PERIOPERATIVE MANAGEMENT AND CRITICAL CARE FOR PATIENTS WITH LIVER DYSFUNCTION

Ph.D. Thesis

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Budapest

2024

"The only difference between screwing around and science is writing it down."

Adam Savage

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1 LIST OF ABBREVIATIONS

ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
CI	Confidence interval
CPFA	Coupled plasma filtration and adsorption
CRP	C-reactive protein
CRRT	Continuous Renal Replacement Therapy
CVVH	Continuous veno-venous hemofiltration
CVVHD	Continuous veno-venous hemodialysis
CVVHDF	Continuous veno-venous hemodiafiltration
CVVHF	Continuous veno-venous hemofiltration
CVVRRT	Continuous veno-venous renal replacement therapy
ERAS	Enhanced Recovery After Surgery
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
ICU	Intensive care unit
IDOL	Inducible degrader of low-density lipoprotein
IV	Intravenous
JBI	Joanna-Briggs Institute (Critical Appraisal Tool of)
MD	Mean difference
OR	Odds ratio
PaO2/FiO2	Ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RCT	Randomized controlled trial
ROB	Risk of bias
ROBINS-I	Risk of Bias in Non-randomized Studies - of Interventions

SLED Sustained low-efficiency dialysis

2 STUDENT PROFILE

2.1 Vision Statement

My vision is to realize and popularize the "scientist-physician" concept, wherein the distance between bedside practice and clinical research is minimized. I believe that all healthcare practitioners, especially physicians, are responsible for practicing evidence-based medicine and contributing to medical literature in any shape or form to the best of their ability.

2.2 Mission Statement

My mission is, and always has been, to challenge conventions and complacency. In the context of my Ph.D. studies, I've always aimed to revise 'what we know to be true' and to pursue 'what could have been'.

2.3 Specific Goals

My specific goals during my Ph.D. studies were to approach liver injury and dysfunction from two directions: to critically appraise the evidence on a guideline-derived patient safety measure and to summarize and contextualize clinical literature on the use of a novel treatment to shed light on its eventual protocolization.

2.4 Scientometrics

Number of all publications:	9
Cumulative IF:	54.60
Av IF/publication:	6.06
Ranking (Sci Mago):	D1: 3, Q1: 6, Q2: -
Number of publications related to the subject of the thesis:	2
Cumulative IF:	8.6
Av IF/publication:	4.2
Ranking (Sci Mago):	D1: -, Q1: 2, Q2: -
Number of citations on Google Scholar:	14

Number of citations on MTMT (independent):	9
H-index:	2

2.5 Future Plans

I intend to complete my anesthesia and intensive care training at Semmelweis University and continue my scientific career here. I have two ongoing studies: the prognostic factors for mortality in acute-on-chronic liver failure and the comparison of different modalities in blood glucose level and insulin therapy management in the intensive care unit. Both projects are meta-analyses. Furthermore, I have the draft of a randomized controlled trial, written as part of my Clinical Science Scholars Program postgraduate training at Harvard University. This study would investigate the hypothesized superiority of an invasive, multimodal, individualized, goal-directed fluid therapy for patients with sepsis in the intensive care unit. Lastly, I plan to continue my career in the Centre for Translational Medicine as a facilitator for learning and speaking the ‘language of science’ at the bedside.

3 SUMMARY OF THE PH.D.

3.1 Why We Did It

We believe in evidence-based medicine in anesthesia and intensive care medicine. The cornerstone of evidence-based medicine is the internationally utilized practical guidelines that help us standardize and optimize our approach to healthcare. Therefore, we aimed to investigate the validity of the evidence and recommendation levels of one guideline-derived medical intervention and to summarize and contextualize clinical evidence on a medical intervention not yet protocolized, to inform policymakers.

3.2 What We Did

With study 1, we performed an interventional meta-analysis of randomized controlled trials based on the Enhanced Recovery After Surgery (ERAS) protocol on liver surgery, investigating the efficacy of preoperative high-dose glucocorticoid administration in reducing postoperative complications, which are thought to be the consequence of liver injury, at least partly. We compared any type of high-dose glucocorticoid administration in major hepatic resections and liver transplantations and assessed whether there was a significant reduction in overall postoperative complications.

With study 2, we collected all relevant original research papers on the use of any hemoadsorption therapy for critically ill patients who developed an acute liver dysfunction within the context of critical illness and multiorgan dysfunction sequelae, as opposed to long-term deterioration of chronic liver diseases. This study investigated the effects of hemoadsorption therapy by contextualizing the clinical parameters observed before and after the therapy. As the intervention is novel, and the pathological entity is relatively rare, multifactorial, and deadly, no large-scale randomized controlled trials were published before our publication.

3.3 What Did We Find

In study 1, we observed a tendency to perform better than placebo plus standard of care in reducing overall postoperative complication rate, and a significant reduction in the observed wound infection rate. There were no significant differences in safety outcomes. Risk of bias

analysis and assessment of the level of evidence certainty showed that trials conducted on this research question suffered from several methodological errors, resulting in important inconsistencies and uncertainty in several domains.

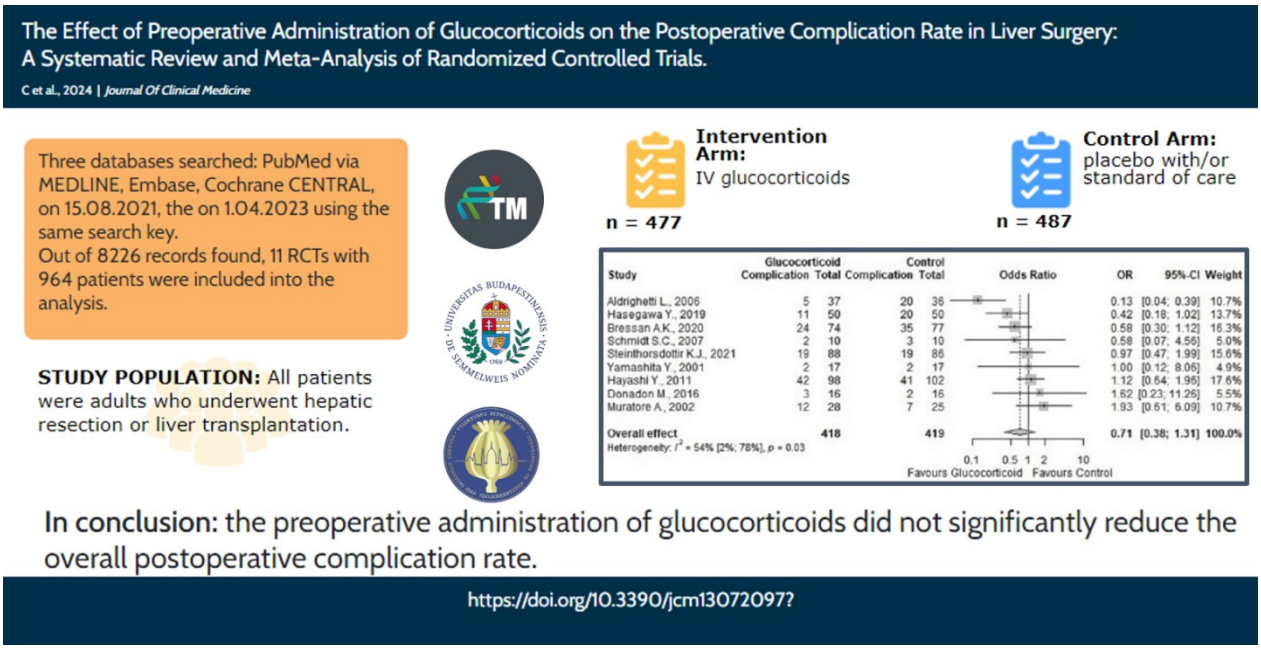
In study 2, we observed a statistically significant effect of the hemoadsorption therapy in reducing serum bilirubin, aspartate transaminase, and the need for vasopressor support, all important markers of liver dysfunction and critical illness. Data on mortality or successful bridge-to-transplantation was unavailable, leading us to recommend specific research questions for the future.

3.4 Our Main Conclusion

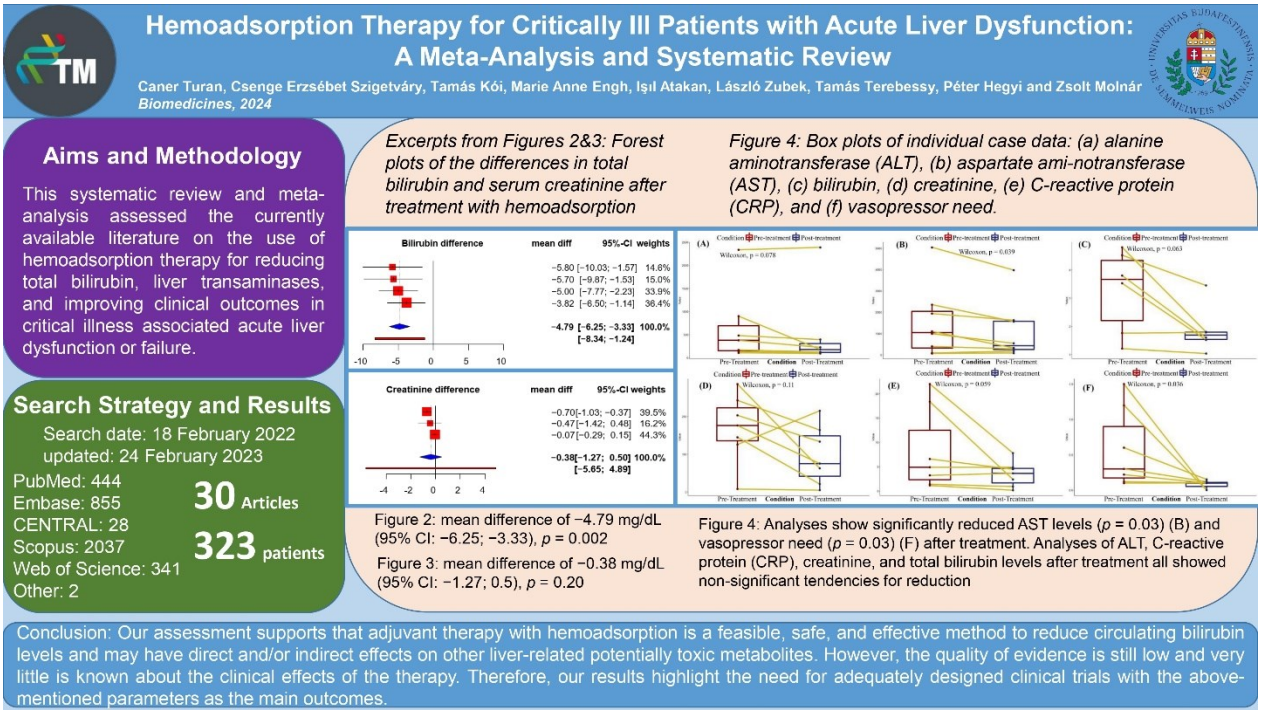
Through our studies, we made several important recommendations for both practitioners and researchers. We highlighted the need for protocolizing a potentially life-saving therapy such as hemoadsorption. We generated counter-arguments to previously published studies reporting significant benefits of preoperative glucocorticoid administration in liver surgery. We urged the scientific community to resolve this highly important uncertainty in a widely used international practical guideline.

4 GRAPHICAL ABSTRACTS OF THE STUDIES

4.1 Study 1



4.2 Study 2



5 INTRODUCTION

5.1 Overview

Liver dysfunction preceding surgical intervention, or acutely manifesting following critical illness, is an exceptionally dangerous phenomenon due to the ‘circular causality’ of liver diseases: as the liver mediates many processes implicated in both recovery and further deterioration, disturbance of its many functions creates an unpredictable chain of complications for the patient, often resulting in even more severe liver injury, thus even worse complications. The practitioner must carefully manage this potentially life-threatening ‘downward spiral’ perioperatively and in the intensive care unit.

5.2 Perioperative Perspective on Liver Diseases

In cases of direct injury to the liver, such as liver surgery, certain extrahepatic tissue-level complications manifest, such as postoperative collections, sepsis, organ space and wound infections, and ultimately, mortality [1,2]. Despite many improvements in liver surgery, the prevalence of such complications remains as high as 48% [3]. Furthermore, there is ample evidence in the literature postulating that the aforementioned downward spiral comprised of the cascade of dysfunctional systemic metabolic and hematological responses to injury underlies these interventions' difficult and high-risk nature [4].

5.3 Perioperative Glucocorticoids Administration in Liver Surgery

Glucocorticoids, namely methylprednisolone and hydrocortisone, both virtually ubiquitous in clinical practice, have been investigated for their anti-inflammatory effects to halt the development of the hyperinflammatory state after liver injury [5,6,7]. This research topic has been investigated worldwide since 1996 and was protocolized for clinical practice in 2016 with the publication of the Enhanced Recovery After Surgery (ERAS) guideline on liver surgery [8].

The 2016 ERAS protocol recommends preoperative administration of high-dose glucocorticoids with a moderate level of recommendation and a weak level of evidence. Randomized controlled studies (RCTs) and meta-analyses of randomized controlled studies have all found conflicting results, with the most recent one by Hao-Han et al. in 2021 reporting a statistically significant

improvement in overall postoperative complication rate. However, several inconsistencies and the absence of four additional RCTs in this meta-analysis necessitated a renewed critical appraisal of the current literature.

5.4 Critical Care Perspective on Liver Dysfunction

Acute liver dysfunction associated with critical illness in patients admitted to the intensive care units (ICU) is a frequent and deadly condition, with a prevalence and mortality up to 20% and 11% respectively [9,10,11]. This is thought to be a phenomenon distinct to an acute complication of a chronic liver disease, rather, a part of the multiorgan failure sequelae brought on by the entity of critical illness itself [12]. Such a condition also brings with it a dysregulated inflammatory process wherein typical pathways of inflammatory cytokines and mediators are disturbed to the point of excess reactive oxygen species at the tissue level and rapidly advancing end-organ dysfunction, manifesting in encephalopathy, permanent neurological and other organ damage, and ultimately, mortality due to multiple organ failure. This distinction is crucial in planning the consecutive steps of patient management, as these patients often require comprehensive diagnostics, monitoring, and treatment strategies.

5.5 Hemoadsorption Therapy in Acute Liver Dysfunction

Until recently, there were no specific treatments for acute liver dysfunction associated with critical illness. Furthermore, the unreliability of the standard monitoring techniques such as serum bilirubin and clinical diagnosis of hyperbilirubinemia, makes it exceedingly difficult to be ‘proactive’ against acute liver dysfunction, rather forcing the clinician to be ‘reactive’ to it [13,14].

Hemoadsorption is a novel extracorporeal blood purification technique mainly employed for cytokine removal to manage hyperinflammation [15,16,17]. As the state of hyperinflammation is also believed to contribute to acquired acute liver dysfunction in critically ill patients [18], theoretically, reducing toxic liver-related metabolites and cytokines in the blood could potentially improve liver function in these patients. However, there is limited evidence supporting its

effectiveness, and despite its growing use and increasing data, a comprehensive review of hemoadsorption in this context is still lacking.

6 OBJECTIVES

6.1 Study 1

We aimed to summarize and contextualize the existing evidence, based on two hypotheses: (1) preoperative glucocorticoid administration can reduce the complication rate following any type of liver surgery; (2) the effect of glucocorticoids on some complications will be different than on the overall complication rate. Our overall goal with this study was to provide clarification and a critical appraisal to policy-makers.

6.2 Study 2

We aimed to assess the effect of hemoadsorption therapy on critically ill patients with acute liver dysfunction associated with critical illness. We statistically analyzed clinical outcomes, the removal of total bilirubin, and the reduction in liver enzymes. Our overall goal with this study was to guide practitioners and researchers using hemoadsorption therapy for their patients by summarizing and contextualizing the current practice, literature, and any uncertainty in evidence quality and to inform the design of prospective clinical trials to answer specific, patient-related research questions.

7 METHODS

Both studies were conducted with full adherence to the Cochrane Handbook for Systematic Reviews of Interventions [19], and were protocolized according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement [20]. Both studies were also prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO), with the following identifiers for the first and second study, respectively: CRD42021284559, CRD42022286213.

7.1 Study 1

7.1.1 Search Strategy

A systematic search was conducted on the 15th of October, 2021. We used three electronic databases: MEDLINE via PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). No filters or restrictions, such as language or date were used to maximize the reproducibility of our systematic search. The systematic search was reproduced once on April 1st, 2023, to ensure no other RCTs were published between the finalization of the manuscript and its submission for publication. The following search key was utilized: (((hepatic OR liver) AND (surgery OR resection OR operation OR intervention)) OR hepatectomy) AND (steroid OR corticosteroid OR glucocorticoid OR methylprednisolone OR hydrocortisone OR cortisol) AND random*. A modified search key was used for the search on Embase: ((hepatic OR 'liver'/exp OR liver) AND ('surgery'/exp OR surgery OR 'resection'/exp OR resection OR 'operation'/exp OR operation OR 'intervention'/exp OR intervention) OR 'hepatectomy'/exp OR hepatectomy) AND ('steroid'/exp OR steroid OR 'corticosteroid'/exp OR corticosteroid OR 'glucocorticoid'/exp OR glucocorticoid OR 'methylprednisolone'/exp OR methylprednisolone OR 'hydrocortisone'/exp OR hydrocortisone OR 'cortisol'/exp OR cortisol) AND random*. References from the selected articles were also searched for additional studies to be included in the selection process.

7.1.2 Eligibility Criteria

We defined the eligibility criteria using the PICOS framework as per Cochrane recommendations. The following framework was utilized: population (P): adult patients of either sex undergoing liver surgery, including open or laparoscopic hepatic resection or liver transplantation; intervention (I): preoperative administration of any type of high-dose glucocorticoids; control (C): placebo or non-administration; main outcome (O): overall postoperative complication rate, with the rates of distinct complications and safety outcomes such as length of hospital stay being secondary outcomes; and setting (S): perioperative hospital care. Only randomized controlled trials were eligible for inclusion in this study.

7.1.3 Selection Process

Two independent review authors selected articles based on predetermined selection criteria, first by their titles and abstracts and then by their full texts, with inter-reviewer agreement calculated by Cohen's Kappa. An agreement of more than 0.8 was sought to judge whether the selection criteria were sufficiently reproducible.

7.1.4 Data Collection Process

Three independent review authors collected data from the included articles in two teams using a preset data table. This table was then compared to spot and correct any errors in data collection. The following data items were collected: (1) study characteristics: first author, the year of publication, study design, study population (number, age, and sex), study period, study country, and institute; (2) postoperative complications: overall postoperative complication rate, wound infection, septic/infectious complications, bile leakage, pleural effusion, gastrointestinal bleeding, intra-abdominal bleeding, high-grade liver failure, and all grades of liver failure; (3) laboratory outcomes (total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), interleukin-6 (IL-6), C-reactive protein (CRP), and prothrombin time–international normalized

ratio (PTT)); (4) perioperative outcomes (length of hospital stay, total operative time, intraoperative blood loss, blood transfusions, and blood products used (FFP or RBC).

7.1.5 Study Risk of Bias and Certainty of Evidence Assessment

Two independent review authors assessed the risk of bias, and level of certainty of the evidence for randomized controlled trials was assessed only by the first author, using the tools recommended by the Cochrane Handbook, namely, the RoB2 [21] with its associated tool and Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessment based on the GRADE Handbook [22], and using GRADEPro [23], respectively. Results from the risk of bias assessments were compared to detect any discrepancies. The risk of bias and GRADE assessments were visualized in the published manuscript.

7.1.6 Statistical Analysis

Meta-analyses were performed for all outcomes presented in the study design section of the prospectively registered protocol, given that at least three included articles presented data in a format that allowed for pooling. Data without measures of distribution, no specified units of measure, or inconsistent reporting were not eligible for pooling. If the reported outcome measures differed, estimations were made to convert medians with ranges into means with standard deviations, given that the reported data were of sufficient quality for the estimation. Adjustments and statistical models were used wherever appropriate for meta-analysis. To calculate and report the effect size estimation, odds ratio (OR) with 95% confidence interval (CI) were used for dichotomous outcomes; mean differences (MD) with 95% CI were used for continuous outcomes. Statistical heterogeneity was assessed in all cases using Cochrane Q and I^2 tests.

7.2 Study 2

7.2.1 Search Strategy

Two separate systematic searches were performed, once before and once after the publication of this study. The two searches were performed on the following dates: 18th of February 2022 and 24th of February 2023. Both searches utilized the same five electronic databases: Medline (via PubMed), Embase, Scopus, CENTRAL, and Web of Science. Systematic search also included manual searching of the CytoSorb Literature Database and the reference lists of the included studies.

No filters or restrictions were used in either search. Both instances of systematic search utilized the following search key: oXiris OR Jafron OR CytoSorb OR hemadsorption OR hemoadsorption OR “blood purification” OR “cytokine removal” AND liver failure OR “liver injury” OR liver dysfunction OR “hepatocellular injury” OR hepatic insufficiency OR hepatic dysfunction OR “acquired liver injury”.

7.2.2 Eligibility Criteria

We included any type of published original research data. These publications included clinical trials, cohort studies, registry analyses, case reports and case series. Publications with no original research data, such as other reviews, editorials, commentaries, letters, and communications, were excluded. We defined the eligibility criteria using the PICO framework as per Cochrane recommendations. The following framework was utilized: population (P): adult patients with acute liver dysfunction or failure associated with critical illness; intervention (I): treated with hemoadsorption using any technology or modality; control (C): if available, standard of care; outcome (O): mortality, bridge-to-transplantation, liver function parameters, critical illness parameters, safety outcomes. We also included studies where any one of the following outcomes were included: vasopressor need, serum bilirubin, liver enzymes before and after therapy.

7.2.3 Selection Process

Three independent review authors divided into two teams performed the selection. Criteria used for the selection were predetermined in the study protocol. An inter-reviewer agreement was calculated by Cohen's Kappa first after the title-and-abstract selection, then the full-text selection. A Kappa of more than 0.8 was eligible to finish any given selection step.

7.2.4 Data Collection Process

Two independent authors collected data from all included studies into a premade data collection sheet. The two sheets were compared to spot any differences that may have resulted during the data collection process. The collected items were: (1) study characteristics and main outcomes; (2) pre-treatment and post-treatment liver function parameters; (3) changes in vital organ function scores; (4) safety outcomes.

7.2.5 Study Risk of Bias and Certainty of Evidence Assessment

As many different study types were included, different tools for risk of bias assessment were utilized in this study. Nevertheless, all tools used were based on the Cochrane Handbook's recommendations. The following tools were used for the given study types: (1) Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) [24] for non-randomized studies such as cohort studies and registry analyses; (2) Joanna-Briggs Institute's Critical Appraisal Tool (JBI) [25] for case reports and case series. GRADE assessment was used to assess the level of certainty of evidence in all cases.

7.2.6 Statistical Analysis

Meta-analysis was performed for all outcomes for which at least three studies of comparable types (cohorts or cases) reported data. Before-after differences were calculated and compared for

continuous outcomes using the classical inverse variance method and Hartung-Knapp adjustment. Where a measure of distribution was not provided, we made observations by inputting −0.5 to 0.9 to correlation models to see if our estimations were sound. Upon validating our mathematical model, we published our estimations using a correlation of 0.8, meaning that we assumed the variables were highly correlated; therefore, we underestimated the effect size.

8 RESULTS

8.1 Systematic Search, Selection, Study Characteristics

8.1.1 Study 1

The systematic search identified 8226 records after automatic and manual duplicate removal. These records were then selected further according to a predetermined selection protocol, ultimately yielding 11 RCTs eligible for inclusion. The detailed record of the selection process is presented in Figure 1.

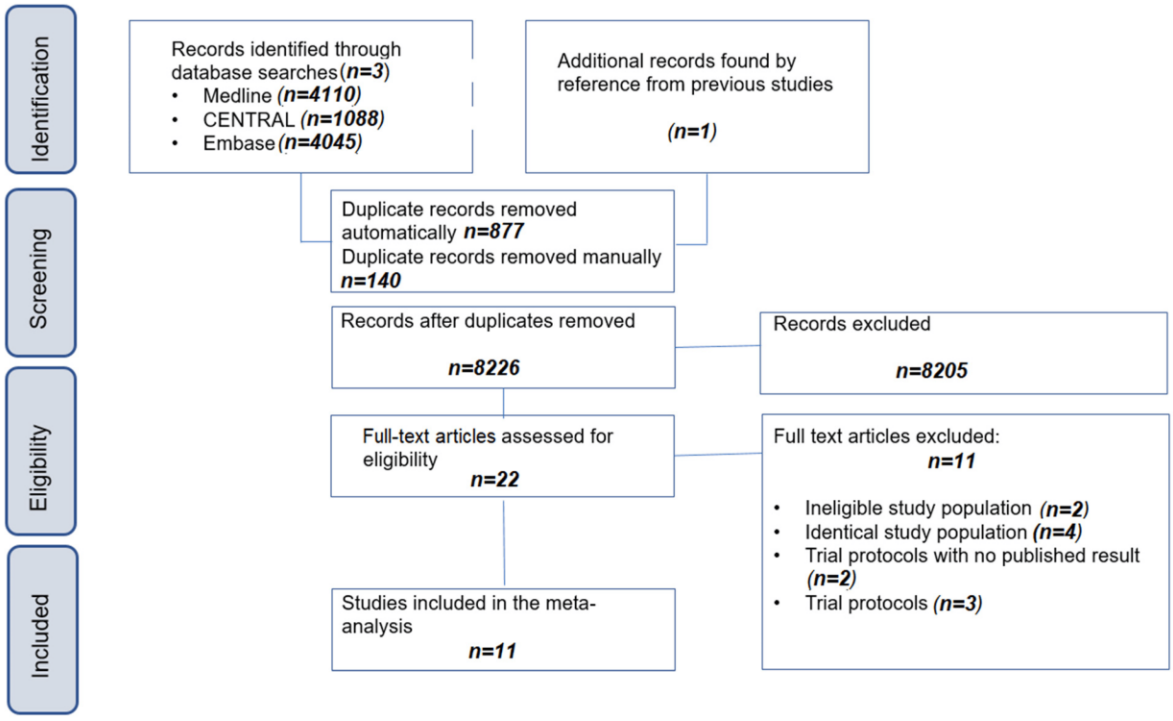


Figure 1. PRISMA flowchart of selection describing the systematic search and selection process

In summary, we managed to analyze data from 964 patients, of whom 477 were in the glucocorticoid group, and 487 in the control group. Baseline characteristics, clinical data, and intervention summaries of the included articles are detailed further in Table 1.

11 studies included in this meta-analysis investigated 964 patients in total, with 477 and 487 patients with no significant between-group heterogeneity in glucocorticoid (treatment) and comparator (placebo or non-administration with standard of care) groups, respectively. The detailed breakdown of study and patient characteristics of the included studies are presented in Table 1.

Table 1. The summary of the studies included (author, publication date, country, patient distribution, and demographic data). RCT: randomized controlled trial, a = mean, b = mean ± standard deviation, c = median (range).

First Author and Publication Date	**Intervention**	**Control**	**Surgery Type**	**Patient Distribution**		**Age, Years**		**Sex, Female % of Total**	
				Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Aldrighetti L. 2006 [26]	IV Methylprednisolone 500 mg	Unclear	Hepatic resection	36	37	61.8 (21–78) c	63 (31–85) c	37.83	38.88

Steinthorsdottir K. J. 2021 [27]	IV Methylprednisolone 10 mg/kg	Standard of care including IV Dexamethasone 8 mg	Open liver surgery without biliary reconstruction	86	88	65.2 ± 11.2 b	64.4 ± 12.0 b	34	30.6
Bressan A. K. 2022 [28]	IV Methylprednisolone 500 mg	Placebo	Hepatic resection	74	77	63.9 a	62.4 a	47.2	38.9
Hasegawa Y. 2019 [29]	IV Methylprednisolone 500 mg	Placebo	Hepatic resection	50	50	67 (59–74) c	68 (62–75) c	38	40
Donadon M. 2016 [30]	IV Methylprednisolone 500 mg	Placebo	Hepatic resection	16	16	65 (27–80) c	63 (22–77) c	44	37.5
Hayashi Y. 2011 [31]	IV Hydrocortisone 500-300-100 mg	Non-administration	Hepatic resection	98	102	69 (39–81) c	70 (35–82) c	No data	No data

	consecutively								
Yamashita Y. 2001 [32]	IV Methylprednisolone 500 mg	Non-administration	Hepatic resection	16	17	56.8 a	60.3 a	31.25	23.52
Muratore A. 2002 [33]	IV Methylprednisolone 30 mg/kg	Non-administration	Hepatic resection	28	25	64.1 a	65.4 a	60.7	32
Onoe S. 2021 [34]	IV Hydrocortisone 500-300-200-100 mg	Placebo	Combined liver and extrahepatic bile duct resection	46	48	70 (39–83) c	71 (39–84) c	33	40
Schmidt S. C. 2007 [35]	Methylprednisolone 30 mg/kg	Placebo	Hepatic resection	10	10	65 a	57 a	60	70

Turner S. 2006 [36]	IV Methylprednisolone 10 mg/kg	Placebo	Orthotopic liver transplantation	17	17	53.4 a	57.7 a	35.3	35.3

8.1.2 Study 2

The second and final round of systematic search yielded 3022 results, of which only two originated from the manual search. Duplicate records were removed first automatically, then manually by the first author. The detailed record of the selection process is presented in Figure 2.

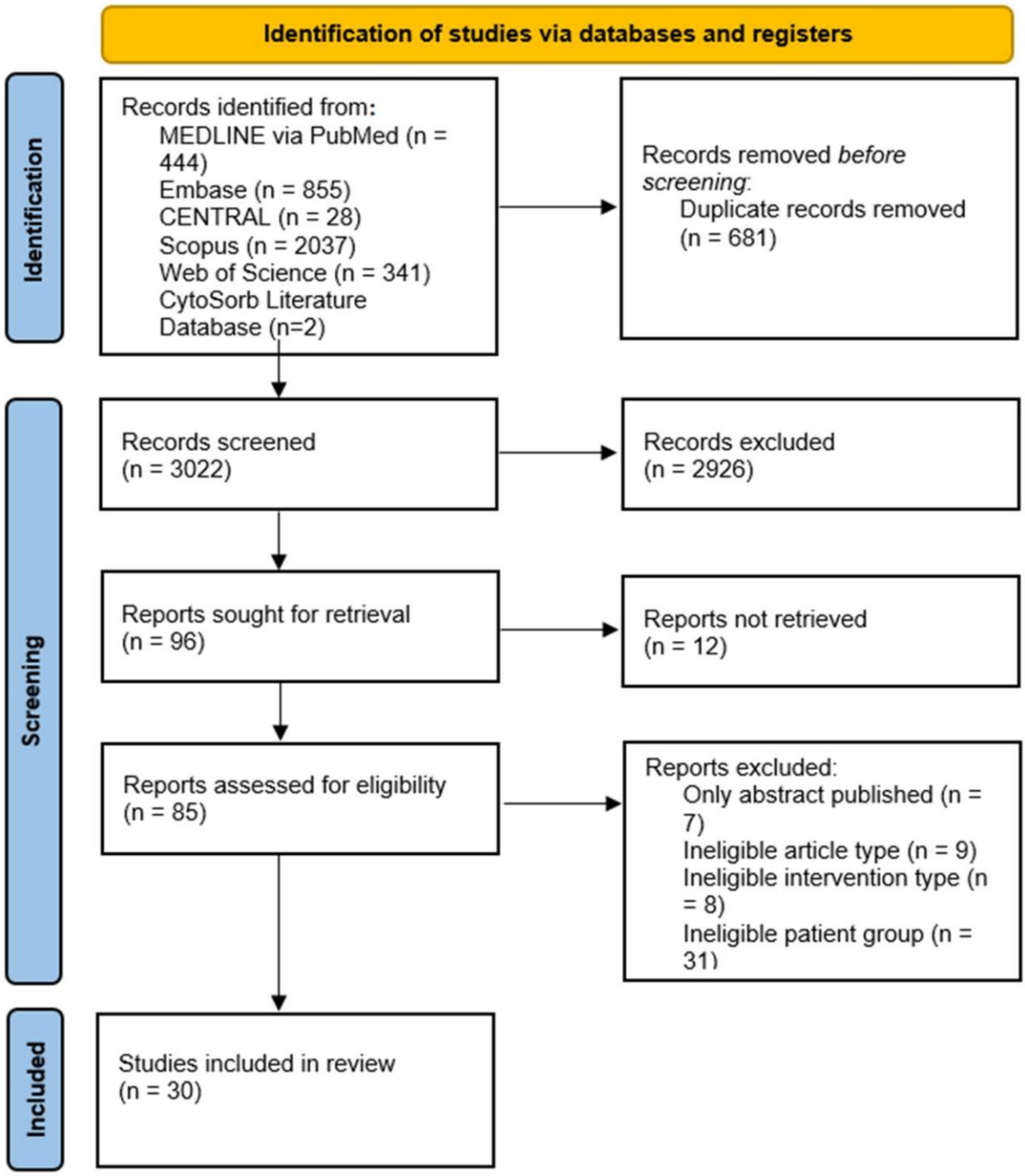


Figure 2. PRISMA flowchart of included studies.

The selection process identified 30 eligible studies published between 2011 and 2022, with an additional 3 studies included from a subsequent systematic search. These studies collectively documented the use of hemoadsorption in 323 patients. Among the studies, 19 were case reports, 7 were case series (totaling 84 patients), 3 were observational studies (130 patients), and 1 was a registry analysis (109 patients). All patients who had liver dysfunction associated with acute critical illness were treated with hemoadsorption techniques: CytoSorb (23 datasets, 232 patients), Coupled Plasma Filtration Adsorption (4 datasets, 88 patients), oXiris (2 datasets, 2 patients), and a combination of CytoSorb and oXiris (1 dataset, 1 patient). Detailed characteristics of the included studies and the baseline patient data are provided in Table 2.

Table 2. Study and baseline characteristics of included studies. a= Individual data, b= range (min–max), c= mean ± standard deviation, d= median (minimum range–maximum range).

Publication Data		**Study Design**	**Number of Patients**	**Age**	**Used Device**	**Intervention**	**Number of Sessions**
First Author	**Year of Publication**						
Gunasekera, A.M. [37]	2022	Case report	1	54 a	CytoSorb	CRRT with CytoSorb	1
Ruiz-Rodriguez, J.C. [38]	2022	Case report	1	50 a	CytoSorb	CVVHDF with CytoSorb	1

Cazzato, M.T. [39]	2019	Case report	1	No data	CytoSorb	CRRT with CytoSorb (24 h)	4
Daza, J.L. [40]	2022	Case report	1	41 a	CytoSorb	SLED combined with CytoSorb (12 h)	2
Hinz, B. [41]	2015	Case report	1	72 a	CytoSorb	CVVHD with CytoSorb (24-6-24 h)	3
Köhler, T. [42]	2021	Case report	1	29 a	CytoSorb	CRRT with CytoSorb (24 h)	Unclear
Lau, C.W.M. [43]	2021	Case report	1	47 a	oXiris	Blood purification with oXiris (5 days in total)	No data
Li, Y. [44]	2020	Case report	1	35 a	oXiris	CVVH with oXiris (24 h)	2

Manohar, V. [45]	2017	Case report	1	22 a	CytoSorb	Extracorporeal cytokine hemofiltration (12 h)	1
Markovic, M. [46]	2020	Case report	1	31 a	CytoSorb and oXiris	CytoSorb (day 1) and oXiris (day 2)	2
Moretti, R. [47]	2011	Case report	1	27 a	CPFA	CPFA (24 h)	5
Piwowarczyk, P. [48]	2019	Case report	1	57 a	CytoSorb	CytoSorb with anticoagulated CVVHD (24 h)	2
Tomescu, D. [49]	2018	Case report	1	17 a	CytoSorb	CytoSorb (before and throughout liver transplantation)	1
Wiegele, M. [50]	2015	Case report	1	44 a	CytoSorb	CytoSorb (6 h)	2

Lévai, T. [51]	2019	Case report	1	42 a	CytoSorb	CytoSorb with anticoagulated CVVRRT	4
Manini, E. [52]	2019	Case report	1	62 a	CytoSorb	CytoSorb with anticoagulated CVVRRT	1
Popescu, M. [53]	2017	Case report	1	47 a	CytoSorb	CytoSorb (24 h)	4
Kogelman, K. [54]	2021	Case report	1	45 a	CytoSorb	CytoSorb with CRRT (in CVVHD mode)	3
Breitkopf, R. [55]	2020	Case report	1	40 a	CytoSorb	CytoSorb with CRRT (in CVVHD mode)	2
Ullo, I. [56]	2017	Case series	9	21–63 b	CPFA	CPFA with citrate anticoagulation	No data

Popescu, M. [57]	2017	Case series	5	49 ± 13 c	CytoSorb	CytoSorb with CVVHF	No data
Popescu, M. and Tomescu, D. [58]	2018	Case series	13	46 ± 17 c	CytoSorb	CytoSorb with CVVHF	No data
Maggi, U. [59]	2013	Case series	2	22–64 b	CPFA	CPFA	3
Popescu, M. [60]	2020	Case series	29	34 ± 14 c	CytoSorb	CytoSorb with CVVHDF	3
Dhokia, V.D. [61]	2019	Case series	3	51–71 b	CytoSorb	CytoSorb with CVVHDF (1); CytoSorb with Prismaflex (1); CytoSorb with CRRT (1)	2

Acar, U. [62]	2019	Case series	4	26–73 b	CytoSorb	CytoSorb with CVVHD	No data
Ocskay, K. [18]	2021	Registry analysis	109	49.2 ± 17.1 c	CytoSorb	Varies: CytoSorb alone or CytoSorb with CRRT	2
Niu, D.G. [63]	2019	Retrospective observational study	76	51.4 ± 15.6 c	CPFA	CPFA with CRRT	No data
Scharf, C. [64]	2021	Retrospective observational study	33	55 (18–76) d	CytoSorb	CytoSorb	1
Praxenthaler, J. [65]	2022	Retrospective observational study	21	74 (58–80) d	CytoSorb	CVVHD with CytoSorb	varies

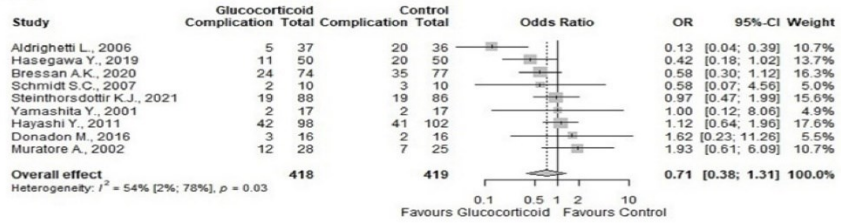
8.2 Results of Analyses

8.2.1 Study 1

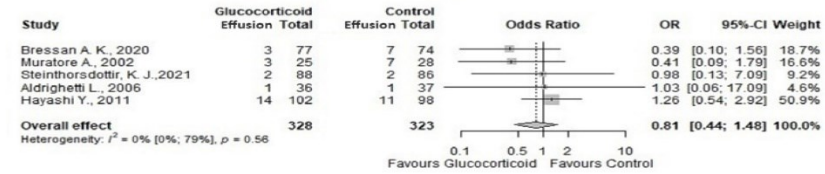
8.2.1.1 Main Outcome

The main outcome of this study was the difference in the odds ratio of the overall postoperative complication rate between the intervention and control groups. Out of the eleven eligible studies in our analysis, nine (n = 836) reported the overall rate of postoperative complications as an outcome [27-35]. This outcome did not differentiate between major and minor complications or varying pathomechanisms. In this pooled analysis, 418 patients received preoperative glucocorticoids in the intervention group, while 419 patients in the control group were given either saline, a placebo, or nothing. The intervention group showed a trend toward a lower overall postoperative complication rate (OR: 0.71; 95% CI: 0.38–1.31, p = 0.23), although this finding was not statistically significant (see Figure 3A). Considerable heterogeneity was observed, as defined by the Cochrane Handbook [I^2 = 54% (2%; 78%), p = 0.03].

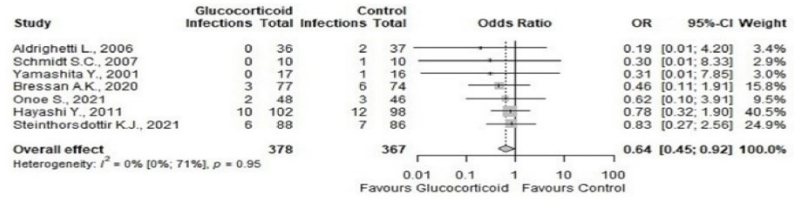
(A)


Study
Glucocorticoid Complication Total
Control Complication Total
Odds Ratio
OR 95%-CI Weight
Aldrighetti L., 2006 5 37 20 36 0.13 [0.04; 0.39] 10.7%
Hasegawa Y., 2019 11 50 20 50 0.42 [0.18; 1.02] 13.7%
Bressan A.K., 2020 24 74 35 77 0.58 [0.30; 1.12] 16.3%
Schmidt S.C., 2007 2 10 3 10 0.58 [0.07; 4.56] 5.0%
Steinthorsdottir K.J., 2021 19 88 19 86 0.97 [0.47; 1.99] 15.6%
Yamashita Y., 2001 2 17 2 17 1.00 [0.12; 8.06] 4.9%
Hayashi Y., 2011 42 98 41 102 1.12 [0.64; 1.96] 17.6%
Donadon M., 2016 3 16 2 16 1.62 [0.23; 11.26] 5.5%
Muratore A., 2002 12 28 7 25 1.93 [0.61; 6.09] 10.7%
Overall effect 418 419 0.71 [0.38; 1.31] 100.0%
Heterogeneity: I^2 = 54% [2%; 78%], p = 0.03
0.1 0.5 1 2 10
Favours Glucocorticoid Favours Control

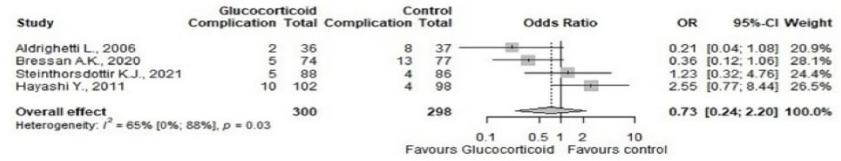
(B)


Study
Glucocorticoid Effusion Total
Control Effusion Total
Odds Ratio
OR 95%-CI Weight
Bressan A. K., 2020 3 77 7 74 0.39 [0.10; 1.56] 18.7%
Muratore A., 2002 3 25 7 28 0.41 [0.09; 1.79] 16.6%
Steinthorsdottir, K. J.,2021 2 88 2 86 0.98 [0.13; 7.09] 9.2%
Aldrighetti L., 2006 1 36 1 37 1.03 [0.06; 17.09] 4.6%
Hayashi Y., 2011 14 102 11 98 1.26 [0.54; 2.92] 50.9%
Overall effect 328 323 0.81 [0.44; 1.48] 100.0%
Heterogeneity: I^2 = 0% [0%; 79%], p = 0.56
0.1 0.5 1 2 10
Favours Glucocorticoid Favours Control

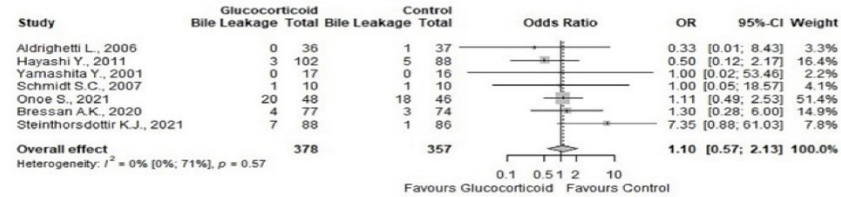
(C)


Study
Glucocorticoid Infections Total
Control Infections Total
Odds Ratio
OR 95%-CI Weight
Aldrighetti L., 2006 0 36 2 37 0.19 [0.01; 4.20] 3.4%
Schmidt S.C., 2007 0 10 1 10 0.30 [0.01; 8.33] 2.9%
Yamashita Y., 2001 0 17 1 16 0.31 [0.01; 7.85] 3.0%
Bressan A.K., 2020 3 77 6 74 0.46 [0.11; 1.91] 15.8%
Onoe S., 2021 2 48 3 46 0.62 [0.10; 3.91] 9.5%
Hayashi Y., 2011 10 102 12 98 0.78 [0.32; 1.90] 40.5%
Steinthorsdottir K.J., 2021 6 88 7 86 0.83 [0.27; 2.56] 24.9%
Overall effect 378 367 0.64 [0.45; 0.92] 100.0%
Heterogeneity: I^2 = 0% [0%; 71%], p = 0.95
0.01 0.1 1 10 100
Favours Glucocorticoid Favours Control

(D)


Study
Glucocorticoid Complication Total
Control Complication Total
Odds Ratio
OR 95%-CI Weight
Aldrighetti L., 2006 2 36 8 37 0.21 [0.04; 1.08] 20.9%
Bressan A.K., 2020 5 74 13 77 0.36 [0.12; 1.06] 28.1%
Steinthorsdottir K.J., 2021 5 88 4 86 1.23 [0.32; 4.76] 24.4%
Hayashi Y., 2011 10 102 4 98 2.55 [0.77; 8.44] 26.5%
Overall effect 300 298 0.73 [0.24; 2.20] 100.0%
Heterogeneity: I^2 = 65% [0%; 88%], p = 0.03
0.1 0.5 1 2 10
Favours Glucocorticoid Favours control

(E)


Study
Glucocorticoid Bile Leakage Total
Control Bile Leakage Total
Odds Ratio
OR 95%-CI Weight
Aldrighetti L., 2006 0 36 1 37 0.33 [0.01; 8.43] 3.3%
Hayashi Y., 2011 3 102 5 88 0.50 [0.12; 2.17] 16.4%
Yamashita Y., 2001 0 17 0 16 1.00 [0.02; 53.46] 2.2%
Schmidt S.C., 2007 1 10 1 10 1.00 [0.05; 18.57] 4.1%
Onoe S., 2021 20 48 18 46 1.11 [0.49; 2.53] 51.4%
Bressan A.K., 2020 4 77 3 74 1.30 [0.28; 6.00] 14.9%
Steinthorsdottir K.J., 2021 7 88 1 86 7.35 [0.88; 61.03] 7.8%
Overall effect 378 357 1.10 [0.57; 2.13] 100.0%
Heterogeneity: I^2 = 0% [0%; 71%], p = 0.57
0.1 0.5 1 2 10
Favours Glucocorticoid Favours Control

(F)

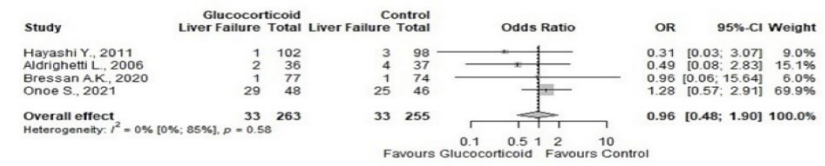

Study
Glucocorticoid Liver Failure Total
Control Liver Failure Total
Odds Ratio
OR 95%-CI Weight
Hayashi Y., 2011 1 102 3 98 0.31 [0.03; 3.07] 9.0%
Aldrighetti L., 2006 2 36 4 37 0.49 [0.08; 2.83] 15.1%
Bressan A.K., 2020 1 77 1 74 0.96 [0.06; 15.64] 6.0%
Onoe S., 2021 29 48 25 46 1.28 [0.57; 2.91] 69.9%
Overall effect 33 263 33 255 0.96 [0.48; 1.90] 100.0%
Heterogeneity: I^2 = 0% [0%; 85%], p = 0.58
0.1 0.5 1 2 10
Favours Glucocorticoid Favours Control

Figure 3. Forest plots of clinical outcomes. (A) overall postoperative complication rate; (B) pleural effusion; (C) wound infection; (D) septic/infectious complications; (E) bile leakage; (F) liver failure of any grade. OR: odds ratio; CI: confidence interval.

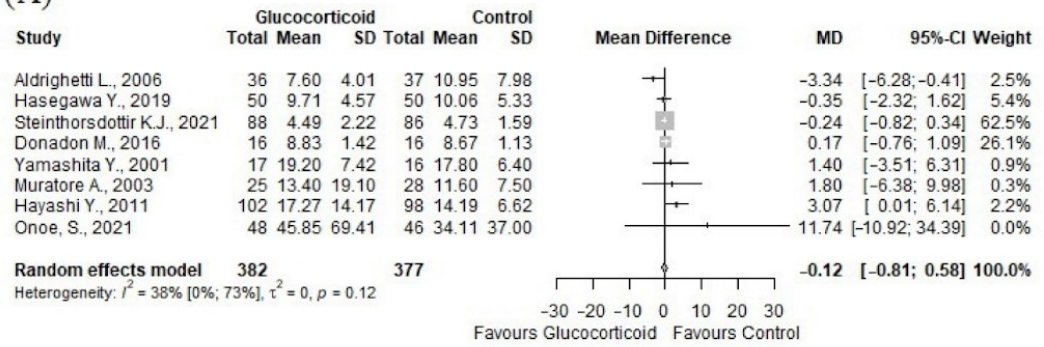
8.2.1.2 Other Outcomes

Five studies [26,27,28,31,33] involving 651 participants evaluated pleural effusion rates as an outcome. Our analysis indicated no statistically significant difference between the groups, though there was a slight trend toward a lower rate in the intervention group (OR: 0.81; 95% CI: 0.44–1.48, p = 0.4963) (see Figure 3B). Wound infection rates were reported in seven studies [26-28,31,32,34,35] with 745 participants. The intervention significantly lowered the incidence of wound infections (OR: 0.64; 95% CI: 0.45–0.92, p = 0.0241) (see Figure 3C). Four studies [26-28,31] with 598 participants reported septic or infectious complications. No statistically significant difference was found between the groups, although there was a trend toward a lower rate in the intervention group (OR: 0.73; 95% CI: 0.24–2.20, p = 0.577) (see Figure 3D). Bile leakage rates were analyzed in seven studies [26-28,31,32,34,35], including 745 participants. Our analysis revealed no statistically significant difference between the groups (OR: 1.12; 95% CI: 0.59–2.13, p = 0.7263), with a slight trend toward a higher rate in the intervention group (see Figure 3E). Liver failure outcomes were reported in five studies [26,28,31,32,34] involving 551 participants, and our analysis found no statistically significant difference between the groups (OR: 0.96; 95% CI: 0.49–1.88, p = 0.9034) (see Figure 3F).

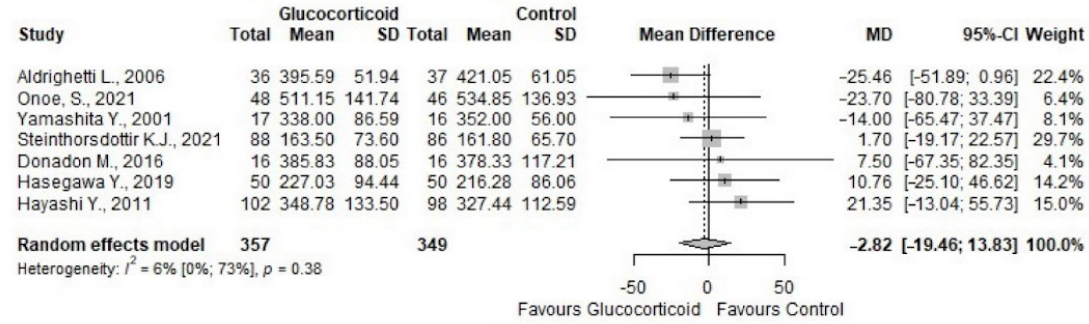
Perioperative outcomes were also assessed in our analysis. No statistically significant differences were found between the glucocorticoid and control groups for these outcomes. Hospital stay duration (in days) was reported in eight studies [27-34] (n = 759), with a mean difference of −0.12 (95% CI: −0.57 to 0.34) (see Figure 4A). Total operative time (in minutes) was reported in seven studies [27-32,34] (n = 709), showing a mean difference of −2.82 (95% CI: −19.46 to 13.83) (see Figure 4B). Blood loss (in milliliters) was analyzed in eight studies [27-34] (n = 857), with a mean difference of 3.41 (95% CI: −33.33 to 40.16) (see Figure 4C). The requirement for intraoperative

blood transfusion was reported in five studies (n = 572), with an odds ratio of 1.04 (95% CI: 0.63 to 1.71, p = 0.89) (see Figure 4D).

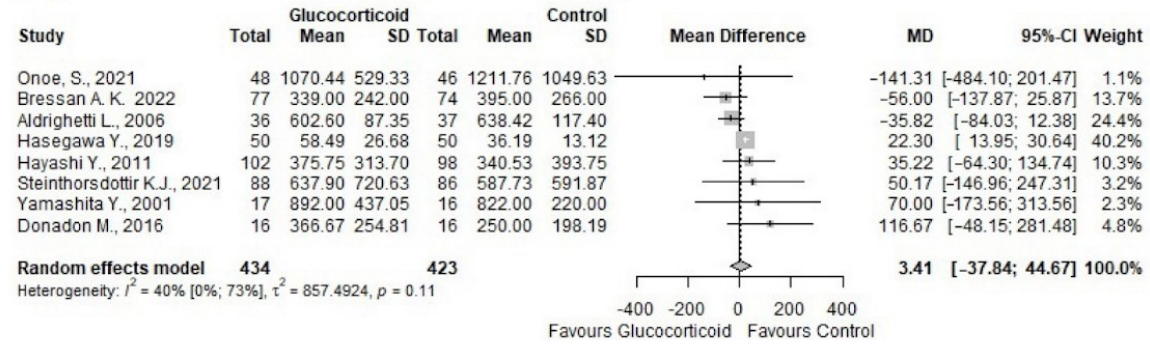
(A)


Glucocorticoid
Control
Study Total Mean SD Total Mean SD
Mean Difference
MD 95%-CI Weight
Aldrighetti L., 2006 36 7.60 4.01 37 10.95 7.98 -3.34 [-6.28; -0.41] 2.5%
Hasegawa Y., 2019 50 9.71 4.57 50 10.06 5.33 -0.35 [-2.32; 1.62] 5.4%
Steinthorsdottir K.J., 2021 88 4.49 2.22 86 4.73 1.59 -0.24 [-0.82; 0.34] 62.5%
Donadon M., 2016 16 8.83 1.42 16 8.67 1.13 0.17 [-0.76; 1.09] 26.1%
Yamashita Y., 2001 17 19.20 7.42 16 17.80 6.40 1.40 [-3.51; 6.31] 0.9%
Muratore A., 2003 25 13.40 19.10 28 11.60 7.50 1.80 [-6.38; 9.98] 0.3%
Hayashi Y., 2011 102 17.27 14.17 98 14.19 6.62 3.07 [0.01; 6.14] 2.2%
Onoe, S., 2021 48 45.85 69.41 46 34.11 37.00 11.74 [-10.92; 34.39] 0.0%
Random effects model 382 377 -0.12 [-0.81; 0.58] 100.0%
Heterogeneity: I^2 = 38% [0%; 73%], τ^2 = 0, p = 0.12
-30 -20 -10 0 10 20 30
Favours Glucocorticoid
Favours Control

(B)


Glucocorticoid
Control
Study Total Mean SD Total Mean SD
Mean Difference
MD 95%-CI Weight
Aldrighetti L., 2006 36 395.59 51.94 37 421.05 61.05 -25.46 [-51.89; 0.96] 22.4%
Onoe, S., 2021 48 511.15 141.74 46 534.85 136.93 -23.70 [-80.78; 33.39] 6.4%
Yamashita Y., 2001 17 338.00 86.59 16 352.00 56.00 -14.00 [-65.47; 37.47] 8.1%
Steinthorsdottir K.J., 2021 88 163.50 73.60 86 161.80 65.70 1.70 [-19.17; 22.57] 29.7%
Donadon M., 2016 16 385.83 88.05 16 378.33 117.21 7.50 [-67.35; 82.35] 4.1%
Hasegawa Y., 2019 50 227.03 94.44 50 216.28 86.06 10.76 [-25.10; 46.62] 14.2%
Hayashi Y., 2011 102 348.78 133.50 98 327.44 112.59 21.35 [-13.04; 55.73] 15.0%
Random effects model 357 349 -2.82 [-19.46; 13.83] 100.0%
Heterogeneity: I^2 = 6% [0%; 73%], p = 0.38
-50 0 50
Favours Glucocorticoid
Favours Control

(C)


Glucocorticoid
Control
Study Total Mean SD Total Mean SD
Mean Difference
MD 95%-CI Weight
Onoe, S., 2021 48 1070.44 529.33 46 1211.76 1049.63 -141.31 [-484.10; 201.47] 1.1%
Bressan A. K. 2022 77 339.00 242.00 74 395.00 266.00 -56.00 [-137.87; 25.87] 13.7%
Aldrighetti L., 2006 36 602.60 87.35 37 638.42 117.40 -35.82 [-84.03; 12.38] 24.4%
Hasegawa Y., 2019 50 58.49 26.68 50 36.19 13.12 22.30 [13.95; 30.64] 40.2%
Hayashi Y., 2011 102 375.75 313.70 98 340.53 393.75 35.22 [-64.30; 134.74] 10.3%
Steinthorsdottir K.J., 2021 88 637.90 720.63 86 587.73 591.87 50.17 [-146.96; 247.31] 3.2%
Yamashita Y., 2001 17 892.00 437.05 16 822.00 220.00 70.00 [-173.56; 313.56] 2.3%
Donadon M., 2016 16 366.67 254.81 16 250.00 198.19 116.67 [-48.15; 281.48] 4.8%
Random effects model 434 423 3.41 [-37.84; 44.67] 100.0%
Heterogeneity: I^2 = 40% [0%; 73%], τ^2 = 857.4924, p = 0.11
-400 -200 0 200 400
Favours Glucocorticoid
Favours Control

(D)

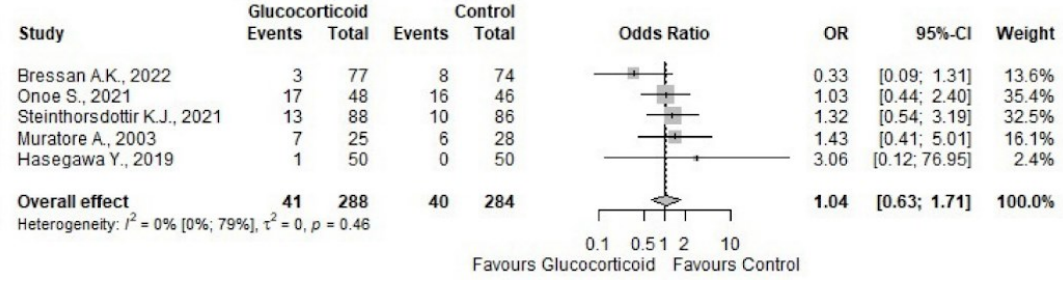

Glucocorticoid
Control
Study Events Total Events Total
Odds Ratio
OR 95%-CI Weight
Bressan A.K., 2022 3 77 8 74 0.33 [0.09; 1.31] 13.6%
Onoe S., 2021 17 48 16 46 1.03 [0.44; 2.40] 35.4%
Steinthorsdottir K.J., 2021 13 88 10 86 1.32 [0.54; 3.19] 32.5%
Muratore A., 2003 7 25 6 28 1.43 [0.41; 5.01] 16.1%
Hasegawa Y., 2019 1 50 0 50 3.06 [0.12; 76.95] 2.4%
Overall effect 41 288 40 284 1.04 [0.63; 1.71] 100.0%
Heterogeneity: I^2 = 0% [0%; 79%], τ^2 = 0, p = 0.46
0.1 0.5 1 2 10
Favours Glucocorticoid
Favours Control

Figure 4. Forest plots of other outcomes. (A) length of hospital stay; (B) total operative time; (C) blood loss (milliliters); (D) need for administration of blood products. OR: odds ratio; CI: confidence interval; MD: mean difference; SD: standard deviation.

8.2.2 Study 2

8.2.2.1 Main Outcome

The primary outcomes assessed in this study were mortality, the rate of bridging to transplantation, and the duration of ICU stay. Due to the scarcity of well-documented original research data in the literature, none of these outcomes could be meta-analyzed as initially intended. Observational cohort studies [62-64] reported an in-hospital mortality rate of 38% (50 out of 130 patients), while case reports and series [37-61] indicated a mortality rate of 23% (19 out of 82 patients). The registry analysis documented a total in-hospital mortality rate of 59.6% (65 cases), with 10 deaths occurring at the end of hemoadsorption therapy (9.2%), 60 deaths during the ICU stay (55%), and 5 more during the post-ICU hospitalization period. This was the only study to report on the length of ICU stay, providing a median duration of 14.0 days (IQR: 7.0–23.0). None of the studies in the analysis provided data on the success rate or any other descriptive outcomes regarding bridging to liver transplantation.

8.2.2.2 Other Outcomes

Among the outcomes, only six laboratory parameters were suitable for meta-analysis. Data from 160 patients demonstrated a significant post-treatment reduction in total bilirubin levels, with a mean difference of −4.79 mg/dL (95% CI: −6.25 to −3.33, p = 0.002) (Figure 5). In the case series involving 38 patients, there was a non-significant decrease in serum creatinine, with a mean difference of −0.38 mg/dL (95% CI: −1.27 to 0.5, p = 0.20) (Figure 6). Additional analyses could be conducted only with individual patient data derived from case reports (Figure 7). Pre- and post-treatment values for each laboratory parameter were aggregated from these case reports and illustrated in box plots. The change in each parameter for individual patients was represented by lines connecting dots that reflect pre- and post-treatment values. These analyses revealed a

significant reduction in AST levels (Wilcoxon p = 0.03) (Figure 4B) and in the need for vasopressors (Wilcoxon p = 0.03) (Figure 4F) after treatment. Analyses of ALT, C-reactive protein (CRP), creatinine, and total bilirubin levels post-treatment showed non-significant trends toward reduction (Figure 4).

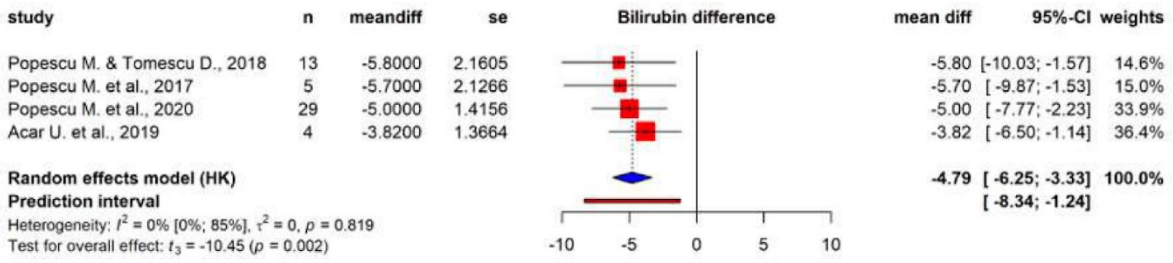


Figure 5. Forest plot of total bilirubin levels pre- and post-treatment with hemoadsorption

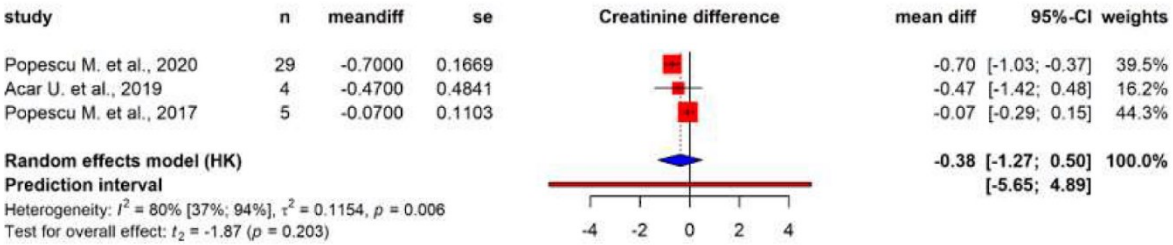


Figure 6. Forest plot of serum creatinine levels pre- and post-treatment with hemoadsorption.

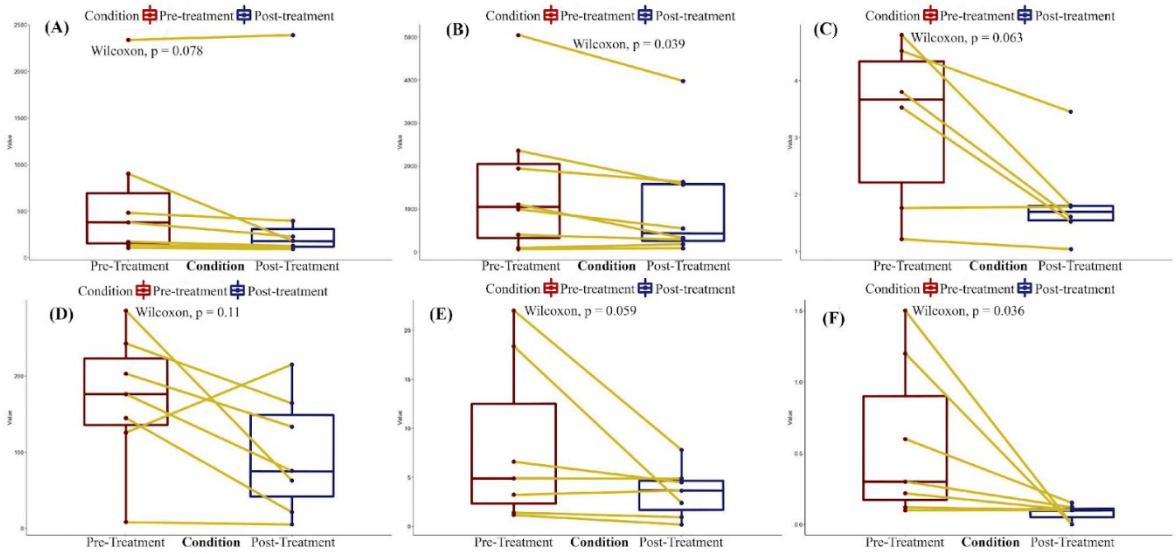


Figure 7. Box plots of individual case data: (A) alanine aminotransferase (ALT), (B) aspartate aminotransferase (AST), (C) bilirubin, (D) creatinine, (E) C-reactive protein (CRP), and (F) vasopressor need. Data were pooled from individual case reports and presented as box plots, representing pre- and post-treatment values. Changes in these parameters for each case are also depicted by lines connecting pre- and post-treatment values.

Only two studies documented changes in SOFA scores before and after hemoadsorption therapy. Ocskay et al. [18] observed a non-significant improvement in SOFA scores among liver failure patients, with a mean difference and confidence interval of 0.5 (−0.3 to 1.3). In contrast, Popescu et al. (2020) [59] reported a significant improvement in CLIF-SOFA scores following hemoadsorption therapy in their case series. Although the retrospective study by Niu et al. [51] indicated a significant improvement in SOFA scores, specific data supporting this finding were not provided. Scharf et al. [63] also found a significant improvement in SAPS-II scores after hemoadsorption, with a mean difference of 6 ± 9 ($p = 0.01$). Among the individual case reports, Cazzato et al. [38] were the only ones to follow up on SOFA scores. Their patients, who underwent hepatic resection and developed acute liver failure postoperatively, showed an improvement in SOFA scores from 4 to 2 after hemoadsorption therapy.

While no study included into this meta-analysis analyzed safety outcomes in a format eligible for a pooled analysis, no device-related adverse events were recorded.

8.3 Assessment of the Risk of Bias and Level of Evidence Certainty

8.3.1 Risk of Bias Assessment

8.3.1.1 Study 1

Risk of bias assessment was performed using RoB2, and the results are presented in Figure 8. Overall, most of the studies included in this analysis were appropriately randomized, and none of the studies had issues related to missing outcomes. The primary risk of bias stemmed from the inadequate detailing of study designs in some instances, leading to potential concerns. Additionally, in certain cases, bias associated with outcome reporting posed a significant risk. Heterogeneity levels were evaluated following the guidelines of the Cochrane Handbook using $\tau 2$, I2, and Cochrane Q test statistics. The overall postoperative complication rate analysis showed moderate heterogeneity (I2 = 54% [2%;78%], p = 0.03), which could be attributed to the inclusion of fewer than ten studies and the pooling of patients who underwent different liver surgeries. Similarly, moderate heterogeneity was noted in the analyses of hospital stay length (I2 = 38% [0%;73%], p = 0.12) and blood loss (I2 = 40% [0%;73%], p = 0.11), likely due to variations in the surgical characteristics of the patients included. The analysis of septic/infectious complications revealed significant heterogeneity (I2 = 65%, [0%;88%], p = 0.03), potentially explained by the relatively small sample size (n = 200), as this analysis included only four studies. No severe heterogeneity was detected in any of the other analyses.

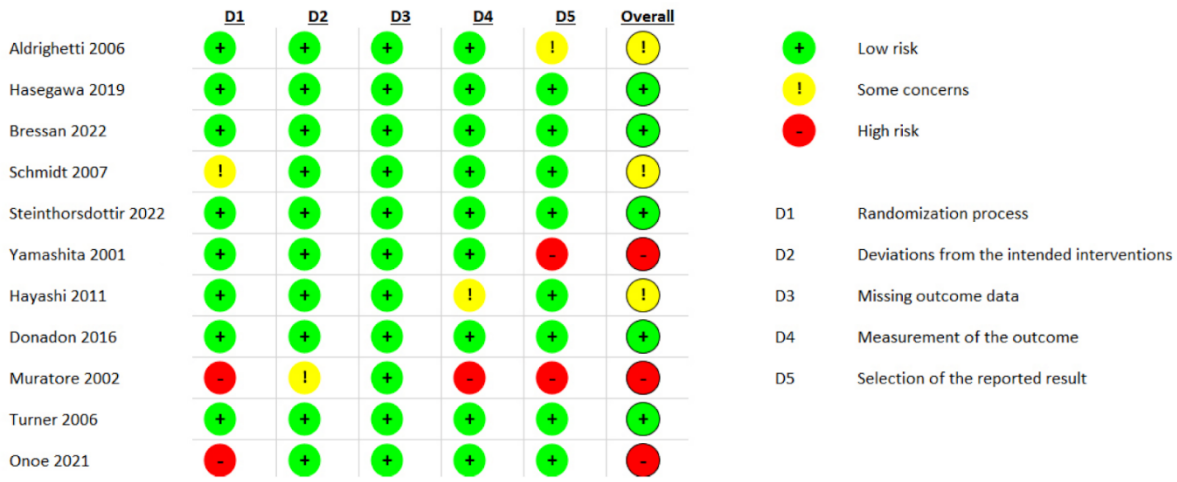


Figure 8. Results of the risk of bias assessments using RoB2

8.3.1.2 Study 2

Risk of bias was assessed using several tools, all as per the recommendations in the Cochrane Handbook. Although the included and pooled studies are of categorically lower quality according to the hierarchy of levels of evidence, the studies themselves were of fair to good quality overall. The results of risk of bias assessments are presented in Figures 9, 10, 11.

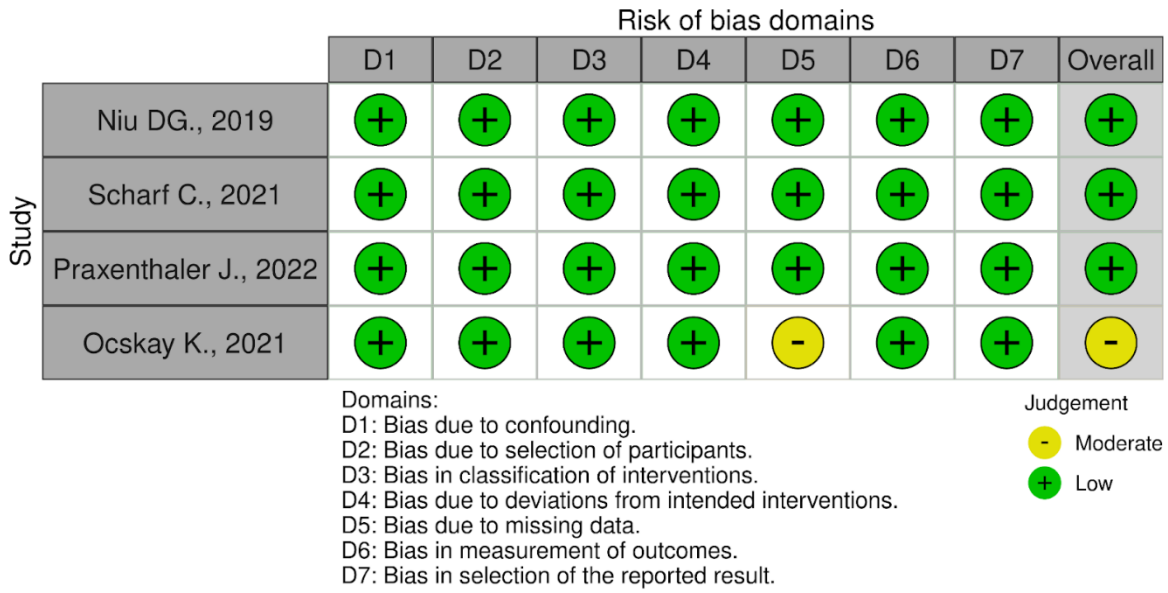


Figure 9. Results of the risk of bias assessments using ROBINS-I

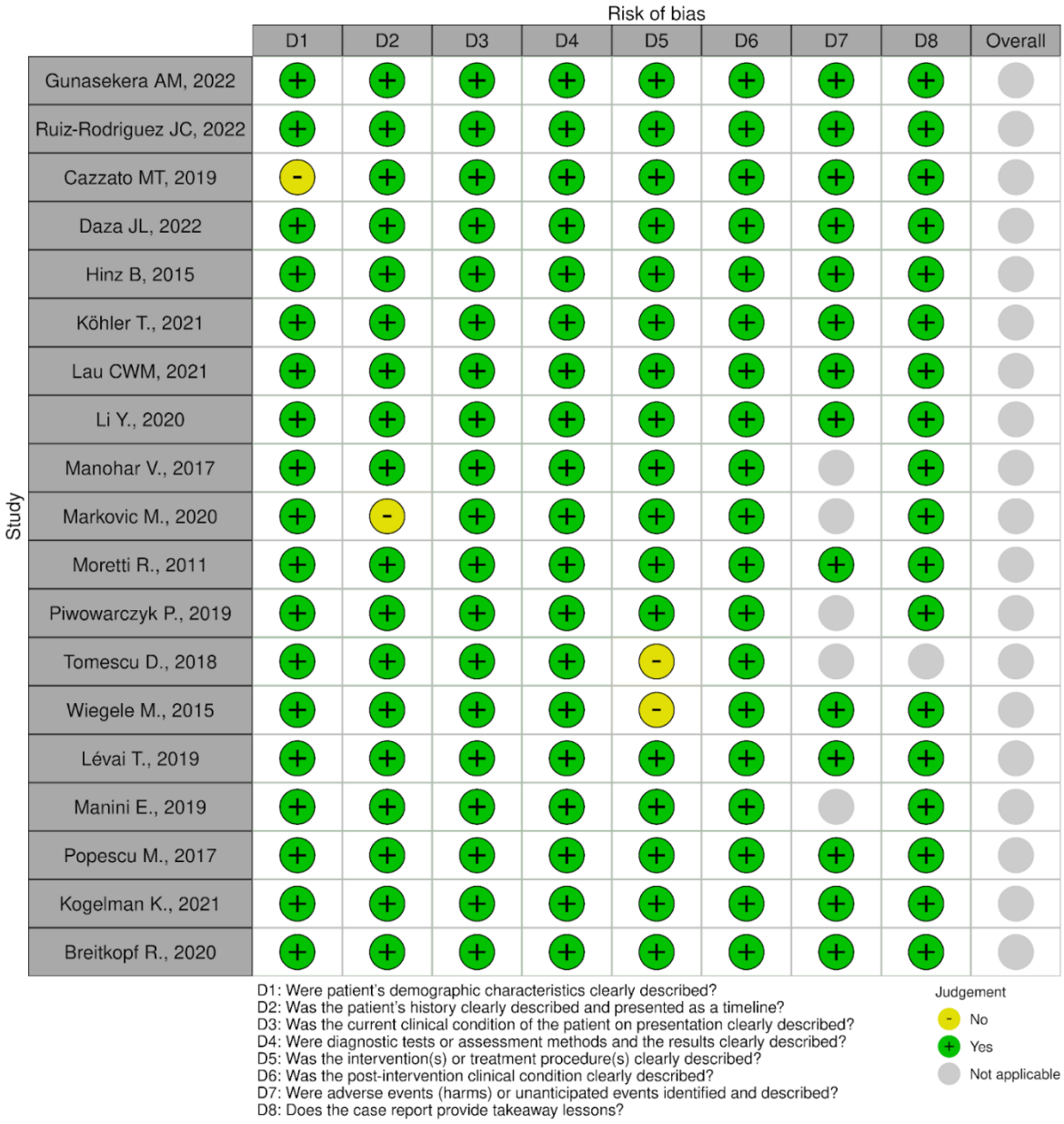


Figure 10. Results of the risk of bias assessments using JBI for case reports

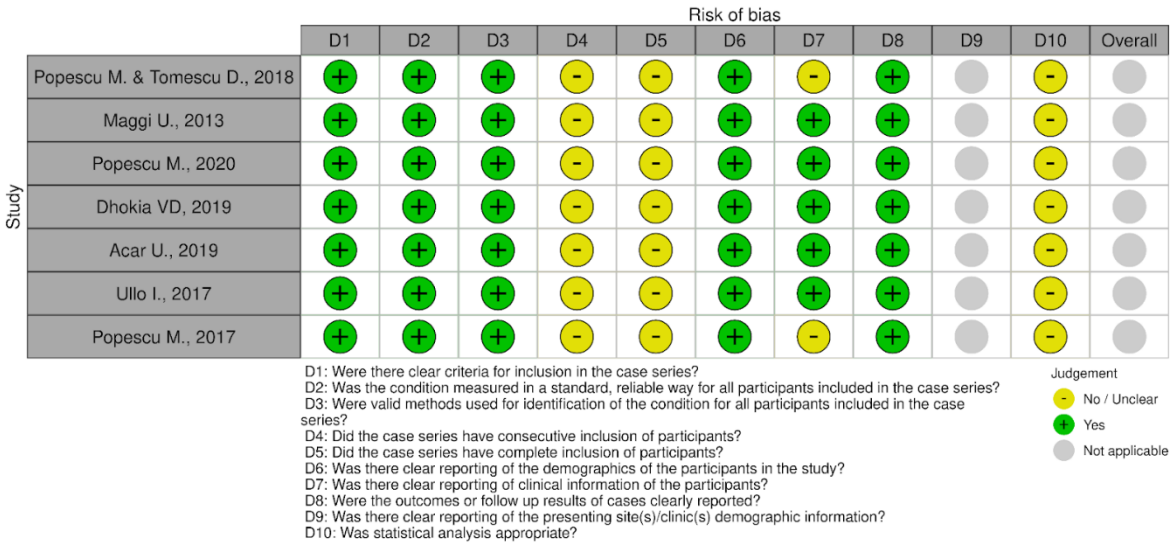


Figure 11. Results of the risk of bias assessments using JBI for case series

8.3.2 GRADE Assessment for Level of Evidence Certainty

8.3.2.1 Study 1

The studies were also assessed for their evidence certainty using the GRADE approach. Overall, the certainty of the evidence was rated as weak to very weak. The most critical issue was concerning the overall postoperative complication rate, which is an indirect and imprecise outcome. Other outcomes also suffered from imprecision and inconsistencies across the pooled studies. Finally, the risk of bias presented an obstacle to achieving higher levels of evidence certainty.

8.3.2.2 Study 2

The quality of evidence has been deemed poor according to the GRADE approach. The fact that all of the studies are retrospective and observational poses significant challenges for drawing dependable conclusions. Additionally, some of the literature on this subject might be categorized

as “gray literature,” which further raises concerns about the reliability and overall quality of the evidence presented.

9 DISCUSSION

9.1 Summary of Findings

Study 1 was the most comprehensive systematic review and meta-analysis on this topic thus far. Our analysis found a tendency towards lower odds of overall postoperative complication with preoperative administration of glucocorticoids for patients undergoing major liver surgery such as hepatic resection or liver transplantation. However, unlike some of the papers included in this study, our findings did not reach statistical significance. This is very important to consider, as it sheds light on the fact that any beneficial effect reported by primary researchers may need to be reinforced by better stratification of patients, larger cohorts, and better reporting of the complications thought to be preventable by the immune-inflammatory modulatory effect ascribed to high-dose glucocorticoids. Interestingly, the wound infection was found to be significantly reduced by the administration of glucocorticoids. This might be due to the low number of studies and patients included in the analysis, especially considering the generally less-than-ideal level of evidence certainty and relatively high risk of bias in these studies, even though they were all randomized controlled trials. Our analyses found no significant benefit in other particular postoperative complications either.

Glucocorticoids have been studied for decades in an attempt to reduce postoperative complications. One of the first clinical studies in this area was performed by Shimada and colleagues and published in 1996 [66]. The present study aimed to evaluate whether glucocorticoids reduced surgical stress by inhibiting cytokine release after surgery. The administration of a single high dose of methylprednisolone ameliorated interstitial inflammation soon in the biopsied liver through down-regulation of secretion levels from macrophage-like cells (Kupffer's and endothelial cell types). Researchers chose steroids because they are potent anti-

inflammatory agents, which were theorized to potentially lead to hepatic stabilization and faster restoration of liver function as a result without the systemic derailment that an inflammatory state would create from uncontrolled immunological response.

Total bilirubin elevation is a marker of failure to maintain the critical balance between production and excretion that is presumed (to various extents) to be partly reflective of hepatic function [67]. When combined with aminotransferases such as ALT and AST, they are already widely used liver health markers in clinical practice. Even though the studies were not as systematic as would be expected from randomized controlled trials, and the data collected were moderately confounded, it is important to note that included studies reported significant benefits to using glucocorticoids. This could indicate a liver-protective effect provided by the intervention, given that an increase in ALT is recognized as a marker of liver disease [68].

CRP, an acute-phase protein produced by the liver, along with IL-6, serves as an indicator of inflammation. Elevated CRP levels have been linked to liver failure [69]. The studies we examined consistently reported significantly reduced CRP levels, suggesting a protective effect on the liver. Also, prolonged prothrombin time is associated with liver failure [70], as the liver produces many factors involved in the coagulation system. However, Hayashi et al.'s findings [31] on the PTT-INR contrast with those of other studies included in this review. As coagulation parameters are also considered a crucial aspect of assessing liver function, future clinical trials should be designed to produce more high-quality evidence regarding the intervention's impact on coagulation.

Study 2 found consistent and statistically significant benefits to using hemoadsorption in patients with critical illness-associated acute liver dysfunction. Liver enzymes, serum bilirubin, and the need for vasopressors, which are all important markers for prognosis, were significantly improved after the treatment. Naturally, such findings need to be validated by future randomized controlled trials. While all of these improvements are highly promising and consistent with experimental research concepts, real-life clinical trials are needed to investigate the patient-level effects of the treatment.

Two distinct pathophysiological stages of inflammation-induced liver dysfunction can be identified based on clinical presentation and laboratory findings. The first stage, known as primary dysfunction or "ischemic hepatitis," occurs within 24 hours after a shock event. This stage is characterized by a significant reduction in liver perfusion leading to centrilobular necrosis, marked by a sharp rise in transaminases (AST, ALT) and only a slight increase in bilirubin levels [71]. Typically, this condition resolves within a few days once tissue-level perfusion is restored. In contrast, secondary liver failure, or cholestatic liver dysfunction, emerges later and is mainly driven by inflammatory mediators. This condition is defined by impaired bile formation and excretion, not due to an obstruction of the bile ducts but rather a non-obstructive buildup of toxic metabolites such as bile acids and bilirubin in the liver. This occurs because of the down-regulation of specific transporter molecules on the biliary side of hepatocytes [72,73]. The average bilirubin levels observed in patients from our meta-analysis were 18.06 ± 13.26 mg/dL before hemoadsorption and 6.15 ± 2.32 mg/dL after hemoadsorption, indicating cholestatic liver dysfunction rather than an ischemic type.

However, this hypothesis is complicated by recent findings by Scharf et al. [64] concerning the effect of hemoadsorption in removing toxic metabolites. In fact, the basic scientific literature to distinguish between the direct removal of substances and secondary effects during hemoadsorption therapy in vivo remains unclear.

i. It is important to highlight the significant lack of robust original research evidence regarding the clinical outcomes of hemoadsorption therapy. Although the device appears to be safe in terms of device-related adverse effects or complications, it is difficult to make this claim in the absence of randomized controlled trials with sufficient sample sizes. The current data on clinical outcomes are either considered low quality according to GRADE criteria or require further validation through additional studies. For instance, the 2019 registry analysis by Ocskay et al. [18] included evaluations made by clinicians on whether hemoadsorption therapy improved, worsened, or had no impact on patients' clinical status. According to the clinicians, 68.9% (n = 75) of patients experienced improvement, 15.6% (n = 17) showed no change, and 4.8% (n = 5) actually

deteriorated. However, the lack of comparative studies prevents definitive conclusions about these outcomes.

9.2 Comparisons with Other International Publications

Study 1 was the most recent systematic review and meta-analysis on the subject of preoperative administration of a high-dose glucocorticoid in liver surgery for their hypothesized liver-protective effects. The four previous studies [74-77] all had different and sometimes conflicting findings. Nevertheless, when the ERAS protocol for liver surgeries was published, these meta-analyses were referred to as justification for the inclusion and discussion of this intervention.

None of these previous studies found significant differences between the intervention and control groups in the complications investigated by our study: bile leakage, liver failure, wound complications, infectious complications, and pleural effusion. This study, was unique among others in that we analyzed these outcomes separately from overall postoperative complication rates. However, the evidence presented in the published randomized controlled trials was often insufficient and/or confounded. One reason for the significant inconsistencies is most likely the changing definitions of postoperative complications. Especially in the postoperative liver failure outcome, there is a large degree of inconsistency due to the different grading and prognostics for what constitutes liver failure.

The most striking difference between our study and the previous studies is with our main outcome. Hao-Han et al. [77] found the intervention significantly reduced the overall postoperative complication rate. We added several recent RCTs and nearly 400 patients, almost doubling the total number of patients meta-analyzed, and could not confirm this finding. Furthermore, we identified

several critical biases and uncertainties in the included studies, which might have been the reason behind the inconsistency across five meta-analyses of randomized controlled trials.

Study 2, in contrast, is the first and only systematic review and meta-analysis on the subject thus far. However, hemoadsorption therapy has also been investigated as an adjuvant therapy in critically ill patients with acute respiratory distress syndrome (ARDS) in a paper published by our research group [78]. This study, a systematic review and meta-analysis, also found hemoadsorption therapy to be significantly beneficial in several outcomes: PaO2/FiO2 ratio, vasopressor need, and CRP levels.

9.3 Strengths

9.3.1 Study 1

Our study included the most recent publications on the topic and analyzed a significantly larger patient population than previous meta-analyses. All the included articles were randomized controlled trials, which we rigorously evaluated using the GRADE approach to assess the certainty of evidence. This evaluation was previously missing in the literature. As a result, our study highlights the most critical areas of uncertainty in the current literature.

9.3.2 Study 2

This study is the first and only meta-analysis on the subject. Incorporating individual patient data and subsequently meta-analyzing several outcomes provided a perspective much larger than previously possible with case reports alone. Furthermore, critical appraisal of these studies and the relatively low risks of bias and methodological rigidity are encouraging for future researchers.

9.4 Limitations

9.4.1 Study 1

The main limitation of our study was the lack of data on certain outcomes and the lack of stratification of study populations. We were unable to perform subgroup analyses as planned, and we could not meta-analyze a part of our outcomes of interest. The generalizability of our findings is also limited due to the fact that we could not separately analyze different, albeit slightly, intervention regimens. There was also considerable heterogeneity between studies which limit the applicability of our findings. Finally, we could not perform an assessment of publication bias due to the low number of studies.

9.4.2 Study 2

The chief limitation of this study is the limitation imposed by the types of studies available in the literature. Randomized controlled trials in this topic were completely missing. Second, several of the included studies could be considered “gray literature”, as it was not always clear whether they had been peer-reviewed, which limit our confidence in their freedom from risk of bias, and thus, limit the generalizability of the findings from the meta-analyses. Third, several included studies fail to report the sex and ethnicity of the patients, which are both important factors to consider in the clinical overview. Finally, as the hemoadsorption therapy in the context of this research question is relatively novel, expensive to administer, not widely available around the world, and is concerned with highly vulnerable patients, large cohort studies with long follow-up times were also unavailable.

10 CONCLUSIONS

10.1 Study 1

Preoperative administration of high-dose glucocorticoids do not reduce overall postoperative complication rate significantly. Although several included articles found significant improvements in laboratory outcomes, these data could not be meta-analyzed due to poor reporting.

10.2 Study 2

We found that hemoadsorption therapy for critically ill patients with acute liver dysfunction significantly improves bilirubin levels, need for vasopressors, and liver enzymes. These findings support the use of hemoadsorption as an adjuvant therapy in this patient population.

11 IMPLICATIONS FOR PRACTICE

11.1 Study 1

It is difficult to recommend preoperative administration of glucocorticoids for patients undergoing hepatic resections or liver transplantation, despite the significant reduction in wound infections and tendency to lower odds of developing overall postoperative complications. The use of this intervention should be limited to the field of clinical research, but not as part of the protocol as suggested by ERAS guidelines.

11.2 Study 2

Considering that there are still many unanswered questions, the use of hemoadsorption therapy for critically ill patients with acute liver dysfunction should be left to the discretion of the practicing physician and the team of intensivists caring for the patient. We recommend the use of hemoadsorption as an adjuvant therapy only.

12 IMPLICATIONS FOR RESEARCH

12.1 Study 1

Our findings confirm and guide the future perspectives of clinical trials in this topic. It is crucially important to standardize data collection and patient stratification in future clinical trials. Furthermore, the lack of standardized definitions for postoperative complications make it difficult to contextualize and apply results from the current body of evidence. However, considering the high-risk nature of these patients and surgeries, and the ubiquity of glucocorticoids in clinical practice, we recommend further randomized controlled trials to detect the patient strata and intervention regimes that are significantly beneficial.

12.2 Study 2

The lack of large-scale clinical trials in this field considerably limits the use of hemoadsorption; therefore, we recommend further research in this area. It should also be noted that longer follow-up times, more rigorous patient selection and documentation, and choosing patient-level outcomes such as organ-support free days and successful bridging-to-transplantation will serve to fill the gap in the clinical literature. We also recommend further experimental research to consider the potential biophysical and biochemical effects of hemoadsorption of variables such as levels of mercaptans, inducible degraders of low-density lipoprotein receptors (IDOLs), albumin binding capacity, and tryptophanes.

13 IMPLICATIONS FOR RESEARCH

13.1 Study 1

We recommend keeping the low levels of evidence certainty and recommendations in the ERAS protocols and urge policymakers to enable further clinical research in this area.

13.2 Study 2

Hemoadsorption therapy is currently not available in many parts of the world due to financial limitations. We urge policymakers to enable clinical researchers access to these devices in order to alleviate this critical condition and to be able to conduct large-scale clinical studies. We also recommend policymakers to consider hemoadsorption as an adjuvant therapy in intensive care units against acute liver dysfunction.

14 FUTURE PERSPECTIVES

Evidence-based medicine is and remains to be the cornerstone of anesthesia and intensive care medicine. Scientific decision-making in these domains affects the prognosis of our patients. Furthermore, practitioners in these fields need to be accountable for their decisions. Our main aim was to approach protocols necessary to practice evidence-based medicine: in one study, we evaluated the validity of a protocolized intervention, and in the other study, we investigated the roadmap to protocolizing an intervention by contextualizing and summarizing currently available literature. I intend to continue the work of practicing and popularizing evidence-based medicine for the entire duration of my medical career.

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BIOMEDICINES 12: 1 Paper: 67, 16 p. (2024)

DOI: https://doi.org/10.3390/biomedicines12010067

IF: 4.7 (2022)

The Effect of Preoperative Administration of Glucocorticoids on the Postoperative Complication Rate in Liver Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Turan, Caner ; Kovács, Emőke Henrietta ; Szabó, László ; Atakan, Işıl ; Dembrovszky, Fanni; Ocskay, Klementina ; Váncsa, Szilárd ; Hegyi, Péter ; Zubek, László ; Molnár, Zsolt

JOURNAL OF CLINICAL MEDICINE 13: 7 Paper: 2097, 15 p. (2024)

DOI: https://doi.org/10.3390/jcm13072097

IF: 3.9 (2022)

Publications unrelated to the thesis

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Kovács, Emőke Henrietta ; Tánczos, Krisztián ; Szabó, László ; **Turan, Caner** ;

Dembrovszky, Fanni ; Ocskay, Klementina ; Lee, Bo-Young ; Hegyi, Péter ; Molnár, Zsolt

BIOMEDICINES 10: 9 Paper: 2194, 20 p. (2022)

DOI: https://doi.org/10.3390/biomedicines10092194

IF: 4.7 (2022)

Hemoadsorption as Adjuvant Therapy in Acute Respiratory Distress Syndrome (ARDS) : A Systematic Review and Meta-Analysis

Szigetváry, Csenge Erzsébet ; **Turan, Caner** ; Kovács, Emőke Henrietta ; Kói, Tamás ;

Engh, Marie Anne ; Hegyi, Péter ; Csukly, Gábor ; Ruszkai, Zoltán ; Molnár, Zsolt

BIOMEDICINES 11: 11 Paper: 3068, 18 p. (2023)

DOI: https://doi.org/10.3390/biomedicines11113068

IF: 4.7 (2022)

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DOI: https://doi.org/10.1186/s13054-023-04677-2

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DOI: https://doi.org/10.1007/s00392-024-02441-2

IF: 5.0 (2022)

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ESC HEART FAILURE Published online: 05 August 2024

DOI: https://doi.org/10.1002/ehf2.14957

IF: 3.8 (2022)

Fluid resuscitation with balanced electrolyte solutions results in faster resolution of diabetic ketoacidosis than with 0.9% saline in adults – A systematic review and meta-analysis

Szabó, Gergő Vilmos ; Szigetváry, Csenge ; **Turan, Caner** ; Engh, Marie Anne ; Farkas, Nelli ; Fazekas, Alíz ; Terebessy, Tamás ; Hegyi, Péter ; Molnár, Zsolt

DIABETES/METABOLISM RESEARCH AND REVIEWS, 2024 Jul;40(5):e3831

DOI: https://doi.org/10.1002/dmrr.3831

IF: 8 (2022)

17 ACKNOWLEDGEMENTS

My work as a Ph.D. student and a young researcher is dedicated, in its entirety, to the people who inspire me to wake up to a better world of tomorrow. None of the things I have achieved would have been possible without the constant love and support of my family and friends.

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Systematic Review

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Caner Turan, Emőke Henrietta Kovács, László Szabó, Işıl Atakan, Fanni Dembrovszky, Klementina Ocskay, Szilárd Váncsa, Péter Hegyi, László Zubek and Zsolt Molnár

MDPI

https://doi.org/10.3390/jcm13072097

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Systematic Review

The Effect of Preoperative Administration of Glucocorticoids on the Postoperative Complication Rate in Liver Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract: Background: Glucocorticoids may grant a protective effect against postoperative complications. The evidence on their efficacy, however, has been inconclusive thus far. We investigated the effects of preoperatively administered glucocorticoids on the overall postoperative complication rate, and on liver function recovery in patients undergoing major liver surgery. **Methods:** We performed a systematic literature search on PubMed, Embase, and CENTRAL in October 2021, and repeated the search in April 2023. Pre-study protocol was registered on PROSPERO (ID: CRD42021284559). Studies investigating patients undergoing liver resections or transplantation who were administered glucocorticoids preoperatively and reported postoperative complications were eligible. Meta-analyses were performed using META and DMETAR packages in R with a random effects model. Risk of bias was assessed using RoB2. **Results:** The selection yielded 11 eligible randomized controlled trials (RCTs) with 964 patients. Data from nine RCTs (n = 837) revealed a tendency toward a lower overall complication rate with glucocorticoid administration (odds ratio: 0.71; 95% confidence interval: 0.38–1.31, p = 0.23), but it was not statistically significant. Data pooled from seven RCTs showed a significant reduction in wound infections with glucocorticoid administration [odds ratio: 0.64; 95% confidence interval: 0.45–0.92, p = 0.02]. Due to limited data availability, meta-analysis of liver function recovery parameters was not possible. **Conclusions**: The preoperative administration of glucocorticoids did not significantly reduce the overall postoperative complication rate. Future clinical trials should investigate homogenous patient populations with a specific focus on postoperative liver recovery.

Keywords: glucocorticoid; liver surgery; perioperative mangement

Citation: Turan, C.; Kovács, E.H.; Szabó, L.; Atakan, I.; Dembrovszky, F.; Ocskay, K.; Váncsa, S.; Hegyi, P.; Zubek, L.; Molnár, Z. The Effect of Preoperative Administration of Glucocorticoids on the Postoperative Complication Rate in Liver Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J. Clin. Med.* **2024**, *13*, 2097. https://doi.org/10.3390/jcm13072097

Academic Editors: Kassiani Theodoraki and Keira Mason

Received: 22 February 2024
Revised: 16 March 2024
Accepted: 27 March 2024
Published: 3 April 2024

1. Introduction

Despite advancements in surgical techniques, liver surgery remains a relatively high-risk procedure, with complication rates reaching up to 48% [1]. The most common complications of liver resections and transplantations include postoperative collections, sepsis, and wound and organ space infections. Underlying the complications are thought to be hepatocellular injury and subsequent inflammation, the accumulation of toxic metabolites due to hepatic dysfunction, and a predisposition to coagulopathy and infections [2,3].

Aside from their other effects, hydrocortisone and methylprednisolone, which are both glucocorticoids, have been investigated in the past in both human and animal models for

their anti-inflammatory properties, which could be helpful in reducing the postoperative hyperinflammatory state [4–6]. Preoperative glucocorticoid administration, based on this pharmacological basis, has been investigated in multiple fields of surgery for its effect on reducing postoperative complication rates [7–10]. However, the efficacy of routine glucocorticoid administration remains controversial.

Clinical trials on preoperative glucocorticoid administration in liver surgery have been ongoing since 1996. The 2016 Enhanced Recovery After Surgery guideline on liver surgery recommends glucocorticoids, albeit with a moderate level of recommendation on a weak level of evidence [11]. This guideline references two systematic reviews by Richardson et al. [12] and Li et al. [13], which contradict each other in their results on postoperative complication rates. Since then, two additional systematic reviews have been published on the subject, in 2019 and 2021, by Yang et al. [14] and Hai et al. [15], respectively. However, these two papers also reported contradicting results.

Therefore, we decided to perform a systematic review and meta-analysis to update the current knowledge on the subject. We aimed to summarize and contextualize the existing evidence, based on two hypotheses: (1) preoperative glucocorticoid administration can reduce the complication rate following any type of liver surgery; (2) the effect of glucocorticoids on some complications will be different than on the overall complication rate. Therefore, we investigated not only the overall postoperative complication rate but also distinct complications and liver function parameters, to inform future clinical research and critically appraise the current level of evidence certainty.

2. Methods

We reported our systematic review and meta-analysis in accordance with the PRISMA 2020 Statement [16] (Table S3: PRISMA 2020 Checklist), and we undertook our research based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [17]. The study protocol was registered on PROSPERO (registration number: CRD42021284559). However, we deviated from the registered protocol concerning reporting our primary outcome, the overall postoperative complication rate. We had initially aimed to report complications following the Clavien–Dindo Classification System [18]. However, this was not possible due to inadequate data availability.

2.1. Search Strategy

Our systematic search was conducted on 15 October 2021, on MEDLINE via PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases, with no filters and no restrictions on date of publication, language, or article type. This systematic search was repeated on 1 April 2023 to detect any new literature eligible for inclusion. During the systematic search, the following search key was used: (((hepatic OR liver) AND (surgery OR resection OR operation OR intervention)) OR hepatectomy) AND (steroid OR corticosteroid OR glucocorticoid OR methylprednisolone OR hydrocortisone OR cortisol) AND random*. A modified search key was used for the search on Embase: ((hepatic OR 'liver'/exp OR liver) AND ('surgery'/exp OR surgery OR 'resection'/exp OR resection OR 'operation'/exp OR operation OR 'intervention'/exp OR intervention) OR 'hepatectomy'/exp OR hepatectomy) AND ('steroid'/exp OR steroid OR 'corticosteroid'/exp OR corticosteroid OR 'glucocorticoid'/exp OR glucocorticoid OR 'methylprednisolone'/exp OR methylprednisolone OR 'hydrocortisone'/exp OR hydrocortisone OR 'cortisol'/exp OR cortisol) AND random*. References from the selected articles were also searched for additional studies to be included in the selection process.

2.2. Eligibility Criteria

Only randomized controlled trials (RCTs) published in peer-reviewed journals and investigating the preoperative administration of glucocorticoids (natural or synthetic) against placebo or non-administration for patients undergoing liver surgery were included in this study. We report the study framework and eligibility criteria according to the PICOS

method, where population (P): adult patients (aged 18 or older) of both sexes undergoing elective or non-elective liver surgery, including open or laparoscopic resection or liver transplantation; intervention (I): preoperatively administered high-dose glucocorticoids as a study drug, regardless of dosing strategy, as opposed to standard of care; control (C): placebo or non-administration; main outcome (O): overall postoperative complication rate (referring to the number of patients who experienced any postoperative complication related to the surgical procedure, including but not limited to infections, bile leakage, liver failure, bleeding, and pleural effusion); and setting (S): perioperative hospital care. We included studies that fit the inclusion criteria regardless of the preoperative dosage strategy. Exclusion criteria were study designs other than RCTs, animal studies, and patients who underwent surgeries that included organs other than the liver. Studies were considered eligible for synthesis if they satisfied the eligibility criteria and reported raw data for any or all outcomes under investigation as per our pre-registered study protocol. Publications in which the study population may have overlapped with an earlier publication were not eligible for inclusion.

2.3. Selection Process

The selection was performed by two teams of independent review authors (CT as review author 1, and IA and EHK as review author 2). Duplicates were detected and removed by both manual and automatic searches. The two reviewer groups then assessed the results for inclusion, first by title and abstract selection, then by full-text selection using EndNote 20 software (Clarivate Analytics, Philadelphia, PA, USA). As agreed, any conflict was resolved by a third independent investigator (FD). To evaluate inter-reviewer agreement, Cohen's Kappa was calculated once after title-and-abstract selection and once after full-text selection, with $\kappa = 0.97$ and $\kappa = 1.0$, respectively. Regarding studies with identical patient populations, the reviewers chose to include only the article with the earlier publication date.

2.4. Data Collection Process

From the eligible articles, data were collected by three authors (CT, IA, and EHK) independently. Disagreements were solved by discussion between the authors. The following data were extracted: (1) study characteristics: first author, the year of publication, study design, study population (number, age, and sex), study period, study country, and institute; (2) postoperative complications: overall postoperative complication rate, wound infection, septic/infectious complications, bile leakage, pleural effusion, gastrointestinal bleeding, intra-abdominal bleeding, high-grade liver failure, and all grades of liver failure; (3) laboratory outcomes (total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), interleukin-6 (IL-6), C-reactive protein (CRP), and prothrombin time–international normalized ratio (PTT)); (4) perioperative outcomes (length of hospital stay, total operative time, intraoperative blood loss, blood transfusions, and blood products used (FFP or RBC).

When unavailable in writing, data estimates from visual sources were collected using software GetData Graph Digitizer version number: v.2.26), although these estimates were not used in the quantitative synthesis.

2.5. Study Risk of Bias and Certainty of Evidence Assessment

Two authors (CT, IA) performed the risk of bias assessment independently, according to the recommendations of the Cochrane Handbook [17], utilizing the RoB 2 tool (ROB2 IRPG beta v6, 25 June 2019) based on the RoB 2 version dated 15 March 2019 [19]. Disagreements were solved by deliberation between the authors. The risk of bias was thus assessed on five distinct domains, including the randomization process, deviations from intended intervention, missing outcome data, the measurement of the outcome, the selection of the reported outcome, and overall bias. The level of certainty of evidence evaluation, using the GRADE assessment based on the GRADE handbook [20], was made using the online software GRADE Pro GDT version 20 [21].

2.6. Statistical Analysis

Meta-analysis was performed for outcomes for which at least 3 distinct included studies reported data. The statistical analyses were made using R (R Core Team 2021, v4.1.1) [22]. For calculations and plots, we used the META (Schwarzer 2022, v5.2.0) [23] and DMETAR (Cuijpers, Furukawa, and Ebert 2022, v0.0.9000) [24] packages.

For dichotomous outcomes, the odds ratio (OR) with a 95% confidence interval (CI) was used to measure the effect. To calculate the odds ratio, the total number of patients in each group and those with the event of interest were extracted from each study. Raw data from the selected studies were pooled using a random effects model via the Mantel–Haenszel method (Mantel and Haenszel 1959; Robins, Greenland, and Breslow 1986; Thompson, Turner, and Warn 2001) [25–27]. If the study number for the given outcome was over five, the Hartung–Knapp adjustment (Knapp and Hartung 2003; IntHout, Ioannidis, and Borm 2014) [28,29] was applied (below six studies, no adjustment was applied). For the pooled results, an exact Mantel–Haenszel method (no continuity correction) was used to handle zero-cell counts (Cooper, Hedges, and Valentine 2009; J. Sweeting, J. Sutton, and C. Lambert 2004) [30,31]. In individual studies, the zero-cell-count problem was adjusted using treatment arm continuity correction. To estimate $\tau 2$, we used the Paule–Mandel method (Paule and Mandel 1982) [32], and the Q-profile method for calculating the confidence interval of $\tau 2$ (Harrer et al., 2021) [33]. Statistical heterogeneity across trials was assessed by means of the Cochrane Q test and the I2 values (Higgins and Thompson 2002) [34]. Raw data were used in all instances; in the case of binary data, numbers of event and non-event and, in the case of continuous data, mean and standard deviation (SD) were used. If the mean and SD were not reported in the article, estimations were made using the given values of medians, quartiles, minimums, and maximums, using the Luo [35] and Shi [36] methods.

Forest plots (Rücker and Schwarzer 2021; IntHout et al., 2016) [37,38] were used to graphically summarize the results.

Outlier and influence analyses were carried out following the recommendations of Harrer et al. (2021) [33] and Viechtbauer and Cheung (2010) [39].

3. Results

3.1. Study Selection and Characteristics

The systematic search yielded 8226 records, and the selection process is detailed in the flowchart according to PRISMA as presented in Figure 1. Overall, 11 articles [40–50] were included in our study. The repeat search did not find any further studies eligible for inclusion.

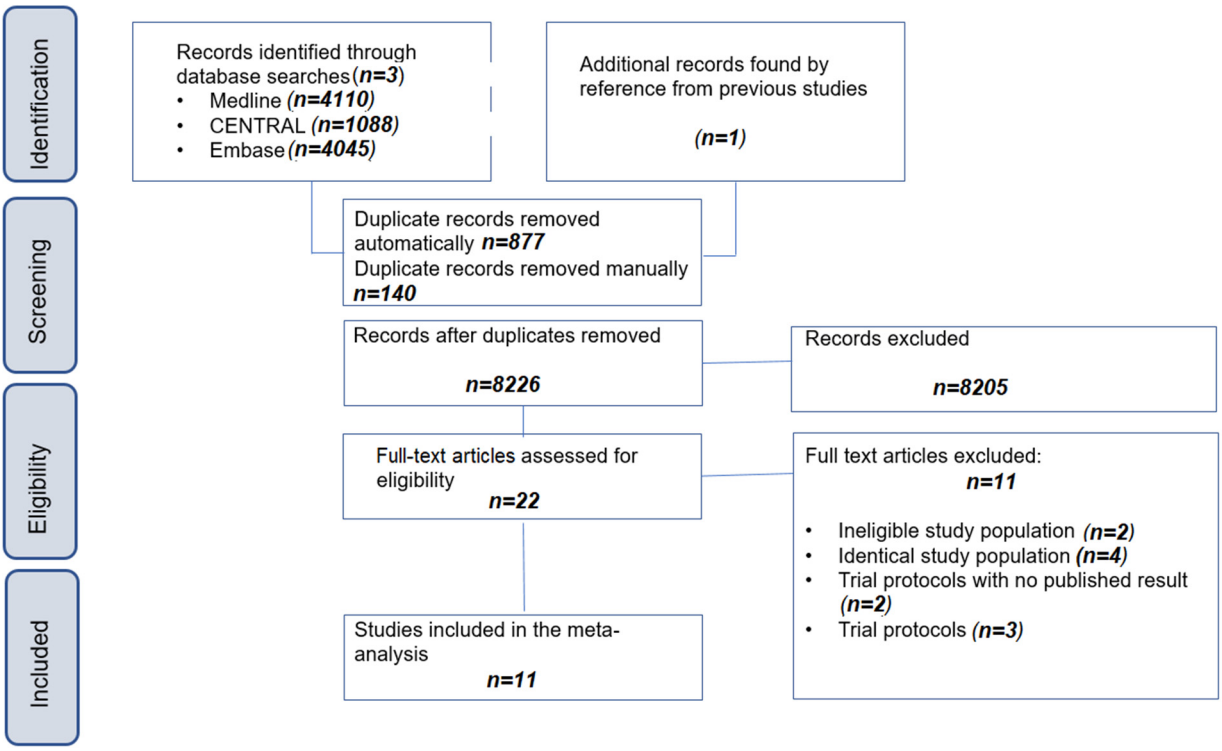

Figure 1. PRISMA flowchart of selection describing the systematic search and selection process.

3.2. Main Characteristics of the Included Studies

In summary, we managed to analyze data from 964 patients, of whom 477 were in the glucocorticoid group, and 487 in the control group. Baseline characteristics, clinical data, and intervention summaries of the included articles are detailed further in Table 1.

Table 1. The summary of the studies included (author, publication date, country, patient distribution, and demographic data).

First Author and Publication Date	Intervention	Control	Surgery Type	Patient Distribution		Age, Years		Sex, Female % of Total	
				Intervention	Control	Intervention	Control	Intervention	Control
Aldrighetti L. 2006 [40]	IV Methylprednisolone 500 mg	Unclear	Hepatic resection	36	37	61.8 (21–78) [c]	63 (31–85) [c]	37.83	38.88
Steinthorsdottir K. J. 2021 [41]	IV Methylprednisolone 10 mg/kg	Standard of care including IV Dexamethasone 8 mg	Open liver surgery without biliary reconstruction	86	88	65.2 ± 11.2 [b]	64.4 ± 12.0 [b]	34	30.6
Bressan A. K. 2022 [42]	IV Methylprednisolone 500 mg	Placebo	Hepatic resection	74	77	63.9 [a]	62.4 [a]	47.2	38.9
Hasegawa Y. 2019 [43]	IV Methylprednisolone 500 mg	Placebo	Hepatic resection	50	50	67 (59–74) [c]	68 (62–75) [c]	38	40
Donadon M. 2016 [44]	IV Methylprednisolone 500 mg	Placebo	Hepatic resection	16	16	65 (27–80) [c]	63 (22–77) [c]	44	37.5
Hayashi Y. 2011 [45]	IV Hydrocortisone 500-300-100 mg consecutively	Non-administration	Hepatic resection	98	102	69 (39–81) [c]	70 (35–82) [c]	No data	No data
Yamashita Y. 2001 [46]	IV Methylprednisolone 500 mg	Non-administration	Hepatic resection	16	17	56.8 [a]	60.3 [a]	31.25	23.52

Table 1. *Cont.*

First Author and Publication Date	Intervention	Control	Surgery Type	Patient Distribution		Age, Years		Sex, Female % of Total	
				Intervention	Control	Intervention	Control	Intervention	Control
Muratore A. 2002 [47]	IV Methylprednisolone 30 mg/kg	Non-administration	Hepatic resection	28	25	64.1 [a]	65.4 [a]	60.7	32
Onoe S. 2021 [48]	IV Hydrocortisone 500-300-200-100 mg	Placebo	Combined liver and extrahepatic bile duct resection	46	48	70 (39–83) [c]	71 (39–84) [c]	33	40
Schmidt S. C. 2007 [49]	Methylprednisolone 30 mg/kg	Placebo	Hepatic resection	10	10	65 [a]	57 [a]	60	70
Turner S. 2006 [50]	IV Methylprednisolone 10 mg/kg	Placebo	Orthotopic liver transplantation	17	17	53.4 [a]	57.7 [a]	35.3	35.3

RCT: randomized controlled trial, [a] = mean, [b] = mean ± standard deviation, [c] = median (range).

3.3. Postoperative Complications

Nine [43–51] (n = 836) out of the eleven eligible articles in our study reported the overall postoperative complication rate as an outcome. This outcome did not distinguish between major and minor complications or different pathomechanisms. In this analysis, 418 patients were in the intervention group and received glucocorticoids preoperatively, and 419 patients in the control group received either saline or a placebo or nothing. There was a tendency toward a lower overall postoperative complication rate in the intervention group (OR:0.71; 95% CI: 0.38–1.31, p = 0.23), but the result did not reach statistical significance (see Figure 2A). There was substantial heterogeneity as defined by the Cochrane Handbook [17] [I^2 = 54% (2%; 78%), p = 0.03].

Five studies [40–42,45,47] (n = 651) reported the rate of pleural effusion as an outcome. Our analysis found no statistically significant difference between the groups with a tendency toward a lower rate in the intervention group (OR: 0.81; 95% CI: 0.44–1.48, p = 0.4963) (see Figure 2B). Seven studies [40–42,45,46,48,49] (n = 745) reported the rate of wound infection as an outcome. Our analysis found that the intervention significantly reduced wound infections (OR = 0.64; 95% CI: 0.45–0.92, p = 0.0241) (see Figure 2C). Four studies [40–42,45] (n = 598) reported septic/infectious complications as an outcome. Our analysis found no statistically significant difference between the groups with a tendency toward a lower rate in the intervention group (OR: 0.73; 95% CI: 0.24–2.20, p = 0.577) (see Figure 2D). Seven studies [40–42,45,46,48,49] (n = 745) reported the rate of bile leakage as an outcome. Our analysis found no statistically significant difference between the groups (OR: 1.12; 95% CI: 0.59–2.13, p = 0.7263) with a tendency toward a higher rate in the intervention group (see Figure 2E). Five studies [40,42,45,46,48] (n = 551) reported liver failure as an outcome. Our analysis found no statistically significant difference between the groups (OR: 0.96; 95% CI = 0.49–1.88, p = 0.9034) (see Figure 2F).

3.4. Laboratory Outcomes

Due to the discrepancy in the methodology of measurements and the reporting of the laboratory outcomes between the included studies, we could not perform a meta-analysis for these parameters. Hence, we included these only in the systematic review. Nevertheless, several individual studies reported statistically significant results. A detailed summary of the measurement time points, results and, where available, p-values of each included study are depicted in Table S1.

3.5. Other Outcomes

Our analysis also included perioperative outcomes. There were no statistically significant differences between the glucocorticoid and control groups with respect to these outcomes. Eight studies [43,44,46–50,52] (n = 759) reported on the length of hospital stay

(days), (MD: −0.12; 95% CI: −0.57–0.34) (see Figure 3A). Seven studies [43,44,46–49,52] (n = 709) reported on the total operative time (minutes), (MD: −2.82; 95% CI = −19.46–13.83) (see Figure 3B). Eight studies [43–49,52] (n = 857) reported on the blood loss (milliliters), (MD = 3.41; 95% CI: −33.33–40.16) (see Figure 3C). Five studies (n = 572) reported on the number of patients who needed to be administered blood transfusion intraoperatively, (OR: 1.04; 95% CI = 0.63–1.71, p = 0.89) (see Figure 3D).

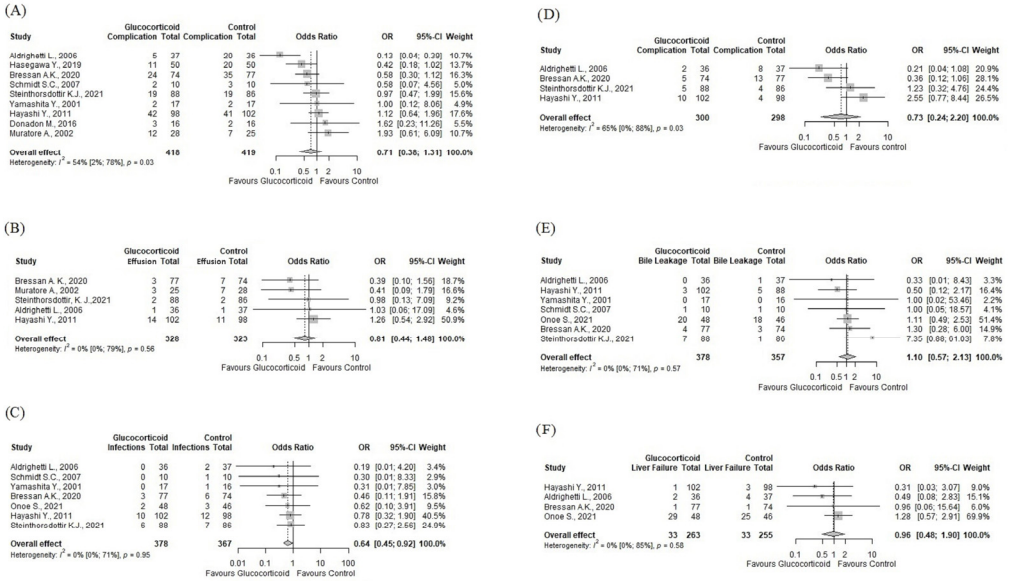

Figure 2. Forest plots of clinical outcomes. (**A**) overall postoperative complication rate; (**B**) pleural effusion; (**C**) wound infection; (**D**) septic/infectious complications; (**E**) bile leakage; (**F**) liver failure of any grade [40–49]. OR: odds ratio; CI: confidence interval.

3.6. Risk of Bias and Study Heterogeneity Assessment

The results of the risk of bias assessment for the outcomes are presented in Figure 4. All outcomes meta-analyzed in this paper received the same score; therefore, Figure 4 represents the results of the assessments of all outcomes.

Overall, most of the included studies were adequately randomized, and no studies had issues arising from missing outcomes. The main risk of bias was related to the inadequate elaboration of the study designs in some cases, which led to some concerns and, in other cases, bias arising from the reporting of the outcomes represented a critical risk.

Levels of heterogeneity are interpreted according to the Cochrane Handbook [17] using τ2, I^2, and Cochrane Q test statistics [32–34]. Moderate heterogeneity (I^2 = 54% [2%;78%], p = 0.03) was observed in the analysis of the overall postoperative complication rate. This may be due to the fact that fewer than ten studies were included in the analysis, and the fact that patients who underwent different liver surgeries were pooled together. Moderate heterogeneity was observed in the analyses of the length of hospital stay (I^2 = 38% [0%;73%], p = 0.12) and blood loss (I^2 = 40% [0%;73%], p = 0.11), possibly due to the difference in the surgical characteristics of the included patients. Severe heterogeneity (I^2 = 65%, [0%;88%], p = 0.03) was observed in the analysis of septic/infectious complications. This could be explained by the size of the patient pool (n = 200), given that this analysis only incorporated four studies. No severe heterogeneity has been detected in any other analyses.

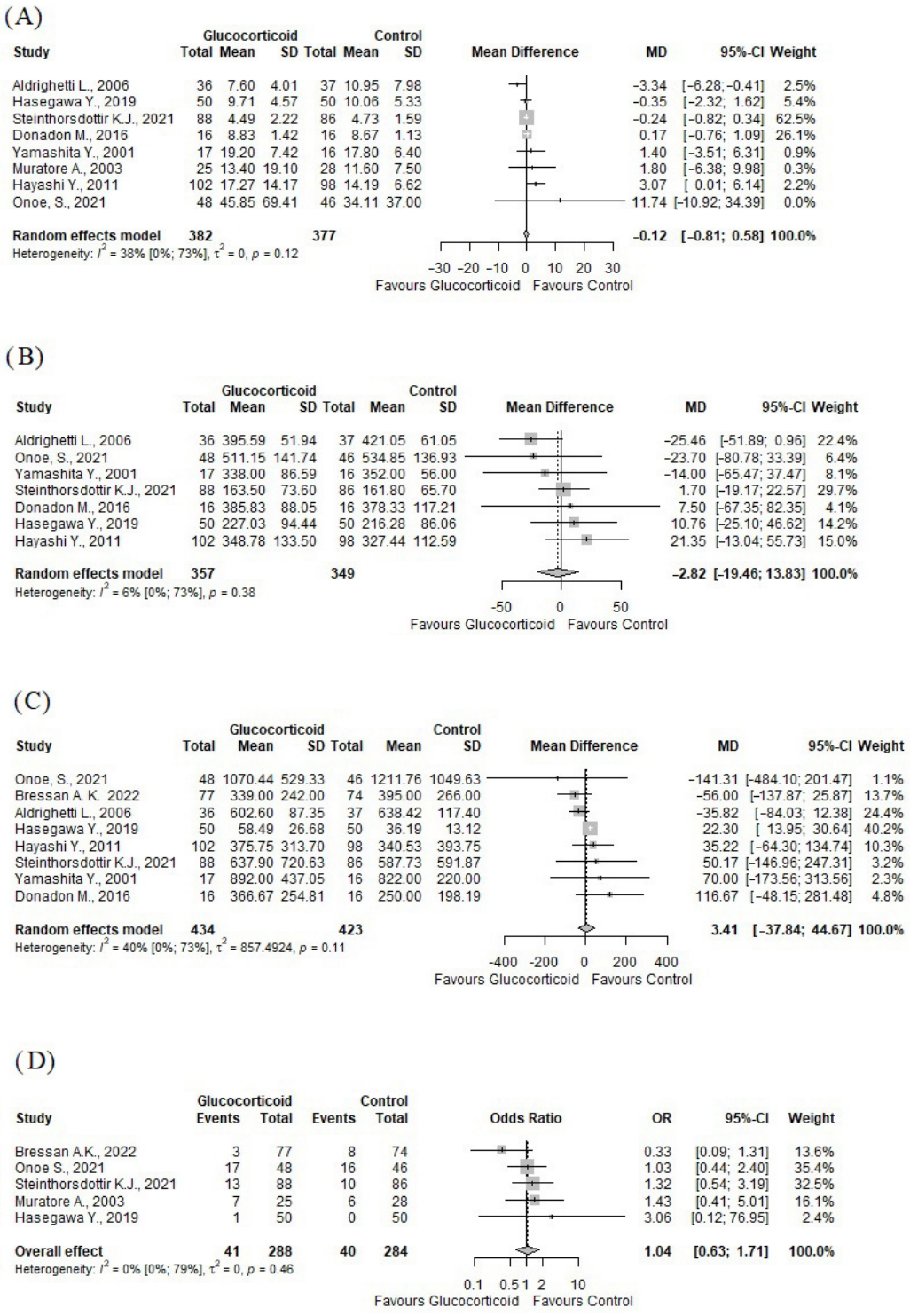

Figure 3. Forest plots of other outcomes. (**A**) length of hospital stay; (**B**) total operative time; (**C**) blood loss (milliliters); (**D**) need for administration of blood products [40–48]. OR: odds ratio; CI: confidence interval; MD: mean difference; SD: standard deviation.

Figure 4. Results of the risk of bias assessments using RoB2 [40–50].

3.7. Certainty of Evidence Assessment

Studies were also evaluated for their level of certainty of evidence using the GRADE assessment system. Results of the GRADE assessment of meta-analyzed outcomes are presented on Table S2. Overall, the certainty of the evidence was assessed as weak to very weak.

4. Discussion

This is the largest and most comprehensive systematic review and meta-analysis on the effects of preoperative glucocorticoid administration in liver surgery to date. Our results revealed that glucocorticoid prophylaxis did not reduce the overall complication rate in patients undergoing major liver surgery (OR: 0.71, $p = 0.23$), and hence its routine use in this patient population is not supported by sufficient evidence.

Liver surgery presents a unique challenge, being unlike most other major abdominal surgeries in the context of postoperative complications. It has been postulated in the past that underlying the relatively high risk involved in liver surgeries is the cascade of dysfunctional systemic metabolic and hematological responses to injury, which is the result of and also the cause of hepatic dysfunction [51]. When the liver parenchyma is injured, the protective functions of the liver, which would have otherwise compensated for the response to insult, may become impaired or dysregulated [52]. The resulting dysfunction is associated with the typical post-hepatectomy complications such as hepatic insufficiency, bile leakage, wound infections, abdominal infections, pleural effusion, pulmonary atelectasis, and hemorrhage [53]. Liver transplantation follows a similar logic, and the complications may be even more severe [54].

Investigations into the use of glucocorticoids for their hypothesized protective effect against postoperative complications have been ongoing for decades. One of the earliest clinical trials was published in 1996 by Shimada et al. [55]. The authors investigated the effects of steroid administration on postoperative cytokine release and found that a short-term pulse of methylprednisolone might be effective in reducing surgical stress by decreasing cytokine release. Steroids were chosen by researchers for their significant anti-inflammatory effects, which have been hypothesized by trialists as being able to reduce the extent of hepatic dysregulation, allow for a more rapid liver function recovery, and reduce the risk of developing systemic dysregulation in relation to the uncontrolled immune response. However, it should be noted that steroids have long been considered a double-edged sword when it comes to use, as their potential side effects are risky and undesirable [4].

Since the two systematic reviews published in 2014, there have been contradictory results published by clinical trialists on the subject of steroids and liver surgery, which necessitated further systematic reviews. While Richardson et al. [12], Li et al. [13], and Yang et al. [14] all reported in their meta-analyses a tendency toward lower overall postoperative complication rates (p-values of 0.09, 0.09, and 0.13, respectively), the recent meta-analysis by Hao-Han et al. [15] found a statistically significant decrease in overall complications

(p = 0.04). However, we cannot validate these results with our updated study. None of the previous meta-analyses were able to detect a statistically significant difference between the intervention and control groups in terms of specific complications, namely, bile leakage, liver failure, wound complications, infectious complications, and pleural effusion. Our analysis of particular complications did not provide a sufficiently high level of evidence, due to the unavailability and/or the improper reporting of these complications. Especially for liver failure, there was an observable difference between the reporting of Onoe et al. [48] and that of other studies. This is possibly due to the different assessments made on what constitutes liver failure. In our meta-analysis, we detected a statistically significant reduction in wound infections, but we have reservations about the quality of the evidence. Firstly, both the sample size and the number of studies are limited, and the intervention groups with zero complications may have introduced a bias toward a reduced odds ratio in the analysis.

Increased total bilirubin is an indicator of an imbalance between production and excretion and, ultimately, is considered a reflection of liver function [56]. Most of the included studies investigated this outcome as a measure of liver health and, except for Muratore et al. [47], found that steroid administration significantly reduced levels of total bilirubin. Combined with aminotransferases ALT and AST, these are indicators of liver health commonly used in clinical practice. Although the investigation was not as thorough, and the findings were not as consistent as with total bilirubin, there were many significant findings of reduced levels of ALT in the intervention groups. This could signal a liver-protective effect that was bestowed by the intervention, since an increase in ALT is found primarily in the liver and is considered a marker of liver disease [57]. C-reactive protein is an acute-phase protein synthesized by the liver and, along with interleukin 6, is a marker of inflammation. Increases in CRP levels have been associated with liver failure [58]. The studies we reviewed consistently reported significantly reduced levels, signaling a protective effect on the liver. Lastly, prolonged prothrombin time is associated with liver failure [59], as the liver produces many of the factors and components of the coagulation system. Hayashi et al.'s finding [45] on the PTT-INR contradicts other articles included in this review. Coagulation parameters should be considered a critical component of the assessment of liver function; thus, future clinical trials should be designed to generate further high-quality evidence on the effects of the intervention on coagulation.

All previous meta-analyses found significantly reduced levels of total bilirubin in the intervention groups. Although we could not perform a meta-analysis on this outcome, available evidence suggests future clinical trials could validate these findings. All meta-analyses, except for that of Hao-Han et al. [15], have also found significantly reduced levels of IL-6 in the intervention groups. However, IL-6 has not been measured in recent clinical trials. We recommend that IL-6 be included in future clinical trial designs as an outcome measure.

The reporting of laboratory measurements as outcomes was not always consistent across the included studies. Although we did not detect a considerable risk of bias using Cochrane's tools, in the clinical context, it might have been more useful to have explicitly detailed and consistent measurements taken throughout the follow-up period. Furthermore, the mathematical analysis of the aggregated data should always be presented in the publication along with distribution, in order to enable reliable meta-analyses. Laboratory outcomes should be examined and reported in a way that is consistent with complications and patient subgroups. Peak values should also be examined alongside means, and the measurements should be documented clearly with their time points to reduce the risk of bias. Measurement results and time points left out of the reports without a clear explanation presented a challenge in conducting our meta-analysis. Another challenge was results reported without reliable distribution figures, which made meta-analyzing these outcomes by pooling medians and means unreliable.

We recommend that trialists design future randomized clinical trials around an internationally acknowledged postoperative complication classification system such as the Clavien–

Dindo Classification System [60] or the Comprehensive Complication Index (CCI) [18], which is an integrated complication-reporting algorithm.

On the other hand, we recommend that future clinical trials put emphasis on differentiating the benefits for patient subgroups, categorized according to the indication for liver surgery, as well as patient severity scoring systems. We recommend utilizing the APACHE IV scoring system [61] for assessing critically ill patients, and the American Society of Anesthesiologists (ASA) physical status classification system [62] to group patients according to the assessed surgical risk. Furthermore, trialists ought to consider the potential difference in benefits derived for patients undergoing liver transplantation versus open or laparoscopic hepatic resections. Researchers may be able to detect differences in benefits derived between different regimes of preoperative steroid administration. Therefore, designing future clinical trials around contrasting single high-dose preoperative administration versus progressively decreasing doses of perioperative administration on subsequent days, as designed by Onoe S. et al. [48], might yield a higher level of evidence.

The ERAS Society's recommendation on perioperative steroid administration in their 2016 guideline [11] is currently stated as a weak recommendation based on a moderate level of evidence. In light of our systematic review and other studies that have been published since 2016, we recommend that the guidelines on this intervention be updated with new levels of evidence and a new grade of recommendation.

4.1. Strengths and Limitations

Our study had certain strengths and limitations that should illuminate clinical decision making and future clinical trial designs. Our study included the most recent publications on the topic and had considerably more patients in the analysis compared to the previous meta-analyses. All included articles were randomized controlled trials which were critically appraised using the GRADE approach to the level of evidence certainty, which was missing from the literature. As such, the qualitative assessment within this manuscript describes where there is uncertainty in the currently available literature.

Our study was limited by data availability, which prevented us from performing subgroup analyses, and meta-analyses on postoperative laboratory outcomes. Differences in intervention regimes may limit the generalizability of our findings. Furthermore, the analyses were limited by the considerable heterogeneity between studies, which limited the applicability of our findings. Finally, we could not perform an assessment of publication bias due to the low number of studies.

4.2. Implications for Practice and Research

We were unable to show any convincing benefits to using glucocorticoids preoperatively in liver surgery, and hence the routine use of preoperative glucocorticoids in major liver surgery cannot be supported by evidence. However, it should be noted that there were no reported cases of adverse events associated with its use either. Therefore, its use should only be warranted within the domain of clinical research.

Further prospective data collection is needed to assess the benefits of perioperative steroid administration on particular postoperative complications. Mainly, the effects on liver dysfunction or failure, shock, septic complications, and coagulation-related complications should be investigated.

It is crucially important to bring scientific results to the bedside [63,64]. As such, research on this particular topic should focus on outcomes that are specific to patient populations and direct clinical outcomes with rigorous postoperative follow-ups.

5. Conclusions

In conclusion, our meta-analysis did not show any statistically significant reduction in postoperative complications for patients undergoing liver surgery, except for in the rate of developing wound infections. However, further investigation is needed to clarify this finding. Most clinical trials reported significant improvements in postoperative laboratory

values at different time points, which signifies a protective effect against liver injury and dysfunction, but further research is needed for a higher grade of evidence.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm13072097/s1, Table S1: Summary table of the laboratory outcomes reported by the included studies, Table S2: Results of the GRADE assessments carried out using GRADEPro GDT software, Table S3: PRISMA 2020 Checklist.

Author Contributions: C.T.: conceptualization, investigation, writing—original draft; E.H.K.: conceptualization, investigation, writing—review and editing; F.D.: methodology, supervision, writing—review and editing; K.O.: methodology, supervision, writing—review and editing; I.A.: investigation, writing—review and editing; L.S.: software, formal analysis, writing—review and editing; L.Z.: review and editing; S.V.: project administration, writing—review and editing; P.H.: project administration, supervision, writing—review and editing; Z.M.: conceptualization, project administration, supervision, writing—original draft. All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Economic Development and Innovation Operational Programme Grant (GINOP-2.3.2-15-2016-00048—STAY ALIVE, GINOP-2.3.4-15-2020-00010 Competence Centre for Health Data Analysis, Data Utilisation and Smart Device and Technology Development at the University of Pécs) and the Hungarian National Research, Development and Innovation Office (Grant No: K 138816).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis.

Conflicts of Interest: The authors declare no conflicts of interest.

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Systematic Review

Hemoadsorption Therapy for Critically Ill Patients with Acute Liver Dysfunction: A Meta-Analysis and Systematic Review

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https://doi.org/10.3390/biomedicines12010067

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Hemoadsorption Therapy for Critically Ill Patients with Acute Liver Dysfunction: A Meta-Analysis and Systematic Review

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Abstract: Critically ill patients are at risk of developing acute liver dysfunction as part of multiorgan failure sequelae. Clearing the blood from toxic liver-related metabolites and cytokines could prevent further organ damage. Despite the increasing use of hemoadsorption for this purpose, evidence of its efficacy is lacking. Therefore, we conducted this systematic review and meta-analysis to assess the evidence on clinical outcomes following hemoadsorption therapy. A systematic search conducted in six electronic databases (PROSPERO registration: CRD42022286213) yielded 30 eligible publications between 2011 and 2023, reporting the use of hemoadsorption for a total of 335 patients presenting with liver dysfunction related to acute critical illness. Of those, 26 are case presentations (n = 84), 3 are observational studies (n = 142), and 1 is a registry analysis (n = 109). Analysis of data from individual cases showed a significant reduction in levels of aspartate transaminase (p = 0.03) and vasopressor need (p = 0.03) and a tendency to lower levels of total bilirubin, alanine transaminase, C-reactive protein, and creatinine. Pooled data showed a significant reduction in total bilirubin (mean difference of −4.79 mg/dL (95% CI: −6.25; −3.33), p = 0.002). The use of hemoadsorption for critically ill patients with acute liver dysfunction or failure seems to be safe and yields a trend towards improved liver function after therapy, but more high-quality evidence is crucially needed.

Keywords: hemoadsorption; liver dysfunction; critical care; database meta-analysis

Citation: Turan, C.; Szigetváry, C.E.; Kói, T.; Engh, M.A.; Atakan, I.; Zubek, L.; Terebessy, T.; Hegyi, P.; Molnár, Z. Hemoadsorption Therapy for Critically Ill Patients with Acute Liver Dysfunction: A Meta-Analysis and Systematic Review. *Biomedicines* **2024**, *12*, 67. https://doi.org/10.3390/biomedicines12010067

Academic Editor: Aleksander F. Sikorski

Received: 16 November 2023
Revised: 15 December 2023
Accepted: 24 December 2023
Published: 27 December 2023

1. Introduction

Critically ill patients admitted to the intensive care unit (ICU) have been shown to be at risk of developing acute liver dysfunction usually as part of multiorgan failure sequelae [1]. Affecting at least 20% of patients, ICU-acquired liver dysfunction therefore has a frequent occurrence in the critically ill population and represents a life-threatening condition associated with a significantly increased risk of death [2,3]. In fact, early liver dysfunction, even after correction for other organ failures, is responsible for a mortality of 11% [4].

During such hyperinflammatory conditions, the liver is both a site of production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and a target organ for the effects of inflammatory mediators derived from extrahepatic sources of infection [5]. When advancing into more severe states, liver dysfunction can lead to hepatic encephalopathy or brain

dysfunction as an expression of acute liver failure [6]. Furthermore, the disruption of the balance of reductive oxygen species is found to be implicated in biochemical and biophysical changes that might play a role in the progression of liver dysfunction into such severe disease states [7,8].

Bedside monitoring of the liver function of critically ill patients is not easy. Bilirubin represents the standard measure for the assessment of liver dysfunction in the ICU and is routinely assessed as part of the sequential organ failure assessment (SOFA) score since increased bilirubin plasma levels reflect a derangement in metabolic processes such as bile formation, bile secretion, and reduced bile flow into the biliary tract, the latter being considered the main component of early hepatic dysfunction under hyperinflammatory conditions [9,10]. However, despite good correlations between bilirubin plasma concentrations and mortality in several critically ill conditions (0.1–0.4 mg/dL total bilirubin was associated with higher cancer mortality (HR, 1.94; $p = 0.016$), whereas ≥0.8 mg/dL was associated with non-cancer, non-cardiovascular mortality (HR, 1.88; $p = 0.002$)) [11], bilirubin is a lagging parameter as there is a significant time lag between imminent or even established liver dysfunction and development of hyperbilirubinemia [12]. Thus, given the lack of diagnostic accuracy of standard laboratory parameters, diagnosis and monitoring of liver dysfunction in critically ill patients remains a major challenge with a very inconsistent definition and lack of clear diagnostic criteria [13].

Up to now, there is no specific therapy for acute liver dysfunction in critically ill patients, integrated management strategies and therapeutic interventions are hardly supported by randomized studies, and treatment is often center-specific [14]. Current clinical practice therefore focuses on timely decisions around transplant in conjunction with optimal multiple organ supportive care and effective therapeutic interventions.

Hemoadsorption is a new extracorporeal blood purification modality. It has been primarily used for cytokine adsorption to control hyperinflammation [15–17]. Acquired acute liver dysfunction in critically ill patients is also thought to be due to hyperinflammation [18]. Therefore, theoretically, clearing the blood from toxic liver-related metabolites and cytokines could be beneficial in improving liver function in this patient population. However, evidence of its efficacy is lacking, and despite its increasing use and accumulating data, a comprehensive summary on hemoadsorption in this setting is missing.

Objectives

The aim of this systematic review and meta-analysis is to assess the effect of hemoadsorption on clinical outcomes and the removal of total bilirubin, as well as the reduction in liver transaminases in critical illness-associated acute liver dysfunction.

2. Methods

We report our systematic review and meta-analysis in accordance with the PRISMA 2020 Statement (Supplementary Table S1: PRISMA 2020 Checklist), and it was conducted following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [19].

2.1. Search Strategy

Two systematic literature searches were conducted on 18 February 2022 and 24 February 2023, using the following databases: Medline (via PubMed), Embase, Scopus, CENTRAL, and Web of Science (PROSPERO registration: CRD42022286213). The following search key was used in these databases: oXiris OR Jafron OR CytoSorb OR hemadsorption OR hemoadsorption OR "blood purification" OR "cytokine removal" AND liver failure OR "liver injury" OR liver dysfunction OR "hepatocellular injury" OR hepatic insufficiency OR hepatic dysfunction OR "acquired liver injury".

CytoSorb Literature Database, and the references of included studies, citing articles, authors' other accessible publications, and ResearchGate were hand-searched for further eligible publications. No filters or restrictions were imposed on the search.

2.2. Eligibility Criteria

Primary research publications with original clinical data were eligible for inclusion in this systematic review. Publications without original clinical data, such as reviews, commentaries, editorials, consensus, and guidelines, were excluded. Inclusion and exclusion criteria were framed beforehand in the PICO model (patients; intervention; control; outcomes). The target population was adult patients with acute liver dysfunction or failure associated with critical illness and treated with hemoadsorption (HA). Selected articles had to report one or more of the following to assess the effect of HA therapy: requirements of vasopressors, serum levels of bilirubin, and the liver enzymes alanine aminotransferase (ALT) or aspartate aminotransferase (AST) for pre- and post-hemoadsorption treatment. Primary outcomes were the change in liver function parameters during HA and mortality. We pooled data from individual cases to assess the variations in vasopressor needs and serum levels of bilirubin, ALT, and AST, before and after treatment with hemoadsorption, without considering the heterogeneity existing among different sources. In addition to the case studies, a pooled analysis was conducted for studies including data on control cohorts. The effect size was expressed as the mean difference in the relative changes of the aforementioned variables from baseline to post-treatment values.

2.3. Selection Process

The selection was performed by two independent review authors (CT as review author 1 and CS as review author 2). The two reviewer groups then assessed the results for inclusion, first by title and abstract selection, followed by full-text selection using the EndNote 20 software (Clarivate Analytics, Philadelphia, PA, USA). Any disagreements were resolved firstly by consensus between the reviewers or by a third independent investigator (FD) when needed. To evaluate inter-reviewer agreement, Cohen's Kappa was calculated with the result being $\kappa = 0.89$ after full-text selection.

2.4. Data Collection Process

From the eligible articles, data were collected by the two review authors (CT and IA). Disagreements between authors were resolved through consensus. The following data were extracted: (1) study characteristics: first author, year of publication, study design, study population (number, age, and sex), study period, study country, and institute; main outcomes (mortality, bridge to liver transplantation, length of ICU stay); (2) pre-treatment and post-treatment liver function parameters: serum bilirubin, ALT, AST, vasopressor need (mcg/kg/min), serum bile acid levels, prothrombin time, D-dimer levels; (3) changes in vital organ function: SOFA scores (Sequential Organ Failure Assessment), SAPS-II (Simplified Acute Physiology Score II), CLIF scores (Chronic Liver Failure Consortium Organ Failure), APACHE (Acute Physiology and Chronic Health Evaluation) scores; (4) safety outcomes: white and red blood cell counts, hemoglobin count, serum albumin, platelet count, neutrophil count. Only data prior to the initiation of hemoadsorption therapy and at the discontinuation of the therapy were collected.

When unavailable in writing, data estimates from visual sources were collected using software (GetData Graph Digitizer version number: v.2.26), although these estimates were not used in the meta-analysis for optimal mathematical accuracy.

2.5. Study Risk of Bias and Certainty of Evidence Assessment

Two authors (CT and IA) independently performed the risk of bias assessment according to the recommendations of the Cochrane Handbook [19] utilizing the Joanna-Briggs Institute's Critical Appraisal Tool [20] for case reports and case series, ROBINS-I Risk of Bias Assessment for cohort studies [21]. Disagreements were resolved by deliberation.

The level of certainty of evidence evaluation was performed using the GRADE assessment based on the GRADE Handbook [22] and was determined using the online software GRADE Pro GDT.20 (GRADEpro Guideline Development Tool version 20, available from gradepro.org).

2.6. Statistical Analysis

Statistical analyses were carried out using the R statistical software (version 4.1.2.) [23]. Meta-analysis was performed for outcomes for which at least three studies reported data. The meta-analysis follows the advice of Harrer et al. [24].

For each continuous outcome, we meta-analyzed the before-treatment mean, the after-treatment mean, and their difference. We used the classical inverse variance method with the restricted maximum likelihood estimator. As only a few studies contributed to the meta-analysis, Hartung-Knapp adjustment was applied. Besides the prediction interval, heterogeneity was assessed by calculating the I^2 measure and its confidence interval and performing the Cochrane Q test. I^2 values of 25%, 50%, and 75% were considered low, moderate, and high heterogeneity, respectively.

In all cases, although standard deviations of the outcome before and after the treatment were available, the standard deviation of the change was missing. Following the instructions of [20], we input several different correlations from the range of −0.5 to 0.9. All the employed correlations provided more or less the same pooled results. The published results were created with an input correlation of 0.8.

Publication bias could not be assessed by visual inspection of the Funnel plot or by performing Egger's test due to the small number of available studies.

From the meta-analyses described above, we excluded studies with one or very few observations. We visualized these excluded results on boxplots, and we tested whether the order of magnitude of the before and after values is different by performing the Wilcoxon test.

3. Results

3.1. Study Selection and Characteristics

The systematic search yielded 3022 records after duplicate removal. The selection process took place in accordance with the protocol registered on PROSPERO. The PRISMA flowchart detailing the selection process is shown in Figure 1.

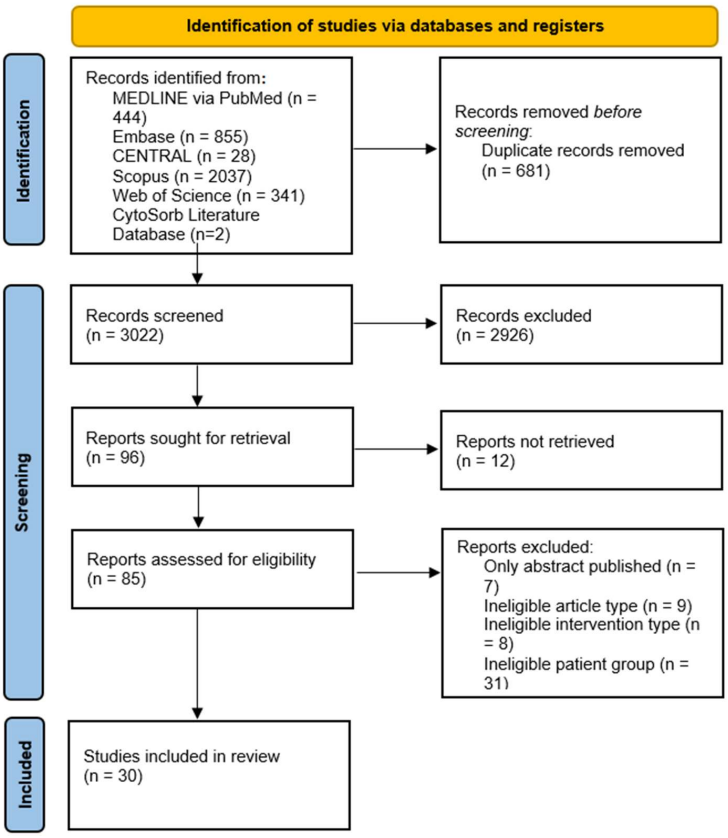

Figure 1. PRISMA flowchart of included studies.

3.2. Main Characteristics of the Included Studies

The selection process yielded 30 eligible publications between 2011 and 2022, and a further 3 publications from the pool retrieved from the repeat systematic search. All publications reported the use of hemoadsorption for a total of 323 patients. Of those, 19 were case reports, 7 were case series (total number of patients, n = 84), 3 were observational studies (n = 130), and 1 was a registry analysis (n = 109). All patients presented with liver dysfunction related to acute critical illness have been treated with HA: CytoSorb (23 datasets, n = 232), Coupled Plasma Filtration Adsorption (4, n = 88), oXiris (2, n = 2), and CytoSorb + oXiris (1, n = 1). The main characteristics of the included studies along with baseline characteristics of the patients are detailed in Table 1.

Table 1. Study and baseline characteristics of included studies.

Publication Data		Study Design	Number of Patients	Age	Used Device	Intervention	Number of Sessions
First Author	Year of Publication						
Gunasekera, A.M. [25]	2022	Case report	1	54 [a]	CytoSorb	CRRT with CytoSorb	1
Ruiz-Rodriguez, J.C. [26]	2022	Case report	1	50 [a]	CytoSorb	CVVHDF with CytoSorb	1
Cazzato, M.T. [27]	2019	Case report	1	No data	CytoSorb	CRRT with CytoSorb (24 h)	4
Daza, J.L. [28]	2022	Case report	1	41 [a]	CytoSorb	SLED combined with CytoSorb (12 h)	2
Hinz, B. [29]	2015	Case report	1	72 [a]	CytoSorb	CVVHD with CytoSorb (24-6-24 h)	3
Köhler, T. [30]	2021	Case report	1	29 [a]	CytoSorb	CRRT with CytoSorb (24 h)	Unclear
Lau, C.W.M. [31]	2021	Case report	1	47 [a]	oXiris	Blood purification with oXiris (5 days in total)	No data
Li, Y. [32]	2020	Case report	1	35 [a]	oXiris	CVVH with oXiris (24 h)	2
Manohar, V. [33]	2017	Case report	1	22 [a]	CytoSorb	Extracorporeal cytokine hemofiltration (12 h)	1
Markovic, M. [34]	2020	Case report	1	31 [a]	CytoSorb and oXiris	CytoSorb (day 1) and oXiris (day 2)	2
Moretti, R. [35]	2011	Case report	1	27 [a]	CPFA	CPFA (24 h)	5
Piwowarczyk, P. [36]	2019	Case report	1	57 [a]	CytoSorb	CytoSorb with anticoagulated CVVHD (24 h)	2
Tomescu, D. [37]	2018	Case report	1	17 [a]	CytoSorb	CytoSorb (before and throughout liver transplantation)	1
Wiegele, M. [38]	2015	Case report	1	44 [a]	CytoSorb	CytoSorb (6 h)	2
Lévai, T. [39]	2019	Case report	1	42 [a]	CytoSorb	CytoSorb with anticoagulated CVVRRT	4
Manini, E. [40]	2019	Case report	1	62 [a]	CytoSorb	CytoSorb with anticoagulated CVVRRT	1
Popescu, M. [41]	2017	Case report	1	47 [a]	CytoSorb	CytoSorb (24 h)	4
Kogelman, K. [42]	2021	Case report	1	45 [a]	CytoSorb	CytoSorb with CRRT (in CVVHD mode)	3
Breitkopf, R. [43]	2020	Case report	1	40 [a]	CytoSorb	CytoSorb with CRRT (in CVVHD mode)	2
Ullo, I. [44]	2017	Case series	9	21–63 [b]	CPFA	CPFA with citrate anticoagulation	No data

Table 1. *Cont.*

Publication Data		Study Design	Number of Patients	Age	Used Device	Intervention	Number of Sessions
First Author	Year of Publication						
Popescu, M. [45]	2017	Case series	5	49 ± 13 [c]	CytoSorb	CytoSorb with CVVHF	No data
Popescu, M. and Tomescu, D. [46]	2018	Case series	13	46 ± 17 [c]	CytoSorb	CytoSorb with CVVHF	No data
Maggi, U. [47]	2013	Case series	2	22–64 [b]	CPFA	CPFA	3
Popescu, M. [48]	2020	Case series	29	34 ± 14 [c]	CytoSorb	CytoSorb with CVVHDF	3
Dhokia, V.D. [49]	2019	Case series	3	51–71 [b]	CytoSorb	CytoSorb with CVVHDF (1); CytoSorb with Prismaflex (1); CytoSorb with CRRT (1)	2
Acar, U. [50]	2019	Case series	4	26–73 [b]	CytoSorb	CytoSorb with CVVHD	No data
Ocskay, K. [18]	2021	Registry analysis	109	49.2 ± 17.1 [c]	CytoSorb	Varies: CytoSorb alone or CytoSorb with CRRT	2
Niu, D.G. [51]	2019	Retrospective observational study	76	51.4 ± 15.6 [c]	CPFA	CPFA with CRRT	No data
Scharf, C. [52]	2021	Retrospective observational study	33	55 (18–76) [d]	CytoSorb	CytoSorb	1
Praxenthaler, J. [53]	2022	Retrospective observational study	21	74 (58–80) [d]	CytoSorb	CVVHD with CytoSorb	varies

[a] Individual data, [b] range (min–max), [c] mean ± standard deviation, [d] median (minimum range–maximum range).

3.3. Primary Outcomes

The main outcomes of this study were mortality, rate of bridge to transplantation, and length of ICU stay. The lack of well-documented original research data in the literature led to none of these outcomes being able to be meta-analyzed as planned. The in-hospital mortality rate was 38% (50/130 patients) in the observational cohort studies [51–53]; 23% (19/82 patients) in case reports and series [27–50]; and the registry analysis by Ocskay et al. [18] reported a total of 65 cases of in-hospital mortality (59.6%): 10 at the end of HA therapy (9.2%), 60 during the ICU stay (55%), and 5 more during the out of ICU hospitalization period. Only Ocskay et al. reported the length of ICU stay (14.0 (7.0–23.0); median and IQR). No studies reported the success rate or any other descriptive outcomes in relation to bridging to liver transplantation.

3.4. Other Outcomes

In order to assess the use of hemoadsorption therapy in a clinical setting, we planned to review a set of exploratory outcomes. These included laboratory outcomes, safety parameters, and changes in vital organ functions.

3.4.1. Post-Treatment Organ Function Parameters

Among these outcomes, only six laboratory parameters could be meta-analyzed. Data pooled from 160 patients showed a significant reduction in total bilirubin levels post-treatment (mean difference of −4.79 mg/dL (95% CI: −6.25; −3.33), $p = 0.002$) (Figure 2). Pooled data from case series ($n = 38$) showed a non-significant reduction in serum creatinine (mean difference of −0.38 mg/dL (95% CI: −1.27; 0.5), $p = 0.20$) (Figure 3). Further analyses could only be performed using individual patient data from case reports (Figure 4). Before and after treatment values for each laboratory parameter were pooled from the case reports and summarized in box plots. Individual patient data concerning the change of these parameters are depicted by lines that connect dots that represent before and after data for

each patient. These analyses showed significantly reduced AST levels (Wilcoxon $p = 0.03$) (Figure 4B) and vasopressor need (Wilcoxon $p = 0.03$) (Figure 4F) after treatment. Analyses of ALT, C-reactive protein (CRP), creatinine, and total bilirubin levels after treatment all showed non-significant tendencies for reduction (Figure 4).

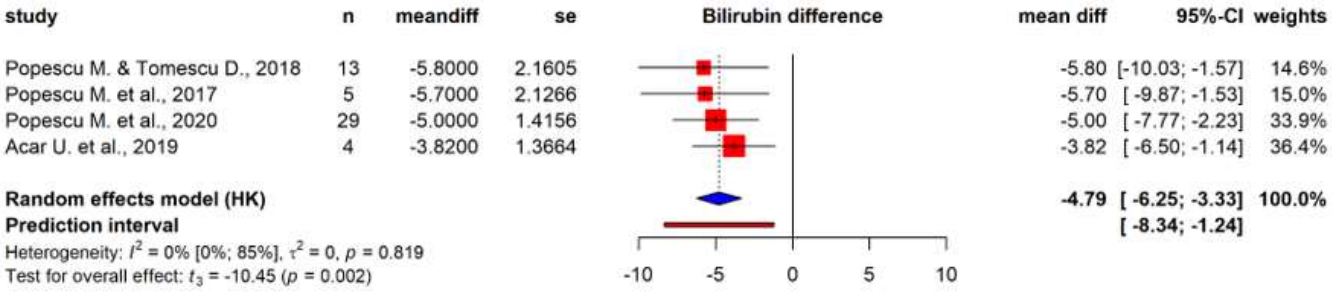

Figure 2. Total bilirubin levels. Forest plot of total bilirubin levels pre- and post-treatment with hemoadsorption [46–48,50].

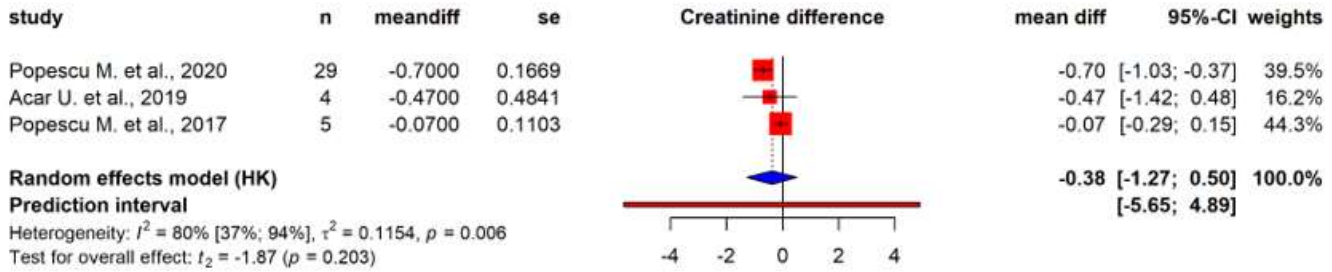

Figure 3. Creatinine levels. Forest plot of serum creatinine levels pre- and post-treatment with hemoadsorption [47,48,50].

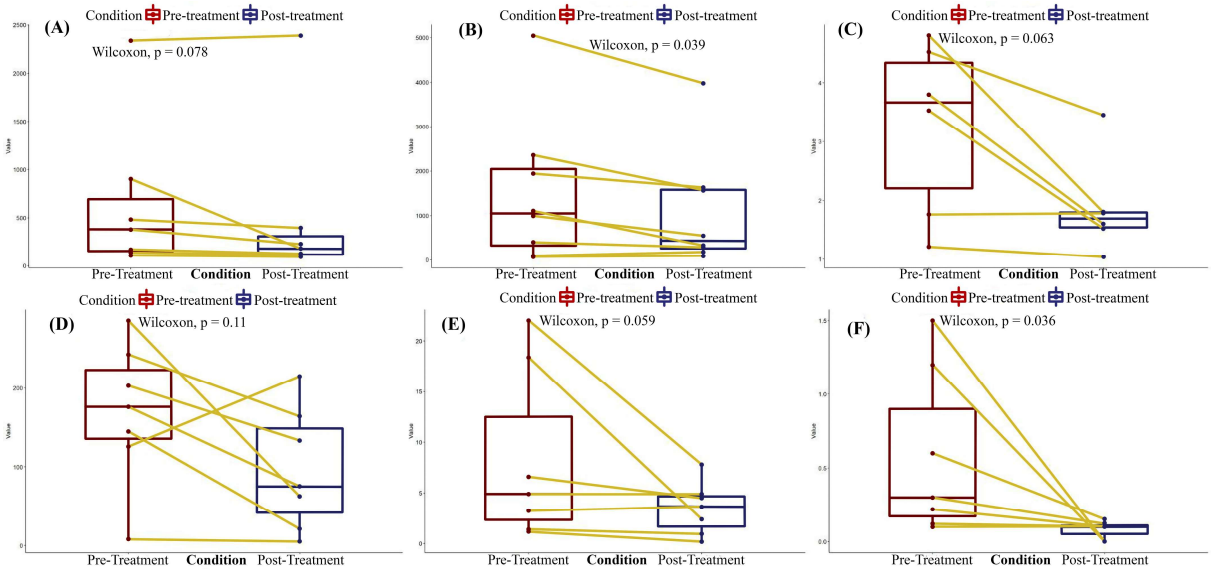

Figure 4. Box plots of individual case data: (**A**) alanine aminotransferase (ALT), (**B**) aspartate aminotransferase (AST), (**C**) bilirubin, (**D**) creatinine, (**E**) C-reactive protein (CRP), and (**F**) vasopressor need. Data were pooled from individual case reports and presented as box plots, representing pre- and post-treatment values. Changes in these parameters for each case are also depicted by lines connecting pre- and post-treatment values.

Currently, data are lacking for D-dimer, serum bile acid levels, and prothrombin time before and after treatment with hemoadsorption. Therefore, a meta-analysis could not be performed for these outcomes.

Other post-treatment organ function parameters extracted from the included articles are detailed in Appendix A Table A1.

3.4.2. Changes in Vital Organ Function

Only two studies reported SOFA score changes before and after HA therapy. Ocskay et al. [18] reported a non-significant improvement in SOFA scores of liver failure patients (mean with a CI: 0.5 (−0.3 to 1.3)), while Popescu et al. (2020) observed a significantly improved CLIF-SOFA score after HA therapy in their case series [48]. The retrospective study by Niu et al. [51] reported a significant improvement in SOFA score, but there are no data available to demonstrate this outcome. Scharf et al. [52] reported a significant improvement in SAPS-II scores after hemoadsorption therapy (mean difference of 6 ± 9, $p = 0.01$).

Among the single-patient case reports, only Cazzato et al. [27] followed up with their patients' SOFA scores. Their patients who underwent a hepatic resection and developed acute liver failure postoperatively improved from a SOFA score of 4 to a 2 after HA therapy.

3.4.3. Safety Outcomes

None of the included studies reported the safety outcomes planned to be presented in this review, but device-related adverse events were not reported in any of the studies.

3.5. Risk of Bias and Level of Evidence Certainty Assessments

The results of the risk of bias assessment and GRADE assessment of the level of evidence certainty are presented in Supplementary Figures S3–S5 and Supplementary Table S1, respectively.

Individual case reports were nearly free from the risk of bias according to our assessment. Case series however suffered from a lack of clearly elaborated patient enrollment strategy across the board. Overall, the risk of bias was not significant for any of the included studies.

Evidence quality is assessed to be poor by the GRADE assessment. Study designs being retrospective and observational present a major challenge in drawing reliable conclusions. Some publications on this topic might be considered "gray literature". As such, the reliability and the quality of the evidence provided should be considered questionable.

4. Discussion

ICU-acquired acute liver dysfunction in the context of a dysregulated host response and hyperinflammation is common and associated with poor short-term outcomes. Notwithstanding clinical advancements to support liver function over the last decades, diagnosis is challenging and therapeutic strategies in the form of liver support therapies are still controversially discussed, since solid data on their efficacy remain sparse.

Therefore, we conducted this systematic review and meta-analysis on the effects of hemoadsorption on liver function in patients with confirmed liver dysfunction of various inflammatory etiologies. We found that the use of hemoadsorption for critically ill patients with acute liver dysfunction or failure seems to be safe and yields a trend towards improved liver function after hemoadsorption.

4.1. Devices

There are a few different hemoadsorption technologies available on the market, of which we identified three devices that were used for ICU-acquired liver dysfunction: CytoSorb, CPFA, and oXiris. Among these, CytoSorb was by far the most frequently used.

4.1.1. CytoSorb

The CytoSorb hemoadsorber is a European CE-marked device capable to adsorb and thus remove cytokines as well as substances such as bilirubin and myoglobin from the blood compartment [54,55]. With more than 180,000 single treatments, this technology is hitherto the most frequently reported hemoadsorption device in clinical practice.

4.1.2. Coupled Plasma Filtration Adsorption

The CPFA cartridge for the removal of cytokines is a blood purification technique that separates whole blood into cellular and plasma components using a high cut-off filter. Subsequently, the plasma is filtered through an adsorbing material that can extract cytokines and then recombine the plasma and cellular components back into whole blood [56].

4.1.3. oXiris

oXiris is a new, high-adsorption membrane filter based on the AN69 polyacrylonitrile hemofilter membrane; in addition, it undergoes additional surface treatment with polyethyleneimine (PEI) lipid A phosphate groups and heparin grafting that combines cytokine and endotoxin removal properties, renal replacement function, and anti-thrombogenic properties [57]. Surface adsorption is purely selective on endotoxin because of the specific configuration of the membrane. Conversely, bulk adsorption is nonselective and can absorb numerous mediators unselectively.

4.2. Outcomes

4.2.1. Bilirubin

One of the most consistent findings in patients with liver dysfunction and treated with hemoadsorption is the effective reduction in bilirubin levels after hemoadsorption, which is strongly supported by the results of our current study.

Two temporally staggered pathophysiological stages of inflammation-induced liver dysfunction can be distinguished in terms of clinical appearance and laboratory assessment. The primary dysfunction, which manifests itself within 24 h after the shock (called "ischemic hepatitis"), leads to a severe restriction of liver perfusion with centrilobular necrosis, accompanied by a massive increase in transaminases (AST, ALT) with only a slight increase in bilirubin [56]. This condition resolves within a few days after the circulation is restored. This is to be distinguished from secondary liver failure or cholestatic liver dysfunction, which is predominantly triggered by inflammatory mediators and is defined by impaired bile formation and excretion. The underlying mechanism is not an obstruction of bile ducts but a non-obstructive accumulation of bile acids and bilirubin in the liver due to a down-regulation of specific transporter molecules at the biliary side of the hepatocyte [9,58]. The mean bilirubin levels in patients included in our meta-analysis were 18.06 $\pm$ 13.26 mg/dL and 6.15 $\pm$ 2.32 mg/dL according to data from individual cases and cohorts before and after HA treatment, respectively. These levels point towards a cholestatic liver dysfunction, rather than an ischemic type.

There is some evidence from experimental studies that high bilirubin concentrations inhibit the non-specific defense mechanisms of neutrophil granulocytes. Because of the antioxidant properties of bilirubin, the bactericidal effect of reactive oxygen species can be inhibited, which enhances the systemic spread of bacteria in an already critical phase [59].

4.2.2. ALT, AST, Bile Acid, Ammonia

However, hemoadsorption may effectively remove not only bilirubin from the blood but also, as shown in two recent in vitro experiments, effectively remove bile acids [60,61]. These results indicate that hemoadsorbents may remove hydrophobic, albumin-bound bile acids better than CRRT filters. Although aminotransferases, levels of bile acid, and serum ammonia are regularly used in clinical practice as markers for liver function, there is hardly any clinical evidence on the effect of hemoadsorption on these parameters. In fact, a recent study found that ammonia elimination is mainly achieved by the dialysis filter rather than

CytoSorb [62]. Furthermore, Scharf et al. hypothesized that the molecular weight of AST, ALT, and GGT makes the transaminase reduction unlikely, and the significant reduction observed suggests a potential improvement in liver function [52]. Therefore, the direct removal of substances versus secondary effects during hemoadsorption therapy remains an unresolved issue. Future studies are needed, in which concentrations of the substances of interest should be measured in the in-flow line (pre-adsorber) and the in the out-flow line (post-adsorber) to determine the clearance of these molecules by the hemoadsorber.

4.2.3. Clinical Outcomes and Safety

This review establishes that there is a critical lack of hard evidence on clinical outcomes associated with hemoadsorption therapy. Although the device itself does not seem to have any adverse effects or complications associated with its use, there is no systematically generated evidence for this claim to be sufficiently reliable. The existing evidence on clinical outcomes is either deemed to be of low quality according to the GRADE assessment or needs to be corroborated and complemented by more studies. The registry analysis from 2019 includes assessments by involved clinicians on whether hemoadsorption therapy improved, deteriorated, or did not affect the clinical status of the patients. While clinicians assessed 68.9% (n = 75) of patients' conditions to have been improved by the therapy, 15.6% (n = 17) of patients did not show any change and 4.8% (n = 5) deteriorated. Due to the lack of comparative studies, it is impossible to draw solid conclusions for such an outcome. However, the current lack of evidence should not be misconstrued as a lack of interest in the topic nor as a demonstration of the inefficacy of the therapy.

4.3. Implications for Research and Practice

Two recent meta-analyses on different extracorporeal liver-support devices showed that this issue is still unsolved, and the level of evidence is so low that recommendations on which approach is the best cannot be made [1,63]. Hemoadsorption is relatively simple to apply, and according to some recent data, it may even be superior to Molecular Adsorbent Recirculating System (MARS). In a recent in vitro study, CytoSorb was found superior to MARS as far as bilirubin, bile acid, ammonia, and cytokine removal are concerned [57]. However, large prospective data or results of randomized trials are still missing. Furthermore, it would also be important to consider alternative study endpoints, such as the change in levels of mercaptans, idols, tryptophane, and albumin binding capacity [64]. Such studies in the future could fill in the gaps in the currently available evidence and knowledge on HA therapy, particularly those associated with clinical outcomes for patients with acute liver dysfunction.

This study has been conducted in the framework of Academia Europaea's position on the cycle model of translational medicine for community healthcare benefit [65,66]. Accordingly, our findings and elaboration are aimed towards summarizing and contextualizing discussions around this highly important subject to generate new hypotheses and guide further research.

4.4. Limitations

The current study has several limitations. First and foremost, the limitation is imposed by the lack of randomized controlled clinical trials in the literature. Second, several of the included studies are case reports and series, which limit the generalizability of the findings from the meta-analyses. Third, several included studies fail to report the sex and ethnicity of the patients, which are both important factors to consider in the clinical overview.

5. Conclusions

The current systematic review and meta-analysis provide further support that adjuvant therapy with hemoadsorption is a feasible, safe, and effective method to reduce circulating bilirubin levels and may have direct and/or indirect effects on other liver-related potentially toxic metabolites. However, the quality of evidence is still low and very little is known about

the clinical effects of the therapy. Therefore, our results highlight the need for adequately designed clinical trials with the above-mentioned parameters as the main outcomes.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/biomedicines12010067/s1, Figure S1. Forest plot of total bilirubin levels pre- and post-treatment with hemoadsorption, using zero correlation model. Figure S2. Forest plot of serum creatinine levels pre- and post-treatment with hemoadsorption, using zero correlation model. Figure S3. Summary table of risk of bias assessment using ROBINS-I for the included non-randomized studies. Figure S4. Summary table of risk of bias assessment according to JBI Manual for Evidence Synthesis (Case reports). Figure S5. Summary table of risk of bias assessment according to JBI Manual for Evidence Synthesis (Case series). Table S1. Summary table of results of GRADE Assessment for the level of certainty of evidence in the included studies. Table S2. HA LIVER PRISMA_2020_checklist. Reference [67] are cited in the supplementary materials.

Author Contributions: All authors' contributions are represented in accordance with the CRediT Author Contribution guidelines. C.T.: conceptualization, investigation, writing—original draft; C.E.S.: conceptualization, investigation, writing—review and editing; T.K.: software, formal analysis, writing—review and editing; M.A.E.: methodology, supervision, writing—review and editing; I.A.: investigation, writing—original draft; T.T.: reviewing and editing; L.Z.: conceptualization, reviewing and editing; P.H.: project administration, supervision; Z.M.: conceptualization, project administration, supervision, writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This project was partially funded by the Hungarian National Research, Development and Innovation Office, Grant No.: K 138816.

Institutional Review Board Statement: In accordance with Good Clinical Practices (GCP) guidelines and applicable regulatory and institutional requirements, written informed consent from study participants was not required.

Informed Consent Statement: Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Data Availability Statement: All data used for the meta-analysis originate from publicly available publications.

Conflicts of Interest: Z.M. is a full-time employee of CytoSorbents Europe GmbH. The other authors state that they have no conflicts of interest.

Appendix A

Table A1. Post-treatment organ function parameters.

First Author, Year of Publication	Bilirubin (mg/dL): Pre-Treatment/Post-Treatment	CRP (mg/dL): Pre-Treatment/Post-Treatment	ALT (U/L): Pre-Treatment/Post-Treatment	AST (U/L): Pre-Treatment/Post-Treatment	Creatinine (mg/dL): Pre-Treatment/Post-Treatment	Ammonia (µmol/L): Pre-Treatment/Post-Treatment	LDH (U/L): Pre-Treatment/Post-Treatment	Vasopressor Dosage (mcg/kg/min)	Mortality	Changes in Vital Organ Function: Pre-Treatment/Post-Treatment
Gunasekera, A.M., 2022 [25]	4.9/4.9	-	2338/2390	5049/3795	4.8/1.8	-	-	-	0	-
Ruiz-Rodriguez, J.C., 2022 [26]	22/7.8	7.7/4.94	-	1938/1625	7.03/CRRT	-	-	1.5/0	0 *	SOFA Score: 15/16
Cazzato, M.T., 2019 [27]	3.22/4.99	-	-	-	3.53/1.52	67/57	-	0.16/0.01	0	SOFA Score: 4/2
Daza, J.L., 2022 [28]	-	145/21	900/179	1100/320	3.8/1.6	-	670/178	1.2/0	1	-
Hinz, B., 2015 [29]	6.58/5.88	203.2/133.4	107.4/100.8	80.4/87.6	1.76/1.78	-	-	0.3/0.15	0	-
Köhler, T., 2021 [30]	1.17/0.19	-	-	-	-	-	-	0.22/0.1	0	SOFA Score: 12/6
Lau, C.W.M., 2021 [31]	-	243/164	-	-	-	-	-	-	0	-
Li, Y., 2020 [32]	-	-	-	-	-	-	-	-	0	CLIF Score: 63/43
Manohar, V., 2017 [33]	-	176.15/74.97	378.5/226.9	992.5/540.1	-	-	-	0.1/0.1	0	-
Markovic, M., 2020 [34]	-	125.5/214.9	482/393	2355/1561	4.52/3.45	-	-	0.6/0.15	1	APACHE-II Score: 35/60
Moretti, R., 2011 [35]	-	-	-	-	-	-	-	-	0	-
Piwowarczyk, P., 2019 [36]	18.41/2.4	-	-	-	-	-	-	-	0	SOFA Score: 16/10
Tomescu, D., 2018 [37]	-	-	-	-	-	-	-	-	0	-
Wiegele, M., 2015 [38]	1.4/0.94	-	137/121	395/285	1.21/1.04	-	-	0.12/0.1	0	-
Lévai, T., 2019 [39]	-	-	-	-	-	-	-	-	0	-
Manini, E., 2019 [40]	-	-	-	-	-	-	-	-	0	-

Table A1. *Cont.*

First Author, Year of Publication	Bilirubin (mg/dL): Pre-Treatment/Post-Treatment	CRP (mg/dL): Pre-Treatment/Post-Treatment	ALT (U/L): Pre-Treatment/Post-Treatment	AST (U/L): Pre-Treatment/Post-Treatment	Creatinine (mg/dL): Pre-Treatment/Post-Treatment	Ammonia (µmol/L): Pre-Treatment/Post-Treatment	LDH (U/L): Pre-Treatment/Post-Treatment	Vasopressor Dosage (mcg/kg/min)	Mortality	Changes in Vital Organ Function: Pre-Treatment/Post-Treatment
Popescu, M., 2017 [41]	-	-	-	-	-	-	-	-	0	
Kogelman, K., 2021 [42]	-	285.9/62.6	-	13,300/198	1.83/no data	-	-	-	0 *	SAPS II Score: 56/37
Breitkopf, R., 2020 [43]	-	-	-	-	-	-	-	-	0	Glasgow Coma Scale: 13/15
Ullo, I., 2017 [44]	-	-	-	-	-	-	-	-	2	
Popescu, M., 2017 [45]	17.5 ± 7.9/ 11.8 ± 6.7	-	-	-	0.83 ± 0.41/ 0.76 ± 0.31	-	-	-	0	
Popescu, M. and Tomescu, D., 2018 [46]	23.6 ± 12.9/ 17.8 ± 11.2	-	-	-	-	-	-	-	0	
Maggi, U., 2013 [47]	-	-	-	-	-	-	-	-	0	
Popescu, M., 2020 [48]	14.2 ± 12.6/ 9.2±9.1	-	-	-	1.9 ± 1.4/ 1.2 ± 0.8	-	-	-	11	CLIF-SOFA Score: 12.0 ± 2.1/10.0 ± 2.6
Dhokia, V.D., 2019 [49]	-	-	-	-	-	-	-	-	0	-
Acar, U., 2019 [50]	18.14 ± 4.47/ 14.32 ± 4.1	979 ± 667/ 982 ± 611	117.88 ± 67.10/ 119.66 ± 73.79	180.11 ± 115.10/ 153.44 ± 78.21			347.11 ± 160.34/ 298.55 ± 53.09	0.02 ± 0.04/ 0.59 ± 1.50	3	-
Ocskay, K., 2021 [18]	-	-	-	-	-	-	-	-	65	SOFA Score: mean = 0.5 (n = 73)
Niu, D.G., 2019 [51]	-	-	-	-	-	-	-	-	14	
Scharf, C., 2021 [52]	-	-	614 ± 1707/ 395 ± 1112	1512 ± 4338/ 1033 ± 3003	-	-	-	-	10 **	SAPS II: 6 ± 9
Praxenthaler, J., 2022 [53]	-	-	-	-	-	-	-	-	-	-

* Mortality event occurred within the follow-up period, but after the completion of the hemoadsorption therapy, from an unrelated reason as described by the authors. ** 7-days mortality irrespective of the completion of the hemoadsorption therapy.

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