Methods: Allogeneic hematopoietic cell transplant (HCT) patients randomized to SIR/TAC received one year of SIR following HCT, while MTX/TAC patients received MTX on days 1, 3, 6, and 11. QOL was assessed with the Functional Assessment of Cancer Therapy – Bone Marrow Transplant Treatment Outcome Index (TOI) prior to HCT and day 30, 90, 180, 270, and 360 following HCT. Random effects models were used to examine longitudinal trajectories of QOL between day 30 and 360 by study arm, controlling for baseline TOI scores.

Results: A total of 74 patients were enrolled (37 per study arm); all contributed data to these analyses. Analyses indicated that the MTX/TAC group showed greater improvement in TOI scores over time compared to the SIR/TAC group ($P = .02$); by day 360, the average difference between groups was 7.18 points ($P = .03$). This effect continued to be significant ($P < .01$) when controlling for clinical differences between groups, including acute GVHD, chronic GVHD, and anemia. Exploratory analyses of subscales comprising the TOI [i.e., Physical Well-Being (PWB), Functional Well-Being (FWB), BMT Scale (BMTS)] indicated that group differences were due to greater improvement in PWB in the MTX/TAC group ($P = .02$). Additional exploratory analyses of items on the PWB scale indicated that members of the SIR/TAC arm were more likely to endorse a lack of energy and nausea over time (ps≤.01). Study arm differences on these items persisted when controlling for acute GVHD, chronic GVHD, and anemia (ps<.01).

Conclusions: Data from the current study indicate that SIR/TAC is associated with less improvement in QOL in the first year post-HCT compared to MTX/TAC. This difference is not attributable to other potential clinical differences between study arms, including acute and chronic GHVD and anemia. Differences in QOL appear to result in part from greater fatigue and nausea in participants treated with SIR, which was administered throughout the one year follow-up period.

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A Population-Based Cohort Study of Malignancies and Late Mortality in Children Treated by Allogeneic Stem Cell Transplantation for Non-Malignant Conditions

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Background: Characterisation of late effects in children undergoing hematopoietic stem cell transplant (HSCT) for non-malignant diseases is challenging due to the small numbers of rare diseases, variations in cancer susceptibility and organ toxicity associated with primary diagnosis as well as non-uniform clinical practice. In addition, limited follow-up in previous studies may have underestimated the risk of second cancers and late deaths in this group of transplant recipients. Our study used population-based registry data to determine the risk of malignancy and late mortality in pediatric patients transplanted for non-malignant conditions.

Methods: 318 Australian allogeneic transplant recipients aged less than 15 years, treated from 1982-2007 for non-malignant conditions, were identified from children's hospitals and the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR). Clinical and demographic data were obtained from the ABMTRR and medical records. Linkage with the Australian Cancer Database and National Death Index was performed to identify all primary invasive cancers and deaths in this cohort. Standardised incidence ratios (SIRs) were generated for second malignancies and deaths in 2-year survivors.

Results: Indications for HSCT included; primary immunodeficiencies (n=130), aplastic anemia (SAA, n=71), inherited marrow failure syndromes (n=51), thalassemia (n=14) and hemophagocytic lymphohistiocytosis (n=14). Over two thirds of recipients were male (69%), while the median age at transplant was 3 years (range 0-14y) A total of 43 patients received radiation therapy as part of their conditioning regimen.

Six malignancies were identified in male patients with various diseases including Fanconi Anemia (2), Severe Aplastic Anemia (1), severe combined immune deficiency (1), Thalassemia (1) and chronic granulomatous disease (n=1). The most common second cancer was squamous cell carcinoma of the tongue. Overall there was a 15-fold increased risk of malignancy compared to the Australian general population (SIR=15.37, 95%CI=6.91-34.21).

Two thirds of patients (62%) survived for more than 2 years after HSCT, while the cumulative incidence of late death was 2.1% at 5 years from HSCT and 6.3% at 10 years from HSCT. Overall, the rate of death was 17 times greater than expected compared to the general population, with cancer being the most common cause of death.

Conclusion: These findings show an increased rate of malignancy and late death in Australian pediatric patients transplanted for non-malignant conditions compared to the general population. This confirms the need for long term surveillance to maximize the early detection of subsequent malignancies, which may occur a decade or more after HSCT.

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A Population-Based Cohort Study of Second Malignancies and Late Mortality in Children Treated by Allogeneic Stem Cell Transplantation for Hematological Malignancies

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Background: Increasing indications for transplant and improvements in early transplant outcomes have lead to an

increasing population of cancer survivors. Much of our knowledge regarding late effects comes from studies in adult recipients or hospital based studies where duration or reliability of follow-up data is limited. The aim of our study was to examine the risk of second malignancy and late mortality in a population-based cohort of pediatric recipients of allogeneic hematopoietic stem cell transplant (HSCT) in Australia.

Methods: Australian pediatric allogeneic HSCT recipients aged less than 15 years and treated for a hematological malignancy from 1982-2007, were identified from pediatric hospitals and the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR). Patient records were linked to records held by the Australian Cancer Database (ACD) and National Death Index to determine second cancers and deaths in the cohort. Standardized rates (SIRs & SMRs) and risk factors were characterised for second malignancies following HSCT and late deaths (deaths occurring 2 or more years after HSCT).

Results: Second cancers were observed in 17 of the 674 (2.5%) HSCT recipients with a primary cancer diagnosis recorded on the ACD. Thyroid cancer was the most common second cancer observed (n=8) followed by brain tumours (n=4). The rate of second cancers occurring after HSCT was 20 times higher than expected based on rates in the age-, sex- and calendar-year matched general population (SIR=20.33, 95% CI=12.64-32). Total body irradiation was associated with a 4-fold increased risk of secondary malignancy, while non-Hodgkin lymphoma patients were 7 times more likely to develop a second malignancy compared to acute lymphoblastic leukaemia patients.

While the overall rate of late death was 36 times greater than the rate seen in the age-, sex- and calendar-year matched general population (SMR=35.93, 95%CI=26.74-48.29), rates of death returned to levels similar to the general population 10 years after HSCT.

Conclusions: This is the first study to use population-based registry data to determine the risk of second cancer and late death in pediatric patients with a hematologic cancer treated by allogeneic HSCT. The increased risk of second cancer and late deaths in this population highlights the importance of long-term follow up, surveillance and early detection of second cancer.

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Association of Pre-Transplant Comorbidities with Long-Term Quality of Life (QOL) Among Survivors After Allogeneic Hematopoietic Cell Transplantation (HCT)

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Whether pre-transplant comorbidities are associated with QOL after allogeneic HCT is unknown. We used the HCT-comorbidity index (CI) in order to investigate possible associations of baseline comorbidities with different domains of QOL among long-term survivors.

All survivors >17 years of age, who were 3-18 years after HCT for hematological malignancy, without active cancers for 2 years, and with internet access were eligible for the study and hence were approached by mail for participation. Assessment was conducted with an online survey that collected information on socioeconomic status, the Short-Form Health Survey (SF-36), Fatigue Symptom Inventory (FSI), Symptom Check List-90-Revised (SCL-90-R) for depression, Cancer and Treatment Distress (CTXD) scale, ENRICHD Social Support Instrument (ESSI), Social Activity Log (SAL), and self-reported comorbidity index (SR-CI) for general health.

Of 1,775 participants approached for the study, 775 were eligible, consented and completed the assessments, of whom 588 were recipients of allogeneic HCT, of whom 398 were given HLA-matched grafts and contributed to this study. Median age at HCT was 43 (3-76) years and median time from HCT was 7.5 (3.1-17.2) years. Diagnoses were mostly myeloid (83%) or lymphoid (16%) malignancies. Baseline HCT-CI scores were 0 vs. 1-2 vs. ≥3 in 47%, 35%, and 18% of survivors, respectively. High-intensity conditioning regimens were used in 88% of the survivors, and grafts were from related donors in 55% of survivors. Rate of post-HCT relapse was 11%.

Linear and logistic regression models were adjusted for pre-transplant characteristics, socioeconomic factors, and relapse after HCT. When scores of QOL measures were assessed on a continuous scale, HCT-CI scores of 0 vs. 1-2, vs. ≥3 were associated with impaired physical health as evidences by decreasing means (SD) of 48.9 (10.4) vs. 47.2 (11.2) vs. 44.9 (10.4), respectively, of the physical component score of the SF-36 ($P = 0.04$). Other QOL measures were assessed as dichotomized outcomes based on standard cut-offs of the population norm. Higher HCT-CI scores were significantly associated with increased depression, increased distress from cancer or its treatment, diminished social support, and higher comorbidity burden among long-term survivors (Table). HCT-CI scores were not associated with the mental component of the SF-36, increased fatigue, or social activities.

This is, to the best of our knowledge, the first evidence that pre-transplant comorbidities, captured by a prognostic comorbidity index, were associated with long-term QOL outcomes for survivors after allogeneic HCT. Prospective studies are warranted to explore associations of comorbidities with QOL early after HCT and to evaluate preventive or rehabilitation interventions that might improve long-term QOL for survivors, particularly those with high pretransplant comorbidity burden.

Table
Associations between HCT-CI risk groups and dichotomized outcomes of QOL among 398 long-term HCT survivors

Dichotomized outcomes based on standard cutoffs from population norms	HCT-CI 0	HCT-CI 1-2	HCT-CI ≥3	Adjusted P-trend
	%	%	%	
SCL-90-R depression 20 >1.74	3	7	9	0.04
CTXD distress >1.11	15	21	23	0.04
ESSI social support < 13.8	11	13	21	0.02
SRCI general health score > 2	31	38	60	0.0005

Logistic regression model: adjusted for age, gender diagnoses, disease status, CMV sero-status, conditioning intensity, doner type, and stem cell source + self-reported race, location per state, rural vs. urban, and years post HCT + relapse.