

GEOGRAPHIC DISPARITIES IN CARDIOVASCULAR DEATH AMONG PATIENTS WITH MYELODYSPLASTIC SYNDROMES

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Introduction

- Acquired somatic mutations in hematopoietic stem cells lead to myelodysplastic syndromes (MDS) and are also associated with accelerated atherosclerosis.
- In subjects without MDS, clonal hematopoiesis (CH) constitutes a potent cardiovascular risk factor.
- In a previous analysis, we demonstrated that an MDS diagnosis was an independent risk factor for cardiovascular disease (CVD) compared to propensity matched non-cancer controls.
- CVD is the most common non-cancer cause of death in MDS, and rural residence has been independently associated with many CVD risk factors.
- There are no studies examining the association of geographic disparities and cardiovascular death in patients with MDS.

Methods

- We identified adult patients diagnosed with MDS between 2001 and 2016 using the Surveillance, Epidemiology, and End Results (SEER) database.
- MDS risk classification into low, intermediate and high, was based on International Classification of Diseases for Oncology 3 Edition (ICDO-3) codes.
- Rural and urban populations were categorized using the US Department of Agriculture's Rural-Urban Continuum Codes (RUCC).
- Primary cause of death reported to State Registries (SEER COD recode) was used for cause-specific survival analysis, calculated from date of MDS diagnosis to date of CVD-related death.
- Cases with missing data on any key variable were excluded from analysis.
- SEER*Stat version 8.3.9 was used to calculate MDS incidence rates.
- Survival analysis employed the Kaplan-Meier method and log-rank test.
- Multivariable Cox-proportional hazards regression estimated the association of rural residence with CVD death adjusting for age, sex, race, ethnicity, MDS risk, and geographic location.

Results

- We included 52,750 patients with MDS, 56.8% were male and 84.8% were white.
- Low, intermediate and high histologic risk were seen in 18.7%, 64.4% and 16.9% respectively.
- Most patients were from urban areas (88%).
- The estimated incidence rate for MDS was 6.7 per 100,000 in both urban and rural populations.
- The rural MDS population was slightly younger (median age 75 vs 77 years, $p < 0.004$) and had a higher proportion of whites (90.5% vs 84%, $p < 0.001$).
- No difference in MDS risk distribution was noted between urban and rural MDS patients (Table 1).

Table 1. Baseline Characteristics of MDS patients.

Characteristic	Urban	Rural	p-value
Total N	46415 (88.0%)	6335 (12.0%)	
Age, median (IQR)	77 (68, 83)	75 (68, 82)	0.004
Age (groups)			<0.001
18-49	1902 (4.1%)	212 (3.4%)	
50-64	6635 (14.3%)	953 (15.0%)	
65-79	19877 (42.8%)	2953 (46.6%)	
80+	18001 (38.8%)	2217 (35.0%)	
Sex			0.365
Female	20016 (43.1%)	2770 (43.7%)	
Male	26399 (56.9%)	3565 (56.3%)	
Race			<0.001
White	38992 (84.0%)	5735 (90.5%)	
Black	3919 (8.4%)	423 (6.7%)	
Other	3504 (7.6%)	177 (2.8%)	
Ethnicity			<0.001
Non-Hispanic	42777 (92.2%)	6167 (97.4%)	
Hispanic	3638 (7.8%)	168 (2.6%)	
MDS Risk			0.151
Low	8651 (18.6%)	1204 (19.0%)	
Intermediate	29865 (64.3%)	4114 (64.9%)	
High	7899 (17.0%)	1017 (16.1%)	

Table 2. Cox Regression for Cardiovascular Death in patients with MDS.

	Adjusted Multivariable Model	
	Hazard Ratio (95% CI)	p-value
Area of residence		
Urban	Ref	-
Rural	1.12 (1.03 - 1.22)	0.011
Age		
18-49	Ref	-
50-64	2.14 (1.65 - 2.77)	<0.001
65-79	5.33 (4.19 - 6.79)	<0.001
80+	13.32 (10.46 - 16.96)	<0.001
Sex		
Male	Ref	-
Female	0.82 (0.78 - 0.86)	<0.001
Race		
White	Ref	-
Black	1.02 (0.93 - 1.12)	0.659
Other	0.82 (0.73 - 0.91)	<0.001
Ethnicity		
Non-Hispanic	Ref	-
Hispanic	0.89 (0.80 - 0.99)	0.035
MDS Risk		
Low	Ref	-
Intermediate	1.17 (1.11 - 1.24)	<0.001
High	1.20 (1.09 - 1.32)	<0.001

Results (continued)

- Unadjusted analyses revealed a trend towards lower overall survival in the rural MDS population (24 vs 25 months, $p = 0.051$).
- After adjusting for age, sex, race, ethnicity, MDS risk category, and area of residence (rural vs urban), rural subjects with MDS had a 12% increased hazard (HR 1.12, 95%CI 1.03 – 1.22) for CVD-related death compared to urban subjects (Figure 1).
- Further, the adjusted HR for CVD-related death was 1.23 (CI95% 1.01 – 1.5) for those who lived in the most rural areas (RUCC codes 8 and 9, less than 2,500 urban population).

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Figure 1. Adjusted CVD-related death survival curves in patients with MDS.

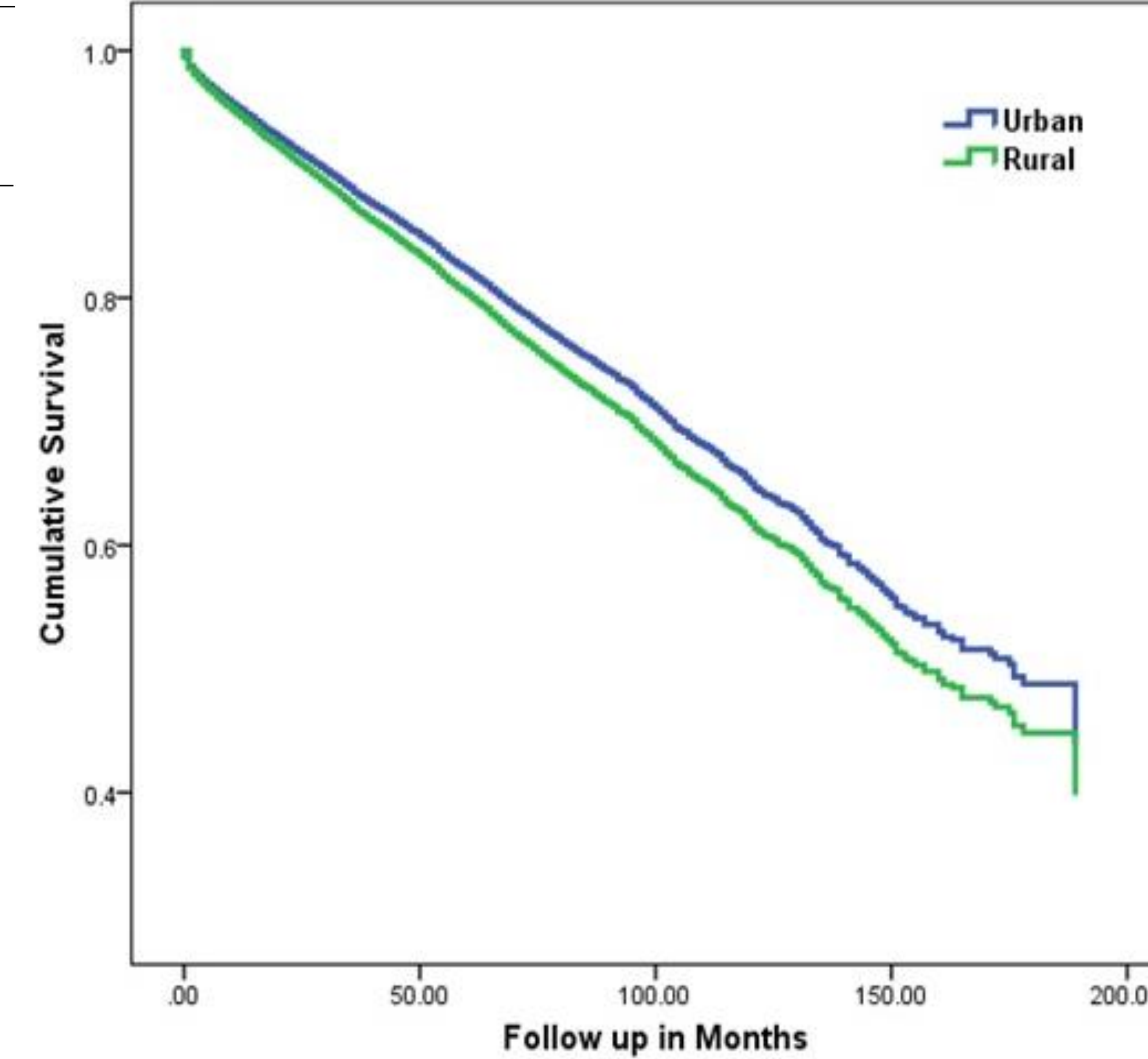
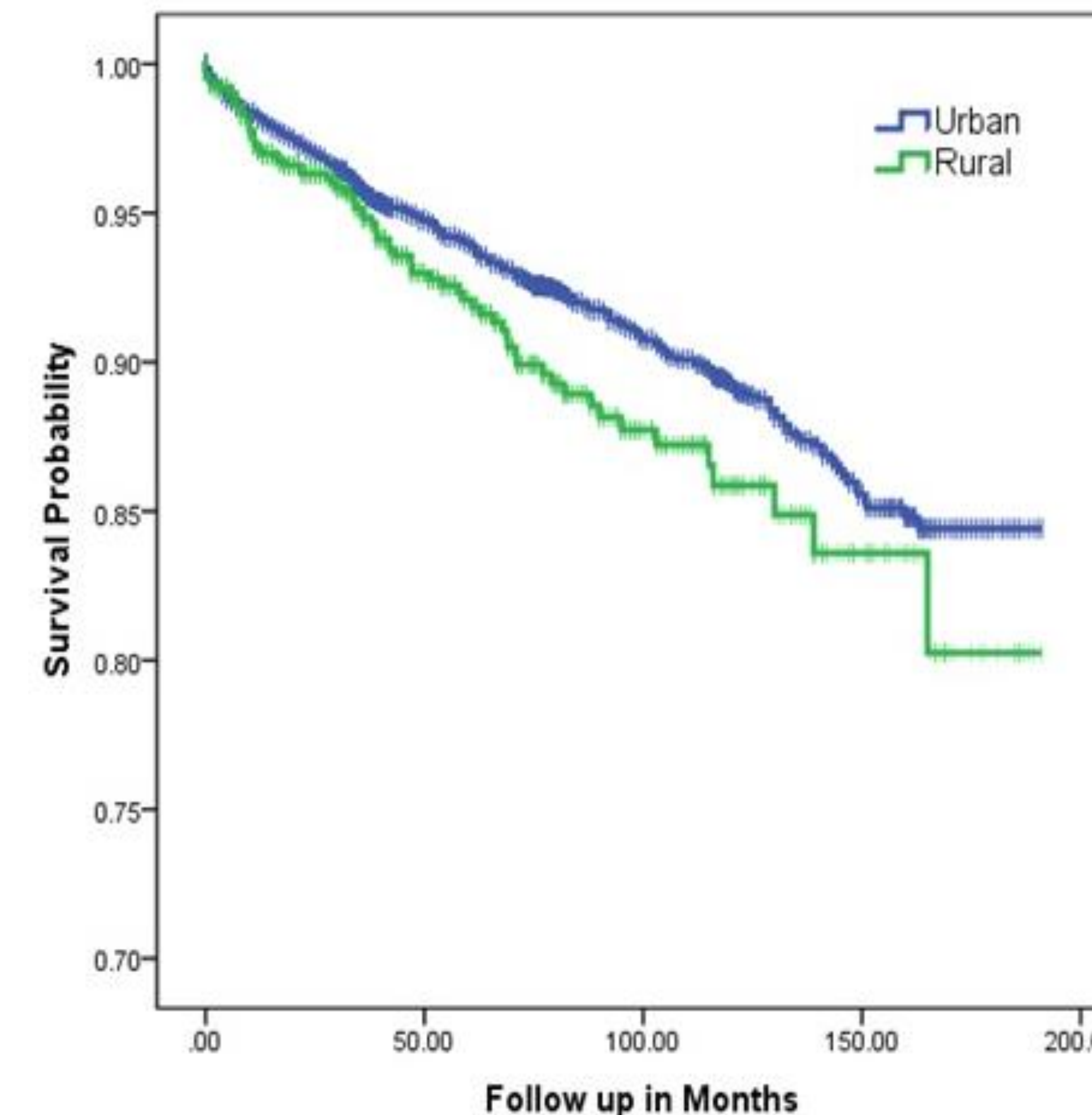


Figure 2. Kaplan Meier curve of CVD-related mortality in MDS patients < 65 years.



Results (continued)

- Among young MDS patients (age < 65), those residing in rural areas had a higher proportion of CVD-related death (6% vs 4.7%, $p = 0.031$) compared to urban subjects.
- Rural young MDS patients also had a significantly lower cardiovascular specific survival compared to MDS patients (Figure 2).
- MDS histologic risk was also a significant risk factor associated with cardiovascular death in the multivariable model (Table 2).
- Compared to low risk MDS, patients with intermediate risk MDS had adjusted HR for CVD-related death of 1.17 (95%CI 1.11 – 1.24).
- Compared to low risk MDS, patients with high risk MDS had adjusted HR for CVD-related death of 1.2 (95%CI 1.09 – 1.32).
- Other factors significantly associated with increased hazard for CVD-related death in the adjusted model were advancing age and male sex.

Conclusions

- In a large population-based study, we found that rural area of residence is significantly associated with a higher burden of CVD-related death in MDS.
- Rural patients with MDS had higher cardiovascular death even after adjusting for demographic risk factors and MDS risk classification.
- Although aging is an important issue in rural areas, the geographical disparities in CVD-related death among MDS patients are not explained by age alone.
- The rural difference in CVD death was notable in young MDS patients less than 65 years old.
- These findings should prompt hematologists caring for patients with MDS from rural areas to rigorously evaluate and address CVD risk factors.
- As novel treatments improve cancer-specific survival in MDS, marginalized populations with different CVD risk profiles may be disproportionately affected by the cardiovascular risk from CH.
- These disparities should be considered when developing MDS surveillance programs.