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Association of frailty status with adverse clinical outcomes in patients with COVID-19: protocol for a systematic review and dose–response meta-analysis

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ABSTRACT

Introduction Frailty status has been recognised as an important prognostic factor of adverse clinical outcomes in various clinical settings. Recently, the role of frailty status in adverse clinical outcomes for COVID-19-infected patients has received increasing attention with controversial results. Hence, we will conduct a comprehensive dose–response meta-analysis to quantitatively evaluate the association between frailty status and adverse clinical outcomes in patients with COVID-19.

Methods The researchers will systematically search PubMed, EMBase, Cochrane Library, ISI Knowledge via Web of Science and MedRxiv or BioRxiv databases (from inception until December 2020) to identify all retrospective and prospective cohort studies. All-cause mortality during hospitalisation will be set as the primary outcome. Univariable or multivariable meta-regression and subgroup analyses will be conducted for the comparison between frail versus non-frail categories. Sensitivity analyses will be used to assess the robustness of our results by removing each included study one at a time to obtain and evaluate the remaining overall estimates of all-cause mortality. To conduct a dose–response meta-analysis for the potential linear or restricted cubic spline regression relationship between frailty status and all-cause mortality, studies with three or more categories will be included.

Ethics and dissemination In accordance with the Institutional Review Board/Independent Ethics Committee of the First Affiliated Hospital of Baotou Medical College, ethical approval is not an essential element for the systematic review protocol. This meta-analysis will be disseminated through publication in a peer-reviewed journal.

PROSPERO registration number CRD42020220226.

Strengths and limitations of this study

- A comprehensive linear or non-linear dose–response analysis between different frail levels and adverse clinical outcomes in patients with COVID-19 will be conducted.
- Sensitivity analyses will be performed to assess the robustness of the association of frailty with all-cause mortality or major adverse cardiovascular event.
- Some frailty scales may not report the different categories (>2) of frailty scores, resulting in insufficient data for dose–response analysis.
- This work could not exclude the potential influence of different frailty scales (Clinical Frailty Scale, Frail Index, FRAIL Scale and Hospital Frailty Risk Score) on frailty in the included studies.
- This work may be biased by the different study designs (retrospective or prospective) for the various frailty scales.

INTRODUCTION

Frailty status is a clinical syndrome with reduced physical activity, decreased physiological response and decreased cognitive function. The clinical significance of frailty has received increasing attention since 2012.[1] The prevalence of in-hospital frailty varies from 15% to 40%,[2] resulting in increased vulnerability to adverse clinical outcomes. Although frailty is more common in older populations, frailty and ageing do not always coexist. Compared to age-matched non-frail patients, frail patients are more susceptible to high morbidity and mortality,[3 4] and even in a dose–response manner.[1] A study also showed that the relationship between frailty status and clinical outcomes in elective cardiac surgery is independent of age.[5] Therefore, frailty is another potentially important factor with prognostic relevance in clinical settings.

Various screening tools, such as the Clinical Frailty Scale (CFS), FRAIL Scale, Frail Index (FI) or Hospital Frailty Risk Score (HFRS), have been used to identify and quantify frailty status.[6–9] Frailty is increasingly recognised as an independent risk factor for adverse clinical outcomes in various cardiovascular clinical practices, such as cardiac surgery, non-cardiac surgery, acute coronary syndrome and chronic heart failure.[10–12]

By 31 October 2020, COVID-19 pandemic had caused 46 501 423 infections and 1 202 031 deaths worldwide in 215 countries.[13] Various risk factors have been indicated for

high mortality including age, hypertension, sex, race and diabetes.[14 15] Recently, the role of frailty status in mortality for COVID-19-infected patients has received growing attention with controversial results.[16–19] Some studies also focused on mortality in different categories (>2) of frailty extent.[18–22] Maltese *et al*[23] performed a related systematic review including only 6 retrospective or prospective trials, 13 editorials, 15 guidelines and 2 case reports; however, no quantitative meta-analysis concerning this important issue has been performed due to the limited data. Hence, we will conduct a meta-analysis with all retrospective and prospective studies to quantitatively evaluate the association between frailty status and adverse clinical outcomes for different frailty scoring systems in patients with COVID-19. Moreover, a comprehensive dose–response analysis for different levels of frailty status will also be performed.

Objectives

This systematic review and meta-analysis will explore the potential dose–response relationship between frailty status and adverse clinical outcomes in patients with COVID-19.

METHODS AND ANALYSIS

Search strategy

This meta-analysis will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guideline.[24] We will search PubMed, EMBase, Cochrane Library, ISI Knowledge via Web of Science and MedRxiv or BioRxiv databases (from inception until December 2020), and the reference lists of the retrieved articles. Table 1 shows the related searching keywords. Figure 1 presents the searching process.

Table 1 Search strategy for PubMed, EMBase, Cochrane Library, ISI Knowledge via Web of Science and MedRxiv or BioRxiv databases

Database	Search items
PubMed	
No.	
# 1	((frail) OR (frailed)) OR (frailty)
# 2	(COVID-19) OR (SARS-CoV-2)
# 3	# 1 and # 2
EMBase	
# 1	frail OR (frailed) OR frailty
# 2	'COVID-19 19' OR 'sars cov 2'
# 3	# 1 and # 2
Cochrane Library	
# 1	frail in All Text OR frailed in All Text OR frailty in All Text
# 2	COVID-19 in All Text OR SARS-CoV-2 in All Text
# 3	# 1 and # 2
ISI Knowledge via Web of Science	
# 1	TOPIC: (frail) OR TOPIC: (frailed) OR TOPIC: (frailty) Timespan: All years. Databases: WOS, BIOSIS, KJD, MEDLINE, RSCI, SCIELO. Search language=Auto
# 2	TOPIC: (COVID-19) OR TOPIC: (SARS-CoV-2) Timespan: All years. Databases: WOS, BIOSIS, KJD, MEDLINE, RSCI, SCIELO. Search language=Auto
# 3	# 1 and # 2
MedRxiv or BioRxiv	
# 1	((frail) OR (frailed)) OR (frailty)
# 2	(COVID-19) OR (SARS-CoV-2)
# 3	# 1 and # 2

Type of participants

Adult patients (age ≥18 years) with COVID-19 infection will be included during hospitalisation.

Patient and public involvement

Patients and/or the public will be not involved in the design, conduct, reporting or dissemination plans of this research.

Type of studies

We will include both retrospective and prospective cohort studies with patients with COVID-19 that have reported the associations of frailty status with the incidence of major adverse clinical outcomes. English-published articles will only be selected. Studies that failed to extract OR or HR and the corresponding 95% CIs for the outcomes of interest will be excluded.

Type of outcomes

The primary outcome will be all-cause mortality during hospitalisation. The second outcome will include major adverse cardiovascular events (MACEs). MACE is a combined endpoint during hospitalisation including all-cause death, myocardial infarction, congestive heart failure, acute renal failure, pulmonary embolism or stroke.

Data extraction

Two independent authors (YW and XZ) will extract the data. A third author (WL) will resolve the disagreements. The extracted data included study design (author, publication year, country, sample size, percentage of frailty status, retrospective or prospective), patient's characteristics (mean age, male proportion, diabetes proportion, hypertension proportion, hyperlipidaemia proportion, smoking proportion, coronary artery disease proportion, previous myocardial infarction, chronic heart failure, atrial fibrillation, history of peripheral vascular disease, history of stroke or transient ischaemic accident, kidney dysfunction, history of lung disease, beta-blocker usage, statin usage, ACE inhibitor/angiotensin receptor blocker

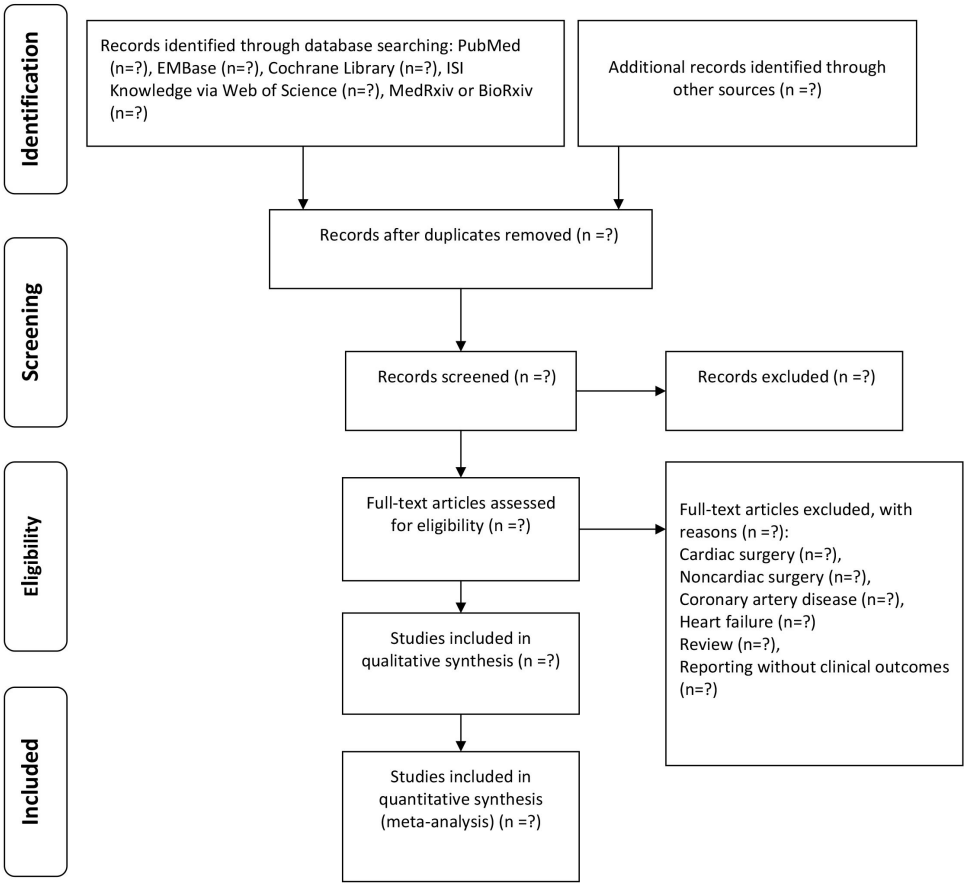

Figure 1 Flow chart of the trial searching process.

usage, calcium channel blocker usage, aspirin usage), follow-up period, frailty scale (CFS, FRAIL Scale, FI or HFRS), cut-off value of frailty scale for definition (CFS >4, FRAIL ≥1, FI >0.2, HFRS ≥5) and the different categories for frailty score.

Risk of bias assessment

The methodological quality of the non-randomised studies will be evaluated in accordance with the Newcastle-Ottawa Quality Assessment Scale[25]: cohort selection (0–4), comparability of the groups (0–2) and quality of the outcomes (0–3). Studies with a score of >7 will be considered high-quality. Moreover, we will also refer to the related parts in *Cochrane handbook* for non-randomised studies before pooling the results.

The quality assessment of randomised controlled trials will be completed using the Cochrane risk of bias tool: randomisation, allocation concealment, blinding, withdrawals and dropouts, and intention-to-treat analysis. We will also list the following items for each study according to National Institute for Healthand Care Excellence(NICE) guideline[26]: inconsistency, indirectness, imprecision, sensitivity, specificity and pooled C-statistic.

Data synthesis

The ORs or HRs and 95% CI in each study will be extracted or calculated from the frailty versus non-frailty categories for the pooled analysis. If necessary, the HR will be calculated using the data from the log-rank test or the Kaplan-Meier survival curve.[27] For the adjusted analysis, the pooled ORs or HRs should have approximately similar covariates. The reference category will be set at the lowest frailty score. The DerSimonian and Laird random-effects model will be used in the pooled analysis for potential clinical inconsistency. Univariable or multivariable meta-regression and subgroup analyses will be conducted for the comparison between frailty versus non-frailty categories including study design and patient's characteristics to explore the potential sources of likely heterogeneity.[28] For multivariable analysis, the data extracted will be from main effect analyses without an interaction. Sensitivity analyses will be used to assess the robustness of our results by removing each included study at one time to obtain and evaluate the remaining overall estimates of all-cause mortality or MACE. Publication bias assessment will be performed by Begg's and Egger's tests. If one study reports multiple categories (>2 categories), we will use the number of events and the total in all of the frailty categories and referent one to calculate the OR for the high versus low analysis. To conduct a dose–response meta-analysis for the potential linear or restricted cubic spline regression relationship between frailty score and all-cause mortality or MACE, studies with three or more categories will be included. At least four studies will be included in the dose–response analysis

for each frailty scale system. The average level of frailty score in each category will be estimated by the mean of the lower and upper levels. If the highest category had an open upper level, the mean level will be estimated to be 1.2× the level of the lower levels.[29] All the pooling analyses will be conducted according to different study types (retrospective or prospective). P value <0.05 (two-sided) will be considered to be statistically significant. All statistical analyses will be performed in Stata software (V.10.0, StataCorp., College Station, Texas, USA) and RevMan software (V.5.0, Cochrane Collaboration, Oxford, UK).

ETHICS AND DISSEMINATION

In accordance with the Institutional Review Board/Independent Ethics Committee of the First Affiliated Hospital of Baotou Medical College, ethical approval is not an essential element for the systematic review protocol. This meta-analysis will be disseminated through a peer-reviewed journal for publication.

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Contributors CZ and HP contributed to the conception and design of the study, and revision of the protocol. The manuscript of the protocol was drafted by HP. YW and XZ will independently search and select the eligible studies and extract the data from the included studies. XZ and WL will assess methodological quality and the risk of bias. All the authors approved the protocol publication.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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