

1 **TITLE:** Critical Illness Risk and Long-Term Outcomes Following Intensive Care in Pediatric
2 Hematopoietic Cell Transplant Recipients

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69 **ABSTRACT**

70 **Background:** Allogeneic hematopoietic cell transplantation (HCT) can be complicated by the
71 development of organ toxicity and infection necessitating intensive care. Risk factors for intensive care
72 admission are unclear due to heterogeneity across centers, and long-term outcome data after intensive
73 care are sparse due to a historical paucity of survivors.

74 **Methods:** The Center for International Blood and Marrow Transplant Research (CIBMTR) was queried
75 to identify patients age ≤ 21 years who underwent a 1st allogeneic HCT between 2008-2014 in the United
76 States or Canada. Records were cross-referenced with the Virtual Pediatric Systems pediatric ICU
77 database to identify intensive care admissions. CIBMTR follow-up data were collected through the year
78 2020.

79 **Results:** We identified 6,995 pediatric HCT patients from 69 HCT centers, of whom 1,067 required post-
80 HCT intensive care. The cumulative incidence of PICU admission was 8.3% at day +100, 12.8% at 1
81 year, and 15.3% at 5 years post HCT. PICU admission was linked to younger age, lower median zip code
82 income, Black or multiracial background, pre-transplant organ toxicity, pre-transplant CMV
83 seropositivity, use of umbilical cord blood and/or HLA-mismatched allografts, and the development of
84 post-HCT graft-versus-host disease or malignancy relapse. Among PICU patients, survival to ICU
85 discharge was 85.7% but more than half of ICU survivors were readmitted to a PICU during the study
86 interval. Overall survival from the time of 1st PICU admission was 52.5% at 1 year and 42.6% at 5 years.
87 Long-term post-ICU survival was worse among patients with malignant disease (particularly if relapsed),
88 as well as those with poor pre-transplant organ function and alloreactivity risk-factors. In a landmark
89 analysis of all 1-year HCT survivors, those who required intensive care in the first year had 10% lower
90 survival at 5 years (77.1% vs. 87.0%, $p < 0.001$) and developed new dialysis-dependent renal failure at a
91 greater rate ($p < 0.001$).

92 **Conclusions:** Intensive care management is common in pediatric HCT patients. Survival to ICU
93 discharge is high, but ongoing complications necessitate recurrent ICU admission and lead to a poor 1-

94 year outcome in many patients. Together, these data suggest an ongoing burden of toxicity in pediatric
95 HCT patients that continues to limit long-term survival.

96 **BACKGROUND**

97 Allogeneic hematopoietic cell transplantation (HCT) offers a potential cure to over thousands of children
98 annually across the world, including those with high-risk leukemia, immunodeficiencies,
99 hemoglobinopathies, and other life threatening disorders.¹ However, a key barrier to HCT success is the
100 development of acute organ failure due to chemotherapeutic toxicity, radiation exposure, infection,
101 genetic predisposition, and impaired or dysregulated immunity.^{2,3} Children requiring intensive care unit
102 (ICU) admission suffer >20% mortality, with rates exceeding 45% when intubation and mechanical
103 ventilation are required.⁴⁻⁶

104 A prominent goal of transplant and intensive care physicians is to quickly and correctly identify high-risk
105 patients to stop the advancement of critical illness and prevent irreversible organ failure.⁷ This is
106 predicated on compelling evidence indicating that organ failure can be modified by promptly recognizing
107 and intervening in its early stages.⁸⁻¹¹ However, predicting who will require intensive care after HCT has
108 been challenging due to relatively small patient numbers spread out across multiple institutions with
109 varying intensive care unit (ICU) admission criteria. Specifically, HCT databases do not capture ICU
110 transfer data and ICU databases do not rigorously phenotype HCT complexity, precluding deeper
111 analyses of risk for critical illness.¹²

112 All major international HCT organizations recommend following all pediatric patients who undergo HCT
113 for long-term cardiopulmonary, renal, and multiorgan toxicities as well as for neurodevelopmental
114 outcomes and health-related quality of life.¹³⁻¹⁵ These recommendations are even more crucial in light of
115 estimates that the number of pediatric survivors of HCT doubled between 2009 and 2020, and will likely
116 double again between 2020 and 2030 to reach an estimated 64,000 patients. However, while recent
117 reports have shown improved survival to ICU discharge, long-term outcomes are lacking since ICU

118 databases do not typically follow patients past ICU discharge.^{4-6,16} In one report of pediatric HCT
119 patients who survived to pediatric ICU (PICU) discharge, survival at 1 year was 40% relative to 1-year
120 survival of 65% in patients who never required PICU admission; this suggests an ongoing burden of
121 chronic organ toxicity in these vulnerable patients.¹⁷ Taken together, these data suggest that both short-
122 and long-term outcomes for critically ill pediatric HCT patients remain suboptimal, and that the toxicity
123 of HCT remains a major barrier to a disease-free childhood for many patients.^{18,19}

124 To address ongoing knowledge gaps regarding risk-factors for critical illness and long-term outcomes, we
125 merged records from two large research databases to determine the incidence of and risk-factors for post-
126 HCT intensive care. We followed patients requiring PICU admission for a median of 5-years to
127 determine long-term outcomes. To assess the burden of chronic toxicities, we also compared survival and
128 organ dysfunction in 1-year transplant survivors according to a preceding need for intensive care in the
129 first year.

130

131 **METHODS**

132 **Data Sources:** The Center For International Blood and Marrow Transplant Research (CIBMTR) is a
133 research collaboration between the National Marrow Donor Program®/Be The Match® and the Medical
134 College of Wisconsin. It comprises over 450 transplant centers worldwide that contribute high-quality
135 longitudinal data on consecutive allogeneic HCT patients. Participating centers contribute data about
136 individual patients and their exposures and outcomes. CIBMTR data is collected and reported at two
137 levels: Transplant Essential Data (TED) and Comprehensive Report Form (CRF). TED data include
138 disease type, age, sex, pretransplant disease stage, and chemotherapy responsiveness, date of diagnosis,
139 graft type, conditioning regimen, posttransplant disease progression and survival, development of a new
140 malignancy, and cause of death. All CIBMTR centers contribute TED data. More detailed clinical
141 information is collected via the CRF mechanism for a subset of randomly selected patients. Observational

142 studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations
143 pertaining to the protection of human research participants. The Virtual Pediatric Systems (VPS) database
144 documents PICU admissions across over 140 pediatric hospitals predominantly in the United States and
145 Canada. Admission characteristics, severity of illness scores, critical care interventions, and critical care-
146 related diagnosis codes are documented by trained analysts at each site, with >95% inter-rater reliability.
147 Patients are followed until hospital discharge.

148 The CIBMTR database was queried for patients who underwent first allogeneic HCT between 2008-2014
149 at an age ≤ 21 years in the United States or Canada and were at a HCT site that also submitted data to
150 VPS. Patients were excluded for allograft source other than bone marrow, peripheral blood, or umbilical
151 cord blood; syngeneic donor; lack of consent to use data; or lack of ≥ 100 days follow-up. Use of
152 intensive care at any point after first allogeneic HCT was identified by matching records between
153 CIBMTR and VPS databases as previously described.⁴ To avoid analyzing low-risk patients, intensive
154 care admissions designated as perioperative or scheduled (>12 hours notice) lasting <2 days were
155 excluded. All PICU admission data were benchmarked to date of first allogeneic HCT since data on
156 repeat allogeneic HCT could not be reliably differentiated from other cellular therapies (eg: donor
157 lymphocyte infusion) in the CIBMTR database during this period of data collection. Patients admitted to
158 an adult ICU were not included. Follow-up data were reported to CIBMTR and were abstracted for this
159 study in the first quarter of 2020.

160 **Outcomes:** The primary outcomes were the need for intensive care and long-term mortality after intensive
161 care. We performed a landmark analysis of all patients alive at transplant day +365 to determine if prior
162 need for intensive care was associated with long-term morbidity and mortality. Approximately half of
163 CIBMTR patients participated in the data-intensive CRF track; for these patients, the occurrence and start
164 date of the following toxicities were collected: congestive heart failure; non-infectious pulmonary
165 dysfunction (interstitial pneumonitis and other non-infectious pulmonary abnormalities including
166 bronchiolitis obliterans, COP/BOOP, and diffuse alveolar hemorrhage); renal failure severe enough to

167 warrant dialysis; non-infectious liver toxicity (including sinusoidal obstruction syndrome, cirrhosis, and
168 other); stroke/seizure; and diabetes/hyperglycemia. Clinical changes in each toxicity, such as worsening,
169 improvement, or resolution, were not captured in CIBMTR.

170 **Covariates:** We considered variables in the following categories. **Demographics:** age at HCT, sex, race,
171 ethnicity, insurance status, zip code median income, weight classification at HCT. **Pre-HCT:** disease,
172 disease status prior to HCT (for malignancy only), HCT Comorbidity Index (HCT-CI), pre-HCT
173 Lansky/Karnofsky, history of pre-HCT mechanical ventilation, history of pre-HCT invasive fungal
174 infection. **HCT-related:** HCT center size, time from diagnosis to HCT (for malignancy only), graft
175 source, donor type/match, allograft manipulation, donor/recipient blood types, donor/recipient CMV
176 status, donor/recipient sex matching, conditioning regimen intensity, conditioning regimen serotherapy,
177 GVHD prophylaxis regimen. **Post-HCT:** achievement of neutrophil engraftment, aGVHD grade,
178 cGVHD grade, hematologic malignancy relapse. **ICU-related:** PICU center size (according to tertile of
179 HCT patient PICU admission volume), age at PICU admission, weight category at PICU admission, time
180 interval between HCT and at PICU admission, Pediatric Risk of Mortality Score-3 (PRISM-3); use of
181 invasive mechanical ventilation (IMV), non-invasive mechanical ventilation (NIV), or renal replacement
182 therapy (RRT); and presence of Gram-positive, Gram-negative, viral, or fungal infection. The PRISM-3
183 score ranges from 0 to 47 and is composed of 17 vital sign and laboratory derangements measured in the
184 first 12 hours of PICU admission.²⁰

185 **Statistical Approach:** Descriptive statistics were used to summarize patient characteristics. Cumulative
186 incidence of being admitted to the intensive care unit was calculated with death being treated as
187 competing risk. Cox proportional hazard model was used to identify factors associated with the need for
188 intensive care. Stepwise model selection was used to identify predictors significantly associated with the
189 outcome. Only variables significant at the 0.05 level were retained in the final model. Overall survival
190 probabilities after intensive care admission were calculated using the Kaplan-Meier estimate. Cox
191 proportional hazard regression with stepwise model selection was used to identify risk factor associated

192 with mortality among patients who were admitted to PICU. Covariates which were not known at baseline
193 (e.g., aGVHD, cGVHD, relapse, use of invasive and non-invasive ventilation) were treated as time-
194 dependent covariates. Next, we explored the difference in survival between patients who were admitted to
195 PICU within 1 year after HCT and those who were not. Only patients surviving to Day +365 post HCT
196 were included in this analysis. Survival after day +365 was estimated using Kaplan Meier curves and
197 factors associated with overall mortality were assessed using Cox proportional hazard regression with
198 stepwise model selection. The development of post-HCT organ toxicities among patients alive at day
199 +365 was assessed in the CRF-track subset of patients using the cumulative incidence function. Nominal
200 significance was considered at a p value <0.05.

201

202 **RESULTS**

203 **Patients:** The final cohort included 6,995 pediatric HCT patients from 69 HCT centers; 1,067 patients
204 required critical care across 79 PICUs (**Figure 1a**). Baseline characteristics of included patients are listed
205 in **Table 1** and **Supplemental Table 1**. The underlying reason for allogeneic HCT was malignancy in
206 57%. Myeloablative conditioning chemotherapy was used in 73% of patients, including total body
207 irradiation (TBI) in 35% of patients. HCT allografts were fully HLA-matched in 54% of patients and
208 obtained most commonly from harvested bone marrow (57%). The largest third of HCT centers (n=23 out
209 of 69) accounted for 67% of all 1st allogeneic transplants performed.

210 **Need for Intensive Care:** Following HCT, the cumulative incidence of PICU admission was 8.3% at day
211 +100 (95% CI 7.7-9.0), 12.8% at 1 year (95% CI 12.0-13.6), and 15.3% at 5 years post HCT (95% CI
212 14.5-16.2, **Figure 1b**).

213 Multivariable analysis with stepwise variable selection identified 15 risk-factors independently associated
214 with the need for intensive care (**Figure 1c; Supplemental Table 2**). Among demographic factors,
215 younger age, lower median ZIP code income, Black race (HR 1.33, 95% CI 1.11-1.59, p=0.002), multi-

216 racial background (HR 2.0, 95% CI 1.50-2.67, $p < 0.001$), and non-Hispanic ethnicity were each associated
217 with PICU admission. Pre-transplant organ toxicity was also associated with greater rates of PICU
218 admission, as measured by an HCT-CI score of ≥ 3 (HR 1.26, 95% CI 1.06-1.49, $p = 0.008$) or a history of
219 mechanical ventilation (HR 1.49, 95% CI 1.24-1.79, $p < 0.001$). Several transplant-related variables were
220 associated with PICU admission, including transplantation at centers in the lowest tertile of transplant
221 volume (HR 1.32, 95% CI 1.07-1.63, $p = 0.009$), HCT for underlying inborn errors of metabolism (HR
222 1.69, 95% CI 1.28-2.23, $p < 0.001$), and recipient CMV positivity (HR 1.46, 95% CI 1.28-1.67, $p < 0.001$).
223 PICU admission was also associated with the use of umbilical cord blood allografts (HR 1.46, 95% CI
224 1.18-1.81, $p < 0.001$) and donors other than HLA-identical siblings (eg: partially matched unrelated donor
225 HR 1.95, 95% CI 1.57-2.43, $p < 0.001$). Finally, the development of post-transplant complications was
226 strongly associated with subsequent PICU admission, including aGVHD grade 3-4 (HR 1.65, 95% CI
227 1.28-2.14, $p < 0.001$), extensive cGVHD (HR 1.80, 95% CI 1.43-2.28, $p < 0.001$), and post-HCT relapse of
228 malignancy (HR 6.26, 95% CI 5.00-7.84, $p < 0.001$).

229 **Outcomes after Intensive Care Admission:** Characteristics of patients at the time of 1st PICU admission
230 are listed in **Table 2**. The per-ICU admission survival rate was 85.7% with a median ICU LOS of 3 days
231 (IQR 1-11). Whereas 14% died in the first ICU admission, 44% survived but required at least one
232 additional PICU admission and 42% of patients survived and did not require PICU re-admission during
233 the study interval. Using CIBMTR longitudinal data, patients were followed from the time of ICU
234 admission to a median 73 months (range 3-147). The OS from the time of 1st PICU admission was 52.5%
235 at 1 year (95% CI 49.5-55.5%), 44.4% at 3 years (95% CI 41.5-47.5%), and 42.6% at 5 years (95% CI
236 39.6-45.6%, **Figure 2a, Supplemental Tables 3-4**).

237 On multivariable analysis, we identified 12 risk-factors independently associated with OS among those
238 requiring intensive care (**Figure 2b, Supplemental Table 5**). Whereas several demographic factors such
239 as age, race, and ethnicity were associated with the need for intensive care admission, once patients were
240 admitted to the ICU, demographics and center size were not independently associated with post-ICU

241 survival. Whereas HCT for inborn errors of metabolism was associated with greater rates of ICU
242 admission, among those admitted to the ICU, HCT for malignant disease was instead associated with
243 worse long-term survival. This was particularly true of malignancy patients with relapsed disease at the
244 time of transplant (HR 2.26, 95% CI 1.40-3.64, $p<0.001$) or relapsed disease after HCT (HR 1.63, 95% CI
245 1.23-2.17, $p<0.001$). In addition to being risk-factors for ICU admission, pre-transplant organ toxicity
246 (HCT-CI ≥ 3 HR 1.42, 95% CI 1.15-1.75, $p<0.001$), use of UCB allografts (HR 1.41, 95% CI 1.08-1.83,
247 $p=0.012$), and allograft donors other than HLA-identical siblings (eg: partially matched unrelated donor
248 HR 1.93, 95% CI 1.45-2.57, $p<0.001$) were each associated with worse post-ICU survival. Interestingly,
249 although 29% of patients did not have neutrophil engraftment at the time of PICU admission, most of
250 these patients achieved neutrophil engraftment during or after ICU stay, and neutrophil engraftment status
251 at the time of PICU admission was not associated with post-ICU survival ($p>0.05$). We considered that
252 post-HCT complications may vary according to time post-HCT, with some complications appearing in
253 the early neutropenic phase and others months later. In this analysis, we found that patients who required
254 PICU admission after day +30 had worse long-term survival compared to those who required PICU in the
255 first 30 days (i.e.: PICU admission 30-99 days post-HCT, HR 1.29, 95% CI 1.0-31.61, $p=0.029$).

256 **Analysis of 1-year Survivors:** Among the subset of the cohort who were alive with follow-up at day
257 +365 (n=5,353 patients), approximately 9% had required intensive care prior to day +365 (n=481). When
258 these 1-year survivors were followed to 5 years post-HCT, the overall survival was approximately 10%
259 lower among those who had required intensive care in the first year (77.1%, 95% CI 73.2-80.8% vs.
260 87.0%, 95% CI 86.1-88%, $p<0.001$), corresponding to a hazard ratio of 1.82 (95% CI 1.50-2.22, $p<0.001$,
261 **Figure 3a, Supplemental Table 6**). Cause-specific mortality among the subset with malignancy showed
262 an approximately 4-fold excess burden of TRM by transplant year 5 in the PICU-exposed group relative
263 to the PICU-unexposed (19.4%, 95% CI 14.1-25.2 vs. 5.6%, 95% CI 4.7-6.6, $p<0.001$, **Figure 3b**). In
264 contrast, rates of relapse after 1 year were comparable regardless of PICU exposure (**Supplemental**
265 **Tables 7-8**).

266 On multivariable analysis, the excess mortality after day +365 among PICU-exposed was most
267 pronounced in those who required PICU after day +30. Specifically, PICU admission between HCT day
268 30-99 (HR 1.89, 95% CI 1.27-2.82) or between HCT day 100-365 (HR 2.20, 95% CI 1.69-2.86, $p<0.001$)
269 were associated with worse outcomes among 1-year survivors, whereas PICU admission in the first 30
270 days post-HCT did not have excess mortality beyond non-PICU patients if alive at 1 year (HR 1.19, 95%
271 CI 0.80-1.78, $p=0.395$). This finding was robust to adjustment for several other factors, including pre-
272 transplant illness severity (HCT-CI, Karnofsky score), transplant variables (recipient CMV+, malignant
273 disease, use of PB or UCB allograft, allograft donor other than HLA-matched sibling), and post-HCT
274 complications (development of cGVHD or relapse prior to one year; **Figure 4c, Supplemental Table 9**).

275 Organ toxicity data from CIBMTR were available on approximately half of the patients. Patients who
276 required critical care in the first year post-HCT showed a greater prevalence of renal failure, diabetes,
277 liver toxicity, stroke/seizure, and non-infectious pulmonary dysfunction at one-year post-HCT ($p<0.001$),
278 demonstrating the burden of illness persisted beyond the immediate PICU admission for some patients
279 (**Supplemental Table 10**). Patients who required critical care in the first year post-HCT also showed
280 significantly greater risk of developing new-onset renal failure after day +365 (increase of 4.9% in PICU-
281 exposed vs. 1.6% in PICU non-exposed, $p<0.001$; **Table 3**). We did not detect a differential increase in
282 the development of diabetes, liver toxicity, stroke/seizure, or non-infectious pulmonary dysfunction after
283 day +365 according to whether PICU was required in the first year, although we could not account for
284 changes or progression in the severity of existing disease.

285

286 **DISCUSSION**

287 We report an approximately 15% cumulative incidence of intensive care admission within 5 years
288 following pediatric HCT, with 85% survival to 1st ICU discharge and 52% survival at 1-year post-1st ICU
289 admission. Importantly, ICU survivors alive at 1-year post-HCT still had worse long-term outcomes

290 including OS, TRM, and new dialysis-dependent renal failure when followed to 5 years post-HCT.
291 Together, these data suggest an ongoing burden of toxicity in pediatric HCT patients that continues to
292 limit long-term survival.

293 First, our report of approximately 8% cumulative incidence of PICU admission within the first 100 days
294 and 15% by year 5 is less than other single-center reports citing 17-35%, which may be due to increased
295 intensity of supportive care outside of the ICU, our exclusion of perioperative and planned ICU
296 admissions, or other factors.²¹⁻²³ Of 69 transplant centers, the third of centers with the highest HCT
297 volume (n=23 centers) accounted for approximately two-thirds of HCT volume and PICU admissions,
298 demonstrating the regionalization of care of these high risk patients. Patients transplanted at a smaller
299 center had increased adjusted risk of ICU admission. The risk for ICU admission associated with younger
300 age and underlying inherited disorders of metabolism may be related to more challenging fluid and
301 airway management in these patients and could be incorporated into patient counseling.²⁴⁻²⁶ The
302 identification of Black and multi-racial background and lower median ZIP code income as risk-factors for
303 post-HCT PICU admission merits further investigation, although these factors were not associated with
304 survival after PICU admission.²⁷⁻³⁰ Finally, the impact of measures of pre-HCT organ toxicity (higher
305 HCT-CI, history of mechanical ventilation) emphasizes the need to optimize organ function in HCT
306 candidates and modify the approach to HCT to increase safety for medically frail patients. Interestingly,
307 time to neutrophil engraftment was not associated with need for intensive care.

308 Of the patients who required intensive care, we identified a significant discrepancy between survival to
309 ICU discharge (86%) and survival to 1-year post-ICU (53%). Previous reports have suggested ICU
310 survival as low as 20-40%, precluding long-term analyses due to so few survivors.^{23,31-34} Our data suggest
311 that while survival to ICU discharge is contemporaneously feasible, nearly half of patients required
312 subsequent ICU readmission during the study interval, which could be due to pre-existing medical frailty
313 or ongoing problems such as alloreactivity or poor immune function. As such, survival with future ICU
314 readmission was the most common outcome (44%), ahead of survival without future ICU admission

315 (42%) or ICU death (14%). Therefore, preservation of organ function during each episode of critical
316 illness is crucial to optimizing survival in future episodes of critical illness.³⁵ Among ICU patients, those
317 with malignant disease, particularly if relapsed going into or after HCT, were of particularly high risk for
318 poor long-term survival due to the competing risks of relapse and TRM. The PRISM-3 score, a metric of
319 multi-organ dysfunction measured in the first 12 hours of PICU transfer, was strongly associated with
320 long-term outcomes independent of the need for mechanical ventilation or dialysis. While this reiterates
321 that it is important to limit the extent and severity of organ dysfunction, it also indicates the importance of
322 the timing of organ dysfunction relative to ICU care. Studies of early transfer prior to clinical
323 decompensation have shown promising results in reducing adverse events.^{36,37} Of note, although 26% of
324 patients had not achieved neutrophil engraftment at the time of PICU transfer, this was not associated
325 with worse mortality, and the majority (73%) went on to achieve neutrophil engraftment, suggesting that
326 aggressive supportive care ought not be withheld from patients purely based on neutrophil engraftment
327 status.³⁸

328 Finally, in a landmark analysis of all HCT patients alive at day +365, we found that those who required
329 intensive care in the first year had 10% greater absolute mortality when followed to 5 years post-HCT
330 compared to patients who did not require intensive care in the first year, which was largely attributable to
331 a 4-fold increased risk of TRM. Studies of long-term outcomes in critically ill children are sparse.
332 *Duncan et al* previously showed worse 1-year outcomes in survivors of intensive care; our study extends
333 these findings to 5-years and emphasizes the chronicity of many post-transplant complications.¹⁷ This
334 risk appeared highest in patients requiring PICU after day +30, again suggesting that transplant
335 complications such as alloreactivity and poor immune function may bear worse prognosis whereas early
336 toxicities related to neutropenia, engraftment, and early fluid overload may be more manageable.

337 Given the high overall survival among patients alive at day +365, we analyzed the incidence of specific
338 organ toxicities, including development prior to and after day +365. As expected, patients who used
339 intensive care in the first year and survived to day +365 had significantly greater rates of organ toxicity in

340 the first year. Whereas *Brogliè et al* recently reported a 12% incidence of non-infectious pulmonary
341 toxicity at 1-year in all pediatric recipients of HCT, our data suggest a much greater burden of
342 approximately 23% at 1-year among those who survived critical illness.² As pulmonary function test
343 (PFT) abnormalities may persist beyond 1-2 years post-HCT in many children, this highlights the need
344 for special attention to follow-up among patients who required intensive care.^{3,39,40} However, after 1-year,
345 there was a relatively small proportion of patients who developed new non-infectious organ toxicities,
346 ranging from 0.6-6%. Interestingly, those who required intensive care in the 1st year had a greater
347 incidence of new-onset dialysis-dependent renal failure after day +365, which is consistent with recent
348 reports and suggests a subset of patients with ongoing progression of AKI/chronic kidney disease
349 pathobiology.⁴¹ Efforts to monitor, mitigate, and address chronic toxicities of pediatric HCT should
350 remain a priority for the field.

351 This is the largest reported cohort of critically ill pediatric HCT patients with high-quality follow-up to 5
352 years post-intensive care. Nonetheless, several limitations warrant discussion. First, transplant and ICU
353 practices may have changed since this cohort was merged; further efforts to streamline multi-database
354 merging so as to deliver more contemporary data are needed. Second, repeat HCT could not be
355 differentiated from donor lymphocyte infusion (DLI) in the CIBMTR database and therefore was not
356 addressed. Third, CIBMTR organ toxicity fields are only reported for research-level participants, include
357 somewhat broad categories, and identify the start point of a complication but do not indicate progression
358 or resolution. Fourth, nearly 1,500 patients were excluded from CIBMTR use due to lack of consent,
359 which might introduce selection bias. Fifth, time from first allogeneic HCT to first PICU admission
360 ranged considerably, and the factors associated with early PICU admission (ie.: within 30 days) may be
361 different than those associated with later PICU admission (i.e.: after day +100).

362

363 **CONCLUSION**

364 In summary, we report an approximately 15% cumulative incidence of intensive care admission within 5
365 years after pediatric HCT, with 85% survival to 1st ICU discharge and 52% survival at 1-year post-1st ICU
366 admission. Major risk factors for critical illness included measures of pre-HCT organ toxicity and
367 predisposition to (or development of) post-HCT alloreactivity or malignancy relapse. ICU survivors alive
368 at 1-year post-HCT had worse long-term outcomes including OS, TRM, and new dialysis-dependent renal
369 failure when followed to 5 years post-HCT. However, accrual of other new organ toxicities was minimal
370 among 1-year survivors. These data can be used for patient prognostication and should be targeted in
371 future investigations focused on improving outcomes following pediatric allogeneic HCT.

372

373 **FIGURE LEGENDS**

374

375 **Figure 1:** (A) Inclusion/exclusion flow diagram. (B) Cumulative incidence of PICU admission after
376 allogeneic HCT. (B) Factors independently associated with post-HCT PICU admission in multivariable
377 competing risk-regression model.

378

379 **Figure 2:** (A) Kaplan Meier estimates of overall survival from the time of PICU admission for all patients
380 (top left) and malignant vs. non-malignant patients (top middle). Cumulative incidence of treatment-
381 related mortality (bottom left) and relapse (bottom middle) among patients transplanted for malignancy
382 are also shown. (B) Factors independently associated with long-term survival from the time of PICU
383 admission to last follow-up in multivariable Cox regression.

384

385 **Figure 3:** (A) Landmark analysis of only patients surviving to HCT day +365. Kaplan Meier estimates of
386 overall survival from transplant day +365 for all patients (top left), those with malignant disease (top
387 middle), and those with non-malignant disease (bottom left), stratified by need for intensive care in the
388 first year post-HCT. Cumulative incidence of treatment-related mortality (bottom middle) among patients
389 transplanted for malignancy is also shown. (B) Among those alive at HCT day +365, factors
390 independently associated with long-term survival from transplant day +365 to last follow-up in
391 multivariable Cox regression.

392

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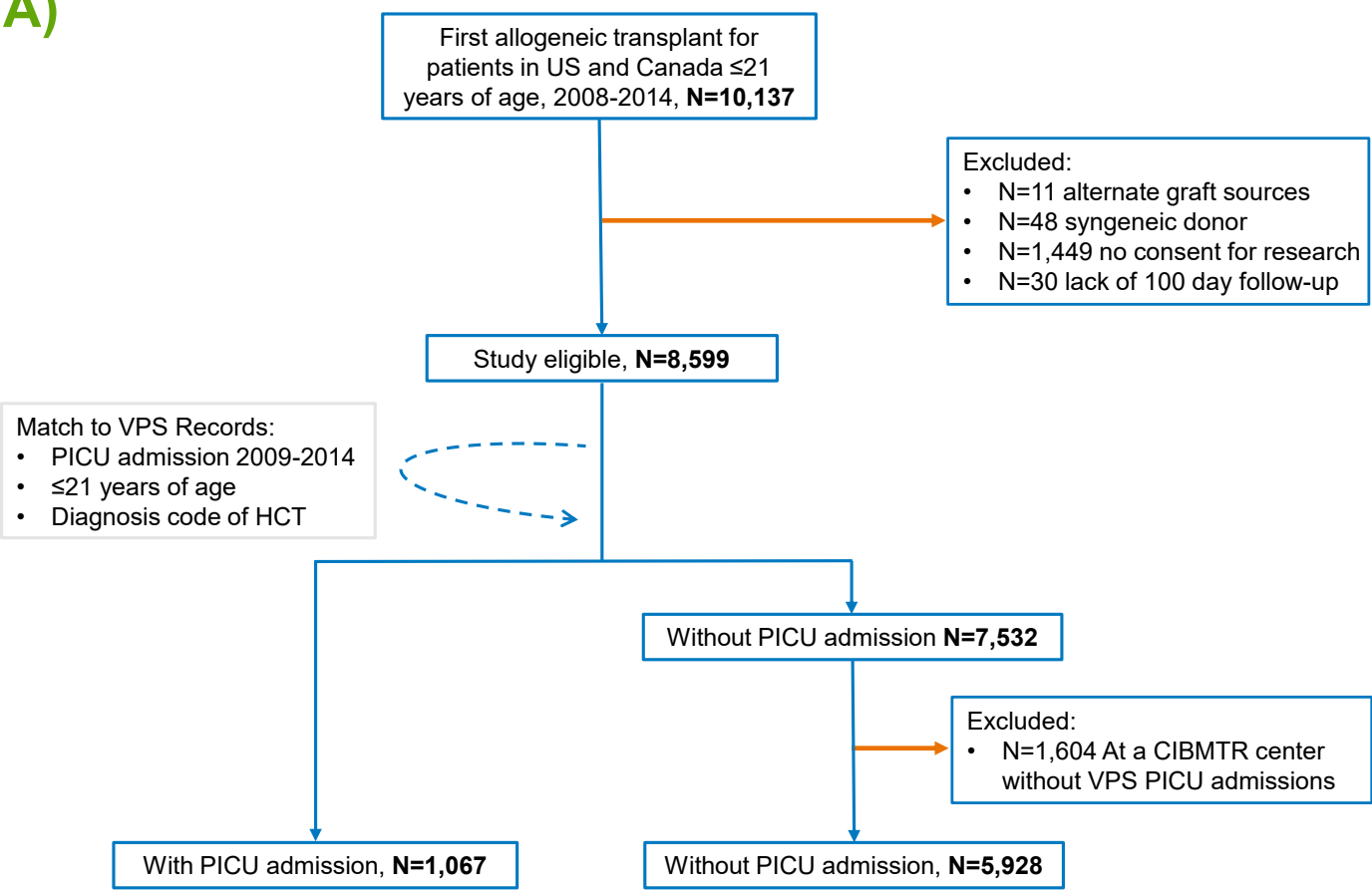
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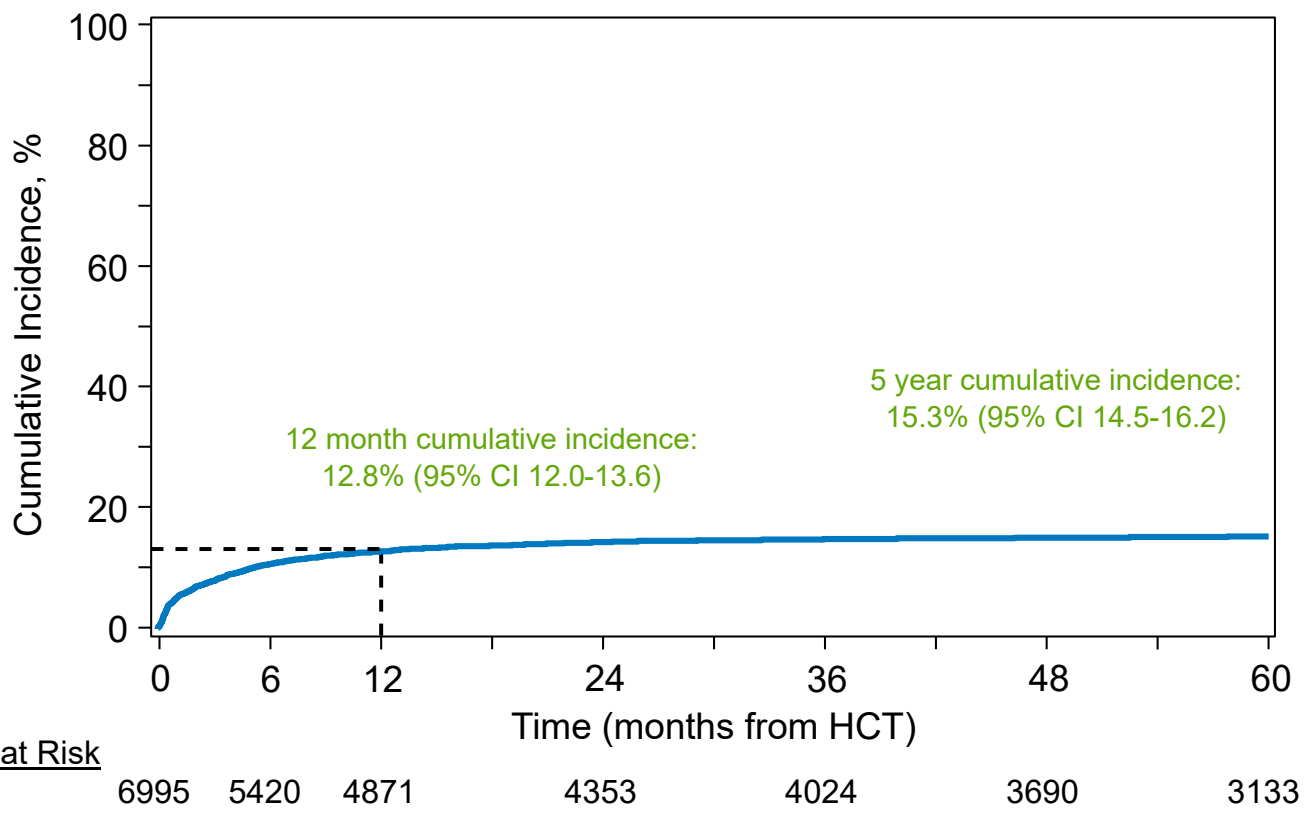
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A)

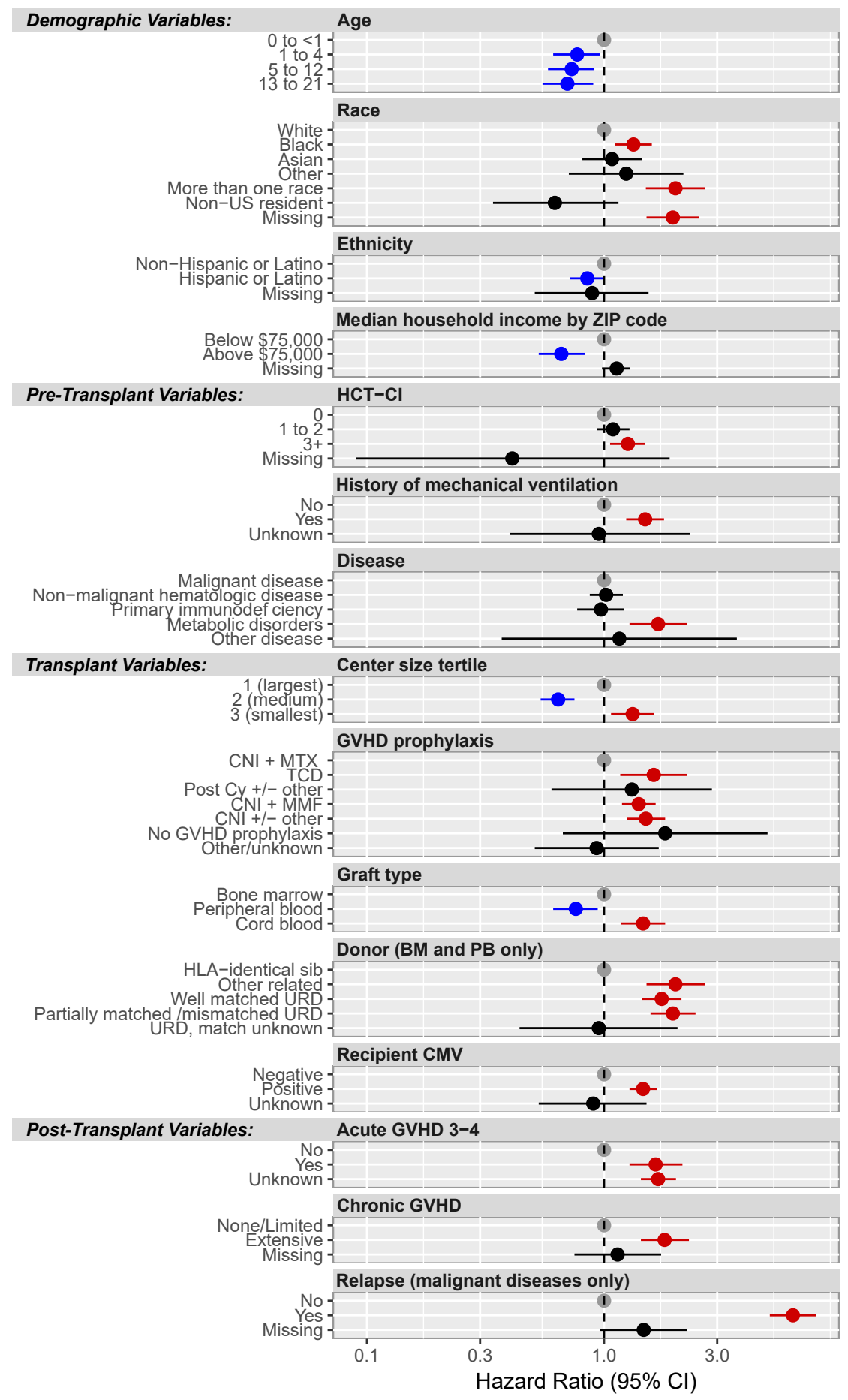


B)

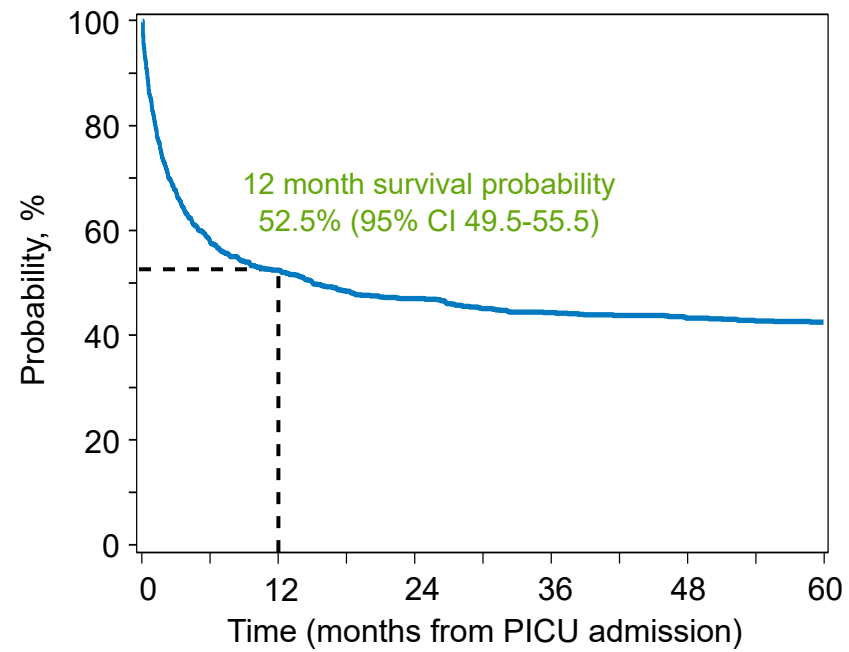
Cumulative Incidence of PICU Admission after Allogeneic HCT



C)

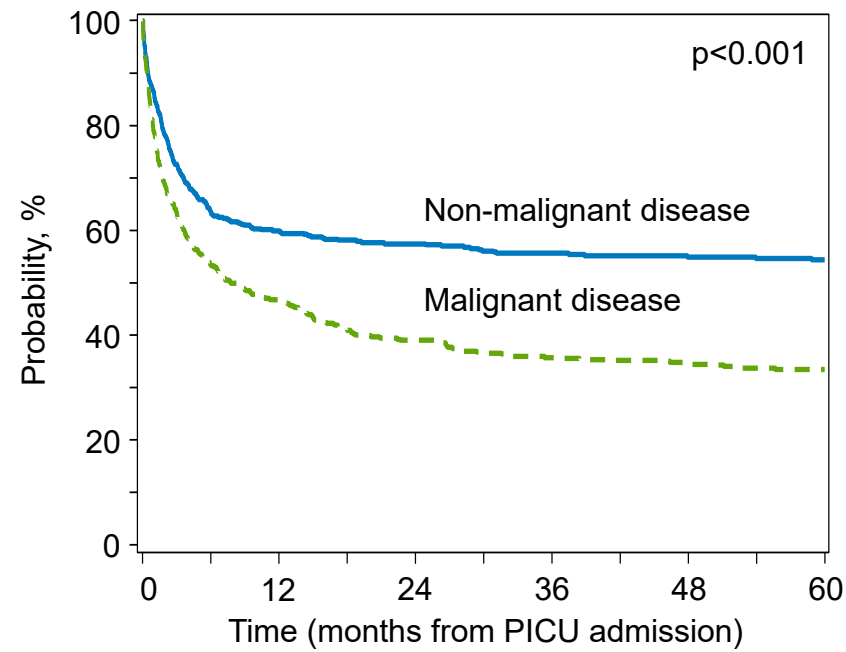


A) Overall Survival of Patients Admitted to PICU



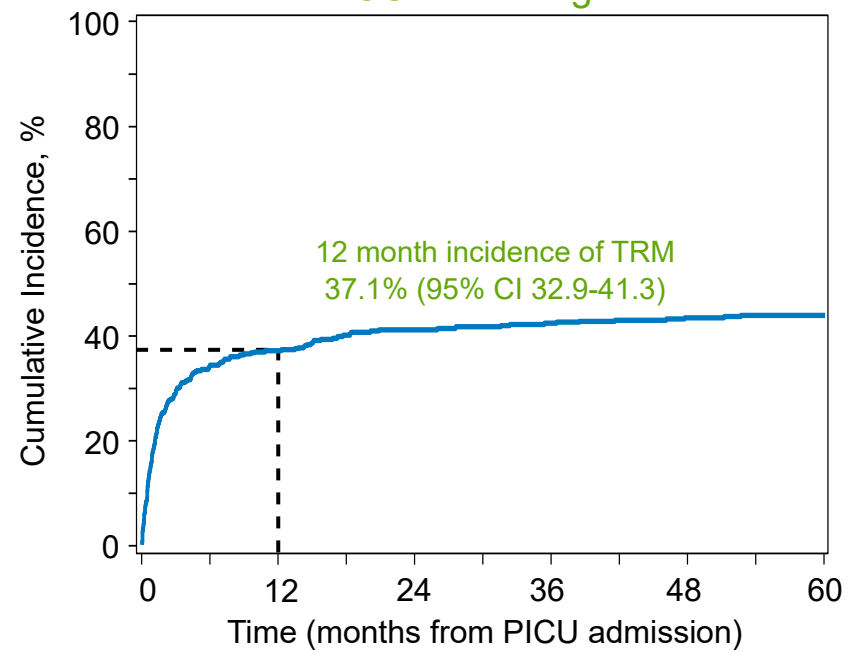
<u>N at Risk</u>	0	12	24	36	48	60
	1067	551	484	444	406	328

Overall Survival of Patients Admitted to PICU



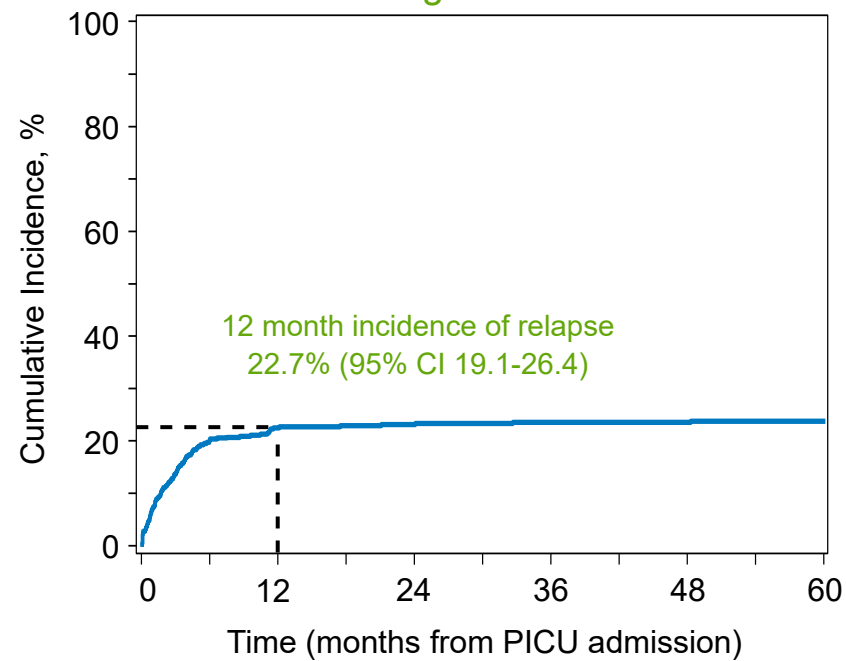
<u>N at Risk</u>	0	12	24	36	48	60
Non-malignant	467	274	256	241	220	188
Malignant	600	277	228	203	186	140

Treatment-Related Mortality of Patients Admitted to PICU with Malignant Disease



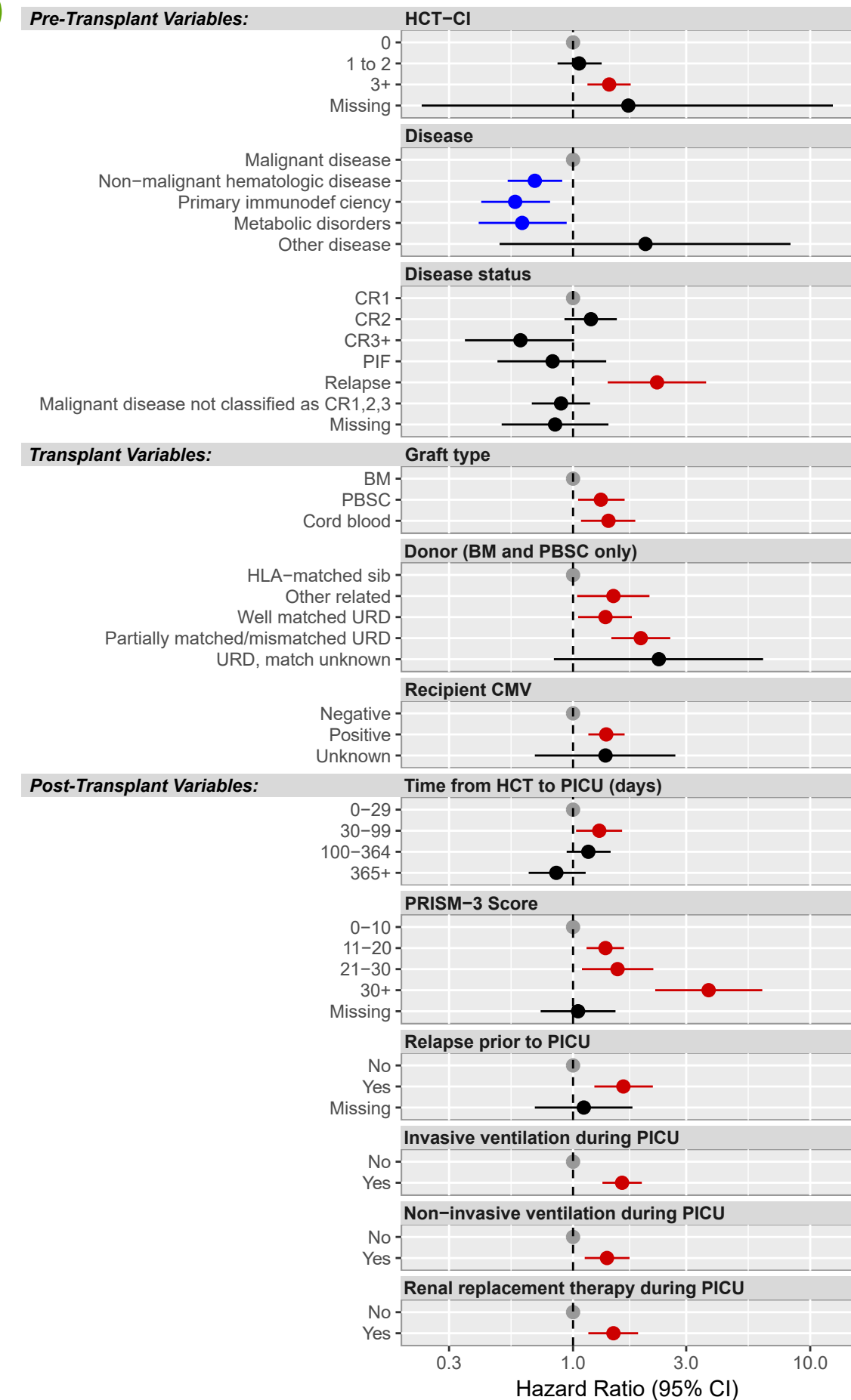
<u>N at Risk</u>	0	12	24	36	48	60
	503	202	174	162	147	109

Relapse of Patients Admitted to PICU with Malignant Disease

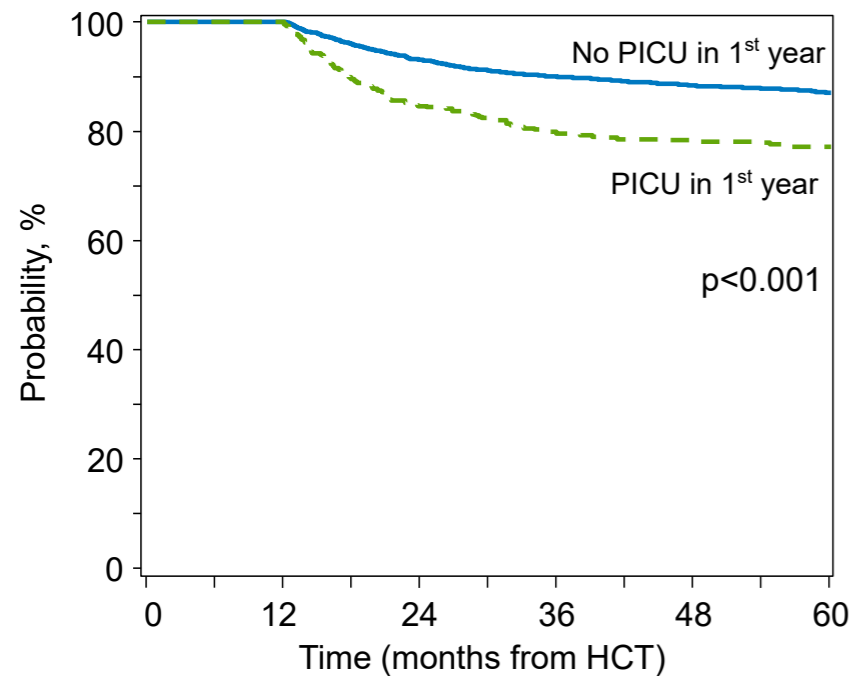


<u>N at Risk</u>	0	12	24	36	48	60
	503	202	174	162	147	109

B)

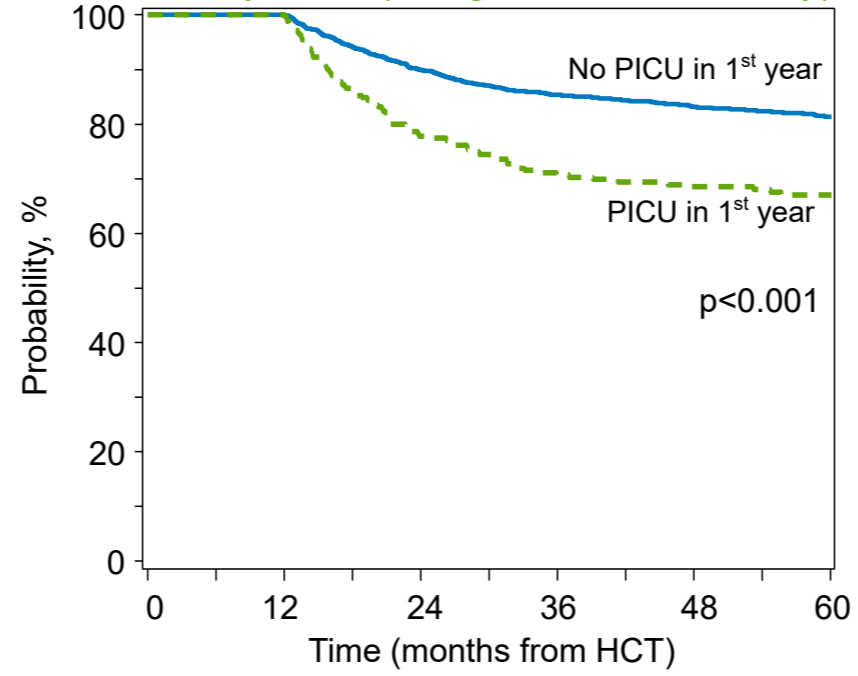


A) Overall Survival of Patients Alive at HCT Day +365



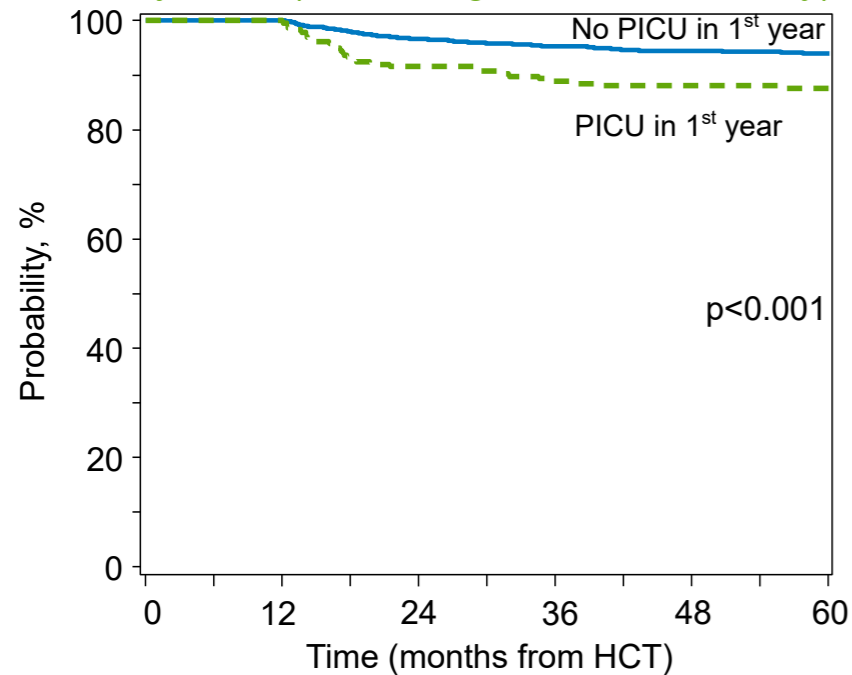
N at Risk		0	12	24	36	48	60
No PICU in 1 st year	4871	4871	4420	4101	3772	3218	
PICU in 1 st year	481	481	401	367	341	298	

Overall Survival of Patients Alive at HCT Day +365 (Malignant Disease Only)



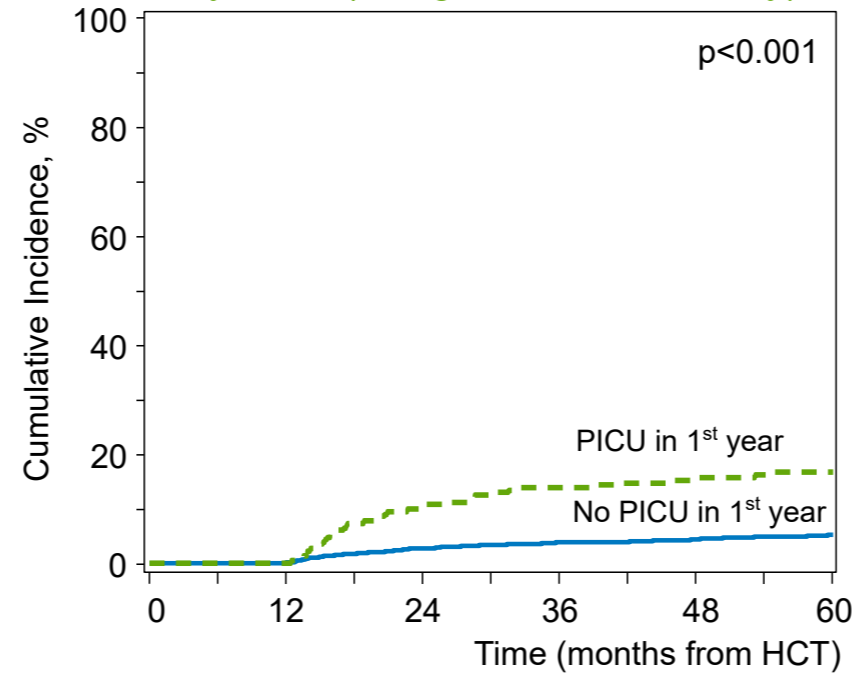
N at Risk		0	12	24	36	48	60
No PICU in 1 st year	2628	2628	2314	2122	1941	1653	
PICU in 1 st year	244	244	188	166	153	126	

Overall Survival of Patients Alive at HCT Day +365 (Non-Malignant Disease Only)



N at Risk		0	12	24	36	48	60
No PICU in 1 st year	2243	2243	2106	1979	1831	1565	
PICU in 1 st year	237	237	213	201	188	172	

Treatment Related Mortality of Patients Alive at HCT Day +365 (Malignant Disease Only)



N at Risk		0	12	24	36	48	60
No PICU in 1 st year	2582	2340	2035	1866	1690	1430	
PICU in 1 st year	236	202	159	142	129	106	

B)

