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Original Article

Symptom Evaluation in Pediatric Oncology Outpatient Setting; A Cross-Sectional Study

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Abstract

Detection and management of cancer-related symptoms is a key component in children's quality of life. We evaluate symptoms and their severity in Iranian pediatric oncology outpatients using Therapy-Related Symptom Checklist for Children (TRSC-C). This was a cross-sectional study conducted in two outpatient pediatric oncology settings. We included all patients aged between 5-17 years. The validated and reliable Persian translated version of TRSC-C was used to study the symptoms. Overall 1425 symptoms were documented from 162 patients (mean age 8.6 ±3.2, acute lymphoblastic leukemia: 76.5%). In 96.3% of patients at least one symptom was present. Twenty (12.34%) patients experienced at least 15 events. Irritable, loss of appetite, cough, pain and hair loss were the top 5 frequent symptoms. The highest mean severity scores were also belonged to irritable, loss of appetite, and hair loss. We found no significant difference between gender, age group or time of the last chemotherapy with mean total severity scores or total number of symptoms (P>0.05). In conclusion, TRSC-C is an appropriate symptom assessment checklist for our settings and it would give us the ability to track symptoms and designate clinical interventions based on the frequent and severe identified symptoms.

Keywords: Pediatric oncology; Symptom frequency; Symptom severity; Therapy-Related Symptom Checklist for Children; TRSC-C.

1. Introduction

Cancer is the main cause of mortality associated with illness in children. However, nowadays it can be optimally cured in up to 80% of pediatric patients [1-3] and the overall survival has improved [3-5].

It was previously demonstrated that the management of cancer-related symptoms is the

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key component in improving children's quality of life [5]. Severe distress resulting from symptoms may delay the scheduled treatments, diminish their effectiveness and prolong the rehabilitation process [6]. Hence, a better understanding and improved assessing, monitoring and managing of adverse effects, is needed for a successful treatment [7-9]. However, symptoms can be easily ignored. First of all, due to the priority of outcome in practice [6, 10], pediatric oncologists and researchers tend to overlook the symptoms [6]. Additionally, sometimes attitudes of parents and children are based on their beliefs in obligatory suffering in cancer treatment, and absence of helpful interventions to relieve the symptoms [11]. Thus, underdiagnosed and under documented symptoms [9, 12] might lead to the limitation of evidence-based data in this field [7]. This sometimes results in unnecessary suffering of children [10]. However, the available information helped the professionals to better realize the needs of children regarding their symptoms so far [13].

Several methods are available for identifying symptoms. Detecting and reporting symptoms by parents and healthcare providers is a common practice. However, there are variations between issues that children, parents [3, 14] and clinician report [3, 15]. Chart review is another standard method. However, despite the accessibility to the vast amount of data [16], under documentation of symptoms still exists [17], especially in the outpatient settings [16]. Since recent studies showed that patients can be a good source for data collection [16] self-report and survey became the most accurate and efficient method in data collection regarding adverse events [15, 16]. This can help to reveal about 92% of the adverse drug events (ADEs) in the outpatient settings [18, 19]. In addition, using checklists have positive effects on various aspects of healthcare quality (i.e. health care services and patients outcomes) [7].

Ever since the importance of self-reporting is verified in adult oncology setting, much effort is dedicated in this regard as a gold standard in ADEs evaluation [1, 20]. Pediatric health-related research, as well, is changing toward obtaining evidences directly from children [21]. It has been documented that children as young as three years old are able to recall and give graphical explanations of adverse events such as illness, violence and disaster experience [22]. However, a meta-analysis which evaluated the utilization of patient-reported outcomes in pediatric oncology, noted the limitation in the number of studies [4] which are much less than optimal [3]. In fact, the issue has not been studied as much as it arises concern in clinicians [23].

Regarding the aforementioned issues, in the present study we intended to evaluate symptoms which pediatric oncology patients are suffering from and their severity in outpatient settings using a self-report tool. Therapy-Related Symptom Checklist for Children (TRSC-C) is a calibrated, easy-to-use symptom checklist which makes it feasible to capture symptoms children [2, 3, 7]. TRSC has also been used in adults [9, 24-26] and via self-report [3, 7]. It has a wide coverage of symptoms and has been used in different languages [2, 3, 7].

2. Materials and Methods

2.1. Setting and Study Design

We aimed to evaluate symptoms experienced by the pediatric oncology in outpatient setting as well as their severity using TRSC-C. This cross-sectional study was carried out from October 2013 to February 2015. The study was conducted in two outpatient pediatric oncology clinics of two academic hospitals affiliated with Iran University of Medical Sciences and Shahid Beheshti University of Medical Sciences, in Tehran, Iran. Patients referred to these clinics for receiving their chemotherapy or follow up visits. The study was approved by the ethic committee of the Tehran University of Medical Sciences.

2.2. Participants

We included pediatric oncology patients between 5 to 17 years old who received chemotherapy regimen from 1 week to 1 month before the study recruitment. Children were excluded if they were unable to communicate independently or with some extent of help from the researcher, or if they had language barrier. Additionally, those who suffered from hearing or speech problems, organic brain syndrome or severe psychiatric disorders were also excluded. Eligible patients were consent by their parents for participating in the study.

2.3. Data Collection

We documented patient's demographic data including age, sex, educational level and their disease characteristics such as diagnosis, duration of treatment and chemotherapy medications during the previous month, from their medical records or parents, whenever it was applicable. Children were asked to answer the scale based on the symptoms that they have experienced since their last chemotherapy administration.

2.4. Questionnaire

To evaluate the symptoms, we used the valid and reliable Persian translation of TRSC-C [27], which has been developed for the evaluation of frequency and severity of symptoms in children undergoing chemotherapy [7]. The checklist was previously used in different languages [2, 3, 7] and was mainly self-administered. However, in children who were unable to read or write the researcher with or without the patient’s guardian, helped the children to fill the checklist by asking the items from children face to face. This was similar to the method

that was applied by Williams et al. who first developed and validate the checklist [7].

The original TRSC-C contains 30 items. However, based on the expert comments on the content validity of the Persian version [27], another question was added to the end of the scale regarding weight gain. Each item of TRSC evaluates the presence of a symptom as well as its severity through a 5 point likert scale, from 0 (none) to 4 (the most severe). Each symptom of the scale is explained by up to 4 kid-friendly terms and phrases. Visual schematic faces were also added to the likert scale in Persian version to make it more comprehensive for young children.

2.5. Statistical Analysis

We used the SPSS version 21.0 for statistical analysis. We reported the frequency and severity of each symptom. In the report, "Total number of symptoms" means the sum of all of the number of symptoms and "Total severity score" is the sum of the severity scores of all of the items. We also calculated the severity of symptoms via the conservative approach which was first used by Williams et al. [2].In this approach we omitted all the "0" scores from reports to assess the severity of a given symptom among patients who reported it.

Chi-square was used to evaluate the correlation between the frequency of each reported symptom in different age groups and within genders. To compare the variables that were not normally distributed, such as the severity score of each symptom, total severity score of TRSC-C and total number of symptoms experienced within sex and age groups, nonparametric Mann-Whitney U and Kruskal Wallis tests were performed respectively. Additionally, differences between total severity scores of TRSC-C and total number of symptoms experienced since the patients' last chemotherapy time (in last 7 days) were calculated by Mann-Whitney U test.

3. Results and Discussion

We included 162 patients with mean age of 8.6 ± 3.2 years. The most frequent diagnosis of patients was Acute Lymphoblastic Leukemia (ALL) (76.5%). Details of patients' demographic data and disease characteristics are listed in table 1.

Only in 18 (%11.1) patients the TRSC-C was completely self-administered. In more than half of the patients (56.8%), the checklists were filled out with the researchers' help. The remaining fifty two (32.1%) checklists were filled with the help of the caregiver and the researcher together.

Overall 1425 Symptoms were documented in 162 patients (8.8 symptoms per patient). In 156 patients (96.3%) at least one symptom regardless of the severity was reported. None of the patients reported all of the 31 symptoms. The highest number of events experienced by one patient was 26 symptoms. Twenty (12.34%) patients experienced at least 15 events.

In table 2 symptoms are listed in descending order based on their frequency. More than 40% of the patients reported at least

Table 1. Demographic and clinical characteristics of patients.

Patients' Characteristics	Number (%)
Gender	
Female	74 (45.7)
Male	88 (54.3)
Age group	
<7 y	57 (35.2)
7-11 y	68 (42.0)
≥12 y	37 (22.8)
Patient education	
Under school age	69 (42.6)
Grade 1-5	60 (37.1)
Grade 6-11	33 (53.4)
Radiotherapy	
Yes	20 (12.3)
No	142 (87.7)
Continuous Oral chemotherapy	
Yes	81 (50)
No	81 (50)
Chemotherapy in last 7 days	
Yes	73 (45.1)
No	89 (54.9)
Diagnosis *	
Hematologic malignancies	151 (93.2)
Others	11 (6.7)
Chemotherapy Agents+	
*Methotrexate**	113 (69.8)
Vincristine	106 (65.4)
6-Mercaptopurine	67 (41.4)
*Cytarabine**	58 (35.8)
Asparaginase	33(20.4)
Cyclophosphamide	31 (19.1)
Doxorubicin	26 (16)
6-Thioguanine	17 (10.5)
Etoposide	10 (6.17)
Others#	23 (14.2)

+ Within the previous month * *Methotrexate* and Cytarabine were used in combination with hydrocortisone as "Triple Intrathecal therapy" in 34 patients. # Including Bleomycin, Vinblastine, Actinomycin, Carmustine (BCNU), Cisplatin, Imatinib, Dacarbazine, PEG-asparaginase.

six symptoms and more than 30% of patients reported at least 12 symptoms. Irritable (34.5%), hair loss (22.2%) and loss of appetite (21.6%) were the symptoms with the most frequent reports of the severity scores of "3" and "4" by patients. More details about the frequency and severity of symptoms are presented in table 2.

Based on the conservative approach [2], the mean severity scores of 15 symptoms out of 31 symptoms was higher than severity score "2". In other words, mean severity of 15 symptoms was reported to be equal to or more than ''quite a bit'' in those who experienced the following symptoms: irritable, hair loss, hard to urinate, loss of appetite, sweating, headache, vomiting, agitation, afraid, jaw pain, difficulty sleeping, feeling sluggish, nausea, pain and difficult swallowing.

Skin changes was the only symptom which was reported significantly more frequently (P =0.01) and more severely (P= 0.01) by boys than girls. Details of the comparisons of symptoms and their p-values are listed in table 3.

In table 4 the frequency and the mean rank of severity score of symptoms in different age groups are presented. There was only a significant difference in the frequency of weight loss (P=0.02), difficulty sleeping (P=0.03) and constipation (P=0.01) among different age groups. We also found that there was a statistically significant difference between the severity of loss of appetite (P=0.02), weight loss (P= 0.02), constipation (P= 0.03) and difficulty sleeping (P= 0.05)

Table 2. Frequency of symptoms and their severity scores.

Symptoms	Frequency N (%)	Severity Score N (%)					Mean ± SD
		0	**1**	**2**	**3**	**4**	
Irritable	94(58.0)	68(42.0)	14(8.6)	24(14.8)	31(19.1)	25(15.4)	1.57±1.55
Loss of Appetite	77(47.5)	85(52.5)	18(11.1)	24(14.8)	11(6.8)	24(14.8)	1.20±1.5
Cough	72(44.4)	90(55.5)	35(21.6)	20(12.3)	7(4.3)	10(6.2)	0.83±1.18
Pain	72(44.4)	90(55.5)	25(15.4)	28(17.3)	11(6.8)	8(4.9)	0.90±1.2
Hair Loss	68(42.0)	94(58.0)	15(9.3)	17(10.5)	9(11.7)	17(10.5)	1.07±1.45
Feeling Sluggish	66(40.7)	96(59.3)	24(14.8)	25(15.4)	7(4.3)	10(6.2)	0.83±1.20
Nausea	62(38.3)	100 (61.7)	22(13.6)	20(12.3)	16(9.9)	4 (2.5)	0.77±1.14
Depression	59(36.4)	103(63.6)	27(16.7)	17(10.5)	9(5.6)	6(3.7)	0.69±1.09
Agitation	56(34.6)	106(65.4)	21(13)	16(9.9)	10(6.2)	9(5.6)	0.73±1.19
Skin Changes	53(32.7)	109(67.3)	17(10.5)	24(14.8)	9(5.6)	3(1.9)	0.64±1.04
Sweating	53(32.7)	109(67.3)	18(11.1)	6(3.7)	19(11.7)	10(6.2)	0.78±1.30
Numbness in Fingers/ and or Toes	49(30.2)	113(69.7)	17(10.5)	23(14.2)	5(3/1)	4(2.5)	0.58±1.01
Weight Loss	48(29.6)	114(70.4)	22(13.6)	13(8)	12(7.4)	1(0.6)	0.54±0.96
Afraid	48(29.6)	114(70.4)	19(11.7)	14 (8.6)	5(3/1)	10(6.2)	0.63±1.16
Difficulty Sleeping	45(27.8)	117(72.2)	13(8)	18(11.1)	11(6.8)	3(1.9)	0.58±1.05
Headache	44(27.2)	118(72.8)	18(11.1)	10 (6.2)	7(4.3)	9(5.6)	0.59±1.14
Difficulty Concentrating	44(27.2)	118(72.8)	20(12.3)	14 (8.6)	3(1.9)	7(4.3)	0.52±1.03
Fever	43(26.5)	119(73.4)	17(10.5)	18(11.1)	6(3.7)	2(1.2)	0.49±0.92
Vomiting	39(24.1)	123(75.9)	14 (8.6)	3 (1.9)	5(3/1)	7(4.3)	0.51±1.06
Constipation	38(23.4)	124(76.5)	12(7.4)	18(11.1)	8(4.9)	0	0.44±0.88
Weight Gain	35(21.6)	127(78.4)	13(8)	14 (8.6)	5(3/1)	3(1.9)	0.42±0.91
Sore Throat	35(21.6)	127(78.4)	21(13)	7(4.3)	4(2.5)	3(1.9)	0.36±0.83
Itching	35(21.6)	127(78.4)	16(9.9)	(10(6.2	(8(4.9	1(0.6)	0.39±0.86
Sore Mouth	33(20.4)	129(79.6)	16(9.9)	9(5.6)	5(3/1)	3(1.9)	0.38±0.87
Shortness of Breath	32(19.7)	130(80.2)	15(9.3)	8(4.9)	6(3.7)	3(1.9)	0.38±0.88
Bleeding	25(15.4)	137(84.6)	17(10.5)	7(4.3)	1(0.6)	0	0.21±0.54
Difficult Swallowing	25(15.4)	137(84.6)	11(6.8)	5(3.1)	7(4.3)	2(1.2)	0.31±0.83
Bruising	23(14.2)	139(85.8)	13(8)	6(3.7)	3(1.9)	1(0.6)	0.23±0.66
Difficulty Standing/ Walking	22(13.6)	140(86.4)	9(5.6)	8(4.9)	3(1.9)	2(1.2)	0.26±0.74
Jaw Pain	21(13.0)	141(87.0)	9(5.6)	4(2.5)	5(3.1)	3(1.9)	0.27±0.81
Hard to Urinate	9(5.5)	153(94.4)	1(0.6)	4(2.5)	2(1.2)	2(1.2)	0.14±0.63

[+] Within the previous month [*] *Methotrexate* and Cytarabine were used in combination with hydrocortisone as "Triple Intrathecal therapy" in 34 patients. [#] Including Bleomycin, Vinblastine, Actinomycin, Carmustine (BCNU), Cisplatin, Imatinib, Dacarbazine, PEG-asparaginase.

among patients in the three age groups.

We found that there was not a significant difference between the mean total severity scores and the mean number of symptoms, in different genders and among different age groups (Table 5).

Additionally, no association was found neither between total severity scores nor total

Table 3. Comparison of frequency and severity of each symptom between different genders.

	Frequency *N (%)*			Severity Score *Mean rank*		
Gender **Symptoms**	**Boy** *Total =88*	**Girl** *Total =74*	*P-value*	**Boy** *Total =88*	**Girl** *Total =74*	*P-value*
Irritable	31 (35.2)	25 (33.8)	0.85	82.7	80	0.67
Loss of appetite	48 (54.5)	29 (39.2)	0.05	87.5	74.3	0.05
Cough	44 (50)	28 (37.8)	0.12	85.3	76.9	0.21
Pain	40 (45.5)	32 (43.2)	0.78	81.5	81.4	1
Hair Loss	35 (39.8)	33 (44.6)	0.54	79.4	83.9	0.49
Feeling Sluggish	35 (39.8)	31 (41.9)	0.79	79.5	83.8	0.51
Nausea	33 (37.5)	29 (39.2)	0.83	80.1	83	0.65
Depression	27 (30.7)	32 (43.2)	0.1	76.4	87.5	0.08
Agitation	50 (56.8)	44 (59.5)	0.73	79.9	83.3	0.63
Skin Changes	36 (40.9)	17 (23)	**0.02**	88.4	73.2	**0.01**
Sweating	25 (28.4)	28 (37.8)	0.2	79.3	84	0.45
Numbness in Fingers/and or Toes	24 (27.3)	25 (33.8)	0.37	79	84.4	0.37
Weight Loss	26 (29.5)	22 (29.7)	0.98	81.5	81.4	0.98
Afraid	23 (26.1)	25 (33.8)	0.29	78.8	84.7	0.32
Difficulty Sleeping	25 (28.4)	20 (27)	0.85	81.7	81.1	0.92
Headache	21 (23.9)	23 (31.1)	0.3	78.4	85	0.26
Difficulty Concentrating	23 (26.1)	21 (28.4)	0.75	80.6	82.5	0.73
Fever	25 (28.4)	18 (24.3)	0.56	82.8	79.8	0.6
Vomiting	25 (28.4)	14 (18.9)	0.16	84.5	77.9	0.23
Constipation	17 (19.3)	21 (28.4)	0.18	78.2	85.3	0.2
Weight gain	16 (18.2)	19 (25.7)	0.25	78.5	85	0.22
Sore Throat	15 (17)	20 (27)	0.12	77.9	85.7	0.14
Itching	19 (21.6)	16 (21.6)	1	81.7	81.2	0.93
Sore Mouth	22 (25)	11 (14.9)	0.11	85.2	77	0.11
Shortness of Breath	18 (20.5)	14 (18.9)	0.81	82.2	80.6	0.76
Bleeding	12 (13.6)	13 (17.6)	0.49	80	83.1	0.51
Difficult Swallowing	12 (13.6)	13 (17.6)	0.49	80.2	82.9	0.57
Bruising	14 (15.9)	9 (12.2)	0.5	82.7	79.9	0.53
Difficulty Standing/ Walking	15 (17)	7 (9.5)	0.16	84.1	78.3	0.19
Jaw Pain	14 (15.9)	7 (9.5)	0.22	83.7	78.8	0.25
Hard To Urinate	6 (6.8)	3 (4.1)	0.44	82.4	80.3	0.46

number of symptoms, with the timing of receiving the last dose of chemotherapy (one week prior to participation in the study vs. receiving the last dose earlier P=0.41 and P=0.79 respectively).

3.1. Discussion

In the current study we investigated the frequency and severity of symptoms in pediatric oncology outpatients, using the Persian calibrated TRSC-C [27]. The checklist is an appropriate and comprehensive symptom checklist which has been translated to other languages and was used in same pediatric settings as well. We found that the symptom occurrence in children undergoing oncology treatment was relatively frequent and common

Table 4. Frequency and mean rank of severity of symptoms among different age groups.

Age group	<7 years (Total=57)			7-11 years (Total=68)			≥ 12 years (Total=37)		
Symptoms	Reported *N(%)*	Not reported *N(%)*	Severity *Mean Rank*	Reported *N(%)*	Not reported *N(%)*	Severity *Mean Rank*	Reported *N(%)*	Not reported *N(%)*	Severity *Mean Rank*
Irritable	34(59.6)	23(40.3)	87.42	39(57.3)	29(42.6)	77.37	21(56.7)	16(43.2)	79.97
Loss of appetite	24(42.1)	33(57.9)	75.12	29 (42.6)	39 (57.3)	77.47	24 (64.9)	13(35.1)	98.73
Cough	27(47.4)	30(52.6)	84.2	31(45.6)	37(54.4)	82.88	14(37.84)	23(62.2)	74.8
Pain	28(49.1)	29(50.9)	86.41	25(36.8)	43(63.2)	74.27	19(51.3)	18(48.6)	87.22
Hair Loss	26(45.6)	31(54.4)	84.89	27(39.7)	41(60.3)	78.64	15(40.5)	22(59.5)	81.54
Feeling Sluggish	20(35.1)	37(64.9)	77.14	27(39.7)	41(60.3)	80	19(51.35)	18(48.6)	90.97
Nausea	19(33.3)	38(66.7)	77.57	24 (35.3)	44 (64.7)	78.5	19 (51.4)	18(48.6)	93.07
Depression	22(38.6)	35(61.4)	83.99	20(29.4)	48(70.6)	75.64	17(45.9)	20(54.1)	88.43
Agitation	20(35.0)	37(64.9)	82.1	23(33.8)	45(66.1)	82.07	13(35.1)	24(64.9)	79.53
Skin Changes	18(31.6)	39(68.4)	81.38	23(33.8)	45(66.8)	81.43	12(32.4)	25(67.6)	81.81
Sweating	20(35.1)	37(64.9)	82.28	26(38.2)	42(61.8)	86.29	7(18.9)	30(81.1)	71.5
Numbness in Fingers/and or Toes	15(26.3)	42(73.7)	79.05	22(32.3)	46(67.6)	82.58	12(32.4)	25(67.6)	83.28
Weight Loss	17(29.8)	40(20.6)	82.17	54(79.4)	14(20.6)	73.69	20(54.1)	17(45.9)	94.82
Afraid	14(24.6)	43(75.4)	77.5	21(30.9)	47(69.1)	82.87	13(35.1)	24(64.9)	85.15
Difficulty Sleeping	18(31.6)	39(68.4)	85.11	12(17.6)	56(82.4)	73.48	15(40.5)	22(59.5)	90.69
Headache	11(19.3)	46(80.7)	74.33	19(27.9)	49(72.0)	82.65	14(37.8)	23(62.2)	90.43
Difficulty Concentrating	17(29.8)	40(70.2)	84.37	17(25)	51(75)	80.04	10(27.0)	27(73.0)	79.76
Fever	17(29.8)	40(70.2)	83.77	17(25)	51(75)	80.83	9(24.3)	28(75.7)	79.23
Vomiting	15(26.3)	42(73.7)	83.39	13(19.1)	55 (80.9)	77.06	11(29.7)	26(70.3)	86.74
Constipation	21(36.8)	36(63.2)	91.39	10 (14.7)	58 (85.3)	75.03	7(18.9)	30(81.1)	78.15
Weight gain	10(17.5)	47(82.4)	78.04	17(25)	51(75)	84.36	8(21.6)	29(78.4)	81.58
Sore Throat	11(19.3)	46(80.7)	79.52	14(20.6)	54(79.4)	80.76	10(27.03)	27(73.0)	85.91
Itching	17(29.8)	40(70.2)	88.63	149(20.6)	45(66.2)	80.65	4(10.8)	33(89.2)	72.08
Sore Mouth	12(21.1)	45(78.9)	82.02	14(20.6)	54(79.4)	82.01	7(18.9)	30(81.1)	79.77
Shortness of Breath	12(21.0)	45(78.9)	83.03	12(17.6)	56(82.3)	79.58	8(21.62)	29(78.4)	82.68
Bleeding	12(21.0)	45(78.9)	85.84	11(16.2)	57(83.8)	82.16	2(5.4)	35(94.6)	73.59
Difficult Swallowing	10(17.5)	47(82.4)	83.32	9(13.2)	59(86.8)	79.92	6(16.22)	31(83.8)	81.59
Bruising	11(19.3)	46(80.7)	85.82	7(10.3)	61(89.7)	78.34	5(13.5)	32(86.5)	80.65
Difficulty Standing/ Walking	11(19.3)	46(80.7)	86.02	5(7.3)	63(92.6)	76.35	6(16.2)	31(83.8)	84.01
Jaw Pain	7(12.3)	50(87.7)	80.9	11(16.2)	57(83.8)	84.02	3(8.1)	34(91.9)	77.78
Hard To Urinate	2(3.5)	55(96.5)	79.96	7(10.3)	61(89.7)	85.24	0(0.0)	37(100.0)	77

with high severity (severity score > "2") in almost half of the experienced symptoms.

3.1.1. Frequency of Symptoms

In comparison with other studies that were conducted using TRSC-C, both the number of frequent symptoms (frequency >40%) as well as their frequency were lower in our study.

In the present study, 6 symptoms were found to have a frequency of more than 40%. Other studies using TRSC-C have reported about 14-18 symptoms that were highly frequent (>40%) [2, 3, 7].The most frequent symptom

Table 5. Mean of total severity scores and total number of symptoms between different genders and age groups.

	Total severity scores (Mean ± SD)	*p-value*	**Total number of AEs (Mean** ± SD)	*p-value*
Gender				
Boy	18.16 ± 12.5	*0.878*	8.82 ± 5.12	*0.953*
Girl	18.47 ± 13.37		8.77 ± 5.16	
Age groups (Mean ± SD)				
<7 years	18.9474±12.26		9.0877±5.01	
7-11 years	17.1765±14.53	*0.141*	8.2353±5.42	*0.235*
≥ 12 years	19.3784±10.44		9.3784±4.76	

AEs: Adverse events

was reported to be 58% in our study vs. 77 to 95% in other studies [2, 3, 7].

Among the mentioned studies, the highest frequency of symptoms (95%) were reported in the study by Williams *et al*. in Thai children [2], in which the TRSC-C was filled by parents. This could be attributed to parents' contribution in the study. Similar findings were obtained in studies which assessed symptoms in pediatric oncology patients using scales other than TRSC-C, and reported the parents' perspectives regarding their children's symptoms [11, 28]. In these studies almost all of the symptoms occurred in more than 40% of patients and the frequency of symptoms ranged almost between 60-90% [11, 28]. In studies which TRSC-C was filled by children with or without additional help, the highest frequency of symptoms was 77-80% [3, 7]. Although these were lower than the reports of the Thai parents' perspectives [2], it was still higher than our study. In studies that reported the pediatrics perspective by the Memorial Symptom Assessment Scale (MSAS), the symptoms frequencies ranged between 6-50% [6, 20, 29].

So far, most of the available data concerning children' health issues are provided from the care givers and/or care providers perspectives [13, 22]. This is often due to their attendance as proxy informants of child's symptom experiences [12]. Although this information is helpful [13], it can be mostly problematic, due to underreporting [11, 12] or over reporting [28] of symptoms.

Another factor that can influence the frequency of symptoms in these patients is the differences of their underlying diseases. It has been previously stated that the patients with hematologic and central nervous systems malignancies experience significantly less symptoms than those diagnosed with solid tumors [20]. In the previously mentioned studies that used TRSC-C, patients with hematologic malignancies were responsible for 45-65% of cases vs. 93% in our study. Thus, we could not compare the differences of symptoms between patients with different malignancies due to the distribution of cancer types in our patients. However, in the previously mentioned studies using TRSC-C the researchers found no statistically significant differences in symptoms between

the two groups [2, 3, 7], while Colins *et al.* attributed the observed different between the groups to the types of chemotherapy regimens as well as the tumor's nature [20].

Additionally, it was suggested that age can alter the frequency of reported symptoms. Surveys on symptoms and problems in children with cancer are mostly conducted by self-administered questionnaires which necessitate some level of cognitive development and reading ability. Even in oral interview, complications may exist in answering, mostly due to the difficulty in understanding the concept and lack of motivation in examination-like situations for younger children [12].

So, due to the different level of cognitive development in older children, they might recognize more and verbalize their symptoms better than their younger counterparts [11, 12]. However, we did not find a significant difference among different age groups in terms of total number of reported symptoms and total scale severity scores. This finding was similar to Williams *et al.* [3] and Collins *et al.* [20] using TRSC-C and MSAS respectively. In contrast, in a study using TRSC-C, it was showed that older children (≥ 12 y) reported significantly more symptoms than younger patients [7], meanwhile in another study, the authors reported contrary results [2]. Since there is a controversy about the correlation of age and symptoms, there is still a need for studies focusing on this issue in this population.

It should be mentioned that we found significant differences among different age groups in symptoms such as weight loss, difficulty sleeping and constipation. Weight loss was mostly reported in 7-11 years old children but difficulty sleeping and constipation were reported significantly higher in youngest children. So, it seems that no specific pattern exists regarding reporting of symptoms in a specific age group.

As noted by Williams et al. [3], we did not find a significant difference between total number of symptoms reported by girls and boys. However, we found that skin change was significantly more frequently reported by boys than girls.

The top 5 frequent symptoms in our study were irritable (58%), loss of appetite (47.5%), cough (44.4%), pain (44.4%) and hair loss (42%). Irritable, hair loss and loss of appetite are also amongst the 5 most frequent symptoms in other studies using TRSC-C [2, 3, 7].

In two studies using TRSC-C, cough was reported by about 30% and pain was reported by about 50% of patients [3, 7]. Although they were not among the most common symptoms, their frequencies were close to ours (44.4%). Cough and pain were also amongst the top 5 most frequent symptom in the study by Collins *et al.* using MSAS [20]. In three studies using MSAS, frequencies of cough and pain were also close to what mentioned previously (cough; 30-40% and for pain; 40-50%) [6, 20, 29].

In the present study we asked patients to report the symptoms that they had experienced since the last dose of chemotherapy. To evaluate the recall bias, we divided patients

regarding the time of their last chemotherapy in two groups. It is generally believed that recall in retrospective studies depends on the studied features i.e. timespan, importance, outcomes on respondents, extents of required details [30], and the age of interviewee [22]. Still, in studies recall is not entirely under control [18]. We compared those who did receive chemotherapy within the last 7 days vs. those who received their regimen earlier and did not find any significant difference regarding this issue. However, It was previously stated that some symptoms were experienced significantly more often in those who received chemotherapy within the last 7 days [29].

All of the symptoms experienced by patients in this study were "very common" (≥ 10%) based on the classification of the Council of International Organizations of Medical Sciences (CIOMS). We only had one symptom (hard to urinate) which was reported in less than 10% which is also amongst the lowest frequency in other TRSC-C studies [2, 3, 7].

3.1.2. Severity of Symptoms

Mean severity scores of symptoms in our study ranged between 0.14 and 1.57, but in other three studies with TRSC-C the mean severity were between 0.12 and 2.57 [2, 3, 7]. Both the lower and the upper range belonged to the study on Thai children [2].

Irritable, loss of appetite and hair loss were the most severe symptoms (mean severity scores>1) in our study respectively and all of them were among the most commonly reported symptoms. These were also among the most severe symptoms in other studies using TRSC-C [2, 3, 7]. However, in contrast to other studies using TRSC-C that reported hair loss as the symptom with the highest mean severity score, we found that irritable was the symptom with the highest mean severity score.

With the conservative approach [2], the mean severity score of about 15 symptoms reached over score "2". This can also reflect the fact that most of the patients marked their severity score as "none". Other studies that implemented the conservative calculation method noted similar findings [2, 7]. In this calculation method, the highest mean severity scores belonged to irritable (2.7), hair loss (2.5), hard to urinate (2.5), loss of appetite (2.5) and sweating (2.4) respectively. The information derived from conservative approach can be used for studies which are developing for or advising severity reduction interventions [2].

We did not find significant differences between total severity scores neither in patients within different age groups nor in different genders. But particular symptoms such as loss of appetite, weight loss and difficulty sleeping were significantly reported with higher severity in children aged more than 12 years. In contrast, constipation was experienced with significantly higher severity in children less than 7 years old. In terms of difference between genders, we found that skin change was reported with significantly higher severity in boys than girls.

Despite the above mentioned findings in our study, other studies using various tools for symptom assessment such as MSAS, TRSC-C and one study with a self-modified questionnaire, did not come across any significant differences between the severity of any given symptoms within different age groups and genders in children [3, 20, 28].
Contributing factors such as age of the children [12] and using care givers/providers as proxy informants [11], which might lead to the differences in frequency of symptoms in children, can also be applicable regarding the severity of symptoms as well.

When we compare results of different studies, another factor that needs to be take into consideration is the cultural bias, which was mentioned by Williams *et al.* in their study on Thai patients using TRSC-C [2]. Cultural bias in cross-cultural assessments, threatens the validity and equivalence of the measuring instruments. This could be due to the cultural specific norms in behavior and language, different social desirability and perception alterations. Cultural bias can emerge in terms of translations, item content, procedure calibration or instrument design [31].

At the end, we should mention our limitation in the current study which was the variations in the treatment regimens of patients. This variation made the analysis of the association between the regimen and the symptoms impossible.

4. Conclusion

In summary, this study is a comprehensive evaluation of the symptoms in Iranian children during oncology treatment in outpatient setting. It seems that the TRSC-C is an appropriate symptom checklist for oncology symptom assessment in the Iranian outpatient pediatric. This study was the first of its kind in Iran and the checklist is also the first calibrated questionnaire regarding this topic in Persian. With this checklist, we are capable to detect patient's symptoms and design clinical interventions based on the severity and frequency of identified symptoms.

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