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Cigarette smoking shortens the survival of patients with low-risk myelodysplastic syndromes

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Abstract

Myelodysplastic syndromes (MDS) are a group of hematological malignancies with poor survival. Although previous studies have identified the prognostic role of multiple demographic and clinical characteristics, the potential role of lifestyle factors has not been evaluated. In this study, we conducted an extensive assessment of the predictors of MDS survival, with a special focus on lifestyle factors. A total of 616 patients (median survival = 4.1 years) were included in the analysis, and multivariate Cox proportional hazard models were utilized to estimate hazard ratios. Compared with non-smokers, MDS patients who smoked at the initial clinical encounter had a significantly increased risk of death [hazard ratio (HR) = 1.46, 95% confidence intervals (CI): 1.07–2.00]. The elevated risk was restricted to men (HR = 1.76, 95% CI: 1.21–2.56) and not observed among women (HR = 0.98, 95% CI: 0.51–1.85). When patients were stratified by the IPSS categorization, a near three fold increased risk of death was associated with smoking among patients with low-risk MDS (HR = 2.83, 95% CI: 1.48–5.39), whereas smoking did not appear to influence the survival of patients with intermediate- or high-risk MDS. This study was the first to identify smoking as a significant and independent predictor of MDS survival, particularly among low-risk patients.

Keywords

Myelodysplastic syndromes; Survival; Smoking

Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of stem cell disorders characterized by ineffective hematopoiesis, peripheral cytopenias, and likely transformation to acute myeloid leukemia (AML) [1]. Recent data from population-based cancer registries in the United States suggest that approximately 80% of MDS patients are 65 years or older at the time of diagnosis (median age at diagnosis = 76 years) and three-year observed survival is only 35% [2]. A number of demographic characteristics and disease-related parameters, including age, sex, percentage of blasts in bone marrow, number of cytopenias, cytogenetic alterations, and comorbidities, have been linked to the survival of MDS [2–5]. The International Prognostic Scoring System (IPSS), which takes into account percentage of blasts in bone marrow, number of cytopenias, and cytogenetic findings [3], has been utilized in recent years to stratify MDS patients into four risk groups (i.e., low risk, intermediate 1 risk, intermediate 2 risk, and high risk), with the median survival ranging from 0.4 years among the high-risk group to 5.7 years among the low-risk group [3].

Smoking is not only a risk factor of AML [6–8] but also a predictor of survival [9, 10]. It has been reported that AML patients who smoked at least 20 pack-years or smoked for at least 30 years had significantly shorter survival [9]. Among AML patients treated with high-dose cytarabine and idarubicin-containing regimens, never-smokers had a significantly longer overall survival and progression-free survival than smokers [10]. However, the potential prognostic role of modifiable lifestyle factors such as cigarette smoking and alcohol drinking has not been investigated in MDS. Using data from a large cohort of MDS patients diagnosed and treated by the same team of hematologists, we conducted an extensive assessment of the predictors of MDS survival, with a special emphasis on cigarette smoking.

Materials and methods

Patients and data collection

The study population consists of 616 MDS patients who were seen by the same team of hematologists at Rush University Medical Center and University of Massachusetts Memorial Medical Center during 1990–2006. All patients had bone marrow biopsy specimens reviewed by the hematopathologists. A 500 cell differential count was performed based on examination of multiple fields of bone marrow aspirate smears. For the diagnosis of morphologic dysplasia in bone marrow, features of dyserythropoiesis, dysgranulopoiesis, and dysmegakaryopoiesis had to be present in $\geq 10\%$ of cells of the respective lineage. Conventional Giemsa banding analysis was performed on 24- and 48-h unstimulated bone marrow cultures. All cases included had the number of metaphases adequate for analysis. Karyotypes were reported using the International System for Human Cytogenetic Nomenclature Criteria [11]. Based on bone marrow morphology, peripheral blood count, and cytogenetic characteristics, all cases were initially classified with the French-American-British (FAB) criteria [12] then reclassified with the 2001 WHO criteria [13, 14], which included (1) refractory anemia (RA); (2) RA with ringed sideroblasts (RARS); (3) refractory cytopenia with multilineage dysplasia (RCMD); (4) refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS); (5) RA with excess blasts-1 (RAEB-1); (6) RAEB-2; (7) MDS associated with isolated del(5q); and (8) MDS, unclassified. An IPSS score was computed for each patient using the algorithm proposed by Greenberg et al. [3]. Cancer history was also collected at the time of diagnosis. Among the 616 patients, 454 had

no history of cancer and were classified as de novo MDS, 110 had other types of cancer prior to developing MDS and were considered therapy-related MDS, and 52 could not be categorized.

Treatment modalities included transfusion of blood products, administration of growth factors, Food and Drug Administration-approved medications for MDS (azacitidine, decitabine, and lenalidomide), and experimental protocols. None of the patients received immune suppressive therapy or underwent hematopoietic stem-cell transplantation. Information on cigarette smoking and alcohol drinking was consistently collected from patients via a structured questionnaire at the initial clinical encounter. The response rate to the questionnaire was approximately 96%.

Patient survival was calculated from the date of MDS diagnosis until death from any cause or until 31 December 2008, whichever was earlier. Date of death was first obtained from medical records; for patients who did not have a date of death recorded, additional search was conducted using the National Death Index for verification of vital status and date of death. We focused on all-cause mortality instead of MDS-specific mortality. The cause of death reporting may not have been reliable and deaths due to MDS may have been miscoded, since MDS is not well-recognized and patients usually die from infections and/or bleeding, which are not specific. In addition, common comorbidities such as congestive heart failure and chronic obstructive pulmonary disease can be severely exacerbated by anemia and infection, which are likely to occur secondary to MDS. Thus, while MDS may be the principal factor leading to a patient's death, it may not be reported as such.

Approximately one-thirds of the patients were also under the care of local hematologists and were transferred to different healthcare facilities when they developed AML, thus we did not have complete information on AML transformation. The study protocol has been approved by the institutional review boards of the institutions involved.

Statistical analysis

Kaplan–Meier product limit was utilized to describe the probability of survival at various times. Log-rank test was used to compare survival curves between different groups. Univariate- and multivariate-adjusted hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazard regression models with follow-up time as the underlying time metric. Age at diagnosis was categorized into five groups: <60, 60–64, 65–69, 70–74, and ≥75 years. Smoking was categorized as never/ever, never/former/current, or combinations of smoking status and level of daily consumption (never smokers, former smokers with < or ≥1 pack/day, and current smokers with < or ≥1 pack/day). We did not construct pack-years of smoking as detailed data on the duration of smoking were not available. Alcohol intake was initially categorized as never/ever and by type and amount of consumption. The type and amount of alcohol consumption did not appear to affect MDS survival, so we decided to only present results with a dichotomous categorization of alcohol intake (i.e., never/ever). Median household income by zip code was obtained by linking patients' residential addresses to the US Census 2000 (<http://www.census.gov/main/www/cen2000.html>) and categorized into tertiles. Tests for trend were conducted by using the original value of each variable on a continuous scale (i.e., means median household income by zip code in dollars, age in years, and IPSS score in continuous format). Due to the relatively small number of patients who were classified as intermediate risk 2 or high risk by the IPSS, these two groups were combined when the impact of smoking on MDS survival was assessed by IPSS risk group. To assess the possibility that smoking may play different roles in de novo versus therapy-related MDS, we conducted additional analyses adjusting for the type of MDS (i.e., de novo, therapy-related, or unknown). Furthermore, the analyses were repeated in patients with de novo MDS and

patients with therapy-related MDS separately. All analyses were conducted using SAS for Windows version 9.1 (SAS Institute, Inc., Cary, NC). All significance tests were two-sided with $\alpha = 0.05$.

Results

Of the 616 patients, 447 (72.6%) had died by December 2008. The median age at diagnosis was 67.3 years, with the majority of patients being white (88.8%) and men (66.6%; Table 1). The median survival was 3.8 years for men and 5.2 years for women (p from log rank test = 0.01). Analyses with univariate Cox proportional hazard models suggested that being men was associated with a 28% increased risk of death (HR = 1.28, 95% CI: 1.05–1.57, Table 1). Compared with RA patients, patients who were categorized as having RCMD, RAEB-1, or RAEB-2 by the WHO recommendation had worse survival. Race, alcohol consumption (never versus ever), and median household income at the zip code level did not appear to be associated with the risk of death among MDS patients (Table 1). We also categorized alcohol consumption based on duration and dose but observed no impact on MDS survival (detailed data not shown).

Age at diagnosis had a significant impact on MDS survival; the older the age, the shorter the survival ($p < 0.01$, Tables 1, 2). IPSS scores differentiated the survival of MDS patients in that intermediate- and high-risk patients had significantly higher risk of death than low-risk patients (Tables 1,2).

The median survival was 3.9 and 4.9 years for patients who smoked and patients who never smoked, respectively (Fig. 1, p from log rank test = 0.13). After simultaneously adjusting for sex, age at diagnosis, and IPSS score, the variables that were associated with the risk of death in univariate analyses, MDS patients who smoked at the time of the first clinical encounter had a significantly increased risk of death (HR = 1.46, 95% CI: 1.07–2.00, Table 3), and the risk estimate was higher for male patients (HR = 1.76, 95% CI: 1.21–2.56). Compared with never smokers, patients who were smoking at least 1 pack/day at the first clinical encounter had significantly increased risk of death (HR = 1.73, 95% CI: 1.19–2.52), whereas those who had quit smoking had risk estimates similar to that of non-smokers (Table 3).

When the analyses were stratified by IPSS risk groups, current smokers, especially current smokers who smoked at least 1 pack/day, showed increased risks of death across different IPSS risk groups. However, the negative prognostic effect of smoking only reached statistical significance in the IPSS low-risk group (current smokers: HR = 2.83, 95% CI: 1.48–5.39; current smokers who smoked at least 1 pack/day: HR = 3.20, 95% CI: 1.55–6.61, Table 4).

Adjusting for treatment modalities had no appreciable impact on the results of different analyses. The observed HRs were essentially unchanged when we adjusted for the type of MDS (i.e., de novo, therapy-related, or unknown). When analyses were stratified by the type of MDS, smoking remained to be a statistically significant, negative prognostic factor for de novo MDS ($n = 454$). While a similar pattern was also observed among patients with therapy-related MDS ($n = 110$), the differences did not reach statistical significance (detailed data not shown).

Discussion

To our knowledge, this is the first study to assess the role of modifiable lifestyle factors in MDS survival. Our findings suggest that smoking is associated with a shorter survival of MDS patients, especially among men and patients in the IPSS low-risk group. Men are more

likely to smoke [15] and have shorter MDS survival than women [2]. In this study, the ratio of male to female patients was approximately 2:1, and the percentages of ever smokers were 72.2 and 52.9% for men and women, respectively. A 78% increased risk of death was observed among male patients who smoked at least 1 pack/day at the initial clinical encounter, compared with male patients who never smoked. Female patients who smoked at least 1 pack/day also appeared to have a higher risk of death than those who never smoked, but the difference did not reach statistical significance. It is interesting that former smokers (i.e., patients who had smoked at some point in their life time but already quit smoking at the initial clinical encounter) had risk of death similar to non-smokers, regardless of sex.

In the United States, the prevalence of smoking is inversely associated with socioeconomic status [15]. In the present study, the residential addresses of 59% of the patients were in zip codes that had median household income greater than 41,994 dollars, the median household income in the United States in 2000 (<http://www.factfinder.census.gov/servlet/SAFFacts>). We adjusted for median household income at the zip code level as a way to control for the possible impact of socioeconomic status and the deleterious effect of smoking on MDS survival persisted (detailed data not shown).

Previous studies have linked smoking with specific cytogenetic abnormalities involving chromosome 7 (mainly -7/7q-) and 8 (trisomy 8 and t(8;21)(q22;q22)) among AML/MDS patients [16, 17]. Chromosome 7 abnormalities have been categorized as poor-risk karyotype according to IPSS, and any patient with chromosome 8 abnormalities in a non-complex karyotype would be categorized as intermediate risk. In this study, when the effect of smoking on MDS survival was evaluated in subsets of patients with and without chromosomal abnormalities, the negative prognostic impact of smoking was observed in both subsets (detailed data not shown). It has also been reported that the prognostic impact of cytogenetic abnormalities on MDS survival is modified by sex and smoking [18]. In this study, the hazard ratio associated with smoking was elevated in both men and women, although it did not reach statistical significance among female patients.

The mechanism as to how smoking affects MDS survival is unclear. Tobacco is a risk factor for a wide range of diseases, such as cardiovascular diseases, respiratory infections, and many types of cancer [19, 20]. MDS patients who smoked could have other comorbidities and be more vulnerable to the side effects of cancer treatment. Smoking is also associated with immunologic perturbations, including alterations in T-cell subsets and a lower percentage of natural killer cells [21, 22], resulting in a general suppression of the immune system [22]. It is understandable that the impact of smoking was more pronounced in the IPSS low-risk group, since the patients in the low-risk group live longer (median survival = 5.7 years) [3] and there is a window of time for prognostic factors to exert their effect. For patients in the IPSS high-risk group, the aggressive natural history of disease leads to much shorter survival (median survival = 0.4 years) [3] with less opportunity for lifestyle factors to exert an effect. We focused on all-cause mortality instead of MDS-specific mortality. Smoking-related mortality can be a competing risk of MDS-specific mortality, especially among patients with longer duration of survival. Therefore, our finding could have potentially inflated the influence of smoking, as smokers tend to have a shorter life expectancy than non-smokers irrespective of MDS.

This study is unique in that it addressed the prognostic role of modifiable lifestyle factors in a large number of MDS patients who were seen by the same team of hematologists. The patients were well categorized in terms of their cytogenetic abnormalities, WHO subtypes and IPSS risk groups. The subjects included in this analysis were hospital-based, not population-based. Compared with MDS patients from population-based cancer registries [2], patients included in this analysis had a similar racial distribution but a slightly skewed

gender distribution (i.e., more men). This likely reflected referral patterns. The information on smoking was systematically assessed at the initial clinical encounter, which usually occurred around the time of diagnosis. It is possible that some patients might have changed their smoking habit later on. Nevertheless, if any change had occurred, it is more likely that a patient had quit smoking or reduced the amount of smoking, which would have resulted in an underestimate of the effect of smoking in the current analysis. Due to the lack of information on the duration of smoking, we were unable to assess any dose–response relationship. However, current and heavy smokers had higher risks of death than past and light smokers, which supported the validity of the findings. Although the analysis adjusted for multiple factors that have been shown to affect MDS survival, such as age at diagnosis, sex, and IPSS risk categorization (which combines many clinical characteristics and has been used widely in prognostic studies of MDS), we were unable to assess the potential role of individual-level social economic status, comorbidities or treatment. Due to the relatively small number of patients with therapy-related MDS, analyses involving this patient group did not have sufficient statistical power. Future studies aiming at identifying the prognostic factors of MDS would benefit from systematically ascertaining comorbid conditions, while the impact of treatment is best assessed in randomized clinical trials.

In conclusion, this study provides strong evidence that smoking is a significant and independent negative predictor of MDS survival, especially among male patients and patients in the IPSS low-risk group. It would be useful for clinicians to inquire about smoking status. Smoking cessation is an important health message to convey to every individual, and it seems to be similarly relevant to MDS patients.

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References

1. Corey SJ, Minden MD, Barber DL, Kantarjian H, Wang JC, Schimmer AD. Myelodysplastic syndromes: the complexity of stem-cell diseases. *Nat Rev Cancer*. 2007; 7:118–129. [PubMed: 17251918]
2. Ma X, Does M, Raza A, Mayne ST. Myelodysplastic syndromes: incidence and survival in the United States. *Cancer*. 2007; 109:1536–1542. [PubMed: 17345612]
3. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997; 89:2079–2088. [PubMed: 9058730]
4. Bennett, J. The myelodysplastic syndromes: pathobiology and clinical management. In: Cheson, B., editor. *Basic and clinical oncology*. Vol. 27. Marcel Dekker; New York: 2002.
5. Wang R, Gross CP, Halene S, Ma X. Neighborhood socioeconomic status influences the survival of elderly patients with myelodysplastic syndromes in the United States. *Cancer Causes Control*. 2009; 20:1369–1376. [PubMed: 19455395]
6. Pogoda JM, Preston-Martin S, Nichols PW, Ross RK. Smoking and risk of acute myeloid leukemia: results from a Los Angeles County case-control study. *Am J Epidemiol*. 2002; 155:546–553. [PubMed: 11882528]
7. Fernberg P, Odenbro A, Bellocchio R, et al. Tobacco use, body mass index, and the risk of leukemia and multiple myeloma: a nationwide cohort study in Sweden. *Cancer Res*. 2007; 67:5983–5986. [PubMed: 17575169]
8. Kasim K, Levallois P, Abdous B, Auger P, Johnson KC. Lifestyle factors and the risk of adult leukemia in Canada. *Cancer Causes Control*. 2005; 16:489–500. [PubMed: 15986104]
9. Chelghoum Y, Danaila C, Belhabri A, et al. Influence of cigarette smoking on the presentation and course of acute myeloid leukemia. *Ann Oncol*. 2002; 13:1621–1627. [PubMed: 12377652]
10. Varadarajan R, Licht A, Hyland AJ, et al. Smoking adversely affects survival in acute myeloid leukemia patients. *ASH Annu Meet Abstr*. 2009; 114:979.

11. International Standing Committee on Human Cytogenetic Nomenclature, Mitelman F (1995) ISCN 1995: an international system for human cytogenetic nomenclature (1995): recommendations of the international standing committee on human cytogenetic nomenclature; Memphis, Tennessee, USA. 9–13 Oct 1994; Karger, Base:
12. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol.* 1982; 51:189–199. [PubMed: 6952920]
13. Harris NL, Jaffe ES, Diebold J, et al. The World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues. Report of the clinical advisory committee meeting, Airline House, Virginia, November, 1997. *Ann Oncol.* 1999; 10:1419–1432. [PubMed: 10643532]
14. Vardiman JW, Harris NL, Brunning RD. The world health organization (WHO) classification of the myeloid neoplasms. *Blood.* 2002; 100:2292–2302. [PubMed: 12239137]
15. Thorne SL, Malarcher A, Maurice E, Caraballo R. Cigarette smoking among adults—United States, 2007. *JAMA.* 2009; 301:373–375.
16. Bjork J, Albin M, Mauritzson N, Stromberg U, Johansson B, Hagmar L. Smoking and myelodysplastic syndromes. *Epidemiology.* 2000; 11:285–291. [PubMed: 10784245]
17. Bjork J, Johansson B, Broberg K, Albin M. Smoking as a risk factor for myelodysplastic syndromes and acute myeloid leukemia and its relation to cytogenetic findings: a case-control study. *Leuk Res.* 2009; 33:788–791. [PubMed: 19019430]
18. Mauritzson N, Johansson B, Rylander L, et al. The prognostic impact of karyotypic subgroups in myelodysplastic syndromes is strongly modified by sex. *Br J Haematol.* 2001; 113:347–356. [PubMed: 11380398]
19. United States. The health consequences of smoking a report of the Surgeon General. Atlanta, Ga: U.S. Public Health Service, National Center for Chronic Disease Prevention and Health Promotion; 2004. Public health service. Office of the surgeon general. National center for chronic disease prevention and health promotion (U.S.).
20. World health organization. IARC. International agency for research on cancer (2002: Lyon); Tobacco smoke and involuntary smoking: views and expert opinions of an IARC working group on the evaluation of carcinogenic risks to humans, which met in Lyon; 11–18 June 2002; Lyon: IARC; 2004.
21. Holt PG. Immune and inflammatory function in cigarette smokers. *Thorax.* 1987; 42:241–249. [PubMed: 3303428]
22. Soperi M. Effects of cigarette smoke on the immune system. *Nat Rev Immunol.* 2002; 2:372–377. [PubMed: 12033743]

Fig. 1.
Survival of MDS patients by smoking status

Table 1

Characteristics of the study population

Characteristics	n (%)	Hazard ratio (95% CI)
Sex, n (%)	616	
Female	206 (33.4)	1.00
Male	410 (66.6)	1.28 (1.05–1.57)
Median age (years) (interquartile)	67.3 (59.3–74.1)	
Age at diagnosis (years)		
<60	162 (26.3)	1.00
60–64	88 (14.3)	1.58 (1.14–2.20)
65–69	117 (19.0)	2.37 (1.77–3.19)
70–74	120 (19.5)	2.74 (2.04–3.68)
75+	129 (20.9)	2.54 (1.90–3.40)
P for trend		<0.01
Race, n (%)		
Non-hispanic white	547 (88.8)	1.00
Other	69 (11.2)	0.92 (0.69–1.22)
Smoke status, n (%)		
Never	211 (34.3)	1.00
Ever	405 (65.7)	1.17 (0.96–1.42)
Former	335 (54.4)	1.06 (0.82–1.38)
Current	70 (11.4)	1.22 (0.98–1.50)
Quit, <1 pack/day	97 (15.7)	1.10 (0.83–1.46)
Quit, ≥1 pack/day	238 (38.6)	1.16 (0.93–1.45)
Current, <1 pack/day	31 (5.0)	0.96 (0.60–1.51)
Current, ≥1 pack/day	39 (6.3)	1.63 (1.12–2.36)
Alcohol, n (%) ^a		
Never	151 (24.5)	1.00
Ever	431 (67.0)	0.99 (0.80–1.23)
Median household income (\$) ^a		
<40,838	193 (31.3)	1.00
40,838–53,893	193 (31.3)	0.88 (0.69–1.11)
>53,893	193 (31.3)	0.98 (0.78–1.23)
P for trend		0.69
WHO classification b, n (%)		
RA	78 (12.9)	1.00
RARS	46 (7.6)	0.81 (0.51–1.27)
RCMD	122 (20.1)	1.52 (1.08–2.14)
RCMD-RS	66 (10.9)	1.21 (0.81–1.80)
5q-	32 (5.3)	1.08 (0.66–1.76)
RAEB-1	118 (19.5)	2.15 (1.53–3.03)
RAEB-2	61 (10.1)	2.83 (1.92–4.16)

Characteristics	<i>n</i> (%)	Hazard ratio (95% CI)
MDS-U	83 (13.7)	0.94 (0.63–1.41)
IPSS, <i>n</i> (%) ^a		
Low risk	157 (25.7)	1.00
Intermediate risk 1	306 (50.0)	1.99 (1.55–2.56)
Intermediate risk 2	118 (19.3)	3.68 (2.75–4.94)
High risk	31 (5.1)	4.83 (3.13–7.44)

^aPercentages did not add up to 100 due to missing values

^bWHO classification: *RA* refractory anemia, *RARS* refractory anemia with ring sideroblasts, *RCMD* refractory cytopenia with multilineage dysplasia, *RCMD-RS* refractory cytopenia with multilineage dysplasia and ringed sideroblasts, *RAEB* refractory anemia with excess blasts, *MDS-U* myelodysplastic syndrome, unclassifiable

Table 2

Selected factors and their association with MDS survival

	Hazard ratio (95% CI)		
	Overall ^a	Male ^b	Female ^b
Sex			
Female	1.00		
Male	1.18 (0.96–1.45)		
Age at diagnosis (years)			
< 60	1.00	1.00	1.00
60–64	1.50 (1.07–2.09)	1.34 (0.89–2.04)	1.64 (0.92–2.94)
65–69	2.15 (1.60–2.90)	2.14 (1.48–3.10)	1.76 (1.02–3.03)
70–74	2.28 (1.69–3.07)	2.35 (1.63–3.38)	1.96 (1.13–3.37)
75+	2.37 (1.77–3.18)	1.94 (1.35–2.79)	3.71 (2.26–6.08)
P for trend	< 0.01	<0.01	<0.01
Smoke status			
Never	1.00	1.00	1.00
Ever	0.99 (0.81–1.22)	1.06 (0.81–1.38)	0.98 (0.70–1.39)
IPSS			
Low risk	1.00	1.00	1.00
Intermediate risk 1	1.85 (1.44–2.38)	1.91 (1.40–2.60)	1.78 (1.13–2.80)
Intermediate risk 2	3.32 (2.47–4.48)	2.74 (1.91–3.94)	6.23 (3.61–10.76)
High risk	4.38 (2.83–6.80)	5.54 (3.25–9.46)	4.14 (1.84–9.33)

^a Hazard ratios and 95% CI were derived from multivariate Cox proportional hazard models, adjusting for sex, age at diagnosis (<60, 60–64, 65–69, 70–74, and 75+), and IPSS risk groups (low, intermediate 1, intermediate 2, high and unknown)

^b Hazard ratios and 95% CI were derived from multivariate Cox proportional hazard models, adjusting for age at diagnosis (<60, 60–64, 65–69, 70–74, and 75+) and IPSS risk groups (low, intermediate 1, intermediate 2, high and unknown)

Table 3

Smoking and MDS survival by sex

Smoking status	Hazard ratio (95% CI)		
	Overall ^a	Male ^b	Female ^b
Never	1.00	1.00	1.00
Ever	0.99 (0.81–1.22)	1.06 (0.81–1.38)	0.98 (0.70–1.39)
Former	0.92 (0.74–1.13)	0.95 (0.72–1.25)	0.98 (0.69–1.41)
Current	1.46 (1.07–2.00)	1.76 (1.21–2.56)	0.98 (0.51–1.85)
Quit, <1 pack/day	0.79 (0.59–1.06)	0.85 (0.58–1.24)	0.76 (0.46–1.24)
Quit, ≥1 pack/day	0.98 (0.78–1.23)	0.98 (0.74–1.31)	1.17 (0.78–1.75)
Current, < 1 pack/day	1.17 (0.73–1.86)	1.74 (1.04–2.92)	0.33 (0.08–1.39)
Current, ≥1 pack/day	1.73 (1.19–2.52)	1.78 (1.13–2.82)	1.65 (0.83–3.29)

^a Hazard ratios and 95% CI were derived from multivariate Cox proportional hazard models, adjusting for sex, age at diagnosis (<60, 60–64, 65–69, 70–74, and 75+), and IPSS risk groups (low, intermediate 1, intermediate 2, high and unknown)

^b Hazard ratios and 95% CI were derived from multivariate Cox proportional hazard models, adjusting for age at diagnosis (<60, 60–64, 65–69, 70–74, and 75+) and IPSS risk groups (low, intermediate 1, intermediate 2, high and unknown)

Table 4

Smoking and MDS survival by IPSS risk group

Smoking status	Low risk		Intermediate-risk 1		Intermediate-risk 2 or high risk	
	n	HR (95% CI) ^a	n	HR (95% CI) ^a	n	HR (95% CI) ^a
Never	59	1.00	109	1.00	42	1.00
Ever	98	1.36 (0.81–2.29)	197	1.08 (0.82–1.43)	107	0.77 (0.52–1.14)
Former	75	1.06 (0.61–1.84)	166	1.07 (0.80–1.42)	92	0.71 (0.47–1.07)
Current	23	2.83 (1.48–5.39)	31	1.16 (0.73–1.85)	15	1.13 (0.61–2.10)
Quit, < 1 pack/day	19	1.01 (0.48–2.13)	48	0.93 (0.62–1.40)	28	0.67 (0.39–1.13)
Quit, ≥ 1 pack/day	56	1.06 (0.58–1.94)	118	1.13 (0.83–1.54)	64	0.73 (0.47–1.14)
Current, < 1 pack/day	9	2.28 (0.89–5.88)	16	0.91 (0.46–1.78)	6	1.03 (0.40–2.64)
Current, ≥ 1 pack/day	14	3.20 (1.55–6.61)	15	1.46 (0.82–2.62)	9	1.20 (0.57–2.54)

^a Hazard ratios and 95% CI were derived from multivariate Cox proportional hazard models, adjusting for sex and age at diagnosis (<60, 60–64, 65–69, 70–74, and 75+)