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Liver biomarkers as predictors of prognosis in heart failure with preserved ejection fraction: a systematic review and meta-analysis

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Abstract

Background Heart failure with preserved ejection fraction (HFpEF) accounts for 50% of heart failure cases, with increasing prevalence due to aging and risk factors such as hypertension and obesity. Liver dysfunction is common in HFpEF and may impact prognosis. This systematic review and meta-analysis aimed to evaluate the prognostic value of liver function markers (albumin, bilirubin, AST, ALT, ALP) in HFpEF patients.

Methods A systematic search of PubMed, Embase, Web of Science, and Scopus was conducted for studies assessing the association of liver markers with adverse outcomes in HFpEF. The primary outcome was a composite of heart failure-related hospitalization or death. Hazard ratios (HR) were pooled using a random-effects model, and heterogeneity was assessed using the I^2 statistic.

Results Twenty studies involving 30,623 patients were included. Serum albumin, the main marker of our study, was significantly associated with a reduced risk of adverse outcomes in a meta-analysis of 16 studies (HR 0.71, 95% CI: 0.61–0.83; $I^2 = 87\%$). After excluding outliers, heterogeneity decreased ($I^2 = 23\%$), and the association remained significant (HR 0.75, 95% CI: 0.69–0.82). Although no significant associations were found for AST, ALT, ALP, or bilirubin with adverse outcomes, the limited number of studies for these markers may have contributed to the lack of statistical significance.

Conclusion Higher serum albumin levels predict better outcomes in HFpEF, while other liver function markers showed limited prognostic utility. Serum albumin may serve as a valuable marker for risk stratification in HFpEF.

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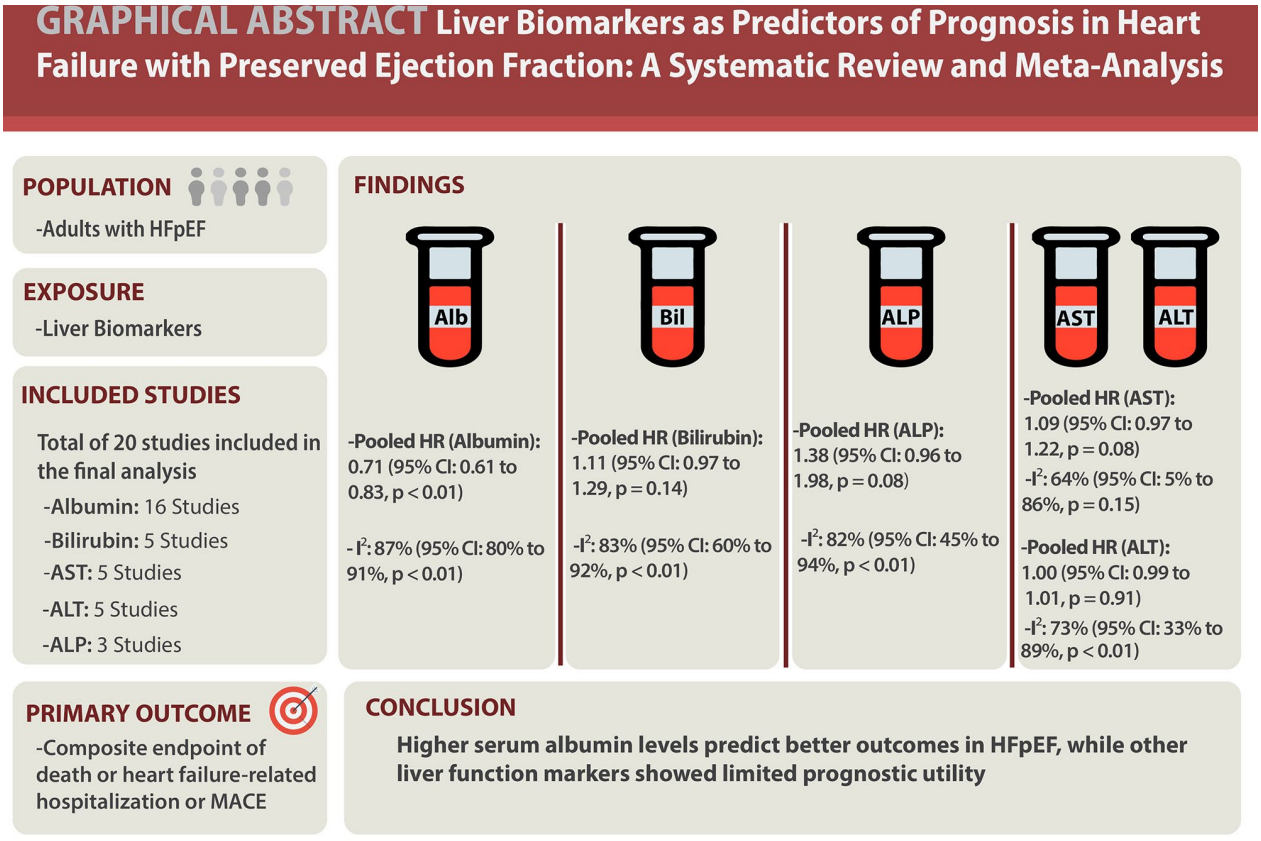
Graphical Abstract



Keywords Heart failure, Preserved ejection fraction, Liver function biomarkers, Serum albumin, Meta-analysis

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a significant and growing public health concern [1]. It accounts for approximately 50% of all heart failure cases, with a prevalence that has been steadily increasing due to the aging population and rising incidence of associated risk factors such as hypertension and obesity [1]. The burden of HFpEF is substantial, leading to high rates of hospitalization, impaired quality of life, and increased mortality [2]. Studies indicate that the prevalence of HFpEF is higher in elderly populations and more prevalent among women, contributing to significant healthcare resource utilization and economic costs [3, 4].

The coexistence of HFpEF and liver dysfunction is increasingly recognized, with shared risk factors like obesity, diabetes, and metabolic syndrome contributing to this overlap [5, 6]. Up to 50% of HFpEF patients may also have Non-alcoholic fatty liver disease (NAFLD) [7]. Liver dysfunction can worsen heart failure symptoms and prognosis, as elevated markers like bilirubin and alkaline phosphatase (ALP) are linked to higher cardiovascular mortality and hospitalization risks [5]. Additionally, hepatic congestion from elevated right heart pressures can further impair liver function, creating a cycle that exacerbates both conditions [8]. Thus, due to the conditions mentioned above, assessing liver function is essential to improve outcomes in HFpEF.

Liver function is assessed using various serum markers, including albumin, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and ALP, each indicating different aspects of hepatic health. Serum albumin is a well-established biomarker of liver function, reflecting the liver's protein synthesis capacity. Reduced albumin levels indicate hepatic dysfunction and have been associated with worse prognosis in HFpEF [9]. Bilirubin measures the liver's ability to process waste, with elevated unconjugated bilirubin indicating non-obstructive conditions, and elevated conjugated bilirubin suggesting obstructive pathologies [10–12]. AST and ALT are enzymes released during liver cell damage, indicating liver injury or inflammation [13]. Gamma-glutamyl transferase (GGT) and ALP are associated with bile ducts, with elevated levels indicating cholestasis or bile duct obstruction [14]. These markers collectively help

diagnose and monitor liver conditions, improving patient outcomes.

Previous studies have explored liver markers in HFpEF patients, noting their prognostic significance. Yoshihisa et al. identified liver fibrosis scores as predictors of mortality [15], while Böhm et al. linked liver function tests (bilirubin, AST, ALT, and ALP) with hospitalization and cardiovascular death [16]. Prenner et al. associated low serum albumin levels with poorer outcomes, including increased mortality and hospitalization [17]. However, no systematic review or meta-analysis has yet evaluated the prognostic value of these liver markers in HFpEF patients.

Given the critical importance of this subject and the current lack of a comprehensive review, which is essential for informed decision-making and effective risk management in patients with HFpEF and impaired liver function, we aim to conduct a thorough systematic review and meta-analysis. This study will evaluate the prognostic significance of liver markers in patients with HFpEF.

Methods

To conduct this systematic review and meta-analysis, we followed PRISMA guidelines. Our methods were prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42024563800).

Search strategy

Four main databases, PubMed, Embase, Web of Science, and Scopus, were systematically searched on August 5th, 2024. Keywords and MeSH terms for liver enzymes, including "Aspartate Aminotransferase," "Alanine Aminotransferase," "Alkaline Phosphatase," "Gamma-Glutamyl Transferase," "Bilirubin," "Albumin," and their synonyms, were connected with OR to find the desired exposures. Additionally, keywords and MeSH terms for "Heart Failure" and its synonyms were connected with OR to find the desired population. The population and exposure keywords were connected with AND and searched in the aforementioned databases. The full search query for all databases is available in the supplementary material.

Selection criteria and screening

The PECOS (population, exposure, comparison, outcome, study type) framework was used to define the selection criteria: (P): any adult with HFpEF defined as having documented symptoms, signs, or guideline-based medication of heart failure with left-ventricular ejection fraction of $>=40$ without any previous episodes of left-ventricular ejection fraction <40 [18]; (E): level of albumin, liver enzymes (i.e. Aspartate Aminotransferase, Alanine Aminotransferase, and Alkaline Phosphatase), and bilirubin; (C): comparison is made between different levels of enzymes thus there is no defined comparison group; (O): primary outcome as defined by the composite endpoint of death or heart failure-related hospitalization or major adverse cardiac event (MACE); (S): any observational or interventional clinical study excluding case-reports and case-series.

Articles were excluded if they did not investigate the HFpEF patients, did not report any of the desired exposures, did not clarify the relation between exposure and outcome with hazard ratios or equivalent statistical methods, or were animal or case-control or case-series studies.

Articles retained through the database search were primarily screened using titles and abstracts by two independent reviewers (P.D. and H.S.). Any conflict was resolved with the help of a third senior reviewer (S.N.). The secondary screening was done using the full text of the articles selected by the primary screening by two independent reviewers (S.N. and M.D.). Any conflict was resolved with the help of a third senior reviewer (P.D.).

Data extraction

Two independent reviewers (A.M. and R.J.) extracted the data using a premade spreadsheet. The spreadsheet obtained the following characteristics of each study: first author, year of publication, country, study design, sample size, age of participants, percentage of male participants, follow-up duration, percentage of hypertensive patients, percentage of diabetic patients, percentage of patients with ischemic heart disease, hazard ratio, and lower and upper 95 confidence interval for each of the exposures concerning each of the outcomes (adjusted and unadjusted values were separated).

Quality assessment

Two reviewers (S.N. and M.D.) employed the Quality in Prognostic Studies (QUIPS) to assess the quality of the included publications [19]. The assessment of the studies involved the utilization of 6 domains that spanned the areas of participation, attrition, prognostic factor measurement, confounding measurement and account, outcome measurement, and analysis and reporting. Discrepancies were addressed through deliberation with a third reviewer (M.T.).

Statistical analysis

Statistical analysis was carried out using R packages. A random-effects model was used because of the heterogeneity of factors impacting exposure variables. HR, with its corresponding 95% confidence interval, was utilized as the effect size for all exposure variables. Heterogeneity was assessed using I^2 statistic. I^2 above 50% was considered significant heterogeneity. The Association between albumin levels, AST levels, ALT levels, ALP levels, and

bilirubin levels and the primary outcome was meta-analyzed using a random-effects model. A leave-one-out (LOO) sensitivity analysis was performed for each of these analyses. In addition, the Funnel plot of studies investigating the association of albumin levels and the primary outcome was elicited. Egger's test was used to test for asymmetry of the funnel plot and reveal any potential publication bias.

Results

After the initial search, 2,099 records were identified from PubMed, Scopus, Embase, and the Web of Science. Following the removal of 197 duplicate studies, 1,812 records were excluded based on title and abstract screening, resulting in 90 studies eligible for full-text review. Of these, 70 studies were excluded for various reasons, as detailed in Fig. 1, leaving 20 studies included in the final analysis. The studies included in this systematic review and meta-analysis were published between 2014 and 2024. The majority of the studies were conducted in Japan (7 studies), followed by China (3 studies), the United States (3 studies), and Multinational studies (3 studies). In total, this review analyzed data from 30,623 patients across both prospective and retrospective study designs. The diagnostic criteria for HFpEF used in these studies were largely consistent, with 14 studies defining HFpEF as left ventricular ejection fraction (LVEF) ≥ 50%, 3 studies using a threshold of LVEF ≥ 45%, and 3 studies defining it as LVEF > 40% with no prior LVEF ≤ 40%. These criteria, along with other baseline characteristics, are detailed in Table 1.

Quality assessment of included articles

The quality of the included studies was generally good, with most studies showing a low risk of bias across key domains such as study participation, outcome measurement, and statistical analysis. However, some studies, such as Matsuo (2021) and Dalos (2019), exhibited high risk in study participation and outcome measurement, respectively. Moderate risk of bias was noted in study attrition and confounding in a few studies, including Bohm (2023) and Liang (2021). Overall, the risk of bias was considered acceptable for the majority of studies. A summary of the quality assessment across all domains is provided in Supplementary Fig. S1 and Table S1.

Albumin

As shown in Fig. 2, utilizing a random-effects model to address study heterogeneity, the meta-analysis incorporated data from 16 studies examining the relationship between albumin levels and the primary outcome. The pooled HR was 0.71 (95% CI: 0.61 to 0.83), indicating a significant association between higher albumin levels and a reduced risk of the primary outcome. However, considerable heterogeneity was observed among the studies, with an I^2 statistic of 87% (95% CI: 80–91%, $p < 0.01$).

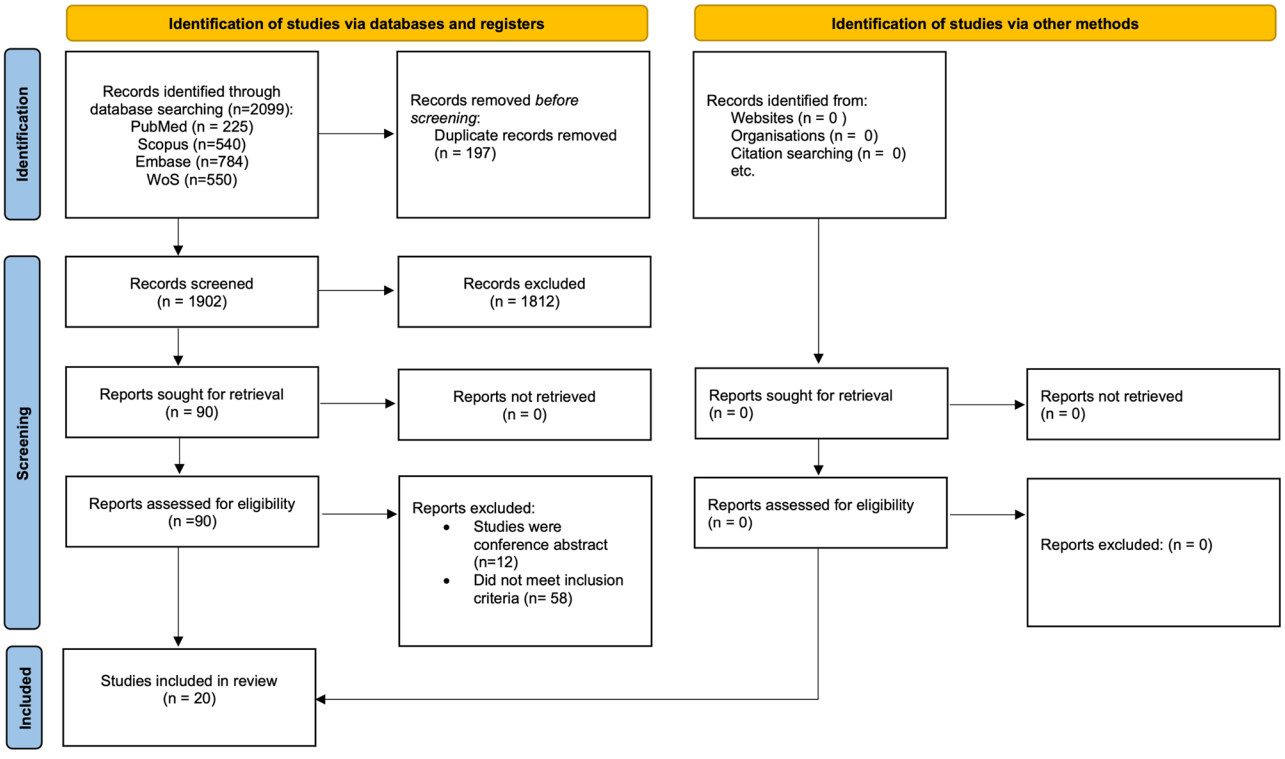


Fig. 1 PRISMA Flow diagram of search strategy and study selection

Table 1 Baseline characteristics of included studies

Author	Year	Design	Location	No. of participants	Mean age (years)	Male (%)	Body mass index (kg/m2)	Hypertension (%)	Diabetes mellitus (%)	Ischemic heart disease (%)	Follow-up duration	Evaluated factor(s)	HFpEF Definition	Reported Baseline Liver Disease	Measured Outcome
Böhm et al. [16]	2023	Prospective	Multinational	5988	71.8 ± 9.3	55.4	N/A	5424 (90.5)	2938 (49)	N/A	N/A	ALP, ALT, AST, bilirubin, and albumin	LVEF > 40%	Patients with liver enzyme levels (AST or ALT) exceeding 3× ULN at screening were excluded	Hospitalization for heart failure, CV death and all-cause mortality
Cheng et al. [51]	2024	Retrospective	China	1258	66.2 ± 13.3	43.4	N/A	752 (59.7)	333 (26.4)	703 (55.8)	1 to 10 years	Albumin	LVEF ≥ 50%	Severe liver dysfunction (ALT or total bilirubin levels > 3× ULN) was an exclusion criterion	All-cause mortality
Cheng et al. [52]	2017	Prospective	Taiwan	870	75.8 ± 13.2	68	24.6 ± 5.0	982 (59)	619 (37)	496 (30)	31.5 ± 27.6 mo	Albumin	LVEF ≥ 50%	Patients with severe liver cirrhosis (Child-Pugh score B or C) were excluded	All-cause mortality
Chien et al. [53]	2019	Retrospective	Taiwan	1120	77.2	39.4	24.6 ± 0.2	808 (72.1)	548 (48.9)	381 (34.)	3.4 years	Albumin	LVEF ≥ 50%	Patients with diagnosed liver cirrhosis from any cause were excluded	Hospitalization for heart failure and all-cause mortality
Dalos et al. [49]	2019	Prospective	Austria	274	71.3 ± 8.4	30.7	30.5 ± 6.8	153 (55.8)	103 (37.6)	67 (24.5)	21.5 ± 18.6 mo	GGT, ALP, ALT, AST, bilirubin, and albumin	LVEF ≥ 50%	Patients with excessive alcohol intake were excluded, and all underwent a complete serologic assessment to rule out infectious, cholestatic, or autoimmune hepatic disorders	All-cause mortality, hospitalization for heart failure and composite of all-cause mortality and hospitalization for heart failure
Fuchida et al. [54]	2021	Retrospective	Japan	206	86	42	22.5 [19.6, 25.5]	134 (65)	52 (25)	43 (21)	10 mo	Albumin	LVEF ≥ 50%	N/A	Hospitalization for heart failure

Table 1 (continued)

Author	Year	Design	Location	No. of participants	Mean age (years)	Male (%)	Body mass index (kg/m2)	Hypertension (%)	Diabetes mellitus (%)	Ischemic heart disease (%)	Follow-up duration	Evaluated factor(s)	HFpEF Definition	Reported Baseline Liver Disease	Measured Outcome
Georgiopoulou et al. [18]	2018	Retrospective	United States	445	73	42.2	30.9 [26.1, 37.8]	404 (90.8)	194 (43.6)	194 (43.6)	2 years	Albumin	LVEF > 40% with no previous report of LVEF ≤ 40%	N/A	Composite of all-cause mortality and hospitalization for heart failure
Hoshida et al. [55]	2020	Prospective	Japan	552	81	46	N/A	447 (86.4)	194 (35.1)	118 (21.3)	1.4 year	Albumin	LVEF ≥ 50%	N/A	All-cause mortality
Liang et al. [5]	2021	Post-hoc	China	3445	N/A	N/A	N/A	N/A	N/A	N/A	N/A	ALP, ALT, AST and bilirubin	LVEF ≥ 45%	Patients with known chronic hepatic diseases (AST or ALT > 3× ULN) were excluded	Cardiovascular mortality, Hospitalization for heart failure and composite of cardiovascular mortality and Hospitalization for heart failure
Liu et al. [37]	2014	Retrospective	China	576	77 ± 10	36	23.3 [20.4, 26.6]	126 (90)	32 (22.9)	18 (12.9)	1 year	Albumin	LVEF ≥ 50%	N/A	All-cause mortality
Matsuo et al. [56]	2021	Retrospective	Japan	140	84	42.9	23.3 [20.4, 26.6]	126 (90)	32 (22.9)	18 (12.9)	1.9 year	Albumin	LVEF ≥ 50%	N/A	All-cause mortality
Nishino et al. [57]	2021	Prospective	Japan	541	86.1 ± 4.2	41.4	23.2 [20.7, 26.4]	461 (85.2)	162 (29.9)	N/A	1.38 ± 0.78 year	Albumin	LVEF ≥ 50%	N/A	Hospitalization for heart failure
Oeun et al. [58]	2022	Prospective	Japan	863	83	44.5	21.4 [19.0, 24.1]	737 (85.7)	291 (34.0)	152 (18.0)	11.4 mo	Albumin	LVEF ≥ 50%	N/A	Composite of all-cause mortality and hospitalization for heart failure
Pocock et al. [59]	2022	Prospective	Multinational	5988	71.8 ± 9.3	55.4	N/A	5424 (90.5)	2938 (49)	N/A	2.1 years	Albumin	LVEF > 40% with no previous report of LVEF ≤ 40%	N/A	All-cause mortality
Prenner et al. [36]	2020	Prospective	United States	118	N/A	N/A	N/A	107 (90.6)	73 (61.8)	40 (33.8)	57.6 mo	Albumin	LVEF > 50%	Subjects with a history of liver cirrhosis were excluded from the analysis	Composite of all-cause mortality and hospitalization for heart failure

Table 1 (continued)

Author	Year	Design	Location	No. of participants	Mean age (years)	Male (%)	Body mass index (kg/m2)	Hypertension (%)	Diabetes mellitus (%)	Ischemic heart disease (%)	Follow-up duration	Evaluated factor(s)	HFpEF Definition	Reported Baseline Liver Disease	Measured Outcome
Prenner et al. [60]	2019	Post-hoc	United States	3254	71	47.17	N/A	2982 (91.6)	1050 (32.2)	N/A	3.3 years	Albumin	LVEF ≥ 45%	N/A	MACE and Composite of all-cause mortality and hospitalization for heart failure
Saito et al. [50]	2021	Prospective	Japan	80	N/A	65	N/A	51 (63.7)	33 (41.2)	23 (28.7)	7.1 mo	GGT, ALT, AST, bilirubin, and albumin	LVEF ≥ 50%	Patients with chronic liver diseases (viral hepatitis, bile duct disease, cirrhosis, or hepatic tumors) were excluded	Hospitalization for heart failure and all-cause mortality
Shen et al. [61]	2021	Prospective	Multinational	4116	71.6	39.6	29.6 ± 5.3	3645 (88.6)	1128 (27.4)	2087 (50.7)	4.4 years	Albumin	LVEF ≥ 45%	N/A	All-cause mortality
Takae et al. [62]	2021	Prospective	Japan	504	71.6 ± 9.4	54.6	24.1 ± 3.6	394 (78.2)	156 (31)	N/A	38.4 mo	ALT and AST	LVEF > 50%	Patients with liver diseases (fatty liver, cirrhosis, hepatitis B or C) were excluded	Cardiovascular events
Zencirkiran et al. [63]	2019	Prospective	Turkey	285	68	45.5	N/A	208 (72.9)	71 (24.9)	63 (22.1)	12 mo	Albumin	LVEF ≥ 50%	N/A	Composite of all-cause mortality and hospitalization for heart failure

Data are presented as mean ± SD, median [Q1, Q3], or number (percent)

Abbreviations: ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transferase; LVEF: Left Ventricular Ejection Fraction; ULN: Upper Limit of Normal; N/A: Not Available; MACE: Major Adverse Cardiac Events; mo: Months; NYHA: New York Heart Association

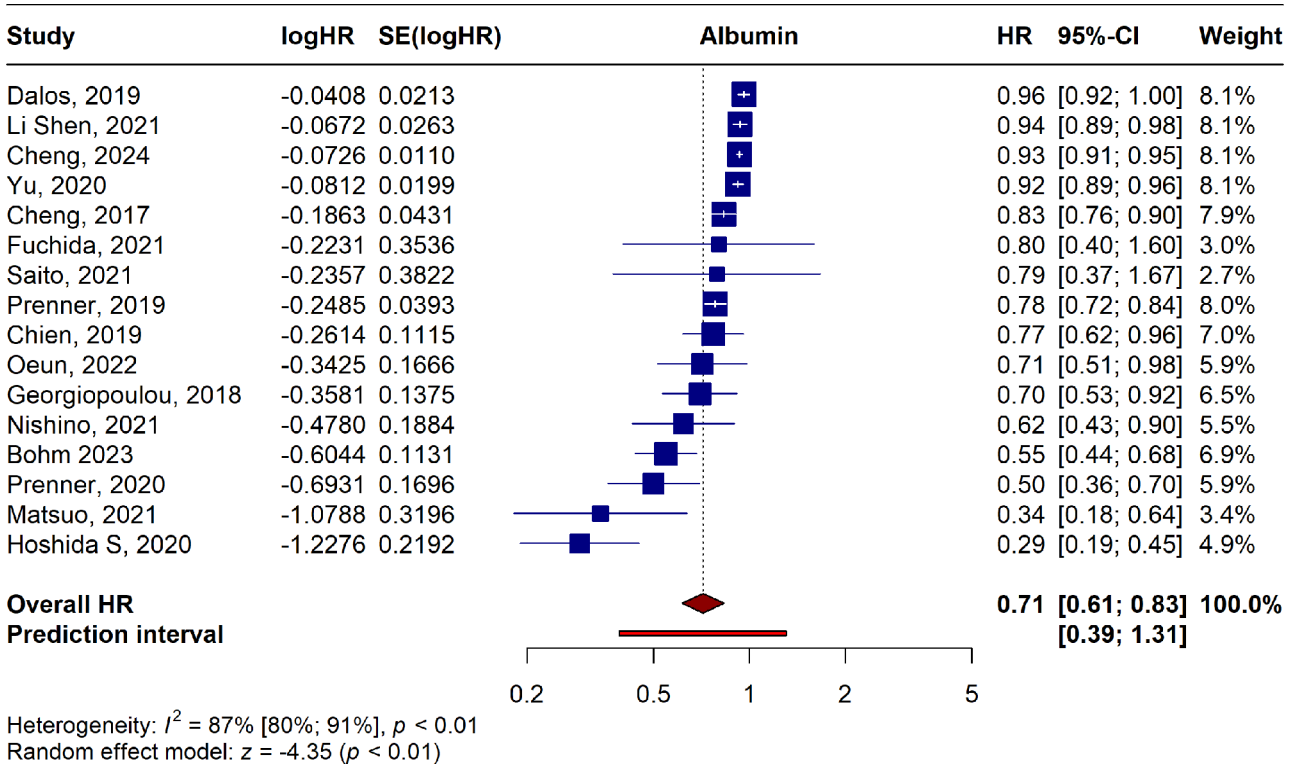


Fig. 2 Forest plot illustrating the pooled HR of serum albumin levels for the primary composite outcome in HFpEF patients, using a random-effects model

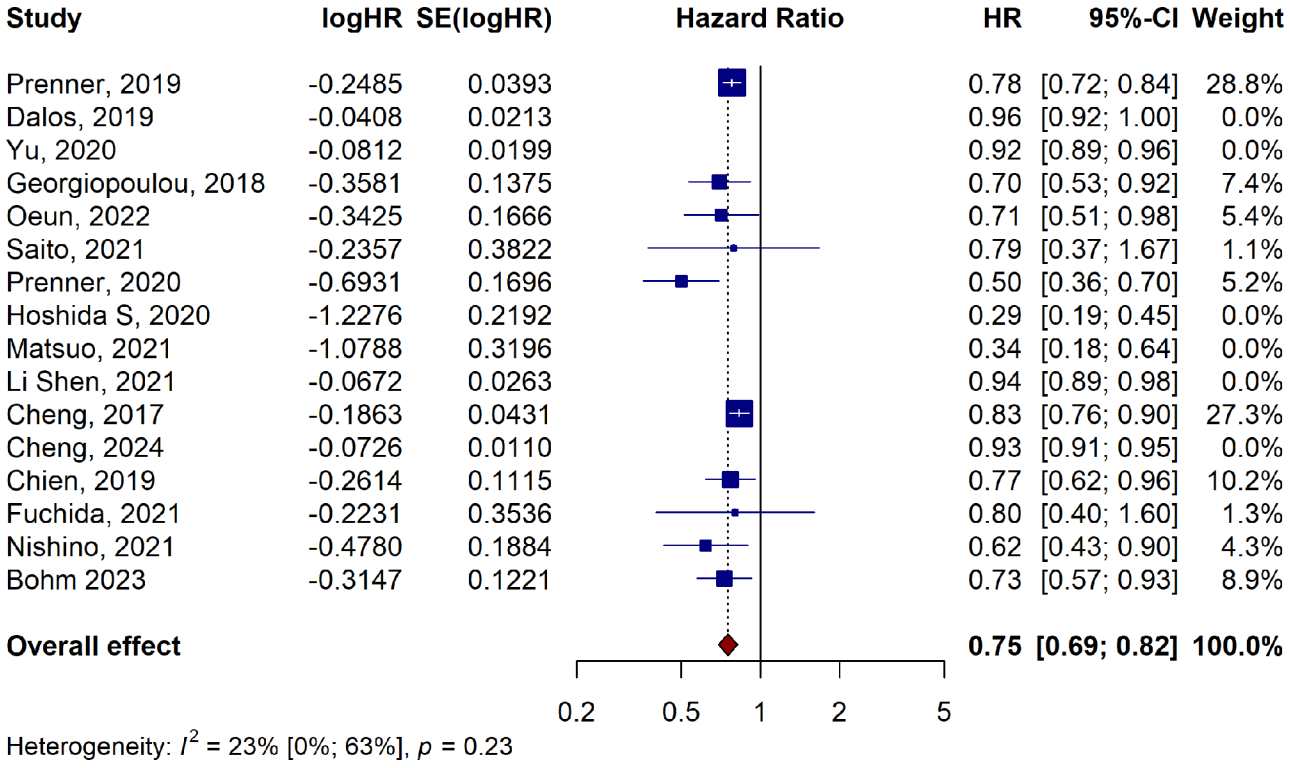


Fig. 3 Forest plot illustrating the pooled HR of serum albumin levels for the primary composite outcome in HFpEF patients after removing six outliers

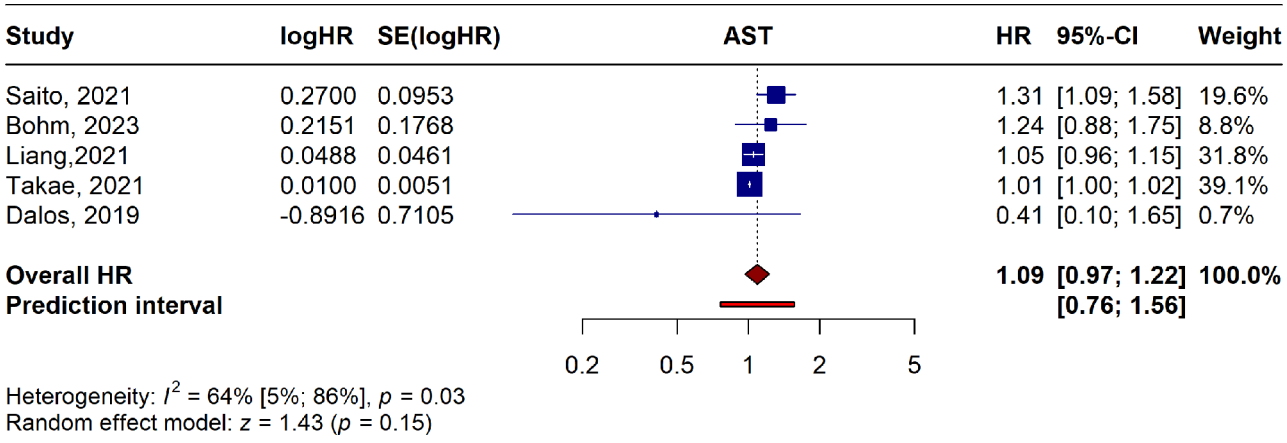


Fig. 4 Forest plot illustrating the pooled HR of AST levels for the primary composite outcome in HFpEF patients, using a random-effects model

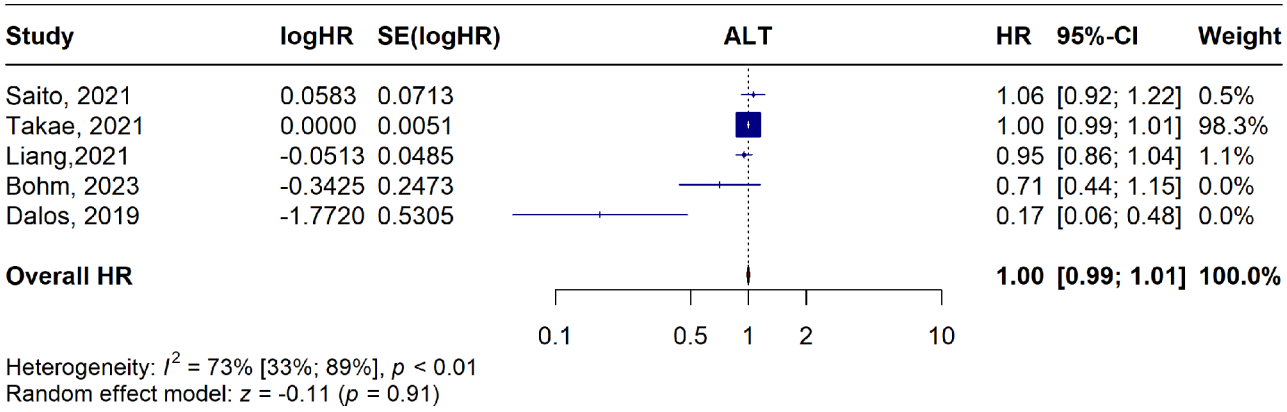


Fig. 5 Forest plot illustrating the pooled HR of ALT levels for the primary composite outcome in HFpEF patients, using a random-effects model

As demonstrated in Fig. 3, after removing six identified outliers— "Dalos, 2019," "Yu, 2020," "Hoshida S, 2020," "Matsuo, 2021," "Li Shen, 2021," and "Cheng, 2024"—the updated analysis included 10 studies. The pooled HR in this analysis was slightly higher at 0.75 (95% CI: 0.69 to 0.82), still showing a statistically significant association. Notably, heterogeneity among the studies decreased considerably, with I^2 reduced to 23.0% (95% CI: 0.0–62.5%), indicating much lower variability across the included studies. The heterogeneity test was non-significant ($p = 0.2311$), further suggesting that removing outliers substantially reduced the between-study variability. As illustrated in Supplemental Fig. S2, the LOO sensitivity analysis confirmed the robustness of the pooled HR of 0.73 (95% CI: 0.64 to 0.85) across all individual studies. Excluding any single study caused only minor changes to the overall effect size, with the HR remaining between 0.72 and 0.80. The study by "Hoshida S, 2020" had the most significant impact on overall heterogeneity. Omitting this study reduced the I^2 statistic from 84.3 to 79.5%, indicating a notable decrease in heterogeneity. As shown in Supplemental Fig. S3, Egger's test for funnel plot asymmetry yielded an intercept of -2.53 (95% CI: -3.57 to -1.48, $p = 0.0003$), suggesting the presence of asymmetry, which could indicate potential publication bias or other sources of bias in the meta-analysis.

AST

Figure 4 presents the meta-analysis using a random-effects model to address heterogeneity, incorporating data from 5 studies examining the association between AST levels and the primary outcome. The pooled HR was 1.09 (95% CI: 0.97 to 1.22), indicating no significant relationship between AST levels and the primary outcome. Moderate heterogeneity was noted, with an I^2 of 64% (95% CI: 5–86%, $p = 0.03$).

In Supplemental Fig. S4, the LOO sensitivity analysis revealed that excluding individual studies considerably impacted heterogeneity, with I^2 values ranging from 17.9 to 71.1%, depending on the omitted study. The pooled HR fluctuated between 1.01 and 1.15, though no exclusion resulted in a statistically significant change in the overall findings. This underscores the substantial influence of certain studies on the variability observed.

ALT

Figure 5 presents the meta-analysis, which applied a random-effects model to address heterogeneity, including 5 studies assessing the relationship between ALT levels and the primary outcome. The pooled HR was 1.00 (95% CI: 0.99 to 1.01), showing no significant association between ALT levels and the primary outcome. Significant heterogeneity was detected among the studies, with an I^2 of 73% (95% CI: 33–89%, $p < 0.01$).

The outlier analysis identified "Dalos, 2019" as an outlier. Upon excluding this study, the revised meta-analysis of 4 studies still yielded a non-significant pooled HR of 1.00 (95% CI: 0.99 to 1.01, $p = 0.93$). Heterogeneity dropped markedly, with I^2 reducing to 18.9% ($p = 0.30$), suggesting that "Dalos, 2019" contributed substantially to the variability.

Supplemental Fig. S5 illustrates the LOO analysis, which showed that removing individual studies had a significant impact on heterogeneity, with I^2 values ranging from 18.9 to 78.8%. Despite these fluctuations, none of the exclusions resulted in a statistically significant outcome. Excluding "Dalos, 2019" led to an HR of 1.00 (95% CI: 0.99 to 1.01) and I^2 of 18.9%, while omitting "Takae, 2021" increased heterogeneity (I^2 = 78.7%) and produced an HR of 0.69 (95% CI: 0.36 to 1.30). These results indicate that certain studies had a greater impact on the observed variability, but their exclusion did not change the overall non-significant findings.

ALP

As shown in Fig. 6, the meta-analysis utilized a random-effects model to account for heterogeneity and included 3 studies assessing the association between ALP levels and the primary outcome. The pooled HR was 1.38 (95% CI: 0.96 to 1.98), suggesting a non-significant association between ALP levels and the primary outcome. Substantial heterogeneity was observed, with an I^2 statistic of 82% (95% CI: 45–94%, $p < 0.01$). No outliers were detected in the random-effects model, reinforcing the consistency of the included studies in the meta-analysis.

As shown in Supplemental Fig. S6, the LOO sensitivity analysis demonstrated that heterogeneity varied significantly depending on the study omitted. Excluding "Liang, 2021" reduced heterogeneity to I^2 = 0% and resulted in an HR of 1.70 (95% CI: 1.35 to 2.15), indicating a stronger and significant association in the absence of this study. On the other hand, omitting "Dalos, 2019" resulted in a reduced HR of 1.36 (95% CI: 0.90 to 2.04), but heterogeneity remained high (I^2 = 90.6%). Excluding "Böhm, 2023" also reduced heterogeneity to 0%, with an HR of 1.12 (95% CI: 1.04 to 1.21). These results indicate that specific studies contributed substantially to the observed heterogeneity.

Bilirubin

Figure 7 illustrates the meta-analysis, which applied a random-effects model to account for heterogeneity, incorporating data from 5 studies examining the association between bilirubin levels and the primary outcome. The pooled HR was 1.11 (95% CI: 0.97 to 1.29), suggesting no statistically significant association between bilirubin levels and the primary outcome ($p = 0.14$). Substantial heterogeneity was observed, with an I^2 statistic of 83% (95% CI: 60–92%, $p < 0.01$).

No outliers were identified in the random-effects model, confirming the consistency of the included studies.

The LOO sensitivity analysis revealed significant changes in heterogeneity when individual studies were excluded. Omitting "Liang, 2021" reduced heterogeneity to I^2 = 0%, and the pooled HR increased to 1.70 (95% CI: 1.35 to 2.15), suggesting a significant association in the absence of this study. Similarly, excluding "Böhm, 2023" also reduced heterogeneity to I^2 = 0%, with an HR of 1.12 (95% CI: 1.04 to 1.21). Omitting "Dalos, 2019" resulted in an HR of 1.36 (95% CI: 0.90 to 2.04), though heterogeneity remained high (I^2 = 90.6%). These results demonstrate that certain studies contributed significantly to the observed heterogeneity (Supplemental Fig. S7).

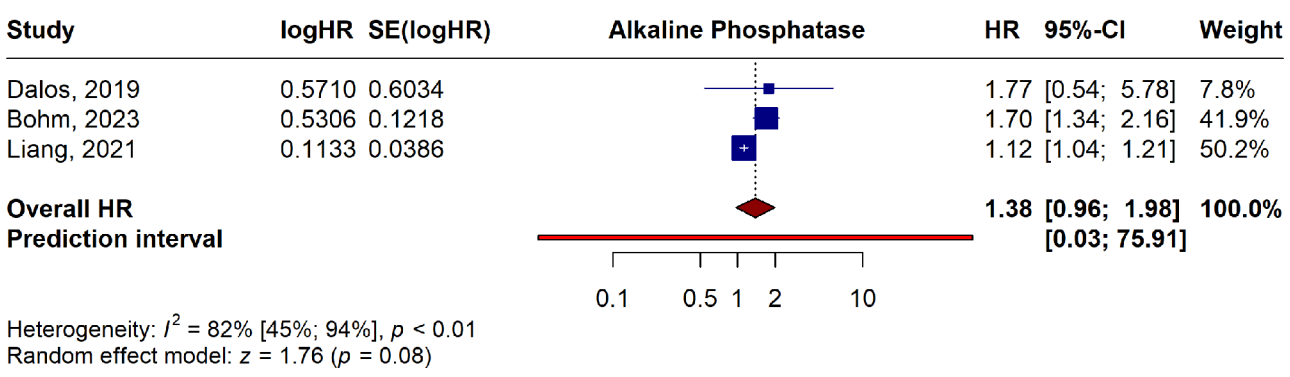


Fig. 6 Forest plot illustrating the pooled HR of ALP levels for the primary composite outcome in HFpEF patients, using a random-effects model

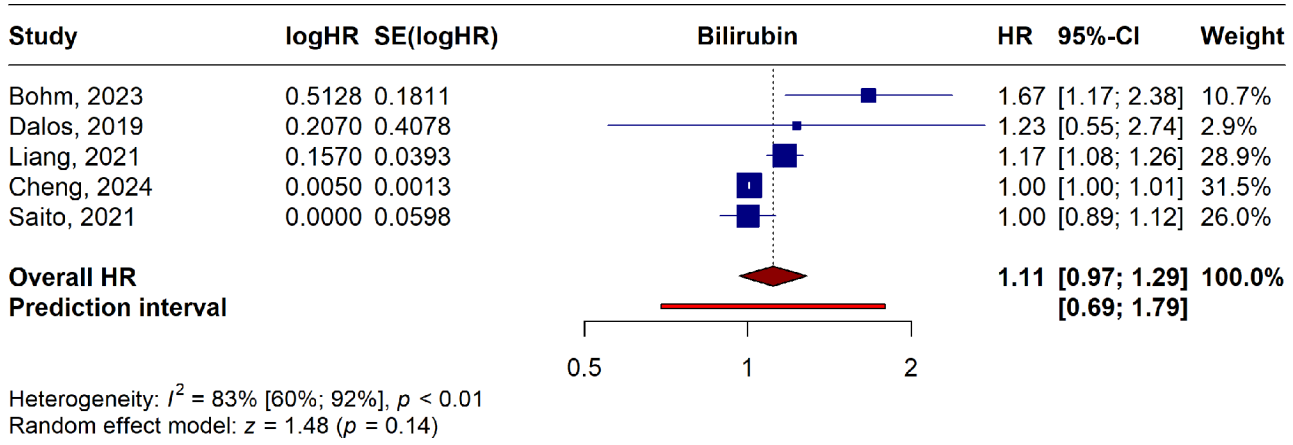


Fig. 7 Forest plot illustrating the pooled HR of bilirubin levels for the primary composite outcome in HFpEF patients, using a random-effects model

Discussion

This systematic review and meta-analysis sought to evaluate the prognostic significance of liver function markers, including serum albumin, bilirubin, AST, ALP, and ALT, in predicting mortality and morbidity in patients with heart failure with preserved ejection fraction. Through a comprehensive meta-analysis of 20 studies, our findings revealed that higher serum albumin levels have a significant protective effect against a range of adverse outcomes, including overall mortality, hospitalization, and major adverse cardiac events. This suggests that serum albumin may serve as a valuable prognostic marker in patients with heart failure with preserved ejection fraction. In contrast, other liver function markers, such as bilirubin, ALT, ALP, and AST, did not show any statistically significant prognostic value for predicting these adverse outcomes.

The interplay between liver function and HFpEF reflects a complex, bidirectional relationship influenced by systemic inflammation, congestion, and metabolic alterations including insulin resistance [20–24]. Zhang et al. demonstrated that liver stiffness (LS), a non-invasive marker of liver fibrosis and congestion, is significantly elevated in HFpEF patients, with more than two-thirds of their cohort showing LS values above the fibrosis threshold of 7.0 kPa. This elevation was closely correlated with left ventricular diastolic dysfunction, left ventricular hypertrophy, and right ventricular dysfunction, suggesting that LS mirrors the hemodynamic and structural abnormalities of HfpEF [8]. Mechanistically, the increased LS in HFpEF is likely driven by chronic venous congestion and endothelial dysfunction. Pulmonary hypertension, right ventricular hypertrophy, and increased central venous pressure further exacerbate hepatic congestion, while systemic endothelial dysfunction, a hallmark of HFpEF, may simultaneously promote liver fibrosis [25, 26]. The study also demonstrated that higher LS values were independently associated with worse short-term outcomes, such as increased hospitalizations and major adverse cardiovascular events (MACE), underscoring the prognostic value of LS as a stable indicator of long-term disease severity compared to dynamic markers like NT-proBNP [8]. Chronic inflammation further bridges liver dysfunction and HFpEF. Zhou et al. highlighted the role of metabolic dysfunction-associated fatty liver disease (MAFLD), a prevalent condition affecting 30% of adults, in exacerbating HfpEF [24]. The systemic low-grade inflammation characteristic of MAFLD, mediated by elevated levels of biomarkers such as high-sensitivity C-reactive protein (hs-CRP), contributes to myocardial remodeling and cardiomyocyte dysfunction [6, 21, 27–33]. Zhou et al. reported that patients with MAFLD and HFpEF exhibited a markedly increased risk of HF hospitalizations, with those in the highest hs-CRP quartile having a 4.4-fold higher adjusted risk compared to the lowest quartile. These findings support the hypothesis that systemic inflammation not only worsens liver function but also accelerates HFpEF progression by impairing myocardial compliance and promoting diastolic dysfunction. Furthermore, the prevalence of HFpEF among patients with MAFLD was estimated at 34%, emphasizing the importance of addressing metabolic and inflammatory mechanisms to mitigate adverse outcomes [24].

The primary finding of this study is that higher serum albumin levels offer protective benefits for patients with HFpEF by reducing the risk of a composite of adverse outcomes, including all-cause mortality, cardiovascular mortality, major adverse cardiac events (MACE), and hospitalization due to heart failure. Conversely, lower serum albumin levels are associated with an increased risk of these outcomes. Given the limited number of studies available for each specific outcome (all-cause mortality, MACE, and heart failure hospitalization), we pooled all studies together to calculate a single overall HR for each liver function marker, including albumin.

Each study contributed to only one outcome, ensuring no repetition, which allowed for a robust evaluation of the prognostic value of serum albumin.

Serum albumin serves as a direct biomarker of liver function, as it is exclusively synthesized by hepatocytes. The serum albumin concentration in the blood reflects the liver's ability to synthesize proteins, which can be compromised in the presence of liver dysfunction. In chronic liver conditions such as cirrhosis, reduced serum albumin levels or hypoalbuminemia are common and signal a decline in the liver's synthetic capacity. Additionally, hypoalbuminemia is often linked to systemic inflammation and malnutrition, both of which are prevalent in liver disease and may negatively influence the prognosis of patients with heart failure with preserved ejection fraction [5, 17].

This study primarily focuses on serum albumin as a marker of liver function and a prognostic marker in HFpEF, highlighting the critical role of liver function in these patients. Serum albumin levels tend to decrease in liver conditions such as cirrhosis, acute liver failure, and chronic hepatitis, and this decline may indicate worsening liver function with broader systemic implications, including on cardiovascular health. Liver dysfunction in HFpEF can trigger systemic inflammation and disrupt fluid balance, both of which can exacerbate heart failure symptoms. Moreover, systemic inflammation and malnutrition are often present in HFpEF, irrespective of liver function status, which can influence the albumin level [34, 35]. Therefore, the prognostic effect of albumin may arise from a combination of the detrimental effects of liver dysfunction, increased systemic inflammation, and malnutrition. So, serum albumin not only indicates liver function in patients with HFpEF, but may also serve as a marker for systemic inflammation and malnutrition regarding cardiac outcomes. However, further investigations are needed to assess the significance of each condition on the overall prognostic value of albumin [36, 37].

Multiple studies have focused on the prognostic significance of serum albumin in patients with HfpEF. In the study by Manolis et al., researchers examined 118 elderly patients with HFpEF to assess the prognostic significance of serum albumin. The study found that lower serum albumin levels were significantly associated with worse outcomes, including higher rates of mortality and complications. The patient population was particularly vulnerable due to advanced age, making the relationship between hypoalbuminemia and adverse outcomes more pronounced [38]. Similarly, the TOPCAT trial analysis by Prenner et al. included a large and diverse cohort of HFpEF patients, where serum albumin levels were again found to be a crucial predictor of adverse cardiovascular events, including heart failure hospitalization and death. The study demonstrated that despite adjusting for other clinical variables, low serum albumin remained an independent risk factor [17]. Additionally, studies have explored the link between serum albumin and specific pathophysiological features of HFpEF. Prenner et al. identified that lower serum albumin levels were associated with increased myocardial fibrosis and adverse pulsatile aortic hemodynamics, which are critical contributors to the disease's progression. This suggests that serum albumin may reflect underlying structural heart abnormalities, further establishing its role as a prognostic marker [36]. The prognostic value of serum albumin extends to heart failure with reduced ejection fraction (HFrEF), with similar findings observed across heart failure phenotypes. A retrospective cohort study of 8,246 patients hospitalized for acute heart failure demonstrated that hypoalbuminemia was a strong predictor of 30-day and 1-year mortality, regardless of the HF phenotype, including both HFrEF and HFpEF. Serum albumin levels below 3.4 g/dL were associated with a two-fold increase in 1-year mortality risk, highlighting its consistent prognostic significance across both phenotypes [39].

While the significant prognostic value of serum albumin in HFpEF is well-established [17, 36, 38], there is limited evidence on whether correcting low albumin levels provides clinical benefits in this population. Currently, no studies have specifically evaluated the impact of albumin supplementation in HFpEF patients. However, research in patients with acute decompensated heart failure (ADHF) has yielded inconclusive results [40–42]. A meta-analysis by Vincent et al. found no consistent evidence supporting albumin supplementation to improve outcomes in hypoalbuminemic HF patients, despite the recognized detrimental effects of hypoalbuminemia on mortality, morbidity, and hospitalization length [41]. Similarly, the PICNIC study subgroup analysis did not show a significant difference in outcomes between normoalbuminemic and hypoalbuminemic HF patients receiving nutritional intervention [42]. In a retrospective cohort study of 1038 ADHF patients, albumin supplementation did not show any advantage in reducing the primary endpoint, which included intubation, emergency renal replacement, or mortality [40]. Taken together, these findings underscore the need for further randomized trials to assess the clinical utility of albumin supplementation, not only in ADHF but also in HFpEF, where data remain scarce.

Beyond heart failure with preserved ejection fraction, serum albumin has been studied extensively as a prognostic marker in various cardiovascular diseases, further validating its clinical significance. In coronary artery disease (CAD), lower serum albumin levels have been associated with a significantly increased risk of adverse cardiovascular outcomes. For instance, patients with low serum albumin levels tend to have higher mortality rates and a greater incidence of MACE, including

myocardial infarction and stroke [43]. Similarly, lower serum albumin levels are linked to poorer outcomes in patients undergoing PCI, including higher rates of MACE. Wada et al. found that among 2,860 patients with coronary artery disease undergoing PCI, lower pre-procedural serum albumin was independently associated with increased long-term MACE risk, including all-cause death and acute coronary syndrome [44]. Shiyovich et al. also showed that post-PCI declines in serum albumin predicted worse long-term outcomes, highlighting the importance of monitoring albumin levels pre- and post-PCI [45].

Several studies have explored the prognostic value of AST, ALT, ALP, and bilirubin levels in patients with various types of heart failure other than HFpEF, yielding mixed results. A recent study from the TOPCAT trial investigated liver function test values, specifically AST, ALT, ALP, and total bilirubin, in patients with HFpEF and without chronic hepatic diseases. The findings suggested that elevated levels of total bilirubin and ALP were significantly associated with increased risks of adverse outcomes, including cardiovascular mortality and hospitalization for heart failure, whereas AST and ALT did not exhibit prognostic significance [5]. Another study from the DAPA-HF trial analyzed liver function tests, including AST, ALT, and bilirubin, in patients with HFrEF and found that total bilirubin and ALP levels were associated with higher risks of adverse outcomes, such as cardiovascular death and hospitalization for heart failure. However, AST and ALT were not found to have significant prognostic value in this cohort [46]. Another study focusing on patients with acute decompensated heart failure (ADHF) reported that elevated total bilirubin was significantly associated with adverse outcomes, such as increased mortality and rehospitalization rates. However, like the previous study, AST and ALT did not show a significant association with clinical outcomes in this context, further suggesting their limited utility as prognostic markers in heart failure scenarios [47]. In our study, although all of these markers (except for ALT, where the HR was 1) showed a very slight worsening effect on the prognosis of HFpEF patients, none were statistically significant. It is important to note that the number of included studies was very limited, and the weight distribution of the included studies, especially for markers like ALT, was highly uneven. These factors likely contributed to the statistically insignificant pooled results. ALT and AST patterns are more commonly associated with left-sided forward failure, which is more characteristic of HFrEF [48]. In contrast, HFpEF is typically associated with chronic venous congestion and liver dysfunction, which are better reflected by cholestatic markers such as bilirubin and ALP [48]. These differences in the underlying hemodynamic changes of HF phenotypes may explain the limited utility of AST and ALT as prognostic markers in HFpEF and further account for the statistically insignificant results in our study.

Although GGT was not included in our meta-analysis due to the limited number of studies reporting its outcomes, two included studies provided valuable insights into its prognostic significance in HfpEF [49, 50]. In a prospective study by Dalos et al., elevated serum GGT levels were independently associated with adverse outcomes, including heart failure hospitalization and all-cause mortality (HR 1.002, $p = 0.004$). Patients with GGT levels above 36 U/L had significantly higher event rates (log-rank $p = 0.012$), and multivariable logistic regression linked elevated GGT to both left- and right-sided cardiac alterations, such as increased right atrial pressure and larger right atrial diameter [49]. Similarly, Saito et al. demonstrated a significant association between GGT and the composite outcome of all-cause mortality and rehospitalization for worsening HF. Univariate Cox proportional hazard analysis revealed that every 10 U/L increase in GGT was associated with a 1.11-fold increased risk of this composite outcome (HR 1.11, 95% CI: 1.04–1.18, $p = 0.001$) [50]. These findings suggest that GGT may serve as a useful biomarker for predicting poor outcomes in HfpEF. Despite these promising results, the limited number of studies highlights the need for further research to validate the role of GGT in HFpEF prognostication.

Limitations

This study has several limitations that should be acknowledged. First, the number of studies available for each outcome and each liver function marker, such as AST, ALT, ALP, and bilirubin, was limited. This scarcity of data restricted our ability to draw robust conclusions about the prognostic value of these markers, especially when compared to serum albumin, which had more substantial evidence supporting its role. Second, the included studies lacked detailed data, preventing us from performing subgroup analyses based on categorical levels of the markers. This limitation further restricted our ability to fully understand how these markers might influence outcomes in HFpEF patients over different timeframes or at varying levels.

Third, high heterogeneity rates were observed across the results of the included studies, with I^2 values reaching as high as 87%. This significant heterogeneity reduces the reliability and generalizability of our findings, reflecting differences in study populations, inclusion criteria, comorbid conditions (e.g., diabetes, obesity, chronic kidney disease), and treatment regimens (e.g., diuretics, RAAS inhibitors, SGLT2 inhibitors). Additionally, variability in biomarker measurement methods and statistical adjustments across studies may have introduced

measurement bias, further contributing to the observed heterogeneity. While sensitivity analyses helped mitigate some of this variability, the initial heterogeneity underscores the need for cautious interpretation of the results. The studies themselves often cited potential reasons for these discrepancies, suggesting that the complex and not yet fully understood relationship between HFpEF and liver function markers like AST, ALT, ALP, and bilirubin may contribute to these variations.

Fourth, only 9 of the included studies explicitly reported baseline liver diseases, while the remaining 11 did not provide this information. Among those that did report, patients with significant liver dysfunction—such as liver tests threefold above the upper limit of normal, severe liver cirrhosis (Child-Pugh B or C), or chronic liver disease like hepatitis—were excluded. This lack of consistent reporting introduces a potential source of heterogeneity and selection bias, as we cannot determine whether subclinical or undiagnosed liver conditions were present in the populations of the remaining studies. This variability may have influenced the interpretation of liver function markers as prognostic tools in HFpEF.

Conclusion

In conclusion, this systematic review and meta-analysis highlights the significant prognostic value of serum albumin in predicting adverse outcomes in patients with HFpEF. Higher serum albumin levels were consistently associated with a reduced risk of overall adverse events, suggesting that serum albumin could serve as a valuable biomarker in the management of HFpEF. In contrast, other liver function markers, such as bilirubin, AST, ALT, and ALP, did not demonstrate consistent prognostic significance in this population, indicating their limited utility as predictors of adverse outcomes in HFpEF.

These findings underscore the importance of serum albumin as a key indicator of both liver function and overall prognosis in HFpEF. Future research should focus on large, well-designed prospective studies to confirm the prognostic value of liver function markers in HFpEF patients. These studies should aim to standardize biomarker measurement protocols, ensuring uniform cut-off values and assay methods across different cohorts. Additionally, more research is needed to determine whether longitudinal changes in liver function markers provide incremental prognostic value beyond baseline measurements. Further investigations should explore whether specific subgroups of HFpEF patients—such as those with different comorbid profiles (e.g., metabolic syndrome, renal dysfunction)—exhibit distinct prognostic patterns based on liver function biomarkers. Finally, multi-marker approaches combining liver function biomarkers with established HF risk predictors (e.g., NT-proBNP, echocardiographic parameters) should be explored to enhance prognostic stratification in HFpEF. Such studies could strengthen the clinical utility of liver function markers in risk assessment and decision-making for this challenging patient population.

Abbreviations

HFpEF	Heart Failure With Preserved Ejection Fraction
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
GGT	Gamma-Glutamyl Transferase
MACE	Major Adverse Cardiac Event
NAFLD	Non-Alcoholic Fatty Liver Disease
CAD	Coronary Artery Disease
PCI	Percutaneous Coronary Intervention
HFrEF	Heart Failure With Reduced Ejection Fraction
ADHF	Acute Decompensated Heart Failure
HR	Hazard Ratio
LVEF	Left Ventricular Ejection Fraction
LS	Liver Stiffness
MAFLD	Metabolic Dysfunction-Associated Fatty Liver Disease

Supplementary Information

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Supplementary Material 1

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Author contributions

P. D. conceptualized the study, collected data, and drafted the manuscript. M. M. collected data, conducted statistical analysis for the meta-analysis, and contributed to data interpretation. H. S., MS. N., R. NJ., M. D., and S. A. M. were involved in data collection, quality assessment of included studies, and writing and editing the manuscript. K. H. provided expert consultation on systematic review methodology, meta-analysis, and heart failure management. M. T. served as the principal investigator, supervised the entire project, developed the systematic review protocol, ensured methodological rigor, and was responsible for the final approval of the manuscript.

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Data availability

This study is a systematic review and meta-analysis, relying on data already provided by previously published studies. All datasets and materials used in this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable. This study is a systematic review and meta-analysis that utilized previously published and peer-reviewed material. Therefore, no ethical approval or consent to participate was required.

Consent for publication

Not applicable. As this study relied solely on previously published data, no individual person's data, images, or videos were included that would require consent for publication.

Competing interests

The authors declare no competing interests.

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