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Empagliflozin Promotes Natriuresis in Diabetic Patients with Cirrhotic Refractory Ascites: A Proof-of-Concept Study

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ABSTRACT

Background & Aims: Interventional studies directly targeting natriuresis in refractory cirrhotic ascites are scarce, and no prospective study has examined whether sodium-glucose transporter 2 (SGLT2) inhibitor-induced glucosuria is associated with changes in renal sodium handling. We conducted a randomized, open-label, proof-of-concept study to characterize the short-term natriuretic response to empagliflozin in patients with diabetes and refractory ascites

Methods: Adults with type 2 diabetes, decompensated cirrhosis, and refractory ascites were randomized 1:1 to empagliflozin 10 mg once daily plus standard care or standard care alone for 10 days. The primary outcome was the between-group difference in mean change in fractional excretion of sodium (FENa, %) from baseline (Day 0) to the mean of post-baseline Days 1, 3, 7, and 10, estimated using a linear mixed-effects model. Key secondary outcomes included 24-hour urinary sodium excretion, 24-hour urine volume, and mean daily paracentesis volume.

Results: Twenty-one participants were randomized (empagliflozin n=10; control n=11). In the empagliflozin group, the between-group difference in mean change in FENa from baseline to the post-baseline mean (days 1, 3, 7, and 10) was +0.44 percentage points (95%CI: 0.05-0.83; p=0.029). Empagliflozin increased 24-hour urinary sodium excretion by +92.1 mmol/24 h (95%CI: 47.1-137.2) and 24-hour urine volume by + 822 mL/24 h (95%CI: 403-1240) versus control. Mean daily paracentesis volume was 0.6 ± 0.4 L/day with empagliflozin and 1.3 ± 0.6 L/day with control (mean difference -0.70 L/day, 95%CI: -1.17 to -0.23). No serious adverse events occurred.

Conclusions: In this open-label, proof-of-concept study, empagliflozin was associated with improved short-term natriuretic indices over 10 days in diabetic patients with decompensated cirrhosis and refractory ascites, without serious adverse events. Larger, blinded, longer-term trials are warranted to confirm these preliminary findings.

Key words: cirrhosis – ascites – sodium-glucose transporter 2 inhibitors – type 2 diabetes mellitus.

Abbreviations: BNP: B-type natriuretic peptide; CI: confidence interval; FENa: fractional excretion of sodium; LMM: linear mixed-effects model; MELD: model for end-stage liver disease; NHE3: sodium-hydrogen exchanger 3; SGLT2: sodium-glucose transporter 2.

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INTRODUCTION

Cirrhosis, particularly in the decompensated phase, is frequently complicated by ascites, a hallmark of poor prognosis and substantial morbidity [1], and is associated with considerable healthcare costs [2, 3].

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, originally developed for type 2 diabetes, have been extensively investigated in metabolic dysfunction associated steatotic liver disease [4]. Importantly, this drug class may also help control cirrhotic ascites by reducing proximal tubular sodium-glucose reabsorption, increasing distal sodium delivery, and restoring tubuloglomerular feedback [5-7]. Prior studies further suggest functional coupling with sodium-hydrogen exchanger 3 (NHE3) [8], providing a mechanistic rationale for a natriuretic effect complementary to loop diuretics [9]. Early clinical signals, including case reports and small series, suggest that SGLT2 inhibition may alleviate ascites and paracentesis needs

[10-13]. However, prospective evidence regarding dynamic changes in urinary sodium remains limited.

Thus, we conducted a randomized, open-label, proof-of-concept study to characterize the short-term natriuretic response to empagliflozin in patients with diabetes and refractory ascites, rather than to establish definitive long-term clinical efficacy.

METHODS

We conducted a randomized, open-label, standard-of-care controlled proof-of-concept study to assess the short-term natriuretic effect of empagliflozin in adults with type 2 diabetes and decompensated cirrhosis with refractory ascites. Written informed consent was obtained from all participants; when decision-making capacity was impaired, consent was obtained from a legally authorized representative. The study was approved by the Clinical Research Ethics Committees of Beijing Youan Hospital (LL-2024-117-K) and Baoding People's Hospital (2024-KLSZ-1), registered at ChiCTR (ChiCTR2500104785), and conducted in accordance with the Declaration of Helsinki.

Hospitalized adults (≥18 years) with type 2 diabetes and decompensated cirrhosis complicated by refractory ascites were eligible. Refractory ascites was defined as ascites unresponsive to high-dose diuretics (spironolactone 80-160 mg/day and furosemide 40-80 mg/day) for ≥1 week or requiring intermittent large-volume paracentesis (4,000-5,000 mL per procedure) with albumin infusion (20-40 g per procedure/day) for 2 weeks, or ascites in patients with uncontrollable diuretic-related complications or adverse drug reactions [14]. Additional inclusion criteria were stable background diuretic therapy and eGFR ≥45 mL/min/1.73 m^2. Exclusion criteria were systolic blood pressure less than 95 mmHg or diastolic blood pressure less than 60 mmHg; history of esophageal or gastric variceal bleeding within the past 3 months; history of grade II or higher hepatic encephalopathy within the past 3 months; patients with liver cancer; alcohol or drug abuse within the past 6 months; use of SGLT2 inhibitors within the past 1 months; model for end-stage liver disease (MELD) score greater than 20 or expected median survival less than 6 months; anemia, with hemoglobin levels less than 7 g/dL; use of diuretics other than spironolactone or furosemide within the past 1 weeks, such as tolvaptan or thiazide diuretics; presence of heart failure with significantly reduced left ventricular ejection fraction, B-type natriuretic peptide (BNP) > 1000 ng/mL within the past 3 months; bladder dysfunction, severe prostatic hypertrophy, or urinary incontinence; history of urinary tract infection in the past 3 months or evidence of a urinary tract infection; fungal vaginitis, phimosis, or balanitis within 3 months; symptomatic hypoglycemia in the past 3 months.

Participants were randomized 1:1 to empagliflozin 10 mg once daily plus standard care or standard care alone from day 1 to day 10 (or until discharge if earlier) using a computer-generated simple random sequence. Allocation concealment was ensured by sealed, sequentially numbered opaque envelopes (Fig. 1). Treating physicians could administer albumin or perform therapeutic paracentesis according to routine clinical practice. The trial was open-label; laboratory personnel followed standardized procedures and were not informed of group allocation.

Day 0 was baseline; days 1, 3, 7, and 10 were prespecified post-baseline visits. Twenty-four-hour urine was collected at baseline and on post-baseline visits (or at discharge if earlier) for measurement of volume, electrolytes, creatinine, and glucose. FENa (%) was calculated from well-mixed 24-hour urine samples and corresponding serum measurements. Vital signs and body weight were recorded daily during hospitalization from routine nursing charts. Paracentesis volumes were extracted from nursing charts. For each participant, mean daily paracentesis volume was defined as the total in-hospital paracentesis drainage volume divided by the number of inpatient study days observed. Days without paracentesis were assigned a value of 0 mL, whereas blank cells after discharge indicate that the participant was no longer under inpatient observation. Participant-level summaries are provided in Supplementary file (Table S2). Adverse events were captured from the EHR through day 10.

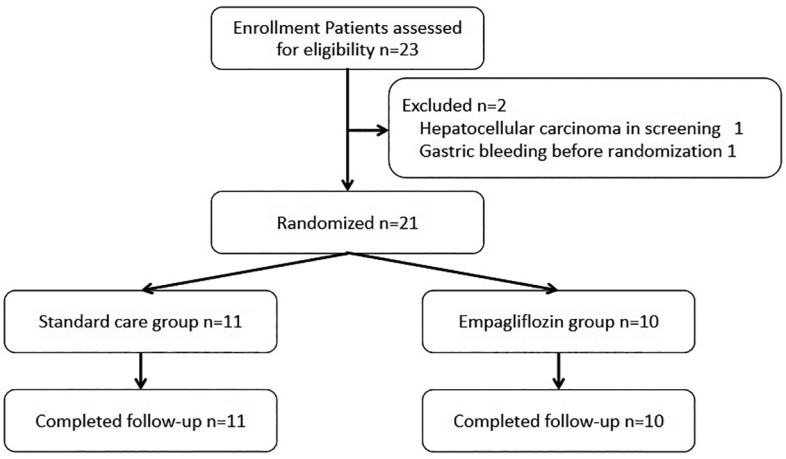

Fig. 1. Study flow chart.

The primary outcome was the between-group difference in change in FENa (%) from baseline to the post-baseline average across days 1, 3, 7, and 10, estimated from a linear mixed-effects model using model-derived marginal means. Secondary outcomes were the corresponding between-group differences in change from baseline to the post-baseline average for 24-hour urinary sodium excretion (mmol/day) and 24-hour urine volume (mL/day). Additional outcomes included body weight, serum electrolytes, paracentesis volume, and safety events.

Statistical Analysis

The primary analysis used a linear mixed-effects model (LMM) with visit as a categorical variable and a participant-specific random intercept. Fixed effects included treatment group, visit (Day 0, 1, 3, 7, 10), and the group-by-visit interaction. The primary estimand was the between-group difference in mean change from baseline, defined as: (average of model-estimated marginal means at days 1, 3, 7, and 10 minus the model-estimated marginal mean at day 0) in the empagliflozin group minus the same quantity in the control group; 95% confidence intervals (CIs) were obtained using linear contrasts. The same LMM framework and estimand definition were applied to secondary outcomes.

If urine collection occurred off-schedule, measurements were assigned to prespecified visits using predefined time windows (day 1 ±1 day, day 3 ±1 day, day 7 ±1 day, day 10 ±1 day); values outside these windows were treated as missing for the corresponding visit. Missing data were summarized by group and visit, and no additional imputation was performed. Sensitivity analyses were based on participant-level summaries and included: (1) ANCOVA of the post-baseline mean adjusted for baseline with HC3 robust standard errors, as a parametric sensitivity analysis; and (2) the Mann–Whitney U test applied to change-from-baseline values, as a nonparametric sensitivity analysis. Given the pilot nature of the study, no formal sample size calculation was performed and p values are descriptive. Analyses were conducted in R 4.4.1.

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or preparation of the manuscript.

RESULTS

Twenty-one participants were randomized to empagliflozin plus standard care (n=10) or standard care alone (n=11). Baseline characteristics were broadly similar between groups (Table I). Completeness of 24-hour urine sample collections by visit is summarized in Supplementary file (Table S5); for FENa and 24-hour urinary sodium, overall completeness across prespecified post-baseline visits was 80% in the empagliflozin group and 89% in the control group.

In the primary linear mixed-effects model, empagliflozin produced a greater increase in FENa than control. From baseline to the average of days 1, 3, 7, and 10, the model-based mean change was +0.53 in the empagliflozin group and +0.09 in the control group, corresponding to a between-group difference of +0.44 percentage points (95%CI: 0.05-0.83; p=0.029) (Fig. 2A, Supplementary file, Table S3).

Empagliflozin increased 24-hour urinary sodium excretion and urine output. The between-group difference in model-based mean change from baseline to the average of days 1, 3, 7, and 10 was +92.1 mmol/24 h (95%CI: 47.1-137.2; p<0.0001) for urinary sodium excretion and +821.7 mL/24 h (95%CI: 403.4-1240.0; p=0.0001) for 24-hour urine volume (Supplementary file, Table S3). Mean daily paracentesis volume was lower in the empagliflozin group (0.6 ± 0.4 L/day) than in controls (1.3 ± 0.6 L/day), with a mean difference of -0.70 L/day (95% CI -1.17 to -0.23) (Supplementary file, Table S2). Sensitivity analyses based on participant-level summaries were consistent (Supplementary file, Table S4A). Descriptive within-group raw changes from baseline are provided separately in Supplementary file, Table S4B.

Table I. Baseline demographics and characteristics

Characteristic	Group	
	Control, N = 11	Empagliflozin, N = 10
Age (year)	61 ± 8	55 ± 6
Gender, n (%)		
female	3 (27)	3 (30)
male	8 (73)	7 (70)
Cause of cirrhosis (HBV=1, alcoholic liver disease=2, other=3), n (%)		
1	5 (45)	5 (50)
2	5 (45)	5 (50)
3	1 (9)	0 (0)
History of diabetes (year)	7.36 ± 8.21	4.00 ± 2.11
Hypertension, n (%)	1 (9)	2 (20)
Chronic kidney disease, n (%)	2 (18)	1 (10)
Alcohol consumption (yes=1, no=0), n (%)	4 (36)	5 (50)
History of cirrhosis (year)	3.91 ± 3.65	5.10 ± 5.17
History of ascites (year)	2.18 ± 2.68	3.00 ± 1.94
Admission body weight (kg)	68 ± 10	69 ± 10
Furosemide daily dose at enrollment (mg), n (%)		
40	7 (64)	7 (70)
60	3 (27)	1 (10)
80	1 (9)	2 (20)
Spironolactone daily dose at enrollment (mg), n (%)		
80	5 (45)	4 (40)
100	3 (27)	4 (40)
120	2 (18)	2 (20)
160	1 (9)	0 (0)
Child-Pugh score, n (%)		
B	4 (36)	2 (20)
C	7 (64)	8 (80)
ALT (U/L)	31 ± 18	33 ± 16
AST (U/L)	44 ± 25	57 ± 29
Tbil (umol/L)	45 ± 29	63 ± 42
ALB (g/L)	28.4 ± 4.9	31.2 ± 3.9
Cr (umol/L)	89 ± 34	71 ± 18
K (mmol/L)	4.01 ± 0.63	3.64 ± 0.61
Na (mmol/L)	133.7 ± 4.4	136.2 ± 4.6

Table I (continued)		
Cl (mmol/L)	101.94 ± 2.88	103.52 ± 3.72
Glu (mmol/L)	8.21 ± 4.30	6.49 ± 1.68
PTA	58 ± 19	61 ± 12
INR	1.55 ± 0.42	1.40 ± 0.21
WBC	4.48 ± 2.31	3.87 ± 1.85
HGB (g/L)	94 ± 19	104 ± 22
PLT	109 ± 64	84 ± 47
HbA1c (%)	6.05 ± 1.62	5.88 ± 0.66
MELD	13.5 ± 4.3	12.3 ± 2.4
FENa (%)	0.40 ± 0.29	0.26 ± 0.14

ALB: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HBV: hepatitis B virus; HGB: hemoglobin; HBA1c: glycated hemoglobin; FENa: fractional excretion of sodium; LMM: linear mixed-effects model; PLT: platelets; WBC: white blood cells; tBil: total bilirubin.

Exploratory analyses suggested relationships between glucosuria and sodium and water handling (Fig. 3). When urinary glucose concentration was used as the exposure metric, it was inversely correlated with urinary sodium concentration (panel A; r=-0.34, 95%CI: -0.59 to -0.04) and FENa (panel D; r=-0.45, 95%CI: -0.67 to -0.17), positively correlated with 24-hour urine volume (panel B; r=0.37, 95%CI: 0.07-0.61), and showed little evidence of correlation with 24-hour urinary sodium excretion (panel C; r=0.04, 95%CI: -0.34 to 0.27). When total 24-hour urinary glucose excretion was used as the exposure metric, there was little evidence of correlation with urinary sodium concentration (panel E; r=0.02, 95%CI: -0.29 to 0.32) or FENa (panel H; r=-0.11, 95%CI: -0.40 to 0.21), whereas positive correlations were observed with 24-hour urine volume (panel F; r=0.77, 95%CI: 0.61-0.87) and 24-hour urinary sodium excretion (panel G; r=0.39, 95%CI: 0.09-0.62).

No serious adverse events occurred in the empagliflozin group. There were no episodes of symptomatic hypoglycemia, hypotension, acute kidney injury, clinically relevant volume depletion, urinary tract infection, or genital infection during the 10-day follow-up. In the empagliflozin group, median 24-hour urinary glucose excretion was 154.09 mmol (IQR 25.29 to 238.85).

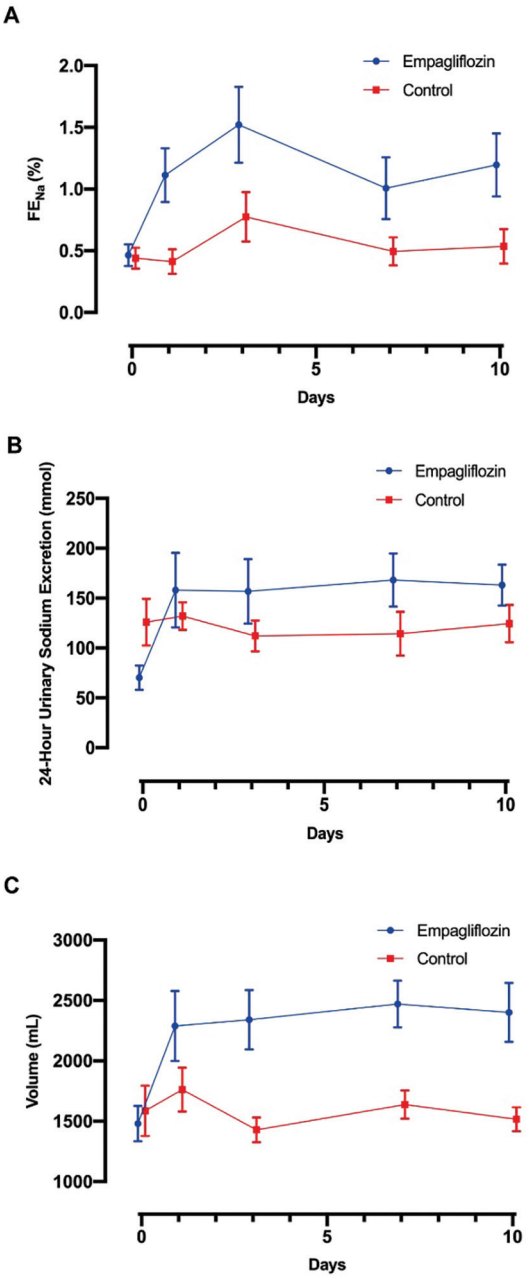

Fig. 2. Changes in FENa, 24-hour sodium excretion, and 24-hour urine volume over time in the empagliflozin and control groups. (A) fractional excretion of sodium (FENa) (%), (B) 24-hour sodium excretion (mmol), and (C) 24-hour urine volume (mL). The blue line represents the empagliflozin group, and the red line represents the control group. Each data point represents the mean, and the error bars indicate the standard error. The figure displays group-wise longitudinal trajectories; the formal model-based between-group differences in mean change from baseline, with corresponding 95% confidence intervals.

DISCUSSION

In this randomized proof-of-concept study of adults with type 2 diabetes, decompensated cirrhosis, and refractory ascites, empagliflozin added to standard care increased natriuresis over 10 days, as reflected by a significant rise in FENa and accompanying increases in 24-hour urinary sodium excretion and 24-hour urine volume. In contrast, participants receiving standard care alone showed no meaningful improvement in these renal sodium and water handling indices. We also observed a lower mean daily ascites drainage requirement in the empagliflozin group. These effects, including higher urine output, lower paracentesis requirement, and improved renal sodium excretion, appear broadly consistent with the limited medical literature currently available on this topic [15-18]. The value of the present study lies in providing prospective controlled pilot data with mechanistically relevant sodium-handling endpoints, but not to claim a novel clinical effect.

From a pathophysiological standpoint, renal sodium retention is central to ascites formation, whereas water retention is largely secondary to sodium accumulation [19]. This concept underpins guideline emphasis on dietary sodium restriction in ascites management [20].

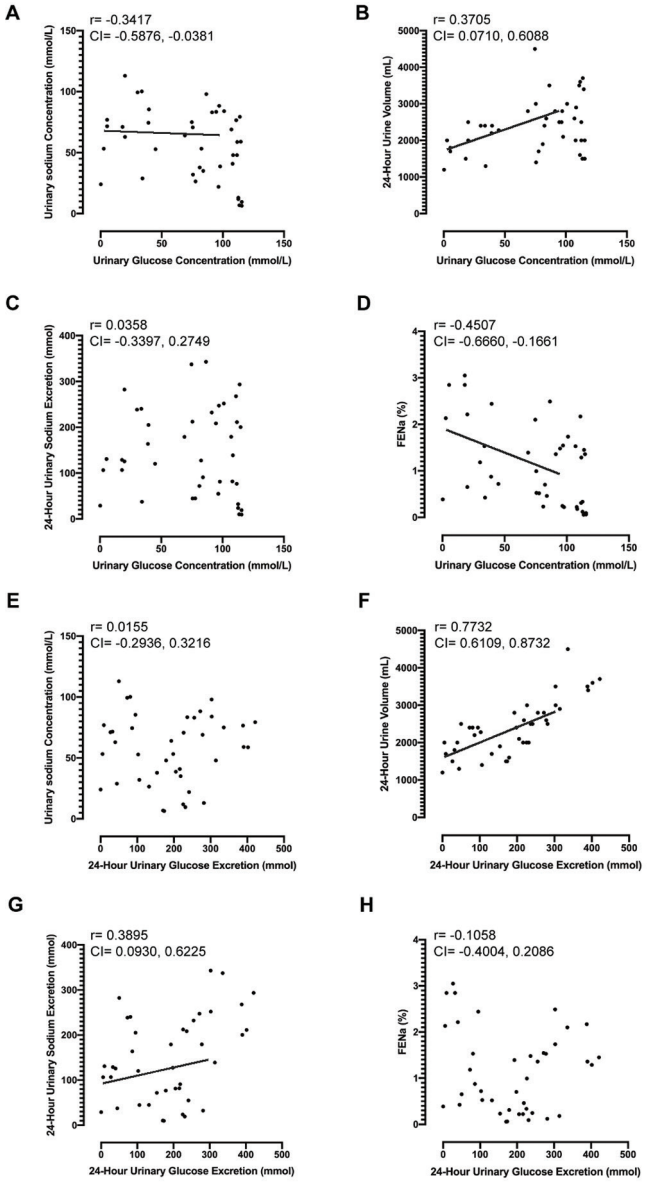

Fig. 3. Correlation analysis between urinary glucose and indicators of sodium and water retention.Panels (A)–(D) show the correlations between urinary glucose concentration (mmol/L) and various sodium retention indicators: (A) urinary sodium concentration, (B) 24-hour urine volume, (C) 24-hour urinary sodium excretion, (D) fractional excretion of sodium (FENa). Panels (E)–(H) show correlations between total 24-hour urinary glucose excretion (mmol) and the same four outcomes, respectively. Each point represents one available post-baseline 24-hour urine collection from the empagliflozin group. Fitted linear trend lines are shown only for correlations whose 95% confidence intervals did not cross zero.

However, in refractory ascites, sodium restriction alone is frequently insufficient because urinary sodium excretion can fall to very low levels, far below typical daily intake [21]. Importantly, enhanced sodium reabsorption in cirrhosis is not confined to the distal nephron and may involve substantial proximal tubular reclamation, a pattern that may contribute to diuretic resistance when therapy predominantly targets distal transport sites [22]. In this context, proximal tubule directed strategies are clinically attractive. As an SGLT2 inhibitor, empagliflozin reduces proximal tubular sodium glucose reabsorption and increases distal sodium delivery, providing a mechanistic rationale for a natriuretic effect that may complement conventional diuretics [23, 24].

A notable aspect of our dataset is the simultaneous assessment of glucosuria metrics and sodium handling indices. These exploratory findings suggest that the natriuretic response to SGLT2 inhibition in cirrhotic ascites may not be simply proportional to the magnitude of glucosuria. While urinary glucose concentration was associated with several indices of sodium and water handling, total 24-hour urinary glucose excretion showed little evidence of correlation with urinary sodium concentration or FENa. This pattern may suggest that the natriuretic response to SGLT2 inhibition in cirrhotic ascites is not simply proportional to the magnitude of glucosuria [25]. linear mixed-effects model These exploratory observations support the possibility that SGLT2 inhibitors exert natriuretic effects through mechanisms that extend beyond osmotic diuresis. This interpretation aligns with the broader clinical experience in heart failure, where benefits of SGLT2 inhibitors appear comparable in patients with and without diabetes [26, 27]. Whether preexisting diabetes or hyperglycemia modulates the natriuretic response to SGLT2 inhibitors in cirrhotic patients also warrants further investigation [28].

The magnitude of glucosuria also has practical safety implications. In our cohort, the upper quartile of 24-hour urinary glucose excretion corresponded to a modest caloric loss relative to typical daily intake, suggesting limited impact on overall energy balance. Consistent with the established insulin independent mechanism of SGLT2 inhibitors, we observed no symptomatic hypoglycemia during the short treatment period. More broadly, the absence of serious adverse events, including renal function deterioration and clinically significant volume depletion, is reassuring for short-term use in this high-risk population, although the sample size and follow-up duration preclude firm safety conclusions.

Several limitations should be considered. First, the sample size was small and follow-up was short, limiting inference about long-term efficacy, durability of natriuresis, and clinical outcomes such as readmissions and survival. Accordingly, the present trial should be interpreted as a proof-of-concept physiological study, but not a definitive efficacy trial. Second, despite randomization, baseline imbalances are possible in a pilot cohort and may influence effect estimates. Third, the trial was open-label, and supportive care, including albumin infusion and paracentesis, was guided by routine clinical judgment rather than protocol, which constrains causal interpretation of drainage differences. Fourth, missing 24-hour urine collections occurred, primarily reflecting the operational challenges of repeated timed collections in hospitalized patients with early discharge.

CONCLUSIONS

The results of this proof-of-concept study suggests empagliflozin may improve renal sodium excretion in diabetic patients with decompensated cirrhosis and refractory ascites, with supportive signals for improved 24-hour urinary sodium and urine volume and reduced drainage requirements. Larger,

longer-term trials are needed to confirm these preliminary findings, evaluate efficacy and safety in non-diabetic patients, and determine whether SGLT2 inhibition can reduce paracentesis requirements and hospital readmissions through sustained natriuresis.

Conflicts of interest: Y.G received consultancy fees from Sinovac and SineuGene within the past 36 months. He currently serves as a medical advisor for Sinovac and Gene Line Bioscience. Additionally, he has received lecture fees from Pfizer within the same period. The other authors have no conflicts of interest to disclose.

Authors' contribution: R.S. and Z.H. conceived the study. R.S. and Y.G collected data. Y.G and L.Z. performed the statistical analysis. R.S. and Y.G drafted the manuscript. Y.G, and Z.H. revised and edited the manuscript. Z.H supervised the study. All the authors read and approved the final version of the manuscript.

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Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-6897

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