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Risk Factors for Delirium in Patients Undergoing Hematopoietic Stem Cell Transplantation

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Abstract

Background—Delirium is common following hematopoietic stem-cell transplantation (HSCT) and is associated with increased morbidity and mortality. Early recognition and treatment have been shown to improve long term outcomes. We sought to investigate the relationship between potential risk-factors and the development of delirium following HSCT.

Methods—Fifty-four inpatients admitted for HSCT were assessed prospectively for delirium every 2-3 days through their inpatient stay using standardized delirium and neuropsychological measures. Patient's self-reports of medical history, medical records, and neurocognitive and psychiatric assessments were used to identify risk factors. Both pre- and post-HSCT risk factors were examined.

Results—Delirium incidence was 35% and occurred with highest frequency in the 2 weeks following transplant. The only pre-transplantation risk factors was lower oxygen saturation ($p=0.003$). Post-transplantation risk factors for delirium included higher creatinine ($p<0.0001$), higher blood urea nitrogen levels ($p=0.005$), lower creatinine clearance ($p=0.0006$), lower oxygen saturation ($p=0.001$), lower hemoglobin ($p=0.04$) and lower albumin ($p=0.03$). There was no observed association with level of cognitive performance, transplant type, disease severity, medical co-morbidity index, age or conditioning regimen.

Conclusion—Routine laboratory values can assist in the identification of high risk patients before delirium onset to improve early detection and treatment of delirium following HSCT.

Keywords

delirium; risk factors; cancer; hematopoietic stem-cell transplantation

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INTRODUCTION

Delirium is the most common neuropsychiatric disorder in cancer patients with an incidence ranging from 18%-85%.[1,2] The incidence is particularly high in patients with hematological (up to 73%) or terminal cancer (up to 85%).[3] The acute and long-term negative outcomes from delirium are numerous and include significant patient distress, a greater mortality risk, longer hospital stay, increased hospital charges, decreased ability for self-care resulting in nursing home placement, increased caregiver burden, long-term cognitive decline and worsened Alzheimer's disease.[4-12] When delirium is recognized, more than half the cases can be reversed through the identification and management of underlying causes and the provision of concurrent symptomatic treatment. Unfortunately, delirium is typically not recognized in cancer patients, with more than 50% of the cases not diagnosed.[5] With early recognition and treatment, some of the burdens of delirium can be decreased.[13] Identification of risk factors can aid in the recognition of delirium in cancer patients.[14]

The majority of studies examining delirium risk factors have focused on elderly hospitalized or medically ill inpatients. Recent studies focusing on risk factors for delirium in hospitalized patients with advanced cancer have published inconsistent results which may reflect the multi-factorial cause of delirium. In cancer patients, delirium has been linked to hypoxia, dehydration (increased creatinine, blood urea nitrogen, or sodium), anemia, decreased magnesium, decreased glucose, and decreased albumin as well as exposure to opioids, corticosteroids, and benzodiazepines.[14-16] To our knowledge there have been three studies published looking specifically at the risk factors for delirium in hematopoietic stem cell transplantation (HSCT) patients and two looked at pre-transplant risk factors. Fann et.al, looked at 90 HSCT patients and reported that the pre-transplant risk factors for delirium onset and severity included lower cognitive function, higher blood urea nitrogen, higher alkaline phosphatase, lower physical functioning and higher magnesium.[17] Re-analysis of the same 90 patient HSCT sample in 2011, focused on post-transplant risk factors and concluded that the only pre-transplant risk factors were higher mean alkaline phosphatase and blood urea nitrogen levels, while the only post-transplant risk factor for delirium onset was higher doses of opioid medications.[18] Beglinger et.al, reported that pre-transplant risk factors for delirium in HSCT patients included decreased white blood cell count, hemoglobin, and platelet count.[6]

Approximately 50,000 patients undergo hematopoietic stem cell transplantation annually around the world. Even if only a third of patients undergoing a HSCT experience delirium, the potential burden and cost to the patient and society is large. There have been studies detailing the phenomenon of delirium in HSCT patients and studies of risk factors for delirium in cancer patients; however, there is limited data on the specific risk factors for delirium in HSCT patients. Identification of delirium risk factors in this population can lead to increased detection and prevention as well as earlier treatment which could have a cascading effect to decrease morbidity, mortality and cost. Our purpose is to replicate and extend previous work characterizing delirium by prospectively identifying delirium following HSCT while looking for pre-and post-transplant risk factors for the development of delirium.

MATERIALS AND METHODS

Patients

Patients were recruited for two delirium related studies before or upon their admission to the University of Iowa Blood and Marrow Transplantation Program for an allogeneic or autologous bone marrow or peripheral blood HSCT from 2004 to 2008. All patients who were scheduled for a transplant during the study enrollment period were evaluated for study eligibility, if they met inclusion criteria they were approached for enrollment. Participants who enrolled in one of two studies during this time where prospectively examined for delirium as well as for the cognitive, psychiatric and metabolic sequelae of HSCT. Following completion of both studies, potential risk factors for delirium (i.,e., laboratory values and vital signs) where retrospectively extracted from the electronic medical record.

Procedures

The protocol and all study procedures were approved by the University of Iowa institutional review board. All patients provided written informed consent and were financially compensated for their participation in the study. Patients were assessed at a pre-transplantation visit ideally before any conditioning treatments occurred (e.g. total body irradiation) with a 90 minute screening battery that assessed cognitive and psychiatric functioning, delirium, demographics and medical information. Patients found to have delirium at the pre-transplantation screening were excluded from the study. During their inpatient stay following HSCT, patients completed a brief battery to monitor for delirium at scheduled two or three day intervals; a full description of the neuropsychological testing procedures completed during those visits are presented elsewhere.[6,19,20] In addition, if staff noticed symptoms of delirium during a non-assessment day, the research team was notified and a visit was scheduled as soon as possible. All cognitive and psychiatric functioning and delirium assessments were conducted by a trained research assistant or neuropsychologist. If a psychiatric consultation was requested during the course of the study the patient received usual treatment with no effect on participation in the study.

Transplantation Assessment/Measurements

Medical history and status—Patients' general and medical backgrounds were assessed using a semi-structured clinical interview at the time of enrollment. Specifics can be found in previously published papers.[6] Information regarding medial co-morbidity was extracted by chart review following the hospital admission and was documented using the hematopoietic cell transplantation specific co-morbidity index (HCT-CI) which is validated in HSCT patients and correlates with survival in this patient population.[21-23] Performance status (i.e., functional level) was measured using the Karnofsky Performance Status (KPS) which was collected from the pre-transplantation medical assessment. The KPS correlates well with the Eastern Cooperative Oncology Group performance status scale (ECOG) and is predictive of treatment failure in elderly cancer patients.[23,24] The types of conditioning regimens, including total body irradiation, were documented.

A retrospective chart review was conducted to compile laboratory test and vital sign data in the 24 hour period prior to the pre-transplantation visit as well as the 24 and 48 hour

intervals prior to post-transplantation delirium assessments. 48 hours was the shortest time between delirium assessments. We did not look at earlier data collection to prevent overlap between collection times and delirium assessments. 24 hour data was collected since it was available for most patients and the literature does not clearly define how long a risk factor needs to be present before delirium occurs. Data collected for the study included laboratory values for hemoglobin, hematocrit, white blood cell count, platelet count, blood urea nitrogen, creatinine, estimated creatinine clearance (calculated using the Cockcroft-Gault formula), magnesium, alkaline phosphatase, albumin, aspartate aminotransferase, alanine transaminase, total bilirubin, sodium, and glucose. Additionally, highest temperatures, highest nursing reported scaled pain levels, and lowest oxygen saturation levels (obtained by bedside oximetry) were collected. If a value was not present in the chart, it was treated as a missing data point in the statistical analysis.

Delirium assessment—The delirium assessment interval was varied since 2 studies were combined and each had a different assessment schedule. All attempts were made to adhere to the scheduled delirium assessment intervals but some assessments were not completed secondary to logistics or patient-centered reasons. On average each patient was assessed two to three times each week following transplant using validated screening instruments. There are no screening tools validated in HSCT patients; however, the most common research tool to diagnosis delirium is the Delirium Rating Scale (DRS) and DRS-Revised [25,26]. These are scales of delirium severity based on all available information from patient interview, family, and nurses' reports, cognitive tests, and medical reports, measured over the previous 24 hour period (DRS cutoff >12; DRS-R cutoff =15 for severity or =18 total score). We also used the Memorial Delirium Assessment Scale (MDAS) [27]which measures delirium presence and severity and can be administered multiple times in one day (cutoff ≥ 8) and is validated in patients with advanced cancer.[28] The following tests were also included in the delirium assessment during the inpatient stay to measure neuropsychological status and assist with delirium assessment: Trail Making Test, Modified Mini Mental Status (3MS), and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): List Learning, Coding, Semantic Fluency and Digit Span. For more details about the neuropsychological battery, please refer to Beglinger et.al.[20]

Statistical Analysis

Patients who surpassed the cutoff value on the DRS or MDAS at any point after transplantation were coded as having delirium. Time to delirium was defined as the time between transplant and a positive delirium assessment. Patients were censored if they had not experienced delirium by the end of the hospital stay. Baseline cognitive, psychiatric, and medical laboratory variables were analyzed univariately with Cox regression to determine their relationship with time to delirium.[29] Post-tranplantation medical laboratory variables were treated as time-dependent in univariate Cox regression models to examine their association with delirium. Multivariate Cox models were created using the most higly significant variables from the univariate analysis. All Cox models used Efron's method for handling ties.[30] A p-value of less than 0.05 was considered significant. All statistical tests were corrected for multiple comparisons using a false discovery rate (FDR) of ≤ 0.05.[31]

RESULTS

Patient Characteristics

A total of 54 patients consented to participate in the two studies. One patient was excluded because of delirium at the time of the pre-transplant assessment. Two patients in the delirium group did not experience a delirium episode during their hospitalization following HSCT (but did at a later date) and have been excluded from the analysis. The remaining patients completed two to four acute-phase assessments after transplantation (mean, 3.3; SD, 1.0). The majority of the patients were male (71%), had lymphomas or leukemia (59%) and received myeloablative therapy (94%). The mean age was 53.3 (SD, 10.7). A greater number of patients received an autologous transplant (57%) than an allogeneic transplant (43%). Patients who underwent an autologous HSCT received high dose, multi-agent chemotherapy for myeloablative therapy. Allogeneic HSCT patients mostly received total body irradiation and high dose chemotherapy or Busulfan-based high-dose chemotherapy. The majority of the transplants were done using peripheral blood hemopoietic stem cells (75%). Patient characteristics are shown on Table 1.

The following case illustrates the delirium risk factors which may occur in a patient following a hematopoetic stem cell transplantation. Mrs. R was a 52 year old married female who had been diagnosed with lymphoma two years prior to transplant. She received two chemotheraputic regimens prior to transplant. At the time of admission to the hospital she had an excellent functional status (KPS 80) and her only medical co-morbidity included fibromyalgia, hypothyroidism and arthritis. Mrs. R's baseline testing showed good cognitive functioning and no evidence of delirium or depression. Her conditioning regimen was myeloablative and included Carmustine, Cytarabine, etoposide and Cyclophosphamide (B-VAC) which she tolerated well. She was given the standard medications following transplant which included prophylactic antibiotics per guidelines (including trimethoprim/sulfamethaxazole, voriconazole, levofloxacin, piperacillin/tazobactam and acyclovir). She received intravenous morphine for mouth and throat pain. Transplant complications were all expected and included pancytopenia requiring transfusion support as well as gastrointestinal toxicity with oral mucositis and diarrhea requiring total parenteral nutrition. Five days after transplant the treatment team remarked that she had a difficult night with a post-transfusion fever (38.5 C) and chest discomfort. That morning her delirium screen was positive (MDAS 9, DRS 8) with deficits in her performance on the Modified Mini Mental Status, Trail Making Test Part A (Trails A), and Repeatable Battery for the Assessment of Neuropsychological Status: Coding and List Recall subtests. No behavioral disturbances are described in the chart. Abnormal labs in the 24 hours proceeding her delirium showed a creatinine (1.6 mg/dl), blood urea nitrogen (40 mg/dl), white blood cell count (0.2 k/mm3), hemoglobin (9.1g/dl), and platelets (8 k/mm3). The remainder of her electrolytes, vital signs, pulse oximetry and pain scores were normal. Over the next day her fever and elevated creatinine had resolved. Unfotunately, her delirium screen remained slightly elevated (but not to the diagnositic cut off) indicating a potential sub-syndromal delirium and she showed continued deficits in her cognitive functioning (deficits in List Recall, Trails A and Coding) which still persisted at discharge two weeks later.

Descriptive Delirium Results

The number of patients who exceeded the cutoff for delirium on either scale at any point during hospitalization following HSCT was 18, or a cumulative incidence of 35% (18/51). The highest prevalence for delirium was in the first 2 weeks following transplant (15/18 84%) and a majority of the delirium was only picked up during one screening visit (12/18 67%) with a mean duration of 2.4 days. The timing is defined in more detail in a previous paper.[20] By combining two studies for the purpose of exploring predictors of delirium we were limited to only looking at two weeks following HSCT (the length of the shorter study) and two subjects with delirium were excluded from the analysis of risk factors because delirium occurred more than 2 weeks after transplant making the total number of patients with delirium 16/51 (31%) for the analysis.

Delirium Risk Factors

Pre-Transplantation—Descriptions and univariate comparisons of pre-transplantation characteristics among patients who had and did not have delirium are shown in Table 1. Using univariate Cox regression, we examined demographic and disease-related variables at baseline: including age, diagnosis, medical co-morbidity using the HCT-CI, functional status using the KPS, and chemotherapeutic agents and found that none of these were statistically significant predictors of delirium in our sample. Cox regression was used to analyze the conditioning agents based on: the number of agents received; whether the agent used crosses the blood brain barrier or has known neurological effects (Carmustine, Etoposide, Cytarabine, Busulfan); and the use of total body irradiation. In addition, there was no association with pre-transplant depression score or cognitive level measured by RBANS, 3MS, and Trails A/B. Univariate comparisons of pre-transplant laboratory values and vital signs did not show an association with delirium with the exception of a lower oxygen saturation (HR 0.66; 95% CI 0.50-0.87; p=0.003). Of the 16 subjects who experienced delirium, 10 had a recorded pre-transplant oxygen saturation. Pre-transplant oxygen saturation predicted delirium at the first visit post-transplant (p=0.03) but not at subsequent visits (2, 3, or 4) and it appeared that oxygen saturation levels at or below 92% were of concern.

Post-Transplantation—Descriptions and univariate comparisons of post-transplantation risk factors among patients who had and did not have delirium are shown in Table 2. Because this is a small exploratory study we are reporting the uncorrected p-values (analysis does not correct for multiple variables) to ensure that any variables which might be related to delirium are highlighted, recognizing that we may have false positives. The corrected p-values (corrected for multiple variables) are also reported in the tables. In univariate tests higher 24- and 48-hour creatinine (p=0.0003, p<.0001), higher 24- and 48-hour blood urea nitrogen (p=0.002, p=0.005), lower 24- and 48-hour creatinine clearance (p=0.0009, p=0.0006), lower 24 and 48-hour oxygen saturation (p=0.010, p=0.001), lower 48-hour hemoglobin (p=0.04) and lower 24-hr albumin (p=0.03) were significant. With the exception of albumin, no values showed significance at only the 24 hour collection time and for simplicity only 48 hour values are displayed in Table 2. Multivariate analysis of 48-hour blood urea nitrogen 48-hour creatinine, and 48-hour oxygen showed that 48-hour blood urea nitrogen and 48-hour creatinine are redundant in the model. For the other two models (one

with 48 hour blood urea nitrogen and 48 hour oxygen and the other with 48-hour creatinine and 48-hour oxygen) both predictors remain significant (Table 3).

DISCUSSION

In the present sample of adult patients undergoing HSCT, the incidence of delirium was 35% and occurred most frequently during the first and second week following transplantation. The frequency of delirum found in this study was lower than the frequency reported by Fann[32], higher than the frequency reported by Prieto[33] but similar to the frequency reported by Beglinger.[6] The similarity with Beglinger is expected due to sample overlap and the low incidence reported by Prieto is likely due to screening only occuring once a week. The median duration of delirium was significantly shorter than reported by Fann (8 days)[17] in HSCT patients but similar to that reported in advanced cancer patients.[15] It is possible that in the decade since the Fann sample was collected, supportive care measures have improved to mitigate the toxicities of the conditioning regimens. With regard to the timing of delirium, results between studies are remarkably consistent, with the highest prevalence of delirium in the first two weeks following transplantation. The converging results of these studies underscore the importance of monitoring for delirium immediately after transplantation because a majority of patients are likely to develop at least mild symptoms which could complicate their care leading to an increase in costs and length of stay. The emerging evidence of the reliability of the timing of delirium may also inform preventative treatment strategies similar to those in elderly patients before they undergo a surgical procedure.[34,35]

For delirium to be diagnosed there has to be an underlying medical abnormality. A person's predilection to the development of delirium is based on both baseline and precipitating factors and risk increases a number of risk factors increase.[36] Baseline factors include things such as age, sex, education, cognitive functioning and are often not able to be mitigated. Precipitating factors which have been identified in cancer patients include medications, infections, hypoxia, hematological vs solid tumors, presence of bony metastases, dehydration, withdrawal, and central nervous system involvement.[8,37] While numerous factors have been postulated to increase the risk of delirium in cancer patients, there is still a lot a variance and little is known about specific risk factors in specific cancer populations. The causes of delirium are numerous and more often than not delirium is believed to be multi-factorial (more than 40%) making it more difficult to treat.[38] This study succeeded in identifying additional precipitating factors for the development of delirium in patients following HSCT.

In this study we found lower blood oxygen saturation and evidence of renal dysfuntion to be correlated with the development of delirium in our HSCT patients. Blood oxygen saturation level is notable because it was the only factor found to be positive both pre- and post-transplant. Reduced oxygen saturation may be a surrogate marker for other underlying conditions such as sepsis or cardio-respiratory insufficiency making it difficult to determine if the delirium is a result of the low blood oxygen saturation or of an underlying process. In this study population we feel sepsis is less likely due to the rigourous screening and surveilence for acute infection and the lack of a significant association between the

development of delirium and an altered white blood cell count (most of the patients demonstrated laboratory evidence of bone marrow suppression). Renal dysfunction (as evidenced by increased blood urea nitrogen and creatinine levels, and lower creatinine clearance in the patients with delirium) was strongly correlated with delirium in the 48 hours prior to the development of delirium. The tendency for patients with renal dysfunction to develop delirium may result from direct biochemical changes associated with the increased lab values, reduced clearance of drugs, or from an underlying medical condition since altered renal blood flow and the resulting renal dysfunction is often a surrogate measure of the severity of various underlying medical diseases. Additionally, a number of factors which can serve as overall markers of disease severity and functional status (hemoglobin, hematocrit and albumin) were less strongly significant. These findings are likely related to the tendency for delirium to be multifactorial.

While our findings partially support Fann's [17] finding that an elevated blood urea nitrogen level pre-transplant is associated with an increased rate of delirium, our pre-transplant markers of renal function were not associated with delirium. This may be related to the small sample size and presence of missing data. We also found additional post-transplant factors which Fann did not identify.[18] While both studies have been undertaken in patients following HSCT, there is a significant difference in the characteristics of the samples. Fann's sample had a preponderance of allogenic (81%) and bone marrow transplants (74%) receiving total body irradiation (59%) while the characteristics of our sample were the opposite (43% allogenic, 13% bone marrow, 12% total body irradiation). It is possible that the type of transplant, type of stem cell used, and type of conditioning may change the risk for delirium. Larger studies are needed to separate out these differences.

While we identified an association between delirium and several precipitating factors in our sample, we were struck by the number of variables which did not show an association with a risk for delirium. Although age has been found to be a risk factor for delirium in cancer patients,[14,39] age has not been a significant predictor of delirium in past studies of HSCT patients, which may reflect that fact that older patients are less likely to receive HSCT. In a frequency distribution of ages in our sample we found that 50% of the delirium occurred in patients under the age of 55 and 14% in patients under the age of 40. It is difficult to find studies which examine delirium in patients under the age of 65 to compare to. Our findings may reflect a unique aspect of delirium in HSCT patients (such as the high dose chemotherapy that is used) or it may be an indicator of the severity of the physiological stressors associated with a HSCT and how acutely medically ill these patients often become following transplant. Medical co-morbidity has been shown to be a risk factor for delirium in elderly medical patients[40] but had not been well studied in patients with cancer. Co-morbidity was not a significant predictor of delirium in our sample even when using a morbidity index specific to HSCT patients. This confirms previous studies in patients following a HCST which did not find disease severity or functional status to be a predictor of delirium[41] possibly reflecting a built-in selection bias for otherwise healthier patients that are candidates for transplantation. It has been unclear as to whether transplant type influences the risk for delirium but our work supports the previously published work that there is not a correlation.[32,33] Chemotherapy is a massive inflammatory insult to the brain and body; therefore, we had expected a relationship between conditioning agents and

delirium, specifically those agents that cross the blood brain barrier. Our finding of a lack of correlation may be related to our sample size and the frequency of each agent used in conditioning patients for transplantation. A larger study may show that the toxicity related to specific chemotheraputic agents is a risk factor for delirium. There is good evidence that pain is related to delirium in medical patients;[42,43] however, we did not see a relationship despite the fact that the patients with delirium had a nurse-reported pain score three times higher than the patients without delirium. While it is possible that patients undergoing a HSCT do not experience much pain we believe the lack of relationship between delirium and pain may be related to the intinsic difficulties in objectively translating patient pain levels to a reliable numeric scale.

This study adds to the growing body of literature on the risk factors and prevelence of delirium in patients receiving HSCT. It is notable that even in our small sample, oxygen levels and creatinine were more predictive of delirium than age, disease severity, or medical co-morbidities. The prospective structure of this study in identifying delirium is a clear advantage; however there are limitiations. Chiefly, is the sample size in comparison to the multiple variables examined. The study was powered to identify only very robust associations and equally important but weaker associations may have been overlooked. The study size was not robust enough to define laboratory values above or below which a prediction for development of delirium can be made; rather we have generated mean values for a group of patients that are different and those values become surrogate markers for derangements in pathology which are statistically correlated with the onset of delirium. The intial study focus was on the prospective identification of delirium and it's neuropsychiatric sequelae and the treatment team was allowed to follow usual clinical care without interference. The retrospective capture of laboratory correlates led to missing values which would have been avoided if we would have designed the study to draw a select panel of labs prior to each delirium evaluation. The delirium evaluations were not performed daily leaving some uncertainty to the exact time of the delirium onset and the possibility of our missing a delirium episode; however, given the duration of delirium in this study as well as our daily chart review and regular contact with the treatment team we believe the chance of having missed a delirium episode is low.

This study has identified common metabolic markers that indicate a risk for the development of delirium in patients following HSCT. The high rate of delirium in the first two weeks following transplant supports the need for close monitoring of this patient population. Early detection is particularily critical as there is growing evidence that successful interventions can improve outcomes for patients with delirium.[34,44] Our findings continue to highlight the differences between the HSCT patient population and other cancer patients. Further research is needed before our findings can be generalized to other patient populations. It is hoped that our findings will lead to prospective studies on treatment and delirium prevention. By identifying high risk patients, clinicians can focus their efforts on modifiable delirium risk factors, such as preventative use of supplemental oxygen for mild hypoxia, close attention to nutritional status with early supplementation based on albumin levels, as well as close attention to renal function and fluid status. These efforts could potentially reduce the rate of delirium in this high risk population. In addition clinicians need to develop a lower threshold

for the recognition and early treatment of delirium which may result in decreased morbidity and mortality in this critically ill population.

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Table 1

Description and Univariate analysis of pretransplant characteristics of patients undergoing HCST (n = 51 patients).

Characteristics	Number of Sample (%) (n=51)	No Delirium (n=35)	Delirium (n=16)	Hazard Ratio (95% CI)	P-value uncorrected	P-value corrected
Age, yrs (range, 21-69)	51 (100%)	35	16	1.02 (0.97-1.08)	0.38	0.64
Mean (SD)		52.4 (10.3)	55.3 (11.8)			
Education, yrs (range,11-21)	51 (100%)	35	16	1.03 (0.87-1.23)	0.69	0.85
Mean (SD)		14.2 (2.5)	14.5 (3.6)			
Gender	51 (100%)	35	16	1.13 (0.39-3.25)	0.83	0.90
Male (reference)	36 (71%)	25	11			
Female	15 (29%)	10	5			
Diagnosis	51 (100%)	35	16		0.07	0.36
Leukemia	11 (22%)	10	1	0.57 (0.18-1.80)	0.34	
Lymphoma	19 (37%)	11	8	0.09 (0.01-0.79)	0.03	
Myeloma	13 (25%)	11	2	0.20 (0.04-1.02)	0.05	
Other (reference)	8 (16%)	3	5	--	--	
Donor Type	51 (100%)	35	16	0.71 (0.26-1.96)	0.51	0.76
Autologous (reference)	29 (57%)	19	10			
Allogeneic	22 (43%)	16	6			
Stem Cell Type	51 (100%)	35	16	0.70 (0.24-2.03)	0.51	0.76
Bone marrow (reference)	13 (25%)	8	5			
Peripheral	38 (75%)	27	11			
Functional Status (KPS)	43 (84%)	29	14	1.03 (0.96-1.10)	0.40	0.66
≤70	2 (5%)	2	0			
80	11 (26%)	8	3			
90	23 (53%)	14	9			
100	7 (16%)	5	2			
HCT-CI Score	50 (98%)	34	16	1.17 (0.33-4.18)	0.81	0.89
0-1	29 (58%)	16	13			
2-3	14 (28%)	14	0			
>3	7 (14%)	4	3			
Conditioning agents*	51 (100%)	35	16			
Number of agents (continuous)	51 (100%)	35	16	1.33 (0.86-2.05)	0.20	0.46
Total Body Irradiation				0.94 (0.21-4.14)	0.93	0.95
No (reference)	45 (88%)	31	14			
Yes	6 (12%)	4	2			
Agent that crosses blood brain barrier**				1.62 (0.52-5.04)	0.41	0.66
No (reference)	18 (35%)	14	4			

Characteristics	Number of Sample (%) (n=51)	No Delirium (n=35)	Delirium (n=16)	Hazard Ratio (95% CI)	P-value uncorrected	P-value corrected
Yes	33 (65%)	21	12			
Neuropsychological***						
3MS total	51 (100%)	35	16	1.04 (0.93-1.16)	0.48	0.74
RBANS total	27 (53%)	19	8	1.01 (0.97-1.04)	0.77	0.89
Trails A Z-score	27 (53%)	19	8	1.22 (0.71-2.10)	0.47	0.74
Trails B Z-score	27 (53%)	19	8	0.98 (0.73-1.31)	0.90	0.92
Psychiatric						
Depression	51 (100%)	35	16	1.78 (0.87-3.62)	0.11	0.36

Table 2

Descriptive and univariate analysis of clinical risk factors for delirium following HSCT (n=51).

Laboratory and Vitals (ref range)	Mean (Range; SD)	Hazard Ratio (95% CI)	P-value uncorrected	P-value corrected
Electrolytes				
Sodium (135-145 mEQ/L)		0.98 (0.87-1.12)	0.80	0.89
Delirium (n =16)	136 (126-141; 3.9)			
No delirium (n=34)	136 (125-142; 3.9)			
Magnesium (1.5-2.9 mg/dL)		2.57 (0.85-7.80)	0.09	0.36
Delirium (n=16)	2.1 (1.3-2.8; 0.3)			
No delirium (n=33)	1.9 (1.5-2.8; 0.3)			
Glucose (65-99 mg/dL)		1.00 (0.99-1.00)	0.48	0.74
Delirium (n=13)	151 (75-262; 52)			
No delirium (n=28)	209 (72-868; 166)			
Metabolic				
Blood urea nitrogen (10-20 ml/dL)		1.05 (1.01-1.09)	0.005	0.05
Delirium (n=16)	27 (8-73; 17)			
No delirium (n=34)	18 (7-61; 11)			
Creatinine (0.7-1.4 mg/dL)		31.8 (5.60-180.79)	<0.0001	0.007
Delirium (n=16)	1.1 (0.6-1.7; 0.3)			
No delirium (n=34)	0.8 (0.5-1.9; 0.3)			
Creatinine Clearance (80-120 mL-min)		0.97 (0.95-0.99)	0.0006	0.01
Delirium (n=16)	96 (40-197; 38)			
No delirium (n=34)	142 (13-334; 57)			
Alkaline Phosphatase (40-129 U/L)		0.98 (0.96-1.01)	0.27	0.54
Delirium (n=11)	67 (44-125; 26)			
No delirium (n=17)	83 (47-146; 33)			
Aspartate Aminotransferase (0-37 u/l)		0.99 (0.96-1.02)	0.60	0.80
Delirium (n=13)	23 (8-62; 17)			
No delirium (n=21)	24 (8-110; 22)			
Bilirubin, Total (0.2-1.0 mg/dL)		0.97 (0.78-1.20)	0.77	0.89
Delirium (n=15)	1.4(0.3-9.6; 2.3)			
No delirium (n=26)	1.7 (0.2-21.1; 4.1)			
Albumin (3.4-4.8 g/dL)		0.43 (0.10-1.75)	0.24	0.51
Delirium (n=6)	3.0 (1.7-3.5; 0.6)			
No delirium (n=18)	3.2 (2.8-4.2; 0.3)			
Hematologic				
White Blood Cells (3.7-10.5 k/mm3)		0.69 (0.32-1.50)	0.35	0.63
Delirium (n=16)	0.4 (0.1-2.5; 0.6)			
No delirium (n=34)	1.4 (0.1-9.0; 2.1)			

Laboratory and Vitals (ref range)	Mean (Range; SD)	Hazard Ratio (95% CI)	P-value uncorrected	P-value corrected
Platelets (150-400 K/mm3)		0.96 (0.92-1.01)	0.14	0.36
Delirium (n=16)	14 (3-45; 12)			
No delirium (n=34)	22 (5-71; 16)			
Hemoglobin (11.9-17.7 g/dL)		0.61 (0.39-0.97)	0.04	0.25
Delirium (n=16)	8.4 (6.7-10.6; 1.0)			
No delirium (n=34)	9.2(7.0-11.6; 1.0)			
Vital Signs				
Weight (kg)		0.99 (0.96-1.01)	0.28	0.54
Delirium (n=16)	83 (57-125; 16)			
No delirium (n=34)	91 (61-143; 21)			
Oximetry (0-100%)		0.82 (0.72-0.92)	0.001	0.02
Delirium (n=15)	92 (79-97; 4.5)			
No delirium (n=32)	94 (89-98; 1.9)			
Pain score (0-10)		1.17 (0.95-1.45)	0.14	0.36
Delirium (n=15)	3.5 (0-8; 2.9)			
No delirium (n=30)	1.7 (0-7; 2.1)			
Temperature (36.1-37.2 C)		1.40 (0.91-2.17)	0.13	0.36
Delirium (n=16)	38.5 (37.6-39.8; 0.7)			
No delirium (n=33)	37.8 (36.5-40.3; 0.9)			

Table 3

Multivariate analysis of 48-hour blood urea nitrogen, creatinine and oxygen level.

Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limits	p-value
Creatinine	25.32	4.45-144.07	0.0003
Oxygen	0.81	0.71-0.92	0.002
Creatinine*	35.13	3.12-396.09	0.004
Blood urea nitrogen*	1.00	0.95-1.05	0.90
Blood urea nitrogen	1.05	1.00-1.09	0.04
Oxygen	0.84	0.74-0.94	0.004

*redundant