DOI:10.14753/SE.2024.3120

PERIOPERATIVE MANAGEMENT AND CRITICAL CARE FOR PATIENTS WITH LIVER DYSFUNCTION

Ph.D. Thesis

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Budapest

2024

DOI:10.14753/SE.2024.3120

"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

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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

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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.

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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.

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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.

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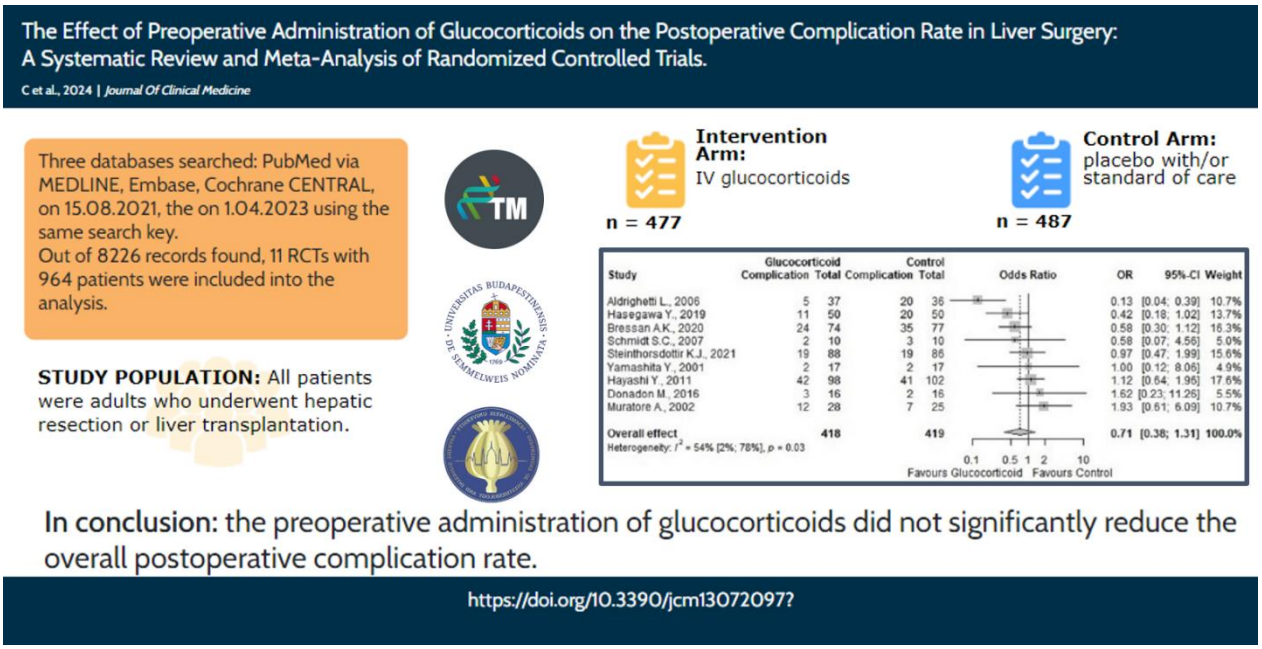
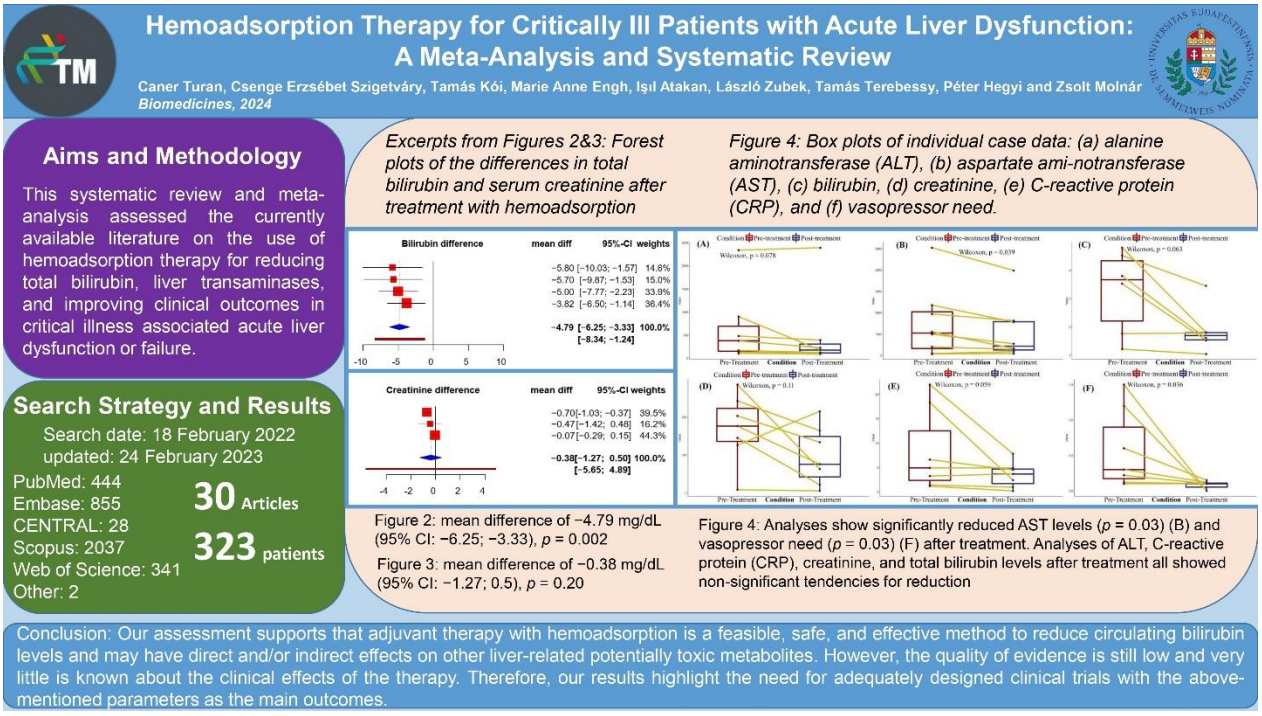
4 GRAPHICAL ABSTRACTS OF THE STUDIES

4.1 Study 1



4.2 Study 2



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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.

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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

DOI:10.14753/SE.2024.3120

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.

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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.

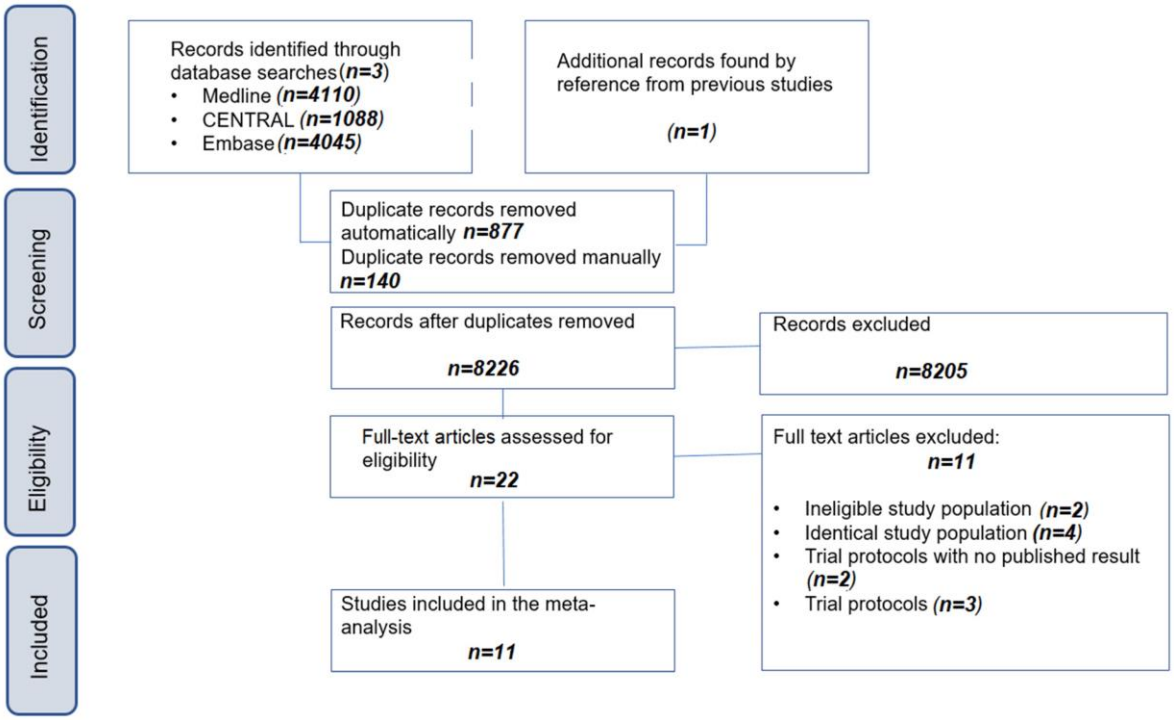

Figure 1. PRISMA flowchart of selection describing the systematic search and selection process

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	Non-administration	Hepatic resection	98	102	69 (39–81) c	70 (35–	No data	No data

	mg consecutively					82) c			
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.

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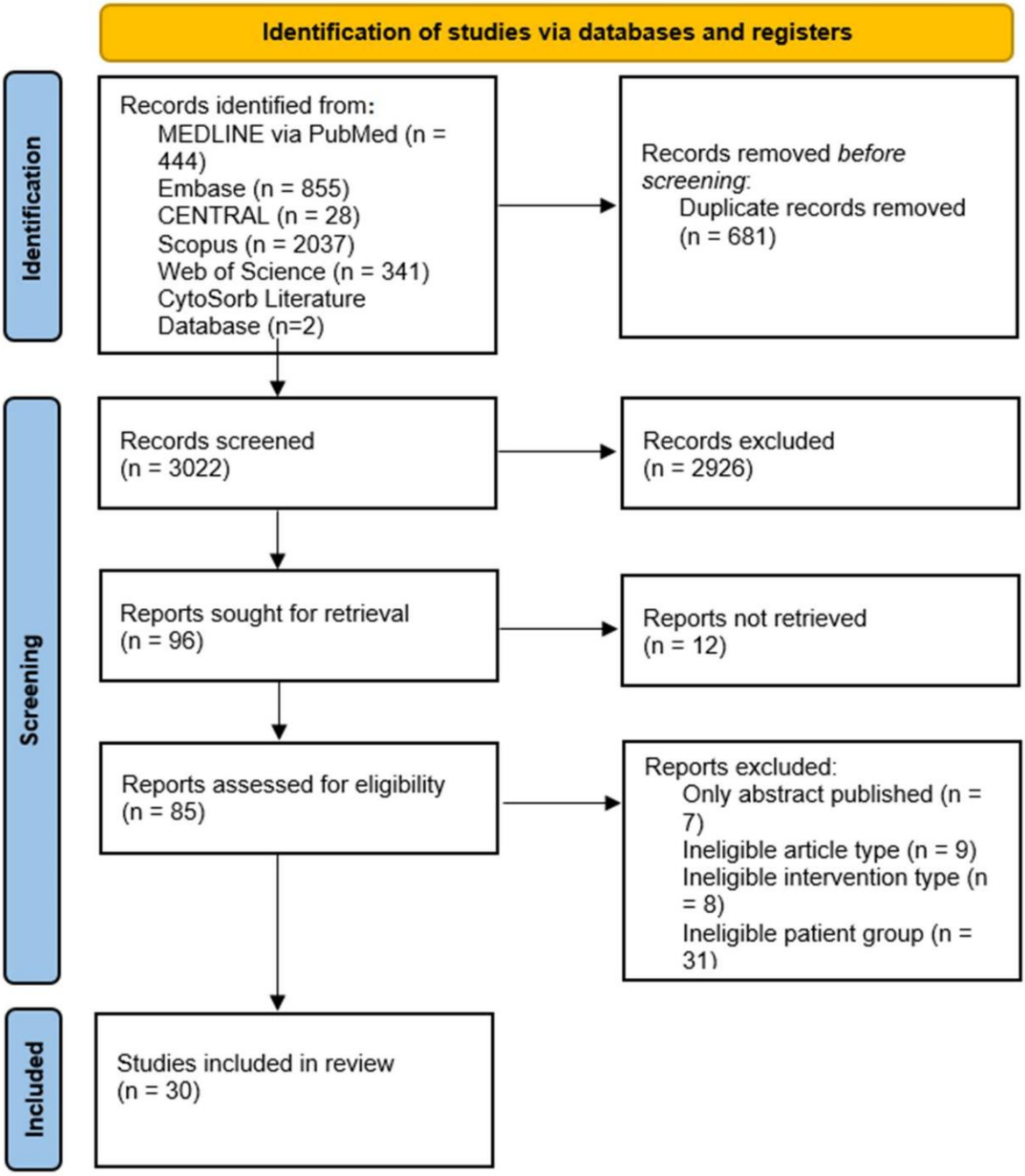

Figure 2. PRISMA flowchart of included studies.

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	2

						with CRRT (1)	
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	21	74 (58–	CytoSorb	CVVHD with CytoSorb	varies

	observation	80)
	al study	d

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].

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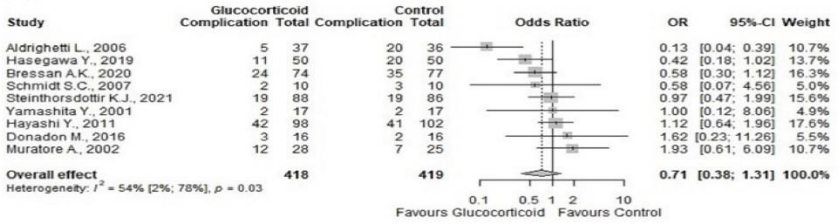
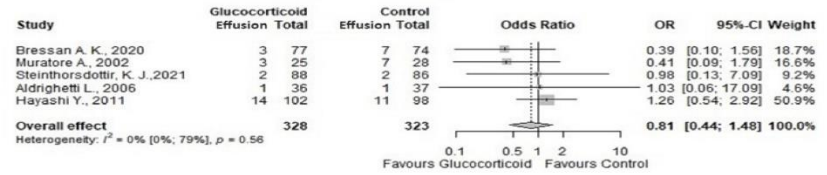


(B)



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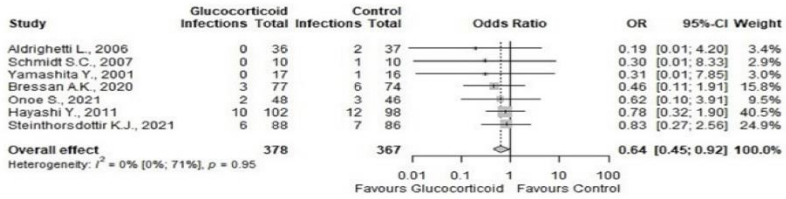

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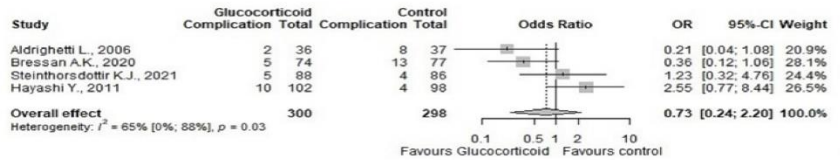

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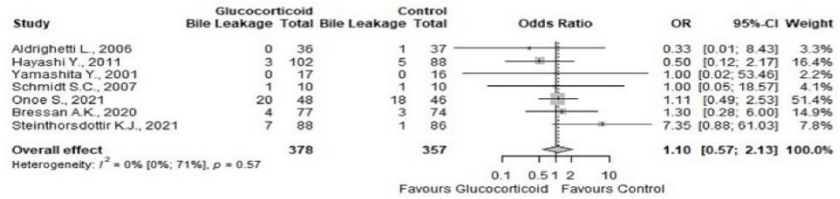

(F)

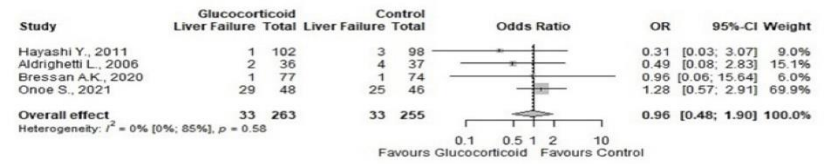

Figure 3. Forest plots of clinical outcomes. (A) overall postoperative complication rate; (B) pleural effusion; (C) wound infection; (D) septic/infectious complications; (E) bile leakage; (F) liver failure of any grade. OR: odds ratio; CI: confidence interval.

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).

DOI:10.14753/SE.2024.3120

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).

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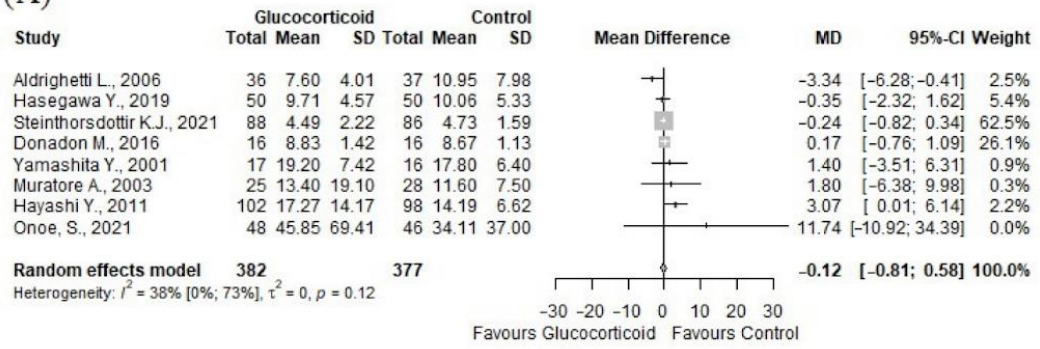
(A)



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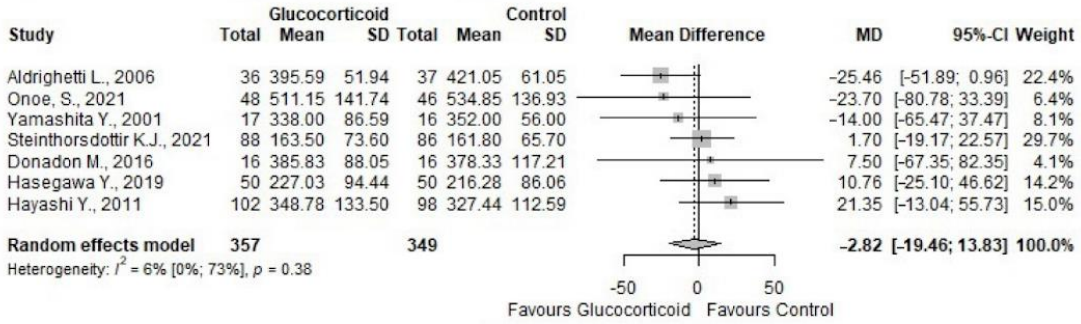

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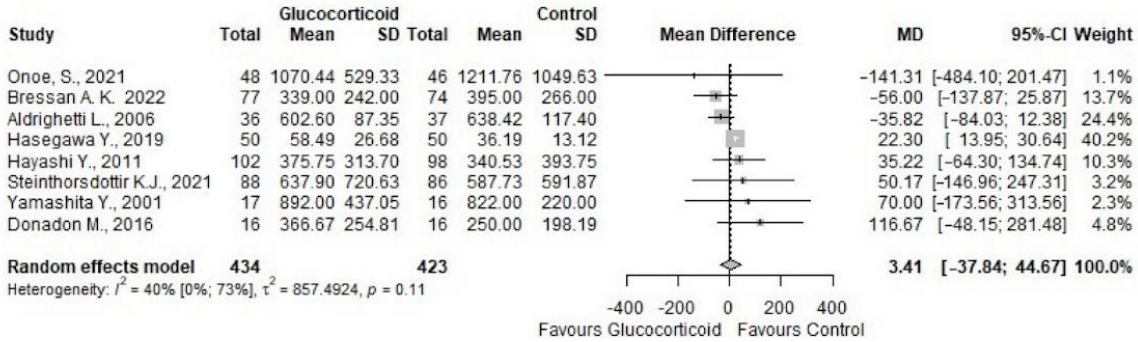

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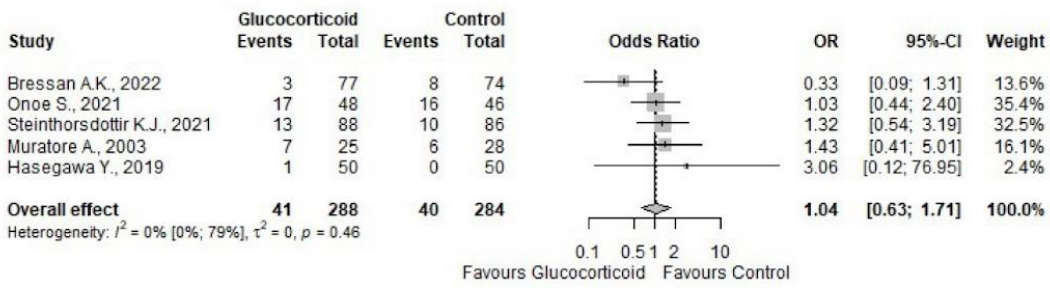

Figure 4. Forest plots of other outcomes. (A) length of hospital stay; (B) total operative time; (C) blood loss (milliliters); (D) need for administration of blood products. OR: odds ratio; CI: confidence interval; MD: mean difference; SD: standard deviation.

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

DOI:10.14753/SE.2024.3120

= 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).

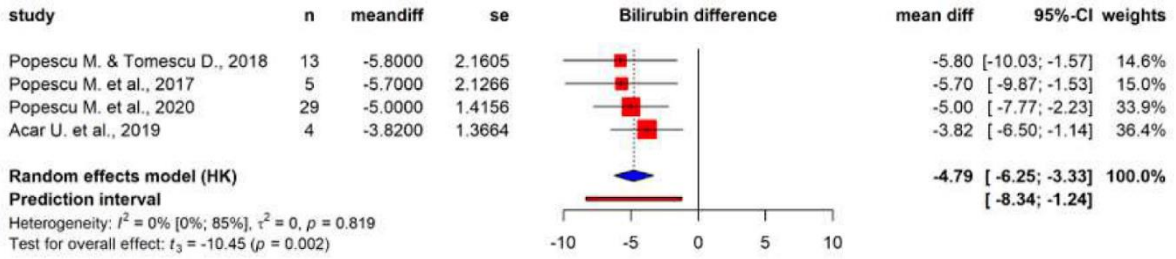

Figure 5. Forest plot of total bilirubin levels pre- and post-treatment with hemoadsorption

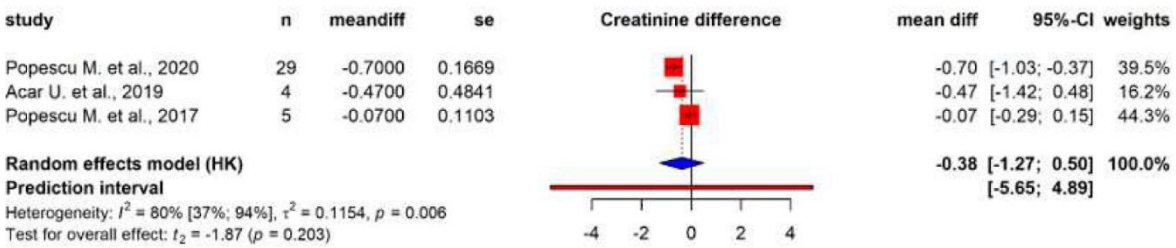

Figure 6. Forest plot of serum creatinine levels pre- and post-treatment with hemoadsorption.

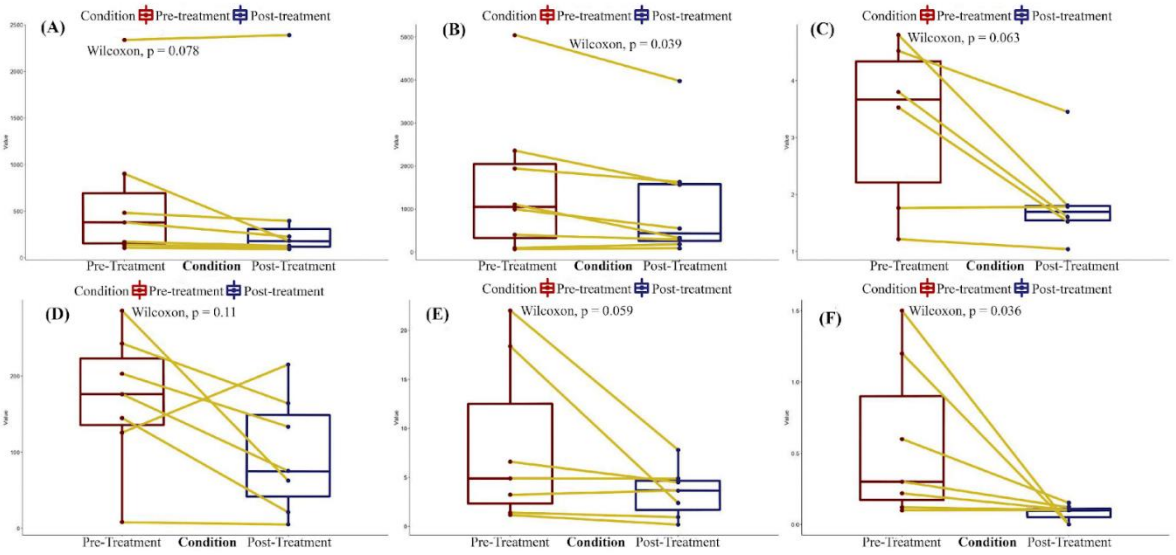

Figure 7. Box plots of individual case data: (A) alanine aminotransferase (ALT), (B) aspartate aminotransferase (AST), (C) bilirubin, (D) creatinine, (E) C-reactive protein (CRP), and (F) vasopressor need. Data were pooled from individual case reports and presented as box plots, representing pre- and 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 τ2, 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.

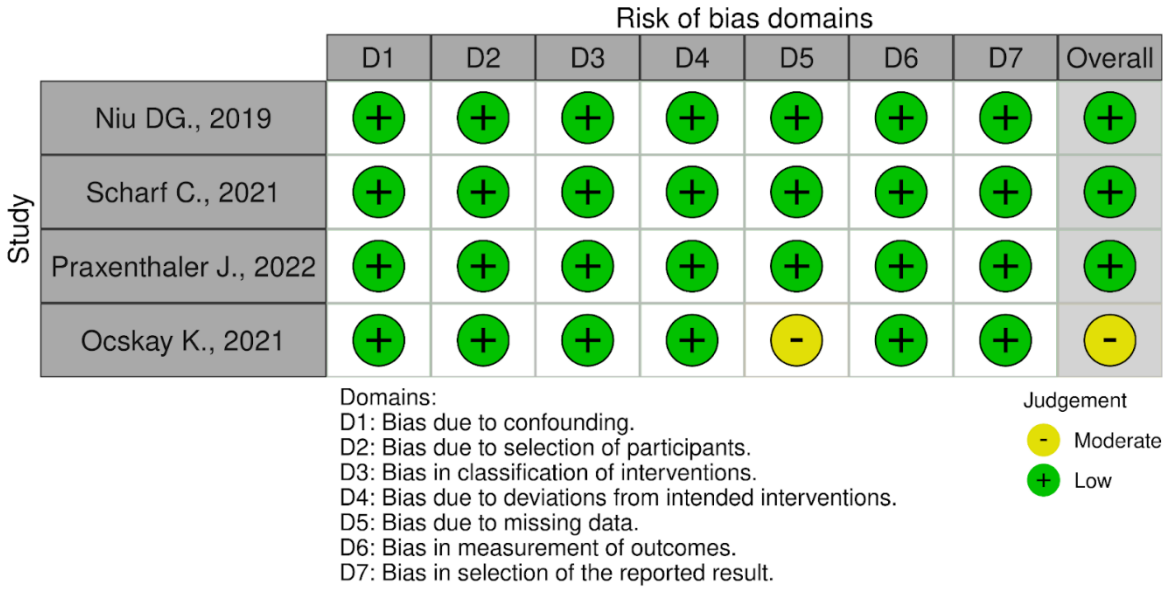

Figure 9. Results of the risk of bias assessments using ROBINS-I

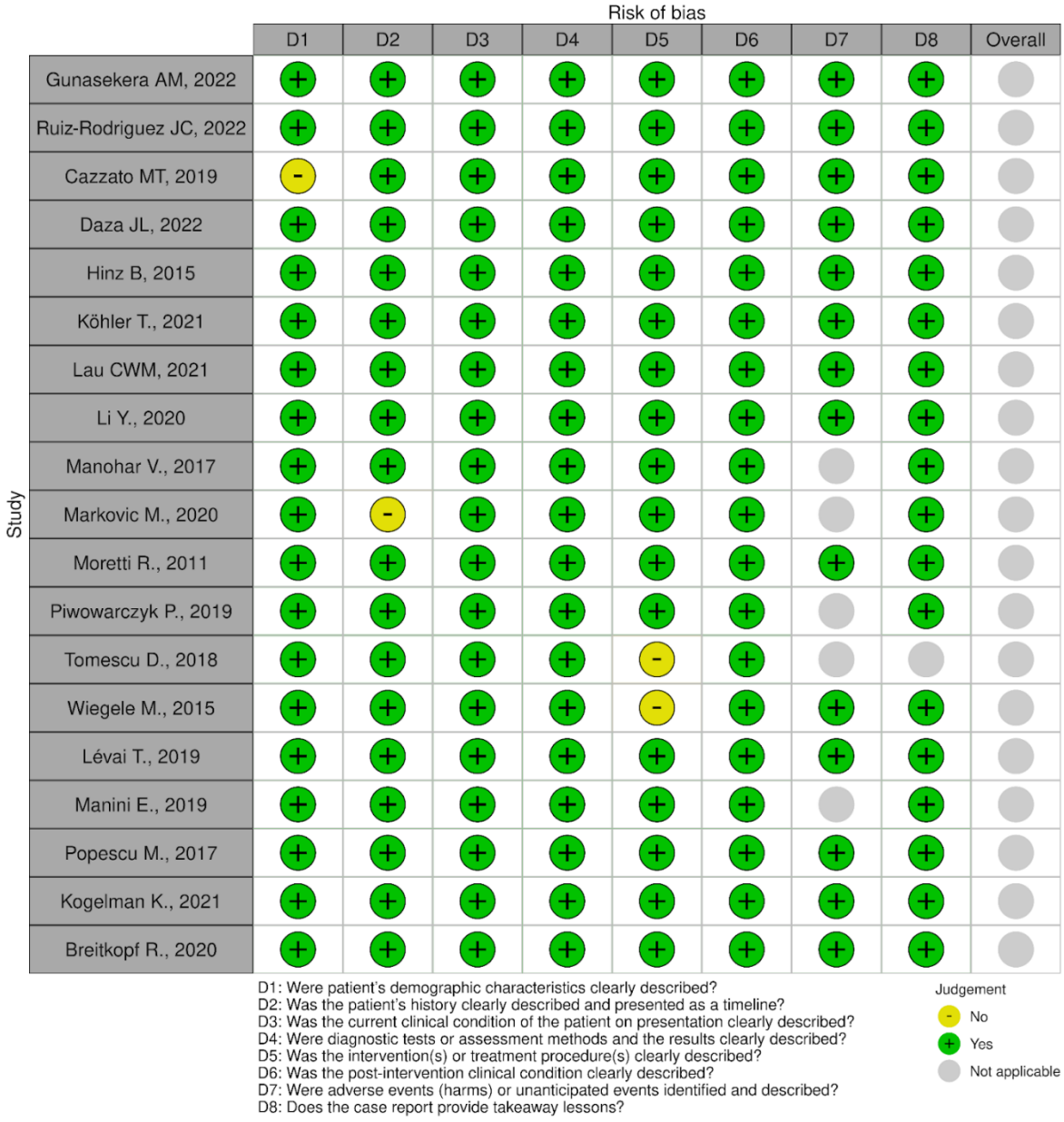

Figure 10. Results of the risk of bias assessments using JBI for case reports

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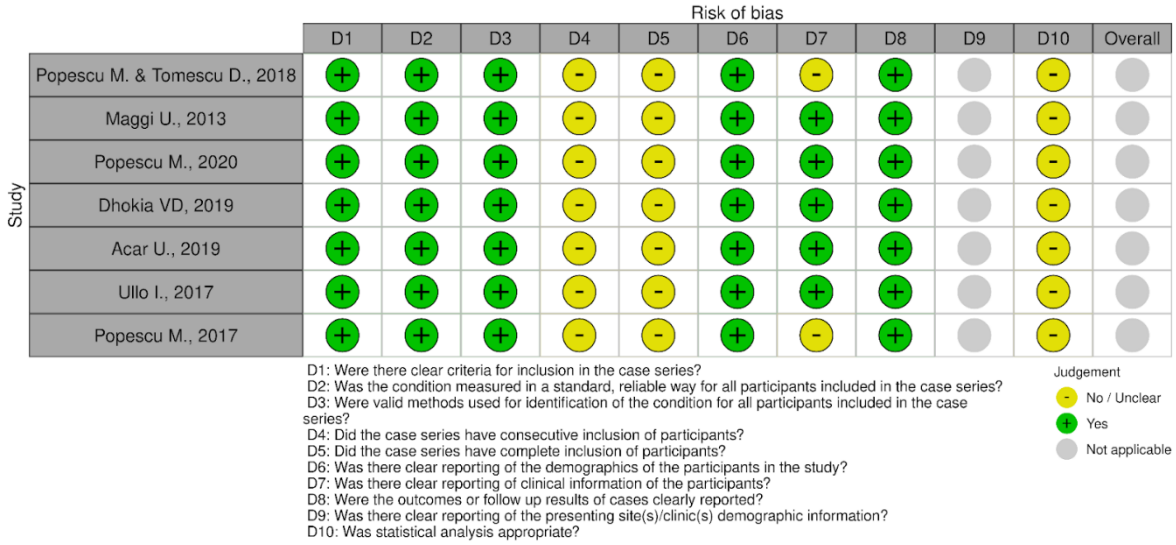

Figure 11. Results of the risk of bias assessments using JBI for case series

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

DOI:10.14753/SE.2024.3120

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

DOI:10.14753/SE.2024.3120

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.

DOI:10.14753/SE.2024.3120

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.

DOI:10.14753/SE.2024.3120

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.

DOI:10.14753/SE.2024.3120

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.

DOI:10.14753/SE.2024.3120

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.

DOI:10.14753/SE.2024.3120

13 IMPLICATIONS FOR POLICYMAKERS

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.

DOI:10.14753/SE.2024.3120

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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16 BIBLIOGRAPHY OF THE CANDITATE'S PUBLICATIONS

Publications related to the thesis

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

Turan, Caner ; Szigetváry, Csenge E. ; Kói, Tamás ; Engh, Marie A. ; Atakan, Işıl ; Zubek, László ; Terebessy, Tamás ; Hegyi, Péter ; Molnár, Zsolt

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

Higher Dose Anticoagulation Cannot Prevent Disease Progression in COVID-19 Patients: A Systematic Review and Meta-Analysis

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)

Procalcitonin-guided antibiotic therapy may shorten length of treatment and may improve survival-a systematic review and meta-analysis

Papp, Márton ; Kiss, Nikolett ; Baka, Máté ; Trásy, Domonkos ; Zubek, László ; Fehérvári, Péter ; Harnos, Andrea ; **Turan, Caner** ; Hegyi, Péter ; Molnár, Zsolt

CRITICAL CARE 27 : 1 Paper: 394 , 15 p. (2023)

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

IF: 15.1 (2022)

Evaluating the predictive value of late gadolinium enhancement assessed by cardiac magnetic resonance on sudden cardiac death in patients selected for implantable cardioverter defibrillator and cardiac resynchronization therapy implantation: a systematic review and meta-analysis

Masszi, Richárd ; Zsigmond, Előd-János ; Ehrenberger, Réka ; **Turan, Caner** ; Fehérvári, Péter ; Teutsch, Brigitta ; Molnár, Zsolt ; Drobni, Zsófia ; Vágó, Hajnalka ; Hegyi, Péter ; Kosztin, Annamária ; Merkely, Béla

CLINICAL RESEARCH IN CARDIOLOGY Paper: in press (2024)

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

DOI:10.14753/SE.2024.3120

IF: 5.0 (2022)

Platelet-rich plasma (PRP) treatment of the ovaries signifcantly improves fertility parameters and reproductive outcomes in diminished ovarian reserve patients: a systematic review and meta-analysis

Éliás, Máté ; Kónya, Márton ; Kekk, Zsófa ; **Turan, Caner** ; Pinto Amorim das Virgens, Isabel ; Tóth, Réka ; Keszthelyi, Márton ; Hegyi, Péter ; Várbíró, Szabolcs ; Sipos, Miklós

JOURNAL OF OVARIAN RESEARCH 17 Paper: 104, 18 p. (2024)

DOI: https://doi.org/10.1186/s13048-024-01423-2

IF: 4.7 (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

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

IF: 8 (2022)

DOI:10.14753/SE.2024.3120

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.