International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Plasma fibrinogen level and mortality in adults with sepsis: a protocol for a systematic review and meta-analysis with threshold synthesis

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 September 2026 and was last updated on 21 September 2026.

INTRODUCTION

Review question / Objective In adults with sepsis, is a low plasma fibrinogen level associated with higher all-cause mortality, and at what level does the risk of death begin to rise? Secondary objectives are to synthesise change points reported by non-linear models, and to assess the association at the upper end of the fibrinogen distribution.

Rationale Plasma fibrinogen is measured in almost every patient with sepsis, but the direction of its association with mortality is disputed and no threshold has been agreed. Available reviews have pooled fibrinogen as a single linear exposure contrast and none has synthesised the change points reported by non-linear models. This review addresses both gaps.

Condition being studied Sepsis and septic shock as defined by the authors of each included study (most used Sepsis-3), and sepsis-associated coagulopathy or disseminated intravascular coagulation where reported. Plasma fibrinogen is the prognostic factor of interest.

METHODS

Search strategy Databases: PubMed/MEDLINE (searched 13 September 2026; 1,077 records); Web of Science Core Collection (11 September 2026; 504); Cochrane Library (12 September 2026; 155); CNKI (12 September 2026; 155); Wanfang (13

September 2026; 814). Coverage from inception; no language restriction.

PubMed/MEDLINE:

(sepsis[MeSH Terms] OR "shock, septic"[MeSH Terms] OR sepsis[tiab] OR "septic shock"[tiab] OR septic[tiab] OR "sepsis-associated coagulopathy"[tiab] OR "sepsis-induced coagulopathy"[tiab] OR "disseminated intravascular coagulation"[tiab] OR DIC[tiab]) AND (fibrinogen[MeSH Terms] OR fibrinogen[tiab] OR hypofibrinogenemia[tiab] OR hypofibrinogenaemia[tiab] OR "plasma fibrinogen"[tiab] OR "fibrinogen level"[tiab]) AND (mortality[tiab] OR death[tiab] OR prognosis[tiab] OR survival[tiab] OR outcome[tiab] OR threshold[tiab] OR cutoff[tiab] OR "cut-off"[tiab] OR nonlinear[tiab] OR "non-linear"[tiab] OR "restricted cubic spline"[tiab] OR "inflection point"[tiab] OR "dose-response"[tiab]) NOT (animals[MeSH Terms] NOT humans[MeSH Terms])

Web of Science Core Collection:

TS=(sepsis OR "septic shock" OR "disseminated intravascular coagulation" OR "sepsis-associated coagulopathy" OR "sepsis-induced coagulopathy") AND TS=(fibrinogen OR hypofibrinogenemia OR "plasma fibrinogen" OR "fibrinogen level") AND TS=(mortality OR death OR survival OR prognosis OR outcome OR "dose-response" OR threshold OR nonlinear OR "cubic spline" OR cutoff)

Cochrane Library:

(sepsis OR septic*) AND (fibrinogen) AND (mortality OR survival OR outcome)

CNKI:

主题:(脓毒症 + 脓毒性休克 + 感染性休克 + 弥散性血管内凝血 + DIC) AND 主题:(纤维蛋白原 + FIB + 纤维蛋白原水平 + 低纤维蛋白原血症) AND 主题:(死亡 + 预后 + 生存 + 阈值 + 剂量反应 + 非线性 + 拐点 + 截断值)

Wanfang:

主题:(脓毒症 OR 脓毒性休克 OR 感染性休克 OR 弥散性血管内凝血) AND 主题:(纤维蛋白原 OR FIB) AND 主题:(死亡 OR 预后 OR 生存 OR 阈值 OR 非线性 OR 拐点)

Note. The PubMed strategy was revised on 13 September 2026 to align the concept blocks across databases; the original strategy (605 records) did not include terms for disseminated intravascular coagulation or for threshold-type outcomes. The aligned strategy returned 1,077 records and superseded the original.PubMed/MEDLINE; Web of Science Core Collection; Cochrane Library; CNKI; Wanfang. Full strings are reproducible and are held by the authors; the concept blocks were: (sepsis OR septic shock OR disseminated intravascular coagulation OR sepsis-associated coagulopathy) AND (fibrinogen OR hypofibrinogenaemia OR plasma fibrinogen) AND (mortality OR death OR prognosis OR survival OR threshold OR cut-off OR non-linear OR restricted cubic spline OR inflection point OR dose-response). Chinese-language strings were used for CNKI and Wanfang. No language or date restriction was applied; coverage was from inception to 13 September 2026.

Participant or population Adults aged 18 years or older with sepsis or septic shock, in any setting (intensive care unit, emergency department or hospital ward). Studies restricted to children, neonates or obstetric populations were excluded.

Intervention Plasma fibrinogen, analysed both as a categorical exposure (a low-fibrinogen group against a reference group) and as a continuous exposure (per 1 g/L decrease). Fibrinogen-based ratio indices reported by included studies (albumin-to-fibrinogen ratio, fibrinogen-to-albumin ratio, fibrinogen-to-prealbumin ratio, fibrinogen-to-C-reactive-protein ratio) were analysed separately because they are not on a common scale. Studies in which fibrinogen was reported only as a within-patient change over time were treated as trajectory studies and contributed to the narrative synthesis rather than to the pooled estimates.

Comparator For the categorical analysis, the higher-fibrinogen or reference group defined by each study; for the continuous analysis, the estimate expresses the change in risk per 1 g/L decrease in fibrinogen.

Study designs to be included Observational studies: retrospective and prospective cohort studies, case-control studies and cross-sectional studies. Interventional studies were excluded.

Eligibility criteria Included: observational studies of adults with sepsis or septic shock that measured plasma fibrinogen and reported all-cause mortality (or a composite outcome including death). Excluded: paediatric, neonatal and obstetric populations; studies in which fibrinogen was not a study variable; studies reporting an

outcome other than death; interventional studies; duplicate reports of the same cohort (the most complete report was retained).

Information sources PubMed/MEDLINE, Web of Science Core Collection, Cochrane Library, CNKI and Wanfang, from inception to 13 September 2026. Embase was not searched because it was not available through the institution's subscription; this is stated as a limitation. Reference lists of included studies and of relevant reviews were also checked.

Main outcome(s) All-cause mortality as defined by each study: in-hospital, 28-day, 30-day or 90-day mortality. Where more than one time point was reported, the time point closest to 28 days was used for the primary analysis and the others in sensitivity analyses.

Additional outcome(s) Change points (thresholds) reported by non-linear models, including restricted cubic splines, generalised additive models, two-piecewise linear regression and group-based trajectory modelling; and mean fibrinogen concentrations in survivors and non-survivors.

Data management Records were deduplicated, then screened in two stages: a bulk review of titles and abstracts, and manual screening of the remaining records against the eligibility criteria. Screening of titles and abstracts, full-text assessment and data extraction were performed by two authors (CW and CX); a third author (YZ) independently verified the extracted values against the source publications. Disagreements were resolved by discussion among the authors. Data were extracted into a standardised form covering study identifiers, design, population, sample size, sepsis definition, fibrinogen assay, cut-off or exposure increment, outcome definition, effect measure with 95% confidence interval, and adjustment variables.

Quality assessment / Risk of bias analysis Risk of bias was assessed within the GRADE framework for prognostic factor reviews rather than with a composite per-study instrument. For every included study we recorded design, whether the estimate was adjusted and for which covariates, outcome ascertainment, and whether the cut-off and outcome window were pre-specified or derived from the data. Certainty of evidence was rated with GRADE; the primary analysis was rated very low.

Strategy of data synthesis Random-effects models (DerSimonian–Laird) with the Knapp–Hartung adjustment because the number of studies was small; ratios log-transformed and pooled with inverse-variance weights. Hazard ratios and odds ratios were pooled together, treating the odds ratio as an approximation of the relative risk, and the analysis was repeated within each effect-measure type. Heterogeneity was quantified with the Q statistic, I^2 and τ^2, and 95% prediction intervals were computed. Estimates reported per unit increase were inverted so that all values express the risk associated with a lower fibrinogen level; studies whose exposure increment could not be established were not pooled and contributed to the threshold analysis instead. Ratio indices were harmonised for direction and pooled only within the same unit. For studies reporting means and standard deviations by survival status, the raw mean difference and the standardised mean difference (Hedges' g) were pooled separately; both are reported as exploratory because they compare group means and are vulnerable to confounding by illness severity. Change points from non-linear models were summarised descriptively (median and range) and were not pooled; cut-offs derived from ROC curves were kept separate because they optimise classification accuracy rather than identify a threshold.

Subgroup analysis Subgroups were population (sepsis, septic shock, sepsis-associated acute kidney injury), geographic region, outcome time point, and whether the estimate was adjusted. Because the review was registered retrospectively, these subgroup analyses are reported as exploratory rather than pre-specified.

Sensitivity analysis Leave-one-out analysis; exclusion of the unadjusted study; restriction to adjusted estimates; and restriction to a single effect-measure type (hazard ratios only, odds ratios only) with and without the study reporting the opposite association.

Language restriction No language restriction was applied to eligible studies. Searches were run in English and in Chinese; the Chinese search strings are retained in their original language for reproducibility.

Country(ies) involved China (the review team's country).

Other relevant information Retrospective registration. The searches were run and the screening, extraction and analyses were completed before this registration. PROSPERO, the registry normally used for systematic reviews,

could not be used because at that time it accepted only intervention reviews and listed prognostic reviews as “Coming soon”. Methodological decisions that were taken after the study results were known, and are therefore reported as post hoc in the final article, were: (i) presenting the categorical low-fibrinogen comparison as a co-primary analysis alongside the continuous analysis after the continuous analysis showed substantial heterogeneity; (ii) keeping the analysis at the upper end of the distribution separate rather than combining it, because the contributing studies disagreed; (iii) reporting the comparison of group means in the supplementary material because it is vulnerable to confounding by illness severity.

Keywords sepsis; fibrinogen; coagulopathy; mortality; threshold; systematic review; meta-analysis.

Dissemination plans The completed review will be submitted as a Systematic Review to Frontiers in Medicine (Intensive Care Medicine and Anesthesiology section). Extracted data, analysis code, supplementary tables and the completed PRISMA 2020 checklist will be provided with the submission; the protocol DOI will be cited in the article and any deviations reported.

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