Results from One Year in the Translational Medicine PhD program in Semmelweis University, Hungary

Colours of Sepsis 23-27 January Ostrava

Caner Turan

About the speaker

My projects

Perioperative Management and Critical Care for Patients with Liver Dysfunction

Projects under my supervision

Cardiology

Anesthesiology and Intensive Therapy

Endocrinology and Gynecology

Emergency Medicine

Caner Turan

Scientific Methodology Supervisor

Clinical physician

TM

OVERVIEW

1. What is Translational Medicine

2. Why we do systematic reviews and meta-analyses

3. Workflow of a meta-analysis

4. The premise of our studies over this year

5. Perioperative management of patients undergoing liver surgery, using glucocorticoid administration

6. A novel technology for managing acute liver dysfunction: Hemoadsorption

Results from One Year in the Translational Medicine PhD program in Semmelweis University, Hungary

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What is Translational Medicine?

A continuous medical education model

- Hybrid system: to educate healthcare professionals to generate and implement science
  - „Evidence based medicine"

- To equip clinical workers with the necessary ability to question and assess every component of the day to day practice
  - „Scientific thinking at the bedside"

- Disseminates the findings of scientific work abroad, **but also at their clinics/departments**

A system which integrates all levels of clinical work, and promotes & develops team-working

- Undergraduate students:
  - Scientific Methodology Learners ; project students
  - MD-PhD Program

- Postgraduate trainees / specialists: PhD students, researchers

- Experienced translational medicine practitioners: Scientific Methodology Experts / Supervisors

- Biostatisticians

- Research workers (registry/clinical trial nurses, data and IT specialists, legal experts)

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What is Translational Medicine?
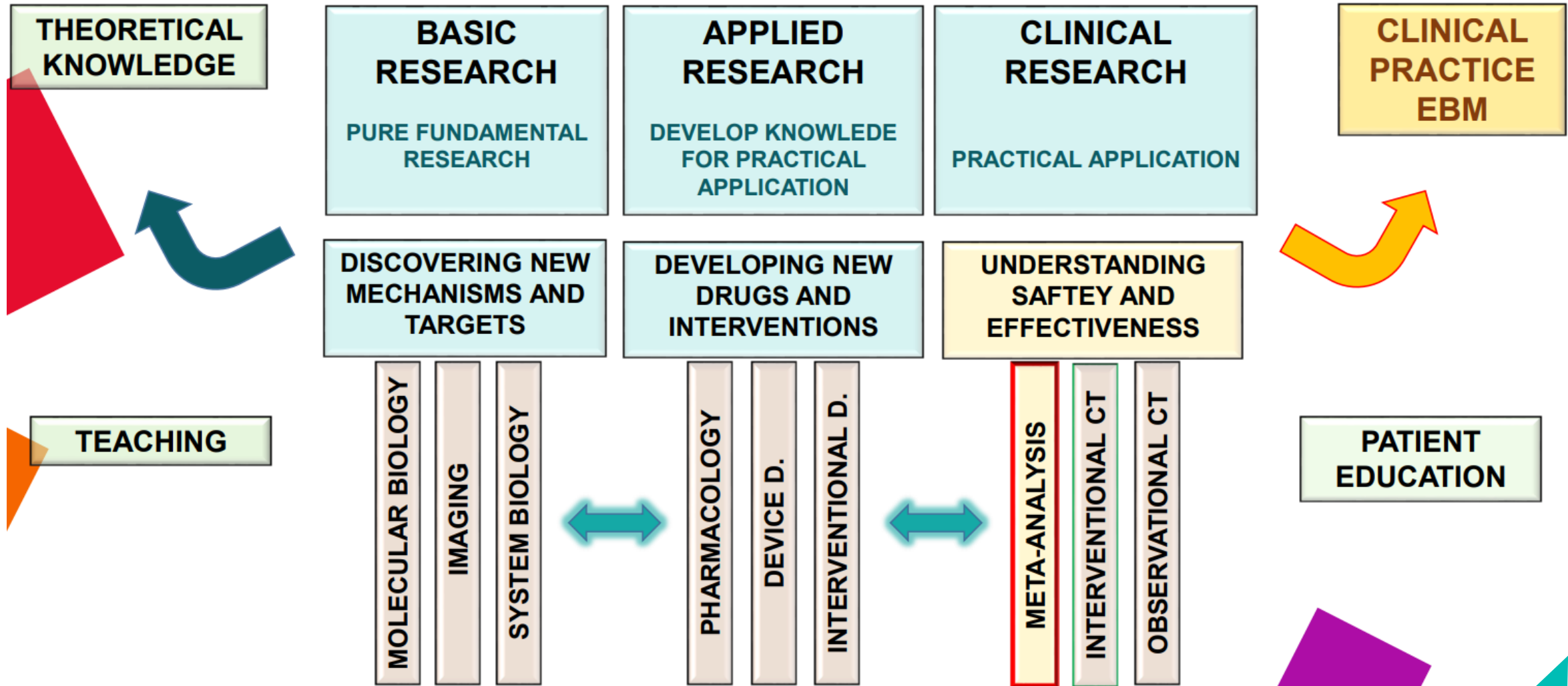
Why we do systematic reviews and meta-analyses?
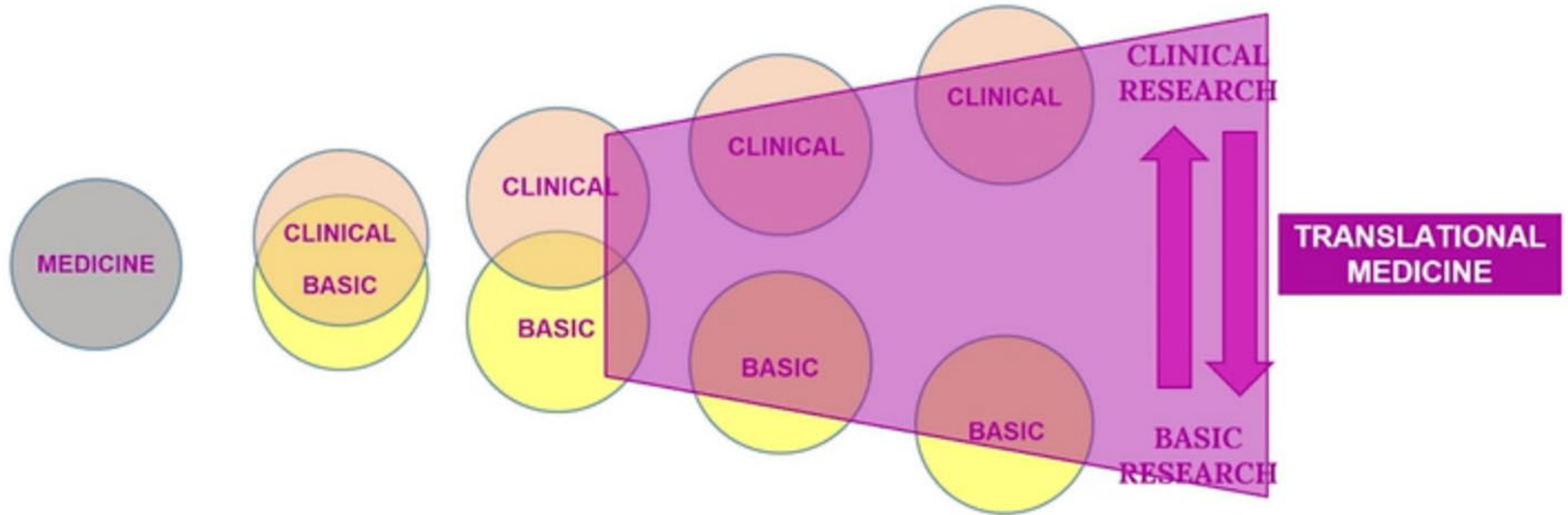
Why we do systematic reviews and meta-analyses?
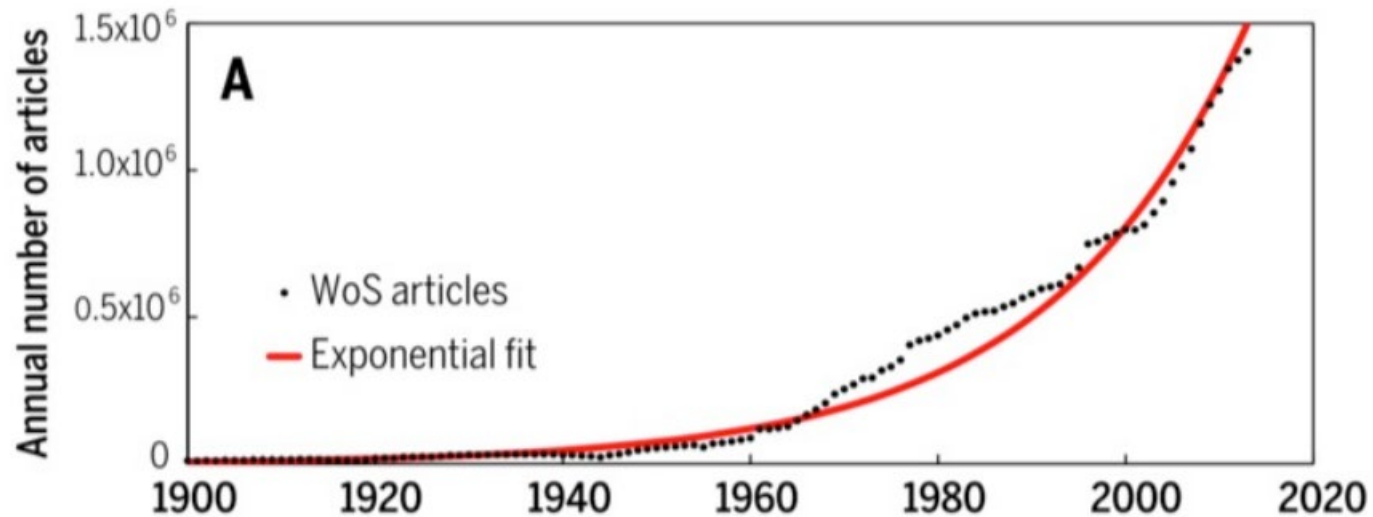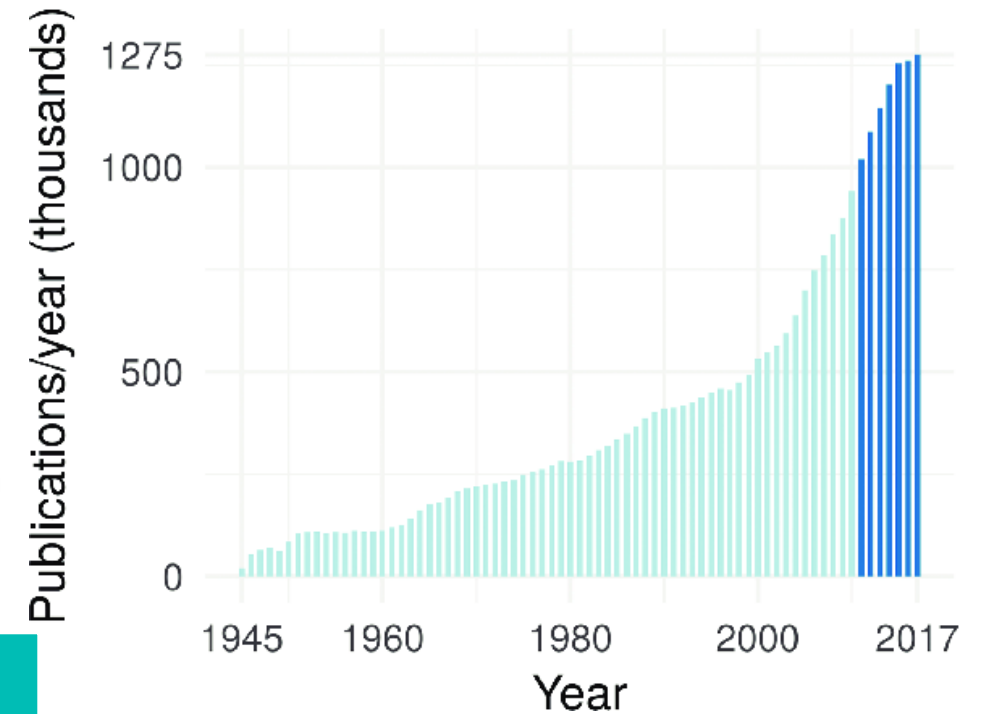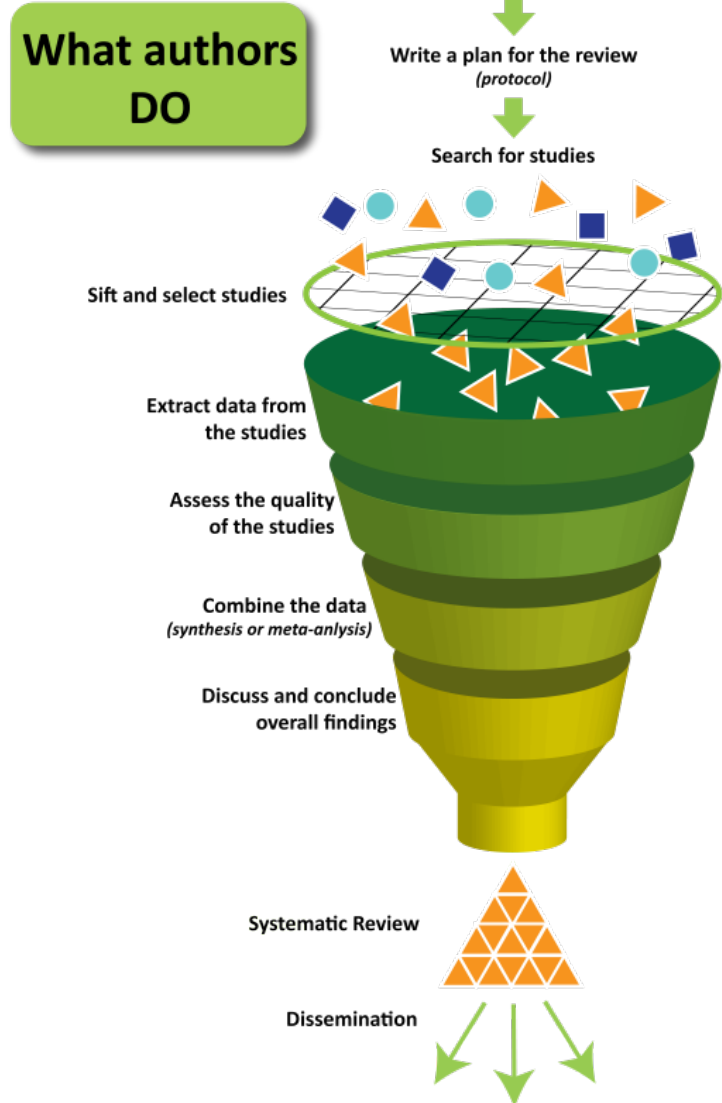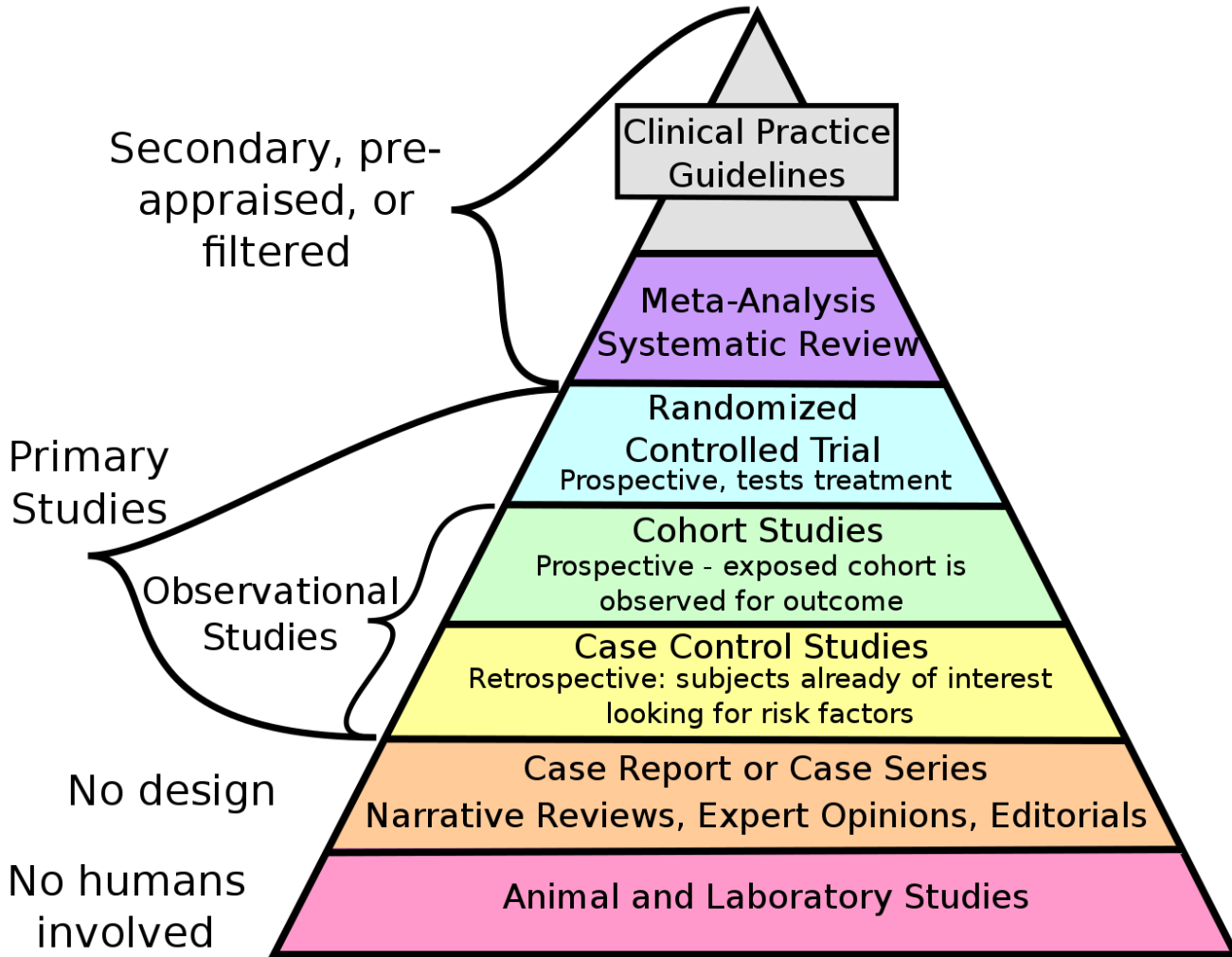
Figure 1. Articles indexed by the Web of Science

Figure 2. Articles published on PubMed each year

We need a way to summarize and contextualize medical knowledge!

Why we do systematic reviews and meta-analyses?

Secondary, pre-appraised, or filtered

Primary Studies

Observational Studies

No design

No humans involved

Clinical Practice Guidelines

Meta-Analysis Systematic Review

Randomized Controlled Trial
Prospective, tests treatment

Cohort Studies
Prospective - exposed cohort is observed for outcome

Case Control Studies
Retrospective: subjects already of interest looking for risk factors

Case Report or Case Series
Narrative Reviews, Expert Opinions, Editorials

Animal and Laboratory Studies

What authors DO

Identify the issue and determine the question

Write a plan for the review *(protocol)*

Search for studies

Sift and select studies

Extract data from the studies

Assess the quality of the studies

Combine the data *(synthesis or meta-anlysis)*

Discuss and conclude overall findings

Systematic Review

Dissemination

Review Question

Patient	Question	Research and Trials	Systematic Review / Meta-Analysis	Policy and Protocol	Repeat

Interventional
- P: patients
- I: Intervention
- C: Comparator
- O: Outcomes

Etiology/Risk
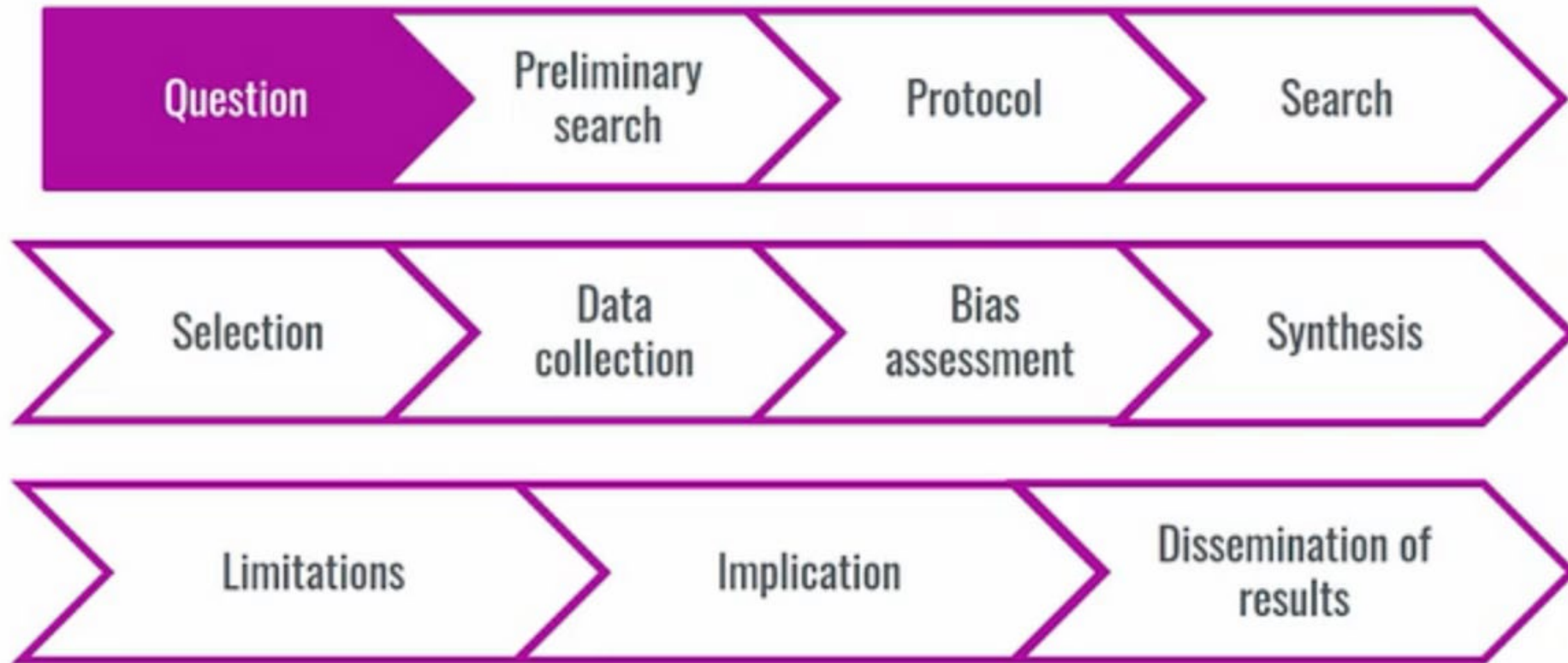- P: patients
- E: Exposure
- [C: Control]
- O: Outcomes

Diagnostic
- P: patients
- I: Index test
- R: Reference test
- D: Diagnosis of interest

Prevalence/Incidence
- Co: Condition
- Co: Context
- Pop: Population

Workflow of a meta-analysis

Choosing a topic for research

- Emergent health concern calls for investigation

- There are gaps in the guidelines

- There are „known unknowns"

- Contradictory alternatives exist in clinical practice

- „Habit" in clinical practice precedes rational „justification"

Choosing a topic for research

F is for Feasibility
- Avoid „empty" reviews; if data is unavailable, consider primary research

I is for Interesting
- Not only for the researcher, but also the partners in healthcare

N is for Novel
- Don't duplicate effort; contribute meaningful work

E is for Ethical
- The purpose and the goal of the review must be fall in line with medical ethics

R is for Relevant
- Involve the partners; we are writing the article for them after all!

Our methodology in action

Preoperative steroid administration for major liver surgery

Guideline

- **Previous clinical trials**: Conflicting results need quantitative & qualitative synthesis

- **ERAS Guideline:**
  Weak recommendation
  Moderate evidence level

Systematic Review

- **Efficacy** in reducing postoperative complications

- **Feasibility** in clinical practice

Hemadsorption therapy for critical illness with acute liver dysfunction

Systematic Review

- **Summary** of evidence

- **Contextualization** of clinical experience

Guideline

- Establishing guidance for **clinical practice**

- **Clarification** of further research required

Our methodology in action

Preoperative steroid administration for major liver surgery

Guideline

- **Previous clinical trials**: Conflicting results need quantitative & qualitative synthesis

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Systematic Review

- **Efficacy** in reducing postoperative complications
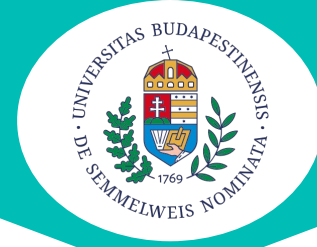
- **Feasibility** in clinical practice

Hemoadsorption therapy for critical illness with acute liver dysfunction

Systematic Review

- **Summary** of evidence

- **Contextualization** of practical experience

Guideline

- Establishing guidance for **clinical practice**

- **Clarification** of further research required

The Effect of Preoperative Administration of Glucocorticoids on the Postoperative Complication Rate in Liver Surgery: a systematic review and meta-analysis

The Problem

Postoperative complication rates for patients undergoing major liver surgery is unacceptably high (~48% complication rate, ~20% mortality) [1]

What we know

Glucocorticoids may be effective in protecting against dysregulated immune response [2]

The missing link

Earlier meta-analyses and clinical trials have contradictory results and recommendations; stronger evidence is needed before implementation into clinical practice

References:
1. Current concepts in acute liver failure, Rovegno et al. 2019, *Annals of Hepatology*
2. Effective prediction of postoperative complications for patients after open hepatectomy: a simplified scoring system based on perioperative parameters, Chen et al. 2019, *BMC Surgery*

Background

Liver surgery can still be dangerous for patients
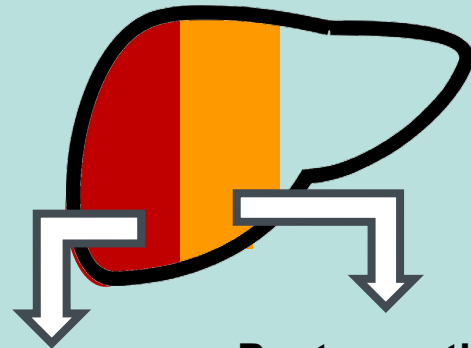
Mortality
20%

Postoperative Complications
48%

Cause

- Operative stress
- Injury to liver parenchyma
- **Dysregulated immune response**

Solution?

- Immune modulation => **Steroids**

Premise

ERAS Society Guidelines
2016
Evidence: Moderate
Grade of recommendation: Weak

2014: Non-significant
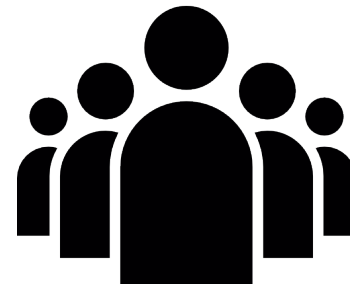**2015:** Non-significant
2019: Non-significant
2021: Significant

4 NEW RCTs

400 NEW PATIENTS

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Research Question

Does preoperative administration of glucocorticoids in liver surgery decrease postoperative complication rates?

P	Patients undergoing liver resections or transplantation
I	Preoperative administration of glucocorticoids *(any modality)*
C	Control group (placebo or non-administration)
O	Primary: overall postoperative complication rate Secondary: intraoperative outcomes, postoperative liver function, length of hospital stay

Hypothesis: Administration of glucocorticoids for patients undergoing liver surgery will reduce the overall postoperative complication rates as opposed to the administration of placebo.

Systematic search

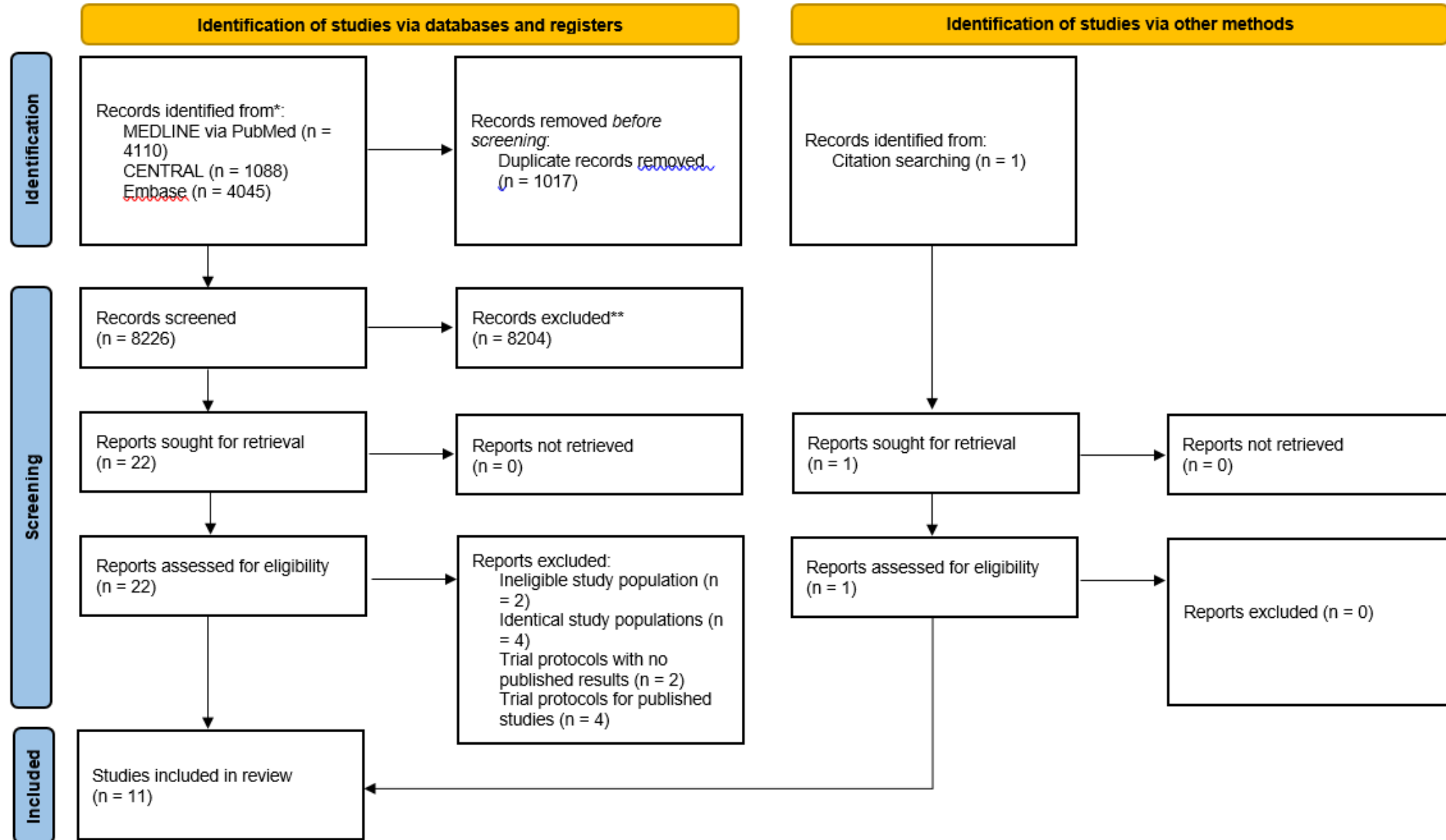**Databases:** Medline (**4110**), Embase (**2314**), Central (**1088**)

Date of search: October 15, 2021

Searchkey:

(((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*

Identification of studies via databases and registers

Identification of studies via other methods

Identification

Records identified from*:
  MEDLINE via PubMed (n = 4110)
  CENTRAL (n = 1088)
  Embase (n = 4045)

Records removed *before screening*:
  Duplicate records removed (n = 1017)

Records identified from:
  Citation searching (n = 1)

Screening

Records screened
(n = 8226)

Records excluded**
(n = 8204)

Reports sought for retrieval
(n = 22)

Reports not retrieved
(n = 0)

Reports sought for retrieval
(n = 1)

Reports not retrieved
(n = 0)

Reports assessed for eligibility
(n = 22)

Reports excluded:
  Ineligible study population (n = 2)
  Identical study populations (n = 4)
  Trial protocols with no published results (n = 2)
  Trial protocols for published studies (n = 4)

Reports assessed for eligibility
(n = 1)

Reports excluded (n = 0)

Included

Studies included in review
(n = 11)

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.
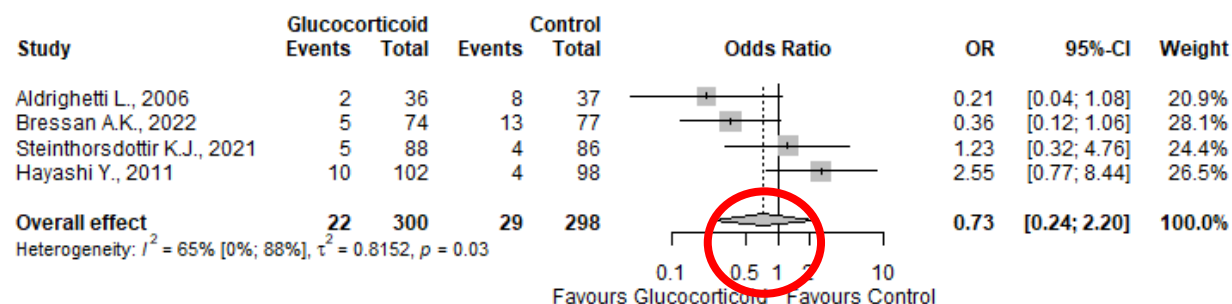
Overall postoperative complication rate

Study	Glucocorticoid Events	Total	Control Events	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., 2022	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., 2003	12	28	7	25		1.93	[0.61; 6.09]	10.7%
Overall effect	**120**	**418**	**149**	**419**		**0.71**	**[0.38; 1.31]**	**100.0%**

Heterogeneity: $I^2 = 54\%$ [2%; 78%], $\tau^2 = 0.3212$, $p = 0.03$

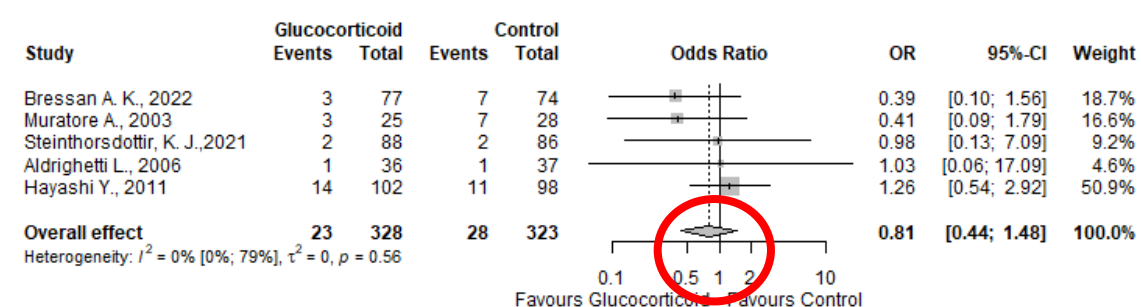Favours Glucocorticoid   Favours Control
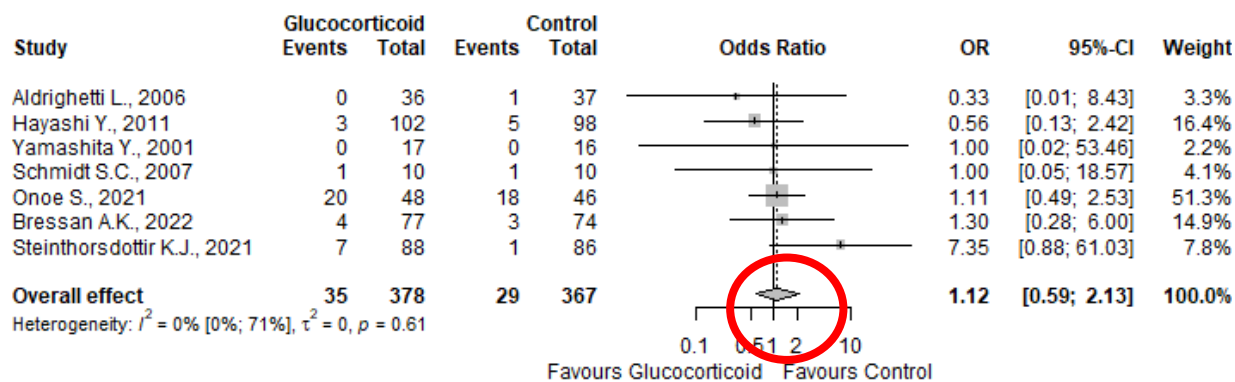
OR = 0.71
p= 0.23

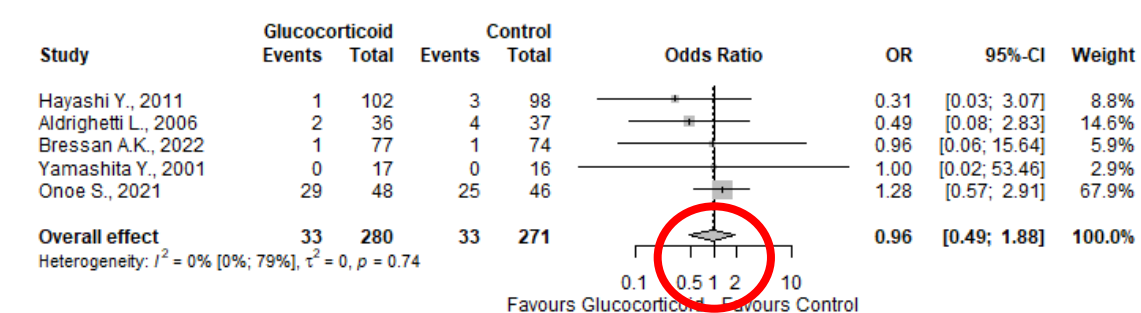# Postoperative complications

Septic/Infectious Complications

Pleural Effusion

Bile Leakage

Liver Failure

Wound Infections

Study	Glucocorticoid Events	Total	Control Events	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., 2022	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	**21**	**378**	**32**	**367**		**0.64**	**[0.45; 0.92]**	**100.0%**

Heterogeneity: I^2 = 0% [0%; 71%], τ^2 = 0, p = 0.95
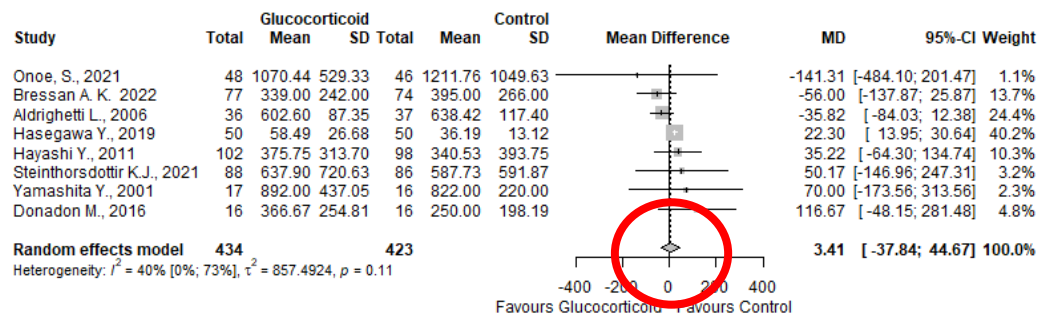
0.01 0.1 1 10 100
Favours Glucocorticoid   Favours Control
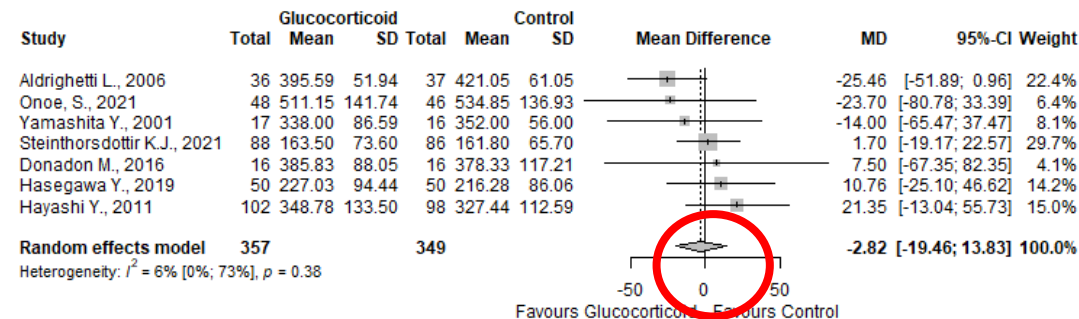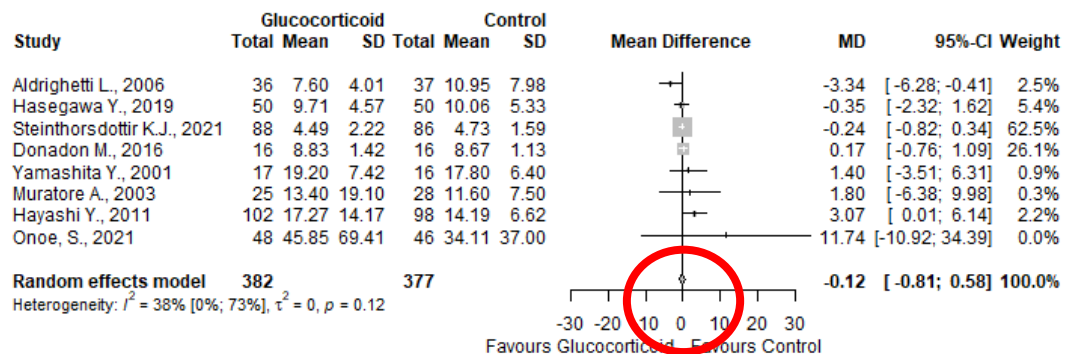
OR = 0.64
p= 0.02

Perioperative outcomes

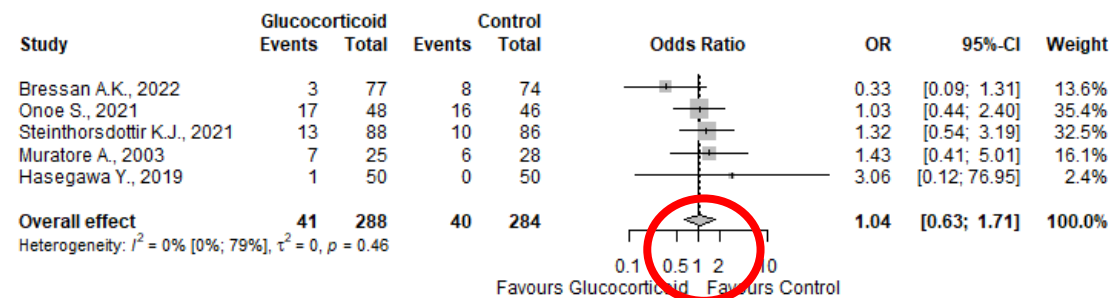## Length of Hospital Stay

Total Operative Time

Blood Loss

Blood Transfusions

Laboratory Outcomes

Article	Study Type	Treatment Used	Treatment Dosage	Patients, control / intervention (#)	Total Bilirubin	ALT	AST	IL-6	CRP	PTT
Onoe, S 2021	RCT	Hydrocortisone	500 mg immediately before hepatic pedicle clamping followed by 300 mg on POD 1, 200 mg on POD 2, and 100 mg on POD 3	46/48	+	+	=		+	=
Steinthorsdottir, K. J. 2021	RCT	Methylprednisolone	10 mg/kg	86/88	+	=				+
Bressan, A. K. 2022	RCT	Methylprednisolone	500 mg IV pre-operatively	74/77	+	=	=			+
Hasegawa, Y. 2019	RCT	Methylprednisolone	500 mg IV pre-operatively	50/50	+				+	+
Donadon, M. 2016	RCT	Methylprednisolone	500 mg pre-operatively	16/16						
Hayashi, Y. 2011	RCT	Hydrocortisone	500 mg immediately before hepatic pedicle clamping followed by 300 mg on POD 1, 200 mg on POD 2, and 100 mg on POD 3	98/102	+	=	=	+	+	+
Yamashita, Y. 2001	RCT	Methylprednisolone	500 mg pre-operatively	16/17	+			+		
Muratore. A. 2003	RCT	Methylprednisolone	30 mg/kg	28/25	=	=	=	+		=
Aldrighetti, L. 2006	RCT	Methylprednisolone	500 mg pre-operatively	36/37	+	+	+	+		+
Schmidt, S.C. 2007	RCT	Methylprednisolone	30 mg/kg	10/10	+	=		+	+	=
Turner, S. 2006	RCT	Methylprednisolone	10 mg/kg	17/17	+					

Legend:
- **+** Significant Improvement
- **=** No Significant Improvement

Overall postoperative complication rate :
Risk of Bias

Study ID	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Yamashita 2001	+	?	+	+	+	!
Muratore 2002	+	+	+	+	+	+
Aldrighetti 2006	+	+	+	+	+	+
Turner 2006	+	+	+	+	+	+
Schmidt 2007	+	+	+	+	+	+
Hayashi 2011	+	+	+	+	+	+
Donadon 2016	+	+	+	+	+	+
Hasegawa 2019	+	+	+	+	+	+
Steinthorsdottir 2021	+	?	+	+	+	!
Onoe 2021	+	+	+	+	+	+
Bressan 2022	+	+	+	+	+	+

+ Low risk
? Some concerns
– High risk

GRADE Assessment

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with preoperative glucocorticoid
Overall postoperative complication rate (PostOp Comp.) assessed with: # (%)	837 (9 RCTs)	⊕⊕⊕◯ Moderate[a]	OR 0.71 (0.38 to 1.31)	370 per 1,000	76 fewer per 1,000 (188 fewer to 65 more)
Septic/Infectious Complications (septic) assessed with: # (%)	598 (4 RCTs)	⊕⊕⊕⊕ High	OR 0.73 (0.24 to 2.20)	97 per 1,000	24 fewer per 1,000 (72 fewer to 94 more)
Wound Infection (wound) assessed with: # (%)	745 (7 RCTs)	⊕⊕⊕⊕ High	OR 0.64 (0.45 to 0.92)	87 per 1,000	30 fewer per 1,000 (46 fewer to 6 fewer)
Bile Leakage (bile) assessed with: # (%)	735 (7 RCTs)	⊕⊕⊕⊕ High	OR 1.10 (0.57 to 2.13)	81 per 1,000	7 more per 1,000 (33 fewer to 77 more)
Pleural Effusion (pleura) assessed with: # (%)	651 (5 RCTs)	⊕⊕⊕⊕ High	OR 0.81 (0.44 to 1.48)	87 per 1,000	15 fewer per 1,000 (47 fewer to 36 more)
All Grades Liver Failure (liver fail) assessed with: # (%)	518 (4 RCTs)	⊕⊕⊕⊕ High	OR 0.96 (0.48 to 1.90)	129 per 1,000	5 fewer per 1,000 (63 fewer to 91 more)
Length of Hospital Stay (LOHS) assessed with: days	759 (8 RCTs)	⊕⊕⊕⊕ High	-	The mean length of Hospital Stay was 0	MD 0.12 lower (0.57 lower to 0.34 higher)
Total Operative Time (op.time.) assessed with: minutes	706 (7 RCTs)	⊕⊕⊕⊕ High	-	The mean total Operative Time was 0	MD 2.82 lower (19.46 lower to 13.83 higher)
Blood Loss (blood loss) assessed with: ml	857 (8 RCTs)	⊕⊕⊕⊕ High	-	The mean blood Loss was 0	MD 3.41 higher (33.33 lower to 40.16 higher)
Blood Transfusion (transfusion) assessed with: # (%)	572 (5 RCTs)	⊕⊕⊕⊕ High	OR 1.04 (0.63 to 1.71)	141 per 1,000	5 more per 1,000 (47 fewer to 78 more)

Conclusion

- Preoperative glucocorticoid administration does not significantly reduce overall complication rate (p=0.23).

- There are no statistically significant differences between particular complications, nor length of hospital stay.

- Level of currently available evidence is insufficient to draw any conclusions regarding the use of glucocorticoids in liver surgery.

Summary

Implication for practice

- Recently made recommendations by reviewers[1] and trialists[2], advocating for the use of glucocorticoids need to be reconsidered in light of new evidence.

Implication for research

- This intervention remains an important field of research considering the high risk of liver surgery and the conflicting results in the literature.

- Based on this systematic review, new clinical trials with robust designs can fill in the gaps of knowledge without repeating the same efforts over and over again.

1. Perioperative steroid administration reduces overall complications in patients undergoing liver resection: A meta-analysis, Hao-Han et al. 2021, *World Journal of Surgery*
2. Preoperative Single-Dose Methylprednisolone Prevents Surgical Site Infections After Major Liver Resection: A Randomized Controlled Trial, Bressan et al., 2022, *Annals of Surgery*

Summary

Strengths

- Only randomized controlled trials were included in the study

- Largest patient pool to date on the subject

- Most broad range of outcomes analyzed on the subject

- Fully compliant with international standards for systematic reviews (Cochrane & EQUATOR Network)

Limitations

- We could not perform subgroup analyses due to poor data availability

- We could not perform meta-analysis on part of our secondary outcomes due to poor data availability

Our methodology in action

Preoperative steroid administration for major liver surgery

Guideline
- **Previous clinical trials**: Conflicting results need quantitative & qualitative synthesis
- **ERAS Guideline:** **Weak** recommendation **Moderate** evidence level

Systematic Review
- **Efficacy** in reducing postoperative complications
- **Feasibility** in clinical practice

## Hemoadsorption therapy for critical illness with acute liver dysfunction

Systematic Review
- **Summary** of evidence
- **Contextualization** of practical experience

Guideline
- Establishing guidance for **clinical practice**
- **Clarification** of further research required

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Background

Critically ill patients may develop liver injury: a deadly condition

Acquired Liver Injury

Acute Hepatic Dysfunction

Acute Hepatic Failure

ICU-acquired Liver Injury

61%   **86%**
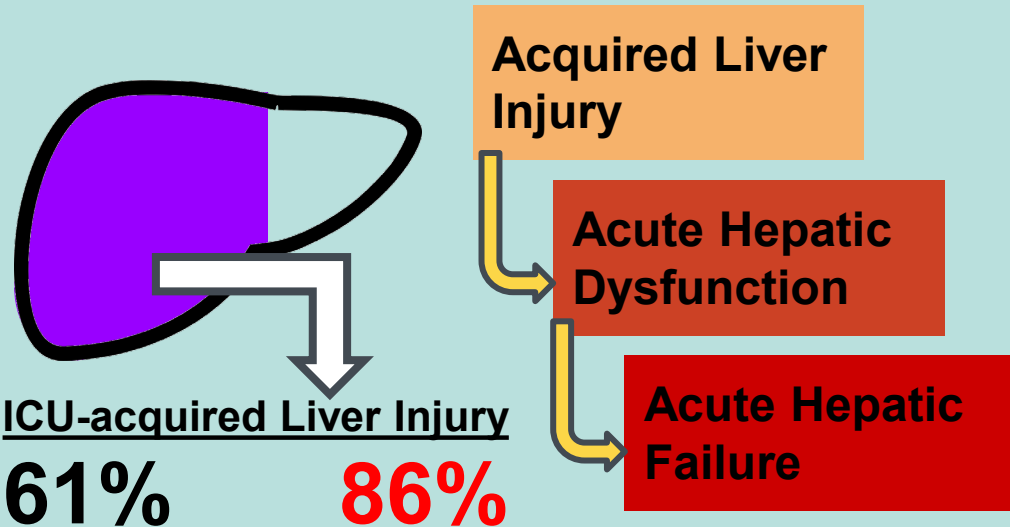
Treatment options

1. **Management of complications**
   a. Metabolic abnormalities
   b. Hepatic encephalopathy
   c. MODS
   d. Hemodynamic management

2. **Bridging to liver transplantation**

3. **Life support**

Hemoadsorption: a novel strategy
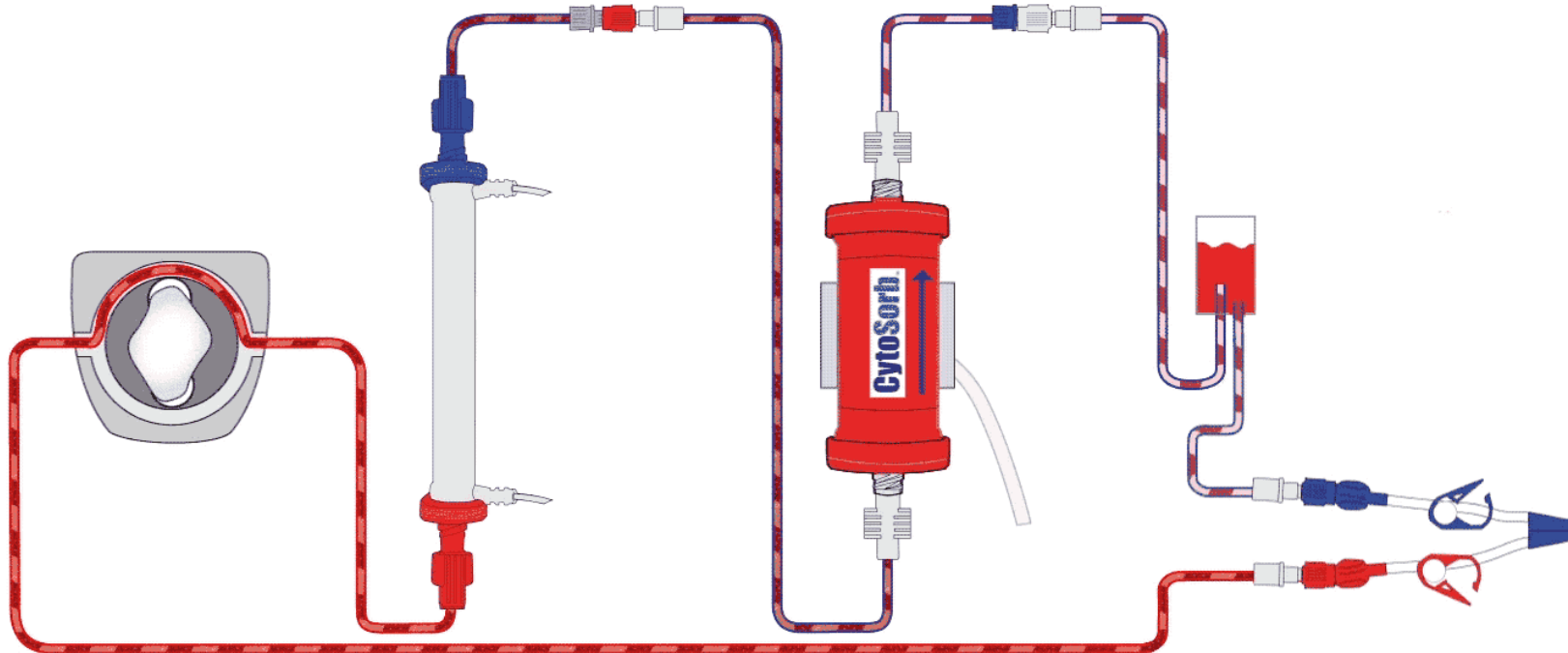
1. Cytokine adsorption

2. Absorption of Inflammatory mediators

3. Reducing bilirubin and other molecules

4. Improvement of liver and kidney functions

    ↓

Bridging to transplant

Research Question

Does hemadsorption therapy effectively reduce the levels of cytokines and liver function related metabolites in critically ill patients with acquired liver injury and lead to better clinical outcomes?

P	Adult critically ill patients with acquired liver injury
I	Hemadsorption therapy
C	Standard care without hemadsorption
O	Primary: mortality; liver function, cytokine levels
	Secondary: bridge to transplantation/recovery, change in vital organ functions, safety outcomes, liver function parameters, length of ICU and hospital stay, mortality

Hypothesis: Hemoadsorption is effective in reducing the circulating cytokines and other inflammatory mediators, improving clinical outcomes
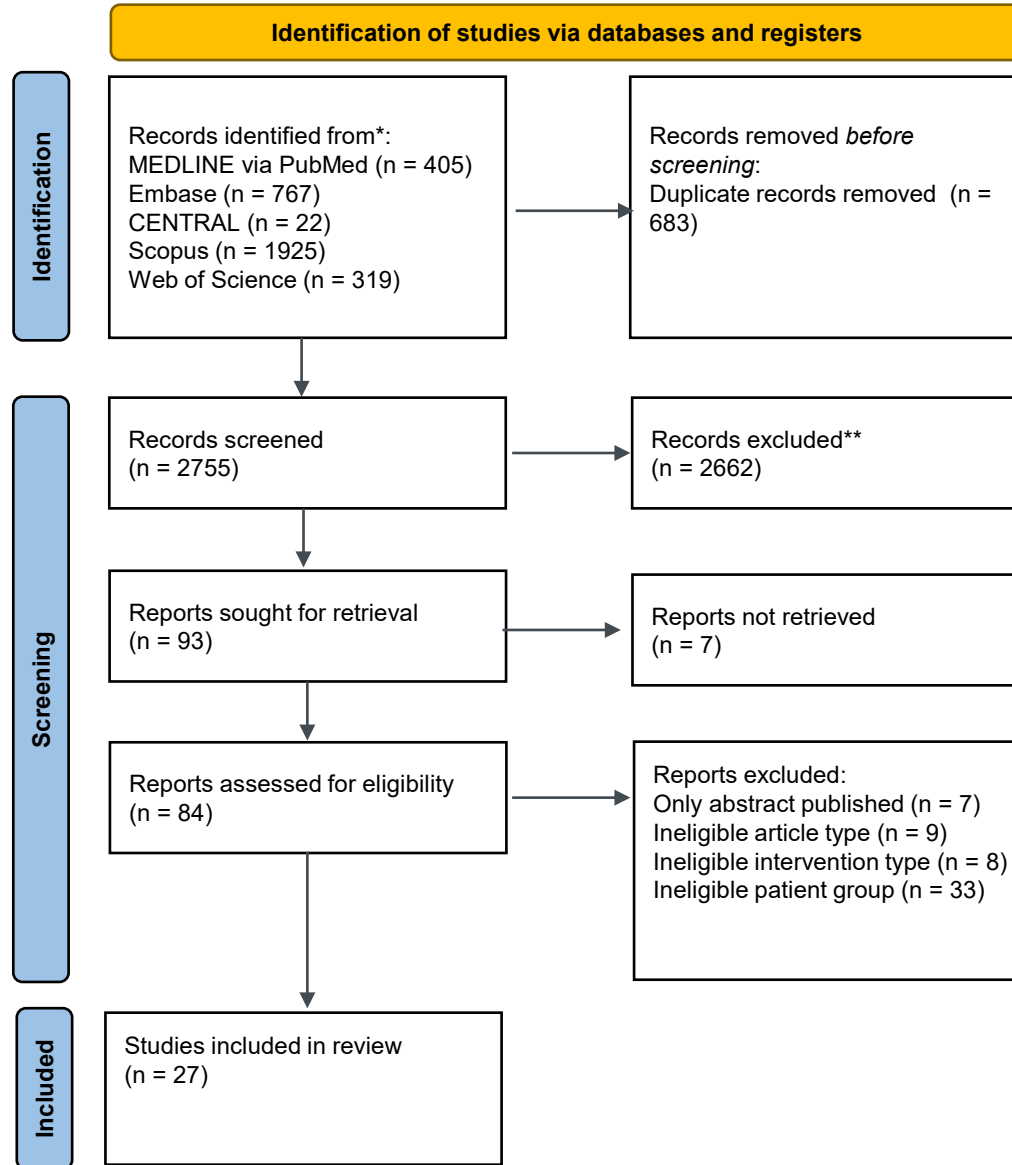
Systematic search

Databases: Medline (**405**), Embase (**767**), Central (**22**), Scopus (**1925**), Web of Science (**319**)

Total search result: 3417

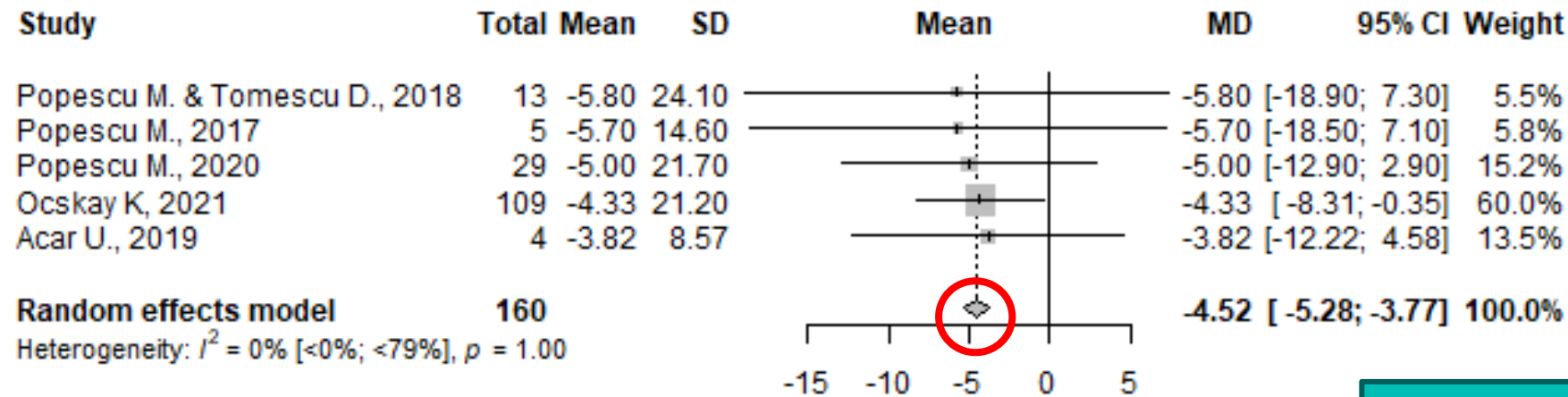**Date of search: November 21 2021**

Searchkey:

(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** liver impairment **OR** "hepatocellular injury" **OR** hepatic insufficiency **OR** hepatic dysfunction **OR** "acquired liver injury" **OR** "hepatic encephalopathy")

Identification of studies via databases and registers

Records identified from*:
MEDLINE via PubMed (n = 405)
Embase (n = 767)
CENTRAL (n = 22)
Scopus (n = 1925)
Web of Science (n = 319)

Records removed *before screening*:
Duplicate records removed (n = 683)

Records screened
(n = 2755)

Records excluded**
(n = 2662)

Reports sought for retrieval
(n = 93)

Reports not retrieved
(n = 7)

Reports assessed for eligibility
(n = 84)

Reports excluded:
Only abstract published (n = 7)
Ineligible article type (n = 9)
Ineligible intervention type (n = 8)
Ineligible patient group (n = 33)

Studies included in review
(n = 27)

Results

Post-treatment Total Bilirubin (mg/dL)
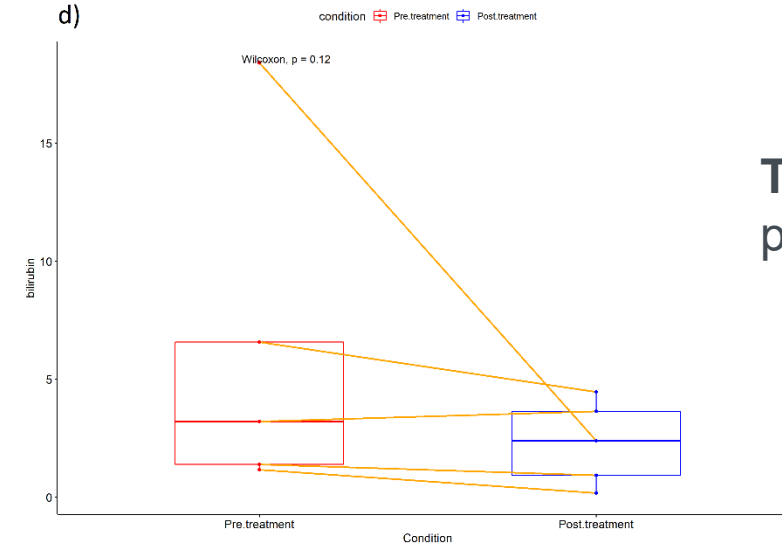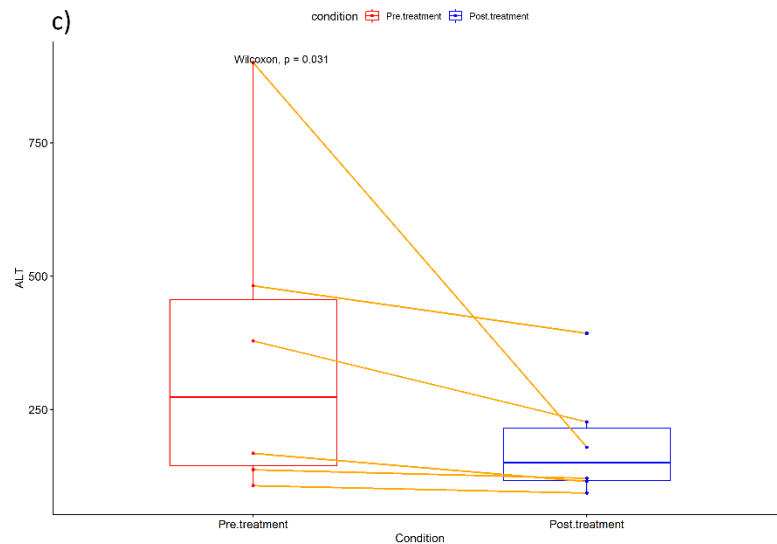

MD = -4.52
p= <.05

Results

Vasopressor Need
p = 0.059
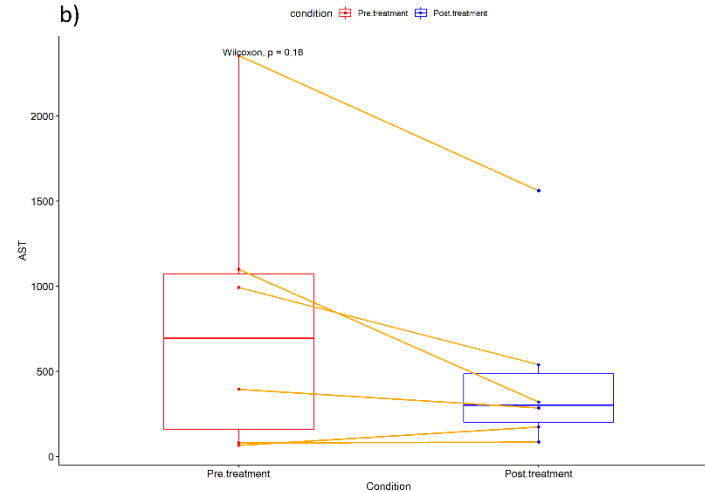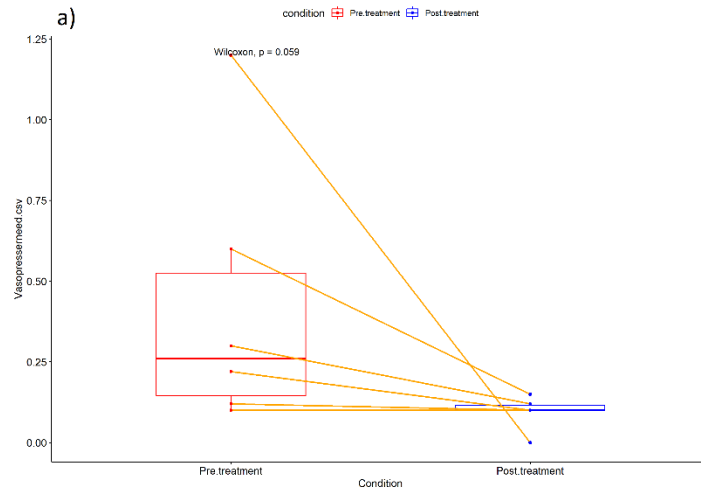
AST
p = 0.16

ALT
p = 0.031

Total Bilirubin
p = 0.12

Conclusion

- Hemoadsorption was safe to use (device related complications)

- The use of hemoadsorption yielded a trend towards improved liver function

- The quality of clinical literature is insufficient in precision and comprehensiveness
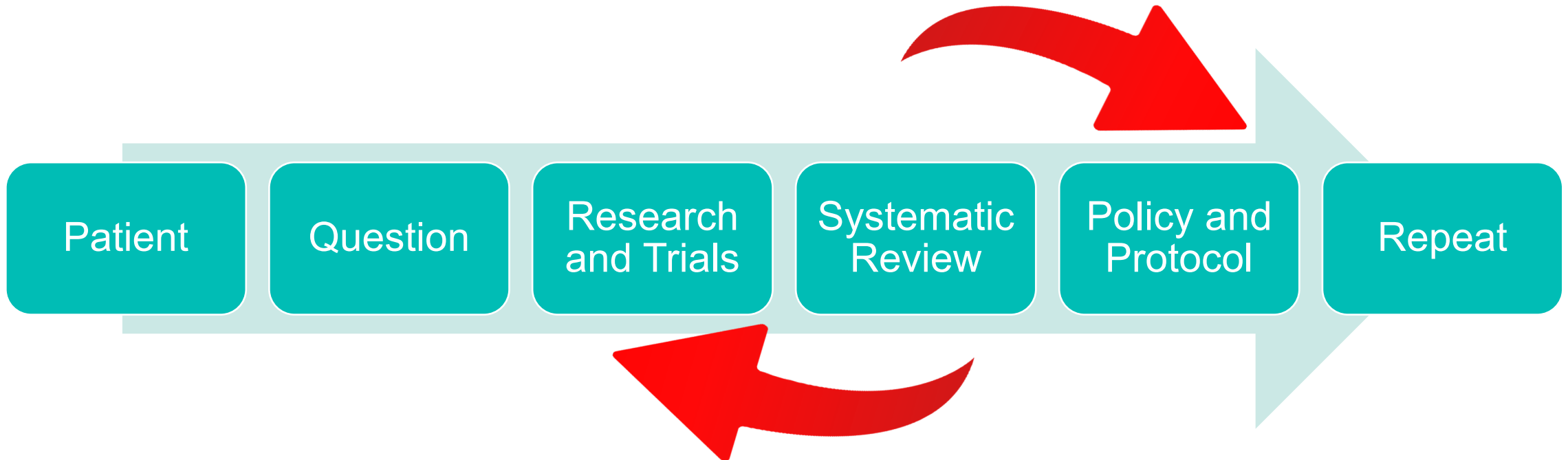
Summary

Implication for practice

- In cases of ICU-acquired liver injury, the use of hemoadsorption therapy is safe and may improve liver function.
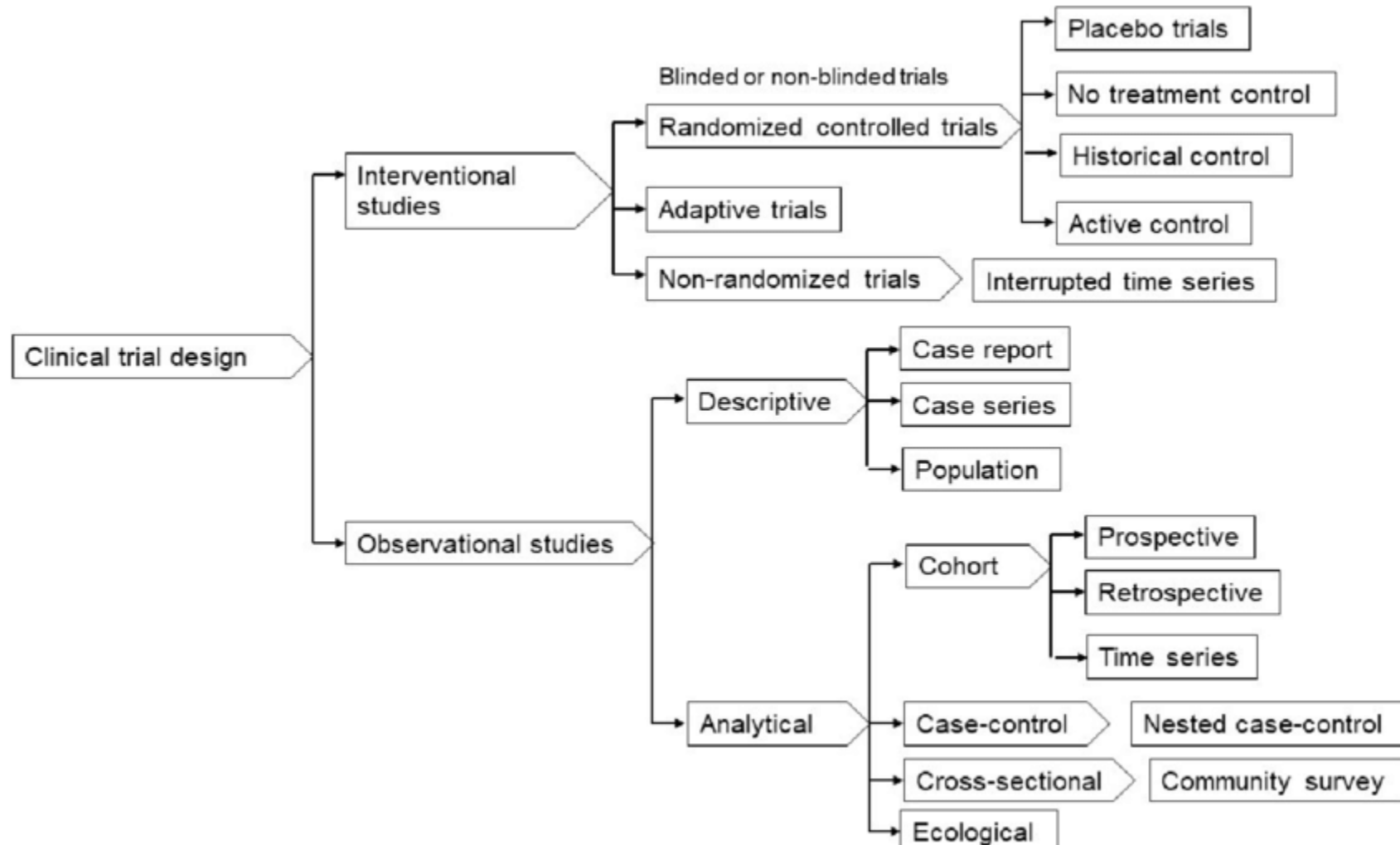
Implication for research

- Our results render the need for adequately designed clinical trials with the parameters investigated in this systematic review as main outcomes.

1. Perioperative steroid administration reduces overall complications in patients undergoing liver resection: A meta-analysis, Hao-Han et al. 2021, *World Journal of Surgery*
2. Preoperative Single-Dose Methylprednisolone Prevents Surgical Site Infections After Major Liver Resection: A Randomized Controlled Trial, Bressan et al., 2022, *Annals of Surgery*

Implications of our work

Patient → Question → Research and Trials → Systematic Review → Policy and Protocol → Repeat
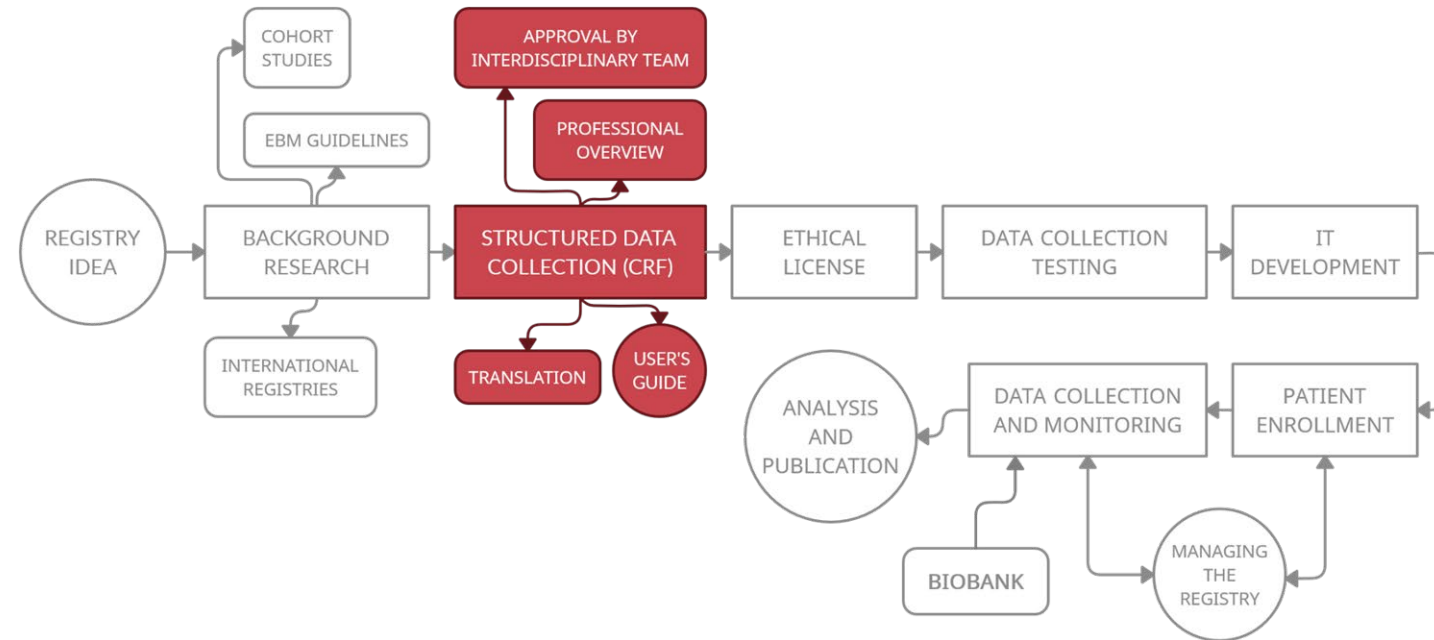
Clinical Trial Design

Registry Design

Case report forms

- Definition
- Design & Structure
- Types of questions and answers

Process up until IT development
- Approval by registry coordinator and interdisciplinary team
- National and international review
- Translation
- Testing before development

Thank you for your attention!