Review article: Practical considerations for fluid resuscitation in cirrhosis

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Summary

Background: Standard clinical methods of assessing volume and providing resuscitation are not always applicable to patients with advanced or decompensated cirrhosis. Despite this being well known from a clinical perspective, there remains relatively little evidence to guide clinicians though fluid management in patients with cirrhosis and, often, multi-organ system dysfunction.

Aims: This review summarises the current understanding of the circulatory dysfunction in cirrhosis, modalities for assessing volume status, and considerations for fluid selection. It additionally provides a practical approach to fluid resuscitation.

Methods: We review current literature on cirrhosis pathophysiology in steady-state and shock, clinical implications of fluid resuscitation, and strategies to assess intravascular volume. Literature reviewed here was identified by the authors through PubMed search and review of selected papers' references.

Results: Clinical management of resuscitation in advanced cirrhosis remains relatively stagnant. Although several trials have attempted to establish the superior resuscitative fluid, the lack of improvement in hard clinical outcomes leaves clinicians without clear guidance.

Conclusions: The absence of consistent evidence for fluid resuscitation in patients with cirrhosis limits our ability to produce a clearly evidence-based protocol for fluid resuscitation in cirrhosis. However, we propose a preliminary practical guide to managing fluid resuscitation in patients with decompensated cirrhosis. Further studies are needed to develop and validate volume assessment tools in the specific context of cirrhosis, while randomised clinical trials of protocolized resuscitation may improve care of this patient population.

1 | INTRODUCTION

Cirrhosis carries high morbidity and mortality in the United States (US), representing approximately 3.8 per 1000 hospitalizations in the US per year and is the fourth leading cause of death among US adults ages 45–64 years old.[1,2] Patients with cirrhosis pose unique clinical challenges secondary to their disordered circulation and the multi-system consequences of advanced cirrhosis. As patients with cirrhosis are often volume overloaded overall and simultaneously have decreased effective arterial volume, their brittle hemodynamics make them prone to bleeding, renal injury, and cardiac overload. Standard clinical methods of assessing volume and providing

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resuscitation are therefore not always applicable. The current literature lacks a comprehensive assessment of available evidence to provide goal-directed care to the patient with decompensated cirrhosis. This review will discuss assessment of volume status and the evidence behind choice of resuscitative therapies in cirrhosis, with an emphasis on critical illness.
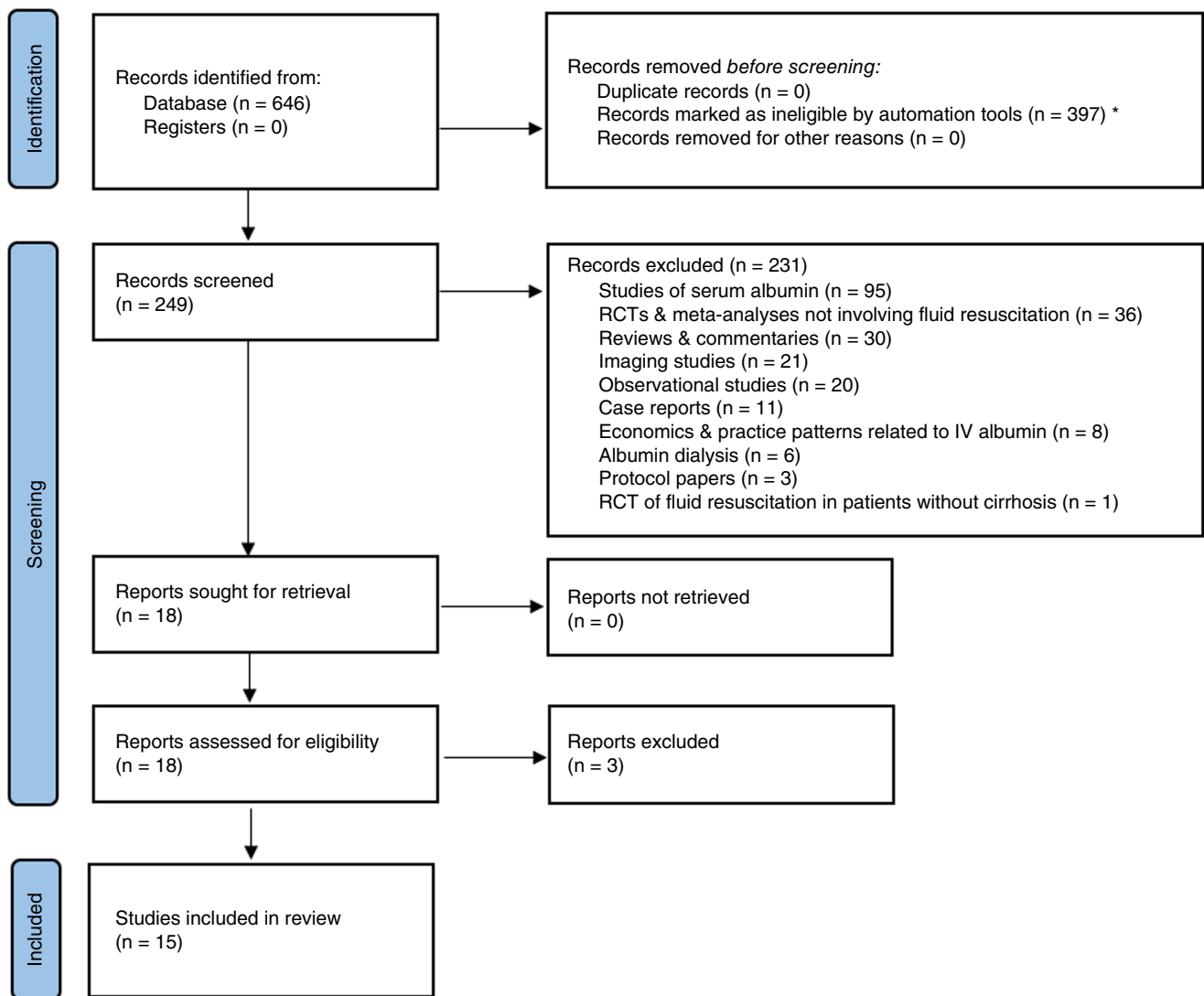
2 | METHODS

The literature reviewed here was identified by the authors through PubMed search (Figure 1) and hand search of the references of the manuscripts identified. We selected randomised clinical trials comparing resuscitation strategies. We discarded studies of fluid resuscitation in animal models, paediatric populations, cost-effectiveness studies, and those comparing the use of vasopressors to fluids. Regarding literature for assessing volume status, we used the search terms "POCUS" "ultrasound" "perfusion" "bioimpedance" "inferior vena cava" "volume status" "cirrhosis" and any combination thereof. We additionally selected papers from the references of manuscripts identified from the primary search.

3 | PATHOGENESIS OF ALTERED HEMODYNAMICS IN CIRRHOSIS

Cirrhosis represents a state of anatomic and functional abnormalities of the liver and portal circulation with ripple effects on central circulatory hemodynamics (Figure 2). Hepatic fibrosis distorts the liver architecture and this is compounded by endothelial

Identification

Records identified from:
  Database (n = 646)
  Registers (n = 0)

Records removed *before screening:*
  Duplicate records (n = 0)
  Records marked as ineligible by automation tools (n = 397) *
  Records removed for other reasons (n = 0)

Screening

Records screened
(n = 249)

Records excluded (n = 231)
  Studies of serum albumin (n = 95)
  RCTs & meta-analyses not involving fluid resuscitation (n = 36)
  Reviews & commentaries (n = 30)
  Imaging studies (n = 21)
  Observational studies (n = 20)
  Case reports (n = 11)
  Economics & practice patterns related to IV albumin (n = 8)
  Albumin dialysis (n = 6)
  Protocol papers (n = 3)
  RCT of fluid resuscitation in patients without cirrhosis (n = 1)

Reports sought for retrieval
(n = 18)

Reports not retrieved
(n = 0)

Reports assessed for eligibility
(n = 18)

Reports excluded
(n = 3)

Included

Studies included in review
(n = 15)

* Excluded: pediatric populations, non-human studies, reviews, commentaries, case reports, surveys, years prior to 1999.

FIGURE 1 PRISMA diagram representing PubMed search for clinical trials comparing colloids and intravenous albumin for fluid resuscitation in cirrhosis. Modified from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.
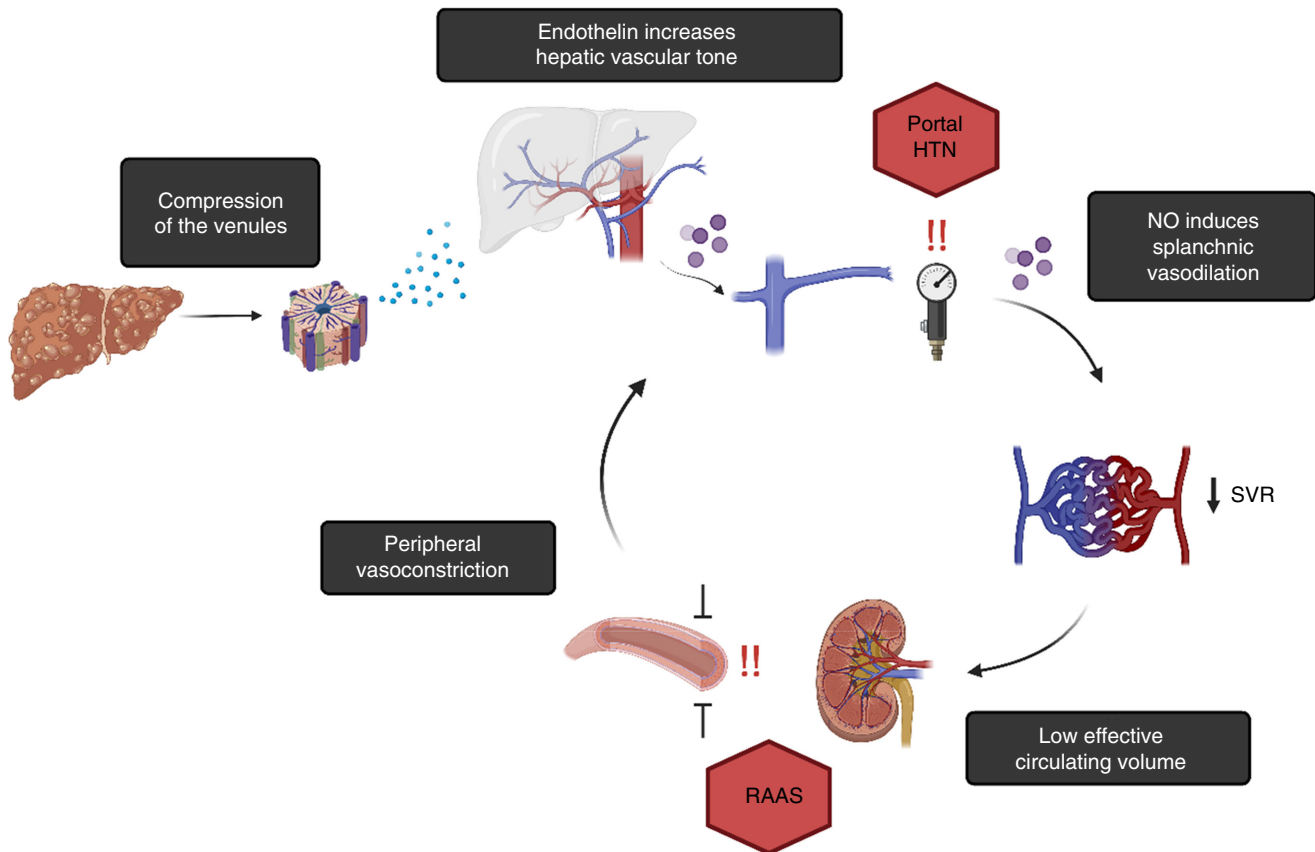
FIGURE 2 Pathophysiology of circulatory dysfunction in cirrhosis. Scarring and fibrosis distort the liver architecture and compress the hepatic venules. Increased production of local vasoconstrictors (ie. endothelin) result in increased intrahepatic vascular smooth muscle tone and portal (sinusoidal) hypertension. Nitric oxide (NO) release in response to increased portal pressure reduces systemic vascular resistance and increases capacitance of the venous circulation via splanchnic vasodilation. The combined effect of decreased systemic vascular resistance and movement of fluid to the extravascular compartment creates an 'effective hypovolemia' (decreased effective circulating volume). Baroreceptor mediated activation of the sympathetic nervous system leads to peripheral vasoconstriction to maintain organ perfusion. Perceived hypovolemia by the kidneys stimulates the renin-angiotensin-aldosterone system (RAAS) to increase salt and water retention. Sustained alternations in hemodynamics lead to irreversible changes in the cardiac and renal physiology and the formation of persistent disease states, such as cirrhotic cardiomyopathy and hepatorenal syndrome. Figure created with BioRender.com.

dysfunction resulting in the development of portal (sinusoidal) hypertension.[3,4] This occurs while there are simultaneous increases in splanchnic vasodilation, capacitance, and pooling.[5] As splanchnic volume and resistance rise, lymphatic capacity is exceeded and ascites forms. The combined effect of decreased systemic vascular resistance and movement of fluid to the extravascular compartment creates an 'effective hypovolemia' (decreased effective circulating volume). Pooling of blood in the splanchnic circulation, low albumin levels (causing persistent edema with low intravascular volume), and high output heart failure are often present in patients who are intravascularly volume depleted. Thus while total blood volume is often increased in cirrhosis, it is predominantly found in the splanchnic compartment, with correspondingly low thoracic blood volume.[6] Chronic effective hypovolemia predisposes patients to rapid development of renal injury when an acute shift in volume occurs, such as with diarrhoea, vomiting, gastrointestinal bleeding, and large volume paracentesis.

Perceived hypovolemia by kidneys stimulates the renin-angiotensin-aldosterone system (RAAS) to increase salt and water retention and contributes to the hypervolemic state seen in patients with cirrhosis.[7] Additionally, baroreceptor mediated activation of the sympathetic nervous system leads to peripheral vasoconstriction in order to maintain organ perfusion. All of this occurs in the context of diminishing albumin concentration, which reduces oncotic pressure and results in third spacing of retained extracellular volume. Overall, these fluid shifts between extracellular compartments exacerbate electrolyte and acid base disturbances.

The chronic hyperdynamic circulation in cirrhosis affects the heart as well and may hasten the progression of the aforementioned perturbations. Cirrhotic cardiomyopathy is characterised by a decreased contractile response to adrenergic stimulation and altered diastolic relaxation, which are visualised with echocardiography.[8,9] Cirrhotic cardiomyopathy can lead to complications including arrhythmias, pulmonary hypertension, hepatorenal syndrome, and sudden cardiac death.[10]

4 | THE NEED FOR PRECISE VOLUME ASSESSMENT IN CIRRHOSIS

Given their increased risk of bleeding, infections, and dehydration (including diuretics and lactulose excess), patients with cirrhosis are prone to intravascular volume depletion. However, it is important to recognise that patients with cirrhosis may also present in states of euvolemia or even volume overload, as they are also prone to decompensated heart failure or cirrhotic cardiomyopathy.[9] The goal of volume resuscitation is to replete intravascular volume and increase peripheral vascular tone.[11] Under- or over-correction of volume status can result in hypoxic end organ injury or tissue edema with venous congestion. Reflexive use of fluids for renal injury as a result of inaccurate assessment of fluid status can delay the initiation of critical therapies, such as vasopressors.

4.1 | The inadequacy of conventional measures

Standard clinical volume assessment includes medical history assessing volume loss or gain and physical examination findings of lower extremity edema, elevated JVP, and an S3 heart sound, which are not reliable in the context of cirrhosis. The volume exam can be highly variable across clinicians. It is supplemented by review of blood pressure, urine output, weight, chest radiography, and laboratory values (lactate, renal function, natriuretic peptide, albumin). These measures provide *indirect* evidence of high or low volume states and are subject to the same inaccuracies as the physical exam due to baseline hemodynamic disturbances in cirrhosis.[12,13] Therefore, additional tools are needed for robust assessment of intravascular volume.

4.2 | The volume status assessment toolbox

In the following section, we review the tools currently available for volume assessment. Each modality described has limitations and should not be used in isolation to determine fluid status. Invasive measures allow clinicians to determine real-time hemodynamic parameters. In contrast, non-invasive measures are often limited by providing single measurements in time. Dynamic fluid response assessments are shown to improve outcomes related to renal function, mechanical ventilation, and length of hospital stay.[14,15] The modalities described below are summarised in Figure 3.

4.2.1 | Central venous pressure

Central venous pressure (CVP) is measured by a catheter inserted into the internal jugular vein. It is a static hemodynamic measure often used to assess right ventricular preload and the risk for hepatic venous congestion and hypoxic injury with fluid administration.[16-19] Traditionally, a low CVP (<6–8 mmHg)

represents low or normal volume status and potential fluid responsiveness, while a high CVP (>12–15 mmHg) indicates hypervolemia. Unfortunately, the predictive value of these ranges for determining fluid responsiveness is low due to overlap with normal ranges in some cases, and they may only be clinically useful at extreme values.[20]

Central venous pressure is limited by both invasiveness and inability to provide continuous monitoring outside of the intensive care setting. Furthermore, the previously established targets for CVP, haemoglobin, and central venous oxygenation in early goal-directed therapy have since been refuted as they have no clinical benefit and can lead to volume overload from excessive fluid resuscitation. A small, retrospective study found that CVP had low predictive value for determining volume responsiveness (an increase in cardiac index by 15%) in patients without cirrhosis in the intensive care unit (ICU).[21] Furthermore, the utility of CVP is limited in patients with valvular pathology, pulmonary hypertension, right ventricular dysfunction, and intrathoracic pressure variability due to mechanical ventilation. However, non-invasive bedside measures of CVP are increasingly being developed and will be discussed further below.

4.2.2 | Pulse pressure variation

Pulse pressure is a derivative measure from arterial line tracings where diastolic blood pressure is subtracted from the systolic blood pressure. It estimates vascular compliance. Pulse pressure variation is calculated over several respiratory cycles by taking the difference between the maximal pulse pressure and the minimal pulse pressure, dividing by the average of the two, and then multiplying by 100.

Under normal physiologic conditions, pulse pressure variability is low, changing no more than 5–10 mmHg throughout the respiratory cycle. Pulse pressure is wide when preload is low, such as with hypotension, tamponade, or constrictive pericarditis. In the absence of tamponade or constrictive pericarditis, a pulse pressure variation of ≥13% is associated with fluid responsiveness.[22] The Valsalva manoeuvre decreases preload and increases pulse pressure variation. A pulse pressure variation of >52% with Valsalva indicates volume responsiveness.[23] Pulse pressure variation has been validated as a measure of fluid responsiveness in a small study of patients with cirrhosis undergoing liver transplant[24] and among those with shock.[25] Its utility is limited in patients with high intra-abdominal pressure (tense ascites), high pulmonary end-expiratory pressure, right ventricular failure, portopulmonary hypertension, and arrhythmias. Patients with cirrhosis commonly experience these comorbidities, which may limit the clinical applicability of pulse pressure variation.

4.2.3 | Pulmonary artery pressure

Pulmonary artery catheterization (also called right heart catheterization) can measure pulmonary artery pressure, guide resuscitation in the setting of pulmonary hypertension, and assess right
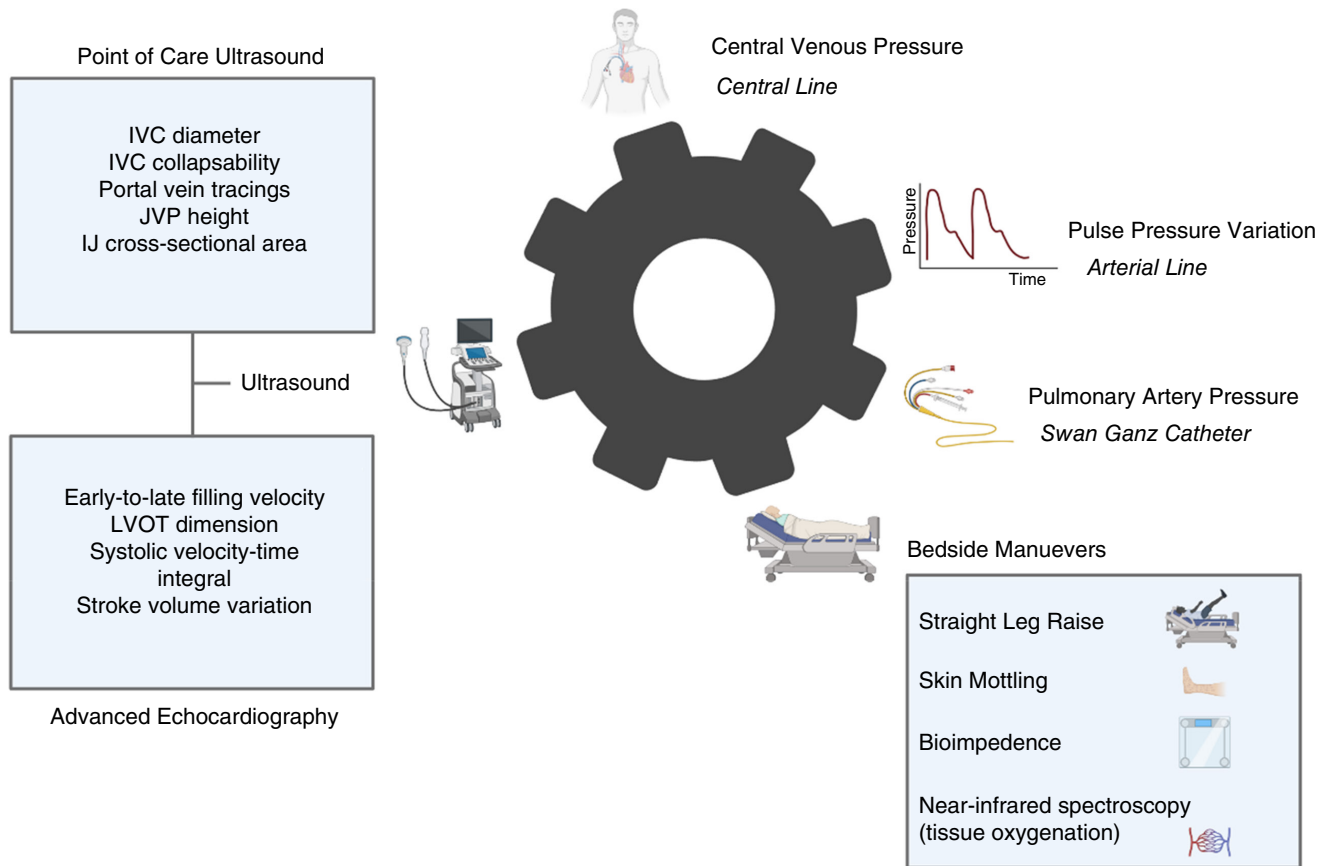
Volume Assessment Toolbox

FIGURE 3 The volume assessment toolbox. Figure created with BioRender.com.

ventricular failure. A normal mean pulmonary artery pressure is 12–16 mm Hg. Low mean pulmonary artery pressures (4–8 mm Hg) may suggest volume depletion. Elevated pressures (>20 mm Hg) may suggest either volume overload or pulmonary hypertension. It is important to recognise that many patients with cirrhosis have underlying pulmonary arterial hypertension (including portopulmonary hypertension) and thus elevated pulmonary artery pressures regardless of fluid status. Measuring pulmonary artery pressure requires either a Swan Ganz or quadruple lumen thermodilution tip catheter advanced into the main pulmonary artery. Pulmonary artery pressures may be assessed by single measurement during right heart catheterization or via continuous monitoring with an indwelling catheter in the critical care setting. Pulmonary artery catheters are preferred over CVP in cirrhosis by some authors due to the limitations of CVP secondary to ascites and left ventricular diastolic dysfunction.[26,27]

Pulmonary artery catheterization and measurement of pulmonary artery pressures are less widely used today due to the lack of clear clinical outcome benefit,[28] but is still recommended in guidelines for management of decompensated cirrhosis in the surgical ICU,[26] for volume assessment in severe or refractory cardiogenic shock,[29] and for patients with pulmonary hypertension. Pulmonary

artery catheterization is helpful for differentiating shock aetiology when a patient has undergone adequate fluid resuscitation.

4.2.4 | Cardiac output

Cardiac output monitoring is considered the gold standard for understanding a patient's hemodynamic state. A normal cardiac output is 4–8 L/min (or a cardiac index of 2.5–4 L/min/m^2). The most common method for measuring cardiac output is with a Swan Ganz (pulmonary artery) catheter using the thermodilution method. The thermodilution method relies on the change in blood temperature in the heart following an injection of cooled saline. This allows for a computerised calculation of flow rates and therefore estimation of cardiac output. As previously noted, pulmonary artery catheterization is a highly invasive procedure that does not consistently improve patient outcomes. Non-invasive measurement of cardiac output is discussed below.

While depressed cardiac output is associated with illness severity and poor outcomes in patients with cardiogenic shock, elevated cardiac output can be seen due to microvascular dysfunction in sepsis. Therefore, interpretation of cardiac output is highly dependent

on the clinical scenario and trends may be more informative than single values.

4.2.5 | Point of care ultrasound

Point of care ultrasound (POCUS) is gaining increasing popularity as a fast, effective, and inexpensive tool for assessing fluid status. For example, clinicians can quickly assess the inferior vena cava (ICV), cardiac function (ejection fraction), lungs (pulmonary edema versus effusions), portal vein pulsatility index, and internal jugular vein size.[30,31] Appropriate application of ultrasound requires careful integration of the findings into the patient's overall clinical picture prior to adjusting the treatment plan. The evidence supporting the use of POCUS for intravascular volume assessment in liver disease is scarce and often case-based.[32–34] When properly applied, however, POCUS can reveal clinician misclassification of fluid status and acute kidney injury (AKI) aetiology among hospitalised patients with cirrhosis.[32] POCUS implementation currently depends on clinician experience – increased training opportunities will be vital to ensuring dissemination, accurate image capture, and interpretation.

IVC diameter and collapsibility

A common use of POCUS is in the assessment of IVC size and dynamics, which are applicable only in spontaneously breathing patients. A small IVC diameter (<2.1 cm) and hyperdynamic collapsibility (>50% inspiratory collapse) may suggest either normal right atrial pressure or intravascular volume depletion. On the other hand, a plethoric and non-collapsible IVC may suggest intravascular volume overload in the correct clinical scenario. More specifically, an IVC diameter of >2.1 cm with <50% inspiratory collapse is commonly used as a surrogate finding for a high right atrial pressure, around 15 mmHg (range 10–20 mmHg).[35] A cross-sectional comparison of IVC diameter, IVC inspiratory collapse, and internal jugular vein height-to-width ratio for estimation of low CVP (<10 mmHg) demonstrated that maximal IVC diameter <2 cm was the most useful predictor of measured CVP (sensitivity 85%, specificity 81%).[36] Among medicine trainees, bedside IVC assessment in admitted patients may be superior to visual examination of the JVP for estimating right atrial pressure >10 mmHg.[37]

Unfortunately, IVC size is not a reliable indicator of cardiac output may not be indicative of the patient's true volume status or fluid responsiveness.[38] For example, in a small, observational study of patients with acute liver failure and shock, IVC distensibility was a poor predictor of fluid responsiveness.[25] IVC indices are better indicators of fluid *tolerance*, meaning that if the clinical situation calls for fluid resuscitation and the IVC is collapsing, then the patient will likely be able to tolerate fluids. The utility of IVC measurement in the setting of significant portal congestion and ascites is debated and the assessment may require additional skill in analysing dynamic IVC indices.[31,33] For example, significant ascites may impair IVC collapsibility due to elevated intraabdominal

pressure regardless of true intravascular volume status.[33,39] Other limitations to the use of IVC diameter for estimating right atrial pressure include a large body surface area, mechanical ventilation, narrowing of the IVC-RA junction, or the presence of webbing in the IVC.[40]

Hepatic vein doppler

Hepatic venous flow patterns can also indicate volume status by estimating right atrial pressure.[41] Under normal conditions, hepatic venous flow has a larger flow wave in systole than in diastole. On doppler, this is visualised as anterograde, phasic flow with waveform deflections below the baseline. In volume overload, there is less right atrial compliance and increased right atrial pressure. As a result, the diastolic flow wave increases relative to the systolic flow rate. The ratio of systolic to diastolic flow declines, until the systolic-diastolic flow ratio is reversed (pressure in the right atrium exceeds IVC pressure). This is visualised on doppler as waveform deflections above the baseline. As blood flows back into the liver during systole, venous congestion worsens. In contrast, in settings with decreased right atrial pressure (volume depletion), the doppler will show downward waveform deflection. In patients with severe liver fibrosis or tumour, hepatic vein doppler is a less reliable indicator of right heart filling. Individual waveforms seen in typical hepatic vein doppler are effaced and the tracing is monophasic with low velocity forward flow.[41] Additional limitations to using hepatic vein doppler include patients with underlying severe tricuspid regurgitation, prosthetic tricuspid valve, and atrial fibrillation. In contrast hepatic vein doppler is less impacted by mechanical ventilation.[42]

Portal vein doppler

Portal venous flow is continuous and non-pulsatile under normal circumstances. It becomes incrementally pulsatile as right atrial pressure and liver congestion increase, due to impaired regulatory capacity of the hepatic sinusoids. Measuring portal vein pulsatility can therefore provide insight into volume status. A pulsatility fraction is calculated by dividing the difference between the highest and lowest velocities in a cardiac cycle by the highest velocity, and then multiplying by 100.[43] Portal vein pulsatility of ≥30% is considered moderately elevated, while pulsatility ≥50% is considered severely abnormal. Unfortunately, there are reports that patients with cirrhosis and portal hypertension may demonstrate pulsatile portal venous flow in the absence of high right atrial pressure.[44] Additionally, pulsatility in these patients may represent local pressure changes rather than transmission of right atrial pressure.

Internal jugular vein indices

The internal jugular vein cross-sectional area will normally increase by 20%–30% following Valsalva among patients with normal right atrial pressure.[45] This is obtained by calculating the percent change in the maximal internal jugular vein cross-sectional area during the Valsalva manoeuvre and at rest. An increase in internal jugular vein cross-sectional area by >17% during Valsalva is sufficient to rule out increased right atrial pressure, as determined by right heart catheterization.[45]

Another technique is to calculate the internal jugular vein aspect ratio (cross-sectional height to width). An aspect ratio of <0.83 correlates a central line measured CVP < 8 mm Hg and likely hypovolemia.[46]

POCUS of the internal jugular vein may also be used to determine JVP height and predict CVP.[47,48] This is commonly performed by scanning the vessel cranially to find the position at which the diameter of the internal jugular vein is smaller than the diameter of the common carotid artery, then adding 5 cm to the measured height from the sternal angle.[47] A study conducted in two US academic institutions demonstrated that ultrasound-measured JVP was predictive of elevated CVP, as measured by right heart catheterization.[47] In contrast, one study noted that while POCUS of the internal jugular vein reliable reproduces JVP, it may underestimate CVP in patients with more extreme elevations in CVP.[49] A systematic review assessing the various internal jugular vein measurements concluded that measurements of collapsibility were superior to static measurements for determining hypovolemia.[50] There was no clear consensus for which measurement is superior for determining hypovolemia, though the authors recommend internal jugular vein height as it is simple to perform.[50] Assessing the internal jugular vein with POCUS is limited by the presence of central venous catheters and it will be elevated in cases of cardiac tamponade regardless of volume status.

4.2.6 | Advanced cardiac ultrasound

Formal transthoracic echocardiography can evaluate cardiac dysfunction in cirrhosis and expand the volume assessment beyond what can be reasonably accomplished by the bedside clinician using POCUS.[51,52] For example, increased left ventricular end diastolic volume and cardiac output suggest development of cirrhotic cardiomyopathy and volume accumulation.

Cirrhotic cardiomyopathy is defined using either systolic or diastolic dysfunction criteria.[9] Systolic dysfunction is defined by either left ventricular ejection fraction ≤50% or absolute global longitudinal strain <18%. Advanced diastolic dysfunction is defined by three of more of the following: septal early diastolic mitral annular velocity (e′) <7 cm/s, mitral inflow early diastolic velocity (E) to e′ ratio ≥15, left atrial volume index >34 mL/m^2, or tricuspid regurgitation velocity >2.8 m/s (in the absence of known primary pulmonary arterial hypertension or portopulomary hypertension).

Additional markers of cardiac dysfunction can also assist in characterising volume status but are not used in the definition of cirrhotic cardiomyopathy. For example, cardiac output can be estimated non-invasively using transthoracic echocardiography through measurement of the left ventricular outflow tract diameter, velocity time integral, and heart rate. Pulsed wave doppler evaluation of these same measures are also used to calculate cardiac output and may be more accurate, potentially improving the assessment of the patient's response to initial resuscitation. Stroke volume variation measured via echocardiography has been studied as a semi-continuous measure of preload and volume resuscitation response in patients undergoing liver surgery.[53] The presence of atrial fibrillation, heart failure, and mechanical ventilation limits accuracy of stroke volume variation in these patients and is further compounded by altered aortic filing due to increased abdominal pressure and reduced vascular tone.[25,53]

4.2.7 | Bedside measurements

At the bedside, measures such as skin mottling score, tissue oxygenation, and bioimpedance testing are non-invasive markers that can be used to guide resuscitation. There are also several simple manoeuvres that can be used to understand a patient's hemodynamic state.

Skin mottling score. Mottling is an irregular, patchy discoloration of this skin that arises due to heterogenous small vessel vasoconstriction. It indicates hypoperfusion of the dermis and may be used as a surrogate marker of organ microcirculation. Skin mottling is typically assessed at a patient's knees and is graded on a scale from 0 to 5, where a higher score indicates more extensive mottling and therefore more widespread perfusion deficits.[54] Increased mottling has been associated with higher lactate, decreased urine output, and mortality among patients with septic shock.[55,56] Among patients with cirrhosis and septic shock, those with skin mottling at the time of intensive care unit (ICU) admission had in-ICU mortality of 83% and none of the patients with persistent skin mottling survived.[54] These mortality rates are higher than those seen in general ICU cohorts even after isolating a subset of patients with cirrhosis.[57] Skin mottling severity may be a useful, early indicator of overall illness severity, regardless of mean arterial pressure (MAP) or concurrent use of vasopressors.[56]

Near-infrared spectroscopy. Near-infrared spectroscopy (NIRS) is a technique used to assess tissue oxygen saturation of haemoglobin and can be measured at various tissue sites. In a small, single center study, the normal range for thenar NIRS tissue oxygenation was 87% (range: 81%–93%), with values of 83% (range: 73%–93%) for mild shock, 80% (range: 68%–92%) for moderate shock, and 45% (range: 19%–71%) for severe shock.[58] Two studies have demonstrated that low NIRS-measured tissue oxygenation (at various locations) predicts mortality in critically ill patients.[59,60] Among patients with cirrhosis, low NIRS-measured tissue oxygenation at the knee correctly identifies patients with worsening hypoxia and predicts mortality.[54] NIRS has the benefit of capturing hypoxia when traditional pulse oximetry does not.[54] There is limited evidence that the accuracy of NIRS decreases in the setting of increased tissue edema among critically ill patients, but the magnitude of this potential effect is not fully understood.[61]

Bioelectrical impedance analysis. Multifrequency bioelectrical impedance analysis determines the distribution of water by measuring total body water, extravascular water, and intravascular water. Compared to patients with compensated cirrhosis, those with decompensated cirrhosis have similar total body water.[62] However, they have a higher proportion of extracellular water, particularly in

the lower extremities and trunk.[62] A small, early study of bioelectrical impedance analysis in patients with cirrhosis compared to controls suggested that the measure is less accurate in those who exhibited signs of fluid overload compared to those who were clinically 'dry', however, this has not been replicated.[63] Patients undergoing hepatectomy for hepatocellular cirrhosis with higher extracellular to total body water ratio were more likely to experience post-operative complications, such as AKI or ascites formation.[64] In our experience, bioimpedance testing is currently not uniformly available across clinical practice settings.

Passive leg raise. Finally, passive leg raise mobilises approximately 300cc of blood back to the heart and is dynamic test of volume responsiveness. Passive leg raise has a 85% sensitivity and 92% specificity for predicting fluid responsiveness, compared to cardiac output.[65] In patients who are intravascularly volume depleted, passive leg raise results in immediate increase in cardiac output.[66] It is less reliable in cases were the patient is severely volume depleted or has tense ascites.[67]

5 | APPROACH TO FLUID RESUSCITATION

5.1 | Selection of resuscitative fluid in cirrhosis

There is a modest body of evidence for fluid selection in critically ill patients without cirrhosis[68–70] and relatively little for those with cirrhosis (Tables 1 and 2).[71,72] The ongoing debate on the use of crystalloids versus colloids in initial volume resuscitation in critical care has led to multiple trials with varied results.[73–76] However, patients with cirrhosis are rarely included in prospective studies of fluid resuscitation comparing crystalloids and colloids.[73,76,77] The findings are nonetheless often extrapolated to guide management of resuscitation in cirrhosis.[11] Figure 4 outlines our proposed algorithm for resuscitation of patients with decompensated cirrhosis.

5.1.1 | Colloids versus crystalloids

Due to their low molecular weight, crystalloids require large volume infusion to produce benefit, which can risk acidemia, hepatic and pulmonary congestion, and tissue edema. Normal saline infusions can provoke hyperchloremic metabolic acidosis and precipitate further renal vasoconstriction, increasing the risk of AKI in an already predisposed population. With any fluid, but particularly with crystalloids, a large proportion will diffuse into the extravascular space after initial intravascular volume expansion and may worsen ascites, peripheral edema, or pulmonary edema. Additionally, due to chronic respiratory alkalosis in cirrhosis, providing base anion-containing fluids (including lactated Ringer's and plasma-lyte) risks worsening alkalosis and potentially lactate accumulation, though the latter is not currently well understood.

Colloids have higher molecular weight, remain in the intravascular space for longer periods, and provide less volume than crystalloids.[78] However, colloids have not been shown to significantly improve short- or long-term outcomes. Thus, due to lower cost, crystalloids are often the first choice for resuscitation in hypovolemia and sepsis.[68]

5.1.2 | Electrolyte and acid–base considerations

In patients who present with non-gap metabolic acidosis and acute kidney injury, isotonic bicarbonate is preferred when the pH is <7.25 and serum bicarbonate <17. In these cases, the patient is often hyperkalemic, which will simultaneously improve with bicarbonate therapy. Among patients with cirrhosis, high anion gap metabolic acidosis is often driven by reduced lactate clearance by the liver and kidneys. It is further exacerbated by acute alcohol ingestion and chronic thiamine deficiency.

On the other hand, patients with cirrhosis can also have a chronic respiratory alkalosis and hypokalemia. This may occur independently, or in association with a distal renal tubular acidosis. Both acidosis and hypokalemia affect ureagenesis, urea clearance, and ammonia production, and consequently the risk of hepatic encephalopathy.[79] Therefore, selecting resuscitative fluids requires consideration pH and potassium rather than serum bicarbonate alone.

5.2 | The role of albumin in liver disease

Albumin is exclusively produced by the liver and modulates plasma oncotic pressure. Albumin also stabilises the endothelium by maintaining the glycocalyx and preserving capillary permeability and has antioxidant thiols which reduce the formation of toxic free radicals.[80–82] Additional non-oncotic properties of albumin are well summarised in two recent reviews.[83,84] Albumin production is reduced in chronic liver disease due to impaired hepatocyte synthetic function as the liver becomes progressively fibrosed and inflamed. Furthermore, the albumin that is produced has impaired function and may not fulfil its many roles as a plasma protein. Therefore, it seems logical to attempt albumin repletion in cirrhosis. The primary disadvantage to large volume or recurrent albumin infusions as they can contribute to chloride excess, pulmonary edema, acid base disturbances, and coagulopathy.[72]

5.2.1 | Albumin as a resuscitative fluid

Albumin was first studied as a resuscitative fluid on a large scale among mild to moderately ill patients without cirrhosis and failed to demonstrate superiority over normal saline.[68] As patients with cirrhosis tend to have multiorgan system dysfunction even in steady state, the trial findings may be less applicable to this population. Two trials in critical care settings of patients with cirrhosis followed (Table 1).[71,72]

TABLE 1 Randomised controlled trials of albumin as a resuscitative fluid in cirrhosis.

Study	N	Study population	Intervention	Primary outcome	Secondary outcomes	Conclusion
Patients with cirrhosis admitted to the ICU						
FRISC Study, *Hepatol Int* 2021[71]	308	Patients with cirrhosis admitted for sepsis-induced hypotension at a single center	5% human albumin vs. normal saline	MAP > 65 mm Hg at 3 h	Serial effect on HR, lactate, and urine output.	Faster and more sustained improvement in MAP for patients receiving albumin.
ALPS Trial, *J Hepatol* 2022[72]	100	ICU patients with cirrhosis admitted with sepsis-induced hypotension	20% albumin vs. plasma-lyte	MAP > 65 mm Hg at 3 h	Serial effect on lactate clearance, RRT requirement, duration of ICU stay, time on mechanical ventilation, and 28-day mortality.	Albumin was superior to plasma-lyte in reversing hypotension. No difference in survival. Higher rates of pulmonary complications with albumin.
Patients with decompensated cirrhosis admitted to general medical wards						
Altman et al, *Eur J Gastroenterol Hepatol* 1998[110]	60	Patients with cirrhosis and tense ascites undergoing large volume paracentesis	Albumin vs. hydroxyethyl starch (HES)	Post-procedural complications	Change in weight, plasma aldosterone concentration, plasma atrial natriuretic factor, coagulation markers, and MAP	No difference in post-paracentesis complications. Albumin was associated with greater weight loss.
Sort et al, *NEJM* 1999[87]	126	Patients with cirrhosis and SBP	IV cefoxatime vs. IV cefoxatime + albumin	Worsening renal function (increased Cr, oliguria). In-hospital mortality.	3-month mortality.	The addition of IV albumin decreased incidence of renal impairment and death.
Gentilini et al, *J Hepatol* 1999[111]	126	Patients with cirrhosis with refractory ascites	Diuretics + albumin vs. diuretics alone	Disappearance of ascites, hospital length of stay		Albumin improved response to diuretics and decreased hospital length of stay.
Garcia-Compean et al, *Ann Hepatol* 2002[112]	69	Patients with cirrhosis and tense ascites undergoing large volume paracentesis	Albumin vs. low-molecular weight dextran	Incidence of paracentesis-induced circulatory dysfunction (change in plasma renin and plasma aldosterone activity)	Weight change, kidney impairment, recurrence of ascites, survival.	Incidence of paracentesis-induced circulatory dysfunction was lower among patients receiving albumin.
Fernanadez et al, *Hepatol* 2005[113]	20	Patients with cirrhosis and SBP	Ceftriaxone + 20% albumin vs. ceftriaxone + HES	Hemodynamic changes at time of SBP resolution (plasma renin activity, MAP, right atrial pressure, pulmonary capillary pressure, heart rate)	Hepatic function, renal function, and coagulation factors.	Albumin, but not HES, was associated with improved systemic hemodynamics. Both groups showed modest improvement in SCr, but no change in hepatic function.

TABLE 1 Continued

Study	N	Study population	Intervention	Primary outcome	Secondary outcomes	Conclusion
Romanelli et al, *World J Gastroenterol* 2006[114]	100	Patients with cirrhosis with first-onset ascites	Diuretics + albumin (weekly or every 2 weeks) vs. diuretics alone	Survival without liver transplantation	Recurrence of ascites, hepatic encephalopathy, variceal bleeding.	Albumin increased transplant-free survival and decreased rates of recurrent ascites.
Alessandria et al, *Dig Liver Dis* 2011[115]	70	Patients with cirrhosis and ascites undergoing large volume paracentesis	8 g of albumin/L ascites removed vs. 4 g of albumin/L ascites removed	Incidence of paracentesis-induced circulatory dysfunction	Kidney failure, hyponatremia.	Incidence of paracentesis-induced circulatory dysfunction was no
Guevara et al, *J Hepatol* 2012[116]	110	Patients with cirrhosis with non-SBP infections	Antibiotics + 20% albumin vs. antibiotics alone	3-month mortality	Change in SCr, new ESKD, and circulatory dysfunction.	Albumin did not decrease 3-month mortality.
Simon-Talero et al, *J Hepatol* 2013[117]	56	Patients with decompensated cirrhosis and hepatic encephalopathy	Albumin vs. isotonic saline plus usual care	Presence of hepatic encephalopathy at hospital day 4.	Severity of encephalopathy, length of stay, 30- and 90-day mortality. Levels of pro-inflammatory cytokines, ammonia, and circulatory dysfunction markers.	Albumin did not decrease time to resolution of hepatic encephalopathy.
Fernandez et al, *Gastroenterology* 2019[85]	96	Patients with decompensated cirrhosis in the Pilot-PRECIOSA and INFECIR-2 studies	Albumin 1 g/kg q2 weeks vs. 1.5 g/kg weekly	Change in serum albumin, plasma renin, cardiocirculatory function, portal pressure, and plasma cytokine levels.		High-dose albumin was associated with normalisation of serum albumin, improved circulatory stability and LV function, and reduced plasma cytokines.
Arora et al, *Hepatology* 2020[81]	80	Patients with cirrhosis undergoing large volume paracentesis	20% albumin vs. no albumin following paracentesis	Incidence of paracentesis-induced circulatory dysfunction	Hemodynamic changes, hyponatremia, encephalopathy, hepatorenal syndrome.	Albumin decreased the incidence of paracentesis-induced circulatory dysfunction.
Fernandez et al, *Clin Gastroenterol Hepatol* 2020[118]	118	Patients with cirrhosis with non-SBP infections	Antibiotics + 20% albumin vs. antibiotics alone	In-hospital mortality.	Grade of circulatory dysfunction, systemic inflammation, 90-day mortality.	The addition of IV albumin did not reduce in-hospital mortality versus antibiotics alone.
ATTIRE trial, *NEJM* 2021[86]	777	Patients with decompensated cirrhosis and serum albumin <3.0 g/dL	20% albumin vs. standard of care for up to 14 days	New infection, kidney dysfunction, or death between days 3–15 of treatment	28-day and 6-month mortality	Albumin infusions to target a serum level of 3.0 g/dL or more was not more beneficial than standard of care.

Abbreviations: ESKD, end-stage kidney disease; HES, hydroxyethyl starch; HR, heart rate; ICU, intensive care unit; LR, Ringers lactate solution; MAP, mean arterial pressure; NS, normal saline; RRT, renal replacement therapy; SBP, spontaneous bacterial peritonitis; SCr, serum creatinine.

The FRISC study randomised patients with cirrhosis and sepsis-induced hypotension to receive 5% albumin or normal saline.[71] The patients who received albumin had higher rates of hypotension reversal at 1 and 3 h of treatment. Additionally, these patients had reduced heart rate, higher MAP, increased urine output, and lower lactate concentration at 3 h compared to those who received normal saline. Patients receiving albumin also demonstrated a small, though statistically significant, improvement in mortality at 1 week post-randomization.[71] However, albumin was associated with increased risk of pulmonary edema. The overall absolute changes in hemodynamics in this study were modest and long-term survival was not studied. Furthermore, patients were eligible to receive fluids at the

TABLE 2 Randomised controlled trials comparing balanced crystalloids as resuscitative fluids in the ICU.

Study	N	Study population	Intervention	Primary outcome	Secondary outcomes	Conclusion
Patients admitted to the ICU, some with cirrhosis						
SPLIT Trial, *JAMA* 2015[73]	2278	ICU patients (1% of each study arm had cirrhosis)	Plasma-lyte vs. normal saline	Proportion of patients with AKI	New RRT and in-hospital mortality	No decreased risk of AKI with balanced solutions.
BASICS Trial, *JAMA* 2021[75]	11,052	ICU patients (2.5% of each study arm had cirrhosis)	Plasma-lyte vs. normal saline	90-day survival	New RRT, AKI at day 3 and 7, SOFA score, and ventilator-free days	No significant reduction in 90-day mortality with balanced solutions.

Abbreviations: AKI, acute kidney injury; HR, heart rate; ICU, intensive care unit; LR, Ringer lactate solution; MAP, mean arterial pressure; NS, normal saline; RRT, renal replacement therapy; SOFA, sequential organ failure assessment.

discretion of the treating provider after 3h, which may have diminished the treatment effect.

In the ALPS trial, patients with cirrhosis and sepsis-induced hypotension were randomised to receive 20% albumin or plasma-lyte.[72] As with the FRISC trial, the patients who received albumin demonstrated earlier improvement in MAP (hypotension reversal). The albumin group also had later dialysis initiation, though overall rates of dialysis were similar between the two groups. Patients who received albumin had similar 28-day survival to the plasma-lyte patients but were also more likely to experience pulmonary complications.[72]

Albumin lacks sufficient trial data to support a superior mortality benefit for initial resuscitation in cirrhosis, but it may have advantages in specific clinical scenarios (Table 1).[85–87] For example, albumin has shown efficacy in preventing renal dysfunction after large-volume therapeutic paracentesis, and in prevention hepatorenal syndrome (HRS) during spontaneous bacterial peritonitis.[87,88] On the other hand, the recent ATTIRE trial showed that targeting an albumin level >3 g/dL with 20% albumin infusion did not reduce incident infection or kidney dysfunction compared to standard care.[86] This study was conducted in patients with decompensated cirrhosis and low baseline serum albumin. Patients who received albumin experienced higher rates of pulmonary edema and volume overload than patients receiving standard of care.[86] In summary, the role of albumin for resuscitation may be limited to select clinical indications and should be used in moderation to prevent adverse events such as pulmonary edema.

5.2.2 | Albumin resuscitation in Hepatorenal syndrome

The clearest indications for albumin in cirrhosis are in the treatment of spontaneous bacterial peritonitis (in conjunction with antibiotics) and acute HRS (HRS-AKI). While AKI is present in about 50% of hospitalised patients with cirrhosis, the specific physiology of HRS represents a unique state of end-organ damage from circulatory compromise.[89] In HRS-AKI, albumin improves perfusion by providing colloid and thereby increasing intravascular fluid retention (plasma expansion) and improving cardiac output. It may also synergistically augment vasoconstrictor therapy,[90] potentially by binding the vasodilators released in cirrhosis and further improving hemodynamics.[84]

While albumin is widely known as part of the HRS treatment protocol, it may not be warranted as therapy in all cases – assessment of volume status remains critical to prevent adverse effects of inappropriate resuscitation. For patients who appear volume depleted, volume resuscitation with 1 g/kg albumin per day is first line treatment in HRS (maximum 100g/day on the first day) and 20–40g/day thereafter as clinically indicated. Once an "albumin challenge" is completed, clinicians must reassess the patient's volume status, MAP, and kidney function to confirm benefit or escalate therapy with intravenous vasopressors.[91] Ultimately, the treatment for HRS is liver transplantation.

Until recently, vasopressors for treatment of HRS-AKI in the United States included oral midodrine (often with intravenous octreotide) or intravenous norepinephrine.[92,93] Terlipressin, a synthetic vasopressin analogue, was approved for treatment of HRS-AKI in the United States in 2022 after the CONFIRM trial showed benefit for HRS reversal over placebo (it has been used in practice in other countries for several years).[94] In this study, both groups were concurrently treated with albumin, and the beneficial effect of terlipressin was attributed to increased splanchnic vasoconstriction, which increases the return of blood to systemic circulation, therapy improving renal perfusion and decreasing stimulation of the renin-angiotensin-aldosterone system.[94,95] Studies comparing the efficacy of terlipressin to midodrine or norepinephrine in HRS-AKI are small and do not support clear superiority of terlipressin as benefits on hard clinical outcomes, such as mortality, are lacking.[96–99]

Terlipressin represents an exciting new avenue for HRS treatment in the United States, but it is not without potential risks. For example, early trials of terlipressin noted increased risk of pulmonary edema.[94] This may be due to increased hydrostatic stress in the pulmonary vasculature, which is not seen with norepinephrine, or an activation of the V1 and V2 receptors on the pulmonary vascular endothelium.[100,101] The higher rates of pulmonary edema in these trials may also be due to the simultaneous high albumin dosing, which was not protocolized in most trials. In the CONFIRM trial, patients in both groups received
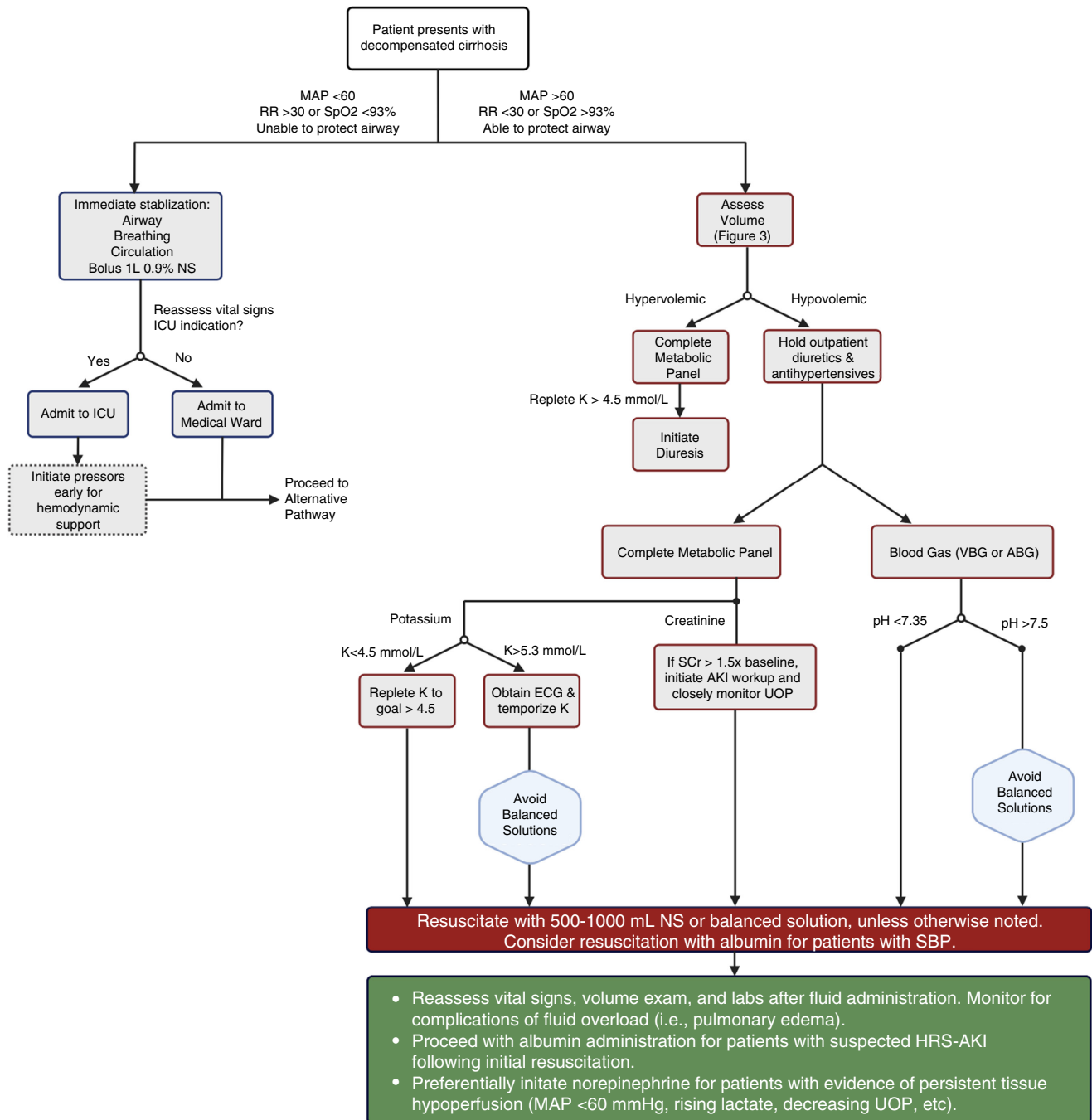
FIGURE 4 Recommended protocol for resuscitation in patients with decompensated cirrhosis. Figure created with BioRender.com.

high doses of albumin prior to randomization (335 g in the terlipressin group, 371 g in placebo).[94,101] Following randomization, receiving terlipressin received a mean total albumin dose of 199 ± 147 g and those in the placebo group received 240 ± 184 g.[94,101] Respiratory adverse events were highest among patients in the terlipressin group receiving the highest albumin doses.[102] Given the adverse events associated with albumin administration seen in the ATTIRE trial, the risk of pulmonary edema with terlipressin may be due to the interaction with concomitant, very high dose albumin rather than solely a drug effect. These studies emphasise the importance of using intravenous albumin in moderation to prevent fluid overload.

6 | ENDPOINTS IN RESUSCITATION

6.1 | Assessing tissue perfusion

Restoring tissue perfusion is the primary goal of volume resuscitation to prevent ongoing end-organ damage, typically by increasing cardiac output. Volume resuscitation in cirrhosis requires close monitoring due to the risks of over-resuscitation in a population with underlying cardiorespiratory comorbidities.[103] However, there is no single marker that fully captures organ perfusion and additional studies of resuscitation endpoints are underway.[104]

In the context of cirrhosis, traditional absolute targets may be less reliable – for example, elevated lactate could be due to impaired clearance rather than ongoing hypoperfusion. Trends in various biomarkers, such as MAP, cardiac output, urine output, lactate, and oxygenation, are likely more clinically relevant than single measurements. This is particularly true given the underlying impaired circulatory function in cirrhosis, which may interfere with the accuracy of arterial lines, cardiac output, and CVP monitoring in these patients.

6.2 | Assessing hemodynamics

Re-evaluating hemodynamic parameters is essential following initial volume resuscitation. However, endpoints for resuscitation based on continuous hemodynamic monitoring (cardiac output, CVP, pulmonary artery pressure, or left ventricular end-diastolic pressure) or MAP are not well established in cirrhosis. Should we tolerate lower MAP goals because baseline blood pressure tends to be lower in cirrhosis, or should we set higher MAP goals due to the high risk of AKI (kidney hypoperfusion) in patients with cirrhosis? Clinical trials comparing fluid resuscitation strategies in cirrhosis employ traditional endpoints such as hypotension reversal (MAP ≥ 65 mmHg) at one- and three-hours post-resuscitation, change in heart rate and urine output, lactate clearance, and short-term mortality (7–28 days).[71,72]

Recommended MAP goals in cirrhosis include a target range of 60–65 mmHg or an increase in MAP by 10–15 mmHg and are based on observational data and expert opinion.[27,105] For example, an retrospective study of patients with cirrhosis in the ICU compared time spent at MAPs ranging from 55 to 75 mmHg and determined that a MAP goal of 65 mmHg was associated with lower ICU mortality in adjusted analyses, whereas other targets were non-significant.[105] These data are limited by the retrospective, observational study design and likely significant residual confounding. A randomised controlled trial of MAP targets (60–65 vs. 80–85 mmHg) in critically ill patients with cirrhosis was presented at the 2021 American Association for the Study of Liver Diseases conference.[106] It showed no difference in 28-day mortality, reversal of shock, or acute kidney injury between the groups using an intention-to-treat analysis. Incidence of intradialytic hypotension was lower and adverse events were higher in patients with a MAP goal of 80–85 mmHg. The trial reported improved secondary outcomes with a MAP goal of 80–85 vs. 60–65 mmHg when using a per-protocol approach. The full manuscript was not available at the time of this review; therefore, it is unknown how well the trial achieved MAP separation between the two groups.

Cardiac output is a dynamic measure that provides immediate feedback following a fluid challenge and an increase in cardiac output (or index) of 15% typically defines a positive response in the existing general ICU literature.[27,107] However, an increase by 15% is unlikely to translate into clinical benefit unless it also results in a sustained increased oxygen delivery, tissue oxygen utilisation, and intravascular fluid retention. Unfortunately, fluid redistribution is common among critically ill patients with vascular endothelial damage, especially in the case of decompensated cirrhosis with ascites. Thus, even under ideal circumstances, not all patients who are 'fluid responsive' will meaningfully increase tissue oxygenation.[108] A small observational study of critically ill patients with acute liver failure and shock requiring pressors found that only 29% of patients increased their cardiac index in response to a 5 mL/kg fluid bolus.[25] Indications for fluid resuscitation in this study included increasing lactate, low central venous saturation, or increasing vasopressor requirements. Unfortunately, neither volume status, vasopressor dose, nor clinical outcomes were captured and thus the importance of this finding is unclear.[25] Other hemodynamic resuscitation endpoints such as CVP and pulmonary artery pressure are even less well studied in the context of cirrhosis.

6.3 | Escalating hemodynamic support with vasopressors

In patients who are unresponsive to volume expansion and show ongoing evidence of organ hypoperfusion, it is essential to initiate vasopressors early. In cases when vasoconstrictor therapy is needed, norepinephrine is the most well studied medication for blood pressure support in decompensated or critically ill patients with cirrhosis. Patients who develop increasing pressor requirements may also need stress-dose steroids for management of adrenal insufficiency, which is a common complication of cirrhosis.[109] In Figure 4, we outline our proposed protocol for resuscitation of patients with decompensated cirrhosis.

7 | CONCLUSION

The unique circulatory dysfunction and metabolic derangements in cirrhosis complicate both volume assessment and volume resuscitation. We encourage clinicians to expand their comfort with tools such as POCUS, tissue oxygenation, and dynamic hemodynamic measures, which may augment the volume exam. This is particularly relevant in cirrhosis as lower extremity edema, elevated JVP, and low blood pressure which may be present in both hypovolemia and hypervolemia in patients with cirrhosis. Clinicians should consider electrolyte and acid base disturbances in their fluid selection, remembering that metabolic acidosis and hypokalemia can provoke hepatic encephalopathy in this population. We recommend normal saline for initial resuscitation, albumin the context of HRS-AKI or spontaneous bacterial peritonitis, and early initiation of vasopressors to avoid the complications of fluid overload (Figure 4). Further studies are needed to develop and validate volume assessment tools in the context of cirrhosis, while randomised clinical trials establishing protocolized resuscitation based on validated assessment of volume and hemodynamics will improve the care of patients with cirrhosis.

AUTHOR CONTRIBUTIONS

Sophie Claudel: Conceptualization (equal); data curation (equal); methodology (equal); writing – original draft (equal); writing – review

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