidence interval) |
|---------------------|--------------------------|---------------------------------------------|
|                     | Age adjusted             | Fully adjusted†                             |
| **Sex**             |                          |                                             |
| Male                | 135/843 (16%)            | 1 (ref)                                     |
| Female              | 107/528 (20%)            | 1.1 (0.9-1.4) P = .3                        |
|                     |                          | 1.1 (0.9-1.3) P = .5                        |
| **Household income quintile‡** |                         |                                             |
| 1 (more affluent)   | 119/415 (29%)            | 1 (ref)                                     |
| 2                   | 42/329 (13%)             | 0.5 (0.4-0.7) P = .3                        |
| 3                   | 34/204 (17%)             | 0.6 (0.4-0.8) P = .3                        |
| 4                   | 26/212 (12%)             | 0.5 (0.4-0.8) P = .3                        |
| 5 (less affluent)   | 14/194 (7%)              | 0.3 (0.2-0.5) P = .3                        |
|                     |                          | Trend = 0.8, P = .0001                     |
| **Personal income quintile** |                         |                                             |
| 1 (more affluent)   | 113/420 (27%)            | 1 (ref)                                     |
| 2                   | 60/317 (19%)             | 0.8 (0.6-1.0) P = .3                        |
| 3                   | 22/216 (10%)             | 0.5 (0.4-0.8) P = .3                        |
| 4                   | 19/205 (9%)              | 0.4 (0.3-0.7) P = .3                        |
| 5 (less affluent)   | 21/196 (11%)             | 0.3 (0.2-0.5) P = .3                        |
|                     |                          | Trend = 0.7, P < .0001                      |
| **Educational level (y in school)** |                       |                                             |
| ≥13 y               | 74/373 (20%)             | 1 (ref)                                     |
| 10-12 y             | 119/599 (20%)            | 1.1 (0.8-1.4) P = .3                        |
| ≤9 y                | 44/379 (12%)             | 0.7 (0.5-1.0) P = .05                       |
|                     |                          | Trend = 0.9, P = .05                        |
| **Living alone**    |                          |                                             |
| No                  | 181/863 (21%)            | 1 (ref)                                     |
| Yes                 | 61/508 (12%)             | 0.6 (0.5-0.8) P = .01                       |
|                     |                          | 0.7 (0.5-0.9) P = .007                      |

†Adjusted for age at diagnosis, MDS subclass, IPSS-R risk class, transfusion dependency, and Charlson comorbidity index.
‡Missing data on income for 17 cases and on education for 20 cases.
Several health-related factors such as nutritional status, obesity, physical activity, smoking, alcohol and drug use could have been taken into account by both physician and patient before treatment decisions, which would have been obvious in the clinical setting, but not measurable in this retrospective registry-based approach. Smoking has previously been linked to survival in lower-risk MDS and could have varied by socioeconomic status in our study. However, the majority of the patients in this study were born before 1940 and in these generations, smoking was more frequent among high-income groups and more evenly distributed among education levels.

The present study is the first nationwide study on the impact of socioeconomic factors on the prognosis of patients with MDS. In summary, poorer socioeconomic status was associated with less intense treatment and shorter survival. Strengths of this study include its large size, the population-based approach and the individual socioeconomic data from reliable sources. Future research is warranted to explore by which exact risk factors the socioeconomic survival differences arise.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Individual participant data will not be shared in order to protect patient privacy.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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