Disability After Stem Cell Transplant in Children

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Chronic Illness is Prevalent in Children Receiving HSCT

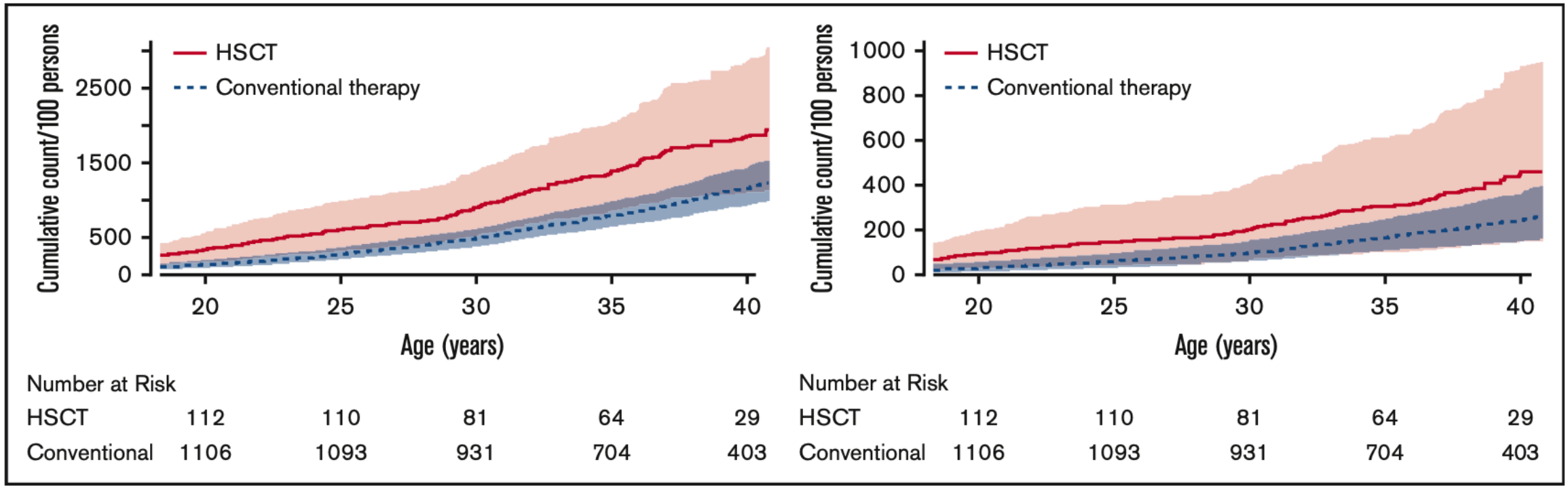
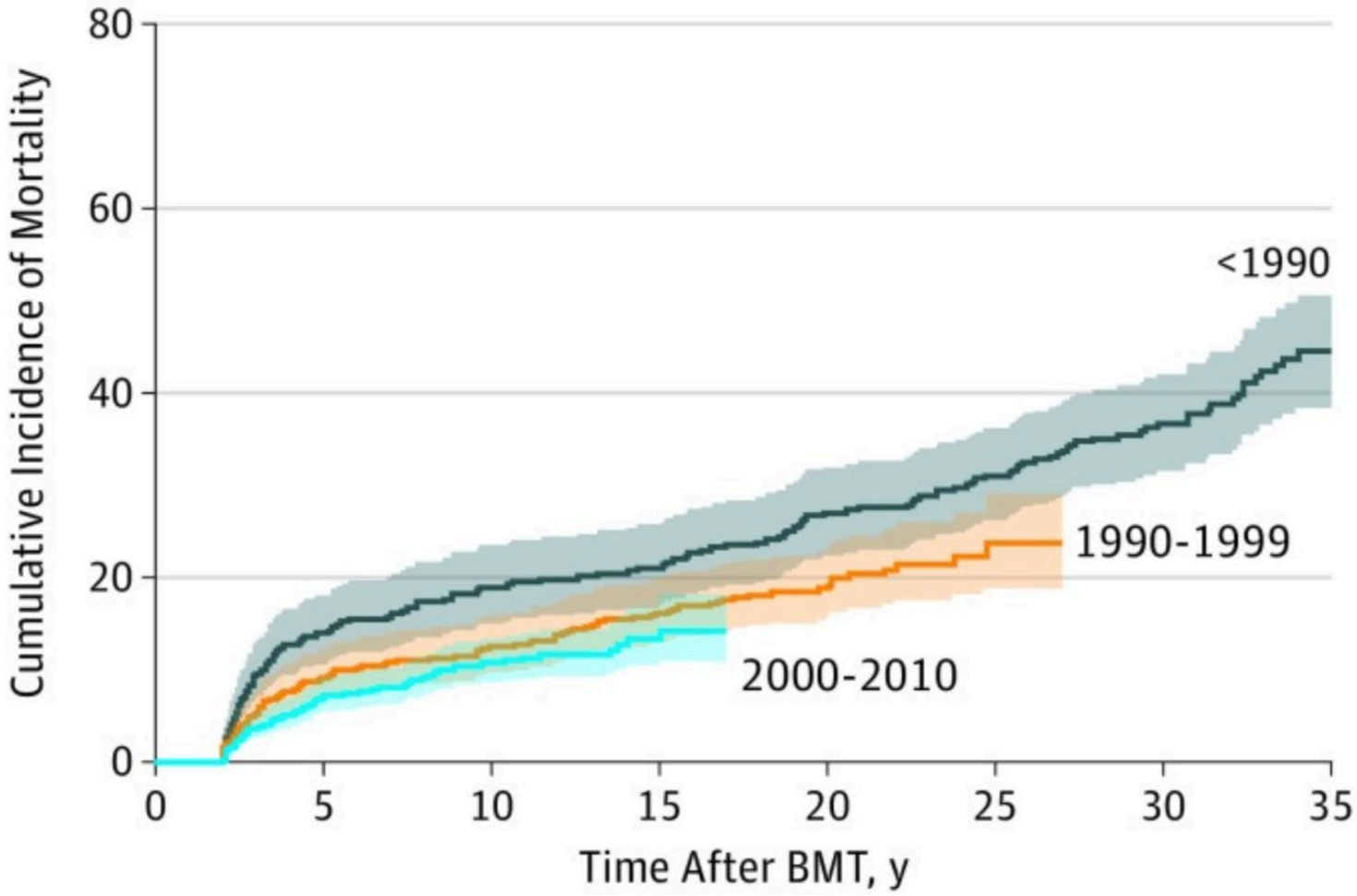


Figure 1. Cumulative burden of chronic conditions among HSCT survivors compared with conventionally treated participants by attained age. (A) Grades 1-4 chronic burden curves. (B) Grades 3-4 chronic burden curves.

Eissa HM et al. blood advances 14 NOVEMBER 2017 · VOLUME 1, NUMBER 24

Mortality is Increased Decades After HSCT in Childhood



No. at risk								
<1990	323	278	262	255	236	223	140	62
1990-1999	407	369	355	340	210	52	0	0
2000-2010	658	611	357	87	0	0	0	0

Holmquist AS et al, JAMA Oncol. 2018; 4(12)

Similarities and Differences in Clinical Factors Influencing Disability In Children and Adults

FACTOR	ADULT	CHILDREN
GVHD	Extremely important	Extremely important
Orthopedic issues	Extremely important, eg arthritis, frailty	Extremely important, eg avascular necrosis of bone, orthopedic complications of primary disease, reduced bone density, frailty
Impact of Critical Illness on Disability	Extremely Important; resilience for physical recovery reduced in older persons	Extremely important; brain development not complete, education delayed, behavioral and social development impaired
Diagnosis	Less important, most transplants performed for malignancy	Extremely important, genetic disorders associated with cognitive deficits, orthopedic complications
Use of Radiation	Less important, brain development already completed	Extremely important; brain development not complete

Diagnoses Associated With High Burden of Late Disability

Diagnosis	Disability
Leukodystrophies	Cognitive impairment, motor impairment, blindness, deafness, progressive peripheral neuropathy (MLD)
Mucopolysaccharidosis type 1	Cognitive impairment, progressive orthopedic impairment, progressive cardiac valve abnormalities,
Sickle Cell Disease	Consequences of prior lung damage, cardiac damage, stroke, avascular necrosis of bone
Fanconi Anemia	Progressive frailty due to metabolic abnormalities, high rate of multiple subsequent squamous cell carcinoma
Dyskeratosis Congenita	Progressive lung fibrosis, liver fibrosis
Brain tumors (autologous transplant)	Cognitive impairment, motor impairment, growth impairment

Importance of Newborn Screening

- Screening of babies for some leukodystrophies, sickle cell disease and mucopolysaccharidosis 1 importantly reduces disability due to earlier referral for transplant
- Gene therapy strategies, if successful, may reduce disability in these populations when used early

Cognitive Difficulties and Access to Appropriate Educational Services

- Causes of cognitive impairment
  - Underlying diagnosis
  - Exposure to radiation
  - Missed education due to illness, immune compromise
  - Infection (encephalitis, sepsis with hypotension)
  - Vascular injury-stroke, thrombotic microangiopathy
- Access to educational services
  - Immune compromise prevents early return to school
  - Remote learning is not great!
  - Complex medical needs limit return to school- intravenous medications and nutrition,

Cognitive Difficulties and Educational Attainment After HSCT: Most Survivors Do Well

- Eligible survivors (HCT at age < 21 year and ≥ 1 year post-HCT) survey of neurocognitive function and quality of life, which included the Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ) and the Neuro-Quality of Life Cognitive Function Short Form (Neuro-QoL)..
- Participants (n = 199, 50.3% female, 53.3% acute leukemia, 87.9% allogeneic transplants) were surveyed at median age of 37.8 years (interquartile range [IQR] 28.5–48.8) at survey and median 27.6 years (IQR 17.0–34.0) from transplant.
- On the CCSS-NCQ, 18.9–32.5% of survivors reported impairments (Z score > 1.28) in task efficiency, memory, emotional regulation, or organization, compared with expected 10% in the general population (all $p < 0.01$).
- In contrast, survivors reported average Neuro-QoL (T score 49.6±0.7) compared with population normative value of 50 ($p = 0.52$).
- In multivariable regression, impaired Neuro-QoL (T score < 40) was independently associated with hearing issues (OR 4.97, 95% CI 1.96-12.6), history of stroke or seizure (OR 4.46, 95% CI 1.44-13.8), and sleep disturbances (OR 6.95, 95% CI 2.53–19.1).

Wu NL et al. Journal of Cancer Survivorship, 2021

Sickle Cell Disease: Can Transplant Reduce Progressive Cognitive Decline?

- Stroke and cognitive decline are hallmarks of sickle cell disease (SCD).
- The natural history predicts progressive loss of 1 intelligence quotient (IQ) point per year attributable to disease- related pathology.
- The Sickle Cell Unrelated Transplant Trial prospectively evaluated cognition and magnetic resonance imaging (MRI) of the brain 2 years following reduced-intensity conditioning followed by unrelated donor HCT.
- Thirteen study participants , mean age 12.5 years, completed pre/post measurements of intelligence.
- Seven had overt stroke pre-HCT; one had an elevated transcranial Doppler velocity with abnormal MRI.
- Average full-scale IQ was stable: 90.9 ± 13 at baseline and 91.2 ± 13 post.
- The average Performance IQ was 89.9 ± 13 versus 90.9 ± 13, and Verbal IQ was 93.4 ± 13 versus 93.2 ± 13 at baseline and post-HCT, respectively.
- Six recipients had stable MRI; two had resolution of all areas of infarction. Three had additional infarcts post-HCT noted at the 2-year timepoint.

King AA et al, Biol Blood Marrow Transplant. 2019

Bone Density is Reduced and Fragility Fractures are Common After Pediatric HSCT: Swauger S et al, TCT, in press

- 237 pediatric transplant recipients from a single center
- 25 (10.5%) had evidence of at least 1 fragility fracture on imaging
- In the patients with at least 1 fragility fracture, 18 (72%) sustained spine fractures.
- The median time to fracture was 5.9 months after HSCT.
- The incidence of fracture was significantly higher in patients with graft-versus-host disease (GVHD) compared with those without GVHD (15% vs 6%;P= .02).
- The cumulative glucocorticoid dose was significantly associated with fracture in patients exposed to glucocorticoids for>3 months (P= .03).

Orthopedic Surgery after HSCT

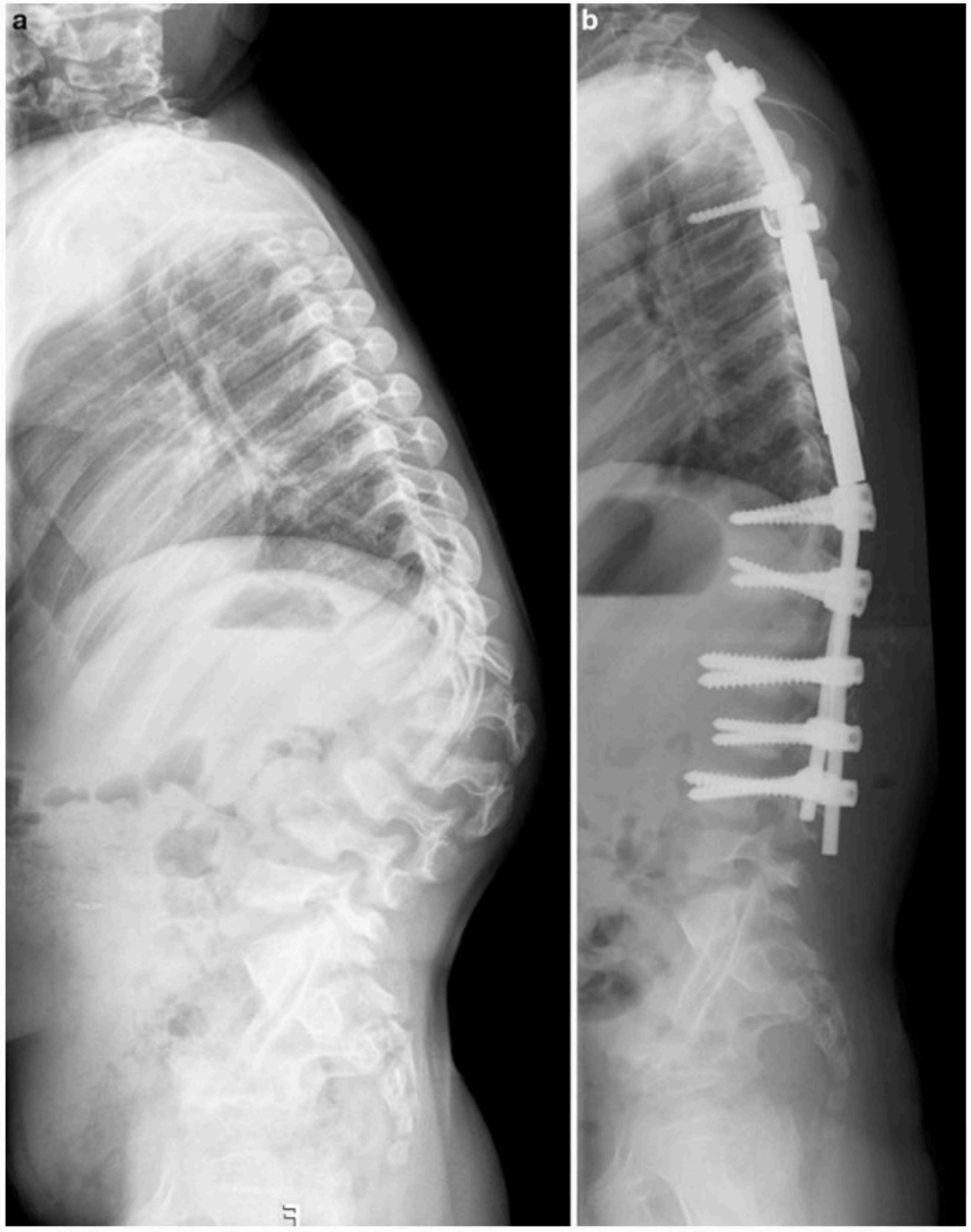


Fig. 4 Example of a thoracolumbar kyphosis. (**a**) Lateral radiograph of the thoracolumbar spine of a 5 year old sitting male patient. There is an obvious kyphosis of 78°, measured between T11 and L2, in addition to anterior beaking of T12 and L1 and severe spondylolisthesis of T11. (**b**) Radiograph after revision of an initial short segment posterior spinal fusion (Th11-L3) in the patient shown in Fig. 4a. To maintain correction, the segment above was fixated with a growing rod system

- Multiple surgeries may be needed as children develop bone abnormalities, each requiring long recovery with intense caregiver needs.
- Growth may mean that repeated surgeries may be needed
- Avascular necrosis is common and can be disabling in adolescents, needing joint replacements

Schmidt M et al.
Orphanet J Rare Dis. 2016; 11(1):93.

Caregivers and Disability

- Children recovering from HSCT need a high level of care (medication, observation for infection, physical therapy at home, doctor visits that typically cannot be shared with school, day care, babysitters or multiple other family members, limiting the ability of primary caregivers to work, particularly in those with GVHD and late complications of primary disease.
- Caregivers may have their own disabilities as they are commonly stressed and traumatized by the experience of HSCT, and often financially challenged by being unable to work. Support for caregivers is essential for recovery of the family unit.

Employment Subsequent to Transplantation in Childhood: Disability Can Persist for Many Years

- The SCT group included 59 adults (18–45 years old treated with allo-SCT in childhood a median of 17 (range 3–28) years earlier.
- The reference group included 296 individuals randomly selected from the general population.
- 54% of long-term survivors were working part- or full-time and 19% were on sick leave or disability pension.
- A larger proportion of the SCT group was on sick leave or disability pension (19% vs. 6%: $p < .001$) than of the reference group.

Winterling J et al. Eur. J. Can. Care, 2018

Fatigue and Disability After Pediatric HSCT

- 76 survivors of pediatric HSCT assessed 5–14 years post-HSCT.
- Survivors exhibited significant fatigue by self and parent-proxy report.
- Excessive daytime sleepiness was reported by 20–33% of survivors.
- Excessive daytime sleepiness was associated with poorer self-reported QOL ($p < .0016$).
- Fatigue was associated with poorer functioning across all domains ($p's < .0016$).
- Fatigue is associated with statistically and clinically greater functional difficulties, highlighting the importance of examining sleep and fatigue and considering interventions to improve alertness.

Graef DM et al. Journal of Pediatric Psychology, 41(6), 2016

Pediatric ICU Admission is Associated With Functional Impairment

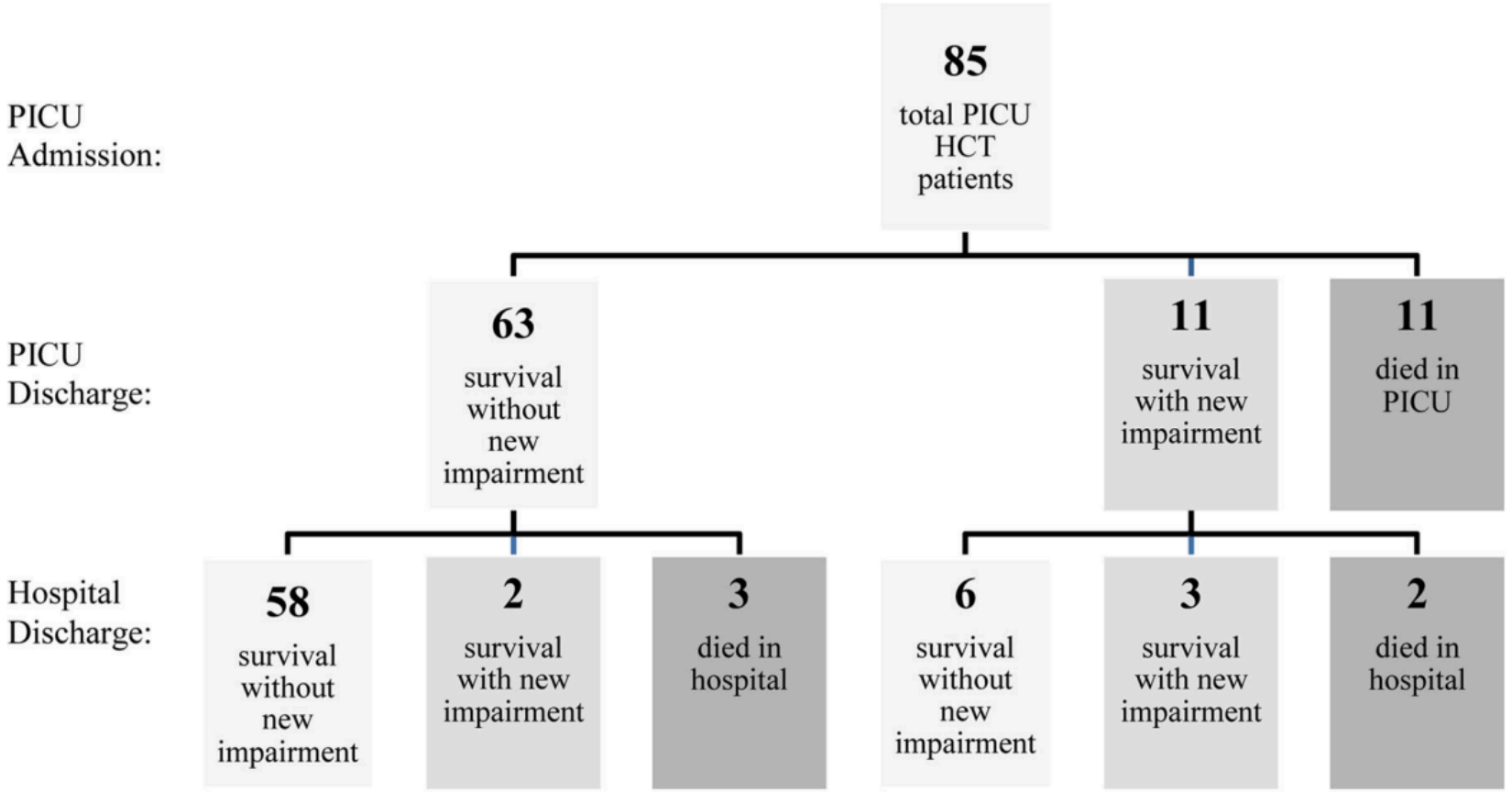


Figure 1. Trichotomous Longitudinal Outcomes of Pediatric Hematopoietic Cell Transplant Patients Admitted to the Pediatric Intensive Care Unit

New impairment defined as increase in Functional Status Scale (FSS) score of at least 3 points relative to pre-hospital baseline.

Zinter MS et al, Biol Blood Marrow Transplant. 2018; 24(2)

Conclusions

- Most children recover well after HSCT, but are at risk of late disability
- Risk of disability associated with
  - Diagnosis
  - GVHD
  - Severe illness during transplant
- Caregiver burden can be extreme, prolonged and disabling in severely affected children