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Supportive Care

Prognostic Factors for Mortality among Day +100 Survivors after Allogeneic Hematopoietic Cell Transplantation

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Although day +100 survival among allogeneic hematopoietic cell transplantation (HCT) recipients has improved over time, longer-term survival remains a challenge. The aim of this study was to identify prognostic factors for survival among patients surviving longer than 100 days using baseline characteristics and factors identified within the first 100 days after transplantation. Of 413 patients undergoing a first allogeneic HCT between 2006 and 2014, 335 survived >100 days post-transplantation. The majority underwent a myeloablative transplantation (75%) with a bone marrow (BM) (52%) graft source. One-year all-cause mortality (ACM) was 29%, with 16% relapse mortality (RM) and 12% nonrelapse mortality. In multivariable analysis, high-risk disease (hazard ratio [HR], 1.55; $P = .003$), non-cytomegalovirus infection (HR, 1.79; $P = .003$), more days hospitalized (HR, 1.16; $P < .001$), and relapse (HR, 4.38; $P < .001$) within the first 100 days were associated with increased risk of ACM. Patients with higher income (HR, .89; $P = .024$) and those who received BM (HR, .52; $P < .001$) or umbilical cord blood (HR, .40; $P = .002$) relative to peripheral blood stem cells had lower risk of ACM. Our study identifies risk factors for adverse long-term survival in 100-day survivors, a time point when patients frequently are discharged from transplantation centers. In addition to disease- and transplantation-related factors, low socioeconomic status was associated with worse long-term survival, highlighting the need for focused efforts to improve outcomes in vulnerable patient populations.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative, but high-risk therapy for patients with advanced hematologic malignancies. Long-term survival and outcomes after HCT remain limited by significant transplantation-related morbidity and mortality as well as disease relapse. Owing to advancements in transplantation, such as high-resolution HLA typing, improved supportive care, earlier referral, and improved understanding of patient and disease factors, day +100 survival has significantly improved over time [1]. Despite these improvements in early survival, longer-term (1 year and beyond) survival has not changed significantly, and additional improvements are still needed [1-4]. Several risk assessment tools have been developed to better prognosticate transplantation outcomes; however, these tools rely primarily on pretransplantation factors, such as patient, disease, and transplantation characteristics [5-14]. We hypothesized that factors and events occurring within the first 100 days after transplantation also may help predict longer-term survival and further inform follow-up care. We undertook this retrospective analysis to identify pretransplantation and day +100 prognostic factors for long-term survival among patients who survive beyond 100 days.

PATIENTS AND METHODS

We identified 355 patients who underwent a first allogeneic HCT between 2006 and 2014 at the Cleveland Clinic and survived >100 days post-transplantation. Data were obtained from our institutional Unified Transplant Database and included patient, disease, and transplantation characteristics, socioeconomic factor, and quality of life (QOL) assessments. The Cleveland Clinic Institutional Review Board approved this retrospective analysis, and informed consent for collection of patient data were obtained in accordance with the Declaration of Helsinki.

Disease status at time of transplantation was classified as low, intermediate, or high according to standard definitions [12]. Comorbidities were scored according to the Hematopoietic Cell Transplantation-Comorbidity Index

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(HCT-CI), with severity graded as low (0), intermediate (1 to 2), or high (≥3) [10]. Recipients of both myeloablative and reduced-intensity conditioning regimens were included in the analysis. Graft-versus-host-disease (GVHD) prophylaxis generally consisted of a calcineurin inhibitor (cyclosporine or tacrolimus), in combination with methotrexate or mycophenolate mofetil. Supportive care was provided according to standard institutional clinical guidelines as described previously [15].

The Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scale was used to assess QOL [16]. Questionnaires were administered prospectively at baseline before transplantation and at day +100 post-transplantation. The FACT-BMT (version 4) is a validated, self-reported QOL questionnaire that includes a BMT-specific subscale. The instrument measures the effect of therapy on domains in physical well-being (PWB), functional well-being (FWB), social well-being (SWB), and emotional well-being (EWB), plus BMT-specific concerns (additional concerns [ACs]). Summary scores include the trial outcome index (TOI = PWB + FWB + AC) and the total score (TS = PWB + FWB + AC + EWB + SWB). Higher scores in all these domains correspond to better QOL.

The following patient, disease, transplantation, socioeconomic, and QOL characteristics were analyzed: age, race, sex, median annual household income, distance between patient's residence and our transplantation center (in miles), performance status, HCT-CI, months from diagnosis to transplantation, diagnosis, disease risk, donor relationship, HLA match, baseline cytomegalovirus (CMV) serostatus of donor and recipient, intensity of conditioning regimen, graft source, and baseline and day 100 FACT-BMT scores. Events occurring within 100 days of transplantation were also analyzed, including days hospitalized during the first 100 days (including the transplantation admission), number of hospital admissions (including the transplantation admission), neutrophil and platelet engraftment, subsequent transplantation due to graft failure, infection (bacterial, CMV viral, non-CMV viral, fungal, and any infection), acute GVHD, and relapse. For the purpose of this analysis, GVHD, infection, and relapse occurring within the first 100 days were analyzed as additional "baseline" variables to assess for longer-term survival. Three continuous baseline variables with outliers were analyzed as ordinal variables so that outliers did not unduly influence results. Specifically, median household income was analyzed with 7 levels (ranging in $10,000 intervals from <$30,000 to ≥$80,000), miles from transplantation center with 6 levels (ranging in 25-mile intervals from <25 to ≥125 miles), and months from diagnosis to transplantation with 9 levels, (ranging in 3-month intervals from <3 to ≥24 months). Median household income was estimated by patient ZIP code of residence at time of transplantation, as determined by 2010 US Census data.

Three mortality outcomes of patients surviving at least 100 days were calculated from the date of transplantation: all-cause mortality (ACM), relapse mortality (RM), and nonrelapse mortality (NRM). The event for RM is death from relapse as primary or secondary cause of death; all other deaths are competing risks. The event for NRM is death from causes other than relapse, with relapse as competing risk. Patients had to survive more than 100 days to be included in this study, so all 3 mortality outcomes are 0% until after day +100. ACM was estimated using the Kaplan-Meier method, and risk factors were identified using Cox proportional hazards analysis. RM and NRM were estimated using the cumulative incidence method, and risk factors were identified using Fine and Gray competing-risk regression. Multivariable risk factors were identified using stepwise analysis. Results are reported as hazard ratio (HRs) and 95% confidence interval (CIs). Analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline and Day +100 Patient Characteristics

Of 413 patients who underwent a first allogeneic HCT between 2006 and 2014, 355 (86%) survived >100 days post-transplantation. Among the 58 patients who died within the first 100 days post-transplantation, the most common causes of death were infection (n = 21; 36%), followed by relapse (n = 14; 21%) and acute GVHD (n = 12; 21%). Table 1 presents baseline characteristics of the 355 study patients. The median age at transplantation was 50 years. The most common indications for transplantation were acute myelogenous leukemia, myelodysplastic syndrome, and acute lymphoblastic leukemia. The majority of patients had a well-matched related or unrelated donor and received a myeloablative transplant.

Events occurring within the first 100 days post-transplantation are also listed in Table 1. Forty-six percent of the patients (n = 162) had either none or 1 hospital admis-

Table 1
Baseline and Day +100 Characteristics of 355 Study Patients

Characteristic	Value
Baseline characteristics	
Age at transplantation, yr, median (range)	50 (18-73)
Sex, n (%)	
Male	199 (56)
Female	156 (44)
Race, n (%)	
Caucasian	318 (90)
African-American	26 (7)
Other	11 (3)
Median annual household income, $	
Median (range)	49,980 (13,316-112,530)
<40,000, n (%)	66 (19)
40-49,999, n (%)	112 (32)
50-69,999, n (%)	129 (36)
>70,000, n (%)	48 (14)
Distance from Cleveland Clinic, miles	
Median (range)	46 (1-1055)
<25, n (%)	100 (28)
25-49, n (%)	92 (26)
50-74, n (%)	72 (20)
>75, n (%)	91 (26)
KPS score (n = 330), n (%)	
Good (80-100)	309 (94)
Poor (<80)	21 (6)
HCT-CI risk category, n (%)	
Low	98 (28)
Intermediate	115 (32)
High	142 (40)
Time from diagnosis to HCT, mo, median (range)	6.5 (.3-163)
Diagnosis, n (%)	
AML	163 (46)
MDS/CMML	89 (25)
ALL	62 (17)
CML	34 (10)
Acute undifferentiated leukemia	7 (2)
Disease risk, n (%)	
Low	170 (48)
Intermediate	65 (18)
High	120 (34)
Donor type, n (%)	
Matched sibling	152 (43)
Matched unrelated	148 (42)
Mismatched unrelated	6 (2)
UCB	36 (10)
Haploidentical	13 (4)
Graft source, n (%)	
BM	189 (53)
PBSCs	130 (37)
UCB	36 (10)
Conditioning regimen intensity, n (%)	
Myeloablative	267 (75)
Reduced intensity	88 (25)
Conditioning regimen, n (%)	
Bu/Cy	166 (47)
Bu/Flu	49 (14)
TBI/VP	48 (14)
Flu/TBI	38 (11)
Flu/Cy/TBI	25 (7)
TBI/VP/ATG	8 (2)
Flu/Cy/TBI/ATG	6 (2)
Others	15 (4)
Baseline CMV serostatus (n = 350), n (%)	
Donor^{+} recipient^{+}	96 (27)
Donor^{+} recipient^{-}	37 (11)
Donor^{-} recipient^{+}	136 (39)
Donor^{-} recipient^{-}	81 (23)
Baseline FACT-BMT score, median (range) (n = 284)	
PWB	23 (5-28)
SWB	24 (7-28)
EWB	18 (5-24)
FWB	17 (4-28)
BMT subscale	70 (32-89)
TOI	111 (47-145)
Total score	153 (77-193)

(*Continued on next page*)

Table 1
(*continued*)

Day +100 characteristics	
Admissions in first 100 days post-transplantation	
Median (range)	2 (0-8)
0, n (%)	6 (2)
1, n (%)	156 (44)
2, n (%)	105 (30)
3, n (%)	64 (18)
≥4, n (%)	24 (7)
Days hospitalized in first 100 days (from day 0), median (range)	29 (0-100)
Events in first 100 days post-transplantation (>1 possible), n (%)	
Neutrophil engraftment	342 (96)
Platelet engraftment	314 (88)
Graft failure	7 (2)
Any infection	229 (65)
Bacterial infection	174 (49)
Viral infection, CMV	92 (26)
Viral infection, not CMV	56 (16)
Fungal infection	14 (4)
Grade II-IV acute GVHD	136 (38)
Grade III-IV acute GVHD	25 (7)
Any chronic GVHD	5 (1)
Relapse	33 (9)
Day +100 FACT-BMT score, median (range) (n = 194) , n (%)	
PWB	22 (4-28)
SWB	24 (9-28)
EWB	20 (8-24)
FWB	17 (2-28)
BMT subscale	69 (34-92)
TOI	109 (46-145)
Total score	154 (80-197)

KPS indicates Karnofsky Performance Status; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; CMML, chronic myelomonocytic leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; Bu, busulfan; Cy, cyclophosphamide; Flu, fludarabine; TBI, total body irradiation; VP, etoposide; ATG, antithymocyte globulin.

sion after transplantation, and 55% (n = 194) had ≥2 admissions. Infections occurred in more than one-half of patients (65%) within 100 days. Thirty-eight percent of the patients developed grade II-IV acute GVHD, and 7% had severe grade III-IV acute GVHD. Nine percent of patients relapsed of their primary disease within the first 100 days.

Table 2
Post-Transplantation Outcomes for Allogeneic HCT Recipients Surviving 100 Days

Outcome	1-year % (95% CI)	2-year % (95% CI)
ACM	29 (24-34)	42 (37-47)
RM	16 (12-20)	22 (18-27)
NRM	12 (9-15)	16 (12-20)
Chronic GVHD (any grade)	35 (30-40)	41 (36-46)

GVHD and Survival Outcomes

Table 2 summarizes 1- and 2-year outcomes among all patients surviving for the first 100 days after HCT. The cumulative incidence of any chronic GVHD was 35% at 1 year and 41% at 2 years. The 1-year ACM was 29%, due relatively equally to both RM (16%) and NRM (12%). The most common causes of death were relapse (n = 92; 49%), followed by infection (n = 31; 17%), pulmonary or other organ failure (n = 33; 18%), and GVHD (n = 19; 10%).

Univariable analysis identified several significant risk factors for mortality. Lower income ($P = .010$), high-risk disease ($P < .001$), older age ($P = .022$), myeloablative conditioning ($P = .006$), PBSC graft ($P < .001$), bacterial ($P = .009$), non-CMV viral ($P = .002$) or any infection ($P = .002$), acute GVHD ($P = .008$), more days hospitalized ($P < .001$), more hospital admissions ($P = .013$), and relapse ($P < .001$) within the first 100 days ($P < .001$) were associated an increased risk of ACM. Lower income ($P = .021$), high-risk disease ($P < .001$), and relapse within the first 100 days ($P < .001$) were also associated with an increased risk of RM. PBSC ($P = .004$), bacterial infection ($P = .022$), non-CMV viral infection ($P = .009$), any infection ($P = .009$), acute GVHD ($P = .001$), more days hospitalized ($P < .001$), more hospital admissions ($P = .040$), and failure to engraft neutrophils within the first 100 days ($P = .022$) were associated with an increased risk of NRM.

Results of multivariable analysis for ACM, RM, and NRM from the date of transplantation are shown in Table 3. High-risk disease ($P = .003$), non-CMV viral infection ($P = .003$), more days hospitalized ($P < .001$), and relapse within the first 100 days ($P < .001$) were all significantly associated with higher risk of ACM, whereas higher income ($P = .024$) and BM ($P < .001$) or UCB ($P = .002$) relative to PBSC were associated with lower risk of ACM. Myeloablative conditioning was no longer a significant factor in multivariable analysis. Figure 1 depicts ACM by median household income, with data categorized into 4 income groups for graphical purposes. Patients with high-risk disease ($P < .001$) and relapse within the first 100 days ($P < .001$) had a higher risk of RM, whereas those with higher income had a lower risk of RM. Patients with acute GVHD ($P = .007$) or more days hospitalized within the first 100 days ($P < .001$) had a higher risk of NRM, whereas those with BM grafts ($P < .001$), UCB grafts ($P = .020$), and neutrophil engraftment within 100 days ($P = .022$) had a lower risk of NRM. Distance from the transplantation center, HLA match, performance status, HCT-CI, CMV status, and fungal

Table 3
Multivariable Analysis Risk Factors for ACM, RM, and NRM

RiskFactors	ACM		RM		NRM	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Median household income (per level increase)	.89 (.81-0.98)	.024	.85 (.73-0.98)	.023	-	-
Disease risk (high/ intermediate + low)	1.55 (1.16-2.08)	.003	2.51 (1.63-3.87)	<.001	-	-
Graft source						
BM/PBSCs	.52 (.38-0.71)	<.001	-	-	.38 (.23-0.63)	<.001
UCB/PBSCs	.40 (.22-0.70)	.002	-	-	.40 (.19-0.86)	.020
Neutrophil engraftment in first 100 days	-	-	-	-	.35 (.15-0.86)	.022
Non-CMV viral infection in first 100 days	1.79 (1.22-2.63)	.003	-	-	-	-
Acute GVHD within first 100 days (per grade increase)	-	-	-	-	1.38 (1.09-1.76)	.007
Days hospitalized in first 100 days (per 10-day increase)	1.16 (1.07-1.25)	<.001	-	-	1.29 (1.16-1.43)	<.001
Relapse in first 100 days	4.38 (2.89-6.63)	<.001	7.60 (4.39-13.1)	<.001	-	-

Median household income levels = < $30000, $30-39999, $40-49999, $50-59999, $60-69999, $70-79999, ≥$8000.

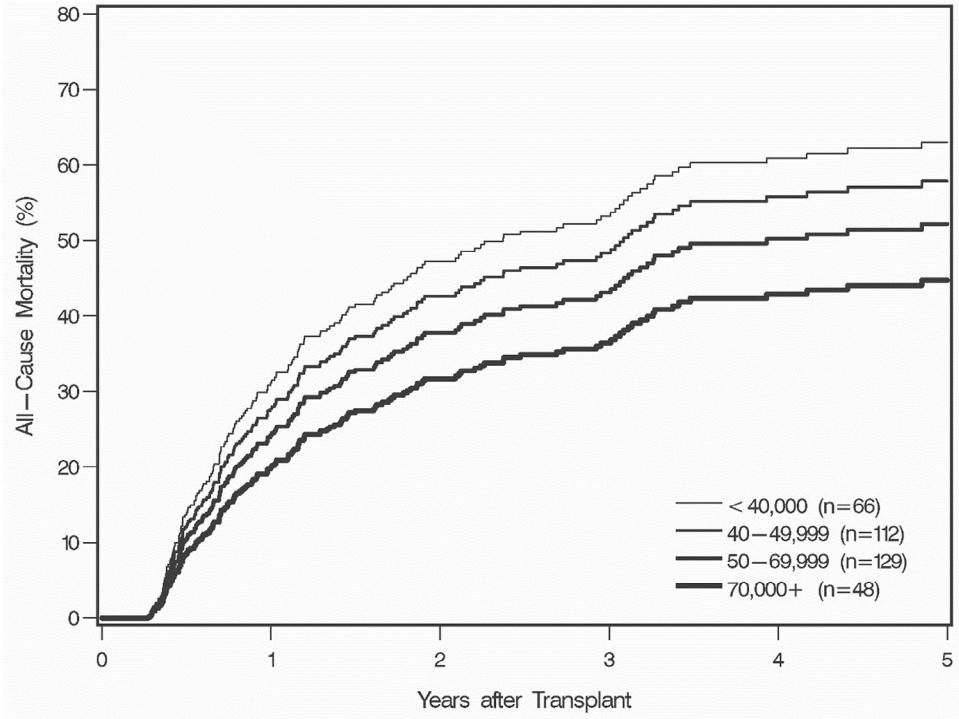

Figure 1. Estimated ACM in relation to median household income. Estimates are based on an average patient profile from a multivariable Cox model accounting for graft source, disease risk, non-CMV viral infections by day +100, number of days hospitalized in first 100 days, and relapse by day +100.

infections were not significant factors in either univariable or multivariable analysis for ACM, RM, or NRM.

In a subset analysis of 284 patients with baseline QOL assessments, no FACT-BMT score was associated with ACM, RM, or NRM ($P = .21$ to .94; data not shown). In a second subset analysis of 194 patients with available day +100 QOL assessments, no FACT-BMT score was associated with RM. In univariable analysis, better PWB (HR .69, $P = .023$) was associated with lower risk of NRM. Better PWB (HR .74, $P = .002$), EWB (HR .70, $P = .016$), BMT subscale (HR .78, $P = .008$), TOI (HR .76, $P = .009$), and total scores (HR .80, $P = .009$) were associated with lower risk of ACM. In multivariable analysis, better day +100 PWB score did not remain prognostic for lower NRM and only showed a trend toward a lower risk of ACM (HR, .83; 95% CI, .67 to 1.02; $P = .07$).

DISCUSSION

Most transplantation centers require allogeneic HCT recipients to attend follow-up at their institution for at least the first 100 days after transplantation. Patients are frequently discharged back to their local physicians at that time, especially if they reside a considerable distance from the transplantation center, and are subsequently co-managed with varying levels of involvement by the transplantation center. Our analysis was built on the premise that identifying 100-day survivors at high risk for adverse outcomes can facilitate the dedication of effort and resources to this group of patients to optimize their survival.

In this landmark analysis of allogeneic HCT recipients who had survived through 100 days, we have identified several disease-, transplantation-, and patient-related factors associated with ACM, RM, and NRM, including disease risk, graft source, infection, GVHD, and days hospitalized. Although relapse remains the biggest cause of treatment failure in this population, and such strategies as targeted post-transplantation maintenance are needed, we also highlight additional risk factors occurring within the first 100 days, such as lower socioeconomic status (SES), as measured by income, that are associated with worse long-term survival. Although many of these factors have previously been associated with increased mortality, this study underscores the importance of identifying transplantation survivors at increased risk of death after 100 days who may benefit from additional resources [8,14,17,18]. Maintaining more frequent outpatient follow-up, improving coordination of care and communication between the transplantation center and referring physician and patient, and dedicating additional psychosocial resources and social work follow up beyond the first 100 days may be considered to benefit high-risk patients.

The influence of SES on outcomes of allogeneic HCT has been reported, including a study by our group examining 283 allogeneic HCT recipients surviving at least 1 year in remission demonstrating associations between low SES and higher risks of ACM and NRM [19]. Two studies from the Center for International Blood and Marrow Transplant Research found an association between income and survival outcomes, independent of race [20] or area of residence [21]. Although a recent secondary analysis from the Blood and Marrow Transplant Clinical Trials Network 0902 Trial did not show an association between SES and clinical outcomes, low SES was associated with poor patient-reported outcome measures, including worse physical functioning, increased distress, and poor sleep quality [22].

Although social disparities contribute to additional risks for individuals with cancer, the psychosocial, environmental, and biological mechanisms remain poorly understood [20]. Nonetheless, an increasing number of reports are linking adverse social conditions with biological pathways. Studies

have shown shifts in gene expression profiles during extended periods of stress, termed the "conserved transcriptional response to adversity" (CTRA). In HCT recipients, Knight et al. found significantly increased pretransplantation CTRA in patients from lower SES backgrounds, and linked this increase to a higher incidence of relapse and decreased leukemia-free survival [23].

These data demonstrate that low SES has a significant negative impact on long-term HCT outcomes, and that there is a need for transplantation centers to examine and optimize the resources available to these individuals. Although early post-transplantation care is typically well coordinated through the transplantation center within the first 100 days, patients with lower SES and potentially poorer access to healthcare and resources are likely to be at higher risk for longer-term complications and may need closer follow-up.

Interestingly, we also found that PBSC as a graft source relative to BM or UCB was associated with worse ACM, mediated primarily by NRM. This is presumably related to a higher incidence of GVHD, as shown in previous studies [24,25]. It is our institutional practice to use BM over PBSCs for myeloablative transplants, and consistent with other data, BM should be the preferred graft source. UCB represented a smaller population and was actually associated with worse ACM within the first 100 days (data not shown), likely due to delayed immune reconstitution and infection, a known limitation of UCB transplants. However, UCB appears to have longer-term benefits in terms of overall mortality and NRM, perhaps due to lower risks of GVHD [26].

Increased hospitalizations, specifically readmissions, have been another recent focus of investigation in allogeneic HCT, as a measure of quality of care, healthcare costs, and predictors of survival [27-29]. Given the risks of morbidity and mortality, HCT is typically associated with high rates of hospital readmissions and prolonged hospitalizations. This analysis included days hospitalized in the first 100 days, because this it is a powerful independent prognostic factor given associations with engraftment, infections, and GVHD, while also serving as a prognostic factor for ACM and NRM; indeed, it may account for other critical events in the first 100 days after transplantation that were not specifically measured. Our group has previously demonstrated that 30-day readmission is an independent predictor of overall mortality, with the use of total body irradiation and occurrence of infection the primary predictors of readmission [28]. Spring et al. [27] also found that active disease at the time of transplantation and the occurrence of infection during HCT admission is associated with readmission by day +100, and that readmission is independently associated with poor overall survival. A second study by the same group evaluating readmission after UCB transplantation demonstrated similar findings, with inferior survival in those who were readmitted within 100 days [29]. They also found that race and income are associated with readmission within 100 days. Not surprisingly, more days hospitalized during the first 100 days post-transplantation reflects the acuity of illness.

A limitation of this analysis is its single-institution, retrospective design. We included both myeloablative and reduced-intensity HCT recipients, and although we did not detect any significant differences in our analysis, there may be different factors influencing long-term outcomes with the different conditioning regimens. In addition, although we perform our reduced-intensity HCTs primarily in the inpatient setting, many centers manage these patients as outpatients, and thus our results might not be generalizable to all patients. In addition, median household income was calculated based on ZIP code of residence, because we did not have actual household income information for patients. However, ZIP code based on census data is a well-validated method for evaluating SES in health services research [30,31]. We also did not have further data reflecting insurance coverage or other resources of HCT recipients. We recognize that several of the factors identified, such as disease risk and relapse and even socioeconomic variables, may be difficult factors to modify.

Nonetheless, this study highlights important factors occurring within 100 days of HCT, which may help predict longer-term outcomes. Although identifying potentially modifiable factors to decrease hospitalizations and improve overall survival remains challenging, this study provides further evidence to help identify at-risk patients who may benefit from more stringent and careful long-term support and follow-up.

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