Hindawi
European Journal of Cancer Care
Volume 2023, Article ID 9955216, 11 pages
https://doi.org/10.1155/2023/9955216

Research Article

The Basic Documentation for Psycho-Oncology in Pediatric Stem Cell Transplantation Recipients: Ratings of Parents and Staff and the Profile of Salivary α-Amylase

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Received 27 January 2023; Revised 14 April 2023; Accepted 3 May 2023; Published 22 May 2023

Academic Editor: Mohammad Reza Kalhori

Background. Hematopoietic stem cell transplantation (HSCT) is a curative treatment option for malignant and nonmalignant diseases that is highly distressing, especially for children. A valid assessment of pediatric patients' distress that is independent from their language skills would be beneficial. Research regarding HSCT-specific self-reporting or rater-reporting instruments is scarce. *Method*. In this single-center prospective study, pediatric patients and young adolescents undergoing HSCT were screened for mental and somatic distress using PO-Bado (Basic Documentation for Psycho-Oncology) ratings from parents and medical caregivers on eight observations days before, during, and up to 200 days after HSCT. Additionally, the stress biomarkers cortisol and α-amylase were monitored on the same observation days. *Results*. A total of 39 pediatric and young adult patients with a median age of 9.3 years (range 0.5–19.0), with 18 females (46%) and 21 males, were enrolled. The perceptions of the patients' somatic and mental distress of parents and medical caregivers of patients were significantly correlated (mental subscale (($r(276) = 0.31$, $p < 0.001$., 95% CI of the correlation: (0.20, 0.41)) and somatic subscale (($r(284) = 0.46$, $p < 0.001$., 95% CI of the correlation: 0.36, 0.54)). The time period between the days of transplantation until day +10 was rated as the most mentally and somatically distressing. *Conclusions*. While the somatic burden declined over time, the mental distress in the patients remained at a stable level, emphasizing the importance of further psychological and psycho-oncological support in these patients. The use of salivary α-amylase as a suitable distress detection marker in pediatric patients undergoing HSCT should be further investigated.

1. Introduction

Hematopoietic stem cell transplantation (HSCT) is a curative treatment option for malignant and nonmalignant diseases that is performed over 400 times per year in children in Germany (2019: 349 allogeneic HSCTs and 96 autologous HSCTs)[1]. Given the persistent burden of a life-threatening disease and its likewise potentially life-threatening cure, the patients experience high psychological and somatic distress when undergoing this intense treatment. They are at particularly high risk of depression, posttraumatic stress disorders, anxiety, and an impaired emotional well-being and quality of life, not only in the acute transplantation period but also in the following years [2–6].

Basic or—if indicated—intensified psychosocial support for pediatric and adolescent patients undergoing HSCT is recommended by the German national S3 Guideline "Psychosocial care in childhood and adolescent oncology" [7].

Research regarding HSCT-specific self-reporting or rater-reporting instruments assessing the children's perceived emotional or physical stress or their health-related quality of life during and after HSCT is scarce and often includes rather punctual observations with a long time lag, e.g. before and six or twelve months after HSCT [8–12]. The data are often limited to older children and their ability to understand and communicate their mental and physical well-being or stress. External observers—i.e., parents and caregivers—might be a beneficial resource in the comprehensive assessment of the mental or somatic condition in this specific patient cohort, especially in younger children and infants. The parents have a thorough understanding of their child's physical and emotional constitution, and the medical staffs (physicians and nurses) have usually a profound experience with many patients undergoing HSCT and its individual burdensome aspects. Both may provide useful information, potentially enabling a reliable identification of patients with a need for further psycho-oncological support and psychosocial care. However, only few works address multirater perspectives and an evaluation of the specific inter-rater differences [8, 12–14].

Pediatric allogeneic and autologous HSCT is performed in specialized treatment centers usually affiliated to university hospitals and it integrates the treatment of international and culturally diverse patients. This can be accompanied by challenges in communicating with the patients and parents, potentially complicating the screening of the patients' need for further support [15]. A valid assessment of patient distress that is independent from their language skills would therefore be beneficial.

In our prospective investigation, we analyzed the mental and somatic distress of a total of 39 pediatric and young adult patients undergoing allogeneic or autologous HSCT as perceived by the patients' parents and their medical caregivers, as well as the patients' blood and salivary stress biomarkers. These studies were conducted at short intervals during the in-patient stay during HSCT and at follow-up until day +200 after HSCT, i.e., the day of in-patient admission (baseline; day −10 before HSCT), on day 0 (day of HSCT), day +10, day +20, day +30, day +60, day +100, and day +200 after HSCT. The primary objective was to describe the course of the mental and somatic distress of pediatric patients before, during, and after HSCT and analyze the inter-rater differences of the external observers. Furthermore, we evaluated age as an influencing factor and the measure of agreement between the distress ratings and stress biomarkers.

2. Methods

2.1. Study Background and Design. In this prospective study, patients of the stem cell transplantation unit of the University Children's Hospital Tübingen were recruited between 2019 and 2020. The inclusion criteria were an age between 0.5 and 20 years at the time of study enrollment and an upcoming allogeneic or autologous HSCT. The exclusion criteria were a diagnosis of a mental disorder according to the ICD-11 (International Classification of Disease-11) before study enrollment [16]. After written informed consent was obtained from the patients and their legal guardians, the patients were enrolled. The observation period started on the day of in-patient admission prior to the commencement of HSCT and ended on day +200 after HSCT. The patients' parents and medical caregivers answered questionnaires and the patients were screened for laboratory markers on a total of eight observation days, i.e., the day of in-patient admission (baseline; day −10 before HSCT), on day 0 (day of HSCT), day +10, day +20, day +30, day +60, day +100, and day +200 after HSCT.

2.2. Questionnaires. The perceived mental and somatic distress of the patients was rated on the specific observation days by the medical staff and one of their parents. The mental and somatic distress was assessed with the standard version of the PO-Bado (Basic Documentation for Psycho-Oncology) cancer-specific screening instrument, developed by Herschbach and colleagues [17–19].

2.3. Laboratory Analyses. On the observation days, the patients were tested for salivary α-amylase and blood levels of cortisol as markers of the stress response, thyroid-function parameters, thyroid-stimulating hormone (TSH), free triiodothyronine (fT_3), and free thyroxine (fT_4). Blood collection was performed around 7 a.m. on the observation days. Measurements obtained during phases of conditioning in which steroids were substituted, as well as during steroid therapies in case of acute GvHD, were excluded from the analyses of cortisol measurements. Normal blood concentrations of the parameters were defined as follows: cortisol 125–400 nmol/L (nanomole per liter), TSH 0.3–4.0 mU/L (milliunits per liter), fT_3 3.5–6.5 pmol/L (picomole per liter), and fT_4 13–26 pmol/L.

2.4. Statistical Analysis. PO-Bado scores for the subscales somatic distress and mental distress were calculated from the ratings done by staff and parents for each participant and point in time according to the manual. For primary analyses, we conducted a baseline correction, subtracting the baseline PO-Bado score (day −10) from the scores of the following days. The baseline-corrected data were then used to fit a linear mixed model [20]. The equation used to fit the model can be described by $\text{score}_{ijk} = \beta_{0j} + \beta_{1j} * \text{day}_k + \vartheta_{0i} + \vartheta_{1i} + \varepsilon_{ijk}$. In this model equation score_{ijk} denotes the baseline corrected PO-Bado score of Patient $i = 1, \ldots, 39$, in rating group $j = 1$ (somatic distress rated by staff), 2 (mental distress rated by staff), 3 (somatic distress rated by parents), or 4 (mental distress rated by parents), at day $k = 0, \ldots, 200$ after HSCT. β_{0j} and β_{1j} denote the fixed effects, where β_{0j} is the intercept estimate (i.e., the baseline corrected PO-Bado score at day 0 after HSCT) and β_{1j} is the slope estimate (i.e., how much the baseline corrected PO-Bado score decreases or increases each day) for the respective rating group j. ϑ_{0i} and ϑ_{1i} describe the individual-specific random intercepts and slopes, while ε_{ijk} is the error term [21–23].

Graphs and statistical tests were created with GraphPad Prism version 8.1.1 (330) for Windows (GraphPad Software. Inc., La Jolla, CA, USA) and R version 3.5.1 (2018-07-02,

Copyright 2018, The R Foundation for Statistical Computing). P values <0.05 (*), <0.01 (**), <0.001 (***), and <0.0001 (****) were defined as statistically significant.

3. Results

3.1. Patient Characteristics. A total of 39 pediatric and young adult patients with a median age of 9.3 years (range 0.5–19.0), with 18 females (46%) and 21 males, were enrolled in this prospective analysis. Of these patients, eight patients (21%) underwent an autologous and 31 patients (79%) underwent an allogeneic HSCT. Detailed patient characteristics can be found in Table 1.

3.2. Course of Mental and Somatic Distress during HSCT. The results of the linear mixed model analysis show significant positive estimates for the intercepts of somatic distress rated by staff and parents, as well as mental distress rated by staff. The intercept estimates for the baseline corrected PO-Bado score signify that there was a significant increase in the rating of distress from baseline to day 0 for those rating groups. The intercept estimates of mental distress rated by parents did not yield a significant result, meaning the distress did not increase nor decrease significantly from the baseline to day 0. For slope estimates—which indicate how much the baseline corrected PO-Bado score decreases each day after HSCT—only the parameter estimates for somatic distress were significant, while the slope estimates for mental distress did not reach significance. This implies that while the rating of baseline-corrected somatic distress decreased after HSCT, the rating of baseline-corrected mental distress did not change significantly (Table 2, Figure 1).

In order to identify age as an influencing factor, the interactions of age as a continuous variable and subscale-rater combinations were added to the mixed linear model as fixed effects. It was shown that age was not an influencing factor in any of the subscale-rater combinations of somatic staff (Figure 1(c)), somatic parents (Figure 1(d)), mental staff (Figure 1(e)), and mental parents (Figure 1(f)), considering a 95% CI. For a clearer depiction in the graphs, age is categorized in groups of 0–5 years, 6–12 years, and ≥13 years.

3.3. Inter-Rater Differences of Parents and Medical Staff. Correlation analyses of the mental and somatic subscales between the ratings of the parents and medical staff showed a significant correlation of both the mental subscale (($r(276) = 0.31$, $p < 0.001$., 95% CI of the correlation: (0.20; 0.41)) and the somatic subscale (($r(284) = 0.46$, $p < 0.001$., 95% CI of the correlation: (0.36, 0.54)). Given that the subscale scores are a combination of items that may be rated differently by staff or parents but still result in the same mean score, the inter-rater reliability was additionally analyzed at the item level with a weighted Cohen's Kappa for each patient and both subscales. Subsequent t-tests showed that the inter-rater reliability was significantly higher for the somatic subscale ($M = 0.38$) when compared to the mental subscale ($M = 0.18$; $t\ (76) = 4.53$; $p < 0.001$) (Figure 2).

3.4. Stress and Thyroid Biomarkers. All children six years of age and older were able to reliably provide saliva samples, while only just under one-third (28.6%) of those under six years of age generated evaluable saliva samples. In the following analyses, all correctly obtained saliva samples are taken into account, so that the results are representative of all children aged six years and older, but only to a limited extent for the group of children up to 5 years. Salivary α-amylase continuously increased from day −10 before HSCT (baseline) (mean 61.6 ± 11.3 units per liter (U/L), range 3.9–225.8 U/L) to an overall peak on day +10 after HSCT (mean 142.1 ± 57.2 U/L, range 5.2–1105 U/L). Given the wide range of results, the mean levels between baseline and day +10 after HSCT were not significantly different ($p = 0.68$). The levels declined until day +20 (mean 52.9 ± 9.6 U/L, range 4.1–138.8 U/L) and continuously increased until day +200 after HSCT (mean 115.5 ± 32.5, range 3.0–467.7 U/L) (Figure 3(a)). At present, there are no reference values for salivary α-amylase, and hence, a description of the detected concentration can only be relative. Based on previous studies, it is recommended to measure the respective relative increase of alpha-amylase of the subject compared to a baseline level instead of considering absolute values [24].

Serum cortisol levels continuously and significantly increased from a mean baseline level of 262.5 ± 24.8 nmol/L (range 14.0–501.0 nmol/L) to a peak value of 489.8 ± 42.6 nmol/L on day +60 after HSCT ($p = 0.0012$). Thereafter, the mean cortisol concentrations decreased to 326.1 ± 48.3 nmol/L (range 54.0–1117 nmol/L) on day +200. A significant increase of the mean cortisol levels beyond the upper normal limit (420 nmol/L) was not reached on any of the observation days (Figure 3(b)).

The TSH blood levels remained similar throughout the whole observation period. Baseline levels started at a mean of 4.4 ± 1.4 mU/L (range 0.1–48.4 mU/L) and slightly and insignificantly ($p = 0.56$) decreased to a mean of 2.6 ± 0.3 (range 0.1–6.6 mU/L) on day +10 after HSCT. None of the determined TSH levels decreased or increased beyond the normal limits (6.3 mU/L) (Figure 3(c)).

FT3 serum levels started at baseline with a mean of 5.0 ± 0.3 pmol/L (range 2.1–7.8 pmol/L) and subsequently decreased to a mean of 4.4 ± 0.2 pmol/L (range 2.5–6.5 pmol/L) on day 0. After a peak on day +10 (mean 5.3 ± 0.2 pmol/L, range 2.9 ± 9.1 pmol/L), mean fT3 levels decreased until day +30 (mean 4.4 ± 0.2 pmol/L, range 1.5–6.4 pmol/L) and continuously increased thereafter until day +200 (mean 5.8 ± 0.2 pmol/L, range 3.7–8.2 pmol/L) after HSCT. None of the determined levels decreased or increased beyond the reference limits (3.5–6.5 pmol/L) (Figure 3(d)).

FT4 baseline levels were 13.2 ± 0.5 pmol/L (range 7.0–24.0 pmol/L) and remained steady until day +30 after HSCT (mean 13.6 ± 0.6 pmol/L, range 9.0–23.0 pmol/L). A peak of fT4 was observed on day +60 (mean 16.6 ± 0.6 pmol/L, range 11.8–23.0 pmol/L), which was significantly higher ($p < 0.0001$) when compared with the baseline levels. Likewise, the levels on day +100 (mean 15.3 ± 0.5 pmol/L, range 11.0–21.0 pmol/L; $p = 0.0004$) and +200 (mean 15.5 ± 0.6 pmol/L, range 9.0–14.0 pmol/L; $p = 0.0186$) after HSCT were significantly higher when compared with the baseline levels (12–23 pmol/L) (Figure 3(e)).

Table 1: Patient characteristics.

	Total		Allogeneic HSCT		Autologous HSCT		p
	n	(%)	n	(%)	n	(%)	
Total	39	(100.0)	31	(100.0)	8	(100.0)	
Age							
Median (range)	9.3 (0.5–19)		6.0 (2.8–19)		9.5 (0.5–18.3)		
Sex							
Male	21	(53.8)	15	(48.4)	6	(75.0)	0.2472
Female	18	(46.2)	16	(51.6)	2	(25.0)	
Diagnosis							
Malignant	26	(66.7)	18	(58.1)	8	(100.0)	**0.0352**
Non-malignant	13	(33.3)	13	(41.9)	0	(0.0)	**0.0352**
Acute lymphoblastic leukemia	6	(15.4)	6	(19.4)	0	(0.0)	0.3133
Acute myeloid leukemia	5	(12.8)	5	(16.1)	0	(0.0)	0.5628
Ewing's sarcoma	2	(5.1)	1	(3.2)	1	(12.5)	0.3725
Myelodysplastic syndromes	2	(5.1)	2	(6.5)	0	(0.0)	>0.9999
Neuroblastoma	6	(15.4)	5	(16.1)	1	(12.5)	>0.9999
Sickle cell anemia	5	(12.8)	5	(16.1)	0	(0.0)	0.5628
Others	13	(33.3)	7	(22.6)	6	(75.0)	**0.0098**
HSCT donor							
Autologous	8	(20.5)	0	(0.0)	8	(100.0)	**<0.001**
Matched unrelated donor	8	(20.5)	8	(25.8)	0	(0.0)	0.1683
Matched sibling donor	10	(25.6)	10	(32.3)	0	(0.0)	0.0862
Mismatched family donor	13	(33.3)	13	(41.9)	0	(0.0)	**0.0352**
Graft-versus-host disease							
Grade I	10	(25.6)	10	(32.3)	n.a.		
Grade II	5	(12.8)	5	(16.1)	n.a.		
Grade III	0	(0.0)	0	(0.0)	n.a.		
Grade IV	0	(0.0)	0	(0.0)	n.a.		
Daycare/school/work							
Daycare/kindergarten	10	(25.6)	8	(25.8)	2	(25.0)	>0.9999
School	23	(59.0)	19	(61.3)	4	(50.0)	0.6937
Others	6	(15.4)	4	(12.9)	2	(25.0)	>0.9999
Parents							
Married	32	(82.1)	26	(83.9)	6	(75.0)	0.6170
Divorced/separated	6	(15.4)	5	(16.1)	1	(12.5)	>0.9999
Widow(er)	1	(2.6)	0	(0.0)	1	(12.5)	0.2051
Death	6	(15.4)	6	(19.4)	0	(0.0)	0.3133

HSCT-hematopoietic stem cell transplantation; n-sample size; p-probability value.

Table 2: Estimated fixed effects of parameters for baseline corrected PO-Bado score.

Parameter	Description	Estimate	SE	df	t	p	95% CI	
							Lower	Upper
β_{01}	Intercept: somatic distress rated by staff	0.80	0.14	12.49	5.69	<0.0001	0.52	1.07
β_{02}	Intercept: mental distress rated by staff	0.36	0.14	12.71	2.55	0.024	0.08	0.64
β_{03}	Intercept: somatic distress rated by parents	0.77	0.14	12.53	5.46	<0.001	0.49	1.04
β_{04}	Intercept: mental distress rated by parents	0.15	0.14	12.68	1.07	0.305	−0.13	0.43
β_{01}	Slope (days): somatic distress rated by staff	−0.004	0.001	106.7	−4.20	<0.0001	−0.006	−0.002
β_{02}	Slope (days): mental distress rated by staff	−0.002	0.001	114.9	−1.72	0.090	−0.003	0.0002
β_{03}	Slope (days): somatic distress rated by parents	−0.004	0.001	102.9	−4.60	<0.0001	−0.006	−0.002
β_{04}	Slope (days): mental distress rated by parents	−0.001	0.001	107.5	−0.97	0.336	−0.003	0.001

3.5. Correlation of Somatic and Mental Distress with Blood Biomarkers. The analyses showed that mental distress as rated by parents and medical staff was rather constant throughout the whole observation period, while somatic distress increased from baseline to peak values between day 0 and day +10 and subsequently decreased over time. Correlation analyses between the ratings of the parents and medical staff showed a significant correlation between both the mental and the somatic subscales, with a higher inter-rater reliability of the latter. To identify correlations of the

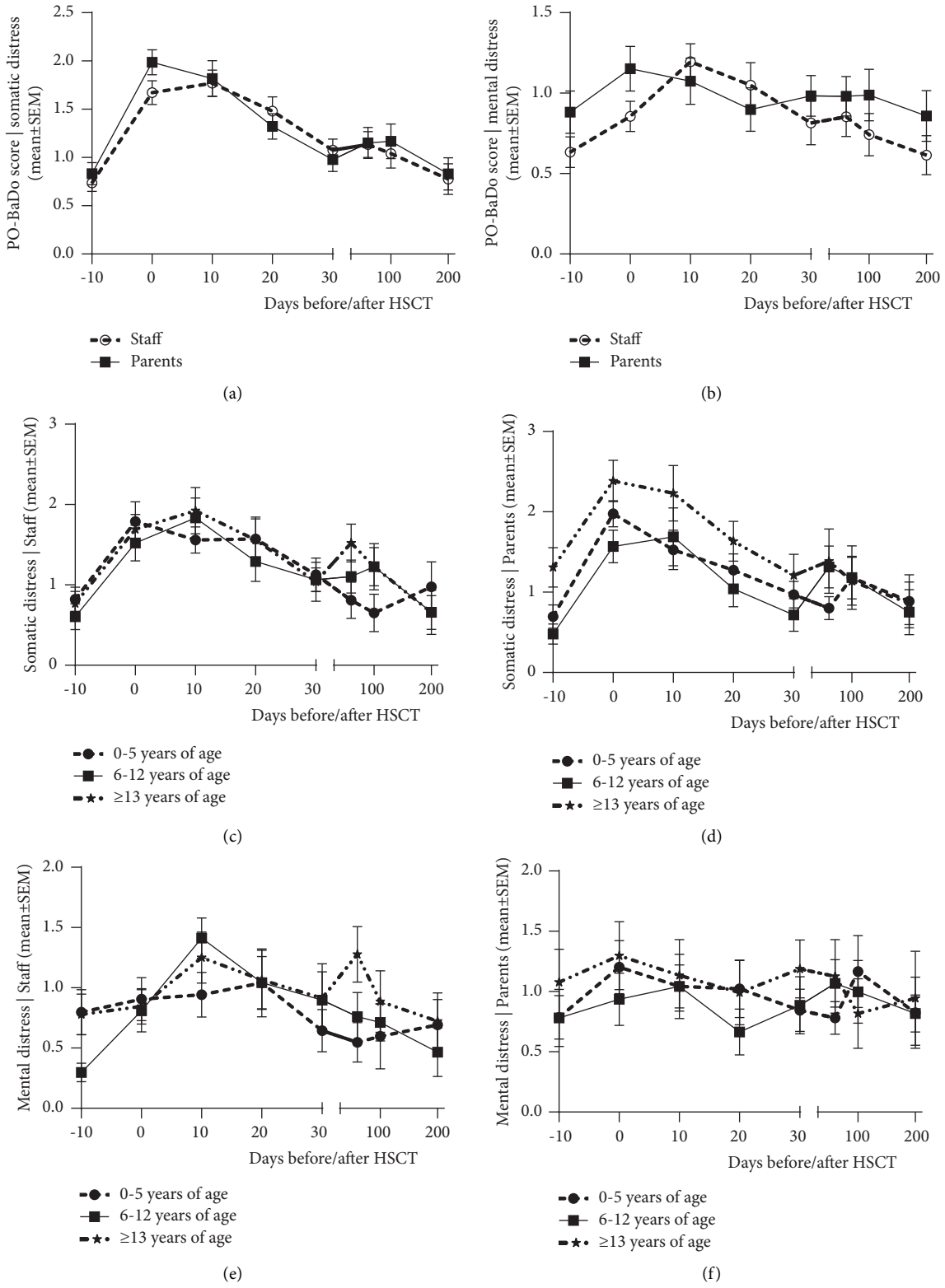

Figure 1: Somatic and mental distress as rated by staff and parents. The graph shows (a) somatic distress and (b) mental distress as rated by the medical staff or the parents of pediatric patients before and after allogeneic or autologous HSCT. Subfigures (c) through (f) show the results regarding somatic (c, d) or mental (e, f) distress considering the different age groups of the patients (0–5 years of age, 6–12 years of age, and ≥13 years of age). The graphs display the respective PO-Bado scores of the days before, during, and after HSCT as mean ± standard error of the means (SEM).

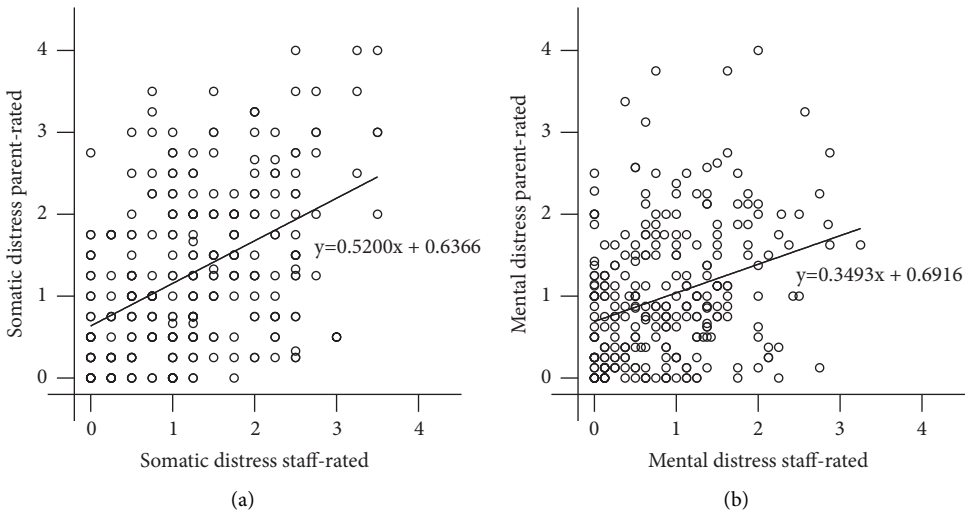

Figure 2: Inter-rater comparisons. The graph shows the inter-rater reliability of somatic (a) and mental (b) distress of pediatric patients before and after allogeneic or autologous HSCT as rated by parents and medical staff. Both the mental subscale (($r(276) = 0.31$, $p < 0.001$., 95% CI of the correlation: (0.20, 0.41)) and the somatic subscale (($r(284) = 0.46$, $p < 0.001$., 95% CI of the correlation: (0.36, 0.54)) were significantly correlated, with a higher inter-rater reliability of the somatic subscale, when compared to the mental subscale.

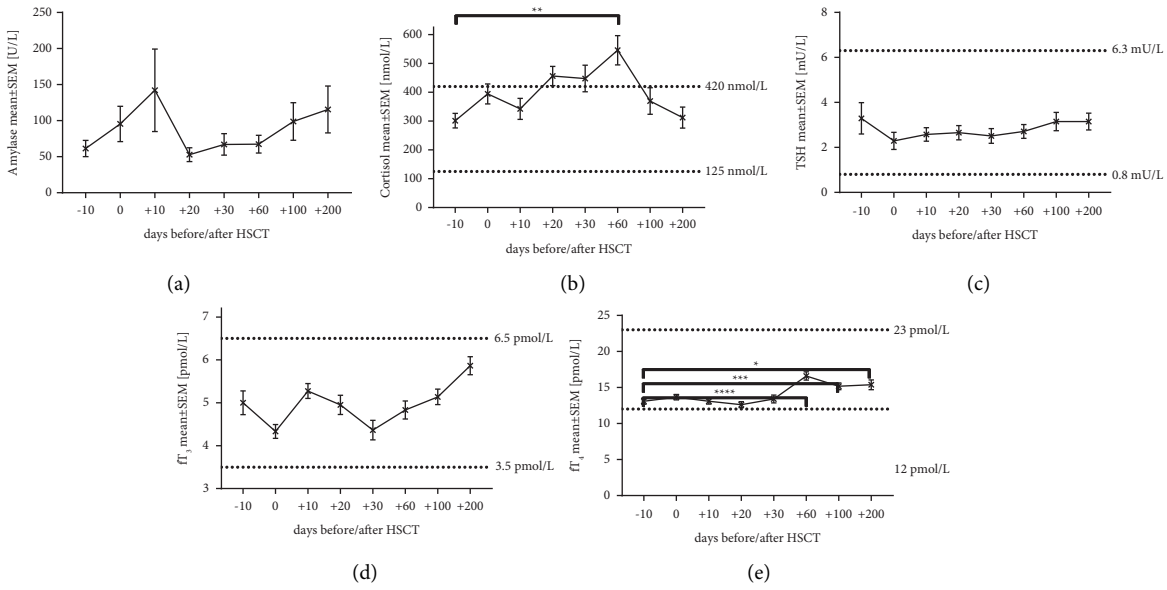

Figure 3: Laboratory markers. The graph shows the mean ± SEM of (a) salivary α-amylase (b) serum cortisol (c) thyroid-stimulating hormone (TSH), (d) free triiodothyronine (fT3), and (e) free thyroxine (fT4) of pediatric patients before and after allogeneic or autologous HSCT. Mean values were tested for significant differences to baseline values on day −10 before HSCT. If not otherwise indicated with symbols and respective brackets, the differences were not statistically significant. Dotted lines indicate upper and lower normal limits. Symbols directly below or above data points indicate significant decreases beyond the normal limits. Indication of the following symbols are $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; and $^{****}p < 0.0001$.

stress biomarkers with the somatic and mental distress, the results of the somatic subscales as rated by medical staff were correlated with the determined parameters that showed relevant changes in the course of the HSCT, i.e., salivary α-amylase (Figures 4(a) and 4(b)) and cortisol (Figures 4(c) and 4(d)).

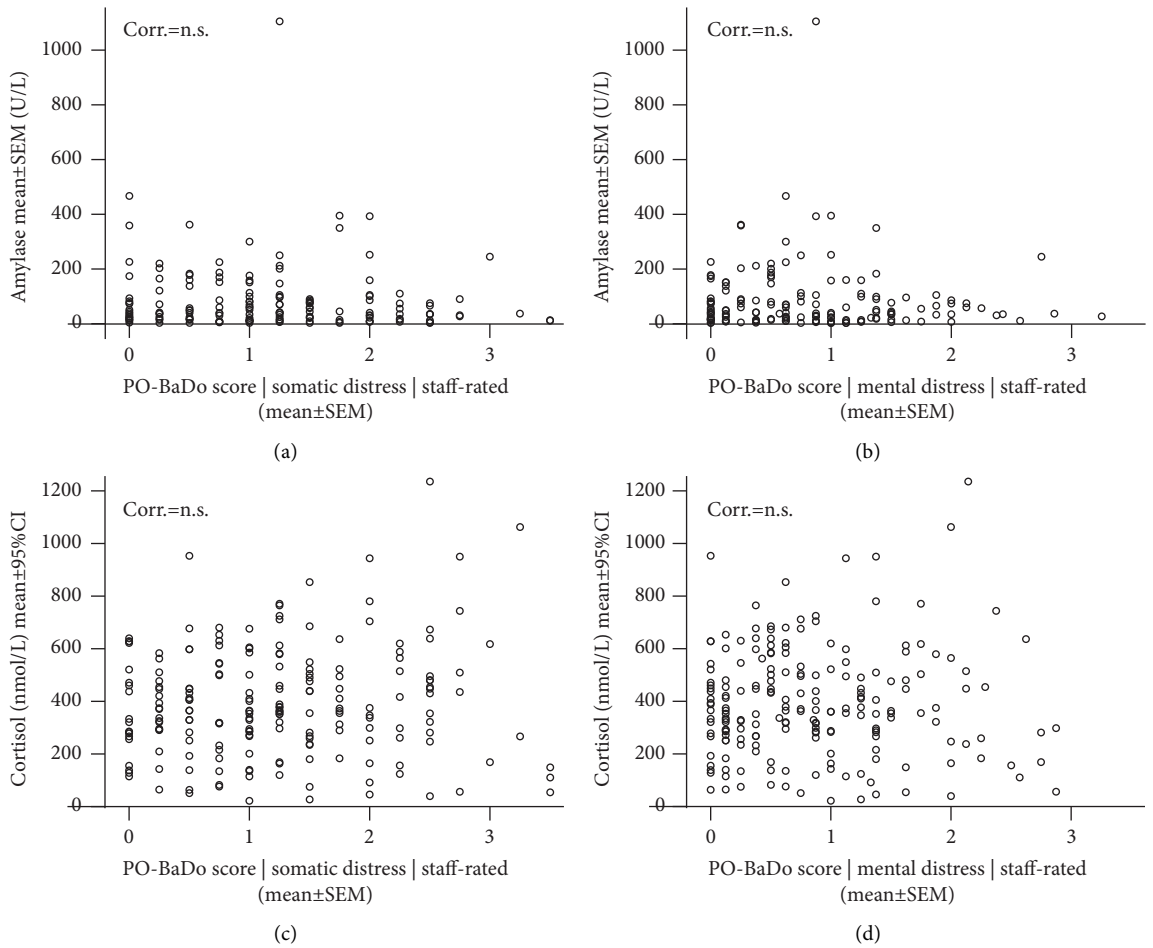

Figure 4: Correlations of PO-Bado scores and laboratory markers. The graph shows somatic (left column) or mental (right column) distress as rated by medical staff in correlation with laboratory results of salivary α-amylase (a, b) and serum cortisol (c, d) of pediatric patients before and after allogeneic or autologous HSCT. The graphs display the respective PO-Bado subscale scores and laboratory results of the days before, during, and after HSCT as mean ± SEM.

4. Discussion

Psycho-oncological support holds strong importance in complementing cancer therapy [25]. In the past two decades, the assessment of the health-related quality of life in pediatric cancer patients has gained considerably in importance [9]. Especially in these patients, a reliable external observer rating provides important data to detect patients at need of further support.

The results of this prospective study show that the somatic burden was rated similarly by parents and medical staff, with worsening at the time of transplantation until day +10 after HSCT. The scores were not significantly different between the two raters, with an overall high degree of alignment over the entire observation period. Although the inter-rater reliability of the mental distress subscale (item-based analysis) was lower when compared to the somatic distress scores, the results of both rater-groups were also not significantly different over the observation period. Contrary to our expectations, patient age was not an influencing factor in these analyses.

Although there were alignments of the somatic and mental distress—especially in the early posttransplant period—the slope estimate analyses of both showed that while the somatic burden declined over time after HSCT, the mental burden of the patients did not significantly change. This implies that the somatic burden of the transplantation is a relevant—but not exclusive—factor in the extent of the mental distress. This clearly shows that the decrease of the individual disease burden does not automatically lead to a decrease of mental distress up to day +200 after HSCT. In a multicenter, prospective study with a total of 165 children undergoing HSCT, the feasibility and the benefits of a multirater assessment of the health-related quality of life as experienced by the patients or rated by parents and nurses were demonstrated. In contrast to our results, the somatic and mental distresses were associated with a higher patient age. Although ratings differed by several factors—e.g., perceptions of the somatic burden—the authors demonstrated the benefit and feasibility of a multirater assessment of the quality of life of pediatric HSCT patients [12].

While quality of life in pediatric patients is mainly due to somatic impairment within the early posttransplantation period, i.e., within the first 30 days after HSCT, mental distress mainly comprises the first 6 months after HSCT. Previous data show a short-term deterioration in quality of life one month after HSCT, followed by improvement as early as 3 months after transplantation to levels better than pretransplant baseline and stability until one year after HSCT [26, 27]. The quality of life in autologous stem cell transplanted adults is higher compared with adults who had an allogeneic stem cell transplant [28]. In pediatric patients with leukemia, distress after induction therapy shows that children with standard-risk ALL experience significant impairment in health-related quality of life at the end of induction but improve rapidly. However, many still suffer from physical and social distress 3 months after therapy, suggesting that family support and physical functioning play a supporting role [29]. Certain influential factors seem to play a role in pediatric patients with ALL with regard to the assessment of quality of life. In high-risk ALL, girls and older children had a poorer quality of life. For standard-risk ALL, those with lower household income and unmarried parents had a poorer quality of life [30]. In addition, interviewed fathers appeared to have lower quality of life perceptions compared with interviewed mothers [31].

The hypothalamus-pituitary-adrenal (HPA) axis and the hypothalamus-pituitary-thyroid (HPT) axis are interdependent key regulators of neurological, neuroendocrine, endocrine, psychological, and immunological functioning [32, 33]. These axes can be significantly altered due to stress disorders, cancer, or inflammation [34–41]. In contrast to alpha-amylase and cortisol, thyroid hormone concentrations can decrease with increased exercise [32, 42]. In the present study, TSH and fT4 showed descriptively lower values between day 0 and day 30 and increased—as did fT3—towards the end of the observation period. Although we identified a significant increase of T4 with a peak on day +60 after HSCT, relevant increases or decreases beyond the normal levels of the thyroid-function markers were not observed. Previous works have described the effects of the conditioning regimen on the gonads and the hypothalamo-pituitary-gonadal control of pediatric and adolescent patients [21–23]. Although hypothyroidism is a known long-term consequence of HSCT in childhood, to date there are no published data on thyroid hormone changes in the first 30 days after HSCT for either adults or children [43–45].

Both salivary α-amylase and cortisol are suggested as useful biomarkers for detecting acute and chronic physical and psychological stress [46–51]. In the present analysis, the levels of the stress biomarker cortisol increased over time and peaked on day +60 after HSCT. In contrast to the cortisol, a peak of the salivary α-amylase levels occurred on day +10 after HSCT, followed by a drop on day +20 after HSCT and then a subsequent and constant increase until the end of the observation period. Accordingly, reference data for the concentration profile of salivary α-amylase during pediatric HSCT were not found in the existing literature.

During allogeneic HSCT, salivary α-amylase levels of 41 adults were significantly higher after one-month post-transplant in comparison to pretransplant baseline levels [52]. During autologous HSCT of 25 adult myeloma patients, a significant difference of the salivary α-amylase levels was not observed between day −3 pretransplant and day +7 posttransplant, which was identified as the day of the maximum severity of oral mucositis [53].

5. Conclusions

The perceptions of the somatic and mental distress of parents and medical caregivers of pediatric patients undergoing HSCT were significantly correlated and not dependent on the patient's age. The time period between the days of transplantation until day +10 was rated as the most mentally and somatically distressing. While the somatic burden declined over time, the mental distress in the patients remained at a stable level until the end of the observation period (6 months after HSCT), emphasizing the importance of further psychological and psycho-oncological support in these patients. The use of salivary α-amylase as a suitable distress detection marker in pediatric patients undergoing HSCT should be further investigated.

Abbreviations

a.m.: Ante meridiem, before noon
CI: Confidence interval
CRP: C-reactive protein
GvHD: Graft-versus-host disease
HSCT: Hematopoietic stem cell transplantation
i.e.: Id est, that is
ICD-11: International Classification of Disease-11
mg/dL: Milligram per deciliter
MMFD: Mismatched family donor
MSD: Matched sibling donor
mU/L: Milliunits per liter
MUD: Matched unrelated donor
n: Sample size
ng/mL: Nanogram per milliliter
nmol/L: Nanomole per liter
p: Probability value
PCT: Procalcitonin
pmol/L: Picomole per liter
PO-Bado: Basic Documentation for Psycho-Oncology
SEM: Standard error of the means
T3: Triiodothyronine
T4: Thyroxine
TSH: Thyroid-stimulating hormone
U/L: Units per liter.

Data Availability

The data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethical Approval

The prospective study was performed in accordance with the Helsinki Declaration adopted by the 18th WMA General

Assembly, Helsinki, Finland, June 1964, and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. The legal basis for the data processing is Art. 6, 7, 9, and 89 of the general data protection regulation (EU) 2016/679 of the EU in combination with §§ 4, 5, 6, 8, 9, 12, and 13 of the Landesdatenschutzgesetzes Baden-Württemberg in its current form of May 25th, 2018. Approval for this analysis was granted by the Institutional Ethics Committee (ID 434/2019BO1).

Consent

Written informed consent to participate in this study and for publication of the data were obtained from all participants and, if necessary, their parents/legal representatives.

Conflicts of Interest

All the authors declare that they have no conflicts of interest.

Authors' Contributions

MD, KMCS, and ST were responsible for the conception and design of this study. All authors collected the data. ST, JX, DW, KMCS, and MD analyzed and interpreted the data. KMCS, MD, ST, and JX wrote the manuscript. All authors were substantially involved in the drafting and/or critical revision of the manuscript. All authors have read and approved the final manuscript.

Acknowledgments

This work was supported by the Förderverein für Krebskranke Kinder Tübingen e.V., Tübingen, Germany.

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