DETERMINING THE APPETITE AND NUTRITIONAL STATUS OF CHILDREN UNDERGOING STEM CELL TRANSPLANTATION

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Abstract

Aim: To determine pre- and post-transplant appetite and nutritional status of children undergoing stem cell transplantation. Methods: This study was conducted between November 2018 and November 2020 with 25 children, aged 8-18 years, diagnosed with cancer without secondary disease and scheduled for stem cell transplantation. Time points: seven days pre-stem cell transplant (T1); transplant day (T2); Day 1 post-transplantation (T3); Day 14 post-transplantation (T4); and Day 30 post-transplantation (T5). Measurements for treating pediatric anorexia and cachexia include: height, mid-upper arm circumference (MUAC); body mass index (BMI); and the Pediatric Functional Assessment Scale (Peds-FAACT). Results: 52% of patients were female, and mean age was 13.2 years. Acute lymphoblastic leukemia was diagnosed in 32% of the children. There was a statistically significant difference between the means of body weight over time ($p<0.001$). By Day 14 post-transplantation, 61% of subjects (n=14) had lost $>$ 5% of body weight. There was a statistically significant difference between distributions of change in food taste over time, and distribution of change in food smell ($p<0.001$, $p<0.001$, respectively). Conclusions: Clinical nutrition teams should closely follow the children's nutritional status, plan appropriate nutritional treatment, perform nutritional care, and evaluate anthropometric measurements.

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Results: 52% of patients were female, and mean age was 13.2 years. Acute lymphoblastic leukemia was diagnosed in 32% of the children. There was a statistically significant difference between the means of body

weight over time ($p<0.001$). By Day 14 post-transplantation, 61% of subjects (n=14) had lost > 5% of body weight. There was a statistically significant difference between distributions of change in food taste over time, and distribution of change in food smell ($p<0.001$, $p<0.001$, respectively).

Conclusions: Clinical nutrition teams should closely follow the children's nutritional status, plan appropriate nutritional treatment, perform nutritional care, and evaluate anthropometric measurements.

Key words: Child, Hematopoietic stem cell transplant, appetite, nutritional status

What's known

Multidisciplinary approach to the nutritional care of children is vital for improving nutritional status after HSCT, as recommended in*Improving Outcomes Guidance for Children and Young People with Cancer* (National Institute for Health and Clinical Excellence (NICE, 2005).

Healthcare professionals need to be aware that malnutrition will lead to more complications in children scheduled for transplantation in stem cell transplant units.

What's new

A nutritional assessment to detect malnourished patients or patients at risk of malnutrition, which includes anthropometric measurements, and observation of changes to smell and taste, should be performed on children in stem cell transplant units.

Nurses need to evaluate changes to smell and taste of children in transplantation units and use of validated scale for appetite of children in stem cell transplant units.

INTRODUCTION

Malnutrition is very common in children who are receiving treatment for cancer.[1] This is due to numerous factors, which may include: changes in taste sensation, side effects of cancer treatment drugs on the gastrointestinal system, increase in metabolic rate and calorie requirement, decrease in food intake due to mucositis, cytokines released, and resulting metabolic disorders.[2,3] Poor nutritional status in children with cancer is associated with increased infections, poor survival, and impaired health-related quality-of-life.[4,5]

The American Society for Parenteral and Enteral Nutrition workgroup defined pediatric malnutrition-undernutrition as an imbalance between nutrient requirement and intake resulting in cumulative deficits of energy, protein, or micronutrients that may negatively affect growth, development, and other relevant outcomes.[6] While the malnutrition rate in pediatric oncology patients ranges widely, from of 6 - 50%, due to the type, stage, location of the tumor, and treatment intensity[1], this rate changes to 18-31% following transplantation.[4,5] Some examples of tumors with high risk of malnutrition among pediatric oncology patients are Wilms tumor, neuroblastoma stage III and IV rhabdomyosarcoma, Ewing sarcoma, medulloblastoma, multiple relapsed leukemia and lymphoma.[7]

Loss of appetite, which is one of the factors leading to malnutrition, and is associated with cachexia (muscle and fat loss), is a common symptom in children with cancer who are undergoing stem cell transplantation.[7-,9] Complications of treatment, such as changes in taste and smell, and oral mucositis, can cause anorexia.[10] A study by Skolin et al. demonstrated that malnutrition occurred in children due to taste change, pain, lack of appetite, nausea and vomiting, fever or a feeling of illness, aversion to hospital food, the ward environment, and gaining some control over the situation were identified as important causes for eating problems by parents.[11] Research has also shown that drugs used in chemotherapy, radiotherapy and stem cell transplant treatment may affect oral food intake by causing taste changes in children, sometimes leading to malnutrition.[11]

The deterioration of nutritional status in a child during cancer treatment negatively affects that child and her family in many ways. For example, it may be associated with biochemical disorders, decreased immune functions, delayed wound healing, and deterioration of drug metabolism. Malnutrition may also impact prognosis, and cause delay in growth and development.[1,12, 13] In addition, decrease in food intake and body

weight associated with anorexia and cancer cachexia can create conflict between the child, the family, and health professionals about eating, changes in body image, and decreased quality of life.[1,9,14]

Since anorexia and cachexia are complex problems, a multidisciplinary team approach is required to determine the underlying causes, to support nutrition, and to keep the child's anthropometric measurements within normal range.[1,12] A multidisciplinary approach is recommended in *Improving Outcomes Guidance for Children and Young People with Cancer* , a guidance developed by the National Institute for Health and Clinical Excellence.[15]

It is the responsibility of the team, consisting of physicians, dieticians, and pediatric oncology nursesm to evaluate the nutritional status and anthropometric measurements of the child before and during the stem cell transplant.[16] Pediatric oncology nurses have direct responsibility for physical and developmental assessment, treatment, education, and anticipatory guidance.[7] They are specifically trained to recognize and manage the complications of childhood cancer and its treatment, including malnutrition and associated symptoms of nausea, vomiting, mucositis, pancytopenia, immunodeficiency, infection, pain, and psychosocial issues. Advanced-practice nurses often have additional responsibility for the comprehensive medical management of children with cancer, coordinating care across inpatient, outpatient, and home settings, while providing preventive services, therapeutic procedures for patients, and education for professional staff.

Nutritional screening and assessment is vital to identifying and managing any cancer-related nutritional problems.[16]For example, pediatric allogeneic hematopoietic stem cell transplant (HSCT) is a lifesaving procedure and curative treatment for hematologic disorders[17], but some symptoms after transplantation can be difficult for children to tolerate, sometimes making nutrition problemmatic.[18]

Evaluation of nutrition in children in the first days after transplantation can be challenging. The daily calorie requirement suitable for the age period of the child, determining which food to include during treatment, and managing of symptoms such as nausea, taste changes, oral mucositis, diarrhea, constipation, and pain affect the treatment process positively by providing better nutrition of the child.[1,8,19,20]

Although there are many studies evaluating anthropometric measurements in children over time during the stem cell transplantation process, there are only a limited number on the relationship between appetite and eating disorder.[20] In this study, the objective was to determine the pre- and post-transplant appetite and nutritional status of children with stem cell transplantation.

PATIENT AND METHODS

Study design and Setting

This descriptive study was carried out between November 2018 and November 2020 in Ankara, Turkey at the Bone Marrow Transplantation Unit of Gulhane Training and Research Hospital, and at Ankara Pediatric Hematology Oncology Training and Research Hospital.

Patients

Inclusion criteria: Children between the ages of 8-18 years, who did not have a secondary disease (such as diabetes, metabolic disease), were diagnosed with cancer, and who were scheduled for stem cell transplantation were included in the study.

Measuring tools

Seven days before stem cell transplant (T1); transplant day (T2); Day 1 post-transplant (T3), Day 14 post-transplant (T4); and Day 30 post-transplant (T5); body weight for age; height for age; MUAC measurement; BMI, and Pediatric Functional Assessment of Anorexia and Cachexia Treatment (Peds-FAACT). World Health Organization (2007) growth charts were used for weight, height, and BMI evaluation.[21] Percentages of weight-for-age (WFA), height-for-age (HFA), BMI and MUAC were calculated. All the cases were evaluated according to the Waterlow and Gomez classifications.[22,23]

2.3.1. Body weight for age: Body weight was measured using an SC-105 model electronic body scale from Bari-Med. Weight was recorded to the nearest 0.1 kg. The literature describes two methods that are frequently used to evaluate risk of malnutrition. In the current study, first is Gomez classification that was used for evaluation of weight for age ratio.[23] The body weight percentile that is below the 90th is considered risky in terms of nutrition. Second, a decrease of more than 5% body weight in a month was considered a nutritional risk.[1] Both of two methods were used in our study. World Health Organization (WHO) growth charts were used for weight evaluation.[21]

2.3.2. Height for age (HFA): Height was measured using the Stadiometer model S100 height rod from Ayrton (Frankfurt, Germany). Height was recorded to the nearest 0.1 cm. The anthropometric indices were calculated using a reference median and classified according to percentiles based on the World Health Organization (WHO) child growth standards.[21] All the cases were evaluated according to the Waterlow classification.[23] For the evaluation of acute and chronic malnutrition, classification was made taking HFA into consideration on the Waterlow classification. A HFA within the ranges 90-95%, 85-90% or below 85% corresponds to mild malnutrition, moderate malnutrition, and severe malnutrition, respectively.

2.3.3. Mid Upper Arm Circumference (MUAC): Arm soft tissue includes subcutaneous adipose tissue and muscle tissue. For this reason, the arm circumference narrows as a result of the reduction of one or both of these two tissues. Upper middle arm circumference is an anthropometric measurement frequently used in children with cancer.[24-27] In this study, the researcher made the measurement while the child was standing upright, and with his or her arm bent 90 degrees at the elbow and the palm facing the ground. A mark was placed on the acromion. The point between the olecranon and the acromion was determined, and the arm was then released. The graduated arm was held at a right angle to the arm. The mid-upper arm circumference was measured with flexible tape to the nearest 0.1 cm at the halfway point between the acromion and olecranon process of the right upper arm.

The anthropometric indices were calculated using a reference median and classified according to percentiles based on the WHO child growth standards.[21]

2.3.4. Body Mass Index (BMI) : BMI was calculated from the weight and height measurements in kg/m^2. World Health Organization (WHO) growth charts were used for BMI evaluation.[21]

2.3.5. Pediatric Anorexia and Cachexia Functional Assessment Scale (Peds-FAACT scale): Children's anorexia-eagerness to eat was evaluated using the Peds-FAACT scale, a useful tool developed by Lai et al. for evaluating anorexia and cachexia in children with cancer.[28] In this scale, the score varies between "0" and "40", with a low value indicating that the risk of anorexia and cachexia is high, and higher values indicating that the nutritional status of the patient is better and the risk of anorexia is low.

Procedure

Weight and height for age were measured and recorded as T1, T2, T3, T4, and T5 by the same researcher. After anthropometric measurements were taken at each time point, the Peds-FAACT scale was completed. Among the anthropometric measurement results, such as height for age, weight for age, and BMI for age, values were evaluated using 2007 standards in the AnthroPlus computer program created for children aged 5-19 years.[21] In current study, >5% loss of weight for age was accepted as undernutrition in pediatric cancer patients undergoing stem cell transplantation.[29]

Research hypotheses

In this current study research hypotheses were:

H_0: There is no difference between pre- and post-transplant appetite and nutritional status in children with stem cell transplantation.

H_1: There is a difference between pre- and post-transplant appetite and nutritional status in children with stem cell transplantation.

Data Analysis

Data were analyzed with IBM SPSS V23. Conformity to normal distribution was examined using the Shapiro-Wilk test. Repeated analysis of variance was used to compare normally distributed data over three or more times. The Pearson correlation coefficient was used to examine the relationship between normally distributed data. The Friedman test was used to compare triple and categorized data according to time. Analysis results were presented as mean ± standard deviation and median (minimum-maximum) for quantitative data, and as frequency (percentage) for categorical data. The significance level was defined as $p < 0.050$.

Ethical Considerations

The study obtained approval from the Ethics Committee (25-46418926), and permission for the study was obtained from both two hospitals. All the participants were informed about the aim and method of this study by the researcher, and gave written informed consent.

RESULTS

Fifty-two percent (52%) of patients were female, and 32% were diagnosed with acute lymphoblastic leukemia. The patients ranged from age eight to age 18, with a mean age of 13.2 years (+ 3.5 months) (Table 1).

There was a statistically significant difference between the means of body weight over time ($p < 0.001$). The average body weight for age at first hospitalization was 47.80 kg + 19.79; the mean weight on day of transplant was 46.46 kg + 19.20; on Day 1 after transplantation, the mean weight was 46.21 kg + 19.48; on Day 14 after transplantation, mean weight was 44.92 kg + 18.92; and 30 days post-transplantation, mean weight was 45.79 kg + 18.29 (Table 2).

There was a statistically significant difference between the means of BMI values according to time ($p<0.001$). At first hospitalization, BMI averaged 19.69 + 4.19. Other results appear in Table 2. There was also a statistically significant difference between the means of MUAC values according to time ($p<0.001$). The mean MUAC at first hospitalization was 25.31 + 6.07. (Other results appear in Table 2).

At Day 14 post-transplantation, there was a loss of more than 5% of body weight in 61% of the children (n=14) as compared to weight at Day 1 of hospitalization post-transplantation (Table 3).

Fifty-two percent (52%) of patients had no change in their food taste at the time of first hospitalization; 64% of patients had minimal change in food taste on the day of transplantation; 44% had a slight and slightly change in food taste on Day 1 post-transplantation; at Day 14, 40% stated that there was some change in food taste; and at Day 30 post-transplantation, 40% had very little change in food taste. There was a statistically significant difference between the distributions of change in food taste over time ($p<0.001$) (Table 4).

Regarding food smell, 56% of patients experienced no change. Table 4 shows the rest of the results at the various time points. There was no statistically significant difference between the distributions of other variables over time ($p>0.05$).

DISCUSSION

In this study, the pre- and post-transplant appetite and nutritional status of children who underwent stem cell transplantation were evaluated over the first month. The fact that the treatment regimen after stem cell transplantation causes symptoms for vomiting, anorexia, oral mucositis, diarrhea, pain, change in taste, and decreased oral intake in children poses a risk for the development of malnutrition.[25,27] Although there are many studies showing decreased appetite associated with cancer and its treatment in children.[27,30,31], there are only a limited number of studies analyzing appetite following stem cell transplantation.[32] The qualitative study by Loves et al. of children with cancer treatment and children with stem cell transplantation found that appetite decreased in children after chemotherapy treatment and stem cell transplantation.[33] In the study by Koç, et al., which evaluated nutritional status after stem cell transplantation, a 46% decrease in energy intake and a 47% decrease in protein intake were found two weeks after the transplant.[26] In our

study, which aligns with Koç's work, the average number of meals eaten by the children decreased versus the number both before and the day of transplantation. Also, the number of meals was < 2 on the 14th day after the transplant, and the children skipped at least one meal Day 1 post-transplant and on Day 30 after the transplant. Parenteral nutrition therapy was initiated in patients who could not be fed enterally due to insufficient oral intake resulting from mucositis, skipping meals and lack of appetite, posing a risk for malnutrition. This process could be managed effectively.

Anthropometric measurements over time

The malnutrition rate in children after transplantation ranges between 20-50%.[3,25-27,30] In the study of Koç, et al., which compared the nutritional status of a study group of 40 children who underwent hematopoietic stem cell transplantation against a control group of 20 healthy children, malnutrition was detected in almost half of the study group.[26] But in determining malnutrition during the transplant process, it is not sufficient to consider body weight as the only anthropometric measurement.[7,24]Body weight may also be affected by hydration during chemotherapy and does not identify any long-term changes in body cell mass.[34] Therefore, in our study, body weight was used as a measurement tool in evaluating growth with height, BMI, MUAC.[1,7,16]

In a study of Zemrani et al. (2020), which evaluated the nutritional status and anthropometric measurements of 27 children who underwent stem cell transplantation, researchers found that the body weight of the children decreased in the first and third months after transplantation as compared to the pre-transplant period.[34] Moreover, at the end of the first year, the body weight z score was higher than the pre-transplant value. In our study, it was determined that the decrease in the average body weight of children on Day 14 post-transplantation was statistically significant. This early recognition of the change in the nutritional status and anthropometric measurements of the children, especially on that 14th day, contributed to the determination of needed nutritional supportren. Daily monitoring of body weight by nurses who care for children after transplantation is an important indicator, as well as other methods, for the nutritional team to assess the need for nutritional support.[20] In the study by Koç et al., which compared the upper middle arm circumference as an indicator of the nutritional status of healthy children with transplantation, there was no difference between the two groups in post-transplant follow-up controls.[26]However, prior to transplantation, the upper middle arm circumference in children to be transplanted was lower than that of the healthy children.

Factors affecting anorexia/cachexia include, but are not limited to, treatment cycle, duration after receiving treatment, and disease severity. As for the peds-FAACT scale, which was developed to detect anorexia/cancer cachexia, the authors stated that scale could not clearly distinguish between patients in different clinical groups due to the limited sample size in each subgroup of the scale.[28] Therefore, the authors suggested conducting studies using the peds-FAACT scale according to treatment regimens, duration after treatment, and disease severity.

Change in sense of taste and smell

Taste change associated with treatment may affect nutritional status and cause malnutrition in pediatric cancer patients undergoing treatment.[10,11,34,35] Children defined food as tasting "funny", "not right", or "different" in the qualitative study by Loves et al., which evaluated the taste changes of children during cancer treatment and HCT process.[33] In the same study, the change in taste caused children to modify their food preferences. One child expressed the change in taste as "[I was] less [hungry] because nothing tasted". In the study by Skolin et al., children who received chemotherapy treatment for cancer and their parents stated that taste change was the key source of nutritional problems.[11]

In addition to taste changes, the smell function can also be affected.[33] In the study by van den Brink et al, which compared the taste and smell functions of 24 healthy controls with 31 children receiving cancer treatment, researchers found that the smell function was affected similarly to our study finding.[10,18] In the same study, approximately one-third of the children reported a decrease in appetite, and 12% stated that there was a bad change in the sense of taste.[10,18] Consistent with the literature, which describes a change in the taste of food on the 14th day post-transplantation, a change in the smell of food on the first and

14th days post-transplantation, and a decrease in the number of meals on the 14th day, the nurses caring for transplanted children should guide the nutrition team to meet the necessary support.

CONCLUSION

Considering that the changes in food taste and odor by the children increase on Day 14 post-transplantation, according to our study results, the health team members in the clinic should closely follow the changes in the nutritional status of the child to ensure timely access to the clinical nutrition team for starting nutritional support. In addition, as part of this effort, it is recommended that anthropometric measurements be evaluated.

A nutritional assessment to detect malnourished patients or patients at risk of malnutrition, which includes anthropometric measurements, and observation of changes to smell and taste, should be performed on children in transplantation units. The current study showed that a multidisciplinary approach to the nutritional care of children is vital for improving nutritional status after HSCT, as recommended in*Improving Outcomes Guidance for Children and Young People with Cancer* (National Institute for Health and Clinical Excellence (NICE, 2005). Healthcare professionals should be aware that malnutrition will lead to more complications in children scheduled for transplantation in stem cell transplant units.

The study has several limitations. First, this study evaluated the nutritional status and appetite status of children for only 30 days post-transplantation. In contrast, the studies in the literature that evaluated the long-term nutritional status of children after transplantation found that anthropometric measurements reached the pre-transplant level approximately one year after transplantation. Since the peds-FAACT scale was used in children with stem cell transplantation, it is recommended that long-term studies be conducted to determine whether there is a relationship between nutritional status and the peds-FAACT scale. Second, considering that the sample group was small, and was not homogenous according to diagnoses, it is difficult to generalize the findings. Thus, it is recommended that a study being planned using a homogeneous sample or a sample grouped according to diagnosis and the type of transplant. Fourth, while the changes in taste and smell were considered, other important factors, such as oral mucositis and nausea were not included in the study. Finally, we recommend that studies be conducted to investigate the relationship between Children's International Mucositis Evaluation Scale (ChIMES)—a scale for detecting oral mucositis before and after transplantation—and Peds-FAACT.

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Table 1. Frequency distribution of demographic data (n=25)

Characteristic	**Characteristic**	**Number (n)**	**Percent (%)**
Gender	**Gender**	**Gender**	**Gender**
	Female	13	52.0
	Male	12	48.0
Diagnosis	**Diagnosis**	**Diagnosis**	**Diagnosis**
	Acute lymphoblastic leukemia(ALL)	12	48.0
	Acute myeloid leukemia (AML)	7	28.0
	Aplastic anemia	4	16.0
	Thalassemia	2	8.0
Clinical variables			
Source of hematopoietic stem cell	**Source of hematopoietic stem cell**	**Source of hematopoietic stem cell**	**Source of hematopoietic stem cell**
	Peripheral stem cell	13	52.0
	Bone marrow	12	48.0
Relationship to donor	**Relationship to donor**	**Relationship to donor**	**Relationship to donor**
	Related	8	32
	Unrelated	17	68
Outcome	**Outcome**	**Outcome**	**Outcome**
	Alive	25	100

Characteristic	**Characteristic**	**Number (n)**	**Percent (%)**
Age (mean ± Standard Deviation / Median (min. – max.)	**Age** (mean ± Standard Deviation / Median (min. – max.)	13.2 ± 3.5	15.0 (8.0 – 18.0)

Table 2. Comparison of quantitative variables according to time (n=25)

Height for age				
Weight for age				
BMI				
MUAC				
Number of meal/day				
Peds-FAACT Scale				

T1: First hospitalization; T2: Transplantation day; T3: First day after transplantation; T4: Day 14 after transplantation; T

Table 3. Malnutrition rates according to different assessments by time (n=25)

Height for age*				
Weight for age**				
Change of weight for age				

T1: First hospitalization; T2: Transplantation day; T3: Day 1 post-transplantation, T4: Day 14 post-transplantation; T5: I

Table 4. Distribution of appetite and nutritional status by time (n=25)

	T1 n %	**T2 n %**	**T3 n %**	**T4 n %**	**T5 n %**	**Test statistics**	**p**
Change in sense of taste							
There is little change	6 (24)[a]	16 (64)[b]	11 (44)[b]	7 (28)[ab]	10 (40)	χ^2=23.068	<**0.001**
There is some change	1 (4)	7 (28)	11 (44)	10 (40)	7 (28)		
There is a lot of change	5 (20)	1 (4)	2 (8)	8 (32)	—		
There is no change in taste	13 (52)	1 (4)	1 (4)	—	8 (32)		
Change in sense of smell							
There is little change	6 (24)[a]	15 (60)[b]	10 (40)[ab]	6 (24)[ab]	7 (28)	χ^2=20.083	<**0.001**
There is some change	2 (8)	7 (28)	12 (48)	14 (56)	9 (36)		
There is a lot of change	3 (12)	1 (4)	2 (8)	5 (20)	—		
There is no change in taste	14 (56)	2 (8)	1 (4)	—	9 (36)		
Appetite							
There is no loss of appetite	12 (48)	8 (32)	10 (40)	5 (20)	9 (36)	χ^2=8.804	0.066
There is little loss of appetite	7 (28)	14 (56)	13 (52)	10 (40)	9 (36)		
There is a modarete loss of appetite	6 (24)	3 (12)	2 (8)	9 (36)	7 (28)		
There are a lot of loss of appetite	—	—	—	1 (4)	—		

	T1 n %	**T2 n %**	**T3 n %**	**T4 n %**	**T5 n %**	**Test statistics**	**p**
T1: First hospitalization; T2: Transplantation day; T3: Day 1 post-transplantation; T4: Day 14 post-transplantation; T5: day 30 post-transplantation; $\chi 2$: Friedman test statistic; a-b: There is no difference between times with the same letter.	T1: First hospitalization; T2: Transplantation day; T3: Day 1 post-transplantation; T4: Day 14 post-transplantation; T5: day 30 post-transplantation; $\chi 2$: Friedman test statistic; a-b: There is no difference between times with the same letter.	T1: First hospitalization; T2: Transplantation day; T3: Day 1 post-transplantation; T4: Day 14 post-transplantation; T5: day 30 post-transplantation; $\chi 2$: Friedman test statistic; a-b: There is no difference between times with the same letter.	T1: First hospitalization; T2: Transplantation day; T3: Day 1 post-transplantation; T4: Day 14 post-transplantation; T5: day 30 post-transplantation; $\chi 2$: Friedman test statistic; a-b: There is no difference between times with the same letter.	T1: First hospitalization; T2: Transplantation day; T3: Day 1 post-transplantation; T4: Day 14 post-transplantation; T5: day 30 post-transplantation; $\chi 2$: Friedman test statistic; a-b: There is no difference between times with the same letter.	T1: First hospitalization; T2: Transplantation day; T3: Day 1 post-transplantation; T4: Day 14 post-transplantation; T5: day 30 post-transplantation; $\chi 2$: Friedman test statistic; a-b: There is no difference between times with the same letter.	T1: First hospitalization; T2: Transplantation day; T3: Day 1 post-transplantation; T4: Day 14 post-transplantation; T5: day 30 post-transplantation; $\chi 2$: Friedman test statistic; a-b: There is no difference between times with the same letter.	T1: First hospitalization; T2: Transplantation day; T3: Day 1 post-transplantatio T4: Day 14 post-transplantatio T5: day 30 post-transplantatio $\chi 2$: Friedman test statistic; a-b: There is no difference between times with the same letter.