Hemoglobinuria in the Early Poststem-Cell–Transplant Period: Risk Factors and Association with Outcomes

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Key Points
- Post-HSCT hemoglobinuria was associated with graft type (BMT+Cord).
- Post-HSCT hemoglobinuria was associated with early (48–72 hours) post-HSCT AKI.
- Graft type (BMT+Cord) was associated with AKI among patients with hemoglobinuria.

Abstract
Background Information on risk factors of hemoglobinuria after hematopoietic stem-cell transplant (HSCT) and its association with AKI, mortality, and engraftment is limited.

Methods We conducted a retrospective cohort study on all consecutive adults that underwent HSCT from January 6, 1999, to November 6, 2017. The study included 6039 patients that underwent bone marrow transplantation (BMT), umbilical cord blood, and peripheral blood stem-cell transplantation (PBSCT).

Results Early post-HSCT, AKI occurred in 393 (7%) patients, and 52 (0.9%) patients had post-HSCT hemoglobinuria. Post-HSCT hemoglobinuria was associated with graft type (BMT+Cord), underlying disease (lymphoma, acute leukemia), and fludarabine-based conditioning regimen. Post-HSCT hemoglobinuria was associated with early (48–72 hours) post-HSCT AKI. Graft type (BMT+Cord) was associated with AKI among patients with hemoglobinuria. AKI in patients with hemoglobinuria was associated with delayed platelet engraftment and delayed WBC engraftment but not 100-day mortality.

Conclusion Close monitoring is recommended in this patient group to facilitate a good engraftment outcome.

Introduction
AKI is a frequent complication of hematopoietic stem-cell transplantation (HSCT) and is associated with significant morbidity and mortality (1,2). Patients with post-HSCT AKI are at a higher risk for developing other complications, such as infections (3), acute graft versus host disease, and sinusoidal occlusion syndrome (4,5). Traditionally, post-HSCT AKI is defined as an AKI occurring within 100 days after HSCT (6,7) and the incidence can vary, depending on the type of HSCT, from 10% in autologous transplantation to as high as 73% after myeloablative allogeneic transplantation (8). In one study, early-onset AKI was defined as AKI before engraftment, and the reported incidence was 22% (2). In this study, patients who had undergone a allogeneic SCT with early onset AKI had an overall survival of just 57% at 100 days (2). The risk factors for renal failure reported include conditioning regimen, age (9), peritransplant antibiotic choice (aminoglycoside [10], amphotericin B [11]), radiation dose (12), and preexisting CKD (10), among others. Awareness of the precipitating factors can be key in preventing and improving overall outcomes.

At the time of stem-cell infusion, patients are occasionally noted to have discoloration in the urine from hemoglobinuria. The reasons behind the intravascular hemolysis are manifold. HSC are cryopreserved to maintain viability of the progenitor cells. During freezing and thawing, a significant number of red blood cells (RBCs) undergo lysis and the kidneys are exposed to RBC breakdown products (13). The cryoprotectant, DMSO, is also known to cause RBC cell membrane lysis and further exacerbating the intravascular hemolytic process (14). There are a few old studies that have assessed the risk factors of hemoglobinuria in the early post-HSCT period, which included patients that underwent autologous SCT and it was suggested that higher concentration of erythrocytes in the hematopoietic cell infusion can contribute to hemoglobinuria and AKI (15,16). Other causes such as underlying disease (e.g., chronic lymphocytic leukemia, paroxysmal nocturnal hemoglobinuria) (17), fludarabine-based conditioning regimens (18,19), and allogeneic HSCT (20) may be associated with hemolysis, but they have not been assessed as risk factors of hemoglobinuria in the setting of HSCT. The
mechanism of nephrotoxicity of these heme proteins may involve intratubular cast formation, decreased renal perfusion, and direct tubular toxicity resulting from, in part, heme-/iron-driven oxidative stress and impaired mitochondrial oxygen consumption (21,22).

Despite the known association, little has been published on hemoglobinuria and AKI after HSCT. We conducted this retrospective study to investigate the relationship between hemoglobinuria and AKI. The primary objective of our study was to assess if hemoglobinuria is a risk factor for early post-HSCT AKI and, if so, to identify risk factors for hemoglobinuria within 24 hours of HSCT. The secondary objectives of this study were to additionally identify risk factors of AKI in patients with post-HSCT hemoglobinuria and assess outcomes (mortality, engraftment, and infection) with AKI as the predictor.

Methods

Patient Selection

This was a retrospective cohort study of adults who underwent HSCT from January 6, 1999 to November 6, 2017. We identified patients whose electronic medical records had documentation from medical staff on the service of new onset red discoloration of urine within 24 hours after stem-cell infusion. For those that underwent multiple transplantations, only the first hematopoietic cell transplant was considered. We included 6039 adults that underwent HSCT during this period (47 with cord blood SCT, 310 with bone marrow transplantation [BMT], and 5682 with peripheral blood SCT [PBSCT]). We also excluded patients that refused consent for review of their records for research purposes. Figure 1 details our study population selection. The Mayo Clinic Institutional Review Board approved the study (Institutional Review Board number 17-007308) under a waiver of informed consent as minimal risk to participants.

Data Collection

We used the Mayo Clinic’s Advanced Cohort Explorer database search tool for data abstraction from the electronic medical records. We extracted data on demographic characteristics, underlying disease, conditioning therapy (fludarabine based versus not), graft type (BMT and cord blood SCT versus PBSCT), ABO mismatch, and transplant type (allogeneic versus autologous). For patients that had hemoglobinuria as demonstrated by red discoloration of urine, we also extracted the volume of infusion, urinalysis (if available within 48 hours of infusion), serum creatinine for the first 5 post-HSCT days, date of death, and date of white blood cell (WBC) and platelet (PLT) engraftment.

We defined gross hemoglobinuria as red discoloration of urine within 24 hours after hematopoietic cell infusion. Once these patients were identified, we also extracted urinalysis data if available within 24–48 hours of red urine discoloration. However, all patients with red discoloration of urine within 24 hours of SCT were included even if a urinalysis was not available after the hematopoietic cell transplant to confirm the presence of heme pigment without RBCs. In the small number of patients with red urine where a urinalysis was available (seven out of 52, 13%), heme pigment was present in the urine, which reinforced our decision to include in the study the patients that did not have a urinalysis available. Early AKI was defined by the Acute Kidney Injury Network criteria (23) as elevation of creatinine ≥0.3 mg/dl within 48 hours of hematopoietic cell infusion. We also classified the stages of AKI on the basis of the Acute Kidney Injury Network criteria ranging from Stage 1 to 3. Neutrophil engraftment after transplantation was defined as first date of three consecutive neutrophil counts ≥0.5×10^9/L for 3 consecutive days. PLT engraftment was defined as the time after transplantation needed to achieve a blood PLT count ≥50×10^9/L for 3 days without transfusion support in the past 7 days.

Statistical Analysis

Continuous variables were reported as mean±SD or median with interquartile ranges (IQR) and categorical variables were expressed as count (percent). P values were derived from the t test or Wilcoxon test for continuous variables and the chi-squared test or Fisher’s exact test for categorical variables as appropriate. We performed logistic regression to predict hemoglobinuria on the basis of demographic data (age, sex), type of transplant (BMT+ Cord versus PBSCT, allogeneic versus autologous), conditioning regimen (fludarabine based), and underlying disease. Variables that were statistically significant (P<0.05) in the univariate analysis were included in multivariable analysis. We also performed univariate analysis with a chi-squared test to assess the association of early post-transplant AKI with hemoglobinuria.

We performed a subgroup analysis of patients with hemoglobinuria. We undertook univariate analysis for prediction of AKI using the following predictors: demographic characteristics, type of transplant, the volume of infusion, conditioning regimen, and underlying disease. We did not perform multivariable analysis because the number of patients with AKI was small (17). JMP 13.0.0 computer software (SAS Institute, Cary, NC, USA) was used for the analysis. P<0.05 was considered statistically significant.

Results

From January 6, 1999 to November 6, 2017, 6039 adults underwent HSCT (47 with cord blood SCT, 310 with BMT,
and 5682 with PBSCT). Of these, 52 (0.9%) patients developed gross hemoglobinuria as evidenced by the report of red discoloration of urine within 24 hours of hematopoietic cell infusion. A urinalysis was performed in seven (13%) out of the 52 patients within 24 hours of urine discoloration, which confirmed the presence of hemoglobinuria with the concurrent absence of hematuria (defined as microscopic red blood cells in urine). Out of the 52 patients, only two had creatinine kinase checked within 24 hours of the red discoloration of urine to rule out rhabdomyolysis and it was not elevated. Out of the 47 patients with cord SCT, there were two that developed hemoglobinuria. Because the number of patients with cord SCT was small compared with the other groups, these patients’ data were combined with those that underwent BMT in the statistical analysis. The baseline characteristics of these patients are reported in Table 1.

When we compared the patients with HSCT that developed hemoglobinuria to those that did not, we found no difference in age, sex, and type of transplant (allogeneic versus autologous). However, there was a higher proportion of patients who received BMT and cord transplant in the hemoglobinuria group compared with peripheral blood SCT recipients (42% versus 6% respectively,  P<0.0001). Also, the proportion of patients that received fludarabine-based conditioning regimen was higher in the hemoglobinuria group (17% versus 7%,  P=0.04). Finally, the underlying disease leading to hematopoietic cell transplant was also statistically different between the two groups, with higher percentage of patients with lymphoma in patients that developed hemoglobinuria after transplantation (56% versus 28% others,  P<0.001).

### Risk Factors of Hemoglobinuria in HSCT

Univariate analysis showed graft type (BMT and Cord versus PBSCT), underlying disease (acute leukemia, lymphoma), and fludarabine-based regimen as statistically significant predictors of hemoglobinuria (Table 2). When included in the multivariable logistic regression analysis, we identified graft type (odds ratio [OR], 8.6; 95% confidence interval [95% CI], 4.78 to 15.50) and lymphoma (OR, 8.7; 95% CI, 2.59 to 29.34) (Table 2) as statistically significant predictors of hemoglobinuria. Of the 14 patients that underwent allogeneic HSCT and had hemoglobinuria, only one had a transplant with ABO mismatch (bidirectional). Hence, ABO incompatibility was not included in the analysis.

### Association of Post-HSCT Hemoglobinuria with Early Post-HSCT AKI

Out of the 6039 patients that were included in the study, 393 had early post-HSCT AKI. Of those with AKI, 17 patients had hemoglobinuria. Hemoglobinuria was associated with seven-fold higher odds of AKI compared with those without hemoglobinuria (OR, 7.1; 95% CI, 3.9 to 12.9,  P<0.0001). Stages of AKI noted in patients who were hemoglobinuric versus nonhemoglobinuric are Stage I AKI: 10 out of 17 (59%) versus 361 out of 376 (96%), Stage II AKI: one out of 17 (6%) versus 11 out of 376 (3%), and Stage III AKI: six out of 17 (35%) versus four out of 376 (1%). Stage III AKI when compared with Stage I and II AKI together in patients who were hemoglobinuric versus nonhemoglobinuric was statistically significant: Stage III AKI: six out of 17 (35%) versus four out of 376 (1%), Stage I and II AKI: 11 out of 17 (65%) versus 372 out of 376 (99%),  P<0.0001.

### Risk Factors of AKI among Patients with Post-HSCT Hemoglobinuria

We performed subgroup analysis in patients with hemoglobinuria. The baseline characteristics of these patients are presented in Table 3. There was a higher proportion of patients who are hemoglobinuric and received BMT and cord transplant versus peripheral blood stem cells in the early post-transplant AKI group, compared with those who did not develop AKI (64% versus 31%,  P=0.02). Otherwise, there was no statistical difference with respect to age, sex, transplant type (allogeneic versus autologous), serum bicarbonate levels within 24 hours of transplant, underlying hematologic disease, conditioning regimen, or volume of infusion. In univariate analysis, graft type (BMT and Cord versus PBSCT) was a statistically significant predictor of early post-transplant AKI among patients who were hemoglobinuric (OR, 4.0; 95% CI, 1.17 to 13) (Table 4).

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### Table 1. Baseline characteristics of patients who underwent hematopoietic stem cell transplantation in our cohort between 2009–2017

| Characteristics                  | Hemoglobinuria n=52 | No Hemoglobinuria n=5987 | P Value |
|----------------------------------|---------------------|--------------------------|---------|
| **Demographics**                 |                     |                          |         |
| Age, yr                          | 58 (44–65)          | 58 (50–64)               | 0.35    |
| Sex, F                           | 27 (52%)            | 2388 (40%)               | 0.08    |
| Graft type (BM+Cord)             | 22 (42%)            | 335 (6%)                 | <0.0001 |
| Transplant type (allogenic)      | 14 (27%)            | 1027 (17%)               | 0.08    |
| **Disease**                      |                     |                          | <0.001  |
| Acute leukemia                   | 7 (13%)             | 644 (10%)                |         |
| Lymphoma                         | 29 (56%)            | 1656 (28%)               |         |
| Myeloma                          | 3 (6%)              | 2367 (40%)               |         |
| Other                            | 13 (25%)            | 1299 (22%)               |         |
| **Conditioning regimen**         |                     |                          |         |
| Fludarabine-based regimen        | 9 (17%)             | 416 (7%)                 | 0.01    |

Values reported as median (interquartile range) or n (%) for continuous or categorical variables, respectively. F, female; BM, bone marrow.
Association of AKI with Post-HSCT Course among Patients with Hemoglobinuria

WBC, PLT engraftment, and 100-day mortality were evaluated between the two groups of patients with post-HSCT hemoglobinuria (AKI versus non-AKI). At 30 days, WBC engraftment was noted in 12 out of 52 (71%) patients who were hemoglobinuric with AKI versus 33 out of 35 (94%) of patients who were hemoglobinuric without AKI (\(P=0.02\)). During the same time frame, PLT engraftment was noted in eight out of 17 (47%) patients who were hemoglobinuric with AKI versus 27 out of 35 (77%) of patients who were hemoglobinuric without AKI (\(P=0.03\)). Mortality in the first 100 days was higher among patients who were hemoglobinuric with AKI, three out of 17 (17%), versus patients who were hemoglobinuric without AKI, one out of 35 (3%), but this difference was not statistically significant (\(P=0.07\)).

Discussion

In this large cohort of patients that underwent HSCT over a period of 18 years, we found that a patient’s graft type, fludarabine-based conditioning regimen, and underlying hematologic disease (lymphoma) are risk factors associated with hemoglobinuria in the early (within 24 hours) post-HSCT period. Graft type (BMT+Cord) showed the strongest association with hemoglobinuria among patients undergoing HSCT, which also persisted in multivariable analysis, and it was identified as a statistically significant risk factor for early post-HSCT AKI among patients with hemoglobinuria. Post-HSCT hemoglobinuria was noted in 0.9% of the patients in this cohort, which makes it a rare complication of HSCT. However, hemoglobinuria was associated with a higher rate of early AKI (within 48 hours of HSCT), and a statistically significant higher stage (Stage III versus Stage I and II) of AKI as compared to patients

| Table 2. Risk factors for hemoglobinuria in patients who underwent hematopoietic stem cell transplant |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Characteristics                          | Univariate Analysis | Multivariable Analysis |
|                                            | Odds Ratio (95% Confidence Interval) | P Value | Odds Ratio (95% Confidence Interval) | P Value |
| Demographics                             |                      |       |                                |       |
| Age, yr                                  | 0.99 (0.97 to 1.01)  | 0.24  |                                |       |
| Sex, F                                   | 1.63 (0.94 to 2.81)  | 0.08  |                                |       |
| Graft type (BM+Cord)                     | 12.37 (7.06 to 21.68)| <0.0001 | 8.6 (4.78 to 15.50) | <0.0001 |
| Transplant type (allogeneic)             | 1.77 (0.96 to 3.3)   | 0.07  |                                |       |
| Disease                                  |                        |       |                                |       |
| Acute leukemia                           | 8.57 (2.21 to 33.25)  | 0.002 | 2.48 (0.55 to 11.12) | 0.24  |
| Lymphoma                                 | 13.81 (4.20 to 45.43) | <0.0001 | 8.9 (2.66 to 30.01) | 0.0004 |
| Myeloma                                  | 1.00 (reference)     | 1.00  |                                |       |
| Other                                    | 7.89 (2.24 to 27.7)  | 0.001 | 3.99 (1.07 to 14.84) | 0.04  |
| Conditioning regimen                     |                        |       |                                |       |
| Fludarabine-based regimen                | 2.8 (1.35 to 5.79)   | 0.005 | 2.39 (0.97 to 5.8)  | 0.06  |

F, female; BM, bone marrow.

| Table 3. Baseline characteristics of patients with hemoglobinuria |
|---------------------------------------------------------------|-----------------|-----------------|-----------------|
| Characteristics                          | AKI n=17 | No AKI n=35 | P Value |
| Demographics                             |            |               |       |
| Age, yr                                  | 58 (29–63) | 59 (36–65) | 0.72  |
| Sex, F                                   | 6 (41)    | 20 (57)     | 0.28  |
| Graft type (BM+Cord)                     | 11 (64)   | 11 (31)     | 0.02  |
| Transplant type (allogeneic)             | 7 (41)    | 7 (20)      | 0.11  |
| Bicarbonate levels                       | 23 (21–26)| 25 (22–26)  | 0.67  |
| Additional bicarb administration         | 6 (35)    | 8 (23)      | 0.35  |
| Disease                                  |            |               | P=0.98 |
| Acute leukemia                           | 3 (17.65) | 5 (14.29)  |       |
| Lymphoma                                 | 9 (53)    | 20 (57.14) |       |
| Myeloma                                  | 1 (6)     | 2 (6)       |       |
| Other                                    | 3 (23)    | 8 (23)      |       |
| Conditioning regimen                     |            |               |       |
| Fludarabine-based regimen                | 5 (39)    | 5 (14)      | 0.20  |
| Volume infusion (ml)                     | 398 (319–522)| 529 (370–697)| 0.55  |

Values reported as median (interquartile range) or n (%) for continuous or categorical variables respectively. F, female; BM, bone marrow.
without hemoglobinuria. In patients who were hemoglobinuric, AKI was associated with a decreased 30-day PLT and neutrophil engraftment when compared with non-AKI group, but we did not find statistical association of hemoglobinuric AKI with 100-day mortality.

Hemoglobinuric AKI involves three major pathways: renal vasoconstriction, direct tubular toxicity, and intratubular cast formation. After uptake of hemoglobin by the proximal tubules via the megalin/cubilin receptors, free heme is released from intracellular hemoglobin. Additionally, heme is also released intracellularly in injured proximal tubules from intracellular heme proteins, especially CYP 450 enzymes, because these heme proteins are among those with the weakest union between the heme and protein moieties (24). Heme is cytotoxic because of its lipophilicity, its capacity to denature cellular proteins, and its prooxidant and proinflammatory actions (21,22,25).

Defining patients at risk for hemoglobinuria is necessary in preventing AKI in patients with high-risk HSCT. Our finding of BMT as a risk factor for hemoglobinuria has been described in the literature. Alessandrino et al. in their study of 126 patients found that all those who underwent BMT developed hemoglobinuria as compared with none in the PBSCT group (16). They attributed it to the presence of a higher concentration of RBCs in patients’ bone marrow samples. ABO incompatibility is another potential consideration because alloimmune hemolysis in major ABO incompatibility may originate from RBCs present in the infused sample (26). In contrast to the 14 patients in our study that underwent allogeneic HSCT and had early hemoglobinuria, only one had a transplant with ABO mismatch (bidirectional). At our institution, we routinely perform RBC reduction in all grafts involving major ABO incompatibility, which may have mitigated this risk of hemolysis. Hemolysis in the setting of minor red cell incompatibility typically manifests about 7–14 days post-transplant, whereas autoimmune hemolysis occurs 41–170 days post-HSCT (27). Autoimmune hemolysis may occur in chronic lymphocytic leukemia (17) and non-Hodgkin’s lymphoma (28,29). Our study found both acute leukemia and lymphoma to be a risk factor for post-transplant hemoglobinuria in univariate analysis, although the association with acute leukemia did not persist in the multivariable analysis. Fludarabine-based conditioning regimens may lead to autoimmune hemolysis (18,19), which was also found to be associated with hemoglobinuria in univariate analysis but not in multivariable analysis in our study.

In our study, patients that developed hemoglobinuria had a seven-fold higher risk of developing an AKI event. Hypovolemia would increase this risk, and volume expansion may mitigate or even prevent hemoglobinuria-induced AKI (30). The rationale for volume expansion is that increased urinary flow minimizes the contact time of the heme proteins with the tubular cells and prevents intratubular cast formation. Urine alkalization may increase the solubility of heme protein and prevent AKI in rat models with myoglobin-induced AKI (31). In our institution, all patients receive intravenous bicarbonate infusion, given as 0.45% saline with 75 mEq of sodium bicarbonate shortly before and after the transplant. Our data also demonstrated there was no difference in the serum bicarbonate levels between patients with hemoglobinuria who developed AKI compared with those who did not. Urinalysis was available in only seven (13%) out of the 52 patients that developed hemoglobinuria, and thus we cannot reach any conclusions about the effects of bicarbonate administration in these patients and whether it achieved urine alkalization.

We also found that among patients with hemoglobinuria, development of AKI was associated with decreased 30-day PLT and neutrophil engraftment when compared with non-AKI group. The delay in PLT and neutrophil engraftment in this subgroup of patients may result from AKI-induced inflammatory cytokines (32) that have been shown to affect post-HSCT PLT engraftment (33). Delayed PLT engraftment is associated with increased incidence of chronic graft versus host disease and decreased survival in the post-HSCT period (34), although the underlying mechanism is not clear. Several studies also report AKI post-HSCT (within the first 100 days) as being associated with increased mortality (35–37). This association was even stronger when the AKI episode occurred in the pre-engraftment period (2). Interestingly, we did not see

### Table 4. Risk factors for acute kidney injury among patients with hemoglobinuria

| Risk Factors                          | Univariate Analysis |  
|--------------------------------------|---------------------|
|                                      | Odds Ratio (95% Confidence Interval) | P Value |
| **Demographics**                     |                     |        |
| Age, yr                              | 1.00 (0.96 to 1.04) | 0.73   |
| Sex, F                               | 0.5 (0.16 to 1.7)   | 0.28   |
| Graft type (BM+Cord)                 | 4.0 (1.17 to 13)    | 0.03   |
| Transplant type (allogeneic)         | 2.8 (0.78 to 9.99)  | 0.11   |
| Bicarbonate per 1 mmol/L             | 0.95 (0.79 to 1.15) | 0.62   |
| Additional bicarb administration     | 1.84 (0.51 to 6.5)  | 0.35   |
| **Disease**                          |                     |        |
| Acute leukemia                       | 1.2 (0.07 to 19.63) | 0.90   |
| Lymphoma                             | 0.9 (0.07 to 11.25) | 0.93   |
| Myeloma                              | 1.0 (reference)     |        |
| Other                                | 1 (0.07 to 14.64)   | 1.00   |
| Fludarabine-based regimen            | 2.4 (0.61 to 10.22) | 0.20   |
| Volume infusion (ml)                 | 0.999 (0.996 to 1.002) | 0.52   |

F, female; BM, bone marrow.
statistically significant association with 100-day mortality in our patient group. This last finding was rather unusual as it is well established that AKI is associated with increased mortality in multiple clinical settings, including patients that undergo HSCT (1,2). A possible explanation for this observation is that in only seven out of the 17 patients with hemoglobinuria exhibited Stage II or III AKI, and previous studies demonstrate that increased mortality generally occurs in Stage II and III AKI in patients undergoing HSCT (1). An additional possibility is that heme proteins and heme potentially induce the cytoprotective gene, heme oxygenase-1 (HO-1), in the kidney and other organs. Such induction of HO-1 reduces the severity of AKI and mortality in preclinical models of heme protein-, ischemic-, and sepsis-related AKI (22,38). We speculate that such induction of HO-1 may prevent the increased mortality that may be otherwise observed in our patient population.

As a retrospective single-center cross-sectional study, there are certain limitations. First, we relied on the provider documentation of urine discoloration to assess hemoglobinuria because a urinalysis was available in only seven out of the 52 patients with post-transplant red urine discoloration. Therefore, it is possible we may have missed some patients with hemoglobinuria, or some patients with red discoloration of urine did not have hemoglobinuria. For this reason, we performed a rigorous chart review and we only included the patients where, according to the documentation of the treating clinician, the red discoloration of urine was noted immediately after the infusion of stem cells and it was not mentioned in the chart of the patient before the infusion of stem cells. Second, we were able to evaluate a relatively limited number of risk factors (e.g., graft type, underlying disease, and conditioning regimen), and were unable to assess certain variables such as infusion volume. The volume of HSCT infusion given is proportional to the amount of DMSO contained, which can also result in hemolysis (13). Collection of these data in the whole cohort of patients was not feasible, and for this reason, it was assessed as a predictor of AKI in the subgroup of patients that developed hemoglobinuria.

So how can we prevent the development of hemoglobinuria-related AKI in patients with HSCT? Maintaining adequate volume expansion is obvious, but with our understanding of the underlying mechanism, we could consider the use of an antioxidant/cytoprotective agent such as deferoxamine. Deferoxamine is an iron chelation agent that is administered to patients with transfusion-related iron overload (39). Preclinical studies demonstrate a protective effect in myohemoglobinuric AKI by decreasing the iron-dependent cytoxicity in renal tubules (40,41). The efficacy of deferoxamine to prevent hemoglobinuria-induced AKI should be assessed in a prospective study that should ideally include patients undergoing HSCT infusion with risk factors of early post-transplant hemoglobinuria as identified in this study.

In conclusion, in this large cohort of patients undergoing HSCT spanning 18 years, we found post-HSCT hemoglobinuria was associated with early post-HSCT AKI and delayed PLT and neutrophil engraftment. We found post-HSCT hemoglobinuria was associated with graft type (BMT and Cord), conditioning regimen (fludarabine based), and underlying hematologic disease (lymphoma). Also, early post-HSCT AKI among these patients who were hemoglobinuric was associated with graft type (BMT and Cord) as well and these patients will need utmost care in preventing a renal event. With the deeper understanding of the mechanism of heme-mediated damage, further investigation should focus on extrapolating a more targeted preventative measure.

Disclosures
K. Nath reports being a scientific advisor or member of the Journal of the American Society of Nephrology and Mayo Clinic Proceedings. N. Leung reports consultancy agreements with AbbVie, Lilly, and Omeros; reports having an ownership interest in Checkpoint Therapeutics; and reports receiving research funding from Alnylam and Omeros; reports being a scientific advisor or member of the Journal of Nephrology. All remaining authors have nothing to disclose.

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Author Contributions
P. Kompotiatis was responsible for data curation, formal analysis, and wrote the original draft; N. Leung conceptualized the study; and all authors reviewed and edited the manuscript.

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