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ORIGINAL ARTICLE

Facing the large variety of life-limiting conditions in children

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Abstract

Life-limiting conditions in children in specialized pediatric palliative care (PPC) are manifold. The "Together for Short Lives" (TfSL) association established four disease categories, which represent the most common illness trajectories. Better understanding the palliative care needs and symptoms of children within these TfSL groups will result in improved anticipation of clinical problems and tailored care. During this retrospective single-center cohort study, 198 children, adolescents, and young adults (CAYAs) were in PPC. Mean age at referral was 8.7 years (range 0.0–25.0), mean duration of care 355 days (range 1–2754). One hundred six (53.5%) CAYAs died during the study period. Sixty-five (32.8%) CAYAs were assigned to TfSL-1, 13 (6.6%) to TfSL-2, 49 (24.7%) to TfSL-3, and 71 (35.9%) to TfSL-4. Home visits were conducted on average every 9.6 days in TfSL-1, 18.9 days in TfSL-2, 31.7 days in TfSL-3, and 31.8 days in TfSL-4 (p value < 0.01).

Conclusions: Intensity of palliative care significantly differed between the TfSL groups. Neurological and gastrointestinal symptoms were most prominent across all TfSL groups. Symptom cluster analysis showed distinct clusters in TfSL-1 (cluster 1, fatigue/lack of appetite/nausea/somnolence; cluster 2, dyspnea/fear/myoclonus/seizures/spasticity) and TfSL-3/4 (cluster 1, spasticity; cluster 2, all other symptoms).

What is Known:
- *The four TfSL (together for short lives) groups represent the four most common illness trajectories of pediatric palliative care patients.*
- *Better understanding the palliative care needs and symptoms of children within these four TfSL groups will result in improved anticipation of clinical problems and tailored care.*

What is New:
- *In our study, TfSL-1 represented the largest individual group of patients, also requiring the most intensive care (defined by the number of visits per days of care).*
- *Symptom cluster analysis revealed distinct symptom clusters in TfSL-1 and TfSL-3/4, which can be used to anticipate clinically common challenges in these patients.*

Keywords Pediatric palliative care · Symptom clusters · Together for short lives (TfSL)

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Introduction

There are at least 50,000 children under 19 years across Germany with a life-limiting or life-threatening condition (LLC) who have—according to German law—the right to specialized pediatric palliative care (PPC) services. Recent data obtained by the charity "Together for Short Lives" groups indicate a prevalence of children with LLCs of 33 per 10,000 children and adolescents (aged 0–19 years) in the UK and of 0.27% in the general white population. These numbers are even higher in the South Asian (0.48%) and black (0.42%) population. Moreover, there is a steady increase in prevalence over time in all age groups and particularly in 16- to 19-year-olds [9]. According to the same study group, this broad spectrum of diseases can be divided into four categories, which outline the four types of illness trajectories of children in PPC [1]. These are classified as follows: group 1, life-threatening conditions for which curative treatment may be feasible but can fail; group 2, conditions in which premature death is inevitable; group 3, progressive conditions without curative treatment options; group 4, irreversible but non-progressive conditions causing severe disability, leading to susceptibility to health complications and likelihood of premature death. However, despite this classification, disease trajectories often remain unpredictable and phases of disease stability might alternate with times of acute deterioration. Some children might experience a notable stabilization of their respective conditions without further need of PPC.

The TfSL groups demonstrate the range of conditions children are diagnosed with and are intended to show how children may benefit from full PPC support or elements of PPC during their lives. The grouping is not always easily achieved but is thought to be important for planning including the assessment of needs. Indeed, diagnoses are only part of the process; the severity of symptoms and subsequent complications, as well as the needs of and their impact on the child and the family, need to be taken into account. However, to date, only very limited data exist exploring the differences in symptoms and needs of these children in palliative home care [3].

Children with LLC often face a broad spectrum of interrelated symptoms, with most patients reported experiencing a variety of simultaneous symptoms [3, 8, 14, 21, 25, 26, 31]. Although identification of (distressing) symptoms is an indispensable precondition for effective symptom control, this is often not easily achieved in these children not least as many of them are nonverbal. Moreover, anticipation of foreseeable, highly distressing clinical problems with emphasis on preparing patients and parents is an important goal in PPC [17]. A better understanding of symptom presentation in children with LLC by providing prognostic information can pave the way to a more informed clinical decision-making and, thus, quality of life [7, 27].

Adult patients with incurable cancer likewise typically show a high symptom burden. Symptom management in these patients is shifting from treating single symptoms to managing the dynamic nature of multiple symptom constellations. In addition, recent research has reported on the phenomenon of symptom clustering in these patients [6, 7, 11, 22]. A symptom cluster (SC) is generally defined as two or more concurrent and interrelated symptoms which occur together—with a high degree of predictability—but that do not require a common etiology [2, 7].

For that reason, we analyzed palliative home care provided by one of the largest specialized pediatric palliative care teams (PPCT) in Germany over 4 years corresponding to about 200 children, adolescents and young adults (CAYA) with LLCs. The overall aim of the study was—first—to determine the clinical characteristics, symptoms, and supportive needs at referral to PPC in each TfSL group—second—to compare these data across the four patient groups, and—third—to explore SCs in and between each group.

Patients and methods

This study was conducted as a single-center analysis of patients in the care of the PPCT of the Children's University Hospital Duesseldorf between 01 January 2013 and 15 September 2016. Details on the PPCT and patients' referral are given elsewhere [18, 19]. All children, adolescents, and young adults (0–25 years) (subsequently referred to collectively as "patients" or "CAYAs"), who were referred to palliative home care, were included. Two physicians assigned patients to the four TfSL groups independently. Duration of palliative care was defined as the time between the start of palliative home and community (including hospice) care (of note, this can be dated before the above-mentioned study starts) and the date of data collection (15 September 2016), interruption of care or death, as applicable.

Patient data were routinely entered into a web interface database after each home visit by the members of the PPCT and from there extracted and further processed. The information included demographic data, number and time of home visits and telephone contacts, symptoms, medications, and care tools. Symptoms were graded according to the World Health Organization (WHO) (WHO 0-WHO 4) or otherwise as none/weak/medium/severe or absent/present (if binary). When required, free text entries were transformed into evaluable data for subsequent analyses by a physician.

To estimate symptom burden at referral to palliative care, the median number of symptoms (total of 49) was calculated by counting the number of symptoms documented on each home visit within the first 30 days of care, then divided by the number

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of home visits in that time period. Symptom burden in the last 30 days of care was calculated accordingly. Patients, who were referred to PPC before the start of the electronic documentation, were excluded from the symptom-related analysis only. For reasons of clarity and better comparability of symptoms between the four TfSL groups, the 49 recorded individual symptoms were then classified into nine symptom categories (body temperature instability, gastrointestinal, emotional instability/agitation, general condition, hematopoietic and vascular system, neurological, respiratory, skin affections, urinary tract). Similarly, the medications were classified into 28 drug categories.

For symptom cluster analysis, the clinically most prominent and diverse individual symptoms (i.e., seizures, fear, fatigue, dyspnea, lack of appetite, myoclonus, nausea, somnolence, spasticity) were selected. The number of symptoms selected was limited to nine symptoms for statistical reasons (due to the overall small numbers of patients in each TfSL group).

The study was conducted according to the Declaration of Helsinki and was approved by the ethics committee of Heinrich Heine University Duesseldorf, Germany, (reference number 4969) and written informed consent was obtained.

Statistical methods

Nominal-scaled variables were described by absolute and relative frequencies as well as by bar charts. Continuous and ordinal-scaled variables were described by mean, standard deviation, minimum, maximum, median, Q1, and Q3 as well as by boxplots. Continuously scaled data were analyzed using ANOVA (in case the continuous scaled variable is normally distributed). In case a continuous scaled variable was not normally distributed, the non-parametric Kruskal-Wallis test was applied. Ordinal-scaled data were analyzed using the non-parametric Kruskal-Wallis test. Nominal-scaled data were analyzed using the chi-squared test (4×2, 4×3, 4×4 tables). In the case of expected cell frequencies ≤ 5, Fishers exact test was applied. An alpha level of 0.05 was used. The analyses were not corrected for multiple testing.

Using a hierarchical cluster analysis (block-distance, between-group linkages) of variables representing the cumulative occurrence of each symptom, it was investigated whether specific groups of symptoms exist, which are related to each other, whereby the results for the solutions with three clusters were used for all patients and with two clusters for each subgroup. Statistical analysis was performed using SPSS 20.0 software (Armonk, NY: IBM Corp) and R (R Core Team 2015/18).

Results

TfSL-4 represents the largest patient subgroup

In the study period, the PPCT cared for 198 CAYAs (for diagnoses, please refer to Table 1). One hundred three (52.0%) patients were male, mean age at referral was 8.7 years (range 0.0–25.0 years). Most CAYAs (119; 60.1%) had a German background. Mean duration of care was 355 days (range 1–2754), and the mean number of home visits was 12.5 (range 1–80).

Fifty-eight (29.3%) children were rehospitalized during PPC at least once. Forty (20.2%) children were eventually discharged from PPC (due to disease stabilization $n = 22$, identification of new therapeutic approaches resulting in clinical stabilization $n = 3$, other teams taking over $n = 3$, parental wishes $n = 4$, relocation to a different city/country $n = 3$, health insurance denying coverage of costs $n = 5$) [14].

Less than half of all patients were still alive at the end of the study period (92; 46.5%); 85 (80.2%) out of the 106 CAYAs who died, did so at home/in hospice. Median age at the time of death was 7.1 years (range 0.1–27.6 years), 17 (16.0%) deceased patients were less than 1 year of age.

A total of 65 (32.8%) CAYAs had diagnoses within the spectrum of TfSL-1, 13 (6.6%) within group 2, 49 (24.7%) within group 3, and 71 (35.9%) within group 4. Details on demographic data and TfSL group distribution can be found in Table 2.

TfSL-1 patients had the most intensive contact with the PPC team

In total, the PPC team visited the patients 2472 times during the study period. Most home visits were planned (1912, 77.3%). On average, group 1 patients were seen once every 9.6 days, group 2 patients every 18.9 days, group 3 patients every 31.7 days, and group 4 patients every 31.8 days (p value < 0.01).

Looking at all unplanned home visits, group 1 patients needed one unplanned home visit on average every 33.2 days, group 2 patients every 48.7 days, group 3 patients every 130.0 days, and group 4 patients every 169.2 days only (p value < 0.01).

The pattern for telephone calls was similar, with members of the PPC being on the phone on average once every 8.1 days with group 1 patients, every 10.0 days with group 2, every 20.9 days with group 3, and every 25.8 days with group 4 patients (p value < 0.01). (Fig. 1).

Symptom burden was high in all groups

At the start of PPC, patients presented with a variety of symptoms, the most prominent across all TfSL groups were neurological and gastrointestinal. The subgroups expectedly showed differences in the symptom severity distribution. In group 1 patients—beside pain—the five most commonly recorded symptoms were difficulty moving, paleness, obstipation, nausea, and vomiting; in group 2, these were difficulty moving, agitation, diarrhea, dyspnea, and bleeding/

Table 1 Diagnoses of 198 children, adolescents, and young adults with life-limiting conditions assigned to TfSL groups. All diagnoses, which were assigned to more than one patient, are given. Please refer to the supplement for a full list of diagnoses

TfSL group	Diagnoses	Count
1	Glioblastoma	8
1	Diffuse intrinsic pontine glioma	6
1	Neuroblastoma	6
1	Astrocytoma	5
1	Osteosarcoma	5
1	Rhabdomyosarcoma	5
1	Ewing sarcoma	4
1	Acute lymphoblastic leukemia	3
1	Atypical teratoid/rhabdoid tumor	3
1	Acute myeloid leukemia	2
1	Intracranial germ cell tumor	2
1	Medulloblastoma	2
2	Duchenne muscular dystrophy	3
2	Biliary atresia	2
2	Hyoplastic left heart syndrome	2
2	Unknown syndrome with multiple malformations (mainly cardiac)	2
3	Spinal muscular atrophy	8
3	Mitochondrial disease of unknown etiology	4
3	Metachromatic leukodystrophy	3
3	Alexander disease	2
3	Leigh's disease	2
3	Mucolipidosis type II	2
3	Neuronal ceroid lipofuscinosis	2
3	Nonketotic hyperglycinemia	2
3	Pearson syndrome	2
3	Sphingolipidosis	2
3	Unclear syndrome (mainly metabolic)	2
4	Unclear syndrome with multiple malformations	14
4	Perinatal asphyxia	8
4	Hypoxic brain injury due to near drowning	6
4	Trisomy 18	5
4	Cerebral palsy of unknown etiology	4
4	Posttraumatic brain injury	3
4	Battered child syndrome	2
4	Campomelic dysplasia	2
4	Encephalitis of unknown etiology	2
4	Herpes simplex encephalitis	2
4	Intraventricular hemorrhage	2
4	Neonatal sepsis	2

hematoma. Groups 3 and 4 shared four symptoms (difficulty moving, spasticity, seizures, and paleness); only the fifth symptom was different (dyspnea in group 3 and agitation in group 4).

On average, group 4 patients had the highest symptom load (9.8 recorded symptoms in the first 30 days), followed by group 1 (9.3 symptoms), group 3 (8.0 symptoms), and group 2 (7.9 symptoms) (statistically not significant).

The severity of difficulty moving, seizures, spasticity, and hypersalivation was statistically higher in TfSL-4 compared with TfSL-1/2. TfSL-1 patients on the contrary had more pronounced bleeding/hematoma, nausea, obstipation, and urinary retention compared with the TfSL-3/4 patients.

TfSL-4 patients suffered from more pronounced symptoms, especially in the symptom categories neurological and respiratory symptoms. There were no statistically significant

Table 2 Demographic data and clinical characteristics of 198 children, adolescents, and young adults with life-limiting conditions assigned to TfSL groups

	All children	TfSL group 1	TfSL group 2	TfSL group 3	TfSL group 4
Number	198	65	13	49	71
Gender, male (%)	103 (52%)	39 (60%)	6 (46%)	22 (45%)	36 (51%)
Age at referral of all children, median (range in years)	8.4 (0.0–25.0)	11.2 (0.0–22.5)	8.4 (0.2–23.9)	1.8 (0.0–24.2)	7.1 (0.1–25.0)
No. of patients < 1 year at referral	17 (8.6%)	1 (1.5%)	2 (15.4%)	8 (16.3%)	6 (8.5%)
No. of patients > 18 years at referral	12 (6.1%)	6 (9.2%)	2 (15.4%)	2 (4.1%)	2 (2.8%)
Duration of palliative care, median (range in days)	122 (1–2754)	39 (1–441)	91 (3–545)	288 (1–2248)	268 (2–2754)
Duration of PPC only for deceased children, median (range in days)	44.5 (1–1574)	33 (1–322)	38 (3–181)	86 (1–1382)	114 (2–1574)
Home visits, median (range)	8 (1–80)	7 (1–41)	6 (1–20)	10 (1–80)	8 (1–64)
No. of deceased children (%)	106 (54%)	56 (86%)	7 (54%)	21 (43%)	22 (31%)
Place of death, *n* (%)					
At home	67 (63%)	45 (80%)	5 (71%)	8 (38%)	9 (41%)
In hospice/PCU	16 (15%)	6 (11%)	1 (14%)	3 (14%)	6 (27%)
In hospital	23 (22%)	5 (9%)	1 (14%)	10 (48%)	7 (32%)
Age at death, median (range in years)	7.1 (0.1–27.6)	10.4 (0.1–22.6)	11.2 (0.2–24.1)	1.9 (0.1–26.7)	3.0 (0.2–27.6)

differences between symptom categories in TfSL-1 and TfSL-2, TfSL-2 vs TfSL-3, and TfSL-3 vs TfSL-4 (Table 3).

To analyze the different age groups, we next classified the three groups children (0–< 10 years), adolescents (10–< 19 years), and young adults (older than 19 years). Children, adolescents, and young adults had equal symptom burden within the first 30 days of care with the one exception of neurological symptoms, which were more pronounced in the young adults. Neurological symptoms were the highest scoring symptom category across all three age groups.

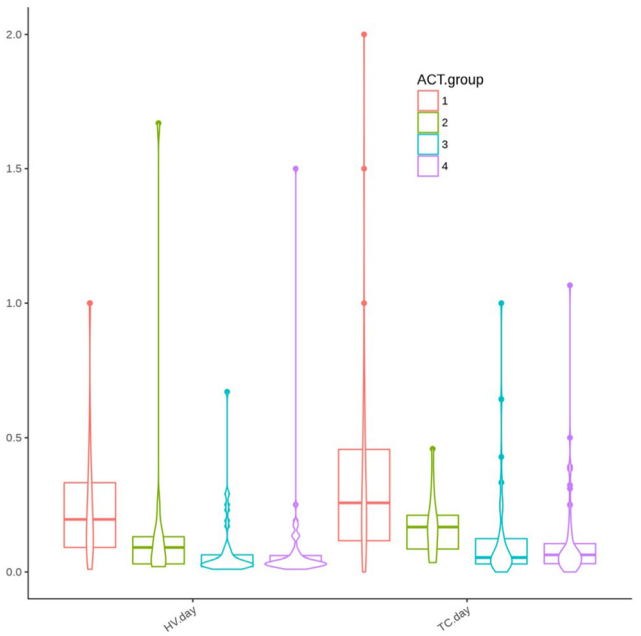

Fig. 1 Number of home visits (HV) and telephone contacts (TC) per days in care. Color code of the four TfSL groups (ACT groups) as indicated

The picture was different during the last 30 days of care. Here, symptom burden had generally decreased in the children and had mostly stayed constant in the adolescents (only neurological symptoms increased). By contrast, symptom burden was markedly higher in the young adult patients in the last compared with the first 30 days of care. This was despite the fact that equal percentages across all three age groups fell into TfSL 1 and 4, respectively (the two largest TfSL groups).

Symptom clusters in TfSL-1 are markedly different from those in TfSL groups 3/4

Symptom cluster (SC) analysis was performed to identify associations among symptoms (i) in all children with LLC and (ii) separately in the four TfSL subgroups (as those patients are expected to present with similar disease trajectories and, therefore, it might be hypothesized also with similar symptom profiles).

In cluster analysis of all children with LLC including dyspnea, fatigue, fear, lack of appetite, myoclonus, nausea, seizures, somnolence, spasticity, and pain, the following three symptom clusters could be defined and are shown by a dendrogram in Fig. 2a. In cluster 1, fatigue, lack of appetite, nausea, and somnolence were co-occurring. Cluster 2 encompassed dyspnea, fear,

Table 3 Comparison of symptoms at the start of PPC between the TfSL groups 1, 3, and 4. Due to low patient numbers, data on group 2 are not shown. Group comparisons are shown horizontally, symptoms vertically (the first two lines refer to symptom categories, the remaining lines to individual symptoms). All statistically significant symptom differences are highlighted in color (all p values < 0.05). Yellow color, group 1 patients were more severely affected by the respective symptom compared with the other groups; blue color, group 1 patients were less severely affected by the respective symptom compared with the other groups

symptom	1 vs 3	1 vs 4	3 vs 4
neurological (general)			
respiratory (general)			
difficulty moving			
hematoma			
hypersalivation			
nausea			
obstipation			
seizures			
spasticity			
urinary retention			

myoclonus, seizures, and spasticity, while the pain was a very independent symptom (cluster 3).

Next, we performed symptom cluster analysis for TfSL groups 1, 3, and 4 including all above-mentioned symptoms except pain with the results with 2 clusters used for each TfSL group. Due to small patient numbers, SC analysis for group 2 patients was not informative and is thus not shown. In TfSL-1, cluster 1 consisted of fatigue, lack of appetite, nausea, and somnolence. Cluster 2 included dyspnea, fear, myoclonus, seizures, and spasticity. While spasticity and myoclonus were similar symptoms, both dyspnea and nausea were independent symptoms. Noteworthy, in contrast to all other TfSL groups, TfSL-1 clearly split into two clusters (Fig. 2b). In TfSL-3/4, spasticity clustered separately from all other symptoms, while no clear clustering of other symptoms could be defined. In TfSL-3, dyspnea and seizures were somewhat independent symptoms compared with fatigue, fear, lack of appetite, myoclonus, nausea, and somnolence (Fig. 2c), while seizures and myoclonus were rather independent symptoms in TfSL-4 (Fig. 2d).

Analgesics and antiepileptics were the most frequently prescribed medications

Given the high symptom burden across all patient groups, a large variety of different medications were prescribed to the patients (range 0–12). Mean numbers of drugs were 4.8 in group 1, 4.8 in group 2, 5.2 in group 3, and 5.1 in group 4 (statistically not significant). Overall, the most frequently administered drugs were analgesics of any kind, antiepileptics, and antacids (see Fig. 3).

Looking at the differences between the groups, non-opioid analgesics were more frequently prescribed to group 1 patients in comparison to group 3 ($p < 0.001$) and group 4 ($p < 0.001$). The same was true for opioid analgesics (group 1 vs 3 $p = 0.008$; group 1 vs 4 $p < 0.001$) and cortisone (group 1 vs 3 $p < 0.001$; group 1 vs 4 $p = 0.001$).

Inversely, skeletal muscle relaxants were most commonly used in group 3 (group 3 vs 1 $p = 0.009$) and group 4 (group 4 vs 1 $p < 0.001$). The same was true for hypnotic drugs (group 3 vs 1 $p = 0.004$; group 4 vs 1 $p = 0.028$).

TfSL-1 patients needed the fewest care tools

In addition to the different medications, a large variety of medical and therapeutic appliances (Fig. 4) was needed by the patients, again with differences between the groups. Mostly group 3/4 had feeding equipment at home, whereas special beds as well as mobility equipment were needed by patients of all groups. None of the group 1 patients was on permanent ventilation. Overall, 40% of all group 1 patients and 11.3% of all group 2 patients had no special medical equipment in the mentioned categories at home, whereas all group 3 and 4 patients needed at least one item (p value for the comparison group 1 vs 3 was 0.001 and group 1 vs 4 was < 0.001).

Discussion

As the TfSL system is based on the theoretical (four) types of illness trajectories of children in LLC [12], one would expect differences in PPC between the four TfSL groups. Our study indeed showed several significant differences. The 98 different diagnoses in this study reflect the large variety of LLCs in children in PPC. Children were roughly equally distributed to

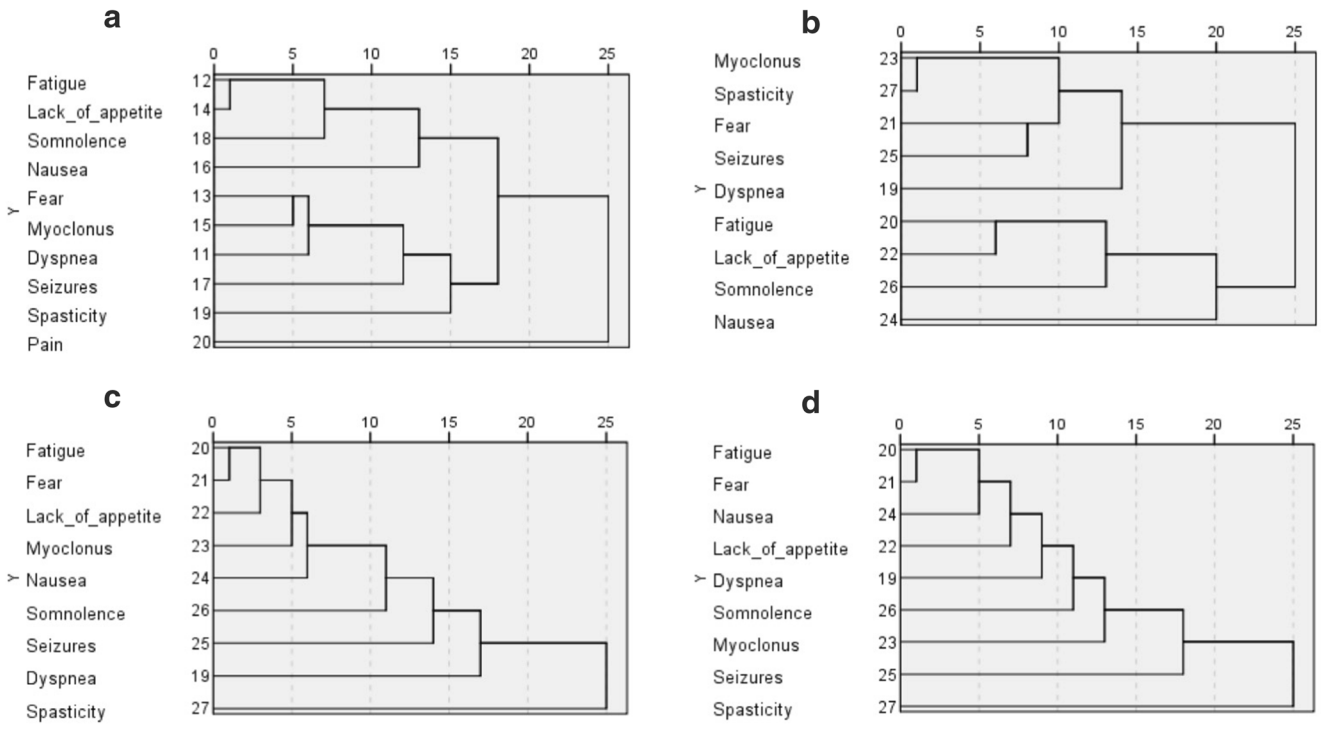

Fig. 2 Dendrograms of symptom clusters of **a** all children with life-limiting conditions, **b** TfSL-1 patients, **c** TfSL-3, and **d** TfSL-4 patients

TfSL-1 and 4 (33% and 36%, respectively), followed by TfSL-3 (25%), whereas only 7% of the patients contributed to TfSL-2. The diagnosis distribution in our study was thereby similar to previous reports on children in PPC [3, 26].

Duration and intensity of care differed significantly between the TfSL groups. Patients in TfSL-1 received the most intensive care. This is reflecting the rapidly progressing diseases and high symptom burden in children with cancer.

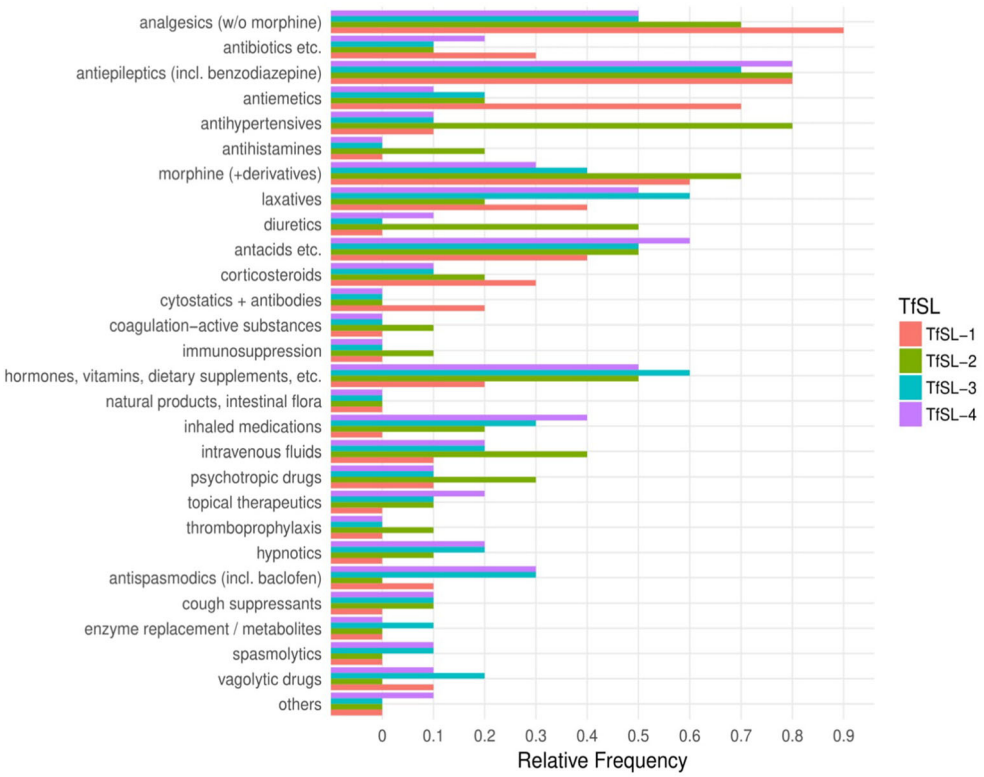

Fig. 3 Overview of the different medication categories. To enable the comparison between the medication categories, relative prescription frequencies are reported (each category in each patient group was scaled to 1, regardless of the number of patients in each group). Multiple answers were possible

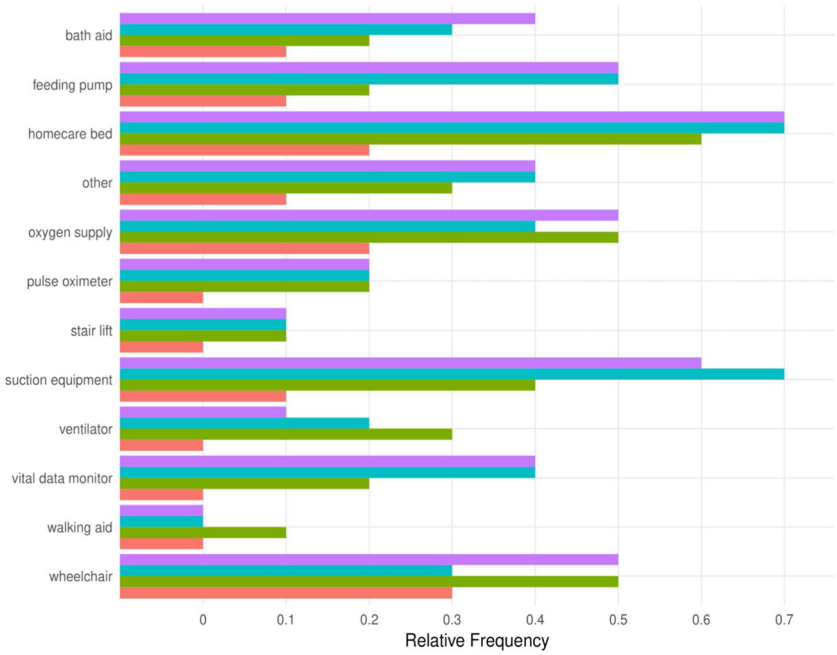

Fig. 4 Overview of the different care tools, which were available to the patients and their families. To enable the comparison, relative frequencies are reported (each category in each patient group was scaled to 1, regardless of the number of patients in each group). Multiple answers were possible (color code as in Fig. 3).

Additionally, oncologic patients, especially those with hematologic malignancies, are referred late to PPC [13, 16], meaning that symptom burden in these patients is usually high already at the onset of palliative care.

By contrast, CAYAs in TfSL-4 and in line with the trend in TfSL-3 received less intensive care. These findings have previously been reported [3]. Most likely due to the low number of patients in TfSL-2, we could only demonstrate trends between TfSL-2 and other TfSL groups but not determine statistically significant differences. However, when interpreting these data, one has to keep in mind that—due to great differences in survival time after referral to PPC between the four TfSL groups—the intensity of care in TfSL-3/4 might be underestimated.

When looking at the symptom load in each patient group, again, this was similar among TfSL-1 and 4 and slightly higher compared to TfSL-2 and 3. However, there is a wide spectrum of predominating symptoms with several differences between the groups. The most frequent symptoms in TfSL-1 were nausea, constipation, urinary retention, and hemorrhages. In our study, the TfSL-1 group is exclusively composed of cancer patients, and our results slightly differ from what has previously been reported in children with advanced cancer [10, 23, 24, 28, 29]. However, in our cohort, there was a predominance of brain tumor patients that might explain some of these differences. Recent research has indicated, that cancer diagnosis and tumor/metastases localization substantially influence symptoms at the end of life in children with cancer [20]. In line with this, previous studies on SCs in adult cancer patients found that the cancer site influenced cluster composition [6, 7]. In our cohort, symptom cluster analysis of TfSL-1 split into two groups of variables pointing towards relevant differences within this group. However, our study was not composed to analyze differences among TfSL-1 patients. Thus, further studies are necessary to explore symptom clusters in pediatric cancer patients.

A large variety of neurological symptoms was significantly more frequent in TfSL-4 and partly in TfSL-3 patients compared with TfSL-1. In addition, most of the children were affected by many simultaneous symptoms. This is not unexpected as most of them suffered from complex neurological conditions.

Usually, CAYAs with LLCs are affected by multiple concurrent symptoms, which are often difficult-to-treat and considerably impair their quality of life. Thereby, symptom research in adult cancer patients has recently focused on multiple symptoms and the occurrence of so-called SC, describing the presence of various concurrent symptoms that are related although may not have a common cause [5, 7]. By identifying and treating such SC, it is hoped to overcome the shortcoming of treating single symptoms for improving the quality of life [4, 5, 30]. To this end and to address the challenging task of treating the multiple/complex symptoms in children with LLCs, we additionally elucidated symptom cluster in the four patient groups. And indeed, as depicted above, different SCs could be identified in TfSL group 1 compared with groups 3/4. Noteworthy, despite significant differences in demographic data, TfSL-3/4 patients shared many symptom commonalities.

Our study for the first-time explored SC in children with LLCs and suggests its existence. Considering the distressing and suffering character of many symptoms in PPC, SC analysis may offer new strategies for the management of multiple symptoms and symptom constellations and guide the challenging task of anticipation and advance care planning in

pediatric palliative care [15, 17]. However, since SC research is still in its early stages, many questions remain open. Above all, yet, it remains unclear whether SC analysis and, thus, treating SC instead of several individual symptoms, may finally contribute to improved quality of life in children with LLC.

Conclusion

In our single-center study, duration and intensity of palliative care significantly differed between the four TfSL groups with TfSL-1 patients needing the most intensive care in the shortest time. Symptom cluster analysis revealed two (different) symptom clusters in cancer patients (TfSL-1). Furthermore, multicenter research on symptom clusters in children with life-limiting conditions is urgently warranted to explore symptom clusters in children with LLC and its impact on treating distressing symptoms and advance care planning.

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Author contribution JIH designed the study, drafted the manuscript, collected, and analyzed data. HW helped with the acquisition of data. JW performed data processing and statistical analysis. GG, LT, and SB cared for the patients, acquired data, and provided important clinical information. TK performed statistical analysis including symptom cluster analysis. GJ is the director of the PPCT, cared for the patients, acquired data, and provided important clinical information. HW, JW, GG, LT, SB, TK, and GJ critically reviewed and revised the manuscript for important intellectual content. MK conceptualized and designed the study, supervised data analysis, and drafted the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Compliance with ethical standards The study was conducted according to the Declaration of Helsinki and was approved by the ethics committee of Heinrich Heine University Duesseldorf, Germany, (reference number 4969) and written informed consent was obtained.

Conflict of interest The authors declare that there is no conflict of interest.

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