

Answering Reviewers

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Warburg effect mimicking inborn errors of metabolism in childhood hematologic malignancies: A case-based systematic review

1. It must be described about the specific terms of the literature search.

Answer: The specific terms for the literature search were added to the MATERIALS AND METHODS section on page 8, lines 4 to 18, as follows:

Data sources and searches

Three authors (Permtawee K, Choed-Amphai C, and Chanthong S) independently conducted searches of the PubMed, Scopus, and Cochrane databases without any time restrictions. The following keywords were used for the search: “lactic acidosis”; “Warburg”; “pediatric”; “child”; “leukemia”; and “lymphoma”. For PubMed, the specific search-term strategy was: ("acidosis, lactic"[MeSH Terms] OR ("acidosis"[All Fields] AND "lactic"[All Fields]) OR "lactic acidosis"[All Fields] OR ("lactic"[All Fields] AND "acidosis"[All Fields]) OR ("warburg"[All Fields] OR "warburg's"[All Fields])) AND ("paediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields] OR ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child's"[All Fields] OR "children's"[All Fields])) AND ("leukaemia"[All Fields] OR "leukemia"[MeSH Terms] OR "leukemia"[All Fields] OR "leukaemias"[All Fields] OR "leukemias"[All Fields] OR "leukemia's"[All Fields] OR ("lymphoma"[MeSH Terms] OR "lymphoma"[All Fields] OR "lymphomas"[All Fields] OR "lymphoma's"[All Fields]) OR ("haematologic malignancy"[All Fields] OR "hematologic neoplasms"[MeSH Terms] OR ("hematologic"[All Fields] AND "neoplasms"[All Fields]) OR "hematologic neoplasms"[All Fields] OR ("hematologic"[All Fields] AND "malignancy"[All Fields]))

OR "hematologic malignancy"[All Fields])). Only articles published in English language were considered for selection.

2. It needs to present the inclusion/exclusion criteria of the subjects in a separate table.

Answer: We have included a summary of the inclusion and exclusion criteria under 'Article Selection' on page 8, lines 25 to 26, and in Table 1, as follows:

Article selection

Inclusion criteria were as follows: type B lactic acidosis in children with hematologic malignancies (including leukemia and lymphoma); and presence of data on clinical course, treatment strategies, and outcomes. Articles which did not meet these criteria were excluded. Summarization of the inclusion and exclusion criteria for this systematic review is presented in Table 1. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guideline^[7].

Table 1 Inclusion and exclusion criteria

Criteria
Inclusion
1. Children, 0 to 18 years
2. Diagnosis of hematologic malignancy, including leukemia and lymphoma
3. Presence of lactic acidosis
4. Availability of clinical course, treatment, and outcome data
Exclusion
1. Adults, > 18 years
2. Diagnosis of other solid tumors
3. Presence of other causes of metabolic acidosis without lactic acidosis
4. Incomplete information regarding clinical courses, treatment, and outcomes

3. Demographic and etiological information for each subject should be presented in a separate table.

Answer: Demographic and etiological information was included for each subject in Table 2 as follows:

Table 2 Demographics, treatments, and outcomes of previously reported children with leukemia/lymphoma and type B lactic acidosis

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4. Although it is not limited to pediatric patients, many cases have been reported about the association between type b lactic acidosis and Warburg effect in patients with leukemia or lymphoma (e.g. Front Oncol. 2018; 8: 232.;J Int Med Res. 2022 Jan; 50(1): 03000605211067749., etc). What clinical implications can the authors argue through this investigation compared to the existing studies?

Answer: In the past decade, hematologic malignancies complicated by lactic acidosis have shown better outcomes in children compared to adults, potentially attributable to disparities in disease status and treatment response. This information was included in the DISCUSSION section on page 12, lines 11 to 19, as follows:

... These findings also differ from those in the adult population. In the past decade, adults with hematologic malignancies who experienced lactic acidosis still had a mortality rate of more than 80%^[30, 31]. Despite the same pathophysiology of this complication in the pediatric and adult populations, disease status and response to treatment may explain the dismal outcome in adults. According to the United States' Surveillance, Epidemiology, and End Results (SEER) program database, survival rates according to age of diagnosis (all patients) at 17 years, 20 years, and 70 years were 75%, 48%, and 15%, respectively. Different treatment regimens and responses were determined to have played significant roles in this survival cliff drop-off^[32]. ...