Study Protocol
version 1.0
Jun 14th, 2022

Title: Diagnostic accuracy of Focused Cardiac ultrasonography for cause of circulatory failure: A systematic review and meta-analysis

Registration information:
Pre-registration site: University Hospital Medical Information Network (UMIN)

Purpose:
Recently, diagnosis using point of care ultrasound (POCUS) has become widespread everywhere. Early diagnosis of the cause of circulatory failure (shock, hypotension, etc.) may allow early intervention and contribute to improving patient outcomes. However, its overall diagnostic accuracy remains unknown.

Methods:
We perform a systematic review and meta-analysis of studies on diagnostic test accuracy (DTA). We adhere to the methodological standards outlined in the Handbook for DTA Reviews of Cochrane and used the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (i.e., PRISMA-DTA) in reporting our findings.

Study eligibility and selection
We will include all studies including prospective, retrospective, and observational (cohort or cross-sectional) studies and secondary analyses of randomized controlled trial data, restricted to the adult human population (ie, ≥18 years old). We will exclude diagnostic case-control studies (two-gate study) and case studies that lacked DTA data, namely, true-positive (TP), false-positive (FP), true-negative (TN), and FN values. Two authors independently will screen each study for eligibility and extract the data. Disagreements among reviewers will be resolved via discussions or by the third reviewer. Excluded studies (with reasons) will be listed in the supplementary file.

Index test

The index test of interest is point-of-care ultrasound including echocardiography for evaluating the cause of circulatory failure, which is performed by physicians in real-time anywhere to distinguish it from consultative ultrasound.

Reference standard

Reference standard in our study is defined as diagnostic results made at a different location or at a different time than the diagnosis made by POCUS. Because there is no single test to identify the cause of circulatory failure, reviewers will accept a reference standard of chart review or blinded expert opinion/consensus.

Target population

The target population to be diagnosed is defined as adult patients with circulatory failure for which the cause has not been identified. The definition of circulatory failure is based on the criteria defined in each study.

Databased searched

To identify all eligible studies, we will search the Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and Web of Science. We will conduct further surveillance searches using the related articles feature. In addition, we will search the following pre-registration sites: the Clinicaltrial.gov, the European Union Clinical Trials Register (EU-CTR), the WHO International Clinical Trials Registry Platform (ICTRP), and the University Hospital Medical Information Network Clinical Trials Registry (UMIN).

Date of search

We plan to search these databases at June 15th, 2022. Two authors will independently scan the titles and abstracts of reports identified by the variety of search strategies described above. If eligibility cannot be determined from the title or abstract, the full paper is retrieved. Potentially relevant studies, chosen by at least one author, are retrieved and evaluated in full-text versions. The articles that meet the inclusion criteria are assessed separately by two authors, and any discrepancies are resolved through discussion.

Data extraction and quality assessment

The following data will be extracted by pre-defined data extraction form: study characteristics (author, year of publication, country, design, sample size, clinical settings, conflict of interest, and funding source), patient characteristics (inclusion/exclusion criteria and patient clinical and demographic characteristics), index test (timing of diagnosis, protocol of ultrasound, and the person who conducted the test), reference standard (timing of diagnosis, information referred for diagnosis, and the person who conducted the diagnosis), and diagnostic accuracy parameters (TP, FP, FN, and TN). Two investigators will evaluate the risk of bias by using the QUADAS-2 tool, which includes four risks of bias domains and three domains of applicability. Any disagreements will be resolved via discussions or by the third reviewer. Assessment findings will be presented using the traffic light plot and summary plot. Given the absence of evidence for publication bias in DTA studies and the lack of reliable methods for its assessment, we will not perform a statistical evaluation of publication bias.

Statistical analysis and data synthesis

The Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy methodology will be applied. Study diagnostic sensitivity and specificity estimates with 95% confidence intervals (CIs) will be captured in paired forest plots to inspect the between-study variance. We apply the bivariate random-effects meta-analysis to pool the sensitivity and specificity and obtain summary point estimates and 95% confidence interval. To be able to pool data we require three or more studies for each threshold. Summary estimates of test accuracy are plotted in the ROC space together with the summary ROC curve and 95% confidence region. All statistical analyses will be conducted with a two-sided alpha error of 5%. All analyses will be performed using R statistical software package (R Foundation for Statistical Computing, Vienna, Austria).

Investigations of heterogeneity

Heterogeneity will be assessed by the visual insight of the forest plot or using the I2 statistical method for diagnostic odds ratio, with I2 > 50% or p-value < 0.05 indicating significant heterogeneity. We will perform subgroup analysis if the following data are available: suspected disease before the ultrasound, presence of ultrasound other than echocardiography, settings in which the

ultrasound was performed, and training program for point-of-care ultrasound.

Sensitivity analysis

We will assess for robustness by excluding studies with a high risk of bias.