**Impact of malnutrition on the pharmacokinetics of chemotherapy in children with cancer: a systematic review**

Sterre Schoon1,2\*, Nthongase Makamo3,4\*, Aniek Uittenboogaard1,5, Melanie B. Bernhardt6, Nmazuo W. Ozuah4,6, Gertjan J.L. Kaspers1,5 and Minke H.W. Huibers1,5  
 1Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands  
2Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands   
3Baylor College of Medicine Children’s Foundation, Malawi  
4Texas Children’s Global Hemtology-Oncology-Pediatric-Excellence (HOPE) Program, Malawi  
5Emma Children’s Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Pediatric Oncology/Global Child health group, Amsterdam, the Netherlands   
6Section of Hematology/Oncology, Department of Pediatrics, Baylor College of Medicine, Houston   
\*Shared first author

Corresponding author:   
Sterre Schoon  
Phone: +31683085749  
Email: [s.schoon@amsterdamumc.nl](mailto:s.schoon@amsterdamumc.nl) (SS)

Abstract word count: 145  
Main Text word count: 2204

Number of Tables: 2  
Number of Figures: 1  
Number of Supporting Information files: 2

Short running title: Malnutrition and chemotherapy in childhood cancer

Key words: malnutrition, pharmacokinetics, children, pediatric oncology, cancer. [[1]](#footnote-1)

**Abbreviations key**

|  |  |
| --- | --- |
| LMICs | Low- and middle-income countries |
| WHO | World Health Organization |
| AUC | Area under the curve |
| HICs | High income countries |
| PRISMA | Preferred Reporting Items for Systematic reviews and Meta-Analyses |
| EPHPP | Effective Public Healthcare Panacea Project |
| BSA | Body-surface area |
| BMI | Body mass index |
| SAM | Severe acute malnutrition |

**ABSTRACT** *Objectives* This systematic review provides an overview of the effect of malnutrition on the pharmacokinetics of chemotherapy in children with cancer. *Methods* PubMed, Embase and Cochrane were searched to identify eligible studies. Malnutrition was referred to as undernutrition, as defined by the World Health Organisation and the Gomez Criteria. *Results* Four studies with a total of 668 children with cancer were included and n=121 (18%) were malnourished. In vincristine, the differences in pharmacokinetic parameters were statistically significant where clearance rates were commonly lower and area under the curve was increased in malnourished children. *Conclusion* The results are suggestive for pharmacokinetic alterations of chemotherapy in malnourished children with cancer. However, the data is scarce, groups are small, and most studies have been performed in high-income countries. Pharmacokinetic research among (severely) malnourished children with cancer is needed in order to improve their outcome, directed by sub-group and ultimately individualized drug dosing.

**1 Introduction**

Malnutrition is one of the largest global health problems in children: it is related to almost half of the deaths in children under the age of five [1-3]. Depending on the region, major differences are seen in the prevalence of malnutrition, with Sub-Saharan Africa (SSA) reporting rates up to 20% in comparison with Europe, where rates do not exceed 2.5% [4]. Children with cancer are at increased risk for malnutrition, but the prevalence rates of malnutrition in these children depend on country and region [5]. Malnutrition can affect 30% to 60% of newly diagnosed children with cancer in low- and middle-income countries (LMICs) and may be exacerbated by delays in cancer diagnosis and treatment [5-8].

A malnourished state results in major metabolic changes, such as decreased plasma protein levels, and may in turn affect body functionalities, such as cardiac, hepatic and renal functions [5,7,9-13]. These changes may affect tolerance and/or efficacy of chemotherapy by altering the pharmacokinetics of these agents – their absorption, distribution, metabolism and elimination [5,9]. Given the therapeutic index of many chemotherapeutic drugs (e.g. doxorubicin) is narrow, small alterations in drug disposition may result in increased toxicity or less activity [10]. Clinical data on the pharmacokinetics of chemotherapeutic drugs in severely malnourished children is lacking. Animal studies have reported prolonged systemic clearance rates and larger area under the curve (AUC) concentrations for anthracyclines and methotrexate in protein-depleted animals compared with normally fed animals [14-16]. Studies in malnourished adults likewise, have described reduced clearance rates and prolonged elimination rates of methotrexate compared to those with better nutritional status [9,17]. However, pediatric pharmacology differs from adults and this must be considered for optimal drug dosing [18].

In this systematic review, we aim to provide an overview of the effect of malnutrition on the pharmacokinetics of chemotherapy in children with cancer. This could serve as a backbone for future research and an important first step in attaining more insight into optimal chemotherapy dosing in malnourished pediatric cancer patients.

**2 Methods**

**2.1 Search strategy**

This systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [19]. PubMed, EMBASE and Cochrane databases were searched in October 2021. The following key search terms were used: ‘pharmacokinetics’, ‘antineoplastic agents’, ‘malnutrition’, and ‘child’. The full search strategies can be found in the supporting information S1.

**2.2 Screening process**

Abstracts were screened independently by two reviewers (SS and NM) according to the following inclusion criteria: assessment of pharmacokinetics; children with cancer; and malnutrition or poor nutritional state. Only studies assessing malnutrition by undernutrition (and not obesity) were included in this systematic review; no further restrictions regarding the definition of malnutrition were applied. Editorial letters, articles written in a language other than English, adult and animal studies, and descriptive reviews were excluded. After title and abstract screening, full-text articles were screened by two reviewers (SS and NM) for eligibility. In cases of disagreement, a third reviewer was consulted (MH) and consensus was retrieved. The reference lists of eligible articles were screened for further inclusions.

**2.3 Quality assessment**

The risk of bias was assessed using the Quality Assessment Tool for Quantitative Studies by the Effective Public Healthcare Panacea Project (EPHPP) [20]. The Quality Assessment Tool for Quantitative Studies includes five components for overall judgement of the studies: selection bias; study design; confounders; blinding; data collection method; and withdrawals and dropouts. Individual componenets as well as final global rating options were strong, moderate, or weak [20]. Studies were considered “strong” if they had no “weak” rating in any of the five components.

**2.4 Data extraction**

Data extraction was performed according to a pre-defined data extraction template. The following data was extracted: author(s), year of publication, population characteristics, type of chemotherapy, pharmacokinetic assessment, nutritional state, and main outcome. The main outcome of this study were any pharmacokinetic parameters in malnourished and non-malnourished children, defined by any pharmacokinetic parameter (e.g., clearance rate, AUC, volume of distribution). When clearance rates were not reported in mL/min/m2, they were calculated using a formula developed by Mostseller to calculate body-surface area (BSA) [21]. Statistical significance was reported by the primary study or calculated using an Independent-Samples T-Test in SPSS (IBM SPSS Statistics for Mac, Version 28.0.1.).

**2.5 Nutritional assessment and definition**

Suboptimal nutritional status or undernutrition is phrased as malnutrition, as defined by the WHO reference [21]. Moderate malnutrition is defined with z-scores below -2 Standard Deviation (SD), and z-scores below -3 SD corresponds to severe malnutrition [21]. If studies described nutritional status using BMI-for-age or z-scores, the WHO’s growth reference data was used to identify malnutrition [21]. Secondly, if studies used relative weight to describe nutritional status, the Gomez classification was used. The Gomez classification system defines relative weight below 90% as malnutrition, based on a weight for age percentage [22].

**3 Results**

**3.1 Search results**

Screening of the databases resulted in 399 records (Figure 1). After the removal of duplicates, 295 records were screened on abstract and title, which resulted in 93 records. Thirteen articles could not be retrieved, and 80 papers were assessed for eligibility (Figure 1). Seventy-seven records were excluded due to the following reasons: reviews (n=13); editorial letter (n=1); not fitting the inclusion criteria (n=61); articles written in a foreign language (n=2). One study was identified through the references of eligible studies, although it did not meet the inclusion criteria since it did not include malnourished children and was therefore excluded (Figure 1). Eventually, four studies were included in this systematic review.

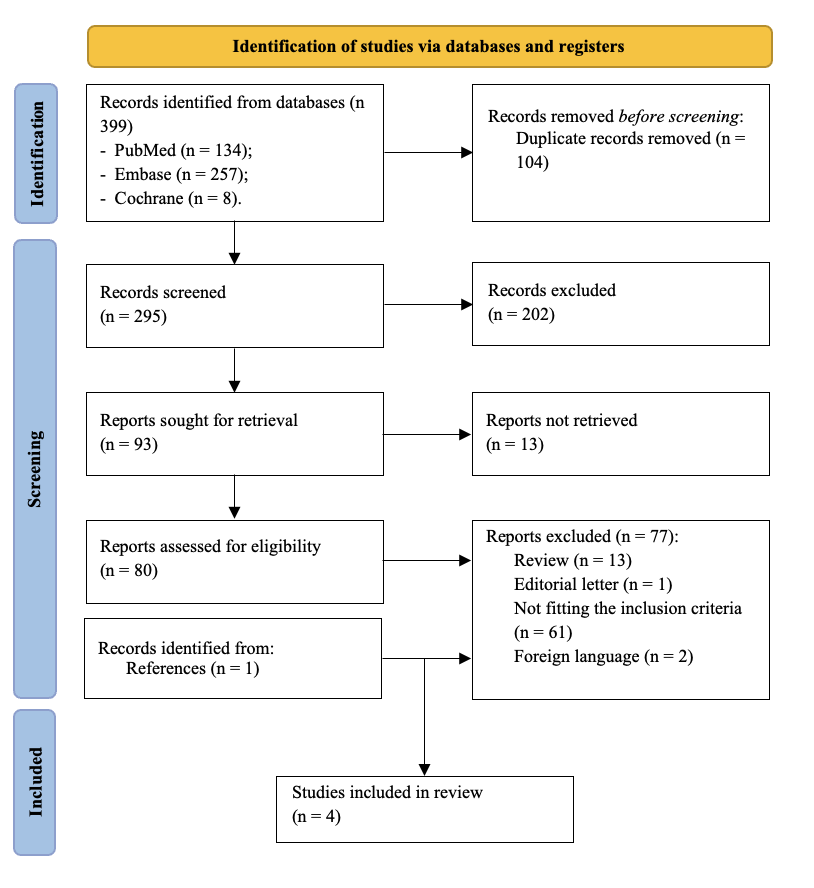
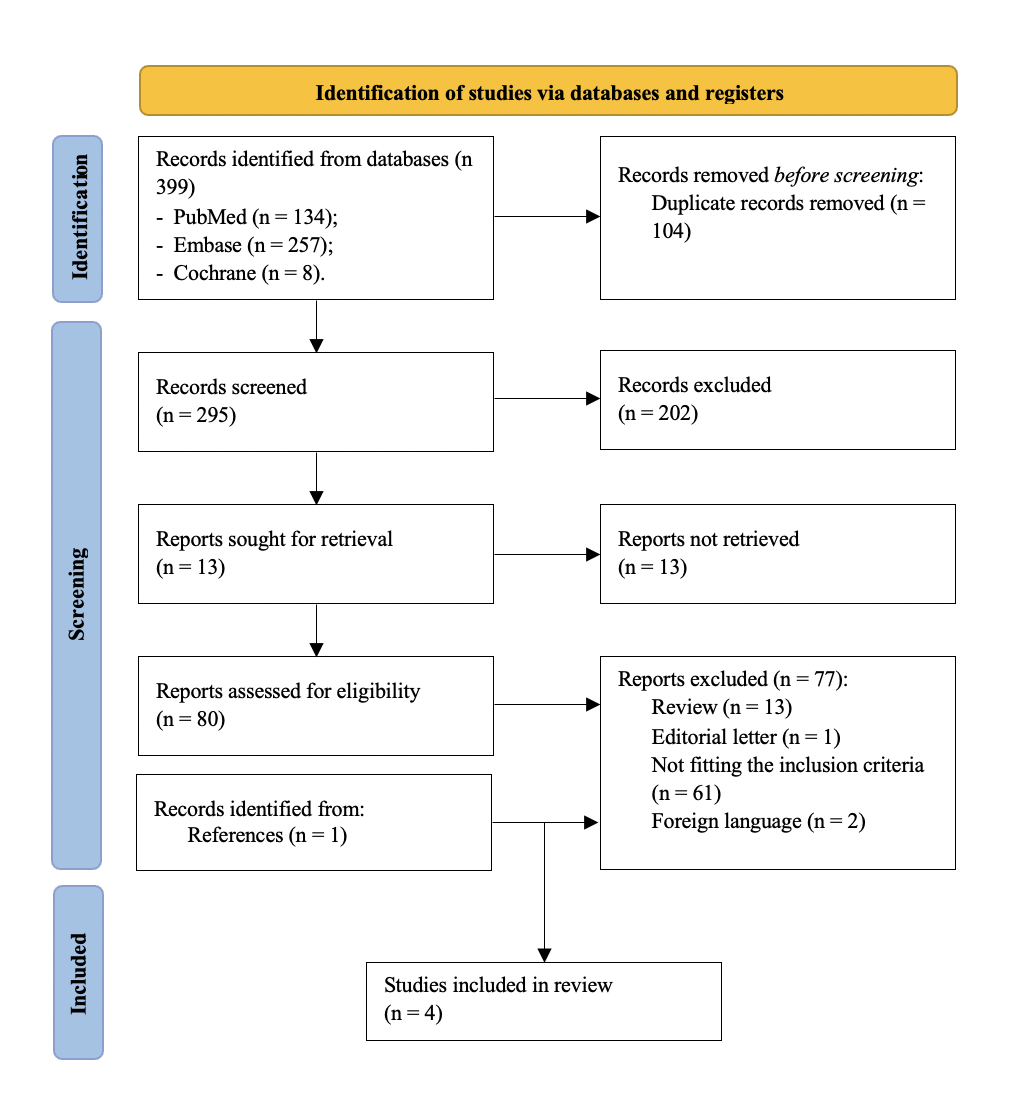
**3.2 Quality assessment**

FIGURE 1 PRISMA flow chart describing the screening process and identification of relevant studies for this review [21].

Two [23,24] studies received a strong global risk of bias rating and two [25,26] received a moderate global risk of bias rating (supporting information S2).

**3.3 Study and patient characteristics**

Study and patient characteristics of the included studies are described in Table 1. Articles were published between 1987 and 2009. Three studies were prospective observational studies and one study was retrospective. The number of patients included ranged from 6 to 621 and all were treated with chemotherapy for their malignancies (Table 1) [23-26].

The definition of nutritional status differed among the studies. Hijiya *et al.* (2006) and Thompson *et al.* (2009) used BMI-for-age percentiles to define malnutrition and found respectively 102 (16%) and 5 (22%) patients to be malnourished [3,23,24]. Israels *et al.* (2010) and Kumar *et al.* (1987) found 11 (58%) and 5 (83%) patients to be malnourished, according to z-scores for (corrected) weight for height and relative weight, respectively [25,26] (Table 1). No study in this systematic review included severely malnourished children according to the WHO’s reference for malnutrition [21].

TABLE 1 Study and patient characteristics for included studies

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Author and year of publication | Hijiya *et al*. (2006) [24] | Israels *et al.* (2010) [25] | Kumar *et al.* (1987) [26] | Thompson *et al.* (2009) [23] |
| **Study design** | Retrospective | Prospective | Prospective | Prospective |
| **No. of patients** | 621 | 19 | 6 | 22 |
| **Age in years (range)** | 1-21 | 0-18 | 1-15 | 1-21 |
| **Male, n (%)** | 342 (55) | 11 (68) | 4 (67) | 16 (73) |
| **Ethnicity, n (%)** | White, 495 (80) Black, 91 (14)  Other, 35 (6) | Malawian, 11 (58) UK, 8 (42) | NA | NA |
| **Type of cancer, n (%)** | ALL, 621 (100) | Wilms tumor, 19 (100) | Unknown | ALL, 4 (18) Lymphoma, 12 (55) Sarcoma, 4 (18) Neuro-/hepatoblastoma, 2 (9) |
| **Nutritional status, no. (%)** | Undernutrition, 102 (16) Normal, 400 (64) At risk of overnutrition, 64 (11) Overweight, 55 (9) | Undernutrition, 11 (58)  Normal, 8 (42) | Undernutrition, 5 (83) Normal, 1 (17) | Undernutrition, 5 (22) Normal, 15 (68) Overnutrition, 2 (10) |
| **Type of chemotherapy** | Methotrexate, etoposide, teniposide, cytarabine, mercaptopurine | Vincristine | Methotrexate | Doxorubicin |
| **Treatment protocol or dose of chemotherapy** | St Jude Total Therapy protocol XII, XIIIA, XIIIB, XIVa | 1.5 mg/m2 by IV bolus | 50 mg/m2 by IV bolus | 1- or 2-day schedule of doxorubicin infusion <24h (dose NA) |

**3.4 Pharmacokinetic analysis**

aProtocols were based on induction with high-dose methotrexate followed by consolidation therapy with etoposide, teniposide, cytarabine or mercaptopurine.   
UK = United Kingdom; NA = no data available; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; IV = intravenously.

All chemotherapy was administered intravenously, except for mercaptopurine, which was administered orally (Table 1) [24]. Two studies used a compartmental analysis for the assessment of pharmacokinetics [23,24]. Israels *et al.* (2010) assessed pharmacokinetics via a non-compartmental analysis [25]. Kumar *et al.* (1987) calculated pharmacokinetic parameters using standard formulas [17,26].

**3.5 Pharmacokinetic parameters**

Hijiya *et al.* (2006) and Thompson *et al.* (2009) reported pharmacokinetic parameters according to their BMI categories [23,24]. The other two studies reported pharmacokinetic parameters for each patient since they had a small sample size [25,26]. Mean systemic clearance rates, volume of distribution and/or AUC are summarized in Table 2.

TABLE 2 Pharmacokinetic parameters of various anticancer drugs

aP-values obtained between four groups. At risk for overweight and obesity groups are not shown in Table 2.  bVd is noted in the initial phase, thus its behavior in the central component.   
cBased on one patient.  
NA = no data available; BMI = body mass index; Cl = clearance; AUC = area under curve; Vd = volume of distribution; SD = standard deviation; NS = not significant.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study/Drug | Pharmacokinetic parameters | Malnutrition | Normal nutritional status | P-value |
| **Methotrexate** Hijiya *et al*. (2006) [24] Kumar *et al.* (1987) [26] | **Mean Cl (±SD) (in mL/min/m2)  Mean Cl (±SD) (in mL/min/m2) Vd (±SD) (in L)b** | 111.1  1.0 (0.7)  18.2 (13.0) | 114.1   1.0c 20.9c | 0.47a  0.43 0.43 |
| **Vincristine** Israels *et al.* (2010) [25] | **Mean Cl (±SD) (in mL/min/m2) Mean AUC (±SD) (in μg/mL min)** | 244.9 (76.0) 6.3 (2.3) | 519.0 (200.9) 3.4 (2.1) | <0.05 0.04 |
| **Doxorubicin** Thompson *et al.* (2009) [23] | **Mean Cl (±SD) (in mL/min/m2) Vd (±SD) (in L/m2)b** | 401.7 (8.5) 7.0 (3.4) | 436.7 (4.5) 7.3 (2.0) | NSa NSa |
| **Etoposide** Hijiya *et al.* (2006) [24] | Total XIIIB  **Mean Cl (±SD) (in mL/min/m2)** | 43.6 | 48.7 | 0.41a |
| **Cytarabine** Hijiya *et al.* (2006) [24] | Total XII  **Mean Cl (±SD) (in mL/min/m2)** | 852.2 | 773.8 | 0.56a |
| **Teniposide** Hijiya *et al.* (2006) [24] | Total XII  **Mean Cl (±SD) (in mL/min/m2)** | 14.2 | 14.0 | 0.35a |

Israels *et al.* (2010) reported a statistically significant difference in mean clearance rates of vincristine between malnourished Malawian and non-malnourished UK patients (Table 2) [25]. In addition, nutritional status was found to significantly contribute to the difference in AUC between patient populations, with AUC for vincristine about two times higher in malnourished patients compared to the non-malnourished patients (p=0.04) [26]. Kumar *et al.* (1987) reported a significant negative correlation of -0.7 for relative weight with elimination half-lives while showing no significant correlation between relative weight and volume of distribution [26]. Hijiya *et al.* (2006) and Thompson *et al.* (2009) reported lower, but not significant, clearance rates for methotrexate, doxorubicin and etoposide in the malnourished patients compared to non-malnourished groups, except for cytarabine and teniposide which did not show lower clearance rates in the malnourished groups [23,24].

**4 Discussion**

This systematic review identified that pharmacokinetic parameters varied among children with normal nutritional status and those suffering from malnutrition, but this effect was only statistically significant for vincristine. Of note, data was very limited since only four could be studies included [23-26].

Reduced clearence rates and prolonged elimination of drugs have been described in malnourished adults but not confirmed in the children among the selected studies in this systematic review [9,17,23-26]. The one study with balanced populations of malnourished versus non-malnourished children was the only study that demonstrated a significant difference in pharmokinetics of vincristine [25]. Secondly, none of the included studies reported on severly malnourished patients which may be an additional explanation of not finding significant differences.

Malnutrition causes a decrease in glomular filtration of the kidneys, and a decrease in liver function with lowering of plasma protein levels; all potentially resulting in lower clearance rates of chemotherapy [27,28]. Decreased serum protein levels − in particular albumin − are a critical observation in malnutrition and can occur in over 60% of patients [5]. This leads to reduced protein binding, resulting in an increase in plasma-free drugs and increased volume of distribution, with increased potential for drug-related toxicities [6,25]. Several studies have demonstrated the high risk for treatment toxicities in patients with malnutrition receiving chemotherapy: for example, a significant association was observed between profound neutropenia and malnutrition among Malawian children with cancer [29]. Similarly, in Nicaragua, increased treatment-related morbidity with a significant contribution from severe infection and sepsis was reported in malnourished children [30].

Improvement in outcome among children with cancer in LMICs is highly needed. Survival rates in these countries remain poor at 10-20% in comparison to the excellent survival in HICs (>80%) despite the fact that 80% of the children with cancer live in these poorer countries [5,7,26,27]. To reduce this inequality, the WHO in 2020, launched a Global Initiative for Childhood Cancer (GICC), which pursues a survival rate of 60% by 2030 for all children worldwide with one of the six common types of childhood cancer [38]. A better understanding of optimal dosing of chemotherapy in children in LMIC’s, with high prevalence of malnutrition, will be crucial to balance the risks of toxicity and efficacy, and improve survival outcomes.

The role of pharmacogenomics on pharmacokinetics should also be considered as a confounder, since black children are more likely to be malnourished than children of other ethnicities and potentially show different pharmacogenomics [29,31]. Small variations between populations are of great importance, given the possible narrow therapeutic index of most chemotherapeutic drugs, such as anthracyclines [32]. The role of CYP450 enzymes in metabolism of chemotherapy is important with respect to population differences [25]. Renbarger *et al.* (2008) reported a significant difference between African American and Caucasian pediatric cancer patients regarding vincristine- associated neurotoxicity. Caucasian patients experienced higher drug exposure from decreased clearance, which led to more neurotoxicity [33]. These results are possibly related to variations in CYP450 enzyme expression between populations. A study from Kenya showed a total of 91% of the patients being CYP3A5 expressors, a member of the CYP450 enzymes [34]. Although, a meta-analysis on pharmacogenetics and vincristine induced peripheral neurotoxicity (VIPN) showed no significant correlation between CYP3A5 expression and occurrence of VIPN [35]. Interestingly, one of the studies included in this review reported lower clearance rates for African patients compared to UK patients which was not expected based on published literature [25]. Based on literature, it would be expected that the African population in this study would have reported higher clearance rates due to higher expression of CYP3A4. However, since all included African children in this study were malnourished, clearence rates might have been influenced based on the nutritional status. [25]. Variations in pharmacogenomic parameters express the importance to take genetics into account when assessing the pharmacokinetics in a LMIC population.

The strength of this study is that it was conducted following the PRISMA guidelines and a standardized risk of bias tool [19,20]. However, the study is limited by an inclusion of only four studies and none of them included severly malnourished children. Although malnutrition among children with cancer is more prevalent in LMICs, most studies on its impact on pharmacokinetics have been conducted in HICs. The degree of malnutrition reported in this systematic review may not therefore be representative of the true pharmacokinetic effect of malnutrition, particularly in LMICs, and may underestimate the impact of this entity on drug disposition. Currently, no data exists on the effect of severe acute malnutrition (SAM) on drug disposition in children with cancer although it is general knowledge that childhood cancer is an important risk factor for SAM, especially in LMICs [4].

This review on the impact of malnutrition on the pharmacokinetics of chemotherapy in malnourished children with cancer was undertaken to help inform the development evidence-based dose adjustments based on nutritional status. Unfortunately, the best available evidence consists of few studies with small sample sizes despite the global burden of malnutrition among children with cancer. Further research, especially in LMICs, is highly recommended to gain insight into the need for treatment adjustments. Ultimately, evaluating pharmacotinetics of chemotherapy in malnourished children adds great value to the field as we aim for safe and effective treatment for children with cancer worldwide.

**5 Conflict of Interest Statement**

All authors declare that they have no competing interests.

**Acknowledgements**

None.

**References**

1. Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet 2013;382(9890):427-51.
2. WHO. Children: improving survival and well-being. September 8, 2020. Accessed December 21, 2021. <https://www.who.int/news-room/fact-sheets/detail/children-reducing-mortality>.
3. WHO. Malnutrition. June 9, 2021. Accessed November 30, 2021. <https://www.who.int/news-room/fact-sheets/detail/malnutrition>.
4. Roser M, Ritchie H. Hunger and undernourishment. 2019. Accessed May 8, 2022. <https://ourworldindata.org/hunger-and-undernourishment>.
5. Sala A, Pencharz P, Barr RD. Children, cancer, and nutrition--A dynamic triangle in review. Cancer 2004;100(4):677-87.
6. Rodriguez-Galindo C, Friedrich P, Morrissey L, Frazier L. Global challenges in pediatric oncology. Curr Opin Pediatr 2013;25(1):3-15.
7. Israëls T, Chirambo C, Caron HN, Molyneux EM. Nutritional status at admission of children with cancer in Malawi. Pediatr Blood Cancer 2008;51(5):626-8.
8. Ladas EJ, Arora B, Howard SC, Rogers PC, Mosby TT, Barr RD. A Framework for Adapted Nutritional Therapy for Children With Cancer in Low- and Middle-Income Countries: A Report From the SIOP PODC Nutrition Working Group. Pediatr Blood Cancer 2016;63(8):1339-48.
9. Murry DJ, Riva L, Poplack DG. Impact of nutrition on pharmacokinetics of anti-neoplastic agents. Int J Cancer Suppl 1998;11:48-51.
10. van Meerten E, Verweij J, Schellens JH. Antineoplastic agents. Drug interactions of clinical significance. Drug Saf 1995;12(3):168-82.
11. Krishnaswamy K. Drug metabolism and pharmacokinetics in malnourished children. Clin Pharmacokinet 1989;17 Suppl 1:68-88.
12. Krishnaswamy K. Drug metabolism and pharmacokinetics in malnutrition. Trends in Pharmacological Sciences 1983;4:295-99.
13. Oshikoya KA, Senbanjo IO. Pathophysiological changes that affect drug disposition in protein-energy malnourished children. Nutr Metab (Lond) 2009;6:50-50.
14. Charland SL, Bartlett D, Torosian MH. Effect of protein-calorie malnutrition on methotrexate pharmacokinetics. JPEN J Parenter Enteral Nutr 1994;18(1):45-9.
15. El-Demerdash E, Ali AA, El-Taher DE, Hamada FM. Effect of low-protein diet on anthracycline pharmacokinetics and cardiotoxicity. J Pharm Pharmacol 2012;64(3):344-52.
16. Cusack BJ, Young SP, Loseke VL, Hurty MR, Beals L, Olson RD. Effect of a low-protein diet on doxorubicin pharmacokinetics in the rabbit. Cancer Chemother Pharmacol 1992;30(2):145-8.
17. Rajeswari R, Shetty PA, Gothoskar BP, Akolkar PN, Gokhale SV. Pharmacokinetics of methotrexate in adult Indian patients and its relationship to nutritional status. Cancer Treat Rep 1984;68(5):727-32.
18. Seyberth HW, Rane A, Schwab M. (2011). *Pediatric Clinical Pharmacology.* Springer-Verlag Berlin Heidelberg.
19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj 2021;372:n71.
20. EPHPP. Quality Assessment Tool for Quantitative Studies. 2010. Accessed November 19, 2021. <https://www.ephpp.ca/quality-assessment-tool-for-quantitative-studies/>.
21. WHO. BMI-for-age (5-19 years) - simplified field tables. 2017. Accessed November 30, 2021. <https://www.who.int/toolkits/growth-reference-data-for-5to19-years/indicators/bmi-for-age>.
22. Gomez F, Galvan RR, Cravioto J, Frenk S. Malnutrition in infancy and childhood, with special reference to kwashiorkor. Adv Pediatr 1955;7:131-69.
23. Thompson PA, Rosner GL, Matthay KK, et al. Impact of body composition on pharmacokinetics of doxorubicin in children: a Glaser Pediatric Research Network study. Cancer Chemother Pharmacol 2009;64(2):243-51.
24. Hijiya N, Panetta JC, Zhou Y, et al. Body mass index does not influence pharmacokinetics or outcome of treatment in children with acute lymphoblastic leukemia. Blood 2006;108(13):3997-4002.
25. Israels T, Damen CW, Cole M, et al. Malnourished Malawian patients presenting with large Wilms tumours have a decreased vincristine clearance rate. Eur J Cancer 2010;46(10):1841-7.
26. Kumar RV, Gokhale SV, Ambaye RY, Shetty PA. Pharmacokinetics of methotrexate in Indian children and its relationship to nutritional status. Chemotherapy 1987;33(4):234-9.
27. Batchelor HK, Marriott JF. Paediatric pharmacokinetics: key considerations. *Br J Clin Pharmacol*. 2015;79(3):395-404. doi:10.1111/bcp.12267
28. Pharmacokinetics in children. MSD Manual Web Site. <https://www.msdmanuals.com/professional/pediatrics/principles-of-drug-treatment-in-children/pharmacokinetics-in-children#v1085289>. Published 2020. Accessed August 15, 2022.
29. Israëls T, van de Wetering MD, Hesseling P, van Geloven N, Caron HN, Molyneux EM. Malnutrition and neutropenia in children treated for Burkitt lymphoma in Malawi. Pediatr Blood Cancer. 2009 Jul;53(1):47-52.
30. Pribnow AK, Ortiz R, Báez LF, Mendieta L, Luna-Fineman S. Effects of malnutrition on treatment-related morbidity and survival of children with cancer in Nicaragua. Pediatr Blood Cancer. 2017 Nov;64(11). doi: 10.1002/pbc.26590. Epub 2017 Apr 27. PMID: 28449403.
31. Kadan-Lottick NS, Ness KK, Bhatia S, Gurney JG. Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. Jama 2003;290(15):2008-14.
32. O'Donnell PH, Dolan ME. Cancer pharmacoethnicity: ethnic differences in susceptibility to the effects of chemotherapy. Clin Cancer Res 2009;15(15):4806-14.
33. Renbarger JL, McCammack KC, Rouse CE, Hall SD. Effect of race on vincristine-associated neurotoxicity in pediatric acute lymphoblastic leukemia patients. Pediatr Blood Cancer 2008;50(4):769-71.
34. Skiles JL, Chiang C, Li CH, et al. CYP3A5 genotype and its impact on vincristine pharmacokinetics and development of neuropathy in Kenyan children with cancer. Pediatr Blood Cancer 2018;65(3).
35. Uittenboogaard A, Neutel CLG, Ket JCF, Njuguna F, Huitema ADR, Kaspers GJL, van de Velde ME. Pharmacogenomics of Vincristine-Induced Peripheral Neuropathy in Children with Cancer: A Systematic Review and Meta-Analysis. Cancers (Basel). 2022 Jan 26;14(3):612.
36. Otiti MI, Allen SJ. Severe acute malnutrition in low- and middle-income countries. Paediatrics and Child Health 2021;31(8):301-307.
37. Müller O, Krawinkel M. Malnutrition and health in developing countries. CMAJ. 2005 Aug 2;173(3):279-86.
38. WHO. Global initiative for childhood cancer. 2020. Accessed November 6, 2021. <https://www.who.int/publications/m/item/global-initiative-for-childhood-cancer>.

1. Previously published as oral abstract on September 26, 2022 at the congress of International Society of Pediatric Oncology: *Impact of malnutrition on pharmacokinetics of chemotherapy in children with cancer: A systematic review.*  [↑](#footnote-ref-1)