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Meta-Analysis

Perioperative administration of albumin in adult patients undergoing liver transplantation: A systematic review

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ABSTRACT

Hypoalbuminemia is a risk factor for mortality in patients with end-stage liver disease (ESLD) and in those undergoing orthotopic liver transplantation (OLT), since it represents a biomarker of post-operative delayed functional recovery of the graft. Despite albumin infusion during and after OLT is frequently adopted in recipients with hypoalbuminemia, it remains unclear whether this procedure could improve post OLT clinical outcomes. Observational studies indicated that treatment with albumin after OLT might be beneficial in reducing ascites and acute kidney injury (AKI) development. However, considering potential complications and the cost of albumin therapy, the decision to use albumin after OLT should be based on careful consideration of patient's individual needs and risks. In addition, the threshold plasma value of albumin below which it could be clinically useful to infuse albumin has not been clearly defined. This systematic review, prepared in accordance with the PRISMA 2020 guidelines, aimed to assess the efficacy of albumin infusion in patients undergoing OLT, in the prevention or treatment of ascites, AKI, and ischemia reperfusion syndrome, as well as its potential impact on patient survival. Furthermore, this review aimed to illustrate the pathophysiological bases justifying the use of albumin infusion in a subset of patients receiving OLT.

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1. Introduction

Hypoalbuminemia is a common finding in patients with end-stage liver disease (ESLD) and represents an independent risk factor for mortality [1]. Hypoalbuminemia can persist even after orthotopic liver transplantation (OLT) as a sign of delayed graft function [2]. Despite albumin infusion was recommended in patients with decompensated liver cirrhosis [3,4], and sometimes adopted after OLT [5], specific indications for albumin infusion in the context of OLT remained a matter of debate [6].

This systematic review, prepared in accordance with the PRISMA 2020 guidelines, aimed to assess the efficacy of albumin infusion in the prevention or treatment of ascites, acute kidney injury (AKI), and ischemia reperfusion syndrome (IRS), as well as its potential impact on survival in patients undergoing OLT. Furthermore, this review aimed to illustrate the pathophysiological bases that could justify albumin infusion in a subset of patients receiving OLT.

2. Materials and methods

2.1. Literature search strategy

An electronic, systematic, and comprehensive literature review was conducted and reported following the PRISMA 2020 guidelines and AMSTAR 2 (Assessing the methodological quality of systematic reviews) guidelines [7]. The literature in the Medline (through PubMed) database was searched from its detection to May 2024. References from included studies were also checked to identify any additional relevant papers. The following search terms were used: "acute kidney injury", “ischemia-reperfusion syndrome”, “ascites”, "hypoalbuminemia", “liver transplantation”. The full search strategy for PubMed is detailed in the appendix 1. The study protocol was registered on PROSPERO (ID: CRD42023445635).

2.2. Selection process

All the identified records were de-duplicated by two authors (R.V. and D.P.) using Rayyan (http://rayyan.qcri.org) and followed by a manual search. After de-duplication, the remaining titles and abstracts were screened independently by two authors (R.V. and D.P.), using Rayyan, to identify potentially eligible studies. Any disagreement over the eligibility was resolved by discussion with a third author (V.G.). The full text of the selected studies was retrieved and independently assessed for eligibility by two authors (R.V. and D.P.), and any disagreement was resolved by discussion with a third author (V.G.).

2.3. Eligibility criteria

Randomized controlled trials (RCTs) and non-randomized studies of interventions (NRSI), including prospective and retrospective studies, assessing the effect of albumin infusion on the development of acute AKI, ascites and IRS in adult patients (aged 18 years and older) who underwent OLT were considered eligible for the analysis.

Studies evaluating patients aged under 18 years and patients with decompensated cirrhosis who received intravenous albumin without undergoing OLT, non-English papers, case reports, and studies not involving humans were excluded.

2.4. Data extraction

Data were extracted into an Excel sheet (Microsoft Excel Version 17, Microsoft Corporation 19) and analyzed using Revman version 5.4 (version 5.4 (The Cochrane Collaboration, available at revman.cochrane.org). Data extracted included: author, year, design of the study, number of patients, age, sex, body mass index (BMI), Model for End-stage Liver Disease (MELD) score/Child-Pugh score, and cold ischemia time. Intraoperative parameters included total fluid administration, and intraoperative and postoperative albumin infusion. The postoperative data included length of stay (LOS) in the intensive care unit (ICU) and in the hospital, postoperative complications (early allograft dysfunction [EAD], biliary complications, AKI, ascites, and IRS), the need for retransplant, graft and patient survival.

2.4.1. Outcomes measured

2.4.1.1. Primary outcomes. The following outcome measures were retrieved if reported by each study:

1. Albumin supplementation and prevention of ascites development after OLT.
2. Albumin supplementation and prevention of AKI, defined according to the Risk, Injury, Failure, Loss of kidney function classification [8] and End-stage kidney disease (RIFLE) classification [9].
3. Albumin supplementation and prevention of IRS, defined as a pathological process that involves ischemia-mediated cellular damage followed by a paradoxical exacerbation upon reperfusion of the liver [10].

2.4.1.2. Secondary outcome.

1. Albumin supplementation and overall survival

For these variables the frequency of the effect was retrieved, and when available, the measure of the effect was also reported as Odds Ratio (OR) with a 95 % confidence interval (CI).

2.5. Study risk of bias assessment

The risk of bias was assessed using the Cochrane Risk of Bias Assessment tool 2 (Cochrane collaboration, 2019) for randomized trials, and tabulated using ROBVIS tool [11]. The assessment considered five domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of systematic bias. For each study the risk of bias was ranked as low, high, or with some concerns.

3. Results

3.1. Description of included studies

The electronic database search yielded 574 records. Additionally, 7 records were identified through snowball searching. Following checks for duplicates (one duplicate was found), 580 records were screened for title and abstract. After screening for titles and abstracts, 19 reports were sought for retrieval, while 13 were excluded (Fig. 1). The reasons for reports exclusion are detailed in the supplementary table 1. Furthermore, 3 registered trials were retrieved while searching for ongoing trials evaluating albumin supplementation during and/or after OLT. The characteristics of the registered trials are summarized in the supplementary table 2.

3.1.1. Characteristics of the studies selected

Among the 6 studies selected for this review, which included 592 patients, four were RCTs [12–16], and two were NRSI [17,18]. The main characteristics of the study design and the main demographic and clinical data of patients enrolled in each study are reported in table 1 and in table 2 respectively, while in the supplementary table 3 are reported the sample size, the registration number and the sponsorships of the studies selected Table 3.

Table 1
Design characteristics of the studies included in the review.

Author	Year	Country	Study design	Aim	Inclusion criteria	Exclusion criteria	Intervention group	Control group
Mukhtar et al. [13]	2009	Egypt	RCT	Evaluate the effect of perioperative administration of Hydroxyethyl starch (HES) compared to albumin on renal function after liver transplant surgery	Adult patients with end-stage liver disease scheduled for living donor liver transplantation (LDLT)	Patients aged < 18 years, patients undergoing retransplantation, with a history of previous upper abdominal surgery, with portal vein thrombosis, with primary renal dysfunction and hepatorenal syndrome	Infusion of 6 % HES 130/0.4 during the intraoperative period and first 4 postoperative days	Infusion of albumin 5 % during the intraoperative period and first 4 postoperative days
Tehran et al. [14]	2022	Iran	RCT	Evaluate the effect of intraoperative administration of low dose albumin-gelatin compared to albumin-normal saline and injection on renal outcomes after liver transplant surgery	Adult patients with end-stage liver disease scheduled for deceased donor liver transplantation	Patients aged < 18 years, patients undergoing LDLT or retransplantation, concurrent liver and kidney transplantation, patients with previous abdominal surgery and preexisting renal dysfunction.	Infusion of modified gelatin and low dose albumin during the intraoperative period	Infusion of 1 % albumin on normal saline during the intraoperative period
Kim et al. [15]	2023	South Korea	RCT	Evaluate the effect of intraoperative administration of 20 % albumin compared to crystalloid solution on renal outcomes after liver transplant surgery	Adult patients scheduled for liver transplantation	Patients with preoperative serum albumin >4.0 g/dL	Infusion of 20 % albumin during the intraoperative period	Infusion of balanced crystalloid solution during the intraoperative period
Oh et al. [16]	2024	South Korea	RCT	Evaluate the effect of postoperative administration of albumin and ringer lactate solution compared to ringer lactate solution as ascites replacement therapy. The primary outcome of interest was time to first flatus during recovery. The secondary outcome was incidence of acute kidney injury.	Adult patients scheduled for living donor liver transplantation.	Patients with a history of abdominal surgery, renal dysfunction requiring hemodialysis, or hypersensitivity to human albumin were not eligible. Patients who unexpectedly required gastrointestinal surgical procedures. Patients aged < 18 years old.	Replacement of 70 % of ascites: - 30 % with 5 % albumin - 40 % with ringer lactate solution	Replacement of 70 % of ascites with ringer lactate solution
Ertmer et al. [18]	2015	Germany	NSRI: Retrospective cohort study	Evaluate the effect of human albumin substitution on organ function in patients undergoing orthotopic liver transplantation (OLT)	Adult patients scheduled for liver transplantation	Patients requiring excessive transfusion (more than two units of blood products each 24 h after the first postoperative day), patients dead within the first 48 h after admission to intensive care unit (ICU), or patients with serum albumin concentration at admission > 5.0 g/dL.	Postoperative infusion of 100 g/d human-albumin 20 %	No infusion
Hand et al. [17]	2015	United States of America	NDRI: Retrospective cohort study	Evaluate the effect of colloid administered during liver transplantation on incidence of acute kidney injury.	Adult patients scheduled for liver transplantation	Patients undergoing simultaneous dual-organ (liver and kidney) transplant, patients aged < 18 years, and patients with incomplete "critical" data.	Infusion of 5 % albumin during the intraoperative period	• Infusion of 5 % albumin and 6 % hydroxyethyl starch (HES) during the intraoperative period • Infusion of 6 % hydroxyethyl starch (HES) during the intraoperative period

RCT: randomized controlled trials; NRSI: nonrandomized studies of intervention.

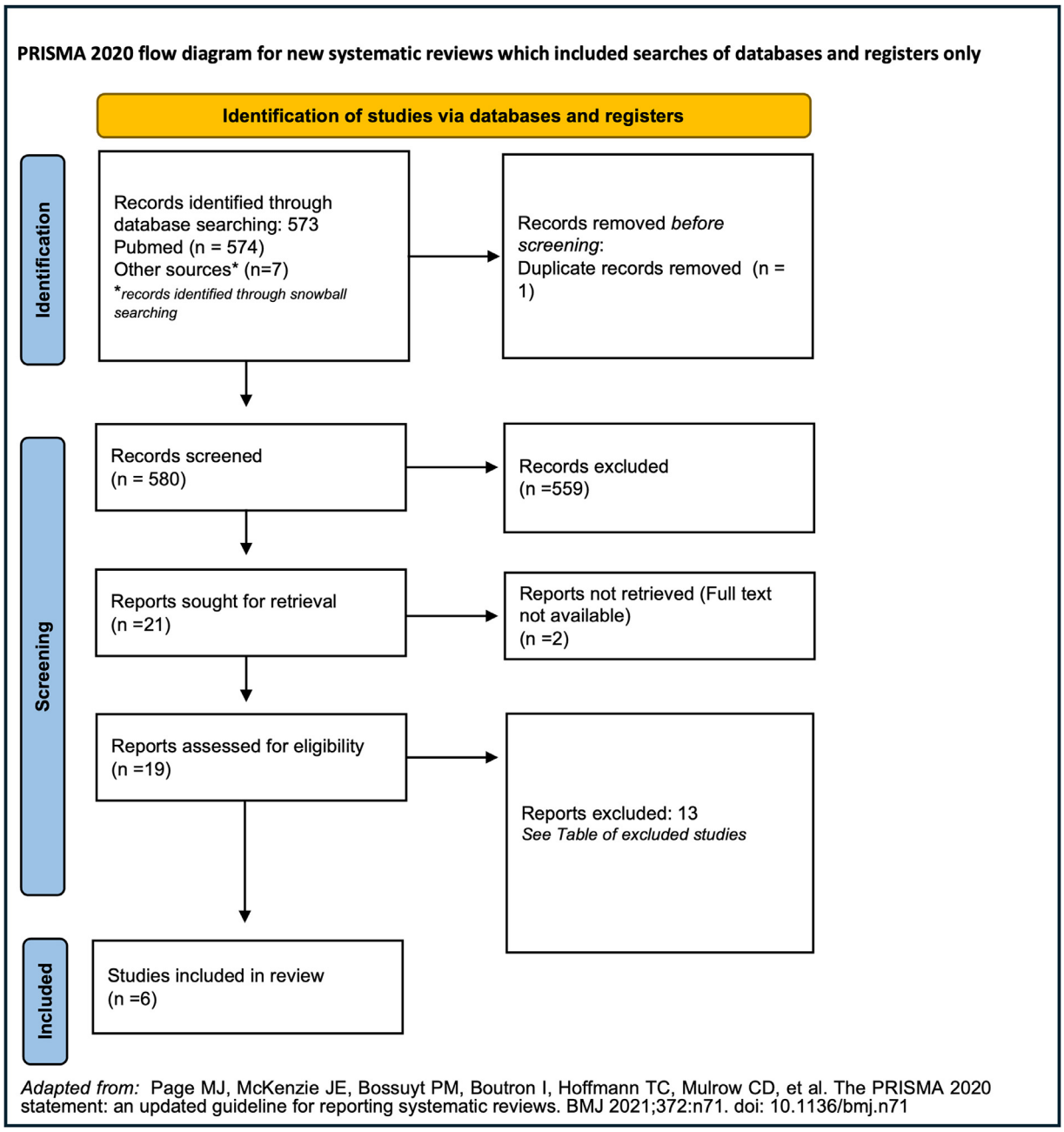

Fig. 1. PRISMA 2020 flow diagram for the proposed systematic reviews, which included searches of databases and registers only.

Table 2
Main demographic and clinical parameters of patients included in the studies selected for the review. Continuous variables are reported as means ± standard deviation or medians (Interquartile range). Categorical variables are reported as frequencies.

Author	Age (years)		Gender male (%)		BMI		MELD score	
	Control group	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group	Intervention group
Mukhtar et al. [13]	51 ± 6	55 ± 5.8	16 (80)	19 (95)	29.9 ± 5.3	26.2 ± 4	15 (12–19)	15 (8–20)
Tehran et al. [14]	46.34 ±14.55	43.72 ± 13.29	42 (60)	44 (62.9)	24.93 ± 4.55	25.01 ±4.15	17.58 ±7.22	18.02 ±6.19
Kim et al. [15]	57 (48–62)	58 (50–63)	37 (56.1)	33 (47.1)	23.9 (21.6–27.0)	23.1 (21.2–25.1)	15 (12–24)	16 (9–30)
Oh et al. [16]	56.9 ± 9.4	56.9 ± 6.8	23 (69.7)	23 (76.7)	23.9 ± 3.6	25.1 ± 3.2	12.6 ± 5.6	11.8 ± 6.4
Ertmer et al. [18]	56 ± 8	55 ± 10	12 (80)	11 (73)	27 ± 7	27 ± 4	18 ± 11	20 ± 13
Hand et al. [17]	55 ± 10	53 ± 11 56 ± 10	36 (72)	55 (56) 15 (62)	NA	NA	22 ± 5	22 ± 4 21 ± 5

NA: not available; BMI: Body mass index; MELD: Model for End stage Liver Disease.

Table 3
Measures of different clinical outcomes reported in the studies selected for the review. Data in the control and intervention group are presented as numbers (percentages).

Author	Acute kidney injury					Ischemia reperfusion syndrome					Ascites				Overall survival				
	Control group	Intervention group	*OR*	*IC*	*P*	Control group	Intervention group	*OR*	*IC*	*P value*	Control group	Intervention group	*OR*	*IC*	*P*	Control group	Intervention group	*OR*	*IC*	*P*
Mukhtar et al. [13]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tehran et al. [14]	18 (25.7 %)	22 (31.2 %)	NA	NA	0.84	25 (35.70 %)	18 (25.70 %)	NA	NA	NA	NA	NA	NA	NA	NA	68(97.1 %)	67 (95.7 %)	NA	NA	NA
Kim et al. [15]	40 (60 %)	39 (56 %)	0.9	0.4–1.9	0.73	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Oh et al. [16]	10 (31.3 %)	6 (20 %)	NA	NA	0.312	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ertmer et al. [18]	NA	NA	NA	NA	0.12	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	13	14	NA	NA	0.52
Hand et al. [17]	25 (50 %)	55 (56 %)	1.77	0.55–5.7	0.340	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	50 (100 %)	99(100 %)	NA	NA	NA
		15 (61 %)	2.94	1.13–7.7	0.027												24 (98 %)			

NA: not available. OR: odds ratio; IC: confidence interval.

The overall quality of the studies was judged to have some concerns, since two studies [15,16] ranked as with low risk of bias, and two studies [13,14] were judged to have main sources of bias being the selection of reported results, due to the absence of a preexisting analysis plan and protocol (Fig. 2).

3.1.1.1. Primary outcomes.

1. *Albumin supplementation and prevention of ascites development after OLT*
   None of the included studies evaluated the effect of albumin infusion on the prevention or resolution of ascites after OLT. Nevertheless, one study [16] evaluated, through indirect outcomes measures (amount of the liquid fluid drained by the abdominal tube), the effect of the infusion of 5 % albumin plus lactated ringer's solutions, compared to lactated ringer's solution alone. No significant differences regarding the liquid volume drained by the abdominal tube between the two groups at the first (p=0.294), second (p=0.539), and third (p=0.550) post operative day were observed.
2. *Albumin supplementation and prevention of AKI development*
   Four RCTs [13–16] evaluating the association between albumin supplementation during and after OLT and the incidence of AKI were identified. Data from these studies were not homogeneous, since a discrepancy existed regarding the timing of albumin infusion, the dose administered, and the baseline patients' characteristics, as well as the assessment of clinical outcomes. Therefore, a meta-analysis of risk measurements was not undertaken. In 3 [14–16] of these trials, human albumin infusion (at the concentrations of 20 % [14], 10 % [16], and 5 % [15]) was not shown to significantly reduce the incidence of AKI post OLT. One study [13] evaluated the effect of the infusion of 5 % human albumin compared to third-generation hydroxyethyl starch (HES) (6 % HES 130/0.4) started in the perioperative period and maintained for 4 days in conditioning renal function. No significant differences between the two groups regarding serum creatinine levels, creatinine clearance, and cystatin C plasma levels, were observed.
   Contrasting results emerged from the analysis of the two retrospective studies [17,18], which reported a non-significant reduced risk of renal impairment and AKI in patients who received higher amounts of albumin infusion and whose albumin serum levels were more elevated. However, the subgroup of patients receiving the infusion of 6 % HES during the intraoperative period, experienced a significant higher risk for developing AKI compared to patients receiving 5 % albumin (OR: 2.94, 95 % IC: 1.13–7.7, p value= 0.027).
3. *Albumin supplementation for the prevention of IRS development*
   Only one [15] of the included studies, assessed the effect of intraoperative colloid infusions on the incidence of IRS. The group of patients receiving modified gelatin and low dose albumin, compared to those receiving 1 % albumin on normal saline during the intraoperative period, seemed to develop a less severe form of IRS. However, both measures of statistical significance and measures of effect are not reported.

3.1.1.2. Secondary outcome.

1. Albumin supplementation and overall survival

Data regarding the impact of albumin infusion on the overall survival were reported in two studies [14,15], but none of them reported the measures of effect. In the study of Tehran et al. [14] no significant advantage of gelatin compared to crystalloids or albumin infusion on the risk of mortality was observed.

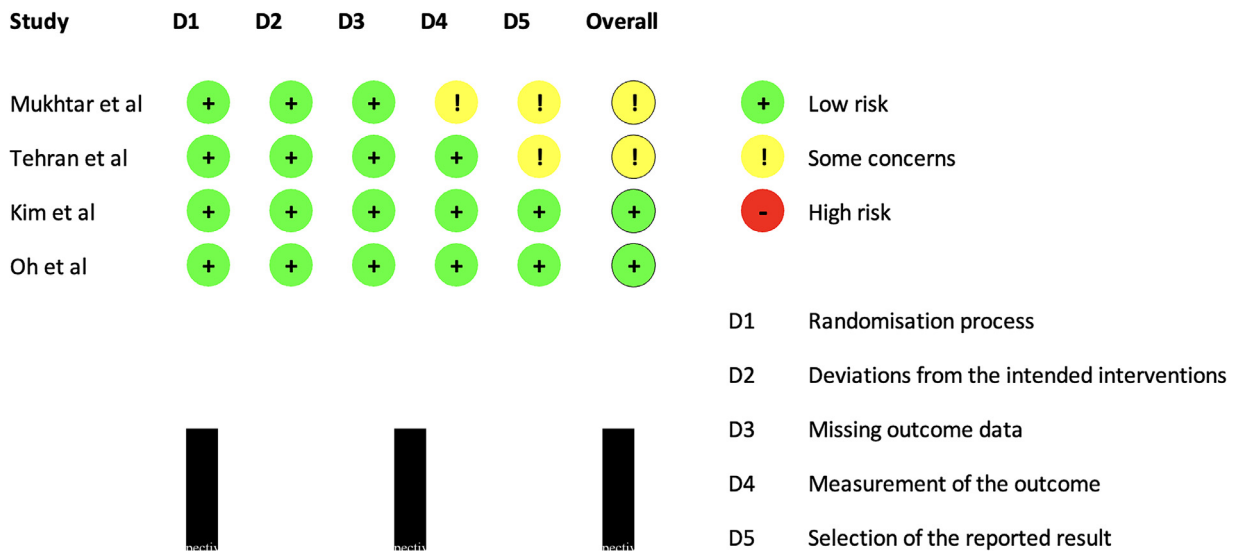

Fig. 2. Graphical representation of the risk of bias assessment in the randomized controlled trials included in the review.

4. Discussion

This systematic review was conducted to verify whether albumin infusion in patients undergoing OLT could be useful to prevent ascites, AKI, and IRS, as well as to improve post OLT survival.

Persistent ascites after OLT occurs in 6–7 % of patients [19,20] and is thought to be due to persistent portal hypertension, renal and cardiac dysfunction, commonly observed in patients with pre-transplant decompensated cirrhosis [21], infections and allograft dysfunction [22]. It negatively affects patients' survival [20] and is associated with renal impairment, increased incidence of peritonitis, and prolonged hospitalization [23]. Although no solid scientific evidence supported the albumin infusion to prevent or treat ascites after OLT, albumin infusion is adopted by several liver transplant centers in treating ascites after OLT, particularly if serum albumin level is <2.5 g/dL [5]. Further randomized and prospective studies specifically designed to assess the impact of albumin infusion in patients with persistent or *de novo* ascites after OLT should be performed. Only through these types of studies it will be possible to evaluate in detail the oncotic and anti-inflammatory properties of albumin and verify whether these will have an effect in the prevention or treatment of ascites in the context of OLT.

The incidence of postoperative renal impairment after OLT is common, as high as 70 %, and is associated with considerable morbidity and mortality [24]. Data from retrospective studies suggested that albumin concentration affected early kidney function and long-term survival after OLT [25–27]. These results might perhaps be explained by the protective effects of albumin on kidneys, including antioxidant protection against uremic toxins (the so-called "scavenger effect" of albumin) [28], preventions of apoptosis of renal tubular cells [29], and reduction of the nephrotoxic effects of medications [30,31]. Furthermore, albumin infusion, through the maintenance of adequate intravascular volume, improvement of cardiac output and prevention of hypotension [31,32], shifts the renal blood flow autoregulation curve toward normalization, which results in a significant increase in renal blood flow [28]. This is particularly important during the early postoperative period, when patients can develop an hemodynamic instability [33].

Despite this pathophysiological support, the benefits of albumin supplementation in preventing AKI post-OLT are still questioned. The results of RCTs [13–16] and NRSI [17,18] showed no differences in renal function between patients treated with colloid infusions, albumin, HES and ringer's lactate. However, it is important to highlight that these studies were not homogeneous in terms of albumin dose administered, timing and type of surgery performed. In the study by Tehran et al. [14], a lower dose of albumin compared to that used in the study by Kim et al. [15] was administered during surgery. It is conceivable that the 1 % albumin dose infused, exclusively during surgery, was insufficient for reaching serum albumin levels ≥3 mg/dL, which has been suggested to be protective for the maintenance of normal renal function [34]. In fact, serum albumin level of ≥3 mg/dl has been identified as the threshold that should be obtained by albumin infusion for preventing renal dysfunction after OLT [13–16], and albumin serum levels <3.0 mg/dl have been associated with the development of AKI after living donor liver transplantation [17,18,34]. Unfortunately, in most patients enrolled in the studies, plasma albumin levels ≥3 mg/dl were not reached. In the study of Kim et al. [15], the proportion of patients reaching the serum albumin level ≥3.0 mg/dL was significantly greater in the albumin compared to saline treated group, but this difference significantly narrowed over time after surgery (41.4 % and 10.6 % at 5 min after graft reperfusion; 38.6 % and 9.1 % at the end of surgery, and 61.4 % and 40.9 % at the postoperative day 1). Similar results were obtained in the study of Oh et al. [16], which demonstrated that serum albumin levels were significantly higher in patients receiving in the post operative period an infusion of 5 % albumin plus ringer's lactate compared to those receiving ringer's lactate alone. However, in both groups albumin serum levels did not reach values ≥3.0 g/dL. Moreover, unpublished data reported in the study of Kim et al. [15], showed that serum albumin levels dropped to <3.0 g/dL immediately after surgery in half of the patients, questioning the efficacy of the intraoperative albumin infusion. Accordingly, data from studies evaluating albumin kinetics suggested that albumin serum levels would drop rapidly even in patients with adequate preoperative values, and that albumin infusion would result in higher fluid shifts due to capillary leakage, contributing to a hypovolemic state and triggering a vicious cycle [35].

Several further mechanisms might influence albumin plasma levels during and after surgery, including systemic inflammation, intestine manipulation, IRS, and length of surgery [36]. Regarding the issue of systemic inflammation, it seems that a higher grade of pre-operative inflammatory state, which is typical of patients with higher MELD, would be associated with a marked fall in albumin synthesis [37]. Indeed, in the randomized controlled trial by Kim et al. [15], the effects of 20 % albumin infusion were

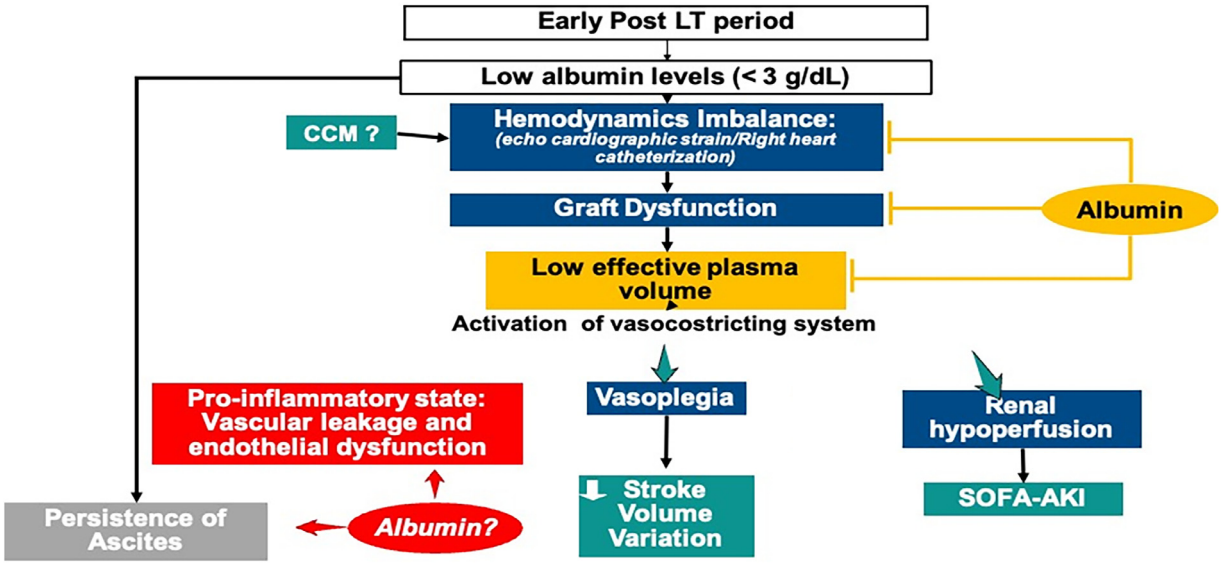

Fig. 3. Potential pathophysiological rationale for the use of albumin after liver transplantation for preventing acute kidney injury (AKI). LT: liver transplantation; CCM: Cardiac Contraction Modulation; SOFA: Sequential Organ Failure Assessment.

shorter in the subgroup of patients with MELD >15 or refractory ascites due to systemic inflammation, which is associated with a marked fall in albumin synthesis and rapid degradation of albumin [37]. Furthermore, on multivariate analysis, decompensated liver cirrhosis resulted as independent risk factor for post-operative AKI. Despite the limited evidence from this study, it is presumable that a greater amount of albumin may be required for these patients. The retrospective studies included in this review [17,18] showed a reduced risk of renal impairment in patients who received higher amounts of albumin infusion and whose albumin serum levels were more elevated, although statistical significance was not reached. Even in this case, a meta-analysis of risk measurements was not done due to the heterogeneity of albumin dose administered and risk association measures used. The discrepancy in results between RCT and NRSI could perhaps be explained by the potential sources of bias and confounding factors. Indeed, all the retrospective studies included a small number of patients, were based on single-center experiences, and did not evaluate the effect of possible confounders (blood loss during surgery and subsequent transfusions, duration of the pre-anhepatic and anhepatic phase) [17,18]. Thus, the great heterogeneity of the studies currently makes difficult to identify the categories of patients who can benefit from albumin infusion for preventing renal dysfunction and AKI in the context of OLT.

Considering data reported in the cited studies, early post operative infusion of human albumin could be suggested for preventing renal dysfunction in patients undergoing OLT since a post-operative serum albumin level ≤3 g/dL represents a risk factor for AKI development. In Fig. 3 a potential pathophysiological rationale for infusing albumin in the early post operative phase after OLT in patients presenting albumin serum levels <3.0 mg/dl is provided. However, further studies evaluating the kinetics of serum albumin during and after OLT in relation to renal function modifications are needed to provide a more solid rationale for albumin infusion during the perioperative phase in patient undergoing OLT.

The pathophysiological mechanisms of IRS after OLT involved a series of complex events, including mitochondrial dysfunction and energy deprivation, metabolic acidosis, oxidative stress, and the upregulation of pro-inflammatory cytokine signal transduction [38,39]. Several types of interventions have been tested for suppressing this phenomenon, including pharmacological treatments during surgery (e.g., simvastatin) [40], and the use of hypothermic machine perfusion for extended criteria donor (ECD). The latter procedure obtained favorable results in animal models, but its real usefulness is still lacking in clinical trials performed in humans [41].

IRS can contribute to hypoalbuminemia after OLT through various mechanisms, including damage to liver cells and systemic inflammatory response triggered by IRS that can disrupt the normal synthesis and metabolism of albumin. Furthermore, IRS can affect the microvasculature of the transplanted liver, including the sinusoidal endothelial cells, with subsequent impairment in the uptake and transport of albumin, further contributing to hypoalbuminemia [39]. The potential impact of combining low dose of albumin infusion plus modified gelatin, compared to albumin alone for preventing IRS development was assessed in only one of the included studies [14], with limited evidence on a beneficial effect.

5. Conclusions

Studies evaluating the effect of albumin administration in the context of OLT [2,6,26,27,42–49] presented a great heterogeneity in terms of design and in the doses of albumin infused. Furthermore, this systematic literature review showed that the plasma albumin value below which the albumin infusion could be useful has not been identified with certainty. Thus, the decision to infuse albumin after OLT should be based on careful consideration of the patient's individual needs and risk factors. Probably, the use of albumin could be advised in the early post operative period in patients with low intravascular volume leading to low cardiac output and serum albumin levels <3 gr/dl, to potentially prevent AKI development.

Finally, it is important to note that the use of albumin after OLT is not without risks. Some studies have suggested that albumin infusion may be associated with an increased risk of infection, bleeding, and other adverse events [50,51]. Additionally, the cost of albumin therapy can be significant, and may not be justified in all cases [52], as demonstrated by a cost analysis by Tigabu et al. [53].

Conflicts of interest

All authors declare that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.11.006.

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