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Impact of malnutrition on survival and infections among pediatric patients with cancer: a retrospective study

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Abstract. – OBJECTIVE: Recognizing and managing malnutrition among hospitalized children affected by cancer is a rising need. Awareness and consideration of malnutrition among clinicians are still largely insufficient. This can principally be explained by the lack of consciousness and the shortage of easy and objective tools to identify malnutrition status. The aim of this study is to explore the impact of malnutrition on survival and infections among a population of pediatric patients with cancer.

PATIENTS AND METHODS: All children aged between 3 and 18 years, newly diagnosed with a malignancy between August 2013 and April 2018, were included in our study. We assessed nutritional risk at diagnosis (with $STRONG_{kids}$), then we evaluated anthropometric measurements (BMI Z-scores and weight loss), data about survival and number of hospitalization for febrile neutropenia (FN) in the first year after diagnosis. Cut-off values for malnourishment were chosen as BMI Z-score ≤-2.0.

RESULTS: One hundred twenty-six pediatric cancer patients were included in the study. At diagnosis 36 pediatric cancer patients (28.6%) were at high risk of malnutrition (STRONGkids 4 or 5), whereas 6 (4.7%) others were malnourished (BMI Z-score≤-2.0). The risk of mortality and the rate of infections (≥3 hospitalizations for FN episodes) were significantly increased by malnutrition and rapid weight loss in the initial phase of treatment (3-6 months after diagnosis). Multivariate analysis confirmed the independent effect of weight loss≥ 5% at 3 months on both survival and infections, and the independent impact of a high risk of malnutrition at diagnosis on infections.

CONCLUSIONS: A personalized evaluation of nutritional risk at diagnosis and a close monitoring of nutritional status during the initial phase of treatment are crucial for ensuring a timely and personalized nutritional intervention, which may potentially improve tolerance to chemotherapy and survival, and prevent prolonged hospitalization for infections in childhood cancer patients.

Key Words:
Malnutrition, Nutritional assessment, Pediatric cancer, Febrile neutropenia, Survival, BMI Z-score, $STRONG_{Kids}$, Personalised medicine.

Introduction

In the last 40 years, the survival rate for many more childhood cancers has considerably increased from 10% to nearly 90% today[1]. Primary reasons for the enhanced cure rate are the progress in early diagnosis, the advance in the modality of treatments and the improvements of supportive care[2]. However, malnutrition remains a common complication in children and adolescents with cancer, with a reported prevalence which varies widely (from 6% to 50%), depending on the type and extension of the disease, the treatment modality and the standard of living[3-5].

Supportive care should provide a proper nutritional assessment and intervention since keeping an adequate nutritional status during cancer treatment plays a crucial role in the treatment response, quality of life (QoL) and cost of care[6]. Pediatric malnutrition in the clinical setting has been defined by the American Society of Parenteral and Enteral Nutrition (ASPEN) as "an imbalance between nutrient requirements and

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intake, result in cumulative deficits of energy, protein or micronutrients that may negatively affect growth, development and other relevant outcomes"[7,8].

The pathogenesis of malnutrition in children with cancer is related to increased needs and energy losses, but also to decreased intake of micro and macro-nutrients[9-11]. Pro-inflammatory cytokines (TNF-α, IL-1, IL-6, IFN-γ released by the tumor) increase metabolic rate and catabolic drive, with accelerated mobilization, oxidation of energy substrates and loss of whole-body proteins[12-14]. Furthermore, common gastrointestinal disorders, due to chemotherapy-induced toxicity (such as vomiting, diarrhea, malabsorption, mucosal damage, gastrointestinal infections), may lead to increased energy losses. Additionally, chemotherapy may produce changing in taste, disorders in appetite sensation, emesis with loss of desire to eat, resulting in a reduced intake of nutrients[15,16]. All these processes lead to cancer cachexia, a complex metabolic syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be entirely reversed by conventional nutritional support, leading to a progressive functional impairment, with weight loss or growth failure, anorexia, muscle wasting, fatigue and abnormal biochemical parameters (such as low serum albumin, anemia, increased inflammatory markers)[17-19].

Malnutrition can adversely affect overall survival, because it may reduce the tolerance to chemotherapy, increasing treatment-related morbidity and decreasing event-free survival[20-23].

Moreover, it may reduce suboptimal tolerated dose and absorption of chemotherapeutical drugs, delaying treatment appointments, with consequent weak treatment response[24,25]. Disease-related malnutrition has been associated with a diminished immunity and an increased risk of infections and febrile neutropenia (FN), due to hormonal changes and compromised cytokine response[9,21,26-28]. In the presence of FN, defined by the occurrence of fever (body temperature ≥38.5°C) during neutropenia status (absolute neutrophilic count ≤0.5 x 10^9/L), it's mandatory to hospitalize the pediatric patient in order to perform endovenous antibiotic therapy[29,30]. Consequently, the number of hospitalization in malnourished children and adolescents with cancer become significantly higher, producing greater treatment costs and worse quality of life (QoL)[31]. In this regard, interventions detecting malnutrition and improving nutritional status may contribute to enhance health outcomes in pediatric patients with cancer. Hospitalized children with cancer should be firstly assessed for nutritional risk and then subjected to a global nutritional assessment[32].

Unfortunately, not all pediatric oncology centers routinely perform a complete nutritional assessment, and there is not a universal algorithm for identifying malnutrition in pediatric oncology patients[33], even if in the last decade several nutritional methods have been released to investigate malnutrition among hospitalized children[34-37]. In this study, we aim to explore the decisive impact of malnutrition on survival and infections among a population of pediatric patients with cancer.

Patients and Methods

This is a retrospective study, performed at the Pediatric Oncology Unit of the Fondazione Policlinico A. Gemelli IRCSS, Catholic University of the Sacred Heart (Rome, Italy).

In the present study, we included all children aged between 3 and 18 years, newly diagnosed with a malignancy between August 2013 and April 2018 and managed in our Hospital. Patients primarily treated in another pediatric oncological hospital and those that did not receive chemotherapy were excluded from the study. Data were collected from medical records stored in our divisional archive and electronic files saved on our informative hospital system.

For each patient, nutritional risk has been assessed with $STRONG_{Kids}$, which was reported on medical records at diagnosis. The $STRONG_{kids}$ score appears a quick, reliable and practical screening tool to use since from the admission in the hospital, to identify a patient with high risk of malnutrition. It is based on 4 items: high-risk diseases (such as malignancies), nutritional intake and losses, weight loss or poor weight gain[34-36]. Subsequently, a global nutritional assessment has been performed, collecting medical and dietary history, physical examination and anthropometric measurements, such as weight, height, body mass index (BMI) Z-scores. Z-scores express in standard deviation (SD) how far from the mean the child is, comparing the individual anthropometric measurement with data from reference age groups. They are available in chart form for several anthropometric measurements (such as weight, length or height, BMI)[34].

According to ASPEN, malnutrition can be defined *mild* by a BMI between -1 and -1.9 Z-score, *moderate* by a BMI between -2 to -2.9 Z-score and *severe* by a BMI between ≤-3[38].

Height in meters (m) and weight in kilograms (kg) were calculated using a professional balance beam scale with height rod (Seca 700 Physician's Balance, Seca®, Birmingham, United Kingdom). BMI was calculated as weight divided by height squared (kg/m^2). These data were recorded on the patient's file.

BMI at diagnosis, 3 and 6 months after diagnosis were obtained from patients' clinical reports.

We used the online calculator "*Peditools.org*" to estimate Z-scores for weight, height, and BMI at diagnosis, 3 and 6 months. Cut-off values for malnourishment were chosen as BMI Z-score ≤-2.0 (according to ASPEN definition for *moderate and severe* malnutrition). Besides, we chose to analyze weight loss and BMI Z-score decrease at 3 and 6 months from diagnosis.

Main aims of this study were:

- to describe children's nutritional status at diagnosis and during treatment;
- to correlate survival rates with nutritional status;
- to correlate the hospitalization rate for FN with nutritional status.

Survival was stated as the time from diagnosis until death and expressed in years. The Kaplan-Meier method was used to represent survival curves.

Given the limited number of patients and the large variety of diagnoses, the sample size for each subgroup was small. Therefore, we decide to categorize patients using surrogate markers of gravity, such as the expected 5-year survival rates based on diagnosis (≥ 60%, 40-60%, or <40% of expected survival at five years, according to Loeffen et al[20]) and the emetic risk of treatment (high/moderate, according to Dupuis et al[39]), both reported in the Electronic supplementary material. Regarding the hospitalization rate for FN, we categorized patients into two groups: those with <3 and those with ≥3 hospitalizations for FN.

The Kolmogorov-Smirnov test was used to evaluate if the continuous variables had a normal distribution. Continuous variables were then summarized in mean and standard deviation (SD) or median and interquartile range (IRQ) or range. Categorical ones are summarized in number and percentages. Differences between groups on survival and on hospital admissions for FN were assessed in univariate and multivariate Cox regression analyses, yielding hazard ratio (HR) and 95% confidence intervals (95% CI). The significance level of all tests was determined at $p<0.05$. Statistical analyses were conducted using STATA® Software (Version 14.0, Stata Corporation; College Station, TX, USA). The study was conducted according to the ethical standards of our University.

Results

Patients and Disease Characteristics

The present study included 126 pediatric patients receiving treatment for a malignancy. Table I shows patient and disease characteristics.

Sixty-four patients (50.8%) were male patients and 62 patients (49,2%) were female. Ninety-four patients (74.6%) were native from Italy.

The median age at diagnosis was 10 years (range: 3.0-17.0). Patients aged between 5 and 15 years was the largest group (72; 57.2%), followed by adolescents older than 15 years (30; 23.8%) and by children younger than 5 years (2; 19%).

Median follow-up from diagnosis was 2.43 years (range 0.33-4.66).

Most of the patients (54, 42.8%, n=54) were affected by solid tumors (rhabdomyosarcoma, Ewing sarcoma, Wilm's tumor, neuroblastoma, osteosarcoma), whereas 30.2% (n=38) of them were affected by CNS tumors (medulloblastoma, low-grade and high-grade glioma, germ-cell tumors) and 27% (n=34) by hematological malignancies (acute lymphoblastic leukemia, Hodgkin's and non-Hodgkin's lymphoma).

Forty-three patients (34.1%) were metastatic at diagnosis, but only 31 (24.6%) of those expected 5-year survival rates based on diagnosis <40%.

Concerning the emetic risk of treatment, the majority of patients (n=83, 65.9%) underwent high emetic-risk chemotherapy, whereas the 43 others (34.1%) experienced moderate emesis-risk chemotherapy.

Regarding treatment, 17 patients (13,5%) underwent hematopoietic stem cell transplantation (HSCT), of which 2 were allogeneic and 15 were autologous.

Surgery was performed in 44.5% (n=56) of patients, whereas radiotherapy in 42.8% (n=54). 19% (n=24) of patients underwent either radiotherapy and surgery.

At the time of analysis, 33 patients (26.2%) had died (6 of them less than 12 months after diagnosis), 87 (69%) had completed treatment and 6 (4.8%) were still receiving treatment. The main cause of death was malignancy itself, whereas tumor progression occurred in 23 patients (72.7%), followed by severe infections in 8 patients (24.3%) and other causes (1 severe heart failure and 1 cerebral hemorrhage).

Table I. Patients and diseases characteristics (n=126).

		No. (%)	Median (range)
Sex			
	Male	64 (50.8)	
	Female	62 (49.2)	
Origin			
	Italian	94 (74.6)	
	Non-Italian	32 (25.4)	
Age at diagnosis (years)			10 (3-17)
	<5	24 (19)	
	5-15	72 (57.2)	
	>15	30 (23.8)	
Follow-up (years)			2.43 (0.33-4.66)
Diagnosis			
	Solid tumors	54 (42.8)	
	EW	22	
	RMS	13	
	NB	8	
	OS	7	
	WT	4	
	CNS tumors	38 (30.2)	
	MB	14	
	LGG	13	
	GCT	7	
	HGG	4	
	Hematological malignancies	34 (27.0)	
	ALL	19	
	HL	8	
	NHL	7	
Metastatic disease at diagnosis		43 (34.1)	
Surgery		56 (44.5)	
RT		54 (42.8)	
Surgery + RT		24 (19)	
5-y-survival rates based on diagnosis			
	≥60%	87 (69)	
	60% - 40%	8 (6.3)	
	<40%	31 (24.6)	
Emetic risk of chemotherapy			
	High	83 (65.9)	
	Moderate	43 (34.1)	
Total of admissions for FN in 1st year after diagnosis		298	
	With bacteremia	61 (20.5)	
Admissions for FN per patient (median, range)			2 (0-8)
	≥3 per patient	54 (42.9)	
	<3 per patient	72 (57.1)	

Abbreviations: EW: Ewing sarcoma, RMS: Rhabdomyosarcoma, WT: Wilm's tumor, NB: Neuroblastoma, OS: Osteosarcoma, MB: Medulloblastoma, LGG: Low-grade glioma, HGG: High-grade glioma, GCT: Germ-cell tumors, ALL: Acute lymphoblastic leukemia, HL: Hodgkin's lymphoma, NHL: Non-Hodgkin's lymphoma, HCST: Hematopoietic stem cell transplantation, RT: Radiotherapy, FN: febrile neutropenia.

A total of 298 admissions for febrile neutropenia (FN) occurred in the first year after diagnosis. 61 out of 298 admissions for FN (20.5%) showed bacteremia.

The median number of admission for FN per patient was 2 (range 0-8). Fifty-four patients (42.9%) had ≥3 admissions for FN in the first year after diagnosis.

Nutritional Status

Table II illustrates patient nutritional status at diagnosis and during treatment.

At diagnosis 90 patients (71.4%) presented a moderate risk of malnutrition ($STRONG_{kids}$ 2 or 3), whereas the other 36 (28.6%) were at high risk

Table II. Patients nutritional status at diagnosis and during treatment.

		No. (%)
At diagnosis		
	$STRONG_{Kids}$ 2-3 (moderate risk of malnutrition)	90 (71.4)
	$STRONG_{Kids}$ 4-5 (high risk of malnutrition)	36 (28.6)
	BMI Z-score from -1 e to 1.9 (mild malnutrition)	16 (12.7)
	BMI Z-score from -2 e to 2.9 (moderate malnutrition)	2 (1.6)
	BMI Z-score ≤-3 (severe malnutrition)	4 (3.1)
At 3 months		
	BMI Z-score ≤-2	18 (14.3)
	Weight loss ≥5%	58 (46.0)
	Weight loss ≥10%	0 (0)
	BMI Z-score decrease ≥1	12 (9.5)
At 6 months		
	BMI Z-score ≤-2	17 (13.5)
	Weight loss ≥5%	63 (50.0)
	Weight loss ≥10%	28 (22.2)
	BMI Z-score decrease ≥1	32 (25.4)

Abbreviations: BMI: Body Mass Index

of malnutrition ($STRONG_{kids}$ 4 or 5).

Six patients (12.7%) presented mild malnutrition (BMI Z-score from -1 to -1.9), 2 patients (1.6%) presented a moderate malnutrition (BMI Z-score from -2 to -2.9) and 4 patients (3.1%) showed a severe malnutrition (BMI Z-score ≤-3). Mean Z-score BMI at diagnosis was 0.35±1.51 (range -6.43-4.3). At 3 months, at least moderate malnutrition (BMI Z-score ≤-2) was found in 18 patients (14.3%), at 6 months in 17 patients (13.5%).

At 3 months after diagnosis 58 patients (46%) reported a weight loss ≥5%, while no patients had weight loss ≥10%; 12 patients (9.5%) had a BMI Z-score decrease ≥1.

At 6 months, a weight loss ≥10% and a BMI Z-score decrease ≥1 were found respectively in 28 (22.2%) patients and in 32 (25.4%) patients at 6 months.

Association Between BMI Z-Score, Weight Loss and Survival

Mortality was significantly higher for patients who were from moderately to severely malnourished (BMI Z-score ≤-2) at 3 months (HR 2.35; 95% CI=1.06-5.23; *p=0.03)* and 6 months (HR 3.03; 95% CI=1.40-6.53; *p=0.005)* after diagnosis (Table III). Patients with a weight loss ≥5% at 3 months after diagnosis showed a worse survival (HR 3.94%, 95% CI=1.82-8.49, *p<0.0001*).

Survival also resulted significantly inferior in the presence of a weight loss ≥10% either at 6 months (HR 2.10%, 95% CI=1.02-4.33, *p*=0.04). Additionally, survival was significantly reduced for patients with a BMI Z-score decrease ≥1 at 6 months (HR 2.42%, 95% CI=1.20-4.88, *p*=0.01). The Figure 1 showed Kaplan-Meier survival curve of patients re-

Table III. Influence of BMI Z-score and weight loss on survival at several times.

		No. (%)	HR	95% CI	*p*
Diagnosis	BMI Z-score ≤ -2	6 (4.7)	2.1	0.64 – 6.89	0.22
3 months	Weight loss ≥5%	58 (46.0)	**3.94**	**1.82 – 8.49**	***<0.0001***
	Weight loss ≥10%	0 (0)	-	-	-
	BMI Z-score ≤-2	18 (14.3)	**2.35**	**1.06 – 5.23**	***0.03***
	BMI Z-score decrease ≥1	12 (9.5)	0.3	0.04 – 2.19	0.24
6 months	Weight loss ≥5%	63 (50.0)	1.04	0.53 – 2.06	0.903
	Weight loss ≥10%	28 (22.2)	**2.10**	**1.02 – 4.33**	***0.04***
	BMI Z-score ≤-2	17 (13.5)	**3.03**	**1.40 – 6.53**	***0.005***
	BMI Z-score decrease ≥1	32 (25.4)	**2.42**	**1.20 – 4.88**	***0.01***

Abbreviations: BMI: Body Mass Index

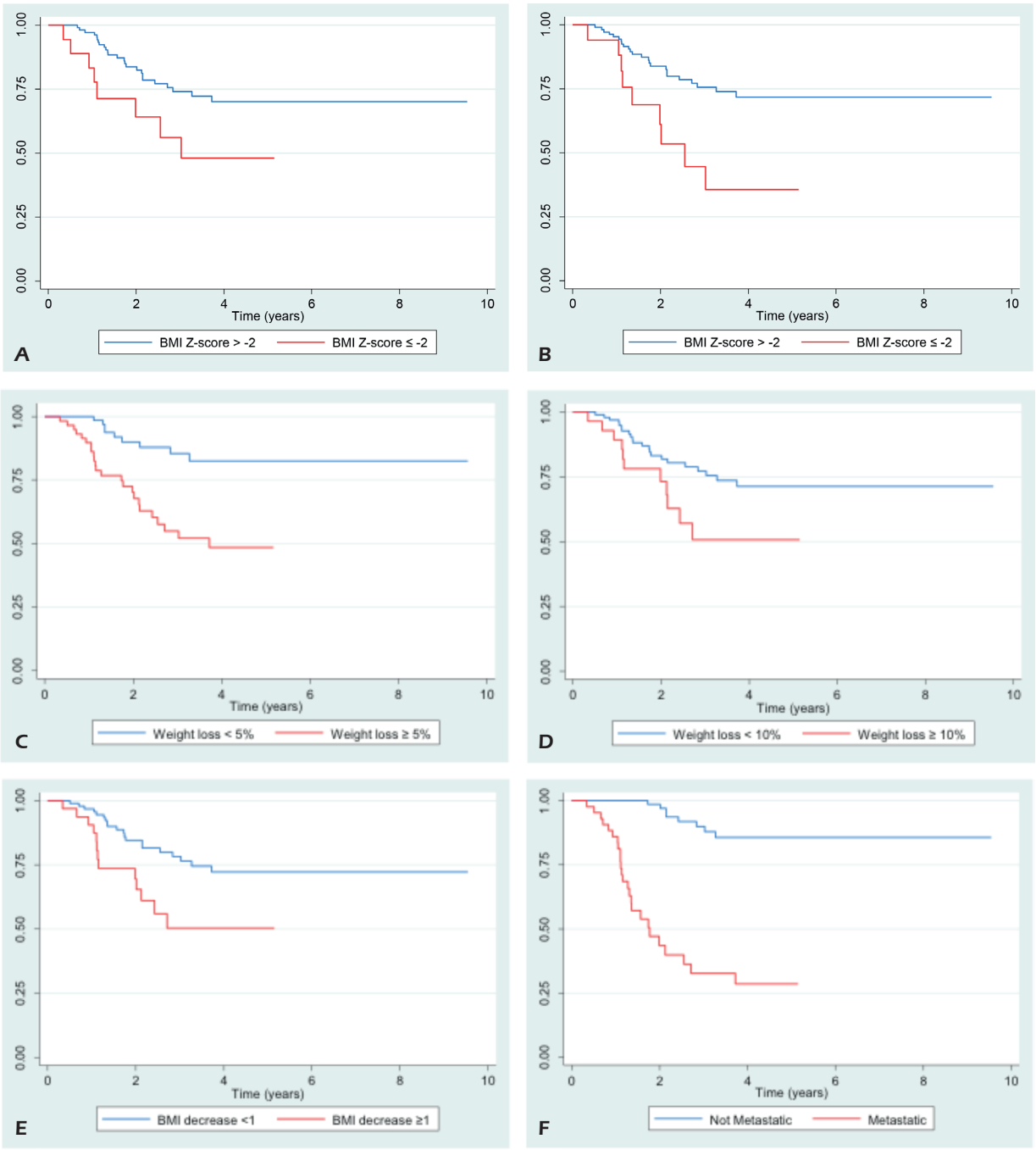

Figure 1. Kaplan-Meier survival curve of patients by (**A**) malnutrition (BMI Z-score ≤ -2) at 3 months after diagnosis, (**B**) malnutrition (BMI Z-score ≤ -2) at 6 months after diagnosis, (**C**) weight loss ≥5% at 3 months after diagnosis, (**D**) weight loss ≥10% at 6 months after diagnosis, (**E**) BMI decrease >1 at 6 months, (**F**) metastases.

spectively by malnutrition (BMI Z-score ≤-2) at 3 months (a) and at 6 months (b) after diagnosis, by weight loss ≥5% at 3 months after diagnosis (c), by weight loss ≥10% at 6 months after diagnosis (d), by BMI decrease >1 at 6 months (e) and by metastasis (f).

At univariate analysis age at diagnosis (HR 1.13%, 95% CI=1.04-1.22, *p=0.005*), non-Italian origin (HR 3.55%, 95% CI=1.77-7.08 *p*<0.0001), hematological malignancies (HR 0.23%, 95% CI=0.07-0.75, *p*=0.01), metastasis at diagnosis (HR 11.08%, 95% CI=4.96-24.78, *p*<0.0001), 5-year survival rates based on diagnosis <40% (HR 7.36%, 95% CI=3.64-14.09, p<0.0001),

Table IV. Univariate and multivariate survival analysis on survival.

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p	HR	95% CI	p
Age at diagnosis (years)	**1.13**	**1.04 – 1.22**	***0.005***	1.04	0.95 – 1.13	0.42
Non-Italian origin	**3.55**	**1.77 – 7.08**	***<0.0001***	1.14	0.47 – 2.74	0.77
Female sex	0.92	0.46 – 1.82	0.81	0.68	0.33 – 1.41	0.31
Hematological malignancy	**0.23**	**0.07 – 0.75**	***0.01***	1.07	0.21 – 5.63	0.94
Metastasis at diagnosis	**11.08**	**4.96 – 24.78**	***<0.0001***	**4.54**	**1.49 – 13.81**	***0.008***
5-y-survival rate <40%	**7.36**	**3.64 – 14.09**	***<0.0001***	2.52	0.78 – 8.14	0.12
High emetic risk	**5.24**	**1.83 – 14.97**	***0.002***	3.11	0.86 – 11.25	0.08
$STRONG_{kids}$=4 or 5	**2.66**	**1.34 – 5.28**	***0.005***	1.16	0.79 – 1.82	0.85
Weight loss ≥5% at 3 months	**3.94**	**1.82 – 8.49**	***<0.0001***	**2.75**	**1.12 – 6.79**	***0.02***

high emetic risk of treatment (HR 5.24%, 95% CI=1.83-14.97, $p<0.002$), $STRONG_{kids}$=4 or 5 (HR 2.66%, 95% CI=1.34-5.28, $p<0.005$) and weight loss ≥5% at 3 months after diagnosis (HR 3.94%, 95% CI=1.82-8.49, $p<0.0001$) were significantly correlated with a lower survival.

At multivariate analysis, only metastasis at diagnosis (HR 4.54%, 95% CI=1.49-13.81, $p=0.008$) and weight loss ≥5% at 3 months after diagnosis (HR 2.75%, 95% CI=1.12-6.79, $p=0.02$) were independently correlated with a worse survival (Table IV).

Association Between Nutritional Status and Hospitalization for FN

Patients from moderately to severely malnourished (BMI Z-score ≤-2) at 3 months *(p=0.001)* and 6 months *(p=0.02)* after diagnosis had a number of hospitalization for FN ≥3 in the first year of treatment. Additionally, number of hospitalization for FN ≥3 was found in patients with a weight loss ≥5% at 3 (HR 14.85%, 95% CI=6.2-35.56, *p<0.0001*), either in the presence of a weight loss ≥10% at 6 months (HR 7.56%, 95% CI=2.79-20.49, *p<0.0001*) and finally in patients with a BMI Z-score decrease ≥1 at 6 months (HR 8.01%, 95% CI=3.11-20.61, *p<0.0001*) (Table V).

At univariate analysis, hospitalization for FN resulted significantly higher (≥3) in patients of non-Italian origin (HR 2.46%, 95% CI=1.09-5.59 *p=0.03*), having metastasis at diagnosis (HR 5.67%, 95% CI=2.54-12.69, *p<0.0001*), 5-year survival rates based on diagnosis <40% (HR 2.71%, 95% CI=1.18-6.25, *p=0.019*), high emetic risk of treatment (HR 3.72%, 95% CI=1.63-8.53, *p=0.002*), $STRONG_{kids}$ = 4 or 5 (HR 13.75%, 95% CI=5.09-37.13, *p<0.0001*) and weight loss ≥5% at 3 months after diagnosis (HR 14.85%, 95% CI=6.20-35.56, *p<0.0001*).

At multivariate analysis, the occurrence of ≥3 hospitalizations for FN showed a significant association with the presence of metastasis at diagnosis (HR 7.27%, 95% CI=1.54-34.38, *p=0.01*), weight loss ≥5% at 3 months after diagnosis (HR 7.72%, 95% CI=2.27-26.2, *p<0.0001*) and a strong correlation with the presence of $STRONG_{kids}$ = 4 or 5 at diagnosis (HR 5.90%, 95% CI=1.56-22.29, *p=0.009*) (Table VI).

Discussion

Our analysis, performed over a period of five years of clinical practice on 126 children neo-diag-

Table V. Influence of nutritional status on the occurrence of ≥3 hospitalizations for FN at several times.

		No. (%)	HR	95% CI	p
Diagnosis	BMI Z-score ≤-2	6 (4.7)	1.35	0.26-6.98	0.72
3 months	Weight loss ≥5%	58 (46.0)	**14.85**	**6.20-35.56**	***<0.0001***
	Weight loss ≥10%	0 (0)	-	-	-
	BMI Z-score ≤-2	18 (14.3)	**8.85**	**2.41-32.47**	***0.001***
	BMI Z-score decrease ≥1	12 (9.5)	0.64	0.18-2.25	0.486
6 months	Weight loss ≥5%	63 (50.0)	0.57	0.28-1.18	0.129
	Weight loss ≥10%	28 (22.2)	**7.56**	**2.79-20.49**	***<0.0001***
	BMI Z-score ≤-2	17 (13.5)	**8.05**	**2.18-29.72**	***0.002***
	BMI Z-score decrease ≥1	32 (25.4)	**8.01**	**3.11-20.61**	***<0.0001***

Table VI. Univariate and multivariate analysis on occurrence of ≥3 hospitalizations for FN.

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p	HR	95% CI	p
Age at diagnosis (years)	1.03	0.95-1.11	0.74	0.99	0.88-1.12	0.90
Non-Italian origin	**2.46**	**1.09-5.59**	***0.03***	2.14	0.59-7.78	0.25
Female sex	0.82	0.40-1.65	0.57	0.55	0.19-1.55	0.26
Hematological malignancy	0.45	0.19-1.06	0.07	1.56	0.30-8.04	0.59
Metastasis at diagnosis	**5.67**	**2.54-12.69**	***<0.0001***	7.27	1.54-34.38	0.01
5-y-survival rate <40%	**2.71**	**1.18-6.25**	***0.019***	0.50	0.08-3.22	0.47
High emetic risk	**3.72**	**1.63-8.53**	***0.002***	3.49	0.86-14.26	0.08
$STRONG_{kids}$ =4 or 5	**13.75**	**5.09-37.13**	***<0.0001***	**5.90**	**1.56-22.29**	***0.009***
Weight loss ≥5% at 3 months	**14.85**	**6.20-35.56**	***<0.0001***	**7.72**	**2.27-26.2**	***<0.0001***

nosed with cancer, showed a 100% rate of patients at risk of malnutrition at diagnosis, respectively 90 (71.4%) at moderate risk ($STRONG_{Kids}$ 2-3) and 36 (28.6%) at high risk ($STRONG_{Kids}$ 4-5). Moreover, at diagnosis 16 patients (12.7%) were already affected by mild malnutrition, 2 (1.6%) by moderate and 4 (3.1%) by severe malnutrition. Our records demonstrate that in a period of 3 and 6 months there is a three-fold increase of the rate of at least moderate malnutrition (BMI Z-score between -2 and -2.9), from 4.7% respectively to 14.3% and 13.5%. Indeed, at 3 months, 58 children (46%) underwent weight loss ≥5%; at 6 months, they were 63 (50%); besides 28 of them (22.2%) had lost ≥10% of their body weight. Due to the retrospective type of analysis, we have no information regarding a possible nutritional support on these categories. Weight loss ≥5% at 3 months and weight loss ≥10% at 6 months after diagnosis were found to be significantly associated with higher mortality. We found a risk of mortality increased of 294% (HR 3.94; 95%CI 1.82-8.49; *p<0.0001*) for patients who lose ≥5% of weight in the first 3 months after diagnosis and a risk of mortality increased of 110% (HR 2.10; 95%CI 1.02 – 4.33; *p=0.04*) for patients who reported a weight loss ≥10% at 6 months after diagnosis.

At the same time, a weight loss ≥5% in the first 3-6 months after diagnosis, very strongly enhanced the occurrence of ≥3 hospitalizations for FN (HR 14.85; 95%CI 6.20-35.56; *p<0.0001*).

To understand the role of covariates on these outcomes we performed a univariate and multivariate analysis, having as main endpoint survival and occurrence of ≥3 hospitalizations for FN. Multivariate analysis confirmed the independent role of weight loss ≥5% at 3 months both on survival (HR 2.75; 95%CI 1.12 – 6.79; *p=0.02*) and on the occurrence of ≥3 hospitalizations for FN (HR 7.72; 95% CI 2.27-26.2; *p <0.0001*). Moreover, regarding the rate of infections, having a $STRONG_{kids}$ of 4-5 at diagnosis increases of 490% (HR 5.90; 95% CI 1.56-22.29; *p=0.009*) the risk of having ≥3 hospitalizations for FN. Our case load confirmed data already present in the literature. Indeed, previously Loeffen et al[20] found that malnutrition at diagnosis and at 3 months was associated with a significantly worse survival. However, in our study, we detected a strong association between malnutrition in the initial phase of therapy (3-6 months after diagnosis) and lower survival, independently of 5-years expected survival based on diagnosis. Consequently, a close monitoring of nutritional status during the initial phase of treatment could provide to enhance survival rates[40-43]. Furthermore, Loeffen et al[20] showed the strong association between a rapid loss of weight in the first 3 months after diagnosis with an increased rate of FN episodes. This data has been confirmed by our results. In addition, we have found that the detection of a high risk of malnutrition at diagnosis ($STRONG_{kids}$ of 4-5) is an independent factor which significantly increases the rate of hospitalization for FN. This awareness may help clinicians to closely identify those patients who are more vulnerable to bacterial infections.

The main point of strength of this study is to have highlighted the role of malnutrition and weight loss on survival and on hospitalization for FN in childhood cancer patients. Due to the potential manageable nature of this risk factor, for the future, a personalized evaluation of our children and adolescents will be mandatory. Furthermore, a nutritional support should be offered to this particularly fragile population. Many

studies have already demonstrated that a careful nutritional intervention may help patients with cancer to better tolerate therapy[43-45].

Some drawbacks, when interpreting our findings, could be raised:

- the poor homogeneity of the sample for the variety of cancer diagnoses with different presentations, courses, and treatments;
- the retrospective nature of the study;
- the lack of data about body composition;
- the lack of information about a nutritional support.

Future studies are needed, including a larger patient number for each malignancy, in order to investigate the role of malnutrition in each type of cancer.

Furthermore, a prospective study should be useful in investigating the correlations between survival and body composition variations during childhood cancer treatment. BMI is considered as an adequate indicator of nutritional status but the combination of body composition and BMI could be accurate nutritional interventions. Body compositions measures are to date considered appropriate to describe nutritional status in children with clinical conditions, such as cancer[46]. Indeed, nutritional intervention should be based either on anthropometric measurements and body compositions status, in order to guarantee a personalized support.

Conclusions

Given the high prevalence of malnutrition in childhood cancer, the impact of malnutrition and a rapid weight loss on survival and infections, a nutritional evaluation should be mandatory from diagnosis and during the treatment. A timely adjustment of nutritional status of pediatric patients receiving chemotherapy not only might improve their survival, but also should prevent infectious disease, giving a reduction of the admissions in the hospital and consequently an improvement of the QoL.

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Informed consent

Informed consent was obtained from all individual participants included in the study and from their parents.

Conflict of Interests

The authors declare that there are no conflicts of interest to disclose.

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