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GLP-1 receptor agonists for organ protection and survival in preclinical models of sepsis: a systematic review and meta-analysis

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Hospital.**ADMINISTRATIVE INFORMATION****Support** - This study received no specific funding.**Review Stage at time of this submission** - Preliminary searches.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100029**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 7 October 2026 and was last updated on 7 October 2026.**INTRODUCTION**

Review question / Objective This review aims to synthesize the effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in animal models of sepsis, with the pooled effect on survival as the primary question, and to examine organ-protective and anti-inflammatory outcomes. The study is being conducted and has not yet been completed; no pooled results are available at the time of registration.

Rationale Sepsis remains a leading cause of death in critical care, and adjunctive treatments that limit inflammation and protect organs are needed. GLP-1RAs have anti-inflammatory, endothelial-protective, and immunomodulatory properties, and a growing number of preclinical studies suggest they improve survival and reduce organ injury in sepsis. The evidence is scattered across heterogeneous models, agents, and dosing schedules and has not been synthesized for

preclinical data alone. This review will quantify the preclinical signal and examine its robustness.

Condition being studied Sepsis and sepsis-induced organ injury in preclinical (animal) models, including live-bacterial infection progressing to systemic sepsis, cecal ligation and puncture, and endotoxemia.

METHODS

Search strategy Four electronic databases were searched: PubMed/MEDLINE, Embase (Ovid), Web of Science Core Collection, and Cochrane CENTRAL, from inception to 19 August 2026, with no animal filter and no date limit. A GLP-1 drug block was combined with a sepsis block using AND. Hyphenation variants, truncation, and toll-like receptor terms were included. Reference lists of included studies and relevant reviews were screened by hand.

PubMed: (#1 drug) "glucagon-like peptide-1"[MeSH] OR "glucagon-like peptide 1

receptor"[MeSH] OR "GLP-1 receptor agonists"[Pharmacological Action] OR GLP-1[tiab] OR GLP1[tiab] OR GLP-1R[tiab] OR GLP-1RA[tiab] OR "glucagon-like peptide-1"[tiab] OR "incretin mimetic"[tiab] OR liraglutide OR semaglutide OR exenatide OR "exendin-4" OR dulaglutide OR tirzepatide OR albiglutide OR lixisenatide OR taspoglutide OR efpeglenatide OR beinaglutide OR retatrutide; (#2 sepsis) "sepsis"[MeSH] OR "shock, septic"[MeSH] OR "endotoxemia"[MeSH] OR "systemic inflammatory response syndrome"[MeSH] OR "bacteremia"[MeSH] OR "lipopolysaccharides"[MeSH] OR "toll-like receptors"[MeSH] OR sepsis[tiab] OR septic[tiab] OR endotoxemia[tiab] OR endotoxin[tiab] OR lipopolysaccharide[tiab] OR LPS[tiab] OR "cecal ligation"[tiab] OR "caecal ligation"[tiab] OR "cecal slurry"[tiab] OR polymicrobial[tiab] OR bacteremia[tiab] OR "toll-like receptor"[tiab]; #3 = #1 AND #2.

Embase, Web of Science (TS=), and Cochrane CENTRAL used the same two concept blocks with database-adapted syntax (Emtree/MeSH, field tags, truncation). Records: PubMed 560, Embase 680, Web of Science 663, Cochrane CENTRAL 63; total 1,966 before de-duplication, 1,064 after.

Embase (Ovid): 1. exp glucagon like peptide 1 receptor agonist/ or exp glucagon like peptide 1/ or exp exenatide/ or exp liraglutide/ or exp semaglutide/ or exp dulaglutide/ or exp tirzepatide/; 2. ("glucagon like peptide 1" or "glucagon-like peptide-1" or GLP-1 or GLP1 or GLP-1R or "incretin mimetic" or exenatide or "exendin-4" or liraglutide or dulaglutide or semaglutide or lixisenatide or albiglutide or taspoglutide or tirzepatide or efpeglenatide or beinaglutide or retatrutide).ti,ab,kw.; 3. 1 or 2; 4. exp sepsis/ or exp septic shock/ or exp endotoxemia/ or exp systemic inflammatory response syndrome/ or exp bacteremia/ or exp lipopolysaccharide/ or exp toll like receptor/; 5. (sepsis or septic* or endotoxemia or endotoxin* or lipopolysaccharide* or LPS or "cecal ligation" or "caecal ligation" or "cecal slurry" or polymicrobial or bacteremia or "toll-like receptor").ti,ab,kw.; 6. 4 or 5; 7. 3 and 6.

Web of Science: TS=(same drug terms as above) AND TS=(same sepsis terms as above).

Cochrane CENTRAL: (#1 same drug terms):ti,ab,kw AND (#2 same sepsis terms):ti,ab,kw.

Participant or population Live-animal models of sepsis or septic organ injury. No restriction on species, strain, sex, or age.

Intervention Systemically administered GLP-1 receptor agonists (for example liraglutide,

semaglutide, dulaglutide, exendin-4, tirzepatide, and engineered formulations), at any dose, route, or timing, provided administration is systemic. Studies using only non-systemic routes (for example intracerebroventricular or intranasal) will be handled separately from the main analysis.

Comparator Concurrent vehicle or placebo control (saline, vehicle, or untreated septic animals).

Study designs to be included Controlled preclinical in vivo studies (for example randomized or non-randomized animal experiments) that compare a systemically administered GLP-1 receptor agonist with a concurrent vehicle or placebo control in an animal model of sepsis and report survival, organ injury, inflammation, or surfactant outcomes. Controlled preclinical in vivo studies comparing a systemically administered GLP-1RA with a concurrent control in an animal model of sepsis, reporting survival, organ injury, inflammation, or surfactant outcomes. Excluded: reviews, editorials, conference abstracts without full text, in vi.

Eligibility criteria Inclusion: full-text available; reported in English; systemic route of administration.

Exclusion: reviews, editorials, and conference abstracts without full text; in vitro-only studies; studies targeting the central nervous system or sepsis-associated encephalopathy (brain, hippocampus, or microglia); studies using only non-systemic routes (for example intracerebroventricular or intranasal); models combining sepsis with a separate comorbidity or injury (for example diabetes, chronic kidney disease, or ischemia-reperfusion); purely mechanistic or receptor-silencing studies with no extractable GLP-1RA versus vehicle organ-protection outcome; and duplicate reports (the most complete report of an overlapping animal cohort is retained, others listed as companion reports).

Information sources PubMed/MEDLINE, Embase, Web of Science Core Collection, and Cochrane CENTRAL, searched from inception to 19 August 2026, with no animal filter and no date limit. A drug block was combined with a sepsis block using AND, including hyphenation variants and toll-like receptor terms. Reference lists were screened by hand.

Main outcome(s) Animal death (survival). Events are defined as death; an odds ratio below 1 indicates protection by the GLP-1RA.

Additional outcome(s) Organ injury (for example histological lung injury score, lung wet-to-dry weight ratio), inflammatory markers (TNF-alpha, IL-6, IL-2), microvascular leak and thrombosis, oxidative stress, and pulmonary surfactant protein (SP-A, SP-B) expression and secretion.

Data management Records retrieved from all databases were imported into Rayyan for de-duplication and screening. Two reviewers independently screened titles, abstracts, and full texts, with disagreements resolved by consensus. Data were extracted into a standardized spreadsheet form and cross-checked by two reviewers. Risk-of-bias assessments and analysis datasets are maintained in separate files for synthesis in Review Manager.

Quality assessment / Risk of bias analysis The methodological quality of included studies will be assessed independently by two reviewers using the SYRCLE risk-of-bias tool for animal studies (ten domains), with disagreements resolved by consensus, and displayed with robvis.

Strategy of data synthesis Dichotomous outcomes (survival) will be pooled as odds ratios using a Mantel-Haenszel random-effects model. Heterogeneity will be assessed with the I-squared statistic. Prespecified sensitivity analyses and subgroup analysis by timing of administration (therapeutic versus prophylactic dosing) will be performed. Publication bias will be examined only if the number of studies reporting the primary outcome is sufficient. Analyses will be conducted in Review Manager (RevMan 5.4).

Subgroup analysis Subgroup analysis by timing of administration (therapeutic, post-insult versus prophylactic, pre-insult). Further subgroups (sepsis model, GLP-1RA class) will be explored where the number of studies permits.

Sensitivity analysis Sensitivity analyses will exclude the single prophylactic study and any high-leverage study whose control group experiences complete mortality, to test the stability of the pooled estimate.

Language restriction English only.

Country(ies) involved Taiwan (primary institution).

Other relevant information The findings will be submitted to a peer-reviewed journal.

Keywords glucagon-like peptide-1; GLP-1 receptor agonist; sepsis; acute lung injury; survival; organ protection; preclinical; meta-analysis.

Dissemination plans The findings will be submitted for publication in a peer-reviewed journal and may be presented at relevant scientific conferences.

Contributions of each author

Author 1 - Sai-Wai Ho - conceived and designed the review, developed the search strategy, and drafted the manuscript.

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Author 2 - Yu-Tzu Li - performed the literature screening, data extraction, risk-of-bias assessment, and statistical analyses, and drafted the manuscript.

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