Hypoalbuminemia as a Predictor of Outcomes in Acute Myeloid Leukemia: A Systematic Review and Meta-Analysis

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Abstract

Background : In acute myeloid leukemia (AML), hypoalbuminemia has been observed at diagnosis and during treatment, often correlating with poor clinical outcomes such as reduced remission rates, increased treatment-related toxicity, and shorter overall survival (OS). This systematic review and meta-analysis aim to investigate the prognostic value of hypoalbuminemia in patients with AML.

Methods : A comprehensive literature search was conducted across PubMed, EMBASE, and Scopus to identify relevant studies published up to January 5, 2025. The search strategy included a combination of Medical Subject Headings (MeSH) terms and keywords such as “hypoalbuminemia,” “acute myeloid leukemia,” “AML,” “serum albumin,” “prognosis,” and “outcomes.” Boolean operators (AND, OR) were applied to refine the search.

Result : This systematic review and meta-analysis included 10 studies with a total sample size of 4,105 participants, of which 2,134 were male, comparing normal albumin levels to hypoalbuminemia across diverse populations. The meta-analysis comparing OS between AML patients with hypoalbuminemia and normal serum albumin levels shows a pooled HR of 1.08 (95% CI: 0.81–1.44).

Conclusions : While this meta-analysis suggests a potential association between hypoalbuminemia and poorer OS and DFS in AML patients, the lack of statistical significance and high heterogeneity caution against definitive conclusions.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by the clonal proliferation of myeloid precursors in the bone marrow, leading to impaired hematopoiesis.[1] Despite advancements in diagnostic techniques and treatment modalities, the

prognosis for AML remains poor, with five-year survival rates varying widely depending on age, comorbidities, and cytogenetic risk factors.[1,2] As a result, identifying reliable prognostic markers is critical for stratifying patients, guiding treatment decisions, and improving outcomes.

Hypoalbuminemia, defined as a serum albumin concentration below the normal range, has emerged as a potential marker of poor prognosis in various malignancies, including hematologic cancers.[3] Serum albumin plays a pivotal role in maintaining oncotic pressure, transporting hormones and drugs, and modulating inflammatory and immune responses.[3] Low albumin levels are often associated with malnutrition, systemic inflammation, and increased disease burden, factors that are known to negatively impact survival and treatment efficacy in cancer patients.

In AML, hypoalbuminemia has been observed at diagnosis and during treatment, often correlating with poor clinical outcomes such as reduced remission rates, increased treatment-related toxicity, and shorter overall survival (OS).[4,5] However, the prognostic utility of hypoalbuminemia in AML has not been systematically evaluated, and its role in clinical decision-making remains underexplored.

Given the complexity of AML and the potential for hypoalbuminemia to serve as a surrogate marker for disease severity and systemic dysfunction, a comprehensive analysis of the existing evidence is warranted. This systematic review and meta-analysis aim to investigate the prognostic value of hypoalbuminemia in patients with AML. By synthesizing data from available studies, this research seeks to evaluate the association between hypoalbuminemia and overall survival in AML patients. Understanding the prognostic implications of hypoalbuminemia in AML could provide valuable insights for risk stratification and management, ultimately contributing to improved patient care and personalized therapeutic approaches.

Material And Methods

A comprehensive literature search was conducted across PubMed, EMBASE, and Scopus to identify relevant studies published up to January 5, 2025. The search strategy included a combination of Medical Subject Headings (MeSH) terms and keywords such as “hypoalbuminemia,” “acute myeloid leukemia,” “AML,” “serum albumin,” “prognosis,” and “outcomes.” Boolean operators (AND, OR) were applied to refine the search. Additionally, the reference lists of eligible studies and review articles were screened to identify further studies meeting the inclusion criteria. No restrictions were placed on language to ensure a comprehensive review. Detailed search strategy was available in **Table 1**.

Table 1. List of search terms applied across each database

Database	Search terms
PubMed	("albumin s"[All Fields] OR "albumine"[All Fields] OR "albumines"[All Fields] OR "albumins"[MeSH Terms] OR "albumins"[All Fields] OR "albumin"[All Fields]) AND ("prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR "prognoses"[All Fields] OR ("outcome"[All Fields] OR "outcomes"[All Fields])) AND ("leukemia, myeloid, acute"[MeSH Terms] OR ("leukemia"[All Fields] AND "myeloid"[All Fields] AND "acute"[All Fields]) OR "acute myeloid leukemia"[All Fields] OR ("acute"[All Fields] AND "myeloid"[All Fields] AND "leukemia"[All Fields]))
Europe PMC	Acute myeloid leukemia AND prognosis OR outcome AND albumin
Scopus	Acute AND myeloid AND leukemia AND prognosis OR outcome AND albumin

Studies were included if they involved adult patients (≥18 years) diagnosed with acute myeloid leukemia, reported hypoalbuminemia as a baseline characteristic or its association with clinical outcomes, and provided quantitative data on outcomes such as overall survival, remission rates, or treatment-related complications. Eligible study designs included observational studies (cohort, case-control, or cross-sectional) and randomized controlled trials (RCTs) with clear methodologies. Articles were excluded if they were case reports, conference abstracts, editorials, or reviews without original data. Studies were also excluded if they lacked quantitative data on hypoalbuminemia or clinical outcomes, involved patients with other hematologic malignancies or secondary AML, or were duplicate studies with overlapping datasets.

Data extraction was performed independently by two reviewers using a standardized form, and discrepancies were resolved by discussion or consultation with a third reviewer. Extracted information included study characteristics (author, year, country, design, and sample size), patient demographics (age, sex, and baseline clinical features), the definition of hypoalbuminemia (threshold used), and clinical outcomes. The primary objective of this study was to assess the association between hypoalbuminemia and OS in AML patients. OS referred to the length of time from the start of treatment or diagnosis until death from any cause. The secondary objective was to evaluate the impact of hypoalbuminemia on disease-free survival (DFS), defined as the time from the start of treatment or diagnosis until the first occurrence of disease recurrence or relapse, or death from any cause, whichever occurred first.

The data extraction process involved gathering essential information from each study. Initially, study identification details were documented, including the study title, first author, year of publication, and journal name. Key study characteristics were extracted, such as study design (e.g., cohort, case-control, or randomized controlled trial), sample size (both total participants and those with

hypoalbuminemia), patient demographics (age range, gender, inclusion/exclusion criteria), and the study setting (e.g., hospital-based, multicenter, or country-specific). Clinical characteristics encompassed the diagnosis of acute myeloid leukemia, the definition of hypoalbuminemia (e.g., serum albumin levels), and any comorbidities present in the study population.

The quality of the included studies was assessed using the QUADAS-2 tool, which evaluates the risk of bias in diagnostic accuracy studies, considering domains such as patient selection, index test, reference standard, and flow and timing. Additionally, the certainty of the evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, which considers factors like study limitations, inconsistency, indirectness, imprecision, and publication bias to determine the overall confidence in the effect estimates. This comprehensive quality assessment ensures the reliability and robustness of the findings in this systematic review and meta-analysis.

The statistical analysis for this systematic review and meta-analysis was performed using RStudio with the meta package. A random-effects model was applied to pool the effect estimates, irrespective of heterogeneity across the studies. The log-transformed hazard ratios (HR) were used to derive the overall pooled effect estimate, with a significance threshold set at a p-value of less than 0.05. Forest plots were generated to visually present the individual study results alongside the pooled estimate, while funnel plots were created to evaluate the potential for publication bias. Bias analysis was conducted using Egger's and Begg's tests, which assess asymmetry in the funnel plot and suggest the presence of publication bias or small-study effects. The random-effects model was selected to account for variability among the studies, with statistical significance determined at a 0.05 level.

Result

The study selection process is depicted in a PRISMA flow chart (Figure 1). Initially, a total of 5,071 records were identified from three databases: PubMed (n = 116), Europe PMC (n = 4,691), and Scopus (n = 264). After removing 65 duplicate records, 5,006 records remained for screening. Out of these, 4,980 records were excluded based on the eligibility criteria. Subsequently, 26 reports were sought for retrieval, all of which were successfully retrieved. These reports were assessed for eligibility, and 16 were excluded for various reasons: 6 did not report survival analysis, 7 only reported the level of serum albumin rather than hypoalbuminemia, and 3 were meeting abstracts. Ultimately, 10 studies were included in the review.[4,6–14] (**Figure 1**).

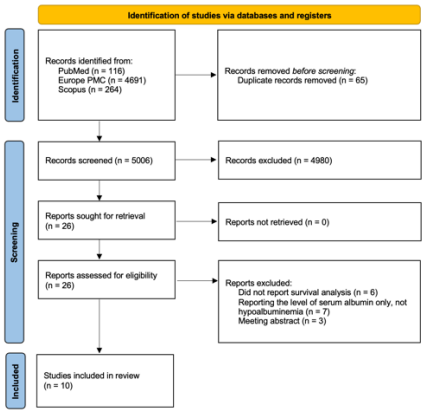

Figure 1. PRISMA flow chart illustrating the study selection process.

This systematic review and meta-analysis included 10 studies with a total sample size of 4,105 participants, of which 2,134 were male, comparing normal albumin levels to hypoalbuminemia across diverse populations. The cutoff values for hypoalbuminemia varied across studies, ranging from 2.5 to 4.0 g/dL. Detailed study demographic was available in **Table 2**.

Table 2. Demographic details of the studies included in the analysis.

Study ID, GRADE	Total cohort	Cutoff	Age	Male
Doucette 2021	715 vs 41	2.5	65.0 (18.0–91.0) vs 60.0 (18.0–85.0)	270 vs 24
⊕⊕⊕				
Wang 2019	139 vs 104	3.5	46 (14–75) vs 55 (17–80)	78 vs 55
⊕⊕⊕⊕				
Fox 2021	138 vs 75	3.5	59 vs 59.7	67 vs 38
⊕⊕⊕				
Kharfan-Dabaja 2011	141 vs 22	3	48 (19-69)	89
⊕⊕⊕⊕				
Chen 2024	299 vs 292	3.5	34 (15 - 54) vs 38 (15 - 54)	174 vs 166
⊕⊕⊕				
Sivgin 2013	60	3.2	26 (IQR 13 - 57)	42
⊕⊕⊕				
Xiao 2022	264 vs 150	3.4	60.8 ± 15.1 vs 56.2 ± 15.7	127 vs 79
⊕⊕⊕				
Murthy 2018	783	3.5	<55 years = 451 ≥55 years = 332	460
⊕⊕⊕⊕				
Artz 2016	784	3.5	50 (18 - 78)	402
⊕⊕⊕				
Yanagisawa 2022	50 vs 70	4	75 (25–88) vs 71 (45–87)	32 vs 51
⊕⊕⊕⊕				

Data presented comparing 'normal albumin levels' to 'hypoalbuminemia'

This systematic review and meta-analysis included 10 studies with a total sample size of 4,105 participants, of which 2,134 were male, comparing normal albumin levels to hypoalbuminemia across diverse populations. The cutoff values for hypoalbuminemia varied across studies, ranging from 2.5 to 4.0 g/dL. The meta-analysis comparing OS between AML patients with hypoalbuminemia and normal serum albumin levels shows a pooled HR of 1.08 (95% CI: 0.81–1.44). This suggests an 8% higher hazard of mortality in patients with hypoalbuminemia, though the confidence interval includes 1.0, indicating no statistically significant association (P = 0.61). Substantial heterogeneity was observed among the studies, with an I^2 value of 93%, suggesting variability due to differences in study characteristics or populations (**Figure 2**).

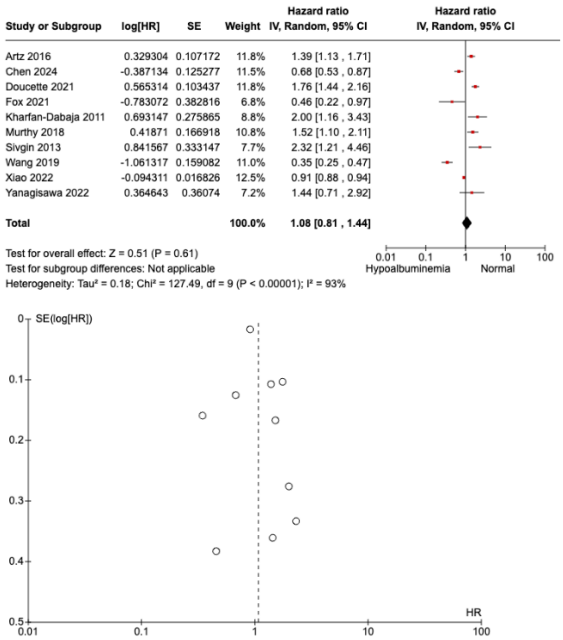

Figure 2. Meta-analysis for OS comparing between AML patients with normal serum albumin level and hypo albumin.

The meta-analysis evaluating DFS between AML patients with hypoalbuminemia and normal serum

albumin levels demonstrates a pooled HR of 1.39 (95% CI: 0.59–3.29). This result suggests a potential increase in disease recurrence or death in hypoalbuminemic patients; however, the confidence interval spans 1.0, indicating no statistically significant difference (P = 0.45). High heterogeneity was present (I^2 = 94%), reflecting significant variability across included studies (**Figure 3**).

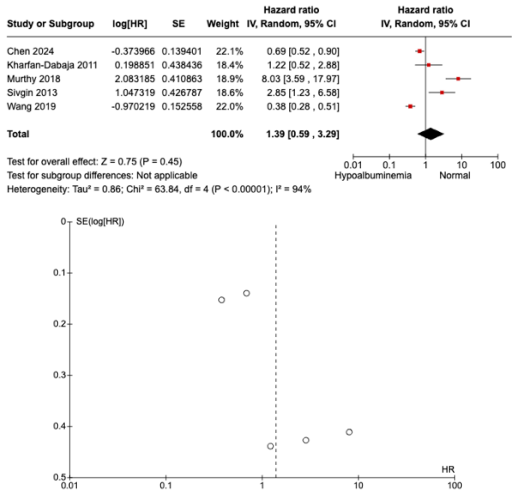

Figure 3. Meta-analysis for DFS comparing between AML patients with normal serum albumin level and hypo albumin.

In terms of bias assessment using QUADAS-2, we found that all included studies were of low to moderate risk of bias. Chen et al (2024) and Artz et al (2016) showing some concern during the bias assessment. Detailed QUADAS-2 was displayed in **figure 4**.[9,13]

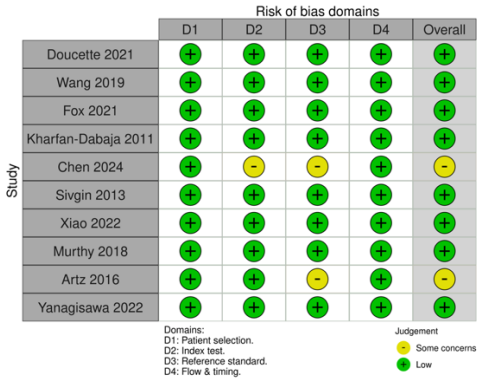

Figure 4. QUADAS-2 assessment from all eligible studies.

Discussion

This meta-analysis evaluates the prognostic significance of hypoalbuminemia in AML, given its potential as a readily measurable biomarker and modifiable risk factor. Identifying factors associated with poor outcomes in AML is essential for enhancing risk stratification and optimizing therapeutic strategies. The pooled HR for OS was 1.08 (95% CI: 0.81–1.44), indicating an 8% higher risk of mortality in patients with hypoalbuminemia compared to those with normal serum albumin levels; however, this result was not statistically significant (P = 0.61). Similarly, the pooled HR for DFS was 1.39 (95% CI: 0.59–3.29), suggesting a possible increase in disease recurrence or death among hypoalbuminemic patients, though this finding also lacked statistical significance (P = 0.45). Both analyses demonstrated substantial heterogeneity, with I^2 values of 93% for OS and 94% for

DFS, indicating considerable variability among the included studies.

Hypoalbuminemia has been associated with poor outcomes in various cancers due to its links to systemic inflammation and impaired nutritional status, both of which are critical factors in AML prognosis.[15] Albumin, as a marker of nutritional and inflammatory status, has been implicated in modulating immune responses and influencing the overall disease trajectory. Some studies included in this meta-analysis reported trends toward poorer survival outcomes in hypoalbuminemic patients, consistent with these biological hypotheses and the pooled HRs observed.

Despite these potential associations, the confidence intervals for both OS and DFS spanned 1.0, indicating no statistically significant relationship between hypoalbuminemia and survival outcomes in AML. Furthermore, several studies found no difference in survival between hypoalbuminemic and normoalbuminemic patients, suggesting the possibility that factors unrelated to albumin levels, such as treatment modalities, disease biology, or other comorbidities, may play a larger role.[16–19] These conflicting findings highlight the variability in the existing literature and the limitations of the available data.

Several limitations must be acknowledged. First, the substantial heterogeneity observed ($I^2 > 90\%$) suggests considerable variability among the included studies in terms of patient populations, definitions of hypoalbuminemia, treatment protocols, and follow-up durations. Second, the limited number of studies and small sample sizes in some cases may reduce the statistical power of the analyses, making it difficult to detect true associations. Third, confounding factors such as comorbidities, baseline disease severity, and variations in therapeutic interventions were not consistently adjusted for across studies. Lastly, the observational design of the included studies limits the ability to establish causality between hypoalbuminemia and survival outcomes.

The clinical applicability of these findings lies in the potential role of hypoalbuminemia as an easily measurable biomarker for assessing prognosis in AML patients. Although the meta-analysis did not establish a statistically significant association between hypoalbuminemia and survival outcomes, the observed trends suggest that serum albumin levels could serve as a proxy for underlying nutritional or inflammatory status, both of which influence disease progression and treatment response.[20] Monitoring albumin levels might help identify patients at higher risk who could benefit from targeted nutritional or supportive interventions to improve their overall condition and potentially enhance treatment tolerance.[21] However, given the substantial

heterogeneity and lack of definitive evidence, these findings should be interpreted cautiously, and further research is necessary before hypoalbuminemia can be routinely used in clinical decision-making for AML.

Conclusion

While this meta-analysis suggests a potential association between hypoalbuminemia and poorer OS and DFS in AML patients, the lack of statistical significance and high heterogeneity caution against definitive conclusions. Future research should focus on large-scale, well-designed studies that address confounding factors and standardize definitions of hypoalbuminemia to better evaluate its prognostic role in AML.

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(Christin Yosefin Jacobs)