Liver Support System and Transplant-Free Survival Patients with Liver Failure: an Evidence-Based Case Report

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ABSTRACT

Background: *The mortality rate in patients with acute liver failure (ALF) and acute on chronic liver failure (ACLF) is still very high. Currently, liver support systems are an alternative therapy in bridging liver transplantation. However, its effectiveness in reducing mortality is still controversial when compared to standard medical therapy (SMT). Our study aims to review the efficacy of liver support system compared to standard medical therapy (SMT) among acute liver failure patients without liver transplantation.*

Method: *We conducted systematic literature searching using PubMed/MEDLINE, EBSCO-CINAHL, ProQuest, and Cochrane databases. Selected articles were examined for duplicates and were screened by abstract and title. Then, we appraised the articles based on the critical appraisal tools from Centre for Evidence-Based Medicine (CEBM) University of Oxford*

Results: *One systematic review and meta-analysis of randomized control trials study was extracted after thorough research. Alhamshi et al showed that extracorporeal liver support has significantly reduced mortality in both ALF and ACLF patients as the primary outcome. Other main findings about adverse events including hepatic encephalopathy, thrombocytopenia, bleeding, and infection were still unclear.*

Conclusion: *The use of liver support system demonstrated better outcome in reducing mortality to standard medical therapy in transplant free patients with liver failure, but best modality recommendation was inconclusive.*

Keywords: *liver support system, extracorporeal liver support, acute liver failure, acute on chronic liver failure*

ABSTRAK

Latar belakang: *Angka kematian pada pasien gagal hati akut (ALF) dan gagal hati akut pada kronis (ACLF) masih sangat tinggi. Saat ini, sistem pendukung hati merupakan terapi alternatif dalam menjembatani transplantasi hati. Namun, efektivitasnya dalam mengurangi angka kematian masih kontroversial jika dibandingkan dengan terapi medis standar (SMT). Penelusuran literatur berbasis bukti ini bertujuan untuk mengetahui peran sistem pendukung hati dibandingkan dengan terapi medis standar (SMT) di antara pasien gagal hati akut tanpa transplantasi hati.*

Metode: *Kami melakukan pencarian literatur secara sistematis menggunakan database PubMed/MEDLINE, EBSCO-CINAHL, ProQuest, dan Cochrane. Artikel yang dipilih diperiksa untuk duplikat dan disaring berdasarkan abstrak dan judul. Kemudian, kami menilai artikel berdasarkan alat penilaian kritis dari Pusat Kedokteran Berbasis Bukti (CEBM) Universitas Oxford.*

Hasil: *Satu tinjauan sistematis dan meta-analisis dari studi uji klinis acak tersamar ganda terpilih sebagai literatur yang relevan dengan pertanyaan klinis. Alhamshi et al menunjukkan bahwa dukungan hati ekstrakorporeal telah secara signifikan mengurangi kematian pada pasien ALF dan ACLF sebagai hasil utama. Namun, temuan utama lainnya tentang efek samping termasuk ensefalopati hepatik, trombositopenia, perdarahan, dan infeksi masih belum jelas.*

Simpulan: *Penggunaan sistem pendukung hati menunjukkan hasil yang lebih baik dalam mengurangi mortalitas terhadap terapi medis standar pada pasien bebas transplantasi dengan gagal hati, tetapi rekomendasi modalitas terbaik tidak meyakinkan.*

Kata kunci: *liver support system, extracorporeal liver support, gagal hati akut, gagal hati akut pada kronis*

INTRODUCTION

Acute liver failure (ALF) and acute on chronic liver failure (ACLF), regardless of the underlying cause, are manifested by severe encephalopathy, coagulopathy, and subsequent multi-system organ failure resulting in a high mortality rate.[1-3] In the CANONIC study, the kidney was the most frequently affected organ (55.8% of patients), followed by liver (43.6% of patients), coagulation (27.7% of patients), brain (24.1% of patients), circulation (16.8% of patients) and lungs (9.2% of patients).[4] In the NACSELD study, 55.7% had grade III-IV hepatic encephalopathy (HE), 17.6% of patients had shock, 15.1% of patients required renal replacement therapy and 15.8% of patients required mechanical ventilation.[5]

Until recent times, liver transplantation is still considered as the main therapeutic modality in acute liver failure with a one-year long-term survival rate exceeding 88%. However, many obstacles are encountered in its application, both the availability of donors and supporting facilities.[6,7] In addition to standard medical therapy (SMT), currently liver support systems are one of the therapeutic options for patients who have not received a liver transplant yet.[8,9]

Extracorporeal liver support systems, in particular albumin dialysis and/or plasma exchange, have been proposed as a new therapeutic option that can be used as a bridge for liver transplantation in patients with acute liver failure with efforts to improve clinical, neurological, and biological parameters.[4,6,9,11] The most studied liver support systems include the adsorbent molecular circulation system (MARS) and the plasma separation and absorption system (Prometheus), which are based on the principle of albumin dialysis.[12,13,15] Prospective trials have demonstrated that MARS can improve cholestasis, hepatic, and renal function and hemodynamic in patients with decompensated cirrhosis; however, the effect on survival is not conclusive.[9,16]

CASE ILLUSTRATION

A 57-years-old male patient came to the ER brought by his family with complaints of confusion, disoriented and somnolent, he had a history of nausea, looked yellow with tea-coloured urine. The patient has had cirrhosis on chronic hepatitis B with a history of regular alcohol consumption. On examination, grade II hepatic encephalopathy, jaundice, ascites with elevated transaminase enzymes (ALT 4375; AST 1593) hyperbilirubinemia (up to 39.53 mg/dL) coagulopathy with INR prolongation 2.8x, reactive HBsAg and HBV DNA increase 5.97 x 106 units (log 6.78) $3.47x10^7$ were found. The patient has been routinely consulted to physician and previously treated with tenofovir disoproxil fumarate, he has been suggested for a liver transplant option but constrained by donor availability. The patient's condition was assessed as acute on chronic liver failure. During treatment, the patient underwent liver support therapy by using plasmapheresis method.

Clinical question: In patients with acute liver failure, are liver support systems more effective in reducing mortality risk than standard medical therapy (SMT)?

METHOD

The selected articles met the eligibility criteria using a systematic review, meta-analysis, and clinical trial method. The inclusion criteria included: clinical trial or meta-analysis study, research subjects were humans with a population of acute liver failure patients, including acute liver failure in chronic liver disease, with intervention of liver supportive therapy in any method compared to standard medical therapy with mortality outcome. The exclusion criteria used were paediatric patients, and had undergone liver transplantation, as well as literature in the form of guidelines and article reviews. We do not limit the selection of articles by year of publication or language.

The literature search was carried out on 11-15 November 2021 in five databases, including MEDLINE, PROQUEST, EBSCO, and Cochrane. The keywords are "acute liver failure" and "liver support" with related terminology (Table 1). The search strategy based on exclusion and inclusion criteria described above (Figure 1). The literature obtained was then screened for titles and abstracts, removed duplications in different databases, and in-depth screening of each intact text was carried out based on the suitability of the clinical question. After literature selection, a critical assessment was carried out by consensus of all authors to assess validity, study results, and clinical application based on the Centre of Evidence-Based Medicine, University of Oxford for both systematic review and meta-analysis studies.

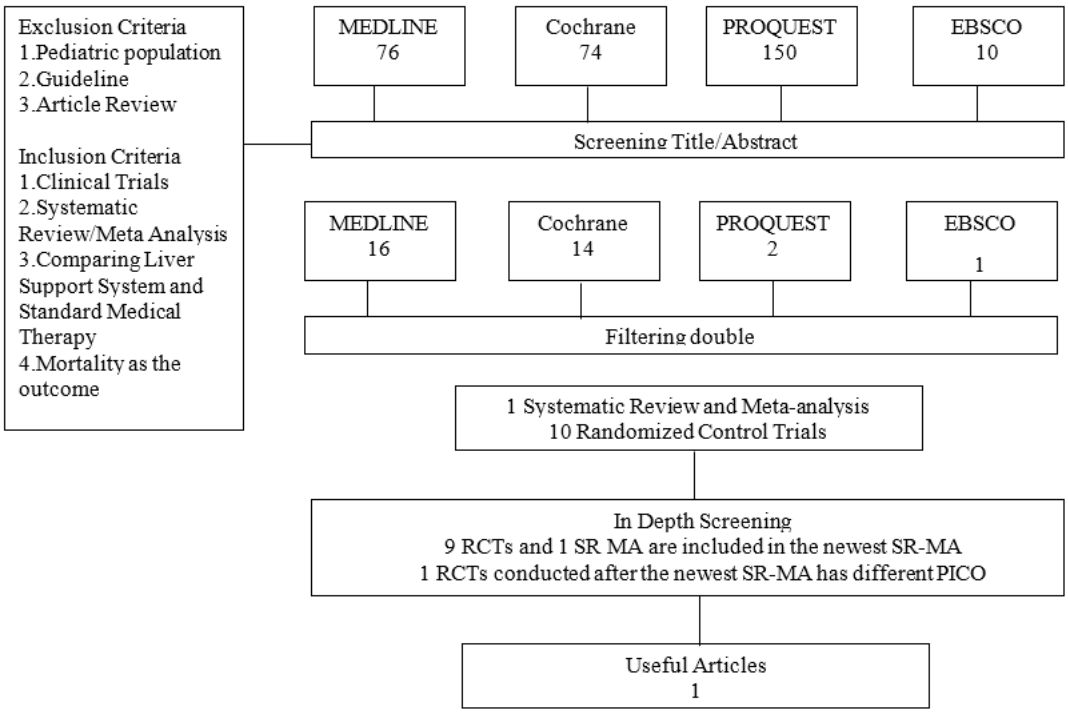

Figure 1. Flowchart of search strategy

Table 1. Terminology used in four databases

Database	Keyword	Hits
MEDLINE	((Acute OR acute-on-chronic) AND (hepatic failure OR liver failure)) AND (plasmapheresis OR plasma exchange OR liver support OR extracorporeal liver) AND (Standard Medical Treatment OR Standard Medical Therapy)	76
Cochrane	((Acute hepatic failure OR acute-on-chronic hepatic failure OR Acute liver failure OR acute-on-chronic liver failure)) AND (plasmapheresis OR plasma exchange OR liver support OR extracorporeal liver) AND (Standard Medical Treatment OR Standard Medical Therapy) in Title Abstract Keyword AND standard medical therapy in Title Abstract Keyword - (Word variations have been searched)	74
EBCO	AB (acute liver failure OR acute on chronic liver failure) AND AB (Liver support OR plasmapheresis OR plasma exchange) AND AB (Standard Medical Treatment OR Standard Medical Therapy)	10
PROQUEST	ab(Acute Liver Failure OR ACLF) AND ab(plasmapheresis) OR ab(plasma exchange) AND ab(adult) NOT (liver transplantations)	150

RESULTS

Based on the literature search strategy, one article met the eligibility criteria based on clinical questions. The summary of the article and its method presented in Table 2. The article is a systematic review or meta-analysis of randomized control trials with level of evidence 1a.

DISCUSSION

The study conducted by Alhamshi et al has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) study protocol. Based on the literature, there was a significant mortality reduction, in both ALF and ACLF patients receiving liver support therapy with various modalities compared to SMT.[6] Heterogeneity based on the Cochran Q-test was not statistically significant for the mortality outcome.[6]

In addition, there was a secondary outcome of hepatic encephalopathy that was more common in patients with liver support systems than those with SMT, but with significant heterogeneity. Another secondary outcome is the accompanying side effects, either bleeding, infection, or thrombocytopenia, the results of which are still unclear.[6]

The subject population was highly broad, included acute liver failure and acute conditions in chronic liver disease, as well as various underlying etiologies affected the potential risk, severity, as well as the different treatment history in each patient.[6] Variations in survival time in various studies also affected heterogeneity.[6] In subgroup analysis, not all subjects could be analysed.[6] Therefore, although this study provides an overview of the benefits of using liver support systems in patients with liver failure in general, its application in daily practice still requires further studies regarding comorbid side effects and the choice of the most superior modality.[6] Careful consideration is needed between the magnitude of the benefits compared to the prognosis of individuals with specific comorbidities considering the costs and facilities are greater than the use of SMT.[6]

Table 2. Design and result of the selected article

Article	Year	Design	Population	Intervention/control	Outcome
Alshamsi et al[6]	2020	SR-MA of RCTs	Randomized controlled Trials of ALF or ACLF from inception through March 13, 2019.	Clinical trials comparing extracorporeal liver support (ECLS) with any methods to standard medical therapy (SMT)	Primary outcome: mortality Secondary outcome: hepatic encephalopathy, bleeding, infection, thrombocytopenia

Table 3. Critical appraisal of the study based on criteria by Centre of Evidence-based Medicine, University of Oxford

Article, design, year	Level of evidence	Sample size	Validity	Importance		Applicability
Alshamsi et al, SR MA of RCTs 20206	1a	25 RCTs (1796 patients)	What question (PICO) did the systematic review address?	It is clearly stated P: adult with ALF or ACLF without liver transplantation I: Any form of liver support (bioartificial or artificial ECLS) C: Standard medical treatment (SMT) O: All-cause mortality or liver-related mortality	1. Mortality (n=1778) RR 0.84; 95% CI (0.74-0.96), p=0,01 Chi^2 34,36 df 23, I^2 33% p=0,06 2. Hepatic Encephalophaty RR 0.71; 95% CI (0.60-0.84) $P < 0.0001$, I^2 0%, 3. Hypotension (n=748) RR 1.46; 95% CI (0.98-2.2), $P = 0.07$, $I^2 = 15\%$	Yes
			Is it unlikely that important, relevant studies were missed?	Yes (it is not included unpublished studies)		
			Were the criteria used to select articles for inclusion appropriate?	Yes	4. Risk of bleeding RR 1.21; 95% CI (0.88-1.66) $P = 0.25$, $I^2 = 31\%$	
			Were the included studies sufficiently valid for the type of question asked?	Yes	5.Thrombocytopenia (n=564) (RR 1.62; 95% CI 1.0, 2.64, $P = 0.05$, $I2 = 62\%$	
			Were the results similar from study to study?	Yes	6. Infection (RR 1.92; 95% CI 0.11, 33.44, $P = 0.65$)	

CONCLUSION

The use of liver support systems is recommended in preventing mortality in patients with acute liver failure and acute liver failure in chronic disease who have not undergone liver transplantation. However, further research on the most effective modalities and the characteristics of the subjects who will benefit most from the treatment options need to be investigated further.

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