Pre- and Post-Transplantation Risk Factors for Delirium Onset and Severity in Patients Undergoing Hematopoietic Stem-Cell Transplantation

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ABSTRACT

Purpose

To determine pre- and post-transplantation risk factors for delirium onset and severity during the acute phase of myeloablative hematopoietic stem-cell transplantation (HSCT).

Patients and Methods

Ninety adult patients with malignancies admitted to the Fred Hutchinson Cancer Research Center for their first HSCT were assessed prospectively from 1 week before transplantation to 30 days after transplantation. Delirium was assessed three times per week using the Delirium Rating Scale and the Memorial Delirium Assessment Scale. Potential risk factors were assessed by patient self-report, charts, and computerized records. Multivariable analysis of time to onset of a delirium episode was undertaken using Cox proportional hazards regression with time-varying covariates. Analysis for delirium severity was carried out using a linear mixed effects model. Validation and sensitivity analyses were performed on the final models.

Results

Forty-five patients (50%) experienced a delirium episode. Pretransplantation risk factors for onset and higher severity of delirium were higher mean alkaline phosphatase and blood urea nitrogen (BUN) levels. Poorer pretransplantation executive functioning was also associated with higher delirium severity. Higher doses of opioid medications were the only post-transplantation risk factor for delirium onset (hazard ratio, 1.05; 95% CI, 1.02 to 1.08). Higher opioid doses, current and prior pain, and higher BUN levels were post-transplantation risk factors for greater delirium severity (all $P < .01$).

Conclusion

Pre- and post-transplantation factors can assist in identifying patients who are at risk for delirium during myeloablative HSCT and may enable clinical interventions to prevent delirium onset or decrease delirium symptoms.

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INTRODUCTION

Delirium is common in patients undergoing myeloablative hematopoietic stem-cell transplantation (HSCT), occurring in up to 50% of patients during the 4 weeks after conditioning and stem-cell infusion.¹ Delirium in patients with cancer has been associated with adverse outcomes, including decreased performance status²; increased pain and use of breakthrough analgesia^{3,4}; longer length of hospital stay^{5,6}; increased distress for the patient, spouse, caregivers, and nurses⁷⁻⁹; and decreased survival.^{2,10,11} Our previous work showed that patients with a malignancy who experienced delirium during myeloablative HSCT were significantly more likely to have impaired neurocognitive

abilities (executive functioning, attention, and processing speed) and persistent anxiety, fatigue, and distress 80 days after transplantation,¹² with some negative effects persisting for up to 12 months.¹³

Identifying predisposing and precipitating factors for delirium may facilitate the identification of high-risk patients and the prevention or early detection of delirium onset.¹⁴ Prior studies examining the risk factors for delirium are limited by small samples, retrospective designs, and limited numbers of potential variables examined. Moreover, few studies have included patients treated with HSCT, who have unique pathophysiologic, treatment, psychosocial, and environmental demands that may influence their neuropsychiatric

condition.¹⁵ Thus, risk factors for delirium need to be examined for this vulnerable population.

Delirium etiology among patients with cancer is multifactorial in two thirds of patients.⁵ Predisposing factors for delirium among these patients include advanced age^{6,16} and impaired physical and cognitive functioning.⁶ Furthermore, there are four groups of precipitating factors for delirium in patients with cancer that occur during the course of treatment.¹⁷ Complications related to the primary cancer that may increase delirium risk include metastatic brain lesions^{5,18} and hypercalcemia, hypoxia, or malnutrition.^{6,16,19} Chemotherapeutic or immunotherapeutic agents (eg, vincristine, interleukin-2, interferon, corticosteroids) may cause toxic CNS effects.^{5,18-21} Infection or hepatic, renal, metabolic, or respiratory complications may cause delirium.^{5,10,18,19} Finally, agents used in supportive care may precipitate delirium, including analgesics (especially opioids), antiemetics, sedatives, and antimicrobials.^{5,10,18,19,21,22}

Previously, we determined pretransplantation factors associated with delirium occurrence and severity in this population.¹ No studies have examined both pretransplantation and longitudinal or time-variant post-transplantation factors associated with delirium onset and severity in patients who have received myeloablative HSCT. Moreover, studies of precipitants of delirium have not assessed the complex inter-relationship between pain and opioids. The primary purpose of this study was to determine the most important factors associated with delirium in the acute post-transplantation period, examining both pre-HSCT and acute time-variant factors contributing to delirium onset and delirium severity. We specifically investigated the interactive effects of pain and opioids on delirium. As a secondary aim, we constructed models for delirium onset and delirium severity that can be tested in future populations.

PATIENTS AND METHODS

Patients

Ninety patients, age 22 to 62 years, treated at the Fred Hutchinson Cancer Research Center were recruited before their first myeloablative allogeneic or autologous marrow or peripheral-blood HSCT. A broad range of cancer diagnoses and conditioning regimens were represented (Table 1).

Procedures

Study procedures were detailed in a previous publication from this cohort.¹ All procedures were approved by the institutional review board, and study patients signed written informed consent before beginning transplantation conditioning. Before conditioning, patients completed a comprehensive battery assessing health-related quality of life, distress, and neuropsychological functioning. At 7 days before transplantation, during conditioning, and through day 30 after transplantation, trained research nurses or investigators assessed patients with a brief delirium (diagnosis, severity), distress, and pain assessment battery targeted to the same time each day on Monday, Wednesday, and Friday. Patients with delirium were able to provide data, except in the most severe cases.

Dependent Variables

Delirium Rating Scale (DRS). The DRS is a 10-item, clinician-rated scale for diagnosing delirium that assesses symptoms over a 24-hour period using information from the patient interview, mental status examination, medical history and tests, nursing observations, and family reports (score range, 0 to 32).²³ The DRS has good construct and criterion validity, including compared with *Diagnostic and Statistical Manual of Mental Disorders* criteria.²⁴ We defined a delirium episode as a DRS score of more than 12^{23,24} for at least two of three consecutive assessments.¹

Memorial Delirium Assessment Scale. The Memorial Delirium Assessment Scale²⁵ is a 10-item, clinician-rated scale that assesses delirium severity (score range, 0 to 30) and has been validated in cancer populations.^{26,27} Delirium severity for each patient was measured as the total score at each observation. If items were missing, the score was prorated.

Pre- and Post-Transplantation Risk Factors

Potential risk factors were chosen based on our prior findings and examination of the delirium literature.

Pretransplantation variables. Pretransplantation variables included demographics (age and sex), executive functioning (Trail Making B test²⁸ T score; higher scores = less impairment), medical status (disease stage, donor cell type, conditioning with total-body irradiation, and liver and renal functioning including mean alkaline phosphatase and blood urea nitrogen [BUN] levels during the week before transplantation), and physical functioning (Medical Outcomes Study 12-item short form [SF-12]²⁹ physical component score; higher scores = better functioning).

Post-transplantation variables. Mean pain score (using a 0 to 10 verbal rating scale) was collected with the delirium assessments three times a week. Both current and prior assessment (lagged) pain scores were included in the delirium analyses to account for the acute and delayed effects of pain and possible correlation between lagged pain and opioid use. Other post-transplantation variables included the following: medications (running average of opioids [10 mg morphine intravenous equivalent³⁰], benzodiazepines [1 mg lorazepam oral equivalent³¹], corticosteroids [1 mg prednisone oral equivalent³⁰], and anticholinergics [total score on anticholinergic drug scale³² excluding any opioids, benzodiazepines, or corticosteroids] in the previous 48 hours, including the day of assessment); cyclosporine blood level exceeding the normal therapeutic range in the previous 7 days, including the day of assessment; peak alkaline phosphatase in the previous 96 hours and peak BUN in the previous 48 hours, including the day of assessment; acute graft-versus-host disease (GVHD) severity, defined as grade of 2, 3, or 4 acute GVHD³³ and allogeneic donor cell type; and any infection within 7 days before the delirium assessment.

Statistical Analysis

Summary descriptive statistics were computed for patients stratified by delirium episode within the first 30 days after transplantation. Multivariable analyses predicting time to onset of a delirium episode used Cox proportional hazards regression with time-varying covariates.³⁴ Analyses predicting delirium severity used a linear mixed effects model with patient-specific random intercepts to allow for within-patient correlation as a result of repeated measures. Assumptions for these models were evaluated using residuals analysis and seemed valid.

Covariates in our multivariable model were selected using a restricted stepwise selection procedure that combined a priori information about variables likely to be important with an automated variable selection algorithm.³⁵ Variables were added to the model in three stages. First, we selected from a defined set of pretransplantation variables based on our prior findings¹ and review of the literature. Then we constrained the model to contain the selected pretransplantation variables and sequentially selected from among the primary post-transplantation variables (medications, BUN, and infection). Finally, we constrained the model to contain all selected baseline and primary covariates while selecting from among a set of secondary covariates (pain, lagged pain, alkaline phosphatase, cyclosporine level, and GVHD). Stepwise model selection was carried out based on the Bayesian information criterion.

We constructed a model for estimating time of delirium onset using variables identified by our final multivariable model. Variable weights are based on a parametric survival model assuming exponentially distributed onset times. To create a parsimonious model, we used average post-transplantation values in estimating variable weights. The performance of the predictive model was evaluated using the c statistic,³⁶ the probability that a patient eventually developing delirium received an estimated delirium onset time less than the estimated onset time for a patient who did not develop delirium.

We carried out model validation to assess performance of our final multivariable models.³⁷ We compared variables selected by the stepwise model

procedure in 1,000 bootstrap replicates of the data set with those included in the model for the original data.

Sensitivity of our final model results to patterns of missing data was evaluated using multiple imputation.³⁸ We compared the results of our restricted stepwise model building using Bayesian information criterion with results obtained using *P* value ($P < .05$) as the selection criterion. All statistical analyses were carried out using R version 2.2.0.³⁹

RESULTS

Patient and Delirium Characteristics

Characteristics of the 90 patients included in the study are listed in Table 1. For post-transplantation risk factors, Table 1 provides the average patient-specific means and between-patient standard deviations estimated as the standard deviation of the patient-specific means. On average, 10.8 post-transplantation assessments were carried out for a length of follow-up of 25.7 days. Summary statistics are also presented separately for 45 patients who experienced a delirium episode during the first 30 days after transplantation and 45 patients who did not experience a delirium episode. Variation in post-transplantation risk factors across the 4 weeks of follow-up is provided in Table 2.

Pretransplantation Risk Factors

Significant pretransplantation variables included in our final multivariable model for delirium onset and delirium severity included higher mean alkaline phosphatase and BUN levels (Table 3). The final model for delirium severity additionally indicated a significant association with lower scores on the Trail Making B neurocognitive test.

Post-Transplantation Risk Factors

Among post-transplantation variables in the multivariable model, only higher doses of opioids were identified as significantly associated with increased hazard of delirium onset. Significant risk factors identified for delirium severity were increased pain and lagged pain, higher opioid doses, and higher BUN levels.

The final multivariable model for predicting delirium severity is comprised of the variables and β coefficients in Table 3, with an intercept of -1.1 . The root mean squared prediction error of this model was 2.38. Using variables from our final multivariable model for delirium onset, we constructed a predictive model for time to delirium onset that can be tested in future populations. The estimated exponential regression model is as follows: days to delirium onset = $\exp(5 - 0.2 \times \text{BUN} - 0.02 \times \text{alkaline phosphatase} + 0.02 \times \text{SF-12 physical component score} + 0.04 \times \text{Trail Making B} - 0.02 \times \text{opioids [10 mg morphine intravenous]} - 0.3 \times \text{pain})$, where BUN, alkaline phosphatase, Trail Making B score, and SF-12 are average pretransplantation values and opioids and pain are average post-transplantation values. The *c* statistic for this model was 0.89. Because values beyond 30 days are extrapolations, these should be interpreted cautiously as indicators of no predicted delirium onset within 30 days, not as precise estimates of onset time.

Sensitivity Analyses

In bootstrap replication, the same set of predictors was selected in more than 80% of bootstrap samples for all variables except SF-12 in the delirium onset model and anticholinergic medications in the delirium severity model. This suggests that these variables may have been

selected as a result of random variation in the data. Multiple imputation indicated that our final models were robust to missing data except for pain in the delirium onset model ($P = .01$) and Trail Making B score in the delirium severity model ($P = .18$), suggesting that these associations may be sensitive to missing data. The *P* value–driven, forward stepwise procedure yielded results that were equivalent, except that in the delirium onset model, pain became significant and in the delirium severity model, Trail Making B score was no longer significant and benzodiazepine use became significant (Appendix Table A1, online only).

DISCUSSION

Pretransplantation risk factors for delirium onset included higher mean alkaline phosphatase and BUN levels. Poorer executive function (Trail Making B test) was additionally a pretransplantation risk factor for delirium severity; however, multiple imputation analyses suggested this result may be attributable to missing data. In contrast to previous analyses examining delirium incidence as the primary outcome,¹ the pretransplantation risk factors in this analysis of time to delirium onset did not include magnesium level or physical or executive function. Executive functioning was also more weakly associated with delirium onset and severity than in previous analyses, suggesting that this relationship may be sensitive to assumptions about missing data. Higher dosages of opioids were the only significant post-transplantation risk factor for delirium onset, with higher levels of pain and lagged pain and higher BUN levels being additional risk factors for delirium severity.

The current investigation builds on previous analyses of this cohort by focusing on longitudinal risk factors and by modeling the timing of delirium onset using survival analysis. These longitudinal analyses are more statistically powerful than our previously reported analyses and allowed us to examine time-varying covariates, facilitating investigation of a larger group of delirium risk factors and construction of models for delirium onset and severity.

Our findings are consistent with research in other cancer populations that found cognitive, liver, and renal impairment to be risk factors for delirium,¹⁰ as well as opioid use, but not benzodiazepine or corticosteroid use.^{22,41} Our model adjusted for current pain and lagged pain, which were significant risk factors for delirium severity but not for delirium onset. Our findings suggest that pain contributes to the severity of delirium symptoms but opioid dosage is a stronger predictor of delirium onset independent of pain intensity. Unlike findings from other populations, use of anticholinergics⁴² and use of benzodiazepines²¹ were not found to be risk factors for time to delirium onset or delirium severity. The lack of significance for anticholinergics may be because we excluded opioids from the anticholinergic score,²¹ whereas some studies included these medications,^{42,43} and adjusted for a broad range of confounders.

Prevention of delirium or decreasing delirium symptoms after HSCT may decrease subsequent distress and functional impairment.^{12,13} The pre- and post-transplantation risk factors will help clinicians identify patients at risk for delirium during their transplantation course and, combined with detection of prodromal delirium symptoms such as attentional, perceptual, and cognitive disturbances,⁴⁴ may enable clinical interventions to prevent delirium onset

Table 1. Summary Statistics for Pretransplantation and Post-Transplantation Variables

Variable	% of Patients With Missing Data*	All Patients (N = 90)		Patients With Delirium Episode† (n = 45)		Patients With No Delirium Episode (n = 45)	
		No.	%	No.	%	No.	%
Before transplantation							
Age, years	0						
Mean			41.5		44.2		38.8
SD			9.9		9.7		9.5
Female	0	36	40	21	46.7	15	33.3
Race	0						
White		85	94.4	42	93.3	43	95.6
Hispanic		3	3.3	2	4.4	1	2.2
Native American		1	1.1	1	2.2	0	0
Other		1	1.1	0	0	1	2.2
Diagnosis	0						
CML		38	42.2	17	37.8	21	46.7
ALL or AML		25	27.8	10	22.2	15	33.3
BR or OV		11	12.2	9	20	2	4.4
MDS or MM		10	11.1	5	11.1	5	11.1
NHL		6	6.7	4	8.9	2	4.4
Stem-cell type	0						
Bone marrow		66	73.3	30	66.7	36	80
Peripheral stem cell		24	26.7	15	33.3	9	20
Donor type	0						
Allogeneic		73	81.1	33	73.3	40	88.9
Autologous		17	18.9	12	26.7	5	11.1
Trail Making B test, T score	4.4						
Mean			51.8		50.2		53.6
SD			11.6		12.7		10.1
Alkaline phosphatase, U/L	3.3						
Mean			63.5		68.4		58.8
SD			27.4		30.7		23.1
Blood urea nitrogen, mg/dL	0						
Mean			12		13.4		10.6
SD			3		3.2		2.1
SF-12, physical component score	3.3						
Mean			48.8		48.3		49.3
SD			9.9		10.4		9.5
Disease stage‡	1.1						
Less advanced		43	48.3	22	48.9	21	47.7
More advanced		46	51.7	23	51.1	23	52.3
Total-body irradiation	0	53	58.9	27	60	26	57.8
After transplantation							
Pain, score	12.4						
Mean			3.2		4		2.5
Between-patient SD			1.8		1.7		1.5
Opioids, mg morphine IV	1.1						
Mean			25.1		38		12.1
Between-patient SD			56.9		76.3		19.2
Benzodiazepines, mg lorazepam PO	1.1						
Mean			2.3		2.2		2.3
Between-patient SD			1.8		1.4		2.1
Corticosteroids, mg prednisone PO	1.1						
Mean			26.1		27.2		25
Between-patient SD			43.1		44		42.5
Anticholinergics, total score	1.1						
Mean			3.4		3.7		3.1
Between-patient SD			1.8		1.8		1.7

(continued on following page)

Table 1. Summary Statistics for Pretransplantation and Post-Transplantation Variables (continued)

Variable	% of Patients With Missing Data*	All Patients (N = 90)		Patients With Delirium Episode† (n = 45)		Patients With No Delirium Episode (n = 45)	
		No.	%	No.	%	No.	%
Alkaline phosphatase, U/L	3.4						
Mean		86.5		91.2		81.8	
Between-patient SD		40.8		45		36.1	
Blood urea nitrogen, mg/dL	9.9						
Mean		23.8		27.1		20.5	
Between-patient SD		13.2		15.2		9.9	
Cyclosporine blood level (above therapeutic range)	0	13	14.4	8	12.1	5	20.8
Infection within 7 days	0	50	55.6	36	54.6	14	58.3
Acute GVHD (grade > 1)	0	61	67.8	44	66.7	17	70.8

Abbreviations: SD, standard deviation; CML, chronic myeloid leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BR, breast carcinoma; OV, ovarian carcinoma; MDS, myelodysplasia; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; SF-12, Medical Outcomes Study 12-item short form; IV, intravenous; PO, oral; GVHD, graft-versus-host disease.

*For pretransplantation variables, percent missing is computed among total number of patients. For post-transplantation variables, percent missing is computed among available observations.

†Delirium episode group includes patients with two of three consecutive assessments with Delirium Rating Scale score > 12.

‡Less advanced disease was defined as ALL or AML in first remission; CML in a chronic phase; or NHL in first remission, untreated first recurrence, or second remission. More advanced disease included all other stages of these diseases, all other types of hematologic malignancies, breast cancer ≥ stage II, and ovarian cancer.⁴⁰

or decrease delirium symptoms. The model by Inouye and Charpentier⁴⁵ of delirium vulnerability (eg, pretransplantation) factors and precipitating (eg, post-transplantation) factors may be relevant in applying these findings in the clinical setting. Applying this model, patients at higher risk for delirium onset as a result of pretransplantation factors will require lower levels of post-transplantation factors to achieve the same hazard of delirium onset as patients with fewer pretransplantation risk factors.

The potentially modifiable pretransplantation risk factors for delirium onset were liver and renal function/dehydration. The most important post-transplantation risk factor for delirium onset was opioid medication dosage. Improved management of common acute sequelae of HSCT often associated with significant pain, such as mucositis and acute GVHD, may lead to a significant reduction of delirium. Inadequately controlled pain may contribute to delirium severity above the contribution of opioid use. Therefore, delirium prevention requires a balance between adequate pain control and avoiding overuse of opioid medication, which may involve the use of nonopioid

analgesia (eg, nonopioid pain medications, hypnosis,⁴⁶ or relaxation and imagery⁴⁷).

The importance of identifying risk factors for delirium symptom severity is supported by growing evidence that morbidity increases with increasing symptom severity, starting at levels defined as subsyndromal delirium.⁴⁸ In addition to pain and opioid use, close monitoring and treatment of liver and renal dysfunction is also important in reducing the severity of delirium symptoms. This is consistent with other reports of dehydration and hepatic abnormalities,¹⁰ perhaps via increase in ammonia and altered drug metabolism, as risk factors for delirium. Hydration has also been associated with decreased rates of impaired mental status in patients with advanced cancer, potentially by promoting the excretion of opioid metabolites.⁴⁹

This study's sample size limited the number of covariates that could be examined. Statistical power in the delirium onset model is a function of the number of observed delirium incidences. Statistical power in the delirium severity model is related to the number of

Table 2. Means and SDs of Post-Transplantation Risk Factors by Week After Transplantation

Risk Factor	Week 1		Week 2		Week 3		Week 4	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Pain, score	3.0	2.1	4.4	2.2	1.5	1.7	1.0	1.1
Opioids, mg morphine IV	11.3	30.5	45.7	74.4	7.6	20.6	0.5	1.5
Benzodiazepines, mg lorazepam PO	3.4	2.8	2.9	3.2	2.3	2.5	0.8	1.3
Corticosteroids, mg prednisone PO	9.0	33.7	18.2	46	33.1	63.1	37.5	56.8
Anticholinergics, total score	3.7	2.1	3.7	2.3	3.1	2.2	1.4	1.6
Alkaline phosphatase, U/L	68.5	27.1	77.1	38.9	94.6	46.2	90.1	46.2
Blood urea nitrogen, mg/dL	16.4	7.5	21.6	15.8	22.6	12.9	23.3	9.7

NOTE. Means were computed for individual patients for each week following transplantation and then mean and standard deviation were computed across these patient means for each week.

Abbreviations: SD, standard deviation; IV, intravenous; PO, oral.

Table 3. Results of Multivariable Models for Time to Delirium Onset and Delirium Severity

Variable	Delirium Onset			Delirium Severity		
	HR	95% CI	P	β	95% CI	P
Before transplantation						
Trail Making B test, T score	0.96	0.93 to 1.00	.06	−0.03	−0.06 to 0.00	.049
Alkaline phosphatase	1.02	1.01 to 1.04	.01	0.03	0.01 to 0.04	< .01
Blood urea nitrogen	1.28	1.14 to 1.43	< .01	0.18	0.06 to 0.30	< .01
SF-12 physical component score	0.98	0.93 to 1.04	.55	0.01	−0.03 to 0.05	.55
Disease stage (more advanced)				0.43	−0.30 to 1.17	.25
Total-body irradiation				0.05	−0.72 to 0.82	.90
After transplantation						
Pain	1.19	0.98 to 1.46	.08	0.20	0.12 to 0.27	< .01
Lagged pain	1.12	0.93 to 1.35	.24	0.16	0.08 to 0.23	< .01
Opioids (10 mg morphine IV)	1.05	1.02 to 1.08	< .01	0.04	0.02 to 0.07	< .01
Anticholinergics				0.03	−0.06 to 0.11	.52
Alkaline phosphatase				−0.01	−0.01 to 0.00	.054
Blood urea nitrogen				0.05	0.03 to 0.06	< .01

NOTE. Delirium onset is modeled using the stepwise Cox proportional hazards model. Reported effects are HRs. Delirium severity is modeled using stepwise linear mixed effects models for Memorial Delirium Assessment Scale (MDAS). Reported effects are linear effects on MDAS. Included variables are those in the final model based on improving fit using the Bayesian information criterion.

Abbreviations: HR, hazard ratio; SF-12, Medical Outcomes Study 12-item short form; IV, intravenous.

patients and the degree of within-patient correlation across assessments. On the basis of the observed correlation, the effective sample size is approximately 168.⁵⁰ Most risk factors investigated had low levels of missing data. However, missing data occurred more commonly for pain, BUN, and alkaline phosphatase. To avoid the possibility of bias introduced by missing data, we used multiple imputation to investigate the sensitivity of our model to the missing data mechanism. Inference from the multiple imputation analysis was similar to that from our primary analysis.

Stepwise model selection may identify spurious relationships between predictors and outcomes caused by random variation in the data set. A bootstrap validation procedure indicated that most of the factors identified by our model are robust to minor variation of the data and are likely to represent real predictors of delirium onset and severity. However, our results should be validated using an external data set.

The definition of delirium onset used in these analyses could potentially violate the proportional hazards model assumption of independence of event and censoring times. This would occur if a patient were censored after a delirium episode had begun but before a second assessment at which the DRS score was greater than 12, preventing us from identifying a delirium episode. However, this is not likely to have affected our analyses because of the small number of possibly affected patients (four of 90 patients). Results of sensitivity analyses indicated that these patients did not impact model inference.

Potential confounding may occur by indication (eg, laboratory tests may have been ordered and medications may have been prescribed in an attempt to manage delirium-related symptoms). This potential bias was addressed by including laboratory values and medication dosing before each index delirium assessment.

Changes in standard treatment since this cohort was enrolled may influence the generalizability of the results. Conditioning regimens now often include nonmyeloablative doses that have lower acute toxicities. Nonetheless, the risk factors detected are still relevant to HSCT recipients who receive myeloablative treatment and may also

be relevant to other treatment regimens; future studies should test these findings.

Future research should examine risk factors for delirium in larger HSCT populations that include nonmyeloablative regimens. Larger samples would allow examination of differential risk factors for specific delirium presentations and outcomes. As prevention and management of pain, mucositis, acute GVHD, and other acute HSCT-related sequelae improve, researchers will be able to examine whether these clinical advances are associated with a concomitant decrease in delirium incidence. Results from this and future studies may lead to prevention studies targeting modifiable risk factors and early detection and treatment models for delirium in patients undergoing HSCT.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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