JOURNAL OF HEPATOLOGY

Response to: A randomized-controlled trial comparing 20% albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension [ALPS trial]

To the Editor:

Sepsis and septic shock in patients with cirrhosis is a leading cause of acute decompensation or acute-on-chronic liver failure and is associated with poor prognosis and increased mortality.[1,2]

In a recent publication, Maiwall *et al.* conducted a randomized-controlled trial to study the efficacy of 20% albumin compared with plasmalyte in 100 patients with cirrhosis and sepsis-induced hypotension [ALPS trial],[3] in terms of increasing mean arterial pressure above 65 mmHg 3 h after infusion. Albumin rapidly restored the hemodynamic parameters but caused more pulmonary complications than plasmalyte. On multivariate analysis, higher sequential organ failure scores, inferior vena cava (IVC) diameter, and shock reversal at 48 hours were independent predictors of mortality.[3]

We would like to discuss some critical aspects regarding the importance of point of care ultrasound (POCUS) in critically ill cirrhotic patients (CICs) with septic shock. POCUS has been defined as the acquisition, interpretation, and clinical integration of ultrasonographic imaging performed by a trained clinician at the patient's bedside.[4]

Maiwall *et al.*, while evaluating the hemodynamic impact of the studied infusions, present ultrasonographic data only on the IVC diameter, which alone has limited value in reflecting central venous pressure (CVP) and describing fluid responsiveness.[3]

The accuracy of POCUS in predicting fluid responsiveness depends on both the measurement site and the ventilatory setting, especially in case of invasive or non-invasive mechanical ventilation (MV).[5] In particular, dilatation of the IVC when high positive end expiratory pressure (PEEP) levels are used, may affect interpretation of changes in IVC diameter.[5]

The measurement of the IVC diameter without data on the concomitant PEEP level and type of ventilatory setting, offers limited clinical information. The authors' statement that an intriguing finding was a near-normal value of the diameter of IVC and CVP in the enrolled patients despite them being in shock is a clear demonstration of this limit.

Furthermore, and as authors themselves stress, a limit of this study is the lack of two important ultrasonographic indices as the IVC-collapsibility index (in spontaneously breathing patients) and the IVC-distensibility index (in MV).[6]

IVC diameter in CICs may also be influenced by increased intra-abdominal pressure due to ascites, pleural effusion, reduction of pulmonary compliance, and features of cirrhotic cardiomyopathy (*i.e.*, diastolic dysfunction).[7]

Besides, the incorporation of sonography as a guide for fluid management in CICs should take into account that volume status in septic shock is a dynamic process. Excess fluid administration can lead to serious complications such as acidosis, changes in the blood coagulative system, accumulation of fluid in the extravascular interstitial space, fluid overload and pulmonary edema. On the other hand, fluid restriction is burdened by marked hypovolemia, hypoperfusion, tissue hypoxia and oxygen debt.

"Hemodynamic optimization" is mandatory in any critical setting, and thoracic ultrasound should be a key component of POCUS in CICs, as it can improve bedside diagnosis of pulmonary disease and evaluation of the hemodynamic status.[5–7]

Lung ultrasound also allows for an evaluation of pulmonary edema through the visualization of the B-lines, vertical artifacts arising from the pleural line detected in the presence of interstitial-alveolar imbibition. Theerawit and Cao demonstrated a variation of the B lines as the patient's fluid state changes.[8,9] The evaluation of dynamic parameters such as fluid responsiveness depends also on the heart-lung interaction. The amount of water that accumulates in the interstitial and in the alveolar space is defined as extravascular lung water (EVLW). Its increase can be caused by increased alveolar-capillary permeability, hydrostatic pressure, or both, and can be evaluated using trans-pulmonary thermodilution techniques. Mayr underlines the potential of different B-lines score for the accurate estimation of the EVLW index and pulmonary vascular permeability index in critically ill patients.[10]

In the ALPS trial, the authors showed a high incidence of pulmonary complications and the need for MV was not negligible, the above discussed concerns assume a great significance.[3] The importance of confirming the clinical diagnosis of pulmonary edema with lung ultrasound documentation of B-lines should be considered, especially in those scenarios in which multiple factors (pneumonia, pulmonary edema, atelectasia), may play a role in the respiratory failure of patients with cirrhosis complicated by septic shock.

We support the systematic use of lung and IVC POCUS as an important low-cost bedside tool to complement clinical assessment of volume status and respiratory function, to guide treatment and to help monitor the response to fluid infusion in CICs with shock. Its widespread availability could help in predicting response to fluids or the severity of lung injury, especially in the setting of patients prone to rapid deterioration.

In order to establish the prognostic role of POCUS in patients with cirrhosis and septic shock, prospective multicenter studies are needed.

Financial support

The authors received no financial support to produce this manuscript.

Conflicts of interest

The authors have read guidance on competing interests, and they declare no competing interests.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All the authors read and discussed the manuscript of Maiwall *et al.* SM and VFT wrote the draft of the Letter to the Editor. ATM

Received 9 June 2022; accepted 1 July 2022; available online 08 July 2022
https://doi.org/10.1016/j.jhep.2022.07.001

reviewed the evidence on the use of ultrasound method. SM submitted the letter. All authors read and approved the final manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.07.001.

References

[1] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021 Nov;47(11):1181–1247. https://doi.org/10.1007/s00134-021-06506-y. Epub 2021 Oct 2. PMID: 34599691; PMCID: PMC8486643.

[2] Wong F, Piano S, Singh V, Bartoletti M, Maiwall R, Alessandria C, et al., International Club of Ascites Global Study Group. Clinical features and evolution of bacterial infection-related acute-on-chronic liver failure. J Hepatol 2021 Feb;74(2):330–339. https://doi.org/10.1016/j.jhep.2020.07.046. Epub 2020 Aug 8. PMID: 32781201.

[3] Maiwall R, Kumar A, Pasupuleti SSR, Hidam AK, Tevethia H, Kumar G, et al. A randomized-controlled trial comparing 20% albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension [ALPS trial]. J Hepatol 2022 Apr 20. https://doi.org/10.1016/j.jhep.2022.03.043. S0168-S8278(22)239-242 Epub ahead of print. PMID: 35460725.

[4] Diaz-Gomez JL, Mayo PH, Koening SJ. Point-of-care ultrasonography. N Engl J Med 2021;385:1593–1602. https://doi.org/10.1056/NEJMra1916062.

[5] Preau S, Bortolotti P, Colling D, Dewavrin F, Colas V, Voisin B, et al. Diagnostic accuracy of the inferior vena cava collapsibility to predict fluid responsiveness in spontaneously breathing patients with sepsis and acute circulatory failure. Crit Care Med 2017 Mar;45(3):e290–e297. https://doi.org/10.1097/CCM.0000000000002090. PMID: 27749318.

[6] Pereira RM, Silva AJLCD, Faller J, Gomes BC, Silva Jr JM. Comparative analysis of the collapsibility index and distensibility index of the inferior vena cava through echocardiography with pulse pressure variation that predicts fluid responsiveness in surgical patients: an observational controlled trial. J Cardiothorac Vasc Anesth 2020 Aug;34(8):2162–2168. https://doi.org/10.1053/j.jvca.2020.02.007. Epub 2020 Feb 12. PMID: 32217045.

[7] Vieillard-Baron A, Evrard B, Repessé X, Maizel J, Jacob C, Goudelin M, et al. Limited value of end-expiratory inferior vena cava diameter to predict fluid responsiveness impact of intra-abdominal pressure. Intensive Care Med 2018 Feb;44(2):197–203. https://doi.org/10.1007/s00134-018-5067-2. Epub 2018 Jan 22. PMID: 29356854.

[8] Theerawit P, Touman N, Sutherasan Y, Kiatboonsri S. Transthoracic ultrasound assessment of B-lines for identifying the increment of extravascular lung water in shock patients requiring fluid resuscitation. Indian J Crit Care Med 2014 Apr;18(4):195–199. https://doi.org/10.4103/0972-5229.130569. PMID: 24872647; PMCID: PMC4033851.

[9] Cao G, Wu Y, Zhao Y, Wang L, Zhang Y. Assessment of extravascular lung water by measuring the number of pulmonary ultrasound B-lines before and after CBP in patients with MODS. Medicine (Baltimore) 2021 Jan 8;100(1):e24181. https://doi.org/10.1097/MD.0000000000024181. PMID: 33429806; PMCID: PMC7793418.

[10] Mayr U, Lukas M, Habenicht L, Wiessner J, Heilmaier M, Ulrich J, et al. B-lines scores derived from lung ultrasound provide accurate prediction of extravascular lung water index: an observational study in critically ill patients. J Intensive Care Med 2022 Jan;37(1):21–31. https://doi.org/10.1177/0885066620967655. Epub 2020 Nov 5. PMID: 33148110; PMCID: PMC8609506.

Sergio Maimone[1,*]
Vincenzo Francesco Tripodi[2]
Anna Teresa Mazzeo[3]
[1]*Division of Medicine and Hepatology, University Hospital of Messina, Messina, Italy*
[2]*Surgery Department, Anesthesia and Intensive Care, University Hospital of Messina, Messina, Italy*
[3]*Human Pathology Department, Anesthesia and Intensive Care, University Hospital of Messina, Messina, Italy*
[*]Corresponding author. Address: Division of Medicine and Hepatology, University Hospital of Messina, Messina, Italy.
E-mail address: smaimone@unime.it (S. Maimone)

Reply to: "Response to: A randomized-controlled trial comparing 20% albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension [ALPS trial]"

To the Editor:

We want to thank Maimone *et al.* for taking keen interest in our recently published ALPS trial, comparing 20% albumin to plasmalyte for fluid resuscitation in sepsis-induced hypotension in critically ill patients.[1] We agree with their suggestions on using point-of-care ultrasound to assess volume status for guiding fluid management in patients admitted to the intensive care unit. Accurate assessment of the fluid status is the key in managing patients with complex hemodynamic alterations associated with organ dysfunction.[2] Unfortunately, we did not protocolize the fluid management in our patients using this technique. Our trial aimed to evaluate the two strategies, *i.e.*, 20% albumin and plasmalyte in patients with sepsis-induced hypotension. Notably patient enrolment, screening and randomization were initiated in the emergency department. As rightly mentioned by the authors, POCUS requires skilled and trained personnel.[3] It is primarily used for assessing dynamic changes in cardiac preload using heart-lung interactions. In addition, it facilitates the differentiation of lung pathologies and can aid in the measurement of inferior vena cava (IVC) diameter. It was not possible to perform a detailed POCUS for all patients included in our trial. However, we reported the assessment of IVC diameter, which we recorded for all patients. In addition, we observed a higher IVC diameter in patients who developed pulmonary complications. Therefore, monitoring the IVC diameter and collapsibility along with detailed POCUS could be very helpful in guiding fluid management in critically ill patients with cirrhosis and sepsis-induced hypotension or acute kidney injury (Fig. 1). In addition, we identified IVC diameter as an independent predictor of 28-day mortality, signifying the clinical relevance of fluid status as a determinant of clinical outcomes.

Received 29 August 2022; accepted 31 August 2022; available online 13 September 2022
https://doi.org/10.1016/j.jhep.2022.08.038