Low serum albumin level predicts mortality at medium and medium-long term following proximal femoral fracture: a systematic review and meta-analysis

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ABSTRACT

Purpose: The aim of this systematic review and meta-analysis was to determine whether serum albumin level (<35mg/L) can predict mortality after proximal femoral fracture surgery in older adults.

Methods: This review adhered to the guidelines outlined in the PRISMA statement. The electronic databases PubMed, EMBASE, Web of Science, and Cochrane were reviewed for studies. The risk of bias was assessed with the ROBINS-I tools. The following relevant data from each included study were extracted and reported by two independent reviewers: study design, sample size, follow-up, age, gender, mortality at last follow-up, odds ratio (OR).

Results: In total, 2,009 studies were identified; 18 original articles satisfied both the inclusion and the exclusion criteria and were included in the final meta-analysis. At 1 month of follow up, among 15,284 patients, the OR was 1.20 (95% CI: 0.86–1.68) with an I-squared statistic of 98.3%. At 1 year of follow-up, among 2,281 patients, the OR was 1.88 (95% CI: 1.00–3.53) with an I-squared statistic of 20.5%. At long-term follow-up (beyond 3 years), among 283 patients, the OR was 5.58 (95% CI: 2.56–12.06) with an I-squared statistic of 0.0%. Evaluation of mortality hazard, among 283 patients, revealed a hazard ratio of was 1.04 (95% CI: 0.89–1.19) with an I-squared statistic of 40.2%.

Conclusion: Over a follow-up period of more than three years, patients with low serum albumin levels have a 5.58 times higher mortality risk than those with normal levels. Additionally, at one year, patients with low serum albumin levels are 1.88 times more likely to die than those with normal levels.

KEYWORDS

Proximal femoral fractures, pertrochanteric fractures, intertrochanteric fractures, hip fractures, albumin, mortality, nutritional state, odds ratio, hazard ratio.

Introduction

Globally, fragility fractures, particularly proximal femoral fractures, are a significant clinical and social concern [1,2]. With the aging of the population, the incidence of these fractures is projected to rise by nearly 60% in the next 20 years [3]. Most hip fracture patients are over 85 years old and have at least two severe comorbidities; around 50% experience moderate to severe functional impairment [4-6]. Morbidity in geriatric hip fractures is increasing with the aging of the population worldwide [7-10].

Given the substantial socioeconomic burden associated with these fractures, extensive efforts have been made to identify predictors that could potentially personalize patient care to reduce costs and improve survival rates for those affected by proximal femoral fractures [11-13].

Serum albumin is an important factor in understanding the prognosis and potential outcomes of patients with hip fractures [14-16]. Albumin is a protein produced by the liver that circulates in the blood. It plays a crucial role in maintaining the osmotic pressure needed for proper distribution of body fluids between body tissues and the bloodstream. Albumin also serves as a carrier protein for hormones, vitamins, drugs, and ions such as calcium. It helps in buffering pH, and is essential for tissue growth and repair. Low levels of albumin in the blood, a condition known as hypoalbuminemia, can indicate various health issues, including liver disease, kidney disease, malnutrition, and inflammation.

Recently, hypoalbuminemia was identified as having an association with pulmonary edema and as a potent prognostic biomarker in heart failure [17]. Moreover, hypoalbuminemia has been found to be associated with increased risk of acute kidney injury in hospitalized patients with a 1.183-fold increased risk of overall mortality in such patients [18]. A systematic review

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previously found that low serum albumin is also significantly associated with increased total mortality in patients after hip fracture surgery, with almost double the risk of mortality reported in patients with hypoalbuminemia versus those with normal serum albumin [19].

The aim of this systematic review and meta-analysis was to incorporate findings from multiple studies, thereby addressing the constraints posed by the limited statistical power of smaller samples, and report updated results. New information about hypoalbuminemia in hip fracture patients may warrant personalized perioperative care strategies including enhanced nutritional support, intensive monitoring, and targeted resource allocation to improve outcomes. Therefore, this systematic review and meta-analysis aimed to quantify the association between preoperative serum albumin levels and mortality risk following proximal femoral fracture surgery in adults aged 65 and older, to establish whether serum albumin can serve as a reliable prognostic indicator of post-surgical survival outcomes.

Materials and methods

This systematic review and meta-analysis adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [20]. The electronic databases PubMed, Embase, Web of Science, and Cochrane were reviewed to identify relevant studies. Only published articles in English were considered among those published from inception of the databases up to July 1st, 2024. The following search terms were employed in combination to identify studies: (albumin OR "serum albumin") AND ("hip fracture" OR "pertrochanteric fracture" OR "intertrochanteric fracture" OR ("proximal femoral fractures").

Eligibility criteria

The reference lists of the selected articles were explored to identify any additional articles not detected in the initial database search. The PICOS-based eligibility criteria were then applied to further refine the selection of articles for inclusion in the meta-analysis, as illustrated in Table I. Inclusion criteria comprised: comparative studies in the literature evaluating odds ratio (OR) and hazard ratio (HR) for mortality in patients undergoing surgery (either hip replacement or osteosynthesis) following proximal femoral fracture with serum albumin level >35mg/L vs. <35mg/L.

Exclusion criteria included *in vitro* studies, case reports, case series with fewer than 10 cases, expert opinions, prior systematic reviews, letters to the editor, and studies whose full text was not obtained. The aim of the current study was to analyze the literature to evaluate the OR and HR of serum albumin levels lower or higher than 35mg/L in relation to mortality.

Table I PICO question of the included studies.

Population	Patients with serum albumin level <35mg/L
Intervention	Proximal femoral fractures
Comparison	Patients with serum albumin level >35mg/L
Outcome	Odds ratio for mortality at 1 month, 1 year, and more than 1 year; hazard ratio
Study	RCTs; cohort studies, case-control studies

Study selection

First, removal of duplicate publications was managed with Zotero (Zotero, Roy Rosenzweig Center for History and New Media, 2016). References were screened by two independent orthopedic residents for titles and abstract. The full texts of studies thought to be eligible for inclusion were obtained. Once the evidence had been screened, the articles were also searched for relevant literature in the citations section. If necessary, the authors of the included studies were contacted to obtain missing or raw data concerning their articles.

Data extraction

The following relevant data from each included study were extracted and reported by two independent reviewers: study design, sample size, follow-up, age, gender, mortality at last follow-up, and OR.

Quality assessment

Two authors assessed the risk of bias for each selected cohort study with the Risk Of Bias In Non-randomized Studies - of Interventions tool (ROBINS-I) [21].

Statistical analysis

A pooled analysis was conducted to compare the OR with the 95% confidence interval (95% CI), which were first transformed into log (OR) and standard error (SE). All analyses were executed using R Statistical Software (v4.1.2; R Core Team 2021) and SPSS Statistics (SPSS, Version 29.0, IBM Heterogeneity among studies was assessed using the I-squared statistic. A random-effects model was employed. A p-value <0.05 was taken as statistically significant.

Results

A total of 2009 studies were initially identified from the four aforementioned databases. Following the removal of 857 duplicate articles, 1152 papers underwent screening based on title and abstract. Subsequently, 96 articles closely aligned with the research content were identified. Upon a comprehensive review of the full-text versions, 78 references were excluded due to not meeting the inclusion criteria. Ultimately, 18 original articles satisfied both the inclusion and the exclusion criteria.

A PRISMA 2020 flowchart summarizes the research strategy (Figure 1) [20]. Following the preliminary screening of titles and abstracts, the complete texts of 18 articles were evaluated in detail for qualitative and quantitative analysis (Table II).

Risk of bias

The quality assessment and selected risk of bias for the studies included in the meta-analysis were classified according to the ROBIN-I risk assessment tool [21].

Figure 1 PRISMA flowchart of the screening process for studies included in the qualitative and quantitative analyses.

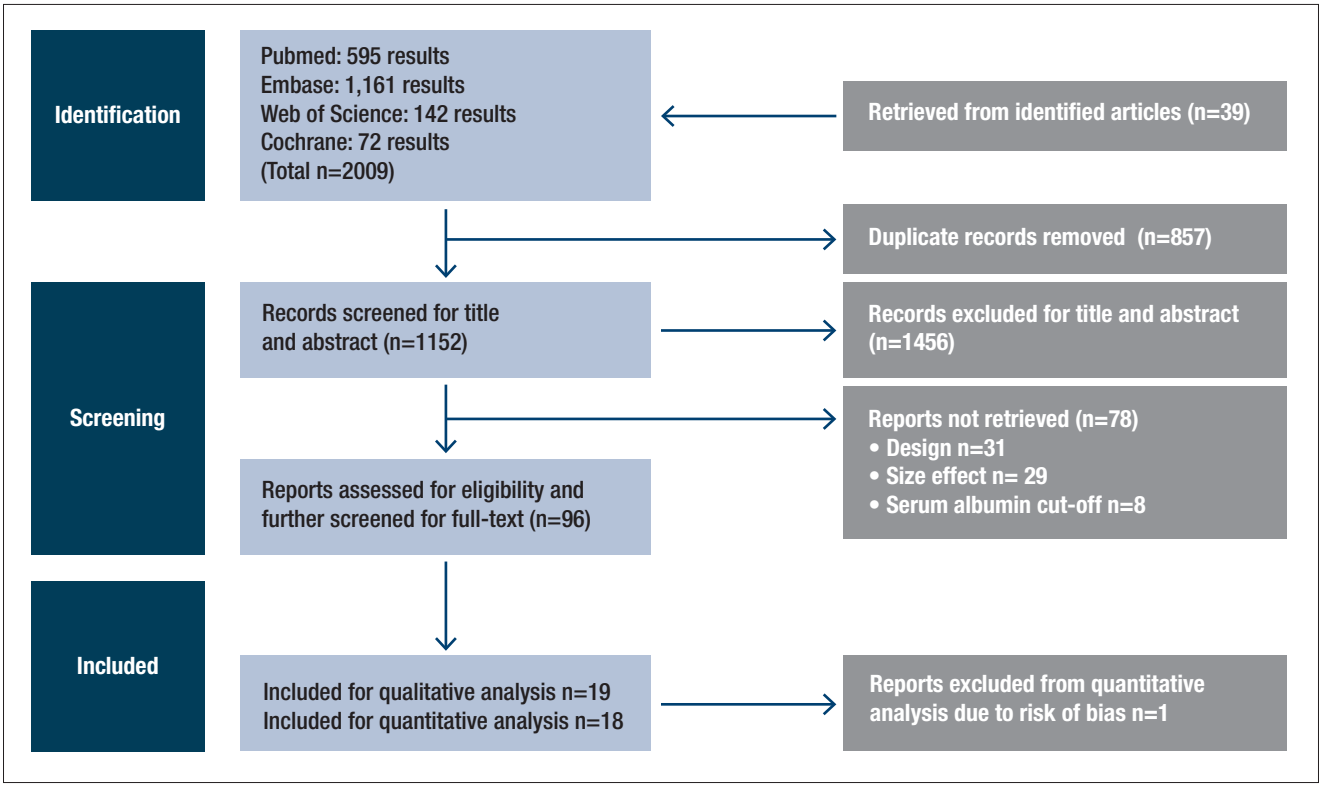


Table II Summary information contained in the studies included in the qualitative and quantitative synthesis.

FIRST AUTHOR (year)	STUDY DESIGN	SAMPLE SIZE	AGE (Y)	MALES (%)	FOLLOW-UP	MORTALITY (%)	INCLUDED IN THE MET-AANALYSIS	SIZE EFFECT
Kieffer (2013) [23]	Retrospective	585	84	22	1 y	27	Y	OR
Helminen (2017) [24]	Prospective	594	≥65	29	1 y	26	Y	OR
Öztürk (2009) [25]	Prospective	74	78	30	1 y	20	Y	OR
Ozel (2023) [41]	Retrospective	275	80	38	1y	34	Y	OR
Chiang (2022) [26]	Retrospective	377	81	28	1y	N/A	Y	OR
Hershkovitz (2010) [37]	Retrospective	376	82	25	2 y	21	Y	OR
Bohl (2017) [22]	Prospective	17651	≥65	59	N/A	N/A	No	OR
Miyanishi (2010) [27]	Retrospective	127	79	19	4 y	48	Y	OR
Lu (2022) [28]	Prospective	156	83	33	3y	24	Y	OR
Aldebeyan (2016) [29]	Prospective	10117	81	30	1 mo.	7	Y	OR
de Haan (2024) [30]	Prospective	3523	84	33	1 mo.	9	Y	OR
Pass (2022) [31]	Retrospective	640	85	28	1 mo.		Y	OR
Chen (2022) [38]	Prospective	1004	80	32	1 mo.		Y	OR
Harrison (2017) [32]	Retrospective	471	82	30	1 y	51	Y	HR
Uriz-Otano (2016) [33]	Prospective	430	84	23	3 y	41	Y	HR
Lu (2016) [34]	Retrospective	174	81	66	1 y	31	Y	HR
O'Daly (2010) [35]	Retrospective	200	81	19	1 y	30	Y	HR
Atay (2010) [36]	Retrospective	240	76	45	2 y	17	Y	HR

Figure 2 Risk-of-bias assessment with ROBINS-I tool shown as a traffic lights chart.

	RISK OF BIAS DOMAINS							
FIRST AUTHOR (year)	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**OVERALL**
Kieffer (2013) [23]	+	-	-	-	-	-	-	-
Helminen (2017) [24]	-	+	-	+	+	-	+	-
Öztürk (2009) [25]	+	+	-	-	-	+	+	-
Ozel (2023) [41]	-	-	-	+	+	-	+	-
Chiang (2022) [26]	+	+	-	-	-	-	+	-
Hershkovitz (2010) [37]	+	+	+	+	+	+	+	+
Bohl (2017) [22]	+	-	!	-	!	-	-	!
Miyanishi (2010) [27]	+	+	+	-	-	-	-	-
Lu (2022) [28]	+	+	+	+	+	+	-	-
Aldebeyan (2016) [29]	-	-	+	+	-	+	+	-
de Haan (2024) [30]	+	+	+	-	-	+	+	-
Pass (2022) [31]	-	+	+	+	+	+	+	-
Chen (2022) [38]	+	+	+	+	+	+	+	+
Harrison (2017) [32]	+	-	+	+	-	-	+	-
Uriz-Otano (2016) [33]	-	+	+	+	+	-	-	-
Lu (2016) [34]	+	-	-	+	+	+	+	-
O'Daly (2010) [35]	-	+	-	-	+	-	+	-
Atay (2010) [36]	-	+	-	+	+	+	+	-

Domains: **D1:** Bias due to confounding. **D2:** Bias due to selection of participants. **D3:** Bias in classification of interventions. **D4:** Bias due to deviations from intended interventions. **D5:** Bias due to missing data. **D6:** Bias in measurement of outcomes. **D7:** Bias in selection of the reported results.

All the studies included in the meta-analysis, except Bohl *et al*. [22], offered robust evidence with the overall assessment of bias indicating a moderate [23-36] or low [37,38] risk of bias as shown in Figure 2. The study by Bohl *et al*.[22] presented major issues and was deemed overall to be at serious risk of bias; for this reason, it was not included in the meta-analysis. Specifically, the intervention group was not clearly defined, and the reported effect estimate was selected on the basis of the results of multiple outcome measurements within the outcome domain [22].

Meta-analysis

- *Odds ratio for mortality at 1 month of follow-up* (Figure 3) A total of 15,284 patients were identified in four studies which evaluated the role of low serum albumin in mortality risk at 1 month of follow-up [29-31,38]. The test of homogeneity was conducted to assess consistency across the studies. The I-squared statistic was 98.3%, which indicates a very high percentage of the variability in effect estimates due to heterogeneity rather than sampling error. The overall OR was 1.20, with a 95% CI ranging from 0.86 to 1.68.

- *Odds-ratio for mortality at 1 year of follow-up* (Figure 4) For the 1-year follow-up, six studies comprising a total of 2,281 patients were analyzed to evaluate the role of low serum albumin in mortality risk [23-26,37,42]. The I-squared statistic was 20.5%, which indicates a low-to-moderate percentage of the variability in effect estimates due to heterogeneity rather than sampling error. The overall OR was 1.88, with a 95% CI ranging from 1 to 3.53.

- *Odds ratio for mortality over long-term follow-up* (Figure 5) For follow-up periods exceeding 3 years, two studies involving a total of 283 patients were assessed [27,28]. The analysis of heterogeneity within the group of studies yielded a percentage of variation due to heterogeneity of 0.0%. The I-squared statistic showed a lack of significant heterogeneity, meaning that all observed variability was within the range expected by chance alone. The overall OR was 5.58, with a 95% CI ranging from 2.56 to 12.06

- *Hazard ratio for mortality* (Figure 6)
A total of 283 patients were identified in five studies which evaluated the role of low serum albumin in mortality risk [32-36]. The analysis of heterogeneity within the group of studies resulted in an I-squared statistic of 40.2% suggesting moderate heterogeneity and implying that there were some differences

Figure 3 Forest plot of mortality at 1 month of follow-up.

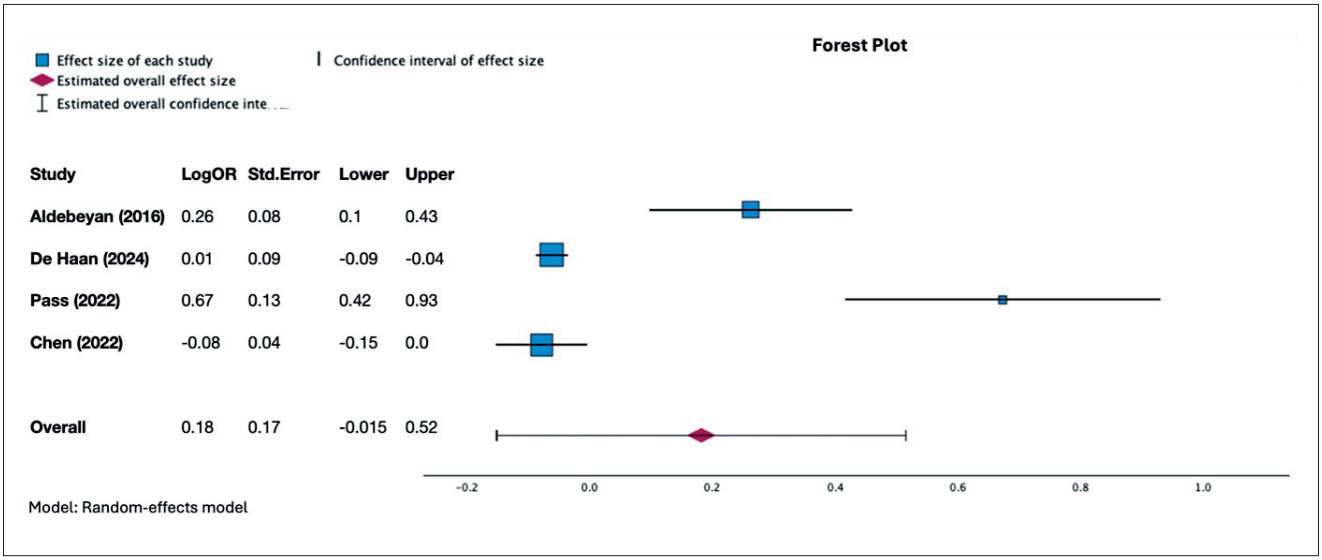


Figure 4 Forest plot of mortality at 1 year of follow-up.

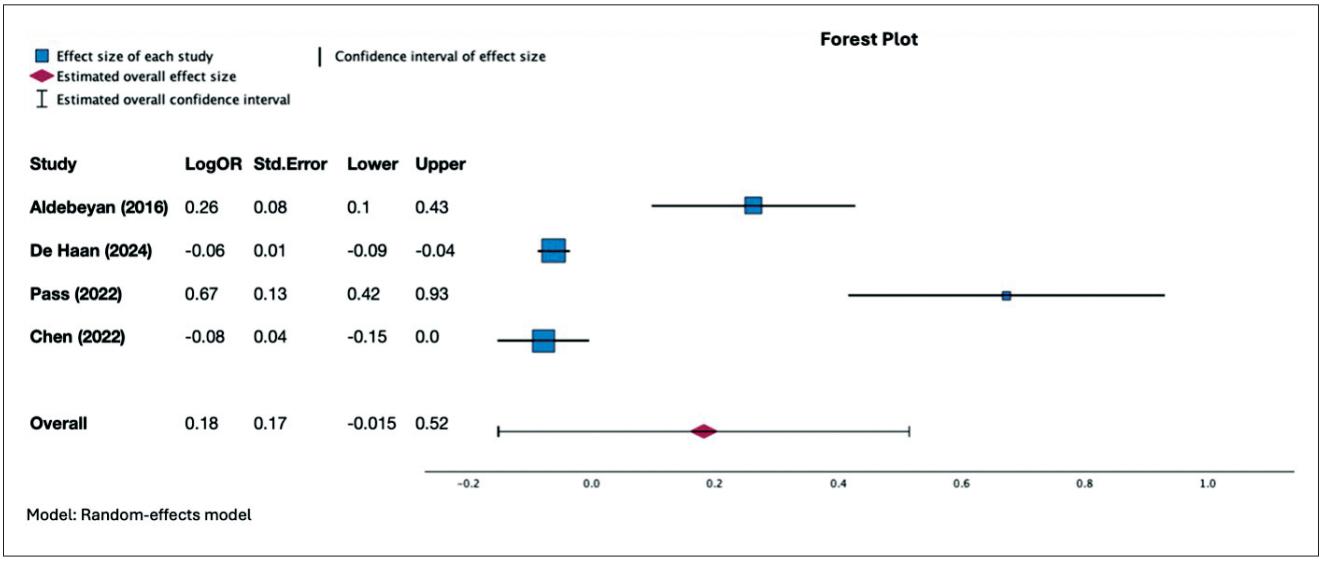


Figure 5 Forest plot of mortality over long-term follow-up.

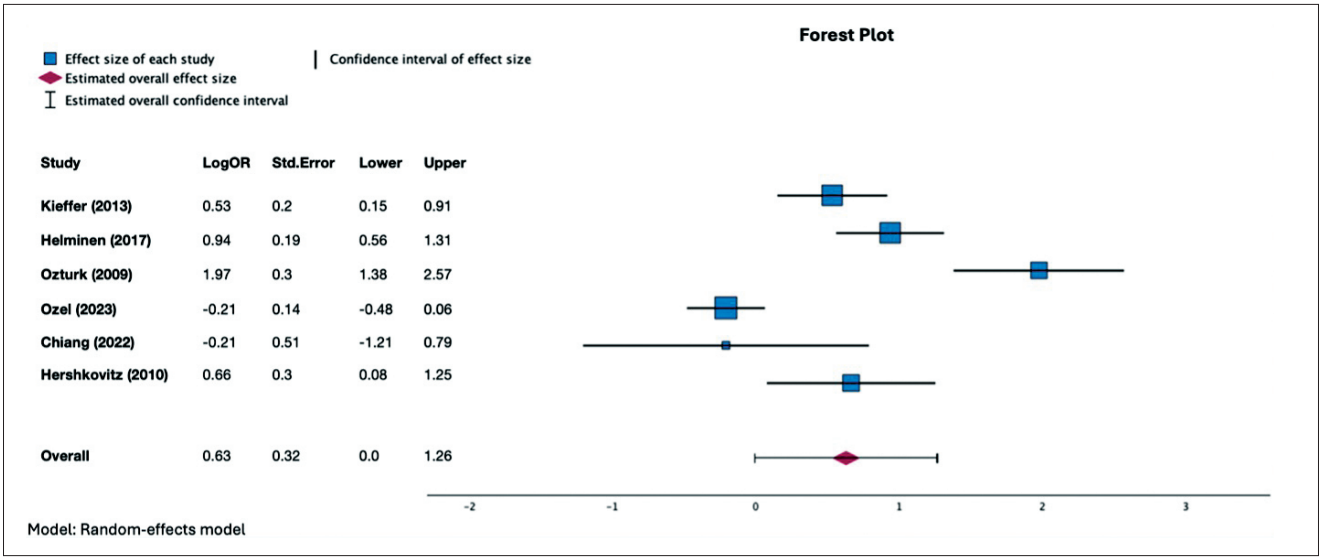
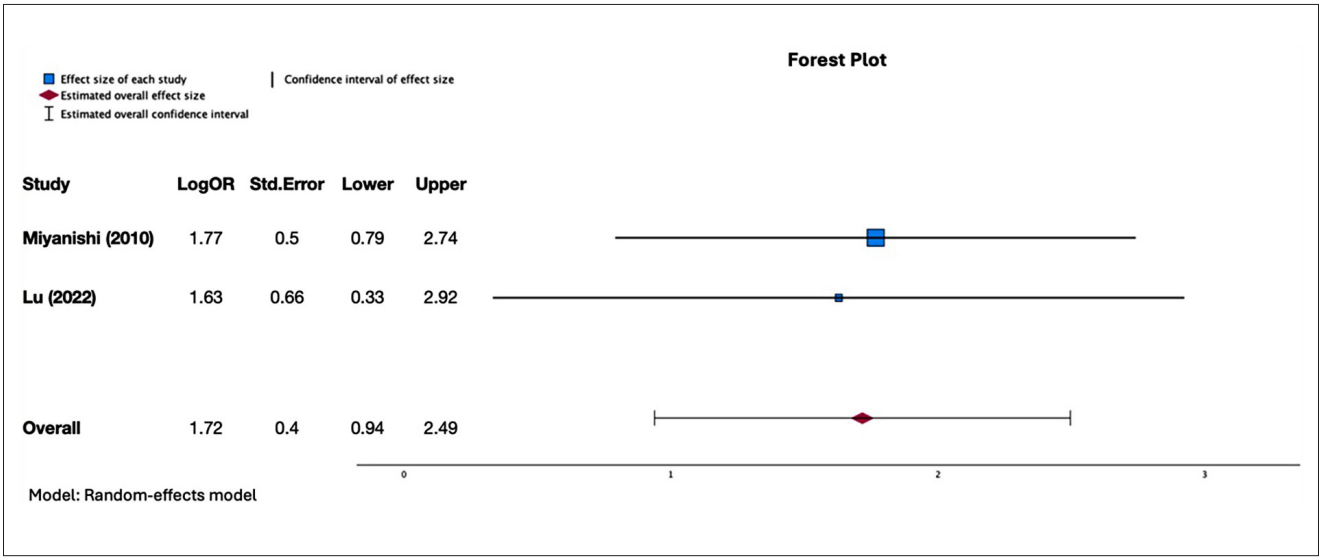


Figure 6 Forest plot of hazard ratios for mortality.



between the studies that could be due to factors other than random variation. The overall HR was 1.04, with a 95% CI ranging from 0.89 to 1.19.

Discussion

The meta-analysis results indicate varying levels of association between low serum albumin <35mg/L and mortality risk at different follow-up points following proximal femoral fractures. At 1 month, the data suggest no significant association between low serum albumin and mortality risk. At 1 year there was a significant association. At more than 3 years, there was a strong and significant association, with low serum albumin levels being linked to a markedly increased long-term mortality risk. The HR for mortality suggests a potential association, but this finding was not statistically significant.

These findings underscore the importance of serum albumin <35 mg/L as a potential prognostic marker of mortality risk, with its impact appearing more pronounced over longer follow-up periods. However, the presence of heterogeneity in some analyses suggests that further research with larger and more homogeneous cohorts is needed to better understand these associations.

The most important and strongest result of this meta-analysis is the association between low serum albumin levels and increased long-term mortality risk over more than 3 years of follow-up. The analysis showed an overall OR of 5.58 with a 95% CI ranging from 2.56 to 12.06, indicating a strong and significant association. This finding is particularly robust given the lack of heterogeneity (I-squared statistic = 0.0%) among the included studies, suggesting that the observed effect is consistent and not influenced by variability between them. Another important finding is the significant association between low serum albumin and increased mortality risk at 1 year. The overall OR was 1.88 with a 95% CI ranging from 1.00 to 3.53, indicating that individuals with low serum albumin have a 1.88 higher risk of dying within one year compared with those with normal levels. The low-to-moderate heterogeneity (I-squared statistic = 20.5%) suggests that this finding is consistent across the analyzed studies.

The OR is a measure used to determine the strength of association or non-independence between two binary data values. It quantifies the odds of an event occurring in one group relative to the odds of it occurring in another group.

The HR, on the other hand, is a measure used primarily in survival analysis to compare event rates between two groups over time. It represents the ratio of hazard rates, which are the rates at which events occur at any given time point.

Another meta-analysis has evaluated whether low serum albumin can predict mortality after hip fracture surgery in older adults [19]. Although this previous meta-analysis was the first to investigate this topic, it has notable methodological limitations. Specifically, it did not provide results for different follow-up periods but rather gave an overall pooled OR that included both 1-month and 4-year results. By pooling results from vastly different follow-up periods (1 month and 4 years), the meta-analysis failed to provide specific insights into how the risk of mortality associated with low serum albumin changes over time. Combining short-term and long-term follow-up data in a single pooled OR can introduce significant heterogeneity, making it difficult to interpret the results accurately. Differences in patient characteristics, perioperative care, and long-term management can vary significantly over such time ranges, leading to inconsistent findings. The current study is updated with more studies and additional data, providing a more comprehensive analysis. The risk of bias was also re-assessed to ensure accuracy and reliability of the findings, offering more specific insights into the association between low serum albumin and mortality risk over distinct follow-up periods.

The significant association at 1 year (OR 1.88) highlights the immediate relevance of serum albumin levels in the short-term prognosis. Clinicians can use this information to make more informed decisions regarding perioperative care, rehabilitation, and follow-up strategies to improve patient outcomes. Regular monitoring of serum albumin levels in patients with

hip fractures can help identify those at higher risk of mortality. This can lead to more personalized and intensive care plans aimed at mitigating risk factors and improving survival rates. Knowledge of a patient's serum albumin levels can inform perioperative care strategies. Patients with low levels may benefit from tailored nutritional support, closer monitoring, and interventions designed to enhance their recovery and reduce complications [39,40]. Finally, hospitals and healthcare providers can use this information to prioritize resources for patients at higher risk. This includes allocating more intensive rehabilitation services, implementing closer post-discharge monitoring, and ensuring adequate nutritional and medical support.

This study has its own limitations, including geographic and ethnic variations, with differences in healthcare systems, genetic factors, and environmental influences across regions and ethnic groups potentially affecting the generalizability of the results. Additionally, potential differences in patient demographics, health status, and treatment regimens across studies might contribute to the observed heterogeneity, impacting the consistency of the findings.

Conclusions

This systematic review and meta-analysis found varying levels of association between low serum albumin <35mg/L and mortality risk at different follow-up intervals following proximal femoral fractures. Over a follow-up period of more than three years, patients with low serum albumin levels showed a 5.58 times higher mortality risk compared with those with normal levels. Additionally, at one year, patients with low serum albumin levels were found to be 1.88 times more likely to die than those with normal levels. Given these findings, routine preoperative serum albumin measurement should be considered a standard screening tool to identify high-risk patients who may benefit from enhanced perioperative care and nutritional optimization strategies. Future large-scale, multicenter studies should investigate whether specific nutritional intervention protocols targeting patients with low serum albumin levels can effectively reduce mortality rates and improve functional outcomes in elderly patients with proximal femoral fractures.

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