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Research Letter

# Complete Resolution of Refractory Ascites and Pleural Effusion with Sustained Improvement in Urinary Sodium Excretion in a Cirrhotic Patient Treated with Empagliflozin

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Sodium-glucose cotransporter 2 (SGLT2) inhibitors, including empagliflozin, dapagliflozin, and sotagliflozin, have shown promising effects beyond glycemic control, notably improving sodium and fluid retention in heart failure.[1] Ascites represents a challenging clinical issue frequently encountered in the decompensated phase of cirrhosis, sometimes becoming resistant to conventional diuretic therapies such as loop diuretics and mineralocorticoid receptor antagonists. Refractory ascites is associated with poor prognosis and often leads to life-threatening complications such as spontaneous bacterial peritonitis.[2] In cirrhosis, refractory ascites results from severe portal hypertension and splanchnic vasodilation, with consequent neurohormonal (RAAS) overactivation and extreme renal sodium retention. Given the shared pathophysiological mechanisms between advanced heart failure and cirrhosis,[3] it has been hypothesized that certain heart failure therapies may be repurposed for the management of refractory ascites in cirrhosis.[4] Among them, SGLT2 inhibitors represent a particularly promising class of agents that may offer therapeutic benefits to cirrhotic patients with ascites. Here, we present a case of decompensated cirrhosis in which treatment with empagliflozin completely resolved concomitant refractory ascites and pleural effusion, with sustained improvement in urinary sodium excretion.

A 59-year-old male with alcoholic cirrhosis complicated by diabetes mellitus was diagnosed with cirrhosis at the time ascites was first detected. Following the diagnosis, the patient abstained from alcohol. Despite standard management, he experienced refractory ascites and pleural effusion that persisted for over six months. These findings were confirmed by computed tomography scans in April 2024 and October 2024 (Fig. 1), which also showed patent hepatic veins and inferior vena cava, with no evidence of venous outflow obstruction. The patient required frequent hospital admissions for repeated paracenteses despite escalating doses of spironolactone (120 mg/day) and furosemide (40 mg/day). Tolvaptan was not administered during this period, as it was not available at our hospital. His total bilirubin levels fluctuated around 30 μmol/L, serum albumin ranged between 30 and 35 g/L, and prothrombin activity varied between 50% and 60%, with a Child-Pugh class of C. Serum sodium ranged from 129 to 133 mmol/L, while serum creatinine and blood urea nitrogen remained within the normal range. Ascitic fluid analysis revealed a serum-ascites albumin gradient of 2.1 g/dL. In subsequent paracenteses, the serum-ascites albumin gradient consistently ranged between 1.8 g/dL and 2.3 g/dL, aligning with portal hypertensive ascites. Fractional excretion of sodium (FENa) remained persistently below 0.3% throughout diuretic therapy.

On October 15, 2024, empagliflozin 10 mg daily was initiated alongside the existing diuretic regimen. Within two weeks, his 24-h urinary sodium excretion increased to over 70 mmol/day, and FENa gradually increased to 1%. By the fourth week of empagliflozin treatment, both ascites and pleural effusion had nearly resolved, and paracentesis was no longer required. Diuretics were completely discontinued in January 2025, and empagliflozin monotherapy was continued. At a follow-up visit in April 2025, computed tomography scans revealed complete resolution of the right-sided pleural effusion and ascites (Fig. 1). At that time, FENa was 0.6%, and 24-h urinary sodium excretion was 100.27 mmol as illustrated in Supplementary Table 1. The patient's liver function showed limited improvement, and hyponatremia persisted as illustrated in Supplementary Table 2.

This patient maintained a durable natriuretic response to empagliflozin even after discontinuation of loop and min-

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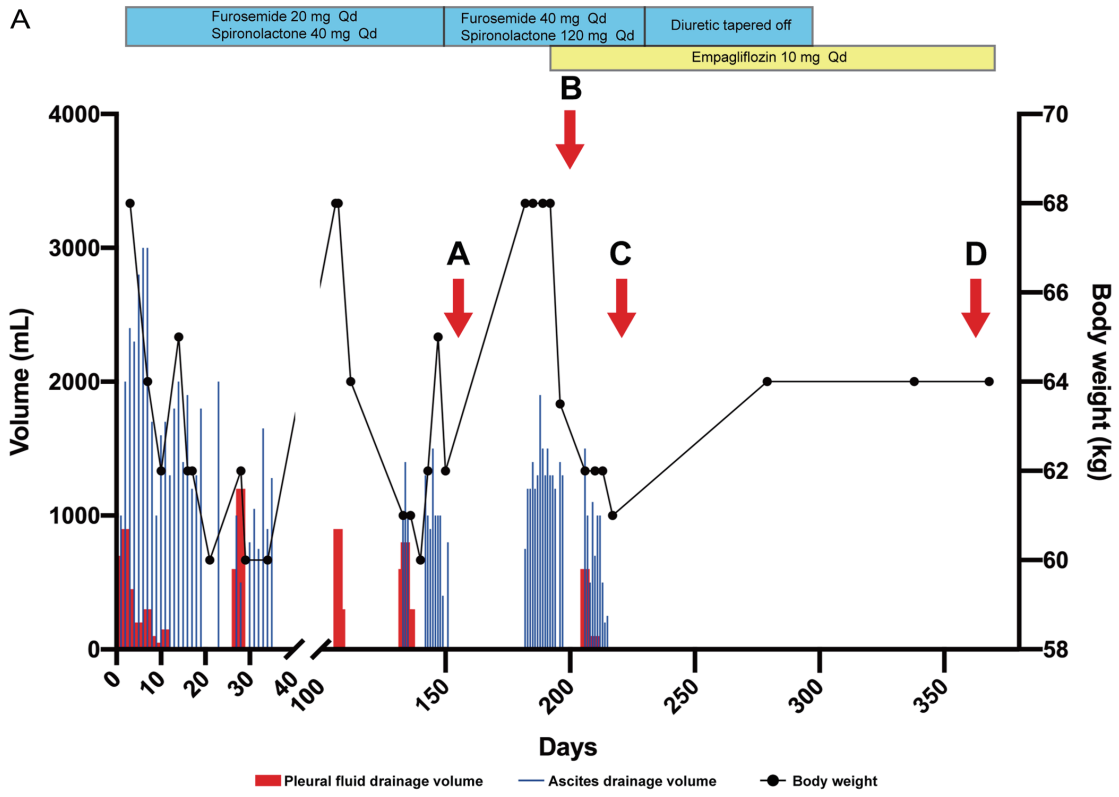
A




B

| | A | B | C | D |
|---|---|---|---|---|
| Urine sodium (mmol/L) | 19.47 | 37.37 | 32.47 | 40.11 |
| FENa (%) | 0.10 | 0.43 | 0.73 | 0.60 |
| 24 H sodium excretion (mmol) | 29.20 | 85.95 | 97.41 | 100.27 |
| 24 H urine volume (mL) | 1500 | 2500 | 3000 | 2500 |

C

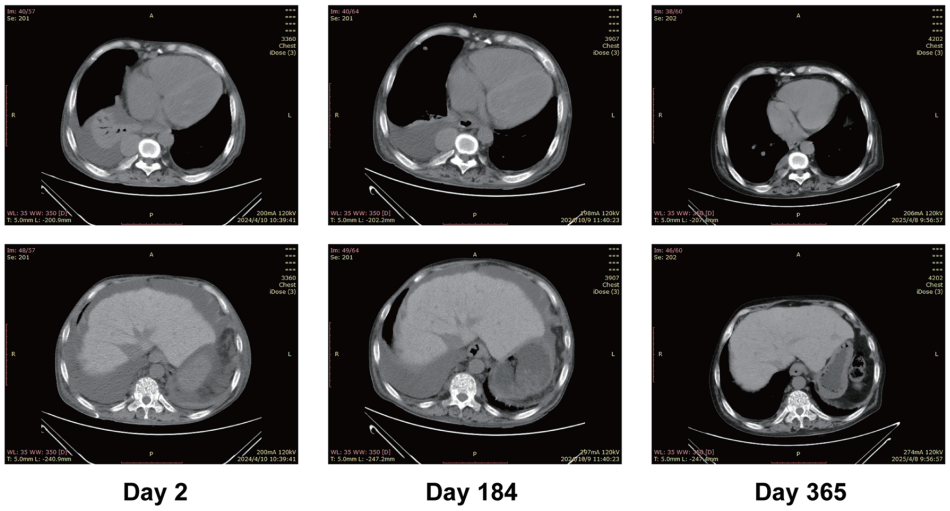



**Fig. 1. Changes in patient's ascitic and pleural fluid drainage, urinary sodium excretion changes, and chest and abdominal computed tomography scans.** (A) Time course of ascitic and pleural fluid drainage along with changes in body weight. (B) Trends in 24-h urinary sodium excretion and daily urine volume. (C) Representative chest and abdominal CT scans before and after empagliflozin treatment. CT, computed tomography.

eralocorticoid receptor antagonists. This observation raises several mechanistic considerations. First, the pivotal approach of managing cirrhotic ascites or concomitant pleural effusion is improving sodium retention. In patients with refractory ascites, diuretic resistance is mainly driven by increased sodium reabsorption in the proximal tubule.[5] This pathophysiological process renders traditional diuretics that target the distal nephron (such as loop diuretics or spironolactone) less effective, as the tubular fluid arriving at the distal tubule is already depleted of sodium ions. In this context, SGLT2 inhibitors, by reducing proximal sodium reabsorption, not only alleviate sodium retention but also enhance tubular sodium delivery to the distal nephron, thereby potentially augmenting the effect of loop diuretics through a synergistic mechanism.[6] Second, while several case reports and small cohort studies have suggested the potential of SGLT2 inhibitors in managing refractory ascites, none have provided detailed insights into the dynamic changes in urinary sodium excretion.[7,8] This sustained natriuretic response to empagliflozin distinguishes it from the typical pattern observed with loop diuretics. Loop diuretics often induce a sharp increase in urinary sodium excretion and volume output shortly after initiation; however, this effect commonly diminishes within a few days due to renal adaptive mechanisms that enhance sodium reabsorption. This attenuation, known as the "braking phenomenon", which is associated with a well-recognized limitation on the long-term efficacy of loop diuretics.[9] Third, SGLT2 inhibitors act in the proximal tubule to inhibit sodium and glucose reabsorption, which leads to increased sodium delivery to the macula densa. This may activate tubuloglomerular feedback and potentially attenuate RAAS activity.[10] The attenuation of RAAS overactivation may reduce sodium reabsorption and thus contribute to the sustained improvement in FENa observed in this case, even after withdrawal of conventional diuretics. This mechanism is currently under evaluation in an ongoing clinical trial (Registration No. ChiCTR2500095222).

Emerging clinical evidence further supports the efficacy of SGLT2 inhibitors in refractory ascites. A recent randomized controlled trial including 42 patients demonstrated that adding empagliflozin to standard care significantly reduced the need for large-volume paracentesis (42.9% vs. 100% in controls) and resulted in complete resolution of ascites in about 24% of patients.[11] In addition, a pilot study by Kalambokis *et al.* reported marked improvement in natriuresis and enhanced circulatory and renal function in cirrhotic patients treated with empagliflozin.[12] Notably, SGLT2 inhibitor therapy was well tolerated in these studies, with only mild adverse effects observed.

In this case, we specifically monitored FENa as a surrogate marker of urinary sodium excretion. FENa is primarily determined by the ratio of urinary sodium to urinary creatinine. As creatinine is not reabsorbed and its urinary excretion remains relatively constant in individuals with stable renal function, and because serum sodium and creatinine levels show minimal fluctuation, FENa serves as a sensitive marker of renal sodium reabsorption. It has been widely used in cardiology to assess sodium excretion in heart failure patients.[13,14] In healthy individuals, FENa is approximately 1%,[15] whereas in cirrhotic patients with ascites, it typically falls below 0.5%, and in those with refractory ascites, it may drop to as low as 0.2%.[16] Whether FENa could serve as a surrogate endpoint for predicting response to SGLT2 inhibitors in cirrhotic ascites remains to be investigated in future clinical trials.

SGLT2 inhibitors may serve as potential adjuncts or even alternatives to conventional diuretic regimens in the treatment of cirrhotic ascites. Nonetheless, their use requires careful monitoring due to potential side effects such as volume depletion, urinary tract infection, ketoacidosis, and acute kidney injury, particularly in patients with unstable hemodynamics. Importantly, recent studies have not found a significant increase in these adverse events associated with SGLT2 inhibitor therapy.[17]

Given the multifaceted renal effects and favorable safety profile of SGLT2 inhibitors in heart failure and chronic kidney disease, further investigation into their use in patients without diabetes is warranted. Whether they can reduce readmissions, decrease the need for paracentesis, or improve hemodynamics in cirrhotic patients remains an open and important research question. Although this report is limited to a single case, our findings are hypothesis-generating and provide proof-of-concept that SGLT2 inhibition can overcome diuretic resistance in cirrhosis. These findings may serve as a basis for future studies aimed at validating therapeutic potential of SGLT2 inhibitors in this population.

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## Conflict of interest

The authors have no conflict of interests related to this publication.

## Author contributions

Manuscript draft: WQ, YunG, and YuanG; data curation: YZ and NB; technical support and resources: WF and WW; study concept and design: YuanG and ZH. All authors have approved the final version and publication of the manuscript.

## Ethical statement

The study was conducted according to the guidelines of the Declaration of Helsinki as revised in 2024 and approved by the ethical committee of Baoding people's Hospital (Approval number: KLSZ-2024-1). Written informed consent for publication was obtained from the patient, and all potentially identifying details have been fully anonymized.

## Data sharing statement

De-identified individual participant data underlying the results reported in this article are available from the corresponding author upon reasonable request for academic purposes. Researchers interested in obtaining the dataset may contact the corresponding author via email.

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