


Factors improving mortality in critically ill patients with liver failure – A systematic review

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ABSTRACT

Background: Acute and chronic hepatic failure can lead to increased mortality in critically ill and perioperative patients. Understanding the pathophysiological principles of these conditions in critically ill patients is of great importance to reduce mortality. The aim of our systematic literature review was to identify all randomized controlled trials on any intervention that had a statistically significant documented reduction in mortality in patients with hepatic failure. **Methods:** We searched PubMed, Scopus and Embase databases for pertinent studies on January 1st 2021. The following studies were included: randomized controlled trials; studies investigating adult critically ill or perioperative patient populations with any form of hepatic failure; mortality as primary or secondary outcome; and statistically significant differences in mortality between the examined groups. **Results:** We finally found nine trials in our systematic review on the effect of antibiotic administration and infectious diseases among patients with cirrhosis (three studies); immune modulation after liver transplantation (one study); administration of colloids in cirrhotic patients (one study); the effect of high-volume plasma exchange in acute liver failure (one study); administration of N-acetylcysteine in acute liver failure (one study); and treatment with terlipressin (two studies). **Conclusion:** In the present review we found only nine randomized studies with a documented survival benefit in patients with liver failure. Strategies that most improved mortality were associated with the outcome of sepsis and renal function.

KEYWORDS

hepatic dysfunction, acute liver failure, cirrhosis, mortality, sepsis, critically ill

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BACKGROUND

Liver failure, which can be acute liver failure (ALF), acute on chronic liver failure (ACLF), or secondary acquired liver injury (i.e., cholestasis and/or hypoxic liver injury), is frequently detected during critical illness and intensive care unit (ICU) stay and is associated with higher mortality [1–4]. Liver failure can be a consequence or even a cause of multi-organ failure (MOF) and critical illness. The incidence of any type of liver failure in the ICU is at least 20%, demonstrating the importance of this condition [5, 6]. Both ALF and ACLF have high mortality rates, ranging from 23% to 86% [7].

Understanding the pathophysiological principles of liver failure and identifying factors that reduce mortality are of great importance, as liver failure is associated with high mortality. Additionally, we should consider some specific conditions that may occur during liver failure, increasing the risk of further complications and worsening the prognosis: increased susceptibility to infections, portal hypertension, ascites, hydrothorax, hepatorenal syndrome or variceal hemorrhage [8].

Current data show a high variability in mortality rates in critically ill patients with liver failure [7]. Moreover, mortality risk stratification is difficult, especially in conditions requiring ICU admission. Scoring systems (e.g., Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score; and Acute Physiology and Chronic Health Evaluation (APACHE) score) targeting to evaluate the potential mortality risk of critically ill patients with ALF or ACLF are not specific to hepatic failure as they also include other organ systems [9, 10]. A retrospective cohort study analyzed predictors of mortality in ACLF patients requiring ICU admission. It was shown that serum lactate levels and the number of organ failures at ICU admission were useful elements of mortality risk stratification [11]. However, as hepatic failure is a complex and heterogeneous condition due to the different liver functions and the wide range of liver failure etiologies, it is challenging to determine which factors and interventions affect mortality. Furthermore, few randomized controlled trials (RCT) are available, and most of our recent knowledge is based on retrospective analyses or observational studies of liver failure outcomes. Indeed, the Guidelines for the Management of Adult Acute and Acute-on-Chronic Liver Failure in the ICU contain a number of recommendations on various aspects of these diseases, but many suggestions are not based on RCTs or high-quality evidence [12].

To our knowledge, strong evidence on factors that reduce mortality in critically ill patients with hepatic failure remains lacking. The aim of the present study was to perform a systematic review and identify all RCT that evaluated any drug, intervention, or method with a statistically significant documented mortality reduction in patients with any form of ALF or ACLF.

METHODS

This review was written according to the Preferred Reporting Items for Systemic Reviews and Meta-analysis (PRISMA) extension statement for reporting systematic reviews ([Additional file 1](#)).

Search strategy

Four researchers searched PubMed, Scopus and Embase databases electronically for pertinent studies on January 1st 2021. Our aim was to identify all RCTs on any intervention affecting mortality in critically ill or perioperative patients with any form of ALF or ACLF.



The complete search strategy and the exact terms used in the literature search can be found in [Additional file 2](#).

After duplicate removal, titles and abstracts were first independently reviewed by four investigators. Disagreements were resolved by consensus and a senior author was consulted. Inclusion criteria included the followings: 1. studies designed as RCTs; 2. studies investigating critically ill or perioperative patients with any form of ALF or ACLF; 3. studies including patients older than 18 years; 4. studies targeting mortality as a primary or secondary outcome; 5. studies that found statistically significant differences in mortality.

There were no restrictions on the language of the publication and the date of publication. Full-text articles were retrieved and independently examined by the same authors as before for eligibility. The process of literature search can be seen in [Fig. 1](#).

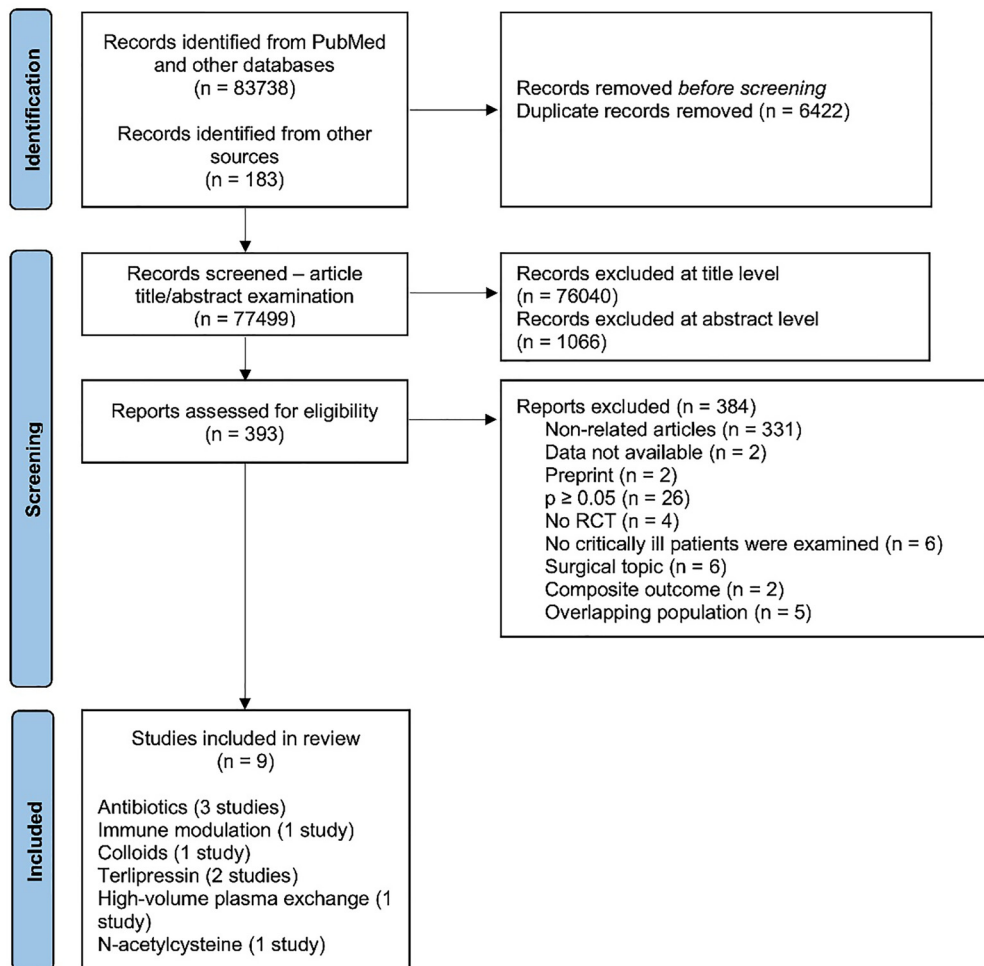


Fig. 1. The steps of the literature search. RCT: randomized controlled trial



Data extraction and study characteristics

Pre-structured forms were applied to extract data by four independent investigators. Disagreements were resolved by involving a senior author. All necessary data from the included studies were recorded in a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA). We followed the PICO (P: patient/population/problem; I: intervention; C: control/comparison; O: outcome) approach during the data extraction process. We collected data on the patient population and patient characteristics (etiology of liver failure, type of liver failure, and circumstances of critical illness or perioperative condition), clinical setting (perioperative or ICU), intervention used to improve outcome and the details of a particular intervention, details of comparison (statistical analysis applied to assess mortality and the level of significance), and relevant outcomes (data describing mortality and predictors of mortality). In addition, details of the articles were extracted and collected, which included the first author, year of publication, the name of the journal in which the study was published, the main question of the article, and details of the RCT design (the intervention and control, blinding, number of patients randomized to each group, and number of centers participating in the trial).

RESULTS

The database search identified 83,738 articles. Finally, nine RCTs were included in our systematic review, covering six areas of interest: administration of antibiotics and the effect of infectious diseases among cirrhotic patients (three studies) [13–15], immune modulation after liver transplantation (one study) [16], colloid administration in cirrhotic patients (one study) [17], the effect of high-volume plasma exchange in acute liver failure (one study) [18], N-acetylcysteine administration in acute liver failure (one study) [19], and terlipressin treatment (two studies) [20, 21]. Table 1 summarizes the characteristics of studies and publications included in our systematic literature review.

The included studies examined different outcomes, however, all of them investigated the effect of a particular therapeutic option on mortality in patients with cirrhosis or ALF. Mortality was defined as primary outcome in two studies [13, 18] and as secondary endpoint in seven studies [14–17, 19–21] (Table 2).

Antibiotic administration

The three studies investigating the effect of antibiotic treatment on mortality were heterogeneous in terms of treatment, settings, and conditions in a total of 316 cirrhotic patients [13–15] (Table 1). Sharma et al. compared the effect of rifaximin and lactulose application versus lactulose alone in patients treated for different levels of hepatic encephalopathy [14]. Rifaximin treatment resulted in better in-hospital survival (in-hospital mortality: rifaximin + lactulose group 23.8% vs lactulose group 49.1%), and sepsis was shown to predict higher mortality (Table 2). Merli et al. examined the effect of broad-spectrum antibiotic treatment versus standard therapy in cirrhotic patients suffering from healthcare-associated infections. Patients in the standard group received either cefotaxime or amoxicillin/clavulanic acid based on the site of infection. Broad-spectrum antibiotic therapy covered imipenem/cilastatin with or without the combination of vancomycin or tygecilin [13]. The in-hospital mortality was significantly higher



Table 1. Characteristics of studies included in our systematic literature review. AB: antibiotic, HCA: health-care acquired, HE: hepatic encephalopathy, HVP: high volume plasma, ICU: intensive care unit, NAC: N-acetylcysteine, Nb: number, O2: oxygen, SBP: spontaneous bacterial peritonitis, vs: versus

1st Author and Year of publication	Journal	Patients	Intervention	Comparator	Setting	Nb. of centers	Nb. of participants	Blinding
Sharma BC et al. 2013 [14]	Am J Gastroenterol	cirrhosis and HE	rifaximin + lactulose	lactulose alone	ICU	1	120	double- blinded
Merli M et al., 2016 [13]	Hepatology	cirrhosis and HCA infection	broad spectrum AB therapy	standard AB therapy	ICU	1	96	no blinding
Sort P et al. 1999 [17]	N Engl J Med	cirrhosis and SBP	cefotaxim + albumin	cefotaxim alone	ICU	7	128	no blinding
Choudhury A et al. 2017 [20]	Liver Int	cirrhosis and septic shock	terlipressin	noradrenaline	ICU	1	84	no blinding
Larsen FS et al. 2016 [18]	J Hepatol	acute liver failure	HVP exchange	standard therapy	ICU	3	182	no blinding
Nabi T et al. 2017 [19]	Saudi J Gastroenterol	acute liver failure	NAC for 72 h	placebo for 72 h	ICU	1	80	no blinding
Arora V et al. 2020 [21]	Hepatology	acute on chronic liver failure	terlipressin	noradrenaline	ICU	1	120	no blinding
O'Grady JD et al. 2002 [16]	Lancet	first orthotopic liver transplantation	tacrolimus	ciclosporin	Perioperative	8	606	no blinding
Terg R et al. 2008 [15]	J Hepatol	cirrhosis and low protein count in ascites	ciprofloxacin	placebo for 12 months	Mixed	2	100	double- blinded



Table 2. Results of the investigation of mortality in the studies included in our systematic literature review. AB: antibiotic, GIB: gastrointestinal bleeding, HE: hepatic encephalopathy, HVP: high volume plasma, KM: Kaplan-Meier analysis, LR: log-rank test, MELD: model for end-stage liver disease, MOF: multi-organ failure, NA: noradrenaline, NAC: N-acetylcysteine, RR: relative risk

1st Author and Year of publication	Group with better survival	Follow-up of mortality	Outcome type of mortality	Statistical analysis for mortality assessment	P value	Predictors of mortality
Sharma et al. 2013 [14]	rifaximin + lactulose	10 days	secondary	Chi-square, KM	0.030	sepsis
Merli et al. 2016 [13]	broad-spectrum AB therapy	in-hospital stay	primary	Chi-square	0.010	sepsis, standard AB therapy
Sort et al. 1999 [17]	cefotaxim + albumin	in-hospital stay	secondary	Chi-square	0.010	
	cefotaxim + albumin	3 months		Chi-square	0.030	renal impairment
Choudhury et al. 2017 [20]	terlipressin	48 h	secondary	KM and LR	0.003	lactate clearance
Larsen et al. 2016 [18]	terlipressin HVP exchange	28 days in-hospital stay	primary	KM and LR chi-square, KM and Cox analysis	0.080 0.008	HVP exchange
Nabi et al. 2017 [19]	NAC for 72 h	in-hospital stay	secondary	Chi-square	0.025	not using NAC, age>60 y, HE 3–4, ascites, MELD-score
Arora et al. 2020 [21]	terlipressin	28 days	secondary	Chi-square, KM and Cox analysis	0.001	MELD-score, HE, NA use
O’Grady et al. 2002 [16]	tacrolimus	1 year	secondary	RR	0.040	sepsis and MOF
Terg et al. 2008 [15]	ciprofloxacin	1 year	secondary	KM and LR	0.040	SBP and sepsis in placebo group, GIB in ciprofloxacin group

in the standard antibiotic therapy group (in-hospital mortality: standard group 25% vs broad-spectrum group 6%) [13]. In addition, standard antibiotic treatment and sepsis were found to be independent predictors of mortality (Table 2). Furthermore, Terg et al. compared the effect of long-term ciprofloxacin prophylaxis versus placebo on the prevention of spontaneous bacterial peritonitis (SBP) in patients with cirrhosis and low ascites protein concentration [15]. They showed not only significantly better one-year survival in ciprofloxacin group (one-year mortality: ciprofloxacin group 14% vs placebo group 34%), but the probability of remaining free from



bacterial infections was also higher among these patients [15]. The main predictors of mortality in the placebo group were SBP and sepsis (Table 2).

Immune modulation

A multicenter trial examined the effect of immune modulation therapy in 606 patients who underwent orthotopic liver transplantation [16]. The effects of tacrolimus and ciclosporin administration were compared. Both groups received concomitant steroid treatment, and patients were followed up for twelve months. The results showed that patients treated with ciclosporin had significantly higher mortality rates (one-year mortality: tacrolimus group 17% vs ciclosporin group 24%). The predictors of mortality were sepsis and multi-organ failure (Table 2).

The administration of colloids

In the only RCT investigating the effect of colloid administration on mortality, albumin and cefotaxime therapy was compared in cirrhotic patients with SBP peritonitis with cefotaxime alone [17]. Albumin was administered in a dose of 1.5 g kg^{-1} BW during the first six hours after admission, followed by 1 g kg^{-1} BW on day three. Both in-hospital (in-hospital mortality: cefotaxime + albumin group 10% vs cefotaxime group 29%) and three-month mortality (three-month mortality: cefotaxime + albumin group: 22% vs cefotaxime group 41%) rates showed better results among albumin treated patients (Table 2). The predictor of three-month mortality was renal impairment that was defined as a nonreversible deterioration of renal function during hospitalization. More precisely renal impairment was diagnosed with a 50% increase in serum creatinine or urea nitrogen level.

The effect of terlipressin

Two RCTs investigated the effects of terlipressin versus noradrenaline in heterogenous settings and patient population, in a total of 204 patients [20, 21]. Choudhury et al. enrolled cirrhotic patients with septic shock and randomized them to either the noradrenaline or the terlipressin groups [20]. Both noradrenaline and terlipressin were administered continuously to achieve a satisfying mean arterial pressure (MAP), defined as $\text{MAP} > 65 \text{ mmHg}$. If hemodynamic instability was persistent despite the monotherapy of vasopressors, salvage treatment was initiated with a combination of terlipressin and noradrenaline. The survival rate at 48 h was significantly better in the terlipressin group (mortality at 48 h: terlipressin group 4.8% vs noradrenaline group 28.6%); however, 28-day survival (mortality at 28 days: terlipressin group 73.8% vs noradrenaline group 85.7%) was similar in both groups [20] (Table 2). In addition, a higher proportion of patients receiving terlipressin were able to reach $\text{MAP} > 65 \text{ mmHg}$. Moreover, lactate clearance (defined as the followings: $\text{lactate baseline} - \text{lactate at time point} / \text{baseline lactate} \times 100$) was found to be an independent predictor of survival after achieving target MAP.

The second RCT examining the effect of vasopressors included patients with a diagnosis of ACLF and hepatorenal syndrome [21]. Patients received either an infusion of noradrenaline or terlipressin. The 28-day survival rate was significantly higher in the terlipressin group (28-day mortality: terlipressin group 51.7% vs noradrenaline group 80%), as was the rate of acute kidney injury reversal. Noradrenaline administration, MELD-score and hepatic encephalopathy were



independent predictors of mortality. The incidence of adverse events was higher in the terlipressin group; however, none of them impacted on mortality [21].

High-volume plasma exchange

One study investigated the effect of high-volume plasma (HVP) exchange on outcome on ALF [18]. A total of 182 patients were randomized to either the standard treatment group or the HVP group. Patients in the standard treatment group were treated according to the local guidelines of the involved ICUs, including the criteria of intubation and mechanical ventilation, hemodynamic supportive therapy, and renal replacement therapy. All patients received N-acetylcysteine for a maximum of five days, regardless of etiology. In addition, patients in the HVP group were treated with HVP for three consecutive days without a defined time interval between the treatments. Patients in the HVP group had significantly better survival during hospital stay (in-hospital mortality: HVP group 41.3% vs standard treatment group 52.2%) and the absence of HVP exchange treatment was an independent predictor of mortality [18] (Table 2).

N-acetylcysteine

Nabi et al. enrolled 80 patients with acute liver failure, who were randomized to N-acetylcysteine or placebo groups [19]. Both N-acetylcysteine and placebo were administered for 72 h continuously. In-hospital survival improved significantly when N-acetylcysteine was used (in-hospital mortality: N-acetylcysteine group 28% vs control group 53%). Additionally, the absence of N-acetylcysteine application, older age, higher MELD-score (MELD-score >30), hepatic encephalopathy and ascites were independent predictors of mortality [19] (Table 2).

DISCUSSION

Key findings

The aim of our systematic literature review was to provide an overview of potential interventions to improve mortality in critically ill patients with ALF or cirrhosis. Nine RCTs were identified focusing on six different areas. Our main findings include, first of all, the effectiveness of antibiotic, especially broad-spectrum antibiotic therapy, in reducing mortality in cirrhotic patients requiring hospitalization or ICU treatment, as well as the potential beneficial role of terlipressin over noradrenaline among cirrhotic patients with sepsis or ACLF. In addition, the application of tacrolimus versus ciclosporin after liver transplantation, albumin, HVP exchange and N-acetylcysteine were shown to reduce mortality in specific aspects of ALF or cirrhosis during hospitalization and ICU therapy. Furthermore, the following independent factors of mortality were described in this patient group in the studies: sepsis, standard antibiotic treatment, SBP, MOF, renal replacement therapy, lower lactate clearance, older age, hepatic encephalopathy stage 3 or 4, ascites, high MELD-score, noradrenaline administration and the lack of HVP exchange. We used a search method that included only RCTs with statistically significant documented differences in mortality, which has been applied in other settings of systematic reviews and added valuable results to the current literature [22-24].



Comparison with previous studies

Infection is one of the most common complications requiring hospitalization in ACLF, which is associated with increased mortality [25, 26]. In addition, SBP can commonly occur in these patients, increasing mortality by 20–40% [27, 28]. These facts have led to the conclusion that proper antibiotic treatment may be beneficial in increasing survival in the presence of cirrhosis.

Previous studies have shown that the pathogens causing SBP in ascites are mostly Gram-negative bacteria [29–31]. On this basis, the European Association for the Study of the Liver (EASL) recommends cefotaxime as the first-line empirical treatment for community-acquired SBP [32]. For healthcare-associated and nosocomial SBP, antibiotic therapy is recommended according to the local resistance rate of the hospital [32]. A randomized controlled trial investigated the efficacy of two regimens of empirical antibiotic therapy for nosocomial SBP [33]. It found that the combination therapy with meropenem and daptomycin had a higher response rate than ceftazidime treatment. A retrospective analysis investigated the sensitivity of pathogens to empirical antibiotics in cirrhotic patients with SBP [34]. The pathogen sensitivity had an influence on patients' mortality and complication rates. The highest susceptibility rates were observed when a combination therapy of meropenem-linezolid or meropenem-daptomycin was applied, whereas piperacillin/tazobactam was the most effective of the monotherapies [34].

The findings of our systematic literature review showed similar results. Three RCTs investigated the effect of antibiotic therapy on mortality among cirrhotic patients. Merli et al. showed a benefit of broad-spectrum antibiotic therapy, similar to the findings of the above-mentioned studies [13]. It should be highlighted that patients in the control group received third-generation cephalosporin, ciprofloxacin, or amoxicillin/clavulanic acid as standard treatment in this study. However, it is questionable in healthcare-associated infections, with the authors explaining this decision by the lack of clear evidence of the efficacy of broad-spectrum antibiotic treatment among cirrhotic patients. Imipenem/cilastatin, with or without antibiotic treatment against multi-resistant *Staphylococcus aureus* (MRSA) significantly reduced mortality compared to standard antibiotic therapy in cirrhotic patients with healthcare-associated infections [13]. This finding can be explained by the fact that broad-spectrum antibiotic treatment was more effective against multi-drug resistant pathogens, which play a crucial role in healthcare-associated infections. This study also showed that sepsis is an independent predictor of mortality in hospitalized cirrhotic patients.

Sharma et al. investigated the effect of rifaximin and lactulose against lactulose alone among patients with hepatic encephalopathy and showed a beneficial effect of antibiotic treatment on mortality [14]. Furthermore, patients not receiving rifaximin were more likely to die in sepsis. Rifaximin is an antibiotic agent with minimal absorption and broad-spectrum activity against Gram-positive and Gram-negative enteric bacteria in vitro. It helps correct imbalances in intestinal microflora and is effective in treating small intestinal bacterial overgrowth. This additional effect of rifaximin on gut microflora and the prevention of endotoxemia may lead to better outcomes in patients who receive not only lactulose alone but lactulose and rifaximin in hepatic encephalopathy. Another RCT examined the efficacy of ciprofloxacin prophylaxis in cirrhotic patients who had low protein levels in ascites [15]. The administration of ciprofloxacin led to reduced rates of bacterial infections, sepsis, and better one-year survival. The available evidence supports the administration of antibiotics in critically ill cirrhotic patients; furthermore, sepsis is a leading cause of mortality in this patient group.



Two heterogeneous RCTs evaluated the usefulness of terlipressin compared to noradrenaline in cirrhotic patients. Choudhury et al. examined cirrhotic patients with septic shock and found not only a 23.8% improvement in 48-h survival but also a lower proportion of variceal bleedings (no variceal bleeding in the terlipressin group compared with 9.5% variceal bleeding in the noradrenaline group) and greater success in achieving a MAP above 65 mmHg [20]. In addition, the rates of adverse events were comparable between the terlipressin and noradrenaline groups, which were mostly minor and similar complications without significant difference between the two groups (peripheral cyanosis: 70.5% in the terlipressin group and 44.4% in the noradrenaline group; lactic acidosis: 11.8% in the terlipressin group and 0 in the noradrenaline group; bradycardia: 11.8% in the terlipressin group and 11.1% in the noradrenaline group; atrial fibrillation: 5.9% in the terlipressin group and 33.3% in the noradrenaline group; ventricular tachycardia: 0 in the terlipressin group and 11.1% in the noradrenaline group). However, there was no significant difference in mortality at 28 days between the two examined groups. Arora et al. investigated the effect of terlipressin and noradrenaline in patients with ACLF with hepatorenal syndrome. In this patient group, they showed a beneficial effect of terlipressin, as the response to terlipressin treatment was more effective with a significant reduction of renal replacement therapy and significantly better survival at 28 days compared to noradrenaline administration [21]. These results correlate with those of previous studies.

Cirrhosis itself leads to hyperdynamic circulation, which may worsen in the presence of an infection [35]. Moreover, a relative vasopressin deficiency occurs in septic shock with a preserved receptor sensitivity [36, 37]. Terlipressin, a vasopressin analog, was not only shown to be effective as a vasopressor in septic shock but even as a vasoconstrictor in variceal bleeding and hepatorenal syndrome [38, 39]. From a pharmacodynamic point of view, terlipressin induces vasoconstriction by inhibiting nitric oxide synthase in vascular smooth muscles and improves responsiveness to catecholamines [36]. Additionally, a retrospective analysis showed that terlipressin was found safe in terms of adverse effects in cirrhotic patients when administered by infusion instead of boluses [40]. It is also well-known that sepsis in cirrhosis may lead to Type-1 hepatorenal syndrome due to reduced systemic vascular resistance, which can be ameliorated by terlipressin and albumin [41].

Sort et al. aimed to evaluate the efficacy of albumin administration in cirrhotic patients with SBP. They found that cefotaxime therapy supplemented with albumin was more beneficial than cefotaxime treatment alone [17]. Patients receiving albumin not only had a reduced incidence of renal insufficiency, but in-hospital and 3-month mortality rates also improved. The pathophysiological explanation for this finding is multifactorial. As we discussed it previously, cirrhosis and ascites are characterized by vasodilatation, hypotension and reduced effective arterial blood volume, which may lead to the activation of renin-angiotensin and sympathetic nervous system [42, 43]. Moreover, when sepsis is present, there is a combination of hemodynamic instability due to sepsis and a hemodynamic instability as a consequence of cirrhosis. Together, these factors result in reduced renal perfusion and glomerular filtration rate. In addition, vasoconstriction activated by the homeostatic response to hemodynamic instability may lead to renal hypoperfusion and even to reduced hepatic blood flow [44, 45]. The potential role of albumin in reducing mortality in this patient group may be based on maintaining effective arterial blood volume and ensuring hemodynamic stability [17].

One RCT investigated the method of immune modulation in patients who underwent their first orthotopic liver transplantation. Better 1-year clinical outcomes were observed in



tacrolimus administration compared to ciclosporine [16]. More favorable 1-year survival and less frequent re-transplantations were observed in the tacrolimus group. Moreover, sepsis and multi-organ failure were found to be the most frequent causes of death in both groups. Immune suppression is a key element of therapy for transplanted patients. This was the first RCT to examine the direct effects of tacrolimus on mortality, as previous randomized trials evaluated mainly the rates of rejection. However, the beneficial effects of tacrolimus have been observed previously: tacrolimus has been shown to be more effective in preventing cellular rejection, steroid-resistant rejection, and chronic rejection [46, 47].

A prospective RCT examined the effect of HVP on mortality in ALF and found significantly better in-hospital survival rates when HVP was applied [18]. Moreover, sequential organ failure assessment (SOFA) scores were lower in patients treated with HVP. ALF results in the accumulation of metabolites and toxins, reduced synthesis of coagulation factors, complement, and lipoproteins, which altogether can lead to severe MOF and death [48]. A major goal of ALF treatment is to restore organ function and prevent MOF until liver regeneration occurs or a suitable donor is available. Plasma exchange therapy with fresh frozen plasma has been shown to be safe and effective in ALF; however, its effect on mortality has not been previously investigated [49, 50]. HVP can reduce the severity of hepatic encephalopathy and vasopressor requirements, and accelerate hepatic nitrogen turnover [51–53]. The beneficial effects of HVP may be explained with its influence on immune modulation, removal of several plasma cytokines and replacement of plasma factors.

A small RCT investigated the effectiveness of N-acetylcysteine in non-acetaminophen-induced ALF [19]. It found that both in-hospital survival and length of hospital stay were significantly better in the group treated with N-acetylcysteine. N-acetylcysteine scavenges free oxygen radicals and refills cellular, mitochondrial, and cytosolic glutathione storage [54, 55]. Furthermore, its anti-inflammatory, antioxidant and vasodilator effects have been previously proved [56, 57]. The beneficial effects of N-acetylcysteine in non-acetaminophen-induced ALF may be explained by the improvement of systemic hemodynamic parameters and tissue oxygen delivery [58–60]. On the basis of this single RCT, N-acetylcysteine may be beneficial in non-acetaminophen induced ALF. However, further investigations are needed to clarify its exact role.

Strengths and limitations

This systematic literature review has several strengths. First of all, it is the first systematic review to evaluate various aspects of methods influencing mortality among critically ill patients with ALF or ACLF. Furthermore, our review is based only on evidence from RCTs. The study not only provides an overview of currently available data, but also highlights areas where further research and information are needed to improve the management of these patients.

The main limitation of this systematic literature review is that it does not provide suggestions on some important areas of the topic. No RCT evaluated the effect of various colloids (except albumin), hemodynamic target parameters, coagulation management methods, renal replacement therapy, nutrition, or respiratory strategies on mortality that may have an impact on the prevention and treatment of MOF and survival. We still rely on lower-quality studies or expert opinions on these topics. However, our findings identify stronger evidence-based therapeutic methods and provide information for future research.



CONCLUSION

We identified nine RCTs in six different areas that evaluated various aspects, drugs, interventions, or methods aimed at improving mortality in patients with different types of liver failure (i.e., ALF, ACLF).

Our main findings include the effectiveness of antibiotic therapy in reducing mortality among cirrhotic patients requiring hospitalization or ICU treatment, as well as the potential beneficial role of terlipressin in cirrhotic patients with sepsis. In addition, administration of tacrolimus after liver transplantation, albumin, HVP exchange and N-acetylcysteine were shown to reduce mortality in specific aspects of hepatic failure during hospitalization and ICU therapy. However, most of these areas remain under-explored and further research is needed in these fields of liver failure management.

Conflict of interests: The authors declare no conflicts of interest.

SUPPLEMENTARY INFORMATION

Supplementary data to this article can be found online at <https://doi.org/10.1556/2060.2023.00211>.

Additional file 1: PRISMA Statement.

Additional file 2: Search strategy.

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