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RESEARCH ARTICLE

Liver tests, cardiovascular outcomes and effects of empagliflozin in patients with heart failure and preserved ejection fraction: The EMPEROR-Preserved trial

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Aim

The prognostic implication of elevated liver tests in heart failure with preserved ejection fraction (HFpEF) is uncertain. This analysis investigates the association of liver markers with hospitalization for heart failure (HHF) and cardiovascular death (CVD), and the treatment effect of empagliflozin across the range of liver marker levels.

Methods and results

The double-blind, placebo-controlled EMPEROR-Preserved (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure with Preserved Ejection Fraction) enrolled 5988 patients with HFpEF (ejection fraction >40%). Patients in New York Heart Association class II–IV and elevated N-terminal pro-B-type natriuretic peptide were randomized to receive empagliflozin 10 mg daily or placebo in addition to usual therapy. Patients with significant liver disease were excluded. The primary endpoint was time to first adjudicated HHF or CVD. We explored the association of liver function abnormalities with heart failure outcomes in patients on placebo, the effects of empagliflozin on liver tests and the treatment effects of empagliflozin on heart failure outcomes across categories of liver laboratory values. High alkaline phosphatase (p trend < 0.0001), low albumin (p trend < 0.0001) and high bilirubin ($p = 0.02$) were associated with poorer outcomes for HHF or CVD, while high aspartate aminotransferase was not, and high alanine aminotransferase was associated with better outcomes. Empagliflozin had no significant effects on liver tests compared to placebo except for albumin which was significantly increased. The treatment effect of empagliflozin on outcomes was not modified by liver tests.

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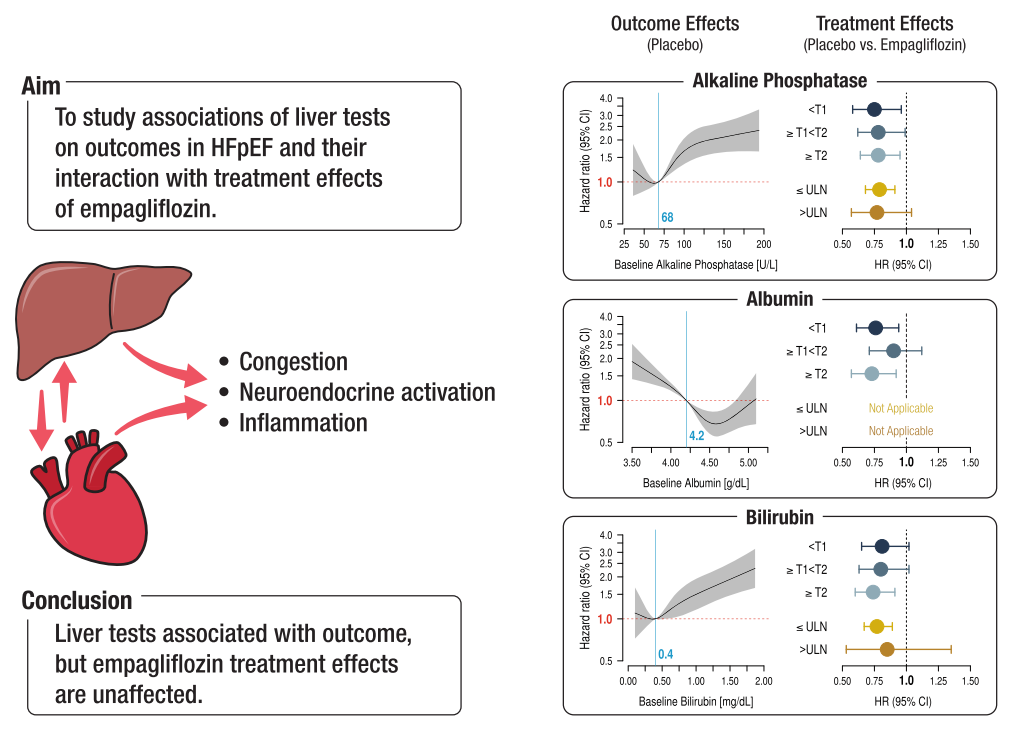
Conclusion Abnormalities of liver function tests are associated differently with heart failure outcomes. Salutary effects of empagliflozin on liver tests were not observed although albumin increased. The treatment benefits of empagliflozin were not affected by baseline values of liver parameters.

Graphical Abstract



Liver parameters and outcomes in heart failure. CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; ULN, upper limit of normal.

Keywords Heart failure • Heart failure with preserved ejection fraction • Liver steatosis • Liver fibrosis • SGLT2 inhibitors • Empagliflozin

Introduction

Liver markers are frequently abnormal in patients with heart failure.[1–3] There are robust observations in acute and chronic heart failure,[4] but data specifically in heart failure with preserved ejection fraction (HFpEF) are sparse.[5] Liver marker abnormalities are suggested to be due to hypoperfusion and congestion[2,3,6,7] and are sensitive to decongestion.[8] Neuroendocrine activation in liver disease can promote pathological cardiovascular phenotypes mediated by changes in inflammation, oxidative stress, autonomic dysregulation, and endothelial dysfunction.[9] These close and complex interactions suggest that pathological liver parameters could have an important impact on outcomes in patients with heart failure. A recent report showed[4] that increased markers of liver disease are negatively associated with outcomes in chronic heart failure and can be improved by sacubitril/valsartan. Dapagliflozin did not change liver markers, specifically bilirubin, which was associated with poorer outcomes.[10] HFpEF is associated with various non-cardiac comorbidities,[11] among them obesity and metabolic disease.[12,13] Current guidelines recommend (class IA) sodium–glucose cotransporter 2 (SGLT2) inhibitors for the treatment of heart failure with reduced ejection fraction (HFrEF)[14,15] since they reduced cardiovascular death (CVD) and hospitalization for heart failure (HHF) in HFrEF.[16,17] In HFpEF, empagliflozin reduced the composite of HHF and CVD.[18] The recent American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines recommend empagliflozin for the treatment of HFpEF (class IIa).[15] In the current study, we assessed the interaction of liver markers on heart failure outcomes as well as on the treatment effect of empagliflozin across the spectrum of liver pathologies in HFpEF.

Methods

Study design

The design and results of the EMPEROR-Preserved trial encompassing 5988 patients have been published previously.[18,19] The ethics committees of each of the participating institutions approved the protocol and all patients gave written informed consent. The registration identifier at ClinicalTrials.gov is NCT03057951.

Study patients and procedures

Patients with heart failure and ejection fraction >40% were screened and those fulfilling all eligibility criteria were randomized double-blind in a 1:1 fashion to receive placebo or empagliflozin 10 mg daily in addition to their usual therapy for heart failure. Patients with or without diabetes were enrolled. The potential for drug-induced liver injury by SGLT2 inhibitors has been continuously monitored by the sponsors and regulators. Therefore, patients with liver tests threefold above the upper limit of normal (3×ULN) at screening were excluded. During follow-up, all accompanying treatments could be altered or initiated according to the changes in the clinical status of the patients at the discretion of the investigator. Patients were assessed at screening and at all clinic follow-up study visits for major outcomes, vital signs, laboratory values including liver values and estimated glomerular filtration rate (eGFR) by the Chronic Kidney Disease Epidemiology Collaboration equation, adverse events and changes in medications or in clinical status that reflected changes in the course of heart failure. All randomized individuals were followed for the occurrence of pre-specified outcomes for the entire duration of the trial regardless of whether the study participants had taken the study medication or were adherent with the study procedures according to the intention-to-treat principle.

Liver tests

Direct and indirect liver tests including alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and albumin were measured in validated laboratories at baseline and at follow-up visits. Liver parameters at baseline were assessed in the overall population, which was then divided into subgroups according to tertiles and normal or pathological values according to the reference values. We studied the risk for the primary endpoint across these subgroups treated with placebo to assess whether liver tests are associated with heart failure events. Next, we evaluated the effects of empagliflozin compared with placebo on liver markers. Finally, we compared the effects of empagliflozin versus placebo on the primary endpoint across tertiles and for normal versus elevated values of liver markers. Additionally, we explored separately patients with increased total bilirubin and increased levels of unconjugated bilirubin in the absence of any other liver diseases versus increased total bilirubin but no increase in unconjugated versus normal bilirubin, as this constellation could reflect Gilbert's syndrome, which could confound the association.

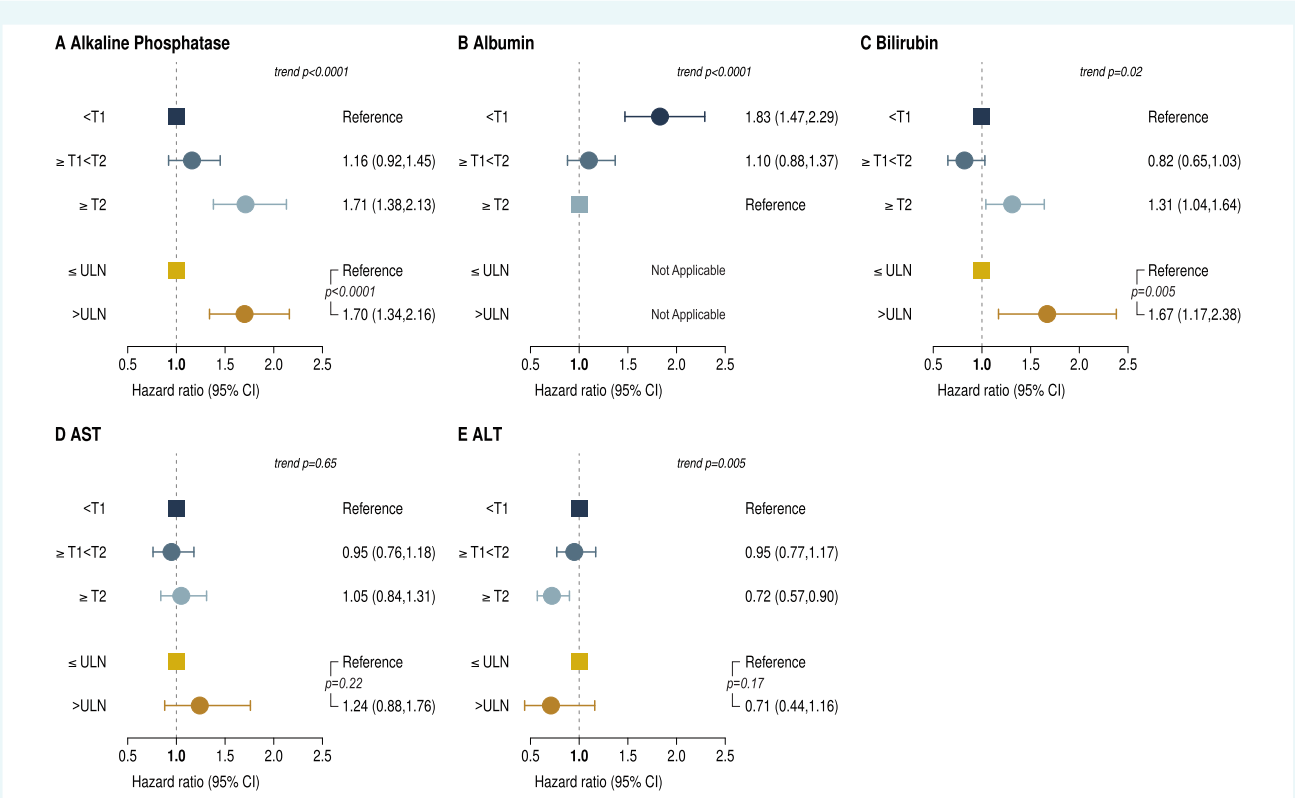


Figure 1 Hazard ratio for the primary outcome within placebo according to tertiles (above) and groups of upper and lower or normal values (below) for alkaline phosphatase (*A*), albumin (*B* – only tertiles), bilirubin (*C*), aspartate aminotransferase (AST), and (*D*) alanine aminotransferase (ALT) (*E*). CI, confidence interval; T, tertiles; ULN, upper limit of normal.

Outcome measures

The primary endpoint was the composite of time to first adjudicated HHF or CVD. In addition, we assessed time to first HHF, CVD and all-cause mortality in the context of patients with elevated bilirubin (see below).

Statistical analyses

For the association of liver tests with outcomes and treatment effects of empagliflozin across liver test categories, Cox proportional hazard regression models with pre-specified covariates of age, sex, geographical region, diabetes status at baseline, left ventricular ejection fraction and eGFR at baseline were used. To account for non-linear relationships, the association between hazard and liver tests as continuous variable was analysed non-parametrically using restricted cubic splines allowing for non-linear relationships. Four knots (5th, 35th, 65th, and 95th percentile of baseline values) were chosen for the analysis. Hazard ratios (HR) and 95% confidence bands were displayed using the 33.3th percentile (T1) as reference (HR = 1). The interaction between liver tests and treatment groups on the occurrence of the pre-specified outcomes was tested using a treatment-by-value interaction term (trend test assuming a linear order across the tertiles). Changes in liver tests were analysed in a mixed model with repeated measures (MMRM). The MMRM models included the same covariates as the Cox model with baseline and baseline-by-visit interaction in addition. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). All reported p-values are 2-sided and $p < 0.05$ was considered as statistically significant in all cases. No adjustments for multiple testing were made due to the exploratory nature of the study.

Role of the funding source

EMPEROR-Preserved was funded by Boehringer Ingelheim and Eli Lilly. The executive committee designed the protocol and identified clinical sites in collaboration with the sponsor. The sponsor was responsible for collection, monitoring and analysis of the data. The manuscript was written by the lead author with contributions from the co-authors.

Results

Change of liver tests by empagliflozin

A total of 5988 patients were randomly assigned to receive either empagliflozin (2997 patients, 10 mg once daily) or placebo (2991 patients).

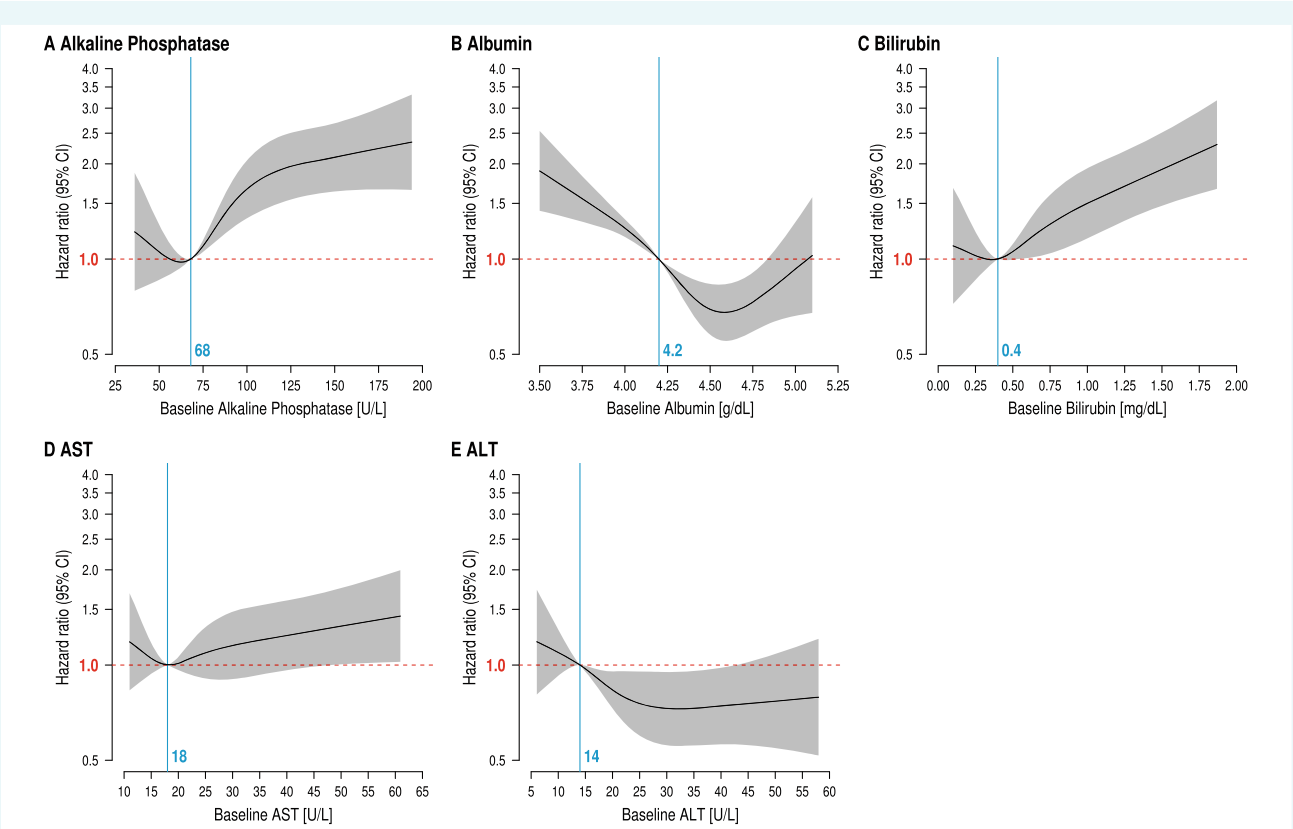


Figure 2 Outcome according to alkaline phosphatase (*A*), albumin (*B*), bilirubin (*C*), aspartate aminotransferase (AST) (*D*), and alanine aminotransferase (ALT) (*E*) as continuous variables. Hazard ratios for the primary endpoint (cardiovascular death and heart failure hospitalization) within placebo are given according to the above mentioned parameters (reference [HR = 1] at T1). Normal ranges: ALT [U/L]: 0–33 (F), 0–41 (M); AST [U/L]: 0–31 (F), 0–37 (M); total bilirubin [mg/dl]: 0.298197–1.2 or 1.22787 (F and M); alkaline phosphatase [U/L]: 35–104 (F), 40–129 (M); albumin [g/dl]: 3.5–5.2 (F and M). CI, confidence interval; F, females; M, males; T, tertile.

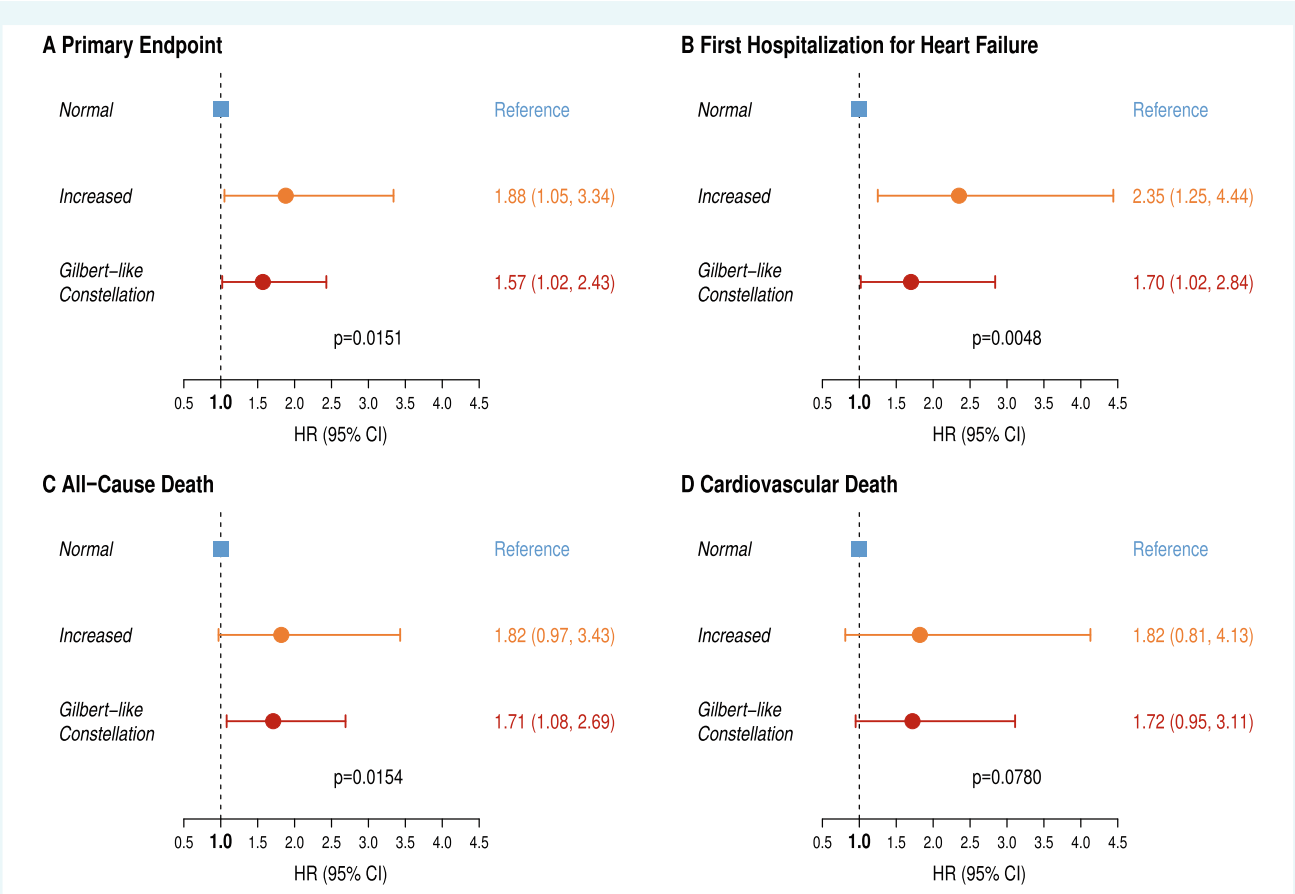


Figure 3 Hazard ratio (HR) for the primary endpoint (*A*), first hospitalization for heart failure (*B*), all-cause death (*C*) and cardiovascular death (*D*) for patients with normal bilirubin levels and increased bilirubin levels separated by a Gilbert-like constellation (increase of unconjugated bilirubin) within placebo. CI, confidence interval.

Online supplementary *Table S1* shows the demographic baseline characteristics across the tertiles of liver function tests. Patients with higher ALP, bilirubin, and AST had higher New York Heart Association (NYHA) functional classification and median N-terminal pro-B-type natriuretic peptide (NT-proBNP), while there was an inverse association with albumin and ALT (online supplementary *Table S1*). As this trial excluded patients with elevated liver values, the minority of patients had values greater than ULN at baseline, placebo/empagliflozin for AST (6.1/6.4%), ALT (4.9/4.9%), ALP (13.0/13.4%), bilirubin (4.9/5.6%), albumin (0.2/0.2%) (data not shown).

High ALP, high bilirubin and low albumin in the third tertile or when levels were above the normal range were associated with higher event rates for the primary outcome (*Figure 1A–C*). No such associations were detected for AST (*Figure 1D*), while high ALT associated with better outcomes (*Figure 1E*). Cubic splines summarize the association of ALP, albumin and bilirubin with poorer outcomes (*Figure 2A–C*). AST (*Figure 2D*) was not associated, while ALT was associated with slightly less primary outcomes (*Figure 2E*).

When assessing patients with increased total and increased unconjugated bilirubin (Gilbert-like constellation), we found that the association with bilirubin with outcomes was similar for the primary endpoint (*Figure 3A*), first HHF (*Figure 3B*), all-cause death (*Figure 3C*) and CVD (*Figure 3D*) regardless of which fraction of bilirubin was increased, indicating that this constellation had no meaningful effects on the bilirubin–outcome association.

We explored the treatment effect of empagliflozin compared to placebo on change in liver parameters. There were no meaningful changes of empagliflozin (vs. placebo) for ALP (*Figure 4A*), bilirubin (*Figure 4C*), and AST (*Figure 4D*). For ALT, there were some minor changes, which should not be considered clinically meaningful (*Figure 4E*). There was a statistically significant effect from week 4 to week 120 for empagliflozin to increase albumin levels (*Figure 4B*), regarded as not clinically meaningful changes. The statistical tests are summarized in online supplementary *Table S2*.

Finally, we explored whether liver tests had an impact on the treatment effect of empagliflozin. The results of the primary endpoint are shown in *Figure 5*. There was no heterogeneity of the treatment effect of empagliflozin at different tertiles of ALP (p trend = 0.75), albumin (p trend = 0.87), bilirubin (p trend = 0.54), AST (p trend = 0.88) and ALT (p trend = 0.17). This relates also for all parameters when values below or above ULN were compared. Also a constellation-like characteristic for Gilbert's

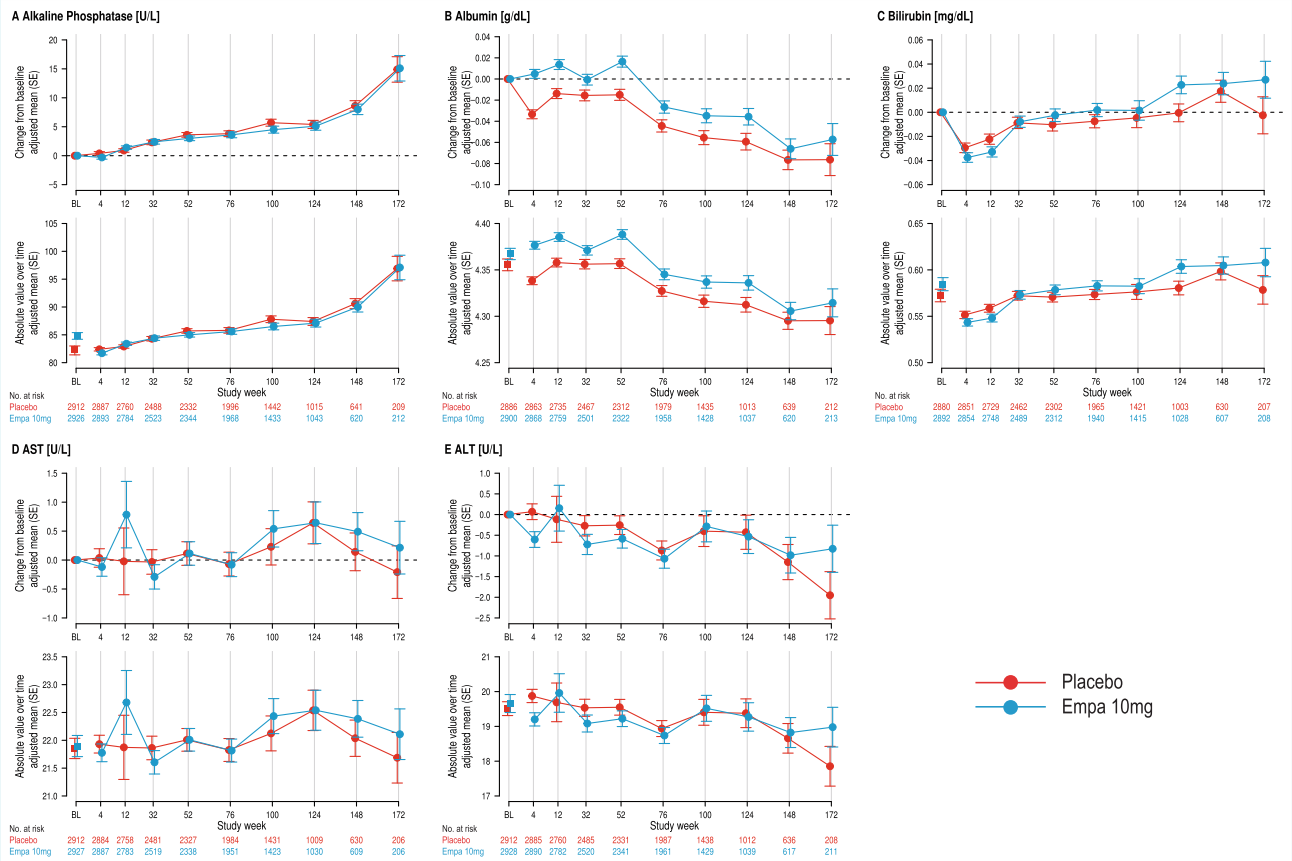


Figure 4 Change from baseline (upper panels) and absolute values (lower panels) for alkaline phosphatase (*A*), albumin (*B*), bilirubin (*C*), aspartate aminotransferase (AST) (*D*), and alanine aminotransferase (ALT) (*E*). SE, standard error.

syndrome did not change the outcome effect of empagliflozin (*Figure 6*).

Discussion

In this analysis from the EMPEROR-Preserved trial, we showed that high ALP and bilirubin and low albumin were associated with high risk for heart failure outcomes in patients with HFpEF, while high ALT was associated with better outcomes. AST was not associated with outcomes. Empagliflozin did not meaningfully change liver tests and the treatment effect of empagliflozin on the primary outcome was not modified by liver tests (*Graphical Abstract*).

Heart failure and liver disease often co-exist with ischaemia and congestion leading to subsequent fibrosis.[20,21] Alongside with heart failure-induced liver damage, non-cardiovascular comorbidities such as metabolic disease and diabetes with obesity and the effect of several drugs[21] are acting in concert resulting in pathologic-hepatic phenotypes. The latter conditions are more prevalent in HFpEF.[10,11]

Liver values are frequently elevated in patients with HFrEF as reported in trials such as DAPA-HF,[10] PARADIGM-HF[4] and CHARM,[22] but in particular in patients with acute heart failure.[6] Many of these factors associate with cardiovascular outcomes such as bilirubin, which is most frequently elevated.[10] This report extends those findings by investigating the association of liver tests with outcomes in a population with HFpEF. Similarly, bilirubin, ALP and low albumin are associated with poorer outcomes. This might be a reflection of haemodynamic compromising such as right-sided congestion, which has been shown to affect liver function and outcomes.[23–25] This is strengthened by the association of tertiles of liver function tests with NT-proBNP and eGFR. Interestingly, ALT was associated with better prognosis, but influence from non-captured conditions like nutrition, liver perfusion, liver conditions such as fatty liver contribution, remains unanswered. Further studies exploring liver status with advanced technologies such as transient elastography or liver biopsy could solve this interesting association. However, similar findings have been reported previously from the TOPCAT study[5] and from the real-world VA Palo Alto Health Care System.[26]

As empagliflozin improved heart failure outcomes, we set out to explore the effects of empagliflozin in HFpEF on liver parameters. Given the fact that SGLT2 inhibitors increase water and sodium excretion and might lead to volume contraction, we only saw an increase over time of albumin at some time

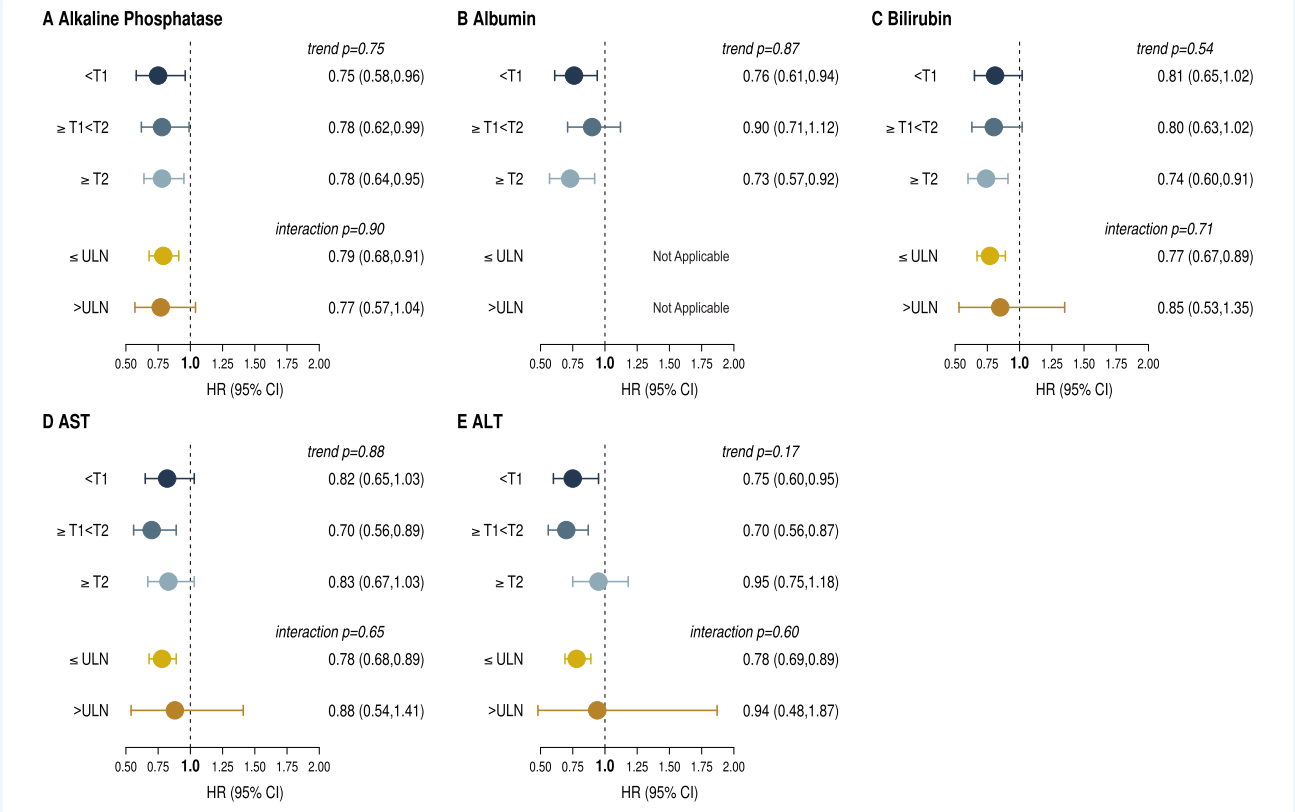


Figure 5 Hazard ratio (HR) for the treatment effect of empagliflozin according to tertiles (above) and groups of upper and lower or normal values (below) of alkaline phosphatase (*A*), albumin (*B*), bilirubin (*C*), aspartate aminotransferase (AST) (*D*), and alanine aminotransferase (ALT) (*E*). CI, confidence interval; T, tertiles; ULN, upper limit of normal.

points but not a reduction of other liver parameters such as bilirubin. This is in agreement with the suggestion that the diuretic effect of empagliflozin is transient and weak in stable chronic heart failure and not strong enough to significantly reduce atrial pressures after 3 months of treatment.[23] Nevertheless, in acute heart failure the situation might be different with a significant improvement in symptoms of congestion as shown in the EMPULSE trial.[8]

Elevated bilirubin is the most prevalent pathological liver marker in heart failure,[9] but might also serve as a biologically active agent. In a condition referred to as Gilbert's syndrome, individuals suffer from mild bilirubinaemia caused by reduced activity of the enzyme UDP-glucuronosyltransferase, which is responsible for the glucuronidation of bilirubin.[27] As unconjugated bilirubin and increased total bilirubin levels in the absence of liver disease could exhibit protective effects on cardiovascular diseases,[28,29] we did a sensitivity analysis in patients in whom this constellation was observed. However, we did not find a different association of bilirubin elevation with a Gilbert's syndrome-like constellation with the primary outcome. Interestingly, empagliflozin did not change serum concentrations of bilirubin in this population unlike sacubitril/valsartan in the PARADIGM-HF study.[4] This might be due to the fact that decongestion as judged from NT-proBNP was stronger with sacubitril/valsartan compared with SGLT2 inhibitors.[30,31]

Finally, we observed that liver values did not influence the magnitude of effects of empagliflozin on HHF or CVD. Therefore, empagliflozin can be used in HFpEF patients independently of slightly elevated (<3× ULN) liver parameters.

Limitations

This is a post-hoc analysis of EMPEROR-Preserved. Thus, the findings should be interpreted with caution. Large scale, long-term follow-up studies utilizing transient elastography and liver biopsies from HFpEF patients under treatment with empagliflozin would be valuable to solve the disparity between liver fat reduction and no changes in liver values. As patients with >3× ULN were excluded from the trial, the results could be different in individuals above these levels. HFpEF is a very heterogeneous syndrome suggesting that findings could not apply to all patients with different phenotypes.

Conclusions

Empagliflozin compared with placebo did not show salutary effects on liver tests in patients with HFpEF. Liver tests did not modify

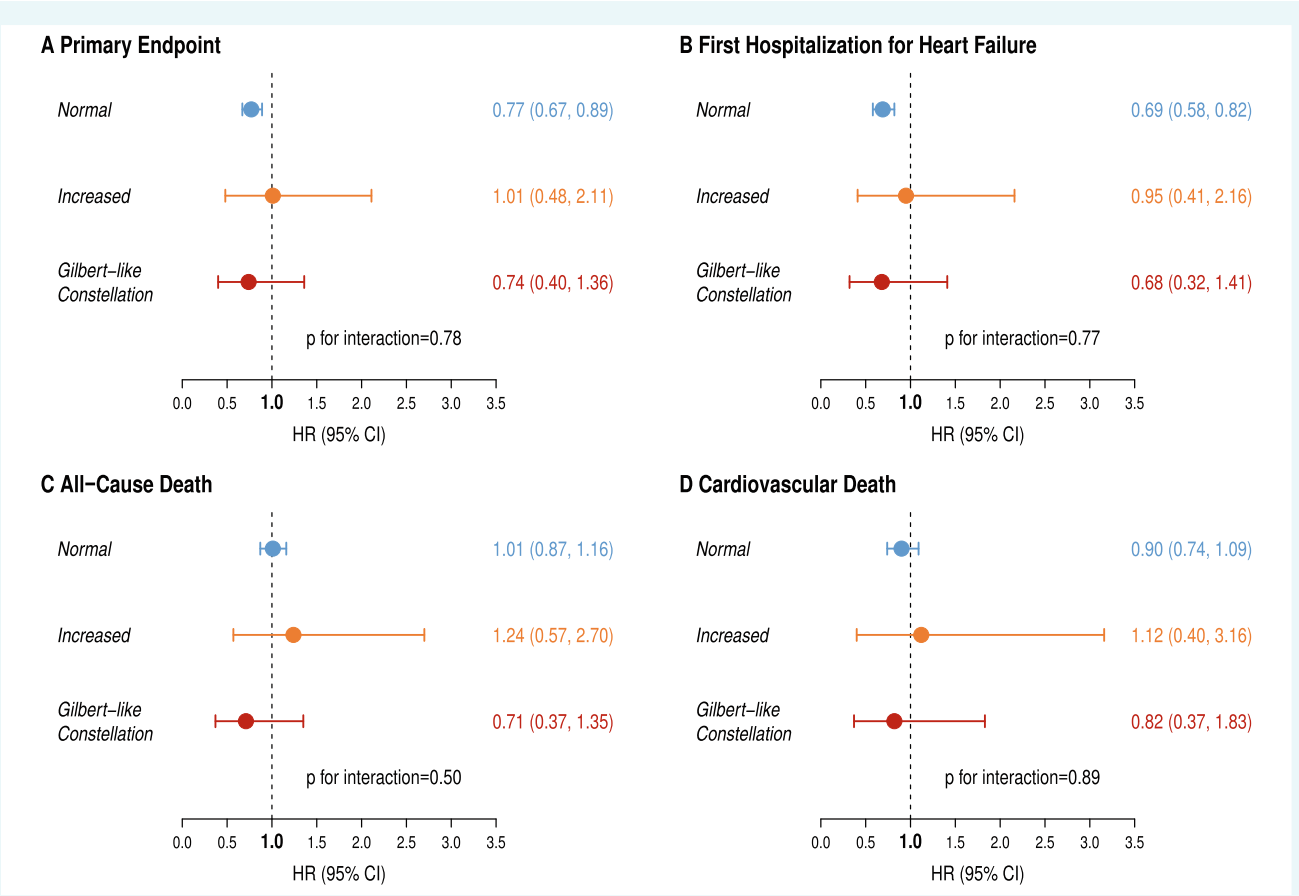


Figure 6 Hazard ratio (HR) for the treatment effect of empagliflozin for patients with normal bilirubin levels and increased bilirubin levels separated by a Gilbert-like constellation for the primary endpoint (*A*), first hospitalization for heart failure (*B*), all-cause death (*C*), and cardiovascular death (*D*). CI, confidence interval.

the treatment benefit of empagliflozin to improve heart failure outcomes, which was consistent in a broad population of patients including those with pathological liver tests.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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