Published in final edited form as:

Pediatr Blood Cancer. 2020 February ; 67(2): e28065. doi:10.1002/pbc.28065.

Hypoalbuminemia in children with cancer treated with chemotherapy

Thomas Williams McLean¹, Ryan Michael Stewart¹, Thomas Patrick Curley¹, Mark Young Dewsnap¹, Sydney Gillian Thomas¹, Thomas Bennett Russell¹, Janet Austin Tooze²

¹Departments of Pediatrics, Wake Forest University School of Medicine, Winston-Salem, North Carolina

²Departments of Biostatistics and Data Science, Wake Forest University School of Medicine, Winston-Salem, North Carolina

Abstract

Background: Hypoalbuminemia is a well-recognized finding associated with cancer, but its prevalence and prognostic significance have not been well studied in children with cancer.

Objective: To determine the prevalence of hypoalbuminemia prior to starting chemotherapy in children with cancer and its association with relapse-free survival (RFS) and overall survival (OS).

Design/method: We performed a single institution, IRB-approved, retrospective review of pediatric oncology patients diagnosed between 1998 and 2012. Five-year survival was estimated using the Kaplan-Meier method; groups were compared using Cox regression.

Results: We identified 659 pediatric patients with a first diagnosis of cancer and a serum albumin level prior to starting chemotherapy. Mean age was 8.6 years (SD = 5.8); 62% were male and 92% were non-Hispanic. Hypoalbuminemia prior to starting chemotherapy was present at least once in 302 (45.8%). The five-year RFS and OS of those with hypoalbuminemia and without hypoalbuminemia were not significantly different. However, patients with severe hypoalbuminemia (defined as a value 10% or more below the lower limit of normal) had inferior RFS and OS for patients with hematologic/lymphatic malignancies, and inferior RFS for patients with metastatic Ewing sarcoma.

Conclusion: Hypoalbuminemia prior to starting chemotherapy in pediatric oncology patients is common (nearly half in this cohort). Severe hypoalbuminemia was associated with inferior 5-year RFS in some subgroups.

Keywords

albumin; cancer; hypoalbuminemia; pediatric; prevalence

Correspondence: Thomas W. McLean, Department of Pediatrics, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157. tmclean@wakehealth.edu.

This research was presented in part at the American Society of Pediatric Hematology/Oncology, 31st Annual Meeting, May 2-5, 2018, Pittsburgh, PA.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

1 | BACKGROUND

Hypoalbuminemia is a well-recognized finding associated with cancer and other chronic illnesses and is generally regarded as a marker of malnutrition. In adults, hypoalbuminemia has been associated with adverse outcomes in patients with cancers of the pelvis, head and neck, gastrointestinal tract, chest (pleural mesothelioma), and bone marrow.^{1–10} Also in adults, hypoalbuminemia has been associated with delayed methotrexate clearance¹¹ and increased surgical site infections after oral cancer surgery.¹² Hypoalbuminemia has been correlated with adverse outcomes (graft-versus-host disease severity and mortality) following hematopoietic cell transplant.^{13,14} Hypoalbuminemia has been associated with adverse outcomes in pediatric patients with Hodgkin lymphoma (HL).¹⁵ In a study of patients aged 2–50 years (median 15 years) with metastatic Ewing sarcoma (EWS), hypoalbuminemia (baseline albumin < 3.5 g/dL) was associated with inferior event-free survival (EFS).¹⁶ In another study of 110 patients aged 2–72 years (median 37 years) with metastatic soft tissue sarcoma, albumin (<4g/dL) was associated with poor EFS, although the number of pediatric patients in that cohort was not reported.¹⁷ Hypoalbuminemia has not been well studied in children with cancer with regard to prevalence and prognostic significance.

The primary objectives of this study were to determine the prevalence of hypoalbuminemia, using age- and gender-specific references, in children with cancer prior to starting chemotherapy, and to determine whether hypoalbuminemia is associated with inferior five-year relapse-free survival (RFS) and overall survival (OS).

2 | METHODS

We performed a single institution, IRB-approved, retrospective review of pediatric oncology patients diagnosed between 1998 and 2012. The year 1998 was chosen because it is the first year for which electronic records were reliably available, and 2012 was chosen to allow for adequate follow up.

Demographic and other data were obtained from our institution's cancer registry, another pre-existing institutional database, and patients' electronic medical records.

Patients were included if they were of age 0–18 years at diagnosis, had a first diagnosis of cancer or other condition requiring chemotherapy (such as Langerhans cell histiocytosis), and received chemotherapy at our institution, Wake Forest Baptist Medical Center, in Winston-Salem, North Carolina (USA). Patients were excluded if they were treated only for relapsed disease or second malignant neoplasm and for missing albumin data.

Hypoalbuminemia was defined as a serum albumin less than normal value for age and gender, based on a contemporary reference.¹⁸ Because hypoalbuminemia was highly prevalent in this cohort, we also defined “severe” hypoalbuminemia for the purposes of this analysis as a value 10% or more below the cutoff for hypoalbuminemia (e.g., if the cutoff was 3.4, we calculated the ceiling of $3.4 \times 90\%$ rounded to 1 decimal place, which is 3.1; see Table 2 for specific cutoffs).

Descriptive statistics (means, medians, standard deviations, and frequencies) were used to describe the study population and the prevalence and distribution of albumin. Prevalence was calculated for the time period defined as the window of 60 days prechemotherapy to the start date of chemotherapy, and compared between gender, race/ethnicity, metastatic disease, and tumor categories by chi-square tests or Fisher's exact tests. Five-year OS and RFS were estimated using the Kaplan-Meier method; groups were compared using Cox regression, in both unadjusted models and overall models adjusted for tumor category. Analyses were adjusted by tumor category to adjust for differing rates of hypoalbuminemia by broad cancer type in estimating the overall value. Patients were censored at date of last contact. A two-sided alpha level of 0.05 was used to indicate statistical significance. All analyses were conducted in SAS (version 9.4, Cary, NC). The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

3 | RESULTS

We identified 707 pediatric patients with a first diagnosis of cancer or other condition possibly requiring chemotherapy. Of these 707 patients, 48 (6.8%) were excluded for reasons including not receiving chemotherapy ($n = 11$), incomplete therapy data ($n = 22$), and missing albumin values ($n = 15$), leaving 659 patients who had a serum albumin level prior to starting chemotherapy. The mean age was 8.6 years ($SD = 5.8$ years) at the time of chemotherapy initiation; 62% were male; 92% were non-Hispanic. The most common diagnosis was acute lymphoblastic leukemia (214 of 659; 32%). Demographic and clinical characteristics are shown in Table 1.

The median time between albumin measurement and start of chemotherapy was 0 days, and although the eligibility criteria included albumin up to 60 days prior to chemotherapy, only five patients had albumin values measured greater than 30 days before chemotherapy, with the maximum at 39 days prior to chemotherapy. Three hundred two of 659 (45.8%) had hypoalbuminemia at least once prior to starting chemotherapy, with higher rates of hypoalbuminemia in hematologic/lymphatic cancers (51.5%) than in solid tumors (37.4%) ($P < .001$) (Table 1). The prevalence of severe hypoalbuminemia (10% or more below the reference range) was lower, at 28.5% ($n = 188$) overall, and higher in hematologic/lymphatic cancers (33.3%) than in solid tumors (21.5%) ($P < .01$). Only two of 39 (5.1%) of children below the age of 1 year had hypoalbuminemia (Table 2).

The median follow-up time was 6.4 years in the full cohort, with a range of two days to 18.5 years; 85.1% had 2 or more years of follow-up. The 5-year RFS of those with and without hypoalbuminemia prior to starting chemotherapy was 73.2% and 73.2%, respectively. With adjustment for broad cancer category type, 5-year survival RFS rates were 70.4% for hypoalbuminemia and 74.0% without hypoalbuminemia, which was not a significant difference (hazard ratio [HR] = 1.17, 95% CI: 0.87, 1.57; $P = .31$; Table 3). No significant differences in RFS by hypoalbuminemia at initiation of chemotherapy were found in hematologic/lymphatic or solid tumor subgroup analyses, or in those with EWS or HL (Table 3). Of the 40 patients with HL, at the time of chemotherapy initiation, 17 (42.5%) had hypoalbuminemia and 23 (57.5%) did not. Of those with hypoalbuminemia, two of 17 (12%)

relapsed, and of those without hypoalbuminemia, one of 23 (4%) relapsed, a difference which was not statistically significant. No significant differences in five-year OS were seen between those with (81.1%) and without (81.1%) hypoalbuminemia prior to chemotherapy initiation in unadjusted models, adjusted models, or by subgroup. For the EWS subgroup ($n = 29$), those with hypoalbuminemia had three times higher risk of death ($HR = 3.17$, 95% confidence interval [CI]: 0.97, 10.34, $P = .056$), which did not meet the cutoff for statistical significance (Table 3).

Both RFS and OS were significantly worse when severe hypoalbuminemia was present for the hematologic/lymphatic subgroup (Table 3). Additionally, when we adjusted the EWS subgroup analysis for metastatic disease, the risk of relapse or death was increased in the severe hypoalbuminemia group ($HR = 4.30$, 95% CI: 1.38, 13.31, $P = .04$), but OS was not significantly different (Table 3). Other analyses stratified by metastatic disease were not significant.

4 | DISCUSSION

In this cohort of pediatric oncology patients, hypoalbuminemia prior to chemotherapy initiation was common (nearly half). Hypoalbuminemia prior to initiation of chemotherapy was not associated with inferior RFS or OS in the entire cohort. However, for patients with the most severe hypoalbuminemia, inferior RFS and OS were observed in the hematologic/lymphatic subgroup. We did not observe an effect of metastatic disease with the exception of the EWS subgroup analysis, which indicated a stronger impact of severe hypoalbuminemia on RFS when adjusted for metastatic disease.

We excluded patients not requiring chemotherapy such as low-risk neuroblastoma, very low risk Wilms tumor, and completely resected low-grade gliomas to focus on the patients with more life-threatening malignancies. We hypothesize that patients not treated with chemotherapy have lower risk disease, lower disease severity, and be less likely to have hypoalbuminemia or be influenced by its presence. Despite central nervous system (CNS) tumors generally being the second most common pediatric malignancy overall, only 34 (5%) of our cohort had a CNS tumor, because many patients with CNS tumors are treated with surgery, with or without radiation therapy, and without chemotherapy, and patients who received no chemotherapy were excluded from this study.

The Common Terminology Criteria for Adverse Events version 5.0¹⁹ simplifies hypoalbuminemia as: grade 1: less than lower limit of normal to 3 g/dL, grade 2: 2 to <3 g/dL, and grade 3: <2 g/dL. Similarly, previous studies (especially those including only adults) have used simplified cutoffs to define hypoalbuminemia. However, serum albumin has significant variation during childhood. For our study, we defined hypoalbuminemia as below normal for age and gender using a contemporary reference,¹⁸ and severe hypoalbuminemia as a value 10% or more below the lower limit of normal.

Serum albumin can be elevated in dehydration (relative increase), and from intravenous albumin infusion. It can be decreased in many conditions including, but not limited to, “liver disease, nephrotic syndrome, poor nutritional status, rapid intravenous hydration, protein-

losing enteropathies (inflammatory bowel disease), severe burns, neoplasia, chronic inflammatory diseases, pregnancy, prolonged immobilization, lymphomas, hypervitaminosis A, and chronic glomerulonephritis.”²⁰

Previous studies, mostly in adults, have associated hypoalbuminemia at diagnosis with inferior outcomes compared to those without hypoalbuminemia. The reasons for this association are unclear. Similar to Biswas et al,¹⁶ we found severe hypoalbuminemia (but not all degrees of hypoalbuminemia) to be a poor prognostic factor in patients with metastatic EWS, even though we had fewer cases (29 vs 150).

We speculate that severe hypoalbuminemia may be a marker for more advanced or aggressive cancer, and thus a worse prognosis. Hypoalbuminemia may reflect poor nutritional status, which could impair chemotherapy tolerance. Finally, patients with hematologic/lymphatic malignancies (which are almost always systemic in children) and metastatic solid tumors may be cachectic, malnourished, and generally sicker than patients with localized, non-metastatic tumors. It is possible that with a larger cohort of patients, additional significant survival differences may have been observed. We used the presence of hypoalbuminemia at least once as a positive result. It is likely that many patients had a single value slightly below normal. Such patients may be physiologically similar to patients without hypoalbuminemia. The findings that severe hypoalbuminemia is associated with inferior survival in some subgroups suggests that the degree of hypoalbuminemia may correlate with prognosis. Such detailed analysis is beyond the scope of this project, but could be investigated in the future.

The strengths of this study are its focus on pediatric oncology patients, relatively robust numbers (659 eligible patients), the inclusion of all chemotherapy-requiring diagnoses, and the use of age- and gender-specific values for albumin. Its primary weaknesses are its single-institution and retrospective nature, and the limited size of the diagnosis subgroups. In addition, we did not collect data on possible contributing factors to hypoalbuminemia such as nutritional status, body mass index, and time to presentation.

In conclusion, hypoalbuminemia prior to initiation of chemotherapy in pediatric oncology patients is common (almost half in this cohort). Mild to moderate hypoalbuminemia is not associated with inferior five-year RFS or OS in analyses adjusted for gender, age at diagnosis, and tumor category. However, severe hypoalbuminemia is associated with inferior RFS and OS in patients with hematologic/lymphatic malignancies, and in patients with metastatic EWS. To fully understand the mechanisms and implications of hypoalbuminemia in children with cancer, additional research is warranted.

Abbreviations:

CI	confidence interval
CNS	central nervous system
EWS	Ewing sarcoma
HL	Hodgkin lymphoma

HR	hazard ratio
OS	overall survival
RFS	relapse-free survival

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TABLE 1

Demographic and clinical characteristics with incidence of hypoalbuminemia (n = 659)

Characteristic	Description n (%) ^a	Incidence of hypoalbuminemia n(%)	P value ^b
Age at diagnosis (years)		^c	–
Mean (SD)	8.1 (5.8)		
Range	0-18		
Gender			.02
Male	407 (62%)	172 (51.6)	
Female	252 (38%)	130 (42.3)	
Race/ethnicity			.39
Non-Hispanic White	487 (74%)	214 (43.9)	
Black	112 (17%)	59 (52.7)	
Hispanic	52 (8%)	25 (48.1)	
Other	8 (1%)	4 (50.0)	
Diagnosis by group			
Hematologic/lymphatic	394 (60%)	203 (51.5)	<.001
Solid tumors	265 (40%)	99 (37.4)	
Solid tumors by metastases			
Metastases present	96 (36%)	38 (39.5)	.57
Metastases absent	169 (63%)	61 (36.1)	
Specific diagnoses			
Acute lymphoblastic leukemia	214 (32%)	106 (49.5)	<.001
Non-Hodgkin lymphoma	86 (13%)	55 (64.0)	
Acute myeloid leukemia	48 (7 %)	23 (47.9)	
Renal tumor	43 (6%)	27 (62.8)	
Hodgkin lymphoma	40 (6%)	17 (42.5)	
Osteosarcoma	36 (5%)	11 (30.6)	
CNS tumor	35 (5%)	8 (22.9)	
Neuroblastoma	33 (5%)	8 (24.2)	

Characteristic	Description n (%) ^a	Incidence of hypoalbuminemia n (%)	P value ^b
Ewing's sarcoma	29 (4%)	11 (37.9)	
With metastatic disease	12 (2%)	5 (41.7)	
Without metastatic disease	17 (3%)	6 (35.3)	
Rhabdomyosarcoma	21 (3%)	8 (38.1)	
Germ cell tumor	18 (3%)	8 (44.4)	
Liver tumor	17 (3%)	7 (41.2)	
Other ^d	16 (2%)	5 (31.3)	
Non-rhabdomyosarcoma soft tissue sarcoma	15 (2%)	4 (26.7)	
Histiocytosis	4 (<1%)	2 (50.0)	
Chronic myeloid leukemia	2 (<1%)	0 (0.0)	
Adrenal cortical carcinoma	2 (<1%)	2 (100)	
Total	659 (100%)	302 (45.8)	

^aUnless otherwise noted.

^bP-value for comparison of hypoalbuminemia prevalence by category from chi-square or Fisher exact test.

^cSee Table 2 for gender- and age-specific values.

^d“Other” diagnoses included seven diagnoses not easily placed into the common diagnoses listed: carcinoma not otherwise specified (NOS), medullary carcinoma NOS, malignant mesenchymoma, pleuroplmonary blastoma, primitive neuroectodermal tumor, retinoblastoma NOS, and small cell carcinoma NOS.

TABLE 2

Prevalence of hypoalbuminemia and albumin values by gender and age category

	Female				Male			
	<1 year	1-3 years	4-6 years	7-18 years	<1 year	1-3 years	4-6 years	7-18 years
	N = 13	N = 68	N = 43	N = 128	N = 26	N = 104	N = 60	N = 217
Age at chemotherapy (years) Mean (SD)	0.5 (0.3)	2.5 (0.8)	5.4 (0.9)	13.4 (3.3)	0.5 (0.3)	2.6 (0.8)	5.3 (1.0)	13.6 (3.4)
Albumin	3.16 (0.78)	3.39 (0.65)	3.38 (0.77)	3.55 (0.59)	3.33 (0.72)	3.46 (0.67)	3.50 (0.69)	3.63 (0.63)
Mean (SD) Median	3.10	3.35	3.60	3.50	3.40	3.60	3.50	3.70
Albumin range	2.0-4.5	1.8-4.8	1.5-4.6	2.2-4.8	1.7-4.9	1.5-4.6	1.7-5.1	1.9-4.9
Hypoalbuminemia, N (%)	1 (7.7%)	34 (50.0%)	20 (46.5%)	75 (58.6%)	1 (3.8%)	37 (35.6%)	27 (45.0%)	107 (49.3%)
Cutoff for hypoalbuminemia ^a	2.1 ^b	3.4	3.5	3.7	2.1 ^c	3.4	3.5	3.7
Albumin among those with hypoalbuminemia	N/A	2.88 (0.39)	2.71 (0.57)	3.14 (0.35)	N/A	2.72 (0.47)	2.90 (0.42)	3.11 (0.44)
Mean (SD) Median		2.95	2.90	3.20		2.90	2.90	3.20
Albumin range among those with hypoalbuminemia	N/A	1.8-3.3	1.5-3.4	2.2-3.6	N/A	1.5-3.3	1.7-3.4	1.9-3.6
Severe hypoalbuminemia, N (%)	0 (0.0%)	19 (27.9%)	14 (32.6%)	50 (39.1%)	1 (3.8%)	23 (22.1%)	17 (28.3%)	64 (29.5%)
Cutoff for severe hypoalbuminemia ^a	1.9 ^d	3.1	3.2	3.4	1.9 ^e	3.1	3.2	3.4
Albumin among those with severe hypoalbuminemia	N/A	2.63 (0.34)	2.45 (0.48)	2.97 (0.30)	N/A	2.46 (0.40)	2.66 (0.36)	2.85 (0.38)
Mean (SD) Median		2.80	2.35	3.00		2.50	2.80	2.90
Albumin range among those with severe hypoalbuminemia	N/A	1.8-3.0	1.5-3.1	2.2-3.3	N/A	1.5-3.0	1.7-3.1	1.9-3.3

^aMust be below the cutoff to be classified as hypoalbuminemia.^bMean of cutoffs—groups collapsed due to small sample size; range of cutoffs is 1.8-2.2.^cMean of cutoffs—groups collapsed due to small sample size; range of cutoffs is 2.0-2.3.^dMean of cutoffs—groups collapsed due to small sample size; range of cutoffs is 1.7-2.0.^eMean of cutoffs—groups collapsed due to small sample size; range of cutoffs is 1.8-2.1.

TABLE 3
Risk of relapse or death (relapse-free survival) and death (overall survival) by hypoalbuminemia

Cancer type	N	Risk of relapse or death (relapse-free survival [RFS]) if hypoalbuminemia present	Risk of relapse or death (RFS) if severe hypoalbuminemia present	Risk of death (overall survival [OS]) if hypoalbuminemia present	Risk of death (OS) if severe hypoalbuminemia present ^d
Overall ^a	659	1.17 (0.87, 1.57) ^b	1.34 (0.98, 1.84)	1.21 (0.85, 1.72)	1.47 (1.01, 2.13) [*]
Hematologic/lymph	394	1.18 (0.76, 1.83)	1.59 (1.02, 2.48) [*]	1.27 (0.71, 2.26)	2.17 (1.22, 3.85) ^{**}
Hodgkin lymphoma	40	3.63 (0.33, 40.27)	7.86 (0.70, 88.29)	N/A ^c	N/A ^c
Solid	265	1.17 (0.78, 1.75)	1.15 (0.72, 1.84)	1.20 (0.77, 1.86)	1.11 (0.67, 1.86)
Solid without metastatic disease	169	1.03 (0.55, 1.91)	0.97 (0.47, 2.03)	1.15 (0.57, 2.32)	1.18 (0.53, 2.61)
Solid with metastatic disease	96	1.39 (0.81, 2.37)	1.41 (0.77, 2.57)	1.22 (0.69, 2.16)	1.06 (0.54, 2.07)
Ewing's sarcoma	29	1.85 (0.63, 5.46)	2.38 (0.65, 8.67)	3.17 (0.97, 10.38)	2.01 (0.54, 7.46)
Ewing's sarcoma with adjustment for metastatic disease	29	1.74 (0.59, 5.10)	4.30 (1.38, 13.31) [*]	2.73 (0.82, 9.08)	2.13 (0.57, 7.98)

^a Adjusted for cancer type (hematologic/lymph, solid; in overall, Cox regression model only).

^b Hazard ratio and 95% confidence interval of event for hypoalbuminemia = yes from Cox regression model.

^c Model could not befit due to only 1 death in subgroup.

^d Severe hypoalbuminemia defined as at least 10% below the bottom of the reference range.

^{*} $P < .05$,

^{**} $P < .01$.