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Impact of Socioeconomic Status on Disease Phenotype, Genomic Landscape and Outcomes in Myelodysplastic Syndromes

Running title

Socioeconomic status and MDS

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Summary

Genetic and epigenetic alterations contribute to the biological and clinical characteristics of myelodysplastic syndromes (MDS), but a role for socioeconomic environment remains unclear. Here, socioeconomic status (SES) for 283 MDS patients was estimated using the Scottish Index of Multiple Deprivation tool. Indices were assigned to quintile categorical indicators ranked from SES1 (lowest) to SES5 (highest). Clinicopathological features and outcomes between SES quintiles containing 15%, 20%, 19%, 30% and 16% of patients were compared. Prognostic scores identified lower-risk MDS in 82% of patients, with higher-risk disease in 18%. SES quintiles did not associate with age, gender, cytogenetics, IPSS, or in sub-analysis (n=95), driver mutations. The odds ratio of a diagnosis of RA was greater than other MDS sub-types in SES5 (OR 1.9, p=0.024). Most patients (91%) exclusively received supportive care. SES did not associate with leukaemic-transformation or the cause of death. Cox regression models confirmed male gender ($p<0.05$), disease-risk ($p<0.0001$) and age ($p<0.01$) as independent predictors of leukaemia-free survival, with leukaemic-transformation an additional determinant of overall survival ($p=0.07$). Thus, if access to healthcare is equitable, SES does not determine disease biology or survival in MDS patients receiving supportive treatment; whether outcomes following disease-modifying therapies are influenced by SES requires additional studies.

Key words: Socioeconomic status, MDS, IPSS, outcomes, healthcare, genomic

Introduction

Myelodysplastic syndromes (MDS) are disorders characterised by different levels of bone marrow failure, dysplasia affecting one or more haemopoietic cell lineages and a variable propensity for transformation to acute myeloid leukaemia (AML) (Nimer *et al*, 2008). Over the last 40 years, a number of studies have enhanced our understanding of the biology of MDS and increased the accuracy of clinical prognostication (Platzbecker, 2015). Earlier studies focussed on morphological (Bennett *et al*, 1982) and cytogenetic characteristics of MDS (Vardiman *et al*, 2002), but the advent of molecular sequencing techniques has helped identify acquired gene mutations in majority of MDS patients, with functional clustering that appears to be clinically relevant (Papaemmanuil *et al*, 2013; Itzykson *et al*, 2013). Thus, driver mutations in haemopoietic stem cells contributing to specific sub-types of MDS have been identified, with the acquisition of additional mutations within this cellular compartment or downstream progenitors associating with transformation to AML. In addition, epigenomic deregulation is being increasingly recognised in the pathogenesis of MDS (Itzykson *et al*, 2013; Itzykson & Fenaux, 2014). The improved understanding of the biological characteristics of MDS is now enabling therapies which result in haematological improvement (reviewed in Garcia-Manero, 2014) or prolong survival in subsets of patients (Fenaux *et al*, 2009).

Despite the plethora of studies investigating genetic and epigenetic changes in MDS, a possible role for environmental factors in altering disease phenotype and/or influencing outcomes has been less well investigated. Whether phenotypic characteristics and genomic alterations observed in MDS, commonly used for prognostication, are influenced by patient socioeconomic status (SES) is therefore unclear. A role for the environment in influencing leukaemogenesis has been

suggested by the differences in the incidence of radiation-induced AML in genetically susceptible mice housed under different conditions (Walburg *et al*, 1968). In these animal models, a pro-inflammatory 'by-stander' cell response to radiation creates an *in vivo* microenvironment favouring AML development (Mukherjee *et al*, 2014). If inflammation were similarly important for the development of *de novo* MDS and AML in humans, SES could be an important contributor to clonal instability since DNA methylation profiling has suggested increased pro-inflammatory gene activity in individuals from lower socioeconomic backgrounds (Stringhini *et al*, 2015). Support for an SES-associated effect on disease biology comes from the observation that mutations in the tumour suppressor gene *TP53* in breast cancer are over-represented in women with severe socioeconomic deprivation (Baker *et al*, 2010; Starks *et al*, 2013).

Whether SES can alter outcome trajectories in MDS patients has not been extensively studied. In patients with solid organ and other haematological neoplasia differences in time to diagnosis, access to clinical care or trials and comorbidity between patients that are SES-dependent are known to affect survival (Kolahdooz *et al*, 2014; Munro, 2005; Roberts *et al*, 2015; Rutherford *et al*, 2013). For example, the lower incidence of childhood acute lymphoblastic leukaemia across levels of increasing relative deprivation could reflect under-diagnosis in lower socioeconomic communities (Kroll *et al*, 2012; Lightfoot *et al*, 2012), and the mortality in AML and myeloma appears to be reduced in higher SES groups in some studies (Kristinsson *et a*l, 2009). In MDS, studies investigating the effects of SES on outcomes (Wang *et al*, 2009; England *et al*, 2013) have yielded conflicting conclusions, possibly due to differences in healthcare funding or organisational structure of healthcare services. Studies on patients treated within the National Health Service (NHS) in the United

Kingdom are relatively less likely to be confounded by these variables since the NHS is free at the point-of-delivery and based on clinical need and not means-tested. In addition, the delivery of secondary health care by a single treatment centre to all patients within the defined catchment area reduces patient selection bias in single-institution studies. These advantages lead us to investigate the effects of SES on clinic-pathological disease characteristics and treatment outcomes including cause of death in MDS patients within NHS Tayside that serves a population of 400,000.

Methods

Patients

Adults diagnosed with MDS including non-proliferative chronic myelomonocytic leukaemia (CMML) between 1996-2012 were identified from the Tayside MDS Registry that contains relevant information on patients diagnosed and managed in NHS Tayside. This Registry has been established with approval from the Tayside Medical Research Ethics Committee. Patients with incomplete datasets and those with refractory anaemia and excess of blasts in transformation (RAEB-t) were excluded. Patient demographics, date of diagnosis, morphological MDS sub-type (FAB or WHO), karyotype, IPSS score (Greenberg *et al*, 1997), AML transformation and date of last follow-up or death were abstracted from the Registry. For acquisition of additional patient data, Caldicott Guardian approval was obtained in compliance with local information governance regulations.

Results of targeted gene sequencing reported previously (Papaemmanuil *et al*, 2013) were used to map the genomic landscape in 95 patients. To enable comparisons with SES, genes were stratified into three functional groups based on the ability to regulate epigenetics, RNA splicing or transcriptional signalling (Bejar and Steensma, 2014).

Cause of death

The cause of death was determined from the final progress note by a hospital-based or community physician. In patients with transformed AML not in remission,

AML was identified as the cause of death. Death associated with progressive cytopenias in the absence of circulating blasts, or cachexia was attributed to MDS. Infections as a cause of death included pneumonia as well as non-pneumonic, systemic sepsis. Patients dying in hospital following surgery were classed as having died of post-surgical complications. Patients older than 80 years, with stable blood counts who experienced sudden death were categorised as having died of ageing.

To investigate associations with SES, causes of death were categorised into those arising as a complication of marrow dysfunction (including pneumonia, infection, bleeding, AML or progressive MDS) or organ failure (cardiac, renal or pulmonary disease). In addition, death due to advanced age, other malignancies, post-surgery, thrombosis, post-operative or unknown causes constituted an 'ancillary' category.

Socioeconomic deprivation data

The SES was inferred from the datazone associated with the patient's residence postcode at the time of diagnosis and the Scottish Index of Multiple Deprivation (SIMD 2009). SIMD is the Scottish Government's official tool for quantifying relative deprivation in Scotland. The tool incorporates several different aspects of deprivation, based on employment, income, health, education, skills and training, geographic access to services, crime and housing and combines these into a single index. Data were derived from the publically available database (http://www.scotland.gov.uk/Topics/Statistics/SIMD/SIMDPostcodeLookup/ScotlandPostcodeLookup). Indices were assigned to quintile categorical indicators

ranked from SES1 (lowest) to SES5 (highest). SES for patients diagnosed in the period prior to the development of the SIMD tool was calculated from the Carstairs index (http://www.isdscotland.org/products-and-Services/GPD-Support/deprivation/carstairs/; Carstairs & Morris, 1990) and assigned to quintiles. Although the Carstairs index uses different criteria, Carstairs SES quintiles ranked from 1 (highest) to 5 (lowest) correlated negatively with those developed using SIMD ($p<0.0001$) suggesting the ability to identify similar SES groups. For this reason, and likely absence of significant changes in post code-affiliated SES over the time period of the study-patient population, the SIMD 2009 tool was extrapolated to measure area SES in all patients.

Statistical analysis

The potential association between SES and co-variates included in the study: patient demographics (age and gender), clinicopathological characteristics (morphological sub-type of MDS, karyotype, genomic analysis and IPSS) and treatment details was investigated using the Chi Square test. All statistical analysis was performed using R software (Version 3.2). In addition, differences in patient outcomes including AML transformation, overall and leukaemia-free survival and causes of death were compared between SES quintiles. Overall survival (OS) was measured as the time from diagnosis to the time of death or last follow-up; leukaemia-free survival (LFS) was calculated from the times between the diagnosis of MDS and AML diagnosis or time of last follow-up. Survival outcomes were analysed using the log-rank test for Kaplan Meier survival curves. Cox regression models were used to estimate the hazard ratio for the significant

co-variates of both OS and LFS. All *p*-values were two-tailed and statistical significance was set at the level of $p < 0.05$.

Results

Patient demographics and disease characteristics (Table I)

Of 305 patients in the registry, 283 Tayside residents were identified as being suitable for the study. Ten local patients were excluded due to insufficient information including absence of marrow examination or failed cytogenetic analysis. The median age of patients in the final cohort was 76 years (range 28-97) with 163 males and 120 females (ratio 1.3:1. The number of patients in SES quintiles 1-5 was 44 (15%), 57 (20%), 53 (19%), 84 (30%) and 45 (16%) respectively.

MDS sub-types included RA (n=94), RARS (n=36), RCMD (n=39), RAEB (n=40), CMML (n=55) and MDS with 5q- (n=5). Disease with fibrosis (n=5) and hypoplasia (n=4), and those with unclassifiable/proliferative disease (n=5) formed a miscellaneous group (n=14). Nine patients had therapy-related MDS. Good, intermediate or poor karyotype was identified in 217, 28 and 38 patients respectively. The IPSS was used to predict low (n=127), intermediate-1 (n=104), intermediate-2 (n=43) or high-risk (n=9) disease. By combining numbers of patients with low and intermediate-1 IPSS scores, 231 patients were classed as having lower-risk MDS; the remainder of the patients with intermediate-2 and high-risk MDS had higher-risk disease (n=52). In the 95 patients who underwent genomic analysis, a total of 198 mutations were identified with commonly mutated oncogenes including *TET2* (22% of total mutations), *SF3B1* (15%), *SFRS2* (11%) and *ASXL1* (10%). Mutations in *U2AF1, DNAMT3A, CBL, RUNX1, EZH2, TP53* and *ZRZR2* accounted for 3-6%, *NRAS, IDH1, KRAS, PHF6, STAG2, CUX1, EP300* and *IDH2*, 1-2% and *BCOR, CEBPA, GATA2, JAK2, KIT, NF1, PTPN11* and *RAD21* for <1% of the mutational spectrum.

Treatment (Table II)

The majority of patients (n=257) exclusively received best supportive care (BSC) with blood products and antibiotics for treatment of infections. In 26 patients, disease modifying therapy was used and 4 patients underwent allogeneic stem cell transplantation.

Transformation to AML and the cause of death

Transformation to AML was observed in 53 patients (19%), with the likelihood being greater in higher-risk MDS (21/52) than with lower-risk disease (32/231, X-squared 15.54, df=1, 95% CI for the difference between proportions of transformation 12-40, $p<0.0001$).

At last follow-up, 247 out of 283 patients (87%) had died. Leukaemic-transformation was the most frequent cause of death (22%) in the entire cohort followed by infection (20%) and advanced age (15%). When the causes of death in patients with lower-risk MDS were examined (Table III), 17% of deaths in this sub-group were related to leukaemic-transformation. Death due to infection including pneumonia (20%), advanced age (16%), progressive MDS (8%), bleeding (7%), non-myeloid malignancies (7%) and cardiac failure (6%) also accounting for fatalities (Table III). In higher-risk MDS, death occurred due to leukaemic-transformation (38%), infection (25%), advanced age (11%), bleeding (4%) or progressive MDS (4%).

SES, MDS phenotype, genomic changes and prognostic scores (Table IV)

To investigate the association between SES and MDS characteristics at diagnosis, patient demographics and clinicopathological variables within different SES quintiles were compared. As shown in Table IV, there was no association between SES and age (X-squared 2.5, df=4, p=0.63) or gender (X-squared=2.4, df=4, p=0.67). A statistical comparison of MDS sub-types and different SES groups was limited by small numbers in some MDS sub-groups. We therefore investigated whether a diagnosis of RA compared to other forms of MDS (non-RA MDS) associated with SES, since the absence of excess blasts, uni-lineage cytopenia and dysplasia can make the diagnosis of RA more challenging than other MDS sub-types (Schiffer, 2006; Malcovati et al, 2013). By Chi-square test, a significant association between RA and SES was detected (X-squared=11.16, df=4, p=0.024). Using ordinal regression modelling for the relation between SES and RA, the odds ratio of a diagnosis of RA was almost double that of non-RA in SES5 compared to other SES groups (odds ratio 1.9, CI 1.2-2.9; p=0.024).

There was no significant association between SES and bone marrow karyotype (X-squared=5.3, df=8, p=0.72) or in sub-analysis (n=95) or the frequency of driver mutations in genes regulating epigenetics, RNA splicing or transcription (X-squared=1.4, df=8, p=0.99). The IPSS score too did not associate with SES, with lower- and higher risk-groups featuring equally in different SES quintiles (X-squared=6.0482, df=4, p=0.19).

SES, treatment and disease outcomes

Disease modifying therapy for lower-risk MDS was offered to 1, 0, 2, 4 and 6 patients in SES quintiles 1-5 respectively; corresponding patient numbers treated for higher-risk MDS were 4, 4, 2, 2 and 1 respectively. These numbers limited a statistically valid investigation of an association between SES and therapy. No association was observed between SES and leukaemic-transformation (X-squared=2.63, df=4, p=0.62) or the cause of death (X-squared=6.49, df=8, p=0.59) (Table IV).

Median survival of the entire cohort was 28.5 months (95% CI 24.6% -35.0%, range, 0.10-280) (Figure 1A). In a log-rank test of OS, age >70 years (p=0.006), higher-risk MDS (p<0.0001), male gender (p=0.022) and transformation to AML (p=0.0003) significantly decreased OS. Multiple Cox regression models were fitted for the co-variates from the univariate analysis and identified male gender (HR 1.3, 95% CI 1.0-1.7, p=0.04), lower-risk disease (HR 0.38, 95% CI 0.27-0.53, p<0.0001, Figure 1B), age ≤70 years (HR 0.59, 95% CI 0.44-0.80, p=0.0007) and AML transformation (HR 1.35, 95% CI 0.97-1.99, p=0.07) as being independent predictors of OS. SES had not influence the OS of the entire cohort (p=0.37) or of patients with lower-risk (Figure 1C) and higher-risk MDS (Figure 1D).

The median LFS was 27.9 months (95% CI 23.6-34.1, range (0.1-199). As with OS, log-rank test indicated the importance of age >70 years (p<0.009), MDS risk-group (p<0.0001) and male gender (p=0.02) on LFS with no influence of SES (p=0.77). Cox regression models further confirmed MDS risk-group (HR 0.3, 95% CI

0.21-0.41, p<0.0001, Figure 1C and D), male (HR 1.29, 95% CI 0.99-1.67 p=.051) and age (HR 0.61, 95% CI 0.45-0.83, p=0.02) as independent predictors of LFS.

Discussion

Based on the established SES-dependent variation in clinicopathological characteristics and outcomes in many diseases (Barker, 1981; Gomez *et al*, 2015; Stringhini *et al*, 2013) including cancer (DeSantis *et al*, 2011; Kolahdooz *et al*, 2014; Lyratzopoulos *et al*, 2012; Roberts *et al*, 2015; Rutherford *et al*, 2013), we hypothesised a role for SES in influencing the biological and clinical heterogeneity in patients with MDS. In previous studies, Wang *et al* (2009) investigated the prognostic role of neighbourhood SES in MDS using data from the Surveillance, Epidemiology and End Results (SEER) cancer registries linked to the national insurance programme Medicare in the USA and identified poorer survival in patients belonging to lower SES groups. While this epidemiological study included a large number of patients, its relevance to areas with alternative mechanisms of health funding is unclear since affordability of therapy can confound interpretation of socioeconomic influences on cancer outcomes. The predictors of survival we have identified in Cox-regression analyses are not new, but importantly, these validate our dataset and its suitability for models to investigate associations between SES and MDS. Thus, the comparable survival outcomes between patients from different SES in our study, combined with the observations from a Canadian cohort of patients (England *et al*, 2013) strongly indicate the ability of equitable healthcare access in MDS to negate adverse outcomes associated with socioeconomic deprivation (Wang *et al*, 2009).

When specific outcomes were studied, in contrast to the study by England *et al*, (2013), we were unable to demonstrate leukaemic-transformation as being more frequent in patients of higher SES. Since all MDS patients in Tayside are treated within NHS Tayside hospitals, the possibility of referral patterns introducing bias in

the Canadian study should be considered. We also failed to identify a contributory role for SES in influencing mortality patterns in both lower and higher risk MDS. In particular, cardiovascular mortality, known to associate inversely with socioeconomic deprivation (Ramsay *et al*, 2015) was low (Dayyani *et al*, 2010) and equally represented in the SES quintiles. Since cardiovascular deaths in MDS patients raise concerns about transfusion-associated iron overload, it would be important to state that barring one patient, the others had significant cardiovascular and valvular disease at the time of MDS diagnosis. Unfortunately, data on co-morbidity on all 283 patients in our cohort was not available, preventing a comprehensive evaluation of its association with SES and contribution to choice of therapy and outcomes. However, the analysis of co-morbidity in a subset of higher-risk patients included in a previous study (Durairaj *et al*, 2013) did not identify any obvious differences in co-morbidity patterns between SES quintiles.

When the morphological MDS sub-type was related to SES, uniquely, RA was more frequently diagnosed in patients from higher SES. Since a diagnosis of RA relative to other MDS phenotypes can often be challenging, it is possible that some patients classed as having RA may not have had true MDS. However, RA patients who were screened for driver mutations all had detectable genomic lesions, validating the morphological diagnosis of RA. Relevant to the possible association of morphological sub-type of MDS with SES, a case-control study from China has suggested that the MDS phenotype can be influenced by occupation, life-style and educational status (generally associated with specific socioeconomic groups), with tobacco smoking, exposure to agricultural chemicals and lower educational achievements associating with RCMD and RAEB (Lv *et al*, 2011). However, the frequency of MDS sub-types by morphology in the Chinese population is not

comparable to that in the West, referral and reporting bias may have skewed Lv *et al*'s study and a clear environmental pre-disposition is absent in an overwhelming majority of MDS patients (Bowen, 2013). Additional studies would be helpful to confirm the association between morphological sub-types of MDS and SES.

In keeping with observations from other studies (Wang *et al*, 2009; England *et al*, 2013), no cytogenetic features or MDS risk scores are unique to patients within specific SES quintiles. Oncogenic gene mutations believed to drive the disease process in MDS also do not have an obvious association with SES when genes are grouped according to function: mutations in genes responsible for RNA splicing, regulation of the epigenome or transcription were equally represented in patients from different SES. In breast cancer, it has been suggested that *TP53* mutations may be over-represented in women facing extreme socioeconomic deprivation (Baker *et al*, 2010; Starks *et al*, 2013). The absence of an obvious genomic link with SES in MDS here could reflect the existence of associations that are unique to a particular malignancy, limited patient numbers or differences in study criteria and analytical models.

The decision to use the SIMD tool to identify area SES and assign SES warrants comment since criteria used to calculate SES often differ between studies. The assigning of any given deprivation score is derived from a person's social characteristics. Thus, information gathered by census, questionnaires or descriptive accounts can all be used to categorise people into ranks of most to least deprived. The SIMD tool uses location as an indicator of deprivation, assuming that people living in the same area (postcode-derived datazones) have broadly similar social circumstances. By using data from seven domains relating to multiple aspects of life, an index that helps create the fullest possible picture of deprivation across

Scotland is generated. The SIMD thus provides a means of analysing deprivation using a national reference. Other tools such as the Carstairs index (Carstairs & Morris, 1990) are often used in similar studies, but this was deemed unsuitable due to the limited data available for the time-periods encompassed by this study. However, for patients whose date of diagnosis permitted an evaluation of deprivation using both the SIMD and Carstairs tools, the SES score based on the Carstairs index was comparable to SIMD data, indicating the applicability of the SIMD tool to historic patients. SIMD 2009 was chosen for this study as this version of the SIMD tool reflected best the time period in which most patients in the study cohort had been diagnosed.

A limitation of our study is the absence of data on historic area SES in individual patients since a comprehensive analysis of SES and MDS biology and phenotype would mandate the identification of deprivation most representative of a patient's socio-economic history *prior* to the diagnosis of MDS. The challenges posed by a review of each patient's social history and mobility meant that the patient's postcode at the time of diagnosis became a surrogate for lifetime location. Therefore the SIMD index will not reflect social mobility, or account for potential anomalies in deprivation within datazones. It is unlikely that standardised patient datasets that include detailed biological variables, on which assessment tools that uniformly assess life-time patient SES in different populations will ever be developed. Thus, while our study has some limitations, it does succeed in establishing the absence of SES influences on MDS outcomes in a health-system providing equitable care, at least in patients exclusively receiving supportive treatments. Whether potentially modifiable, environmental risk factors influence outcomes in MDS patients on therapy remain of interest.

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FM, MJG and ST designed the research study, DTB, AH and NK were responsible for patient-data collection and the MDS Registry, EP and PJC contributed genomic data, KB and ST performed data analysis and interpretation, ST wrote the paper with input from all authors.

Conflict of Interests

The authors do not have any conflicts of interests to declare.

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Table I. Patient demographics and clinicopathological variables (n=283).

Variable	Total
Age (years)	
≤70	73
>70	210
Gender	
Males	163
Females	120
MDS Sub-type	
RA	94
RARS	36
RCMD	39
RAEB	40
CMML	55
5q-	5
Miscellaneous	14
Karyotype	
Good	217
Intermediate	28
Poor	38
Driver mutations	
Epigenetic	85
RNA splicing	70
Miscellaneous	43
IPSS score	
Lower-risk	231
Higher-risk	52
SES	
Quintile 1	44
Quintile 2	57
Quintile 3	53
Quintile 4	84
Quintile 5	45
Treatment	
Exclusive BSC	257
Other	26
AML transformation	53

Table II. Therapies used in managing MDS patients.

Therapy	Patient number
Exclusive best supportive care	257
Danazol	3
Erythropoietin+/- G-CSF	3
Anti-lymphocyte globulin +/- Cyclosporin	4
Low-dose chemotherapy	5
Intensive chemotherapy	9
Amifostine	1
Lenalidomide	1

Table III. Causes of death in lower-risk MDS.

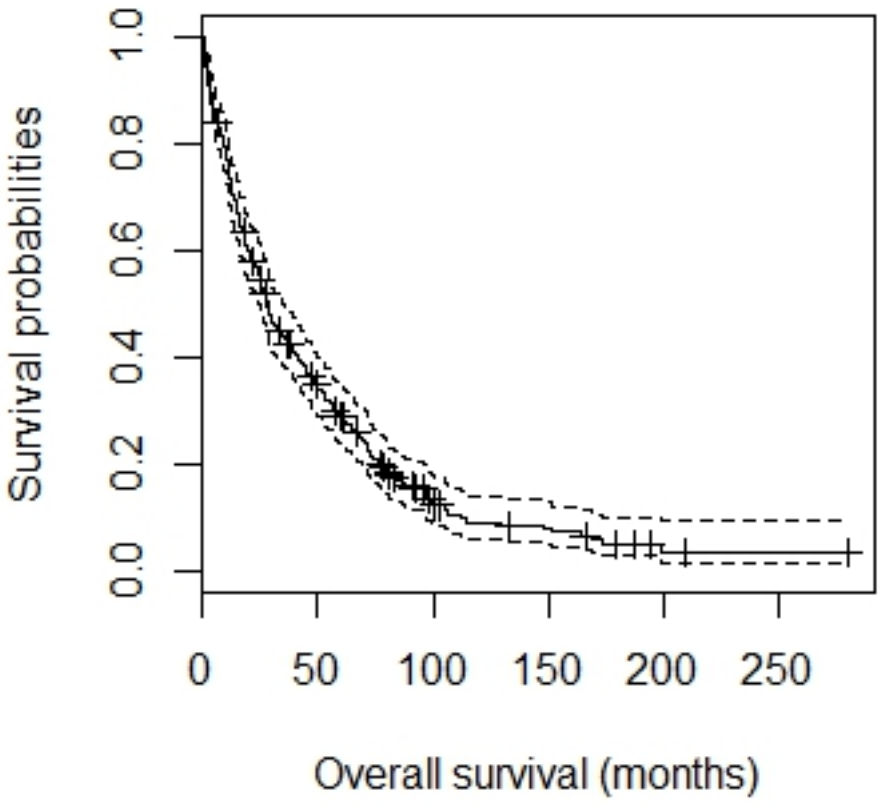
Cause of death	Number (% of total deaths)
Marrow dysfunction	
End-stage MDS	15 (8)
AML	33 (17)
Infection	15 (8)
Pneumonia	23 (12)
Bleeding	14 (7)
Organ failure	
Cardiac failure	11 (6)
Pulmonary disease	4 (2)
Renal failure	6 (3)
Ancillary	
Age	32 (16)
Other malignancies	14 (7)
Post-operative	5 (2.5)
Thrombosis	5 (2.5)
Misc.	8 (4)
Not known	10 (5)

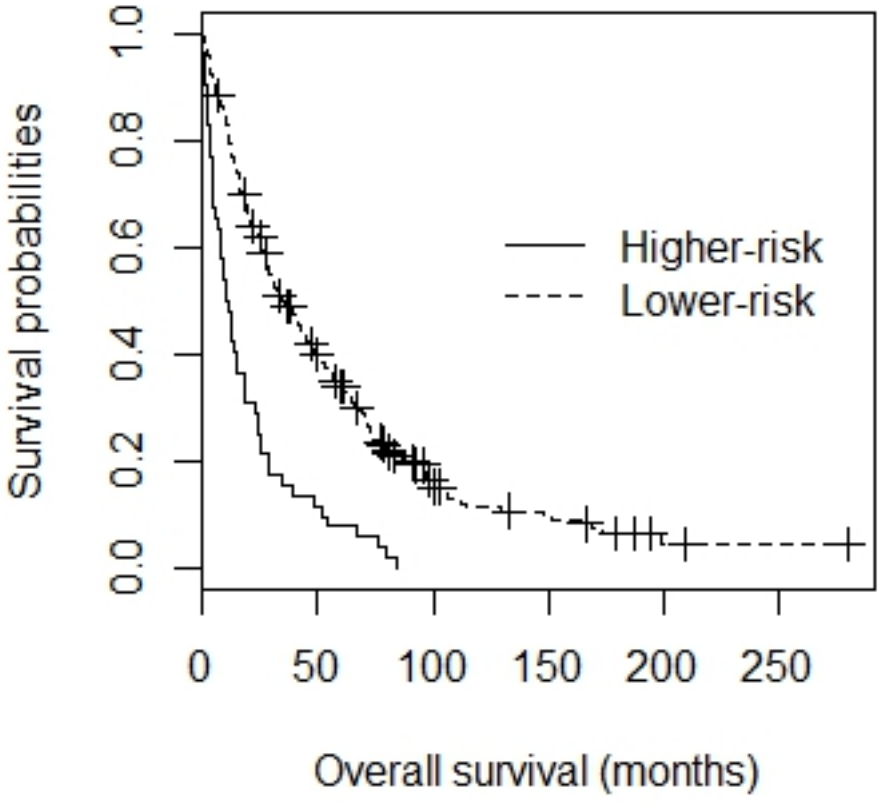
Table IV. Association between SES and clinicopathological variables at diagnosis, prognostic scores, therapy and leukaemic-transformation in MDS.

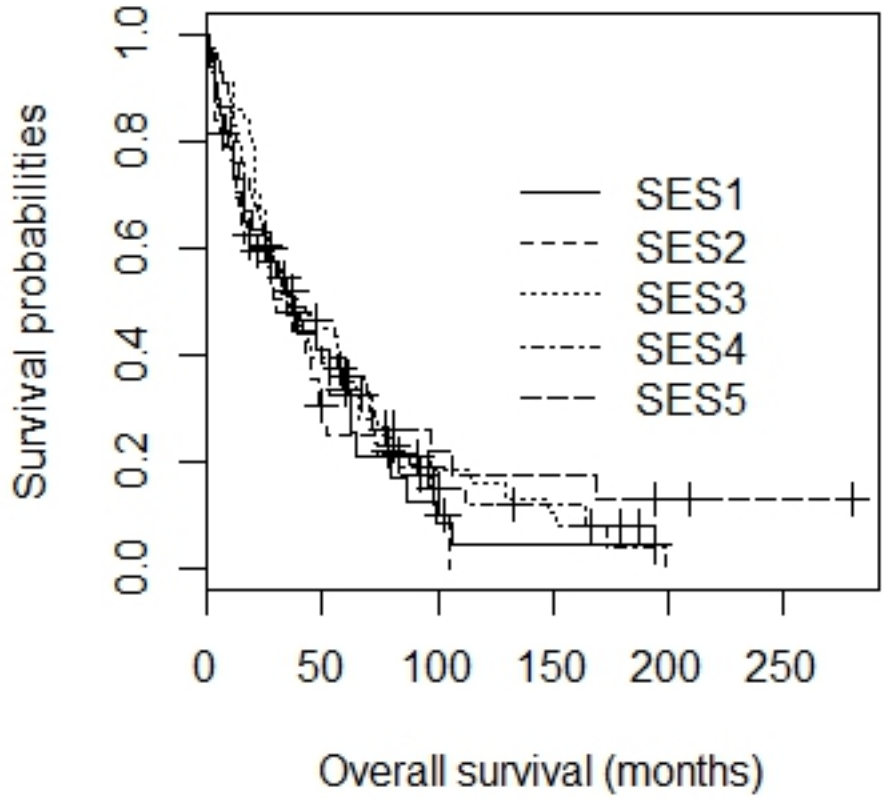
	SES1	SES2	SES3	SES4	SES5	p
Age (years)						0.63
≤70	15	14	15	19	10	
>70	29	43	38	65	35	
Gender						0.67
Males	25	31	27	53	27	
Females	19	26	26	31	18	
Sub-type						0.024*
RA	7	18	19	28	22	
Non-RA MDS	37	39	34	56	23	
Karyotype						0.72
Good	34	41	41	66	35	
Intermediate	4	5	4	8	7	
Poor	6	11	8	10	3	
Driver mutations						0.99
Epigenetic	16	16	14	26	13	
RNA splicing	12	16	12	19	11	
Miscellaneous	9	11	6	11	6	
IPSS score						0.19
Lower-risk	33	43	43	75	37	
Higher-risk	11	14	10	9	8	
Treatment						0.78
BSC	39	53	49	77	39	
Other	5	4	4	7	6	
AML transformation	9	10	12	13	9	0.62
Cause of Death						0.59
Marrow dysfunction	20	25	35	38	20	
Organ failure	4	6	3	8	3	
Ancillary	15	19	11	26	14	

*Patient numbers in individual MDS sub-types within SES quintiles limited a comparative analysis of SES and MDS sub-type, but a significant association between RA and SES was observed compared to non-RA MDS (OR 1.9, p=0.024).

Fig. 1. Kaplan Meier survival curves in MDS patients. Overall survival (OS) for the entire cohort (n=283) (A). OS in with lower-risk MDS was superior ($p<0.0001$) to those with OS higher-risk disease (B). No association between SES and OS was evident in patients with lower-risk (C) or higher-risk MDS (D).


Survival probabilities
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
200
250
Overall survival (months)


Survival probabilities
0.0
0.2
0.4
0.6
0.8
1.0
Higher-risk
Lower-risk
0
50
100
150
200
250
Overall survival (months)


Survival probabilities
0.0
0.2
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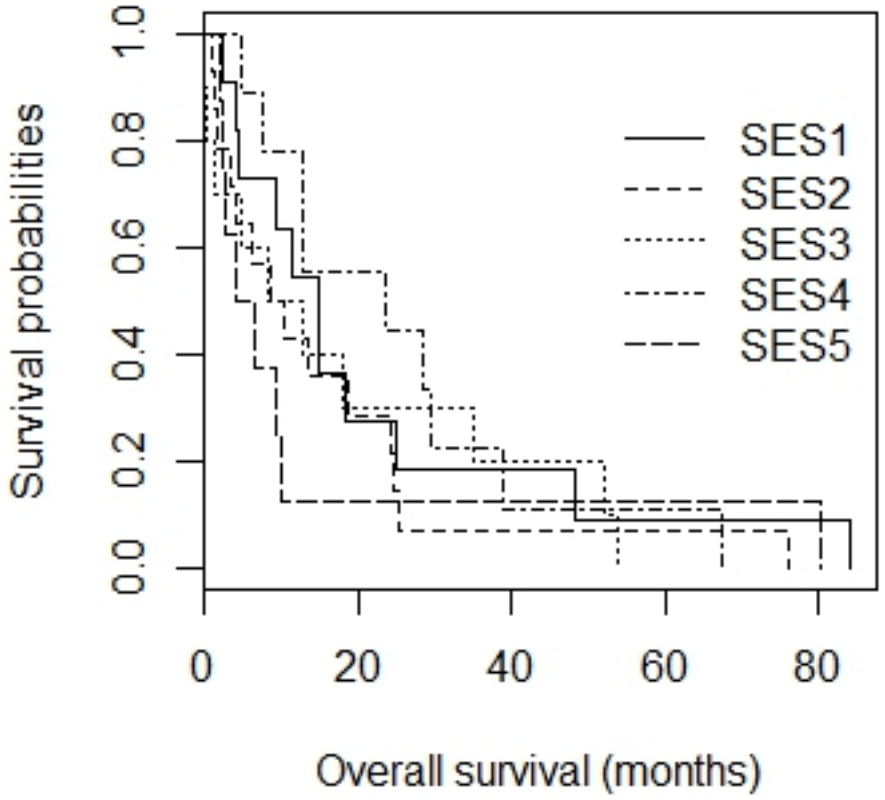
0.8
1.0
SES1
SES2
SES3
SES4
SES5
0
50
100
150
200
250
Overall survival (months)


Survival probabilities
0.0
0.2
0.4
0.6
0.8
1.0
SES1
SES2
SES3
SES4
SES5
0
20
40
60
80
Overall survival (months)