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ORIGINAL ARTICLE

Prognostic factors for survival in children with cancer and febrile neutropenia

Factores pronósticos de sobrevida en niños con cáncer y neutropenia febril

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What do we know about the subject matter of this study?

Febrile neutropenia (FN) as a consequence of cancer treatment in children is linked to morbidity and mortality due to delays or suspension of oncological therapy and the onset of opportunistic infections, impacting survival rates.

What does this study contribute to what is already known?

This survival, historical cohort, prognostic, and analytical study examined risk and protective variables by hazard ratio. A univariate analysis and a Cox multivariate model constructed with variables of clinical interest, expert medical criteria, and statistical significance were also used. This triad had not been studied for survival at the local level in this population. An overall survival of 64.7% at 5 years was observed.

Abstract

Cancer remains one of the most important diseases in public health. **Objective:** To estimate 5-year survival in pediatric cancer patients affected by FN, according to clinical-demographic variables. **Patients and Method:** Survival, prognostic, and analytical study with historical cohort. analytical. Cancer was grouped into leukemias-lymphomas, osteosarcoma, and other solid tumors. Descriptive analysis was performed with Fisher and Kruskal-Wallis tests; prognostic factors like age, type of cancer, and sepsis were analyzed with hazard ratio (HR). The Kaplan-Meier method and the Cox regression model were used for the survival curves. **Results:** We studied 116 subjects diagnosed with leukemia-lymphoma (51.7%), osteosarcoma (25.9%), and other solid tumors (22.4%). The median

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number of days between chemotherapy and the first episode of FN was 5 days [1-7], 7 [7-8], and 7 [5-8], respectively. Overall survival was 64.7% at 5 years. Protective factors according to Cox Model were post-cancer comorbidity (HR 0.33 CI95% 0.16-0.67) and average educational level of the caregiver (HR 0.36 CI95% 0.18-0.73) and risk factors were the presence of another type of solid organ tumor (HR 3.43 CI95% 1.64-7.19), sepsis (HR 2.89 CI95% 1.47-5.70), delay in chemotherapy (HR 2.94 CI95% 1.17-7.40), and invasive fungal infection (HR 3.36 CI95% 1.22-9.22). **Conclusion:** Our study analyzed prognostic factors on survival in children with cancer and FN, finding risk and protective factors consistent with the literature. The presence of a solid organ tumor and sepsis were confirmed as risk factors, while the presence of post-cancer comorbidity and average educational level were protective factors in survival.

Introduction

According to data from the International Agency for Research on Cancer of 2018[1], childhood cancer mortality in children under 15 years of age numbers 74,956 cancer deaths overall[1], 7,297 in Latin America, and 119 cases in Chile. In the first National Childhood Cancer Registry (RENCI) in Chile, for the five years between 2007-2011, an annual average of new cancer cases of 480 was observed, with an overall crude incidence rate of 128.2 per million in children aged under 15 years and an overall survival of 71.4% at 5 years of follow-up after diagnosis[2].

Neutropenia is one of the most frequent consequences of chemotherapy in children with cancer, defined as an absolute neutrophil count (ANC) < 500 cells/mm^3. When the neutrophil count is < 500 cells/mm^3, predisposes patients to infections clinically manifesting as fever, a condition termed febrile neutropenia (FN)[3,4,5,6]. This is the main infectious complication presented by cancer patients during their treatment. FN is classified as low or high risk for invasive bacterial infection, which implies differences in prognosis, treatment, and evolution[5].

In adults, one of the adverse effects of neutropenia is the need to delay chemotherapy or dose reduction[5,6], which can impact the treatment efficacy and thus affect survival[7]. However, research in the pediatric population on the effect of FN episodes on the overall survival of children with cancer is still limited. In Chile, there are no data on this subject. Therefore, it is relevant to study the relationship between FN, the possibility of delaying chemotherapy, and associated survival to have a global view of the behavior of this triad and, thus, contribute with information for the definition of local strategies.

According to clinical-demographic variables, this study aimed to estimate 5-year survival in pediatric cancer patients affected by FN.

Patients and Method

This was a survival, historical cohort, prognostic, and analytical study. With the appropriate authorization of the Principal Investigator and the Human Research Ethics Committee of the Faculty of Medicine of the *Universidad de Chile*, we used the database of children with FN prospectively included in FONDECYT project nº 1090194 between 2009 and 2011. From this base, we used the updated series of children with cancer and FN treated at the *Hospital Dr. Luis Calvo Mackenna* from a non-probabilistic sample. In addition, cancer was grouped into three categories: leukemia-lymphoma, osteosarcoma, and other solid tumors. The *Hospital Dr. Luis Calvo Mackenna* is a public pediatric facility that is part of the National Child Program of Antineoplastic Drugs (PINDA) network.

Exclusion criteria were children with hematopoietic progenitor cell or solid organ transplant before or after cancer diagnosis and up to five years of follow-up. The variable FN was defined as an episode with ANC < 500 cells/mm^3 added to fever, described as an axillary temperature ≥ 38.5ºC or two measurements ≥ 38.0ºC spaced at least one hour apart[3,4,5,6]. The primary response variable was time to death, observable at a maximum follow-up of five years from a cancer diagnosis. The physiological comorbidity variable was defined as the disorder or disease occurring simultaneously, and chemotherapy-related comorbidity is the morbidity that occurs when receiving this treatment.

A descriptive and comparative data analysis was performed (Fisher test for categorical variables and Kruskal-Wallis test for quantitative variables). A p value < 0.05 was considered statistically significant. Regarding the survival analysis, prognostic factors for survival in children with FN were evaluated, estimating the hazard ratio (HR) and both overall and specific survival over five years[9,10,11].

The Kaplan-Meier method was used to estimate the survival curves, and the survival functions were compared using the Cox regression model in accordance

with the proportional hazards assumptions. The Hosmer-Lemeshow test ($p < 0.25$) and the stepwise methodology ($p < 0.05$) were applied to the results of the prognostic variables entered into the univariate Cox model until a final multivariate Cox model was obtained. This model evaluated clinical variables with expert medical criteria and those obtained by the methodology above, regardless of their significance level.

The StataSE version 14.0 statistical software was used for the analyses.

Results

The database, which included 126 subjects, was analyzed. Of these, ten were excluded, eight due to undergoing some type of transplant during follow-up, one due to a kidney transplant before the cancer diagnosis, and one due to incomplete information. There was no loss to follow-up for any of the cases analyzed or death due to another cause. The magnitude of missing data was less than 10%; therefore, it was considered that this did not affect the robustness of the analysis, so the data were not imputed[10,12].

Table 1 shows the sociodemographic variables of the 116 children included in the study. They were distributed in the three cancer categories: leukemia-lymphoma (N = 60, 51.7%), osteosarcoma (N = 30, 25.9%), and other solid tumors (N = 26, 22.4%). Within the group of leukemia-lymphomas, 78.3% of the patients had lymphoblastic leukemia, and 18.3% had myeloid leukemia; in the group of other solid tumors, 26.9% were central nervous system tumors, and 26.9% were soft tissue sarcomas. Children with leukemia/lymphoma and osteosarcoma were younger than those with other solid tumors ($p = 0.002$). The education level of the caregiver was mainly completed secondary education, and there was a tendency towards greater rurality for the leukemia/lymphoma group, a value that was not significant.

Table 2 shows the clinical characteristics of children with FN episodes according to type of cancer.

Table 1. Sociodemographic characteristics in the children studied according to type of cancer

Variable n, (%)	Leukemia and Lymphoma n = 60	Osteosarcoma n = 30	Other solid tumors n = 26	*p value*
Male	35 (58.3)	14 (46.7)	14 (53.8)	0.569
Age in months, median [IQR]*	73 [44.5-118]	74.5 [44.5-118]	133.5 [53-167]	**0.002**
Nationality (Chilean)	58 (96.7)	30 (100)	26 (100)	0.730
Caregiver's Education Level				
Elementary	14 (23.3)	6 (20)	7 (26.9)	0.807
Secondary	30 (50)	17 (56.7)	13 (50)	0.882
Higher education	15 (25)	6 (20)	3 (11.5)	0.406
Geographic area				**0.022**
North	17 (63)	4 (13.3)	8 (30.7)	
Center	41 (68.3)	23 (76.7)	16 (61.5)	
South	1 (1.7)	3 (10)	2 (7.7)	
Region of residence				**< 0.001**
Arica y Parinacota	2 (3.3)	0	0	
Tarapacá	8 (13.3)	0	4 (15.4)	
Antofagasta	7 (11.7)	2 (6.7)	4 (15.4)	
Coquimbo	0	2 (6.7)	0	
Valparaíso	1 (1.7)	4 (13.3)	1 (13.3)	
Metropolitan	19 (31.7)	13 (43.3)	5 (19.2)	
Libertador Bernardo O`Higgins	0	3 (10)	1 (3.9)	
Maule	21 (35)	0	8 (30.7)	
Ñuble	0	1 (3.3)	0	
Biobío	1 (20)	3 (10)	1 (3.9)	
Araucanía	0	2 (6.7)	2 (7.7)	
Lima	1 (1.7)	0	0	
Rurality	17 (28.3)	7 (23.3)	6 (23.1)	0.885

*IQR: Interquartile range (the Shapiro-Wilk test was used to evaluate the normality of the distribution of the age data in months, with a p 0.05, and the Kruskal-Wallis test was used to assess the p value), variable education level n= 111 (missing 4.3% of the data). The Fisher test was used to obtain the p value in the categorical variables. A p value < 0.05 is considered significant.

Table 2. Clinical characteristics of the children studied, according to the type of cancer diagnosis

Variables related to the cancer and its treatment n (%)	Leukemia and Lymphoma n = 60	Osteosarcoma n = 30	Other solid tumors n = 26	*p value*
Comorbidity upon admission	20 (33.3)	8 (26.7)	8 (30.8)	0.835
Comorbidity after diagnosis	47 (78.3)	22 (73.3)	19 (73.1)	0.745
Type of comorbidity after diagnosis				**< 0.001**
Physiological	11 (23.4)	4 (18.2)	15 (78.9)	
Chemotherapy-related	13 (27.7)	14 (63.6)	3 (15.8)	
Days from the onset of symptoms to cancer diagnosis, median [IQR]	18 [10.5-34]	50 [45-82]	42 [27-100]	**< 0.001**
Secondary cancer	0	0	1 (3.9)	0.224
Relapse	33 (55)	6 (20)	9 (34.6)	**0.004**
Days from diagnosis to relapse, average (SD)	824.4 (± 514.8)	676.8 (± 183.1)	538.5 (± 262.4)	0.372
More than one relapse	8 (24.2)	1 (16.7)	1 (11.1)	0.859
High-risk febrile neutropenia in the 1st episode	44 (73.3)	21 (70)	10 (38.5)	0.053
Days from diagnosis to 1st FN episode, median [IQR]	38 [14-72]	35 [16-61]	134.5 [25-218]	**0.009**
Days of chemotherapy to 1st FN episode, median [IQR]	5 [1-7]	7 [7-8]	7 [5-8]	**< 0.001**
N° of episodes of febrile neutropenia, median [IQR]	4 [3-6]	4.5 [3-6]	2 [1-4]	**0.001**
N° of episodes of high-risk febrile neutropenia, median [IQR]	4 [2-6]	3 [2-5]	1 [0-2]	**< 0.001**
N° of episodes of low-risk febrile neutropenia, median [IQR]	0 [0-1]	1 [1-2]	1 [1-2]	**0.002**
N° of patients who have a delay in chemotherapy due to FN	5 (8.3)	4 (13.3)	2 (7.7)	0.701
Invasive bacterial infection in any episode	45 (75)	24 (80)	13 (50)	**0.035**
IBI risk factor in 1st febrile neutropenia episode				
C-reactive protein > 90 mg/L	21 (35)	11 (36.7)	8 (30.8)	0.934
Hypotension	9 (15)	5 (16.7)	3 (11.5)	0.941
≤ 7 days from the last chemotherapy cycle to the start of the fever	49 (81.7)	17 (56.7)	17 (65.4)	**0.034**
Platelets < 50,000 /mm^3	32 (53.3)	16 (53.3)	8 (30.1)	0.122
N° of risk factors for IBI in 1st febrile neutropenia episode	2 [1-3]	2 [1-2]	1 [1-2]	**0.004**
Invasive fungal infection in any episode	13 (21.7)	1 (3.3)	0	**0.003**
Fungal infection proven/probable in any episode	12 (20)	1 (3.3)	0	**0.006**
Sepsis in any episode	23 (38.3)	9 (30)	5 (19.2)	0.221
Finalized treatment	37 (61.7)	19 (63.3)	13 (50)	0.558
Admission to palliative care	14 (23.3)	9 (30)	6 (23.1)	0.783
Days from diagnosis to admission to palliative care, average (SD)	1073.6 (± 780.6)	520.7 (± 401.9)	686.5 (± 325.4)	0.152
Metastasis	0	17 (56.7)	12 (46.2)	**< 0.001**
Metastasis at cancer diagnosis	0	5 (29.4)	4 (33.3)	0.568
Finalized treatment and subsequently presents metastasis	0	1 (5.9)	2 (15.4)	0.607
Death	17 (28.3)	11 (36.7)	13 (50)	0.156
Months from diagnosis until death, average (SD)	23.8 (± 14.7)	28.2 (± 16.7)	22.8 (± 13.6)	0.779
Finalized treatment and subsequently presents relapse (n = 19)	10 (83.3)	1 (33.3)	3 (75)	0.259

*n = 115 (missing 0.9% of the data), **n = 45 (missing 6.2% of the data), IQR: interquartile range, SD: standard deviation, IBI: invasive bacterial infection. The Shapiro-Wilk test was used for the quantitative variables to evaluate normality with a $p < 0.05$. The Kruskal-Wallis test was used for the categorical variables, and the Fisher Test was used to obtain the p value in categorical variables. A p value < 0.05 is considered significant.

The median number of days from symptom onset to cancer diagnosis was 18 days [10.5-34 days] for children with leukemia/lymphoma, 50 days [45-82 days] for osteosarcoma, and 42 days [27-100 days] for other solid tumors ($p < 0.001$). When comparing pre- and post-cancer diagnosis comorbidity, an increase of 135%, 175%, and 137.5% was seen in children with leukemia/lymphoma, osteosarcoma, and other solid tumors, respectively. The presence of relapse was significantly higher in children with leukemia/lymphoma (55%) than in those with osteosarcoma (20%) or other solid tumor (34.6%) ($p = 0.004$). Regarding mortality, 28.3%, 36.7%, and 50% of the children died, respectively (p = NS).

The time from the start of chemotherapy to the presentation of the first FN episode was significantly shorter in children with leukemia/lymphoma than children with osteosarcoma and other solid tumors ($p = 0.000$). The number of FN episodes was significantly higher in children with leukemia/lymphoma and osteosarcoma compared with children with other solid tumors ($p = 0.001$). Invasive bacterial infection was more frequent in children with leukemia/lymphoma and osteosarcoma ($p = 0.035$), and invasive fungal infection in children with leukemia/lymphoma ($p = 0.003$).

Of 116 children followed for five years, with a total risk analysis and time observation of 5,523 months and a final observation at 60 months, 41 died (expecting the event of interest), resulting in a risk time of 1,023 months and an incidence rate of 0.04 (41 cases/1,023 months at risk). At 32 months of follow-up, 75% of the children were alive. The overall and specific survival of oncology patients affected by FN was 64.7% at five years. Out of the 41 deceased patients, all the cases were reviewed, establishing cancer as a cause of death in all of them.

Figure 1 shows survival by type of cancer. In the leukemia/lymphoma group, 75% of the children were alive at 42 months of follow-up; in the osteosarcoma group, 75% of the children were alive at 40 months of follow-up; and in the other solid tumors group, 50% of the children were alive at 44 months of follow-up.

Prognostic factors for survival

To identify prognostic factors for survival according to the number of FN episodes and their duration, adjusting for variables of interest, we first performed a univariate analysis of the variables with the Cox model (table 3). The proportionality of risks was confirmed with the proportional hazards assumption test, where it was noted that age in months is a risk factor, increasing the risk of death by 1% for each additional month of life (HR 1.01; 95%CI 1.00-1.01), together with having had sepsis in some episode, which increases the risk of dying by 2.84 times (HR 2.84; 95%CI 1.54-5.26) and the delay in chemotherapy for FN, which increases the risk of dying by 2.32 times compared with children who did not have a delay (HR 2.32; 95%CI 1.03-5.26). In this analysis, the education level of the caregiver was protective, which significantly decreased the risk of death in children (HR 0.46; 95%CI 0.24-0.88).

The results of the univariate Cox model were subjected to the Hosmer-Lemeshow criterion with a significance level of 0.25. Additionally, the expert medical criterion and the stepwise procedure with a variable

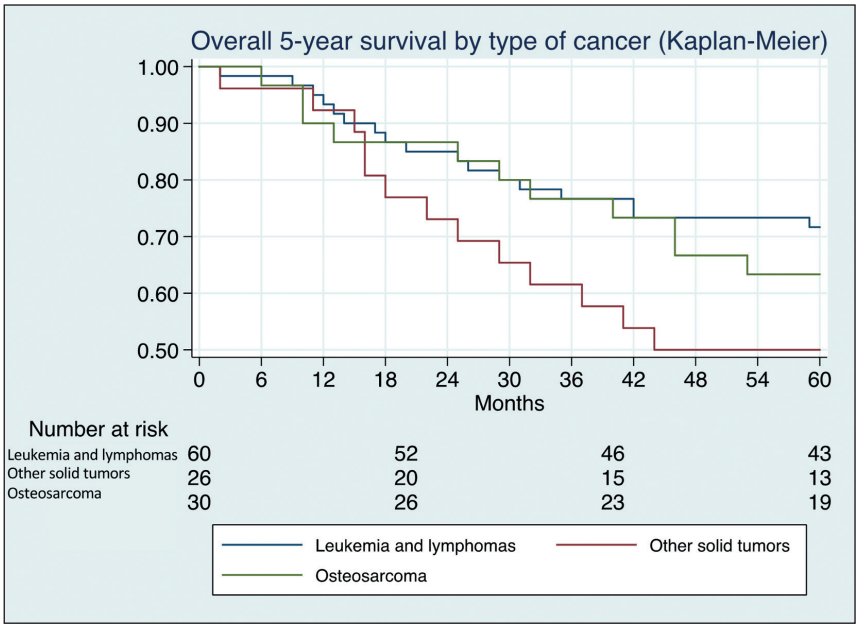

Figure 1. Kaplan-Meier Curve. Overall 5-year survival rate of 116 pediatric cancer patients treated in a public pediatric hospital in Santiago, Chile, according to the type of cancer diagnosis. Comparison of survival curves with the log-rank test p=0.146 (leukemia and lymphomas p=0.12, osteosarcoma p=0.94, other solid tumors p=0.06). Comparison of survival curves using the Wilcoxon test p= 0.165.

Table 3. Cox model. Crude univariate analysis, according to death risk factors, in children with cancer and episodes of febrile neutropenia

Variable	H.R.	[CI 95%]		*p value*
Sex (male)	1.11	0.60	2.06	0.737
Age (months)	1.01	1.00	1.01	**0.007**
Caregiver's education level -Elementary	1.85	0.96	5.58	0.066
Caregiver's education level – Secondary	0.46	0.24	0.88	**0.019**
Education level of caregiver - Higher education	1.38	0.69	2.76	0.357
Rurality	1.33	0.69	2.58	0.384
Comorbidity upon admission	0.68	0.34	1.40	0.305
Comorbidity post cancer diagnosis	0.58	0.30	1.12	0.107
Days from consultation to cancer diagnosis	1.00	0.99	1.00	0.474
Leukemia and lymphomas	0.61	0.33	1.14	0.125
Osteosarcoma	1.02	0.51	2.05	0.938
Other solid tumors	1.83	0.95	3.55	0.070
1st episode of high-risk febrile neutropenia	1.65	0.83	3.30	0.154
Days from diagnosis to 1st FN episode	0.99	0.99	1.00	0.156
Days from last chemotherapy to 1st FN episode	1.01	0.93	1.10	0.770
N° episodes of febrile neutropenia	1.05	0.92	1.19	0.420
N° episodes of high-risk febrile neutropenia	1.09	0.98	1.23	0.113
N° episodes of low-risk febrile neutropenia	0.77	0.57	1.05	0.103
N° of risk factors for IBI	1.34	0.96	1.86	0.076
Invasive bacterial infection in any episode	1.32	0.65	2.71	0.433
Sepsis in any episode	2.84	1.54	5.26	**0.001**
Delay in chemotherapy due to febrile neutropenia	2.32	1.03	5.26	**0.042**
Invasive fungal infection in any episode	1.79	0.79	4.04	0.161
Fungal infection proven/probable in any episode	1.51	0.63	3.59	0.351
Metastasis at cancer diagnosis	1.30	0.50	3.41	0.585

Table 4. Multivariate Cox model. Death risk factors in children with cancer and episodes of febrile neutropenia

Variable	H.R.	[CI 95%]		*p value*
Sex (male)	1.59	0.82	3.11	0.171
Age (months)	1.01	1.00	1.02	**0.005**
Secondary education	0.36	0.18	0.73	**0.005**
Comorbidity post-diagnosis	0.33	0.16	0.67	**0.002**
Other solid tumors	3.43	1.64	7.19	**0.001**
Sepsis in any episode	2.89	1.47	5.70	**0.002**
Delay to chemotherapy due to febrile neutropenia	2.94	1.17	7.40	**0.022**
Invasive fungal infection (proven/probable) in any episode	3.36	1.22	9.22	**0.019**

Multivariate Cox model $p < 0.0001$ with 116 observations. Hosmer and Lemeshow research criteria ($p < 0.25$), stepwise method with a significance level of 0.05, and expert opinion.

retention significance of 0.05 were employed. This resulted in the final multivariate Cox model. When entering the prognostic variables according to statistical and clinical significance (table 4), older age (HR 1.01; 95%CI 1.00-1.02; p = 0.005), age (HR 1.01; 95%CI 1.00-1.02; p = 0.005), having a solid tumor other than osteosarcoma (HR 3.43; 95%CI 1.64-7.19; p = 0.001), having had sepsis in a FN episode (HR 2.89; 95%CI 1.47-5.70; p = 0.002), the delay of chemotherapy following FN episodes (HR 2.94; 95%CI 1.17-7.40; p = 0.022), and having had any episode of invasive fungal infection (HR 3.36; 95%CI 1.22-9.22; p = 0.019). This last variable was incorporated into the model on the recommendation of the experts consulted at the *Hospital Dr. Luis Calvo Mackenna*, gaining statistical significance and becoming a risk factor with relevance for survival.

Discussion

In this study, a series of 116 children with cancer and FN episodes in a pediatric public hospital were analyzed, reporting their survival and prognostic factors that affect it. Overall survival of 64.7% was reported, below that described in the first RENCI report[2], which was 71.4% for children under 15 years of age and lower than that found in pediatric studies carried out in Switzerland (88.2% at 5 years)[13] and the United States (81.3% at 5 years)[14].

Concerning survival and prognostic factors, we found no differences between rural and urban residents as a prognostic factor, possibly because they were treated in referral centers and were housed in foster homes. This differs from what was reported by M. Hashibe et al., in a metropolitan-rural disparity analysis performed on adult residents of Utah, where they found a 5-year relative survival for rural residents, 5.2% lower compared with urban residents[15]. This is similar to Erdmann et al.[16], who evaluated survival in children with central nervous system tumors, reporting an HR 1.38 for those living in rural areas (95%CI 1.00-1.09).

In the same study by Erdmann et al., no relationship was found between the education level of the parents as caregivers and five-year survival[16], which differs from what was observed in our study, where the average education level of the caregiver acts as a protective factor with respect to the primary and higher education level (p = 0.005). These findings could be due to the type of population attending the hospital and correlate with what was reported by the 2017 National Census[17], where 44.6% of the population reported having completed high school education. In our series, 51.7% corresponds to this education level, compared to 20.7% for higher education, so the sample size may have affected the significance of a higher education level for the caregiver. Being part of this middle educational group may facilitate understanding instructions, actively participating in the child's care, educating themselves on issues related to the underlying disease, and seeking help in case of warning signs.

The variable age at diagnosis was found to be a relevant predictive factor for this series after being included in the multivariate Cox model (p = 0.005); however, it loses significance within its 95%CI. Therefore, it is considered relevant but insignificant, similar to what Aljabari et al.[18] reported in their univariate analysis (p = 0.70). These authors found a similar effect for male sex (p = 0.49), which was in line with our findings (p = 0.171). These results are consistent with those reported for age and sex by Mendes Lins et al. in their study of survival and mortality risk factors in pediatric patients with acute myeloid leukemia in a low-middle-income country[19]. Additionally, in the study by Loeffen et al.[20], there were similarities in what was observed for sex (p = 0.547) with this series, and they disagreed in the multivariate analysis for the variable age, where they reported age < 1 year (p = 0.04) as a risk factor. Also, L. Salvo and G. Cavada Ch.[21] reported relevant significance for age (p = 0.00) in a study of prognostic factors for survival in patients older than 15 years with osteosarcoma, which is consistent with the expert opinion.

The results for the series of these variables (age and sex) could be due to the loss of significance when added in the model against other variables due to the sample size, because older patients may have more complex hospitalizations, or because age and sex may not be significant in some types of cancer.

The variable invasive fungal infection (proven/probable) was relevant as a risk factor in agreement with that reported by Dursun et al.[22], with a lower survival at 30 days for patients who developed fungal infection compared to patients without it (p < 0.001), which in that study lost significance when a multivariate model was performed. The presentation of invasive fungal infection in the context of FN is clinically relevant. It is an unfavorable scenario, constituting an important cause of morbidity and mortality in children with cancer[23].

The presence of sepsis is considered a relevant risk factor for survival, as observed by the same study[22] (p = 0.05), which is similar to that reported for this series (p = 0.002) and agrees with the literature[18]. Furthermore, Dursun et al.[22] did not identify cancer type as a prognostic factor, contrasting with our findings, which indicated that possessing a solid tumor, excluding osteosarcoma, was significantly associated with mortality (p = 0.001). This discrepancy may be at-

tributed to the fact that central nervous system tumors represented 26.9% of the cohort of other solid tumors, ranking as the second leading cause of childhood cancer mortality in Chile in 2013[24].

In the study by Kuderer et al.[25] regarding mortality and morbidity in adults with cancer, a multivariate logistic regression analysis was employed to assess predictor factors. They identified various comorbidities as risk factors, yet did not specify whether these occurred prior to or subsequent to the cancer diagnosis, reporting an odds ratio (OR) greater than 1 ($p < 0.001$). This contrasts with the findings in this series, where comorbidity functions as a protective factor. This may be due to differences in the populations themselves or to the fact that having a comorbidity, the children may have more check-ups, and the parents may be more supported by the hospital.

This work is the first national study in a pediatric oncology series that analyzes survival in patients with FN episodes and its prognostic factors, in addition to being able to perform a multivariate Cox model consistent with that reported by other authors. Among the study's limitations is its retrospective design, so there may be missing or incomplete data. In addition, the cases identified are limited to those that were recorded by FONDECYT project nº 1090194, which includes children who presented FN during the study period and does not consider children who did not present FN episodes during the same period; therefore, it is not possible to extrapolate survival to the pediatric oncology population in general.

Considering that the children treated at the hospital are mainly from the reference population of the Eastern Metropolitan Health Service, including Easter Island, and referred from centers in other regions, selection biases could occur in this study. Therefore, some variables, such as different education levels, could be over- or under-represented because the families belong to an area of the country considered to have varying incomes and access compared to other patients from the public healthcare system or patients from an ISAPRE[a].

Another possible limitation is that we did not count the number of episodes of sepsis, bacterial infection, and invasive fungal infection, but only whether these were present in any episode. Having the number of these events could better reflect the effect of these variables on the overall prognosis of survival, in addition to having a scale for objectively evaluating the severity of the FN episode.

This research provides information on the local reality that had not been previously analyzed, with a first look at child survival considering the triad of childhood cancer, prognostic factors, and FN. It is relevant to promote future studies that continue evaluating survival in children with cancer, considering the evolution of therapies, diagnostic techniques, development of risk scales that have been incorporated and developed over the years that could be evaluated for improvement or continuity, and protocols for treatment based on the risk of FN. In addition, it should be noted that in this study, sociodemographic information was available, which allows a more global view, considering the social determinants that could affect survival in childhood cancer. As a suggestion, it is necessary to incorporate a qualitative view to have a comprehensive perspective of FN episodes, the consequences of this type of condition on the child and their family, and what this implies.

The predictor variables identified for the *Hospital Dr. Luis Calvo Mackenna* series, both statistically and clinically, corroborated by experts from the institution, indicate that the presence of a solid organ tumor and sepsis are risk factors, while post-cancer comorbidity and average education level serve as protective factors for survival, aligning with findings in international literature. Therefore, having this information could help to strengthen existing prevention strategies and propose new guidelines.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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[a]Chilean private healthcare system.

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