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Fit Older Adults with Advanced Myelodysplastic Syndromes: Who is Most Likely to Benefit from Transplant?

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Abstract

We conducted a prospective observational study of fit adults aged 60 to 75 with advanced MDS, enrolled hierarchically for adverse MDS risk (intermediate-2 or high-risk international prognostic score [IPSS], low or intermediate-1 IPSS with poor-risk cytogenetics, or therapy-related MDS) or standard risk with severe cytopenia. A total of 290 patients enrolled at two centers: 175 for adverse risk and 115 for standard risk with severe cytopenia. 113 underwent HCT after a median of 5 months; median follow-up for all was 39.5 months. In univariable analyses, the hazard ratio (HR) for death comparing HCT with no HCT was 0.84 (p=0.30). The HR for death was 0.64 (p=0.04) for HCT ≤5 months after enrollment and 1.20 (p=0.39) for HCT >5 months. In multivariable analyses controlling for age, gender, ECOG performance status, cytogenetic risk, and IPSS risk group, HR for death was 0.75 (p=0.13) for HCT compared to no HCT, 0.57 (p=0.01) for adverse MDS risk and 1.33 (p=0.36) for standard risk with severe cytopenia. In this large, prospective cohort of fit older adults with advanced MDS, we found that survival was significantly improved if HCT was performed early or for adverse risk disease but not for standard risk disease with severe cytopenia.

Introduction

The myelodysplastic syndromes are a heterogenous group of hematopoietic stem cell disorders characterized by ineffective hematopoiesis and variable risk of progression to acute myeloid leukemia. Age is an important risk factor for MDS, with a median age at

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diagnosis of approximately 70 years old.[1, 2] Despite progress in diagnosis and treatment,[3, 4] overall survival in advanced disease is approximately 1 year,[5] and the only known curative therapy is hematopoietic stem cell transplantation (HCT).[2, 4] The median age at diagnosis has historically limited the number of patients considered eligible for HCT, due to the increased mortality associated with myeloablative conditioning regimens in older patients.[6]

The introduction of reduced-intensity conditioning (RIC) has made HCT available to more fit, elderly patients. Markov modeling suggests that, for those aged 60 to 70 with intermediate-2 or high-risk IPSS scores, RIC HCT offers a quality-adjusted overall survival (OS) benefit (36 vs 28 months).[7] Prospective clinical data are limited. Early results from the VIDAZALLO trial, which treated patients 55–70 years old with azacitidine induction followed by allogeneic transplant or continuous azacitidine, showed improved survival with HCT (3-year OS 49% versus 22%);[8] however, 33% of patients enrolled did not undergo randomization (mainly due to progression or death), suggesting that early HCT may be crucial.

The SFGM-TC/GFM trial demonstrated an improved 4-year OS for patients 50–70 years old with high-risk MDS who underwent RIC HCT versus those who did not (37% vs 15%);[9] however, HCT eligibility was limited to those with a matched donor. Finally, the RICMAC trial, which compared RIC and myeloablative conditioning (MAC) before HCT in patients with MDS or secondary AML (only 5% were older than 60), found similar 2-year relapse-free and overall survival rates between the approaches (62% vs 58% and 76% vs 63%, differences not significant).[10] While provocative, taken together, the patient populations and/or entry criteria of these studies do not reflect the “real world” population of older adults with MDS who are faced with the decision of whether or not to pursue HCT. We therefore undertook a prospective observational study to examine survival for RIC HCT versus non-HCT approaches for HCT-eligible patients with advanced MDS aged 60 to 75.

Materials/Subjects and Methods

Patient Selection

Data are from the MDS Transplant-Associated Outcomes (MDS-TAO) study. Patients aged 60 to 75 years with diagnosis of MDS, myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U), or chronic myelomonocytic leukemia (CMML), with disease sufficiently advanced to warrant consideration of RIC HCT were prospectively identified at the Dana-Farber Cancer Institute or Massachusetts General Hospital.[11] Adverse-risk disease was defined as intermediate-2 or high-risk IPSS,[5] high-risk cytogenetics,[12] or therapy-related MDS. Standard-risk disease comprised subjects with severe cytopenias or transfusion dependence as defined according to the WHO classification-based prognostic scoring system (WPSS)[13] Patients with IPSS low-risk disease (low or intermediate-1), who did not have severe cytopenias or intermediate/poor cytogenetics as defined above, were not eligible.

Patients were required to be fit enough for HCT, meeting pre-determined measures of hepatic, renal, pulmonary, and cardiac function as well as having an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.[14] Patients also had to be willing to undergo HLA-typing and consider subsequent HCT at the time of enrollment. Patients

whose baseline donor status was already known, or who had undergone prior HCT, were excluded. Complete eligibility details can be found in the Appendix.

Study Design and Procedures

In a prospective cohort design, new patients with advanced MDS from the two participating centers were screened for eligibility. Patients who were not eligible were followed for changes in clinical status (e.g., progression of disease) that might render them eligible over time, at which point they could enter the cohort (see Appendix for CONSORT diagram). All patients who met eligibility criteria (age, diagnosis and disease status, and fitness; not previously undergone a formal donor search or HCT) were approached for enrollment. This was either at the time of their initial appointment or on a rolling basis as their age, disease status, and fitness made them eligible. Appointments could have been with non-transplant or transplant oncologists; patients could not have already considered and declined to pursue transplant at the time of enrollment, but they were not mandated to have a transplant consult. Study entry was defined by when patients became eligible, based on the above criteria, and confirmed with either their transplant or leukemia physician.

After informed consent, eligible participants were followed prior to treatment and during HCT or non-HCT therapy until death. Treatment was not assigned and was at the discretion of the patient and treating physician. For patients >= 60 years old undergoing HCT for MDS, RIC was preferred at the participating institutions throughout the length of the study; however, as this was an observational study, conditioning intensity, GVHD prophylaxis, and post-transplant maintenance therapy were not mandated. Targeted mutation analysis panels for MDS became available in September 2014 and were obtained at the discretion of the treating physician. Results were analyzed for all patients whose testing predated the date of HCT. TP53, JAK2, and RAS pathway mutations were considered adverse-risk; PPM1D was not part of the mutational panel at that time.[15] The study was approved by the Office for Human Research Studies of the Dana-Farber/Harvard Cancer Center and registered at ClinicalTrials.gov (NCT02390414).

Endpoints and Statistical Methods

The primary endpoint was overall survival (OS), defined as time from study entry to death from any cause in the HCT and no-HCT groups. For the HCT cohort only, progression-free survival, cumulative incidence of non-relapse mortality (NRM) and relapse from HCT were also assessed. The study planned to enroll 290 patients. With anticipated enrollment in a 1:2 ratio for HCT to no-HCT, this gave approximately 85% power to detect a 15% difference in 5-year OS between the HCT and no-HCT study groups.[16] Baseline characteristics and mutation analyses were reported descriptively and compared using Fisher's exact test, Chi-square test, or Wilcoxon-Rank-Sum test, as appropriate.

The Kaplan-Meier method was used to estimate OS from study entry, and the log-rank test was used to compare OS based on baseline characteristics. To compare OS between patients with and without HCT, the Mantel-Byar (MB) test[17] was used and corresponding Simon-Makuch (SM) curves[18, 19] were generated by constructing the data in (start, stop) form. Analysis was also performed excluding fourteen patients who died within two months of

study entry (none underwent HCT). Since HCT was treated as a time-dependent variable, the results with and without these fourteen patients were almost identical. Therefore, without loss of generality, these fourteen patients were excluded in the analysis of the MB test and SM curves only. Univariable and multivariable Cox regression analyses were performed to examine the impact of receiving HCT on OS, treating time-to-HCT as a time-dependent variable. For the HCT cohort, cumulative incidence of NRM and relapse were estimated in a competing risks framework treating relapse and NRM as a competing event, respectively.

To explore a potentially time-varying effect of time-dependent factor, HCT, we fit a Cox model with two binary time-dependent covariates: early HCT(t) and delayed HCT(t).[20] Here we defined "early HCT" as HCT performed within 5 months (as the median time to HCT was 5 months); "delayed HCT" was defined as those occurring after 5 months. Risk factors considered in multivariable analysis included age, gender, ECOG performance status, IPSS-based cytogenetic risk, IPSS risk score, and eligibility (MDS disease risk [IPSS intermediate-2 or high, non-IPSS poor-risk cytogenetics, and t-MDS] versus standard risk with severe cytopenias). Prior to modeling, the proportional hazards assumption, linearity assumption for continuous variables, and significance of interaction terms between HCT and covariates were examined.

Finally, we performed landmark analyses[21] at 5, 9, 12, and 24 months after study entry. In this analysis, patients who were alive and at risk at each landmark time point were included and analyzed according to their HCT status at the landmark time regardless of any subsequent shifts in transplant status. All p-values were two-sided, and the significance level was set to 0.05. Multiplicity was not considered. All analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC), and R version 3.2.2 (the CRAN project, www.cran.r-project.org).

Results

Cohort Characteristics

Between May 2011 and May 2018, 303 patients met eligibility criteria, and 290 (95.7%) were enrolled. Baseline characteristics for all patients according to enrollment criteria are shown in Table 1. Baseline characteristics of patients by HCT status are shown in Table S1. By the date of last follow-up (7/1/2019), 177 patients were deceased. The median follow-up time among survivors was 39.5 months (range 7, 96). 113 patients underwent HCT with a median time to HCT of 5 months (range 1, 58). Among these patients, 58 (51.2%) subsequently died. Among the 177 who did not receive HCT, 119 (71.3%) had died. The characteristics of patients who underwent HCT are shown in Table 2; reasons patients did not receive HCT are shown in Table S2.

Targeted mutational analysis panels were available for 139 patients (47.9%), including 52 (46.0%) of the 113 who underwent HCT and 87 (49.2%) of the 177 who did not (p=0.63). Adverse-risk mutations were seen in 53 (38.1%) of the patients profiled: 19 (36.5%) of the 52 who went on to receive HCT and 34 (39.1%) of the 87 who did not (p=0.86). TP53 mutations were found in 20 (38.1%) of the patients profiled: 5 (9.6%) of the 52 who went on to receive HCT and 15 (17.2%) of the 87 who did not (p=0.32). JAK2 mutations were found

in 5 (3.6%) of the patients profiled: 4 (7.7%) of the 52 who went on to receive HCT and 1 (1.1%) of the 87 who did not (p=0.065). In addition, 31 out of 52 (59.6%) in the HCT cohort and 33 out of 87 (37.9%) in the no-HCT cohort had 3 or more mutations (p=0.01; Table S1).

Overall Survival

For the entire cohort (n=290), the median OS was 29 months (95% CI [19, 39.5]; the 3-year OS was 46% (95% CI [40, 52]). Univariable and multivariable Cox models, treating HCT as a time-dependent variable, are presented in Table 3. In univariable analysis, the HR for death in the HCT cohort compared to no-HCT was 0.84 (95% CI [0.61, 1.17], p=0.30). In multivariable analysis, the HR for death in the HCT cohort was 0.75 (95% CI [0.52, 1.09], p=0.13). Excluding the 14 patients who died within two months of the study entry, the HR for death in the HCT cohort was 0.84 (95% CI [0.61, 1.17], p=0.31) in univariable analysis and 0.75 (95% CI [0.52, 1.09], p=0.13) in multivariable analysis. Figure 1A presents the OS of these cohorts using Simon-Makuch curves and their corresponding Mantel-Byar test results (p=0.31). Landmark analyses at 5 months showed benefit for HCT in the overall cohort (p=0.04) and also for landmarks at 9 months (p=0.01) but not 12 or 24 months (Figure S1A). For the HCT cohort, the 3-year PFS from HCT was 53% and 3-year cumulative incidence of non-relapse mortality and relapse were 9.3% and 39%, respectively.

Timing of Transplant

In multivariable analysis excluding 14 patients who died within 2 months without receiving HCT, “early HCT” (≤5 months from study entry) was associated with a lower risk of death compared to no HCT (HR 0.53; 95% CI [0.33, 0.83], p=0.006). “Delayed” HCT (>5 months from study entry) did not demonstrate benefit (HR 1.17; 95% CI [0.75, 1.84], p=0.49). Reasons for delayed HCT are enumerated in Table S3; of 46 patients who received alternative therapies before HCT, 11 responded to pre-HCT treatment and underwent HCT in complete remission. These 11 patients had a favorable hazard ratio (0.53), almost identical to the HR for early HCT. Combining early HCT (N=62) and delayed but in CR (N=11), the difference in OS among the three groups was significant (p=0.01; Figure S2). In multivariable analysis, having an early HCT or a delayed HCT with CR were together associated with lower risk of death (HR 0.52, 95% CI [0.34, 0.81], p=0.004) but those who had delayed HCT without CR did not benefit (HR 1.4, 95% CI [0.88, 2.24], p=0.15). For the HCT cohort, cumulative incidences of relapse and NRM did not differ between early and delayed HCT (Figure S3).

MDS Risk vs. Standard Risk with Severe Cytopenia

For those eligible due to adverse-risk disease, the univariable HR for death between the HCT and no-HCT groups was 0.65 (95% CI [0.43, 0.97], p=0.04) and the multivariable HR was 0.57 (95% CI [0.37, 0.88], p=0.01). For those with standard-risk disease (i.e., eligible due to severe cytopenia alone), the univariable HR for death was 1.24 (95% CI [0.69, 0.2.23], p=0.48) and the multivariable HR for death was 1.33 (95% CI [0.73, 2.42], p= 0.36). Univariable and multivariable results for entry criteria and IPSS categories are summarized in Table 3 and Table S4, and corresponding Simon-Makuch curves are presented in Figures 2A–D. Landmark analyses showed benefit for HCT at 5, 9, and 12 months for the adverse

risk group (p = 0.03, 0.001, and 0.06, respectively) and for the intermediate-2/high IPSS group (p=0.006, <0.0001, and 0.0001, respectively; Figures S1B and S1C).

We next compared OS according to entry criteria for all patients (Figure 3A; comparison by IPSS is presented in Table S5) and among those who did not receive HCT (Figure 3B). For the entire cohort, the 3-year OS estimates for those with adverse-risk and standard-risk disease with severe cytopenia were 43% (95% CI [35, 50]) and 51% (95% CI [40, 80]), respectively (p=0.43, log rank test; Figure 3A; comparison by IPSS is presented in Table S5). For patients who did not undergo HCT, the 3-year OS estimate was 25% (95% CI [16, 35]) for adverse-risk disease and 47% (95% CI [35, 58]) for standard-risk disease (p=0.07, log rank test; Figure 3B). When comparing all patients according to IPSS risk, the 3-year OS estimate was 50% (95% CI [42, 58]) for low/intermediate-1 IPSS and 40% (95% CI [31, 48]) for intermediate-2/high IPSS (p=0.08, log rank test; Figure 3C). Among patients who did not undergo HCT, the 3-year OS estimate was 49% (95% CI [39, 58]) for low/intermediate-1 IPSS and 8.7% (95% CI [29, 19]) for intermediate-2/high IPSS (p<0.001, log rank test; Figure 3D).

Who Benefits from HCT?

Figure 4 is a forest plot that summarizes hazard ratios of HCT compared to no-HCT for OS using a univariable Cox model and Mantel-Byar tests for each subgroup. The populations that appeared to derive a survival advantage from HCT included those with ECOG PS of 1 (p=0.024), those with poor-risk cytogenetics (p=0.015), those with intermediate-2 or high IPSS scores (p<0.001), those with adverse-risk MDS (p=0.037), and male sex (p=0.027).

Discussion

In this prospective observational study of patients aged 60 to 75 with a diagnosis of MDS and related diseases, with disease sufficiently advanced to warrant consideration of HCT, a treatment strategy that included HCT trended toward better overall survival. The benefit for HCT was significant for those enrolled according to adverse disease risk (according to IPSS score, poor cytogenetics, or prior therapy) and for those who received HCT within five months or achieved remission to alternative therapy prior to HCT. Taken together, these data suggest that timely transplant for older adults with MDS who are transplant-eligible due to disease risk, but not due solely to severe cytopenias, improves patient survival.

Determining when the likelihood of long-term benefit outweighs HCT-associated morbidity and mortality is a critical clinical question for older adults with MDS, who often have comorbidities and are frail.[22] The heterogeneous natural history of MDS in this population combined with the rarity of the disease necessitate that the HCT decision for any one patient must be made in the absence of randomized data. While MDS prognostic scoring systems have added predictive ability, they are only one type of information to consider when assessing the fit older patient with MDS for a HCT or non-HCT approach. Timing, conditioning type, and genomics are also important factors, though their precise impact remains uncertain as prospective data is only beginning to be reported.

Until recently, outcomes data on HCT in MDS had largely been from retrospective studies that examined populations much younger than the median age at diagnosis in the "real world."[23, 24] Cohorts that included older adults, including one comparing RIC with MAC and another assessing HCT versus non-HCT approaches, found similar rates of survival with lower intensity treatments. Early increases in non-relapse mortality (NRM) with intensive approaches appeared to be negated by higher rates of relapse in the RIC and non-HCT groups.[25–27] The authors of one such retrospective cohort analysis noted the limitations of this approach where death before transplantation is unknown, the reasons for transplantation are assumed, and selection bias is unavoidable.

Prospective results are also limited. Early results of the VIDAZALLO trial demonstrated improved survival for HCT after azacitidine induction as compared to continuous azacitidine in patients 55–70 years old, but a third of patients did not make it to randomization.[8] The SFGM-TC/GFM trial demonstrated a separation between survival curves in favor of HCT after year 2 but only transplanted those with a fully matched donor.[9] The RICMAC trial demonstrated that OS after RIC is comparable to that of MAC, however this cohort was mostly <60 years old.[10]

A significant strength of our study is that it assesses the impact of HCT and its timing in a prospective cohort that minimizes artificial patient selection and exclusion, addressing the limitations of prior analyses through its rigorous eligibility criteria. Our approach also minimizes selection bias by mimicking the real-world entry point when clinicians consider utilizing HCT. This is perhaps reflected in the low percentage of patients with early death (4.8%). Though the entire study population did not benefit from the incorporation of HCT, those with adverse-risk disease did, supporting the associations seen in Markov models. Moreover, we found clear populations and timing for which HCT improves outcomes in older, fit patients with MDS.

Recommendations regarding the necessary disease risk and appropriate timing of HCT for older patients with MDS currently rely primarily on two decision analyses.[7, 28] The first used Markov modeling to evaluate immediate HCT, HCT at the time of progression to acute leukemia, and HCT at fixed 2-year intervals after diagnosis (but prior to leukemic progression).[29] Delayed transplantation led to an increase in life expectancy for patients with low or intermediate-1 IPSS, while life expectancy was improved with immediate transplantation for patients with intermediate-2 or high-risk disease. The second found risk score-stratified differences in a decision model of RIC HCT versus no HCT for patients aged 60–70 years, with OS in intermediate-2 and high-risk disease favoring RIC HCT (36 versus 28 months) over non-transplantation therapies.[7]

Our study confirms these findings with prospective data, showing that those with intermediate-2 and high-risk disease, and those receiving HCT sooner than 5 months after enrollment, benefited from HCT on both univariable and multivariable analysis. Importantly, our definition of adverse risk included additional clinically important factors, such as therapy-related disease and non-IPSS high-risk cytogenetics that fell outside of the preferred risk score (IPSS) at the time of our study's inception. Moreover, we conjecture that HCT soon after enrollment was beneficial due to the ability to avoid disease progression.

Our work has limitations. First, although the study was performed prospectively and had rigorous inclusion and exclusion criteria that imitated the real-world entry point of when HCT is considered for use in MDS, we cannot exclude bias induced by its observational nature or by patients or physicians advocating more strongly for transplant in the highest risk cases. Second, eligibility was partially determined with the older IPSS risk score[5] and not the more current IPSS-R.[30] This limitation was ameliorated by our inclusion of patients with non-IPSS poor-risk cytogenetics,[12] therapy-related disease, and severe cytopenias, which makes the study population very similar to those who are considered for HCT using the current IPSS-R. Third, while HCT patients were not mandated to receive the same conditioning, cell source, or donor type, which introduces bias, our population was fairly homogenous in their receipt of RIC, use of matched unrelated donors, and use of peripheral blood stem cells. Fourth, we did not measure other important outcomes such as quality of life. Finally, the limited racial and ethnic diversity of our study population and the fact that only two HCT centers were involved may make our conclusions less generalizable to other populations.

In summary, in this large prospective cohort of older, fit adults with advanced MDS, a treatment strategy that included HCT trended toward better overall survival. There were also significant benefits for those receiving HCT within 5 months and for those with adverse disease risk factors as compared to standard risk with severe cytopenias. Future studies should refine which subgroups of adverse risk patients benefit most, how genomics and measurable residual disease can be used to risk stratify consideration of HCT in this patient population, and how recently characterized predictors, such as frailty, may be incorporated into these decisions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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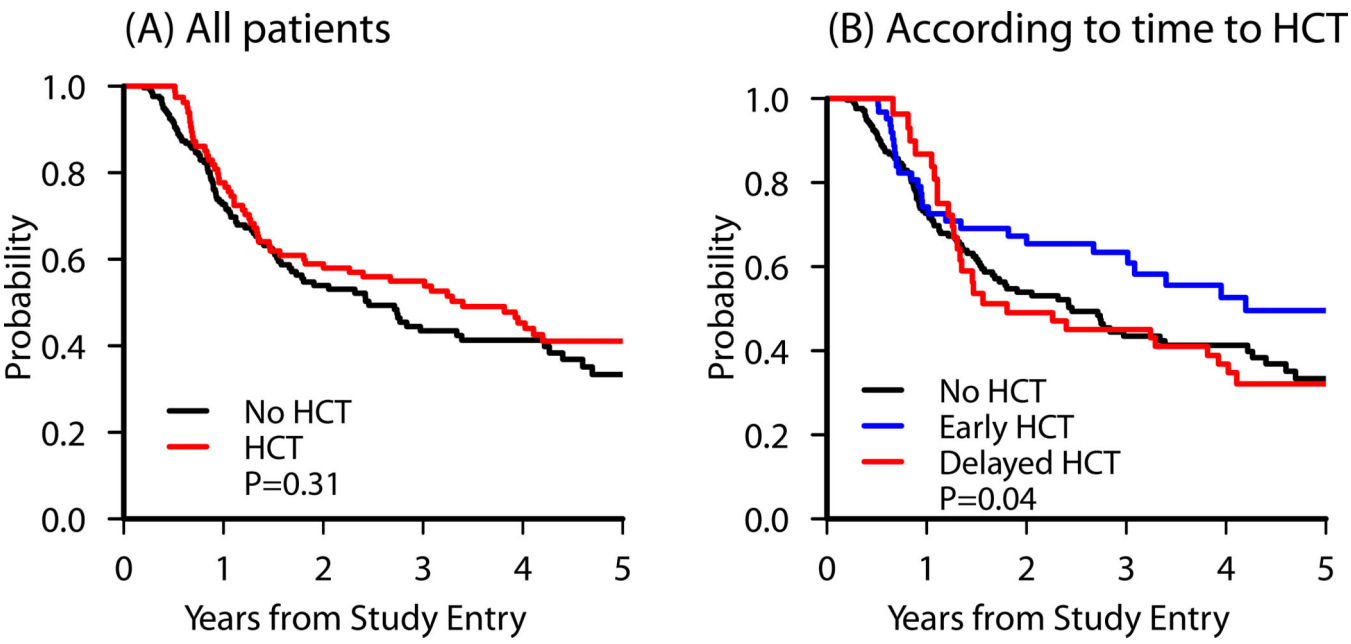

Figure 1. Simon-Makuch Curves for Overall Survival*

*Early HCT denotes HCT within 5 months of study entry; delayed HCT denotes HCT after 5 months. Fourteen patients who died within 2 months of study entry were excluded. Mantel-Byar test was used for group comparison.

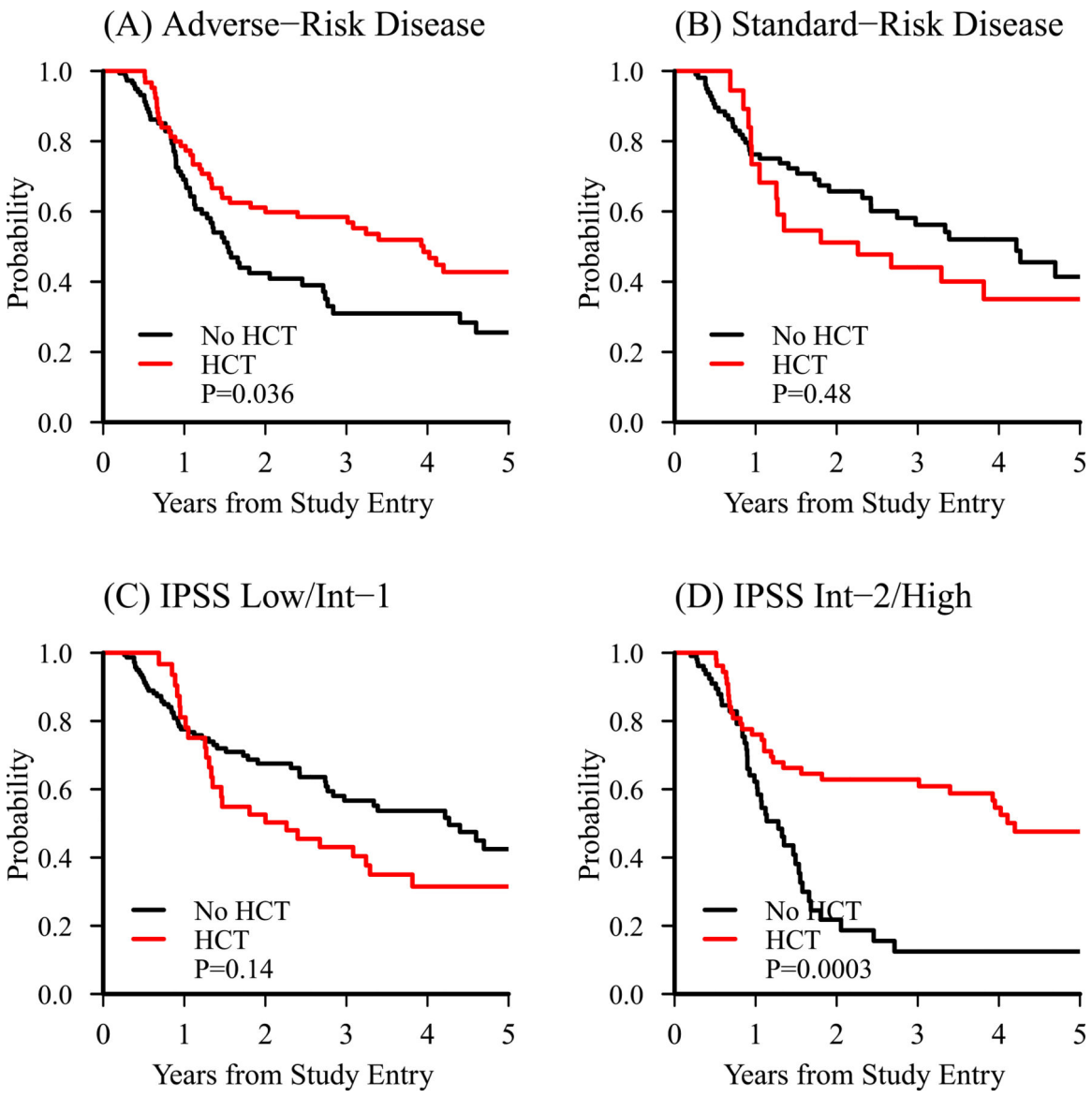

Figure 2. Simon-Makuch Curves for Overall Survival: Subgroup Analysis by Eligibility Criteria and IPSS*

*Fourteen patients who died within 2 months of study entry were excluded. Mantel-Byar test was used to compare HCT vs no HCT for each group.

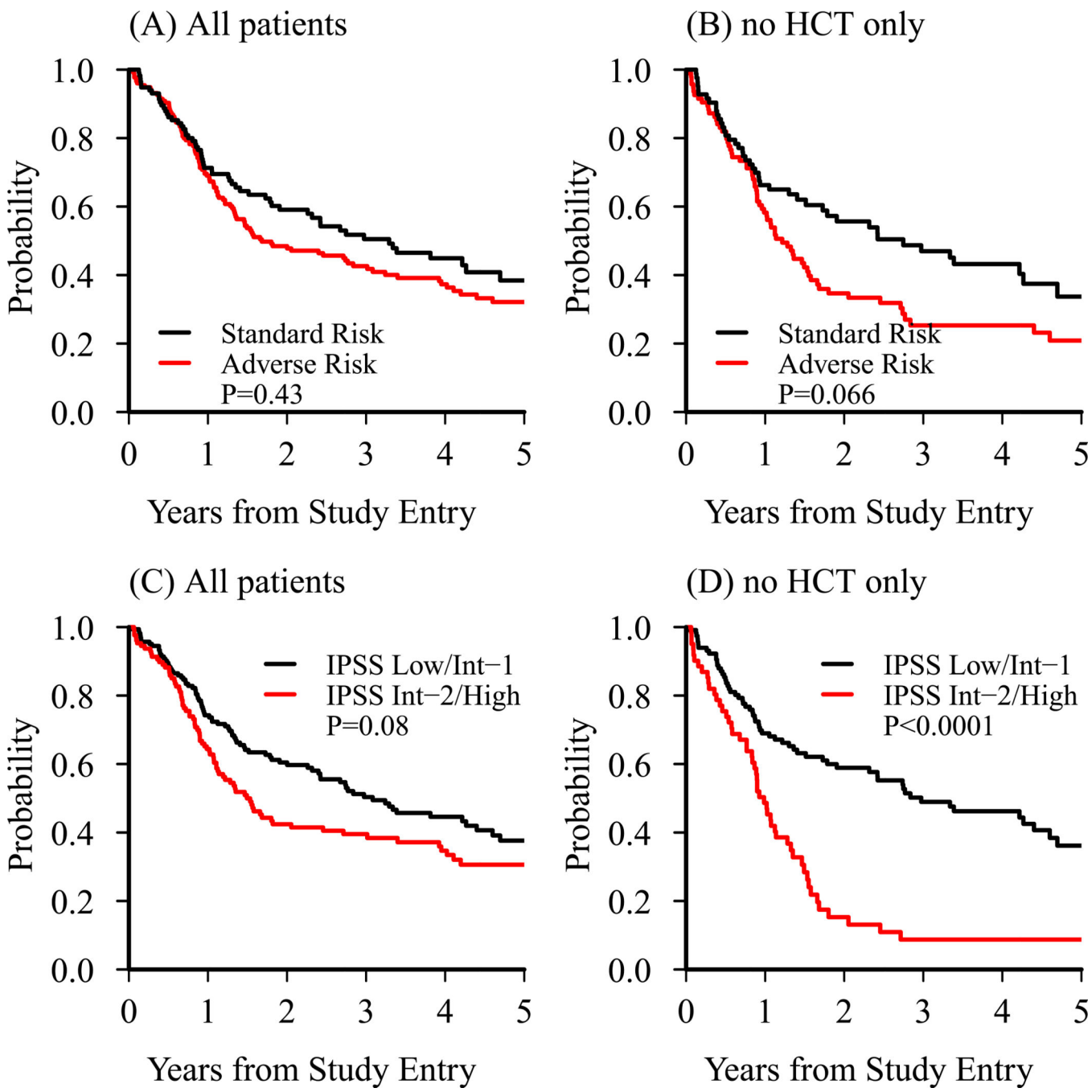

Figure 3. Kaplan-Meier Curves for Overall Survival According to Eligibility Criteria (Adverse MDS Risk versus Standard Risk with Severe Cytopenia) and IPSS for All Patients and Those who Did Not Undergo HCT*

*Log-rank test was used for group comparison.

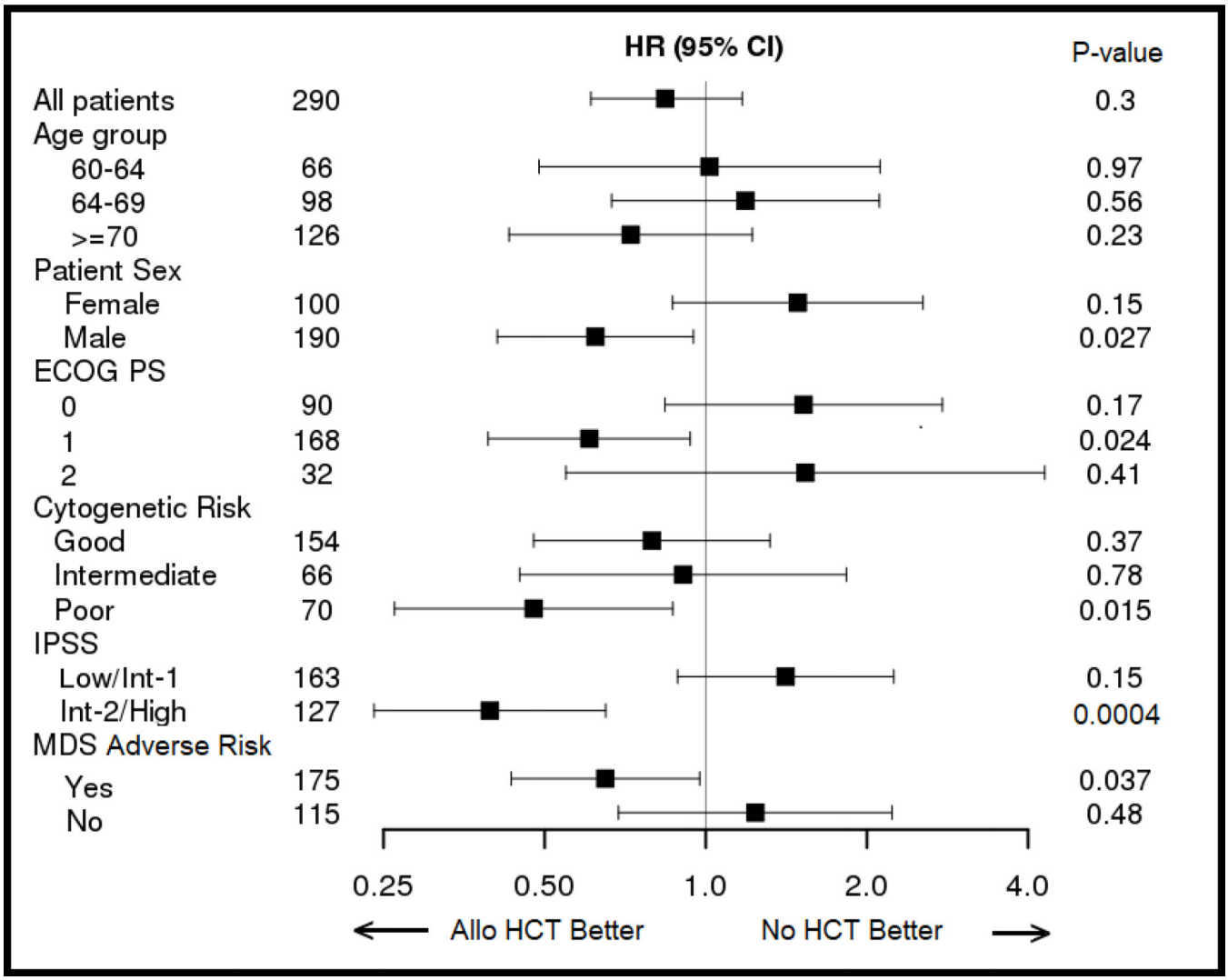

Figure 4. Forest Plot: Which Patients Were Most likely to Benefit from HCT?*

*Mantel-Byar test was used for comparison between no HCT and HCT.

Table 1.

Overall Cohort Characteristics by Entry Criteria Fulfilled

	All		MDS Disease Risk		Severe Cytopenia		
	N	%	N	%	N	%	p-value*
Total	290	100	175	100	115	100	
Transplanted							
No	177	61	94	53.7	83	72.2	0.002
Yes	113	39	81	46.3	32	27.8	
median time to HSCT (mo)	5 (1, 58)		4 (1, 23)		6 (2, 58)		
Age at consent							0.51
median (range)	69 (60, 75)		69 (60, 75)		69 (60, 75)		
Gender							0.47
Male	190	65.5	115	65.7	75	65.2	
Female	100	34.4	60	34.3	40	34.8	
Race							
White	278	95.9	168	96	110	95.7	0.41
Black	9	3.1	4	2.3	5	4.3	
Asian	2	0.7	2	1.1			
Decline to answer	1	0.3	1	0.6			
Eligibility							<0.001
Int-2 or High-Risk IPSS	128	44.1	128	73.1			
Secondary MDS (any	15	5.2	15	8.6			
Poor-prognosis karyotype	32	11	32	18.3			
RBC Transfusion Dep.	42	14.5			42	36.5	
Severe Anemia	26	9			26	22.6	
Severe Thrombocytopenia	41	14.1			41	35.7	
Severe Neutropenia	6	2.1			6	5.2	
Cytogenetic risk							<0.001
Good	154	53.1	50	28.6	104	90.4	
Intermediate	66	22.8	56	32	10	8.7	
Poor	70	24.1	69	39.4	1	0.9	
IPSS							<0.001
Low	43	14.8	4	2.3	39	33.9	
Int-1	120	41.4	44	25.1	76	66.1	
Int-2	107	36.9	107	61.1			
High	20	6.9	20	11.4			
ECOG PS							0.79
0	90	31	52	29.7	38	33	
1	168	57.9	105	60	63	54.8	
2	31	10.7	17	9.7	14	12.2	
3	1	0.3	1	0.6			
TP53 mutation**							0.003

	All		MDS Disease Risk		Severe Cytopenia		
	N	%	N	%	N	%	p-value*
No	119	85.6	65	78.3	54	96.4	
Yes	20	14.4	18	21.7	2	3.6	
UNK	151		92		59		
JAK2 mutation**							1
No	134	96.4	80	96.4	54	96.4	
Yes	5	3.6	3	3.6	2	3.6	
UNK	151		92		59		
RAS pathway**							0.2
No	110	79.1	69	83.1	41	73.2	
Yes	29	20.9	14	16.9	15	26.8	
UNK	151		92		59		
Any adverse mutation**							0.48
No	86	61.9	49	59	37	66.1	
Yes	53	38.1	34	41	19	33.9	
UNK	151		92		59		
Any mutation on NGS**							0.43
No	17	12.2	12	14.5	5	8.9	
Yes	122	87.8	71	85.5	51	91.1	
UNK	151		92		59		
Number of mutations on NGS**							0.17
<3	75	54	49	59	26	46.4	
≥3	64	46	34	41	30	53.6	
UNK	151		92		59		

UNK: unknown

*P-values are provided for information and not for strict comparison between two cohorts. The differences in eligibility criteria, IPSS, cytogenetic risk and HCT are expected.

**P-values for mutations were calculated excluding unknown mutation status. The proportion of unknown mutation status was balanced between two cohorts (52.6% vs 51.3% in MDS risk and severe cytopenia cohorts, respectively).

Table 2.

HCT Cohort Characteristics

	N	%
Total (N)	113	
Age, median (range)	67 (59, 74)	
Patient Sex		
Male	72	64.3
Female	40	35.7
Donor Sex		
Male	70	62.5
Female	42	37.5
Patient and Donor Sex		
Male patient & Female donor	18	16.1
HLA typing (A B DRB1)		
Matched unrelated	85	75.9
Matched related	11	9.8
Mismatch unrelated	8	7.1
Mismatch related	8	7.1
Cell source		
Bone marrow	6	5.4
(PBSC)	106	94.6
Conditioning Intensity		
MAC	12	10.7
RIC	100	89.3
Patient-donor CMV sero status		
Positive	70	62.5
Haploidentical Transplants	9	8.0

HLA: human leukocyte antigen

PBSC: peripheral blood stem cell

Table 3.

Univariable and Multivariable Cox Regression Analyses for HCT versus no-HCT

		Univariable Cox regression analysis				Multivariable Cox regression analysis			
Group	**N**	**HR**	**95% CI**		**p-value**	**HR**	**95% CI**		**p-value**
All patients	290	0.84	0.61	1.17	0.30	0.75	0.52	1.09	0.13
Standard Risk	115	1.24	0.69	2.23	0.48	1.33	0.73	2.42	0.36
Adverse Risk	175	0.65	0.43	0.97	0.04	0.57	0.37	0.88	0.01
IPSS Low/Int-1	163	1.41	0.89	2.25	0.15	1.39	0.85	2.27	0.19
IPSS Int-2/High	127	0.40	0.24	0.65	0.0003	0.40	0.24	0.67	0.0005