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Oxygenation index predicts mortality in pediatric stem cell transplant recipients requiring mechanical ventilation

Rowan CM, Hege KM, Speicher RH, Goodman M, Perkins SM, Slaven JE, Westenkirchner DF, Haut PR, Nitu ME. Oxygenation index predicts mortality in pediatric stem cell transplant recipients requiring mechanical ventilation.

Abstract: The mortality in the ICU for pediatric HSCT recipients remains high. Early pulmonary complications continue to be an obstacle to the survival. We hypothesize OI is a predictor for mortality in critically ill pediatric HSCT recipients. Retrospective review of pediatric HSCT recipients between 2002 and 2010 who required intensive care during the same hospital admission as their transplant. Twenty-eight patients accounted for 31 ICU admissions. Twenty-six (84%) admissions required mechanical ventilation. Ten (38%) mechanically ventilated admissions were placed on HFOV. Mortality of those mechanically ventilated was 70%. An OI ≥ 20 at any point during ventilation was associated with 94% mortality, while an OI ≥ 25 had 100% mortality. There was a significant association between maximum OI at any point during mechanical ventilation and ICU mortality, with the odds of dying increasing by 13% for each unit increase of max OI (OR = 1.13, 95% CI = 1.01–1.26, p = 0.03). An OI of 20 had a sensitivity of 0.89 and specificity of 0.83 for predicting mortality. OI has a strong association with ICU mortality among pediatric stem cell recipients.

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While the success of pediatric HSCT continues to improve, the mortality of these patients in the ICU remains high, especially if these patients require mechanical ventilation. A meta-regression analysis published in 2008 by van Gestel et al. (1) found an overall ICU mortality rate of 60%. This rate increased to 71% if mechanical ventilation was needed. HSCT recipients who require mechanical ventilation have significantly worse outcomes then non-HSCT patients (2). Another study published in the same year found a mortality rate of 42% for HSCT recipients (3). While this value is still lower than that noted for non-HSCT patients, it is by far the best reported survival rate reported in the literature.

As pediatric critical care continues to advance for these patients, the survival rate has increased. Previous recommendations to potentially limit care in some of the pediatric HSCT recipients (4)

Abbreviations: AML, acute myeloid leukemia; ARDS, acute respiratory distress syndrome; FEV1, forced expiratory volume in one second; HFOV, high frequency oscillatory ventilation; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; MAP, mean airway pressure; OI, oxygenation index; PEEP, positive end expiratory pressure; PICU, pediatric intensive care unit; ROC, receiver operating characteristic.

may no longer apply in today's PICU environment where survival rates continue to improve. However, despite improvements from previously reported fatality rates of close to 100%, pulmonary complications have continued to be an obstacle to the success of HSCT. Clinical decisions and family conversations regarding ongoing care may be aided by better tools to predict mortality.

Previous studies have looked for prognostic factors to predict mortality in pediatric HSCT recipients. One found that earlier requirement of critical care, delay before ICU admission, lack of engraftment, hemorrhage, tachypnea, hypoxemia, renal impairment, coagulopathy, mechanical ventilation, and increasing number of organ failure all are risk factors for mortality (5). Numerous studies have shown that pulmonary complications are a significant risk for death (1, 3, 5–7). Cyclosporine/methotrexate for graft versus host disease prophylaxis, a lower pretransplant FEV1, and allogeneic stem cell transplantation have been found to be associated with the development of severe pulmonary complications (8). Scales et al. (9) found that both mechanical ventilation and hemodialysis were independent predictors for death, but no combination of factors could predict 100% mortality. While it seems that pulmonary disease increases the risk of death, tools to identify which patients are less likely to survive have not been found.

OI is a calculated number used by some intensivists to determine the severity of oxygenation failure. It takes into account both the FiO_2 and the MAP necessary to achieve the patient's PaO_2 and is calculated as $OI = MAP \times FiO_2 \times 100/PaO_2$. In 2000, Simma et al. (10) showed that infants on HFOV who survived had a lower OI. Monchi et al. (11) also found OI to be an independent predictor of mortality in adults with ARDS. Trachsel et al. looked at OI as a predictor of mortality in all pediatric patients with acute hypoxemic respiratory failure. They found that a higher OI was associated with a higher mortality, but that there was no OI threshold beyond which death was inevitable (12). We hypothesize that OI is a predictor for mortality in critically ill pediatric HSCT recipients requiring mechanical ventilation.

Patients and methods

A retrospective, single-center study was completed looking at maximum daily OIs in intubated HSCT recipients. We began with a consecutive review of pediatric HSCT recipients at Riley Hospital for Children between January 2002 and July 2009 and then focused on those who required pediatric intensive care during the same hospital admission as their HSCT. Our tertiary care center has 32 PICU beds with approximately 1600 PICU admissions per year. All of these patients were managed by pediatric intensivists with close consultation by pediatric HSCT specialists.

Data were collected from either the electronic medical record or microfilm. The primary end-point was survival to PICU discharge. Patient demographic information, pretransplant data, laboratory values, and respiratory care parameters were collected and used to calculate the OI. The following calculation was used: $OI = ([MAP \times FiO_2]/PaO_2) \times 100$. The maximum daily OI was then recorded.

Age, gender, donor type, source of cells for HSCT, length of time post-transplant at PICU admission, PICU length of stay, duration of mechanical ventilation, mechanical ventilatory parameters, use of nitric oxide, use of HFOV, and mortality were also collected.

Institutional review board reviewed and approved this study.

Statistical analysis

Descriptive statistics are given by means (s.d.) for continuous variables and number (percent) for categorical variables. To determine differences between groups (PICU transplants vs. non-PICU transplants and survivors vs. non-survivors), Student's *t*-tests were used for continuous variables, and Fisher's exact tests, because of some small cell sizes, were used for categorical variables. Logistic regression analyses were conducted to examine whether maximum OI was predictive of death in the PICU. ROC curves were used to further describe the predictive value. All analytic assumptions were checked to ensure proper outcome reporting. Associations were considered significant at a p-value of < 0.05.

Results

Two hundred and eighteen stem cell transplantations were completed from January 2002 to July 2009. One transplant was excluded because of a missing chart. Twenty-eight patients accounted for 31 PICU admissions, giving a PICU admission rate of 14.2%.

Of all PICU admissions, 42% survived to PICU discharge. Of the patients requiring mechanical ventilation, the survival rate dropped to 31%. Of all patients admitted to the PICU, only six (21.4%) were alive six months post-transplant.

All of the patients that were included in the study were admitted to the PICU during the same admission as their HSCT. Twenty-six of the 31 PICU admissions required mechanical ventilation. We focused on the patients with requiring mechanical ventilation for the remainder of the study. Twenty-four of the patients were intubated for respiratory failure. One patient was intubated electively for pain control, while another was intubated for seizures. Table 1 compares patient demographics of those admitted with the PICU that required mechanical ventilation with those that did not. Demographics comparing survivors with non-survivors for

Table 1. Patient demographics comparing those that required mechanical ventilation with those who did not

	Mechanical ventilation (n = 26)	No mechanical ventilation (n = 5)	p-Value
Age in years (s.d.)	7.50 (6.70)	6.33 (6.83)	0.72
Gender (%)			
Female	14 (54)	2 (40)	0.65
Male	12 (46)	3 (60)	
Diagnosis (%)			
AML	10 (38)	2 (40)	0.19
Acute lymphoblastic leukemia	6 (23)	1 (20)	
Chronic myelogenous leukemia	0 (0)	1 (20)	
Hemophagocytic lymphohistiocytosis	3 (12)	0 (0)	
Retinoblastoma	1 (4)	0 (0)	
Neuroblastoma	0 (0)	1 (20)	
Pineoblastoma	1 (4)	0 (0)	
Bone marrow failure	1 (4)	0 (0)	
Hyper-IgM	1 (4)	0 (0)	
Metabolic disorders	3 (12)	0 (0)	
Donor type (%)			
Allogeneic	24 (92)	4 (80)	0.42
Autologous	2 (8)	1 (20)	
Stem cell source (%)			
Bone marrow	12 (46)	1 (20)	0.25
Cord blood	11 (42)	2 (40)	
Peripheral blood	3 (12)	2 (40)	

mechanically ventilated patients are listed in Table 2. The majority of the patients received a stem cell transplant for AML, although there were many different diagnoses. There was no statistical difference between survivors and non-survivors with respect to age at transplant, diagnosis leading to transplant, source of stem cells received, or day post-transplant at PICU admission. There were slightly more females in the non-survivor group, but this did not reach statistical significance. There was also a trend toward longer length of PICU stay in the non-survivors.

The survivors and non-survivors were ventilated in a similar fashion. Duration of intubation and tidal volume did not differ significantly between the two groups. There did seem to be a trend toward higher maximum PEEP in the non-survivor group, but this did not reach statistical significance. None of the survivors received inhaled nitric oxide, although inhaled nitric oxide data were missing for two of the survivors. Table 3 compares the ventilation parameters of the survivors with non-survivors.

Sixteen (89%) of the 18 patients who died in the PICU had a maximum OI of ≥20. An OI ≥ 20 at any point during ventilation in our study population was associated with 94% mortality, while an OI ≥ 25 was associated with 100% mortality. There was a significant association between maximum OI at any point during mechanical ventilation and ICU mortality. For every increase in the maximum OI by 1, the odds

Table 2. Patient demographics for mechanically ventilated admissions (n = 26)

	Survivor (n = 8)	Non-survivor (n = 18)	p-Value
Age at transplant (yr)	5.78 (6.19)	8.74 (6.87)	0.312
Length of stay in PICU (days)	20.50 (15.46)	37.00 (31.27)	0.174
Post-transplant day at PICU admit	31.00 (35.22)	32.11 (28.40)	0.933
Gender			
Female	2 (25)	12 (67)	0.090
Male	6 (75)	6 (33)	
Diagnosis			
AML	3 (37)	7 (39)	0.963
Acute lymphoblastic leukemia	2 (25)	4 (22)	
Congenital thrombocytopenia	1 (13)	0 (0)	
Hemophagocytic lymphohystiocytosis	1 (13)	2 (11)	
Hyper-IgM	0 (0)	1 (6)	
Hurler's disease	1 (13)	1 (6)	
Wolman disease	0 (0)	1 (6)	
Pineoblastoma	0 (0)	1 (6)	
Retinoblastoma	0 (0)	1 (6)	
Source of stem cells			
Bone marrow	4 (50)	8 (44)	0.704
Cord blood	4 (50)	7 (39)	
Peripheral blood	0 (0)	3 (17)	
Reason for PICU admission			
Respiratory failure	7	10	0.246
Sepsis/respiratory failure	0	4	
Renal replacement therapy	0	2	
Altered mental status	0	1	
Gastrointestinal bleed	0	1	
Seizure	1	0	

Statistics for mechanically ventilated patient demographics (n = 26). Values are means (s.d.) for continuous variables and frequency (%) for categorical variables; p-value for continuous variables come from Student's *t*-test and for categorical variables come from Fisher's exact test.

Table 3. Ventilation data comparing survivors with non-survivors

	Survivor (n = 8)	Non-survivor (n = 18)	p-Value
Duration of intubation (days)	17.63 (12.66)	29.94 (29.38)	0.167
Tidal volume in mL/kg	8.07 (1.02)	8.32 (1.55)	0.698
Max peep in cm H_2O	8.57 (3.95)	11.71 (4.25)	0.109
Inhaled nitric oxide*			
Yes	0 (0)	6 (33)	0.277
No	6 (100)	12 (67)	
Max OI	12.36 (6.74)	50.52 (29.85)	< 0.001
Min PaO_2:FiO_2	119.20 (36.80)	81.92 (78.24)	0.277

Statistics for mechanically ventilated patient demographics (n = 26). Values are means (s.d.) for continuous variables and frequency (%) for categorical variables; p-value for continuous variables come from Student's *t*-test and for categorical variables come from Fisher's exact test.
*Inhaled nitric oxide use was missing from two of the survivors.

of dying increase by 13% (OR = 1.13, 95% CI = 1.01–1.26, p = 0.03). An OI of 20 at any point during mechanical ventilation had a sensitivity of 0.89 and a specificity of 0.83 for predicting mortality. Fig. 1 demonstrates the ROC for maximum OI.

We found that the OI was on average higher in those that died than in those that survived. Table 3 shows that the average peak OI during the course of mechanical ventilation was significantly higher in the non-survivors. It was not just the peak OI that was higher. Even early on in the ventilator course (i.e., the first week of ventilation), the mean OI was persistently higher in the non-survivors. See Fig. 2.

Of note, ten patients were placed on HFOV, and none survived to PICU discharge. The decision to start HFOV in patients was at the attending pediatric intensivist's discretion. The average OI at the start of HFOV was 41.4 ± 19.5. The average length of time on HFOV was 10.9 ± 9.0 days.

Discussion

While survival of the pediatric HSCT recipient in the PICU continues to improve, the mortality rate is still high. Predictors of mortality may help better guide care, allow for decisions on appropriate medical interventions, and aid in conversations with patients and families. This study shows peak OI to be a predictor of mortality for HSCT recipients requiring mechanical ventilation. While the study population is small, the results do reach statistical significance.

The ROC curve allows practioners to see the sensitivity and specificity for different values of maximum OI. As each practitioner may have a different threshold for what OI is clinically tolerable, this ROC curve can be useful on an individual level. From this curve, one can also see that by the time the OI reach approximately 35, the specificity for mortality is 100%.

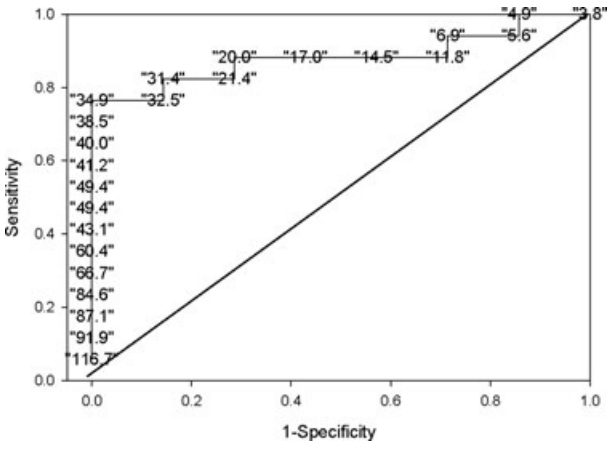

Fig. 1. The area under this curve was found to be 0.91.

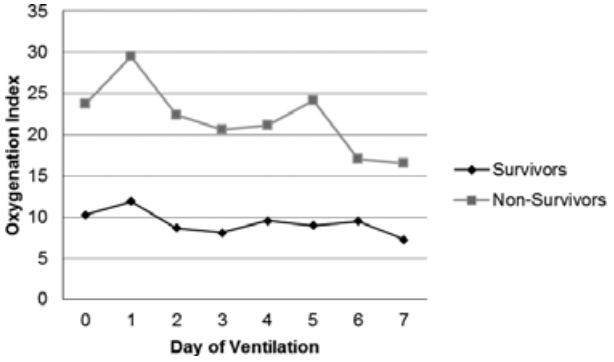

Fig. 2. Comparison of mean OI in survivors and non-survivors during the first week of mechanical ventilation. Note the persistent difference in mean daily OI in the first week of mechanical ventilation between the survivors and non-survivors.

OI is an advantageous tool to help predict mortality because it is an existing measurement that is frequently calculated in patients with hypoxemic respiratory failure. It does not require any expensive equipment or additional monitoring than what is already in place for the routine care of the intubated patient with respiratory failure.

This study falls in line with other studies that have illustrated the predictive power of OI. A multicenter retrospective study found that an OI greater than 28, in the immunocompromised patient, after 24 h on HFOV indicated a 70% probability of death. This probability of death increased to 90% if the OI was greater than 58 after 24 h (13). Our study seems to demonstrate an even stronger association between maximum OI and death; however, we looked at OI at any point during mechanical ventilation. We did not look at OI during a specific time period, so it is unclear from our study if it can be utilized as an early predictor of mortality. The average time before death to reach an OI of 20 was day 22 of mechanical ventilation, but this was highly variable.

Of the 217 HSCT recipients in our study, patients were transplanted for a variety of underlying disease, with AML being the most common. It is not surprising that AML, hemophagocytic lymphohistiocytosis, and metabolic disorders required more critical care as these patients often fare worse because of the aggressiveness of prior chemotherapy and active disease at transplant. Our PICU admission rate seems to be in line with a pediatric stem cell and critical

care review carried out by Gale, which also found an PICU admission rate of 14% (14).

We focused our study on patients that were admitted to the PICU requiring mechanical ventilation during the same admission as their HSCT. This naturally raises the question of how this population compares with HSCT patients who have already been discharged from their HSCT admission and then readmitted for various reasons. One possibility is that our population was more critically ill because of early post-transplant complications, such as lack of engraftment, graft versus host disease, and veno-occlusive disease. It is possible that the PICU complications our patients experienced were more directly related to their HSCT.

Owing to the retrospective nature of the study, mechanical ventilation management was not standardized. However, the average ventilation parameters comparing survivors with non-survivors seem to exhibit an acceptable approach to ventilation in both groups. All the parameters fall into the guidelines previously recommended by the acute respiratory distress syndrome protocol (15). Also secondary to the retrospective nature of the study, a few data points were missing from the data set. Nitric oxide data on two of the surviving patients could not be located. Within the data that were available, none of the survivors received nitric oxide; however, we cannot say with total confidence that this was the case for all survivors. A third limitation with our study is that not all patients had an arterial catheter the entire length of PICU stay. Therefore, a daily PaO_2 was not available for these patients to calculate an OI. While this is problematic with doing an accurate comparison, it is reasonable to assume that patients who did not have arterial lines placed likely did not experience severe oxygenation failure. It is common practice at our PICU to place arterial lines for better monitoring of hypoxemia in patients that experience severe oxygenation failure. This limitation was partially overcome by using the maximum OI value across the study time frame.

Patients who required HFOV had 100% mortality. This striking high mortality raises the concern that possibly we are not employing HFOV appropriately in this particular patient population. The use of HFOV was left to the discretion of the attending pediatric intensivist in charge of the patient's care. Adjustments to HFOV were not standardized as this was a retrospective study. Our average max OI on the day that HFOV was started was 41.4. This high initial OI may indicate that earlier initiation of HFOV may be indicated and potentially could lead to improved outcomes. It is obvious that further investigation into this particular area is warranted. A prospective, randomized controlled study would help better answer this question.

Conclusion

Mortality among mechanically ventilated stem cell transplant recipients remains high. OI has a strong association with PICU mortality among pediatric stem cell recipients with >20 being associated with a 94% mortality and >25 associated with 100% mortality. We also found that for every increase in the maximum OI by 1, the odds of dying increase by 13%. Theses predictors of mortality may better guide care and counseling to families. As PICU management strategies continue to evolve, further investigations are warranted into the timing of treatment and support of this unique patient population, especially in the use of HFOV, which proved universally fatal in this study.

Conflict of interest

There was no financial support provided for this study.

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