

Frailty as a Predictor for Mortality Among Patients With COVID-19: A Systematic Review and Meta-Analysis

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Abstract

Background

A great number of studies have explored the association between frailty and mortality among COVID-19 patients, suggesting inconsistent results. The aim of this meta-analysis was to synthesize the evidence on this issue.

Methods

Three databases, including PubMed, Embase, and Cochrane Library from inception to 20th October, 2020 were conducted to search for relevant literature. The Newcastle–Ottawa Scale (NOS) was used to assess quality bias, and STATA was employed to pool the effect size. Additionally, potential publication bias and sensitivity analysis was performed.

Results

There are 11 studies that were included, with a total of 22105 COVID-19 patients for quantitative analysis. Overall, the pooled prevalence of frailty was 51% (95%CI:42%-60%). Patients infected with COVID-19 with frailty had an increased risk of mortality, compared to those without frailty, and the pooled HR was 2.27 (95%CI:1.79-2.89). In addition, subgroup analysis based on population showed that the pooled HR for hospitalized patients and nursing home residents was 2.24 (95%CI:1.74-2.89) and 2.95 (95%CI:1.19-7.32), respectively. Subgroup analysis using the frailty assessment tool indicated that this association still existed when using the clinical frailty scale (CFS)(HR=2.41;95%CI:1.60-3.62), frailty index(HR=2.95;95%CI:1.19-7.32), hospital frailty risk score (HR=1.96;95%CI:1.79-2.15) and palliative performance scale (HR= 2.89;95%CI:1.42-5.87).

Conclusion

Our study indicates that frailty was an independent predictor for mortality among patients with COVID-19. Thus, frailty could be a prognostic factor for clinicians to stratify high-risk groups, and remind doctors and nurses to perform early screening and corresponding interventions urgently needed to reduce mortality rates in patients infected by SARS-CoV-2.

Background

A global pandemic of the coronavirus disease 2019 (COVID-19) has become since first being reported in Wuhan city, China in December 2019[1]. By now, the total number of confirmed cases is about 40,268,496 worldwide on October 20, 2020, (<https://www.worldometers.info/coronavirus/>), with the highest mortality among older adults from different geographic regions, resulting in a huge burden for every sector of society, especially the global healthcare system. It is reported that older adults living in community-dwelling or nursing homes are the most vulnerable group with the highest mortality rates for covid-19 because of a variety of comorbidities and lower levels of immunologic function, compared to younger adults[2]. Identifying the risk factors for predicting mortality among patients with COVID-19 is very significant for clinicians.

Recently, many factors have been prognosticated for mortality, such as age[3], diabetes[4], hypertension, and obesity[5]. However, it was reported these somatic conditions cannot comprehensively predict worse outcomes for COVID-19 patients. Thus, new prognostic risk factors are required for identifying and stratifying patients.

Older adults are characterized by heterogeneity of health and vigor. Single aspects, such as chronological age and concurrent disease cannot truly reflect overall health status. To solve this condition, frailty syndrome has widely introduced in the last decades. Frailty is defined as a condition characterized by weakness, progressive declined physiologic function and diminished strength, leading to vulnerable and reduced resilience of stressors with an increased risk of adverse outcome[6]. Frailty was confirmed as a predictor of risk, with worse outcomes such as falls, mortality and lower quality of life in different populations[7]. Several studies have presented the association between frailty and mortality in patients with COVID-19, with inconsistent results[8-17]. Given new articles exploring this association between frailty and mortality[18-20], we therefore believe there is an urgent need to summarize the evidence on this important issue. The objective of our study is to systematically review and quantify the results of the associations between frailty and mortality, which could provide evidence-based suggestions for clinicians.

Methods

This meta-analysis followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement. We have registered our protocol in the PROSPERO database.

Search strategy

Three databases - PubMed, Embase, and Cochrane Library - were independently searched by two authors (XPH, CZ) from database inception to 10th October, 2020. We also used a combination of keywords and medical subject headings (Mesh). The search strategy was below frail* or frailty (Mesh) and ("COVID-19" OR "Coronavirus Infection" OR "Coronavirus Infection Disease 2019" OR Coronavirus*). Additionally, we tried to find relevant studies from references and also searched for grey studies using the Google search engine. The detailed search strategy of PubMed was shown in supplemental file1.

Inclusion and exclusion

All observational studies describing the associations between frailty and mortality in patients with COVID-19 were included. We excluded article types such as comments, reviews, conferences, correspondence, editorials, letters to the editor and case reports. In addition, the study presented the effect size of the association by using frailty score as a continuous variable.

Study selection process

Two authors blindly screened the literature with Endnote software after storing all of the relevant articles. The first step was to delete the duplications and then check the articles by title and abstract, finally identifying the full-text with the criterion of inclusion and exclusion. When there seemed to be a disagreement, the third author would participate, to come to a final consensus.

Data extraction

Two authors (XMZ and XHX) independently extracted the variables from the articles that were included, including basic characteristics (author, publication year, average age, prevalence of males/females, sample size, types of individual), study design, prevalence of frailty, frailty assessment scale, outcomes and the effect size for association between frailty and mortality. The third author confirmed the final version of the data when there seemed to be any argument.

Quality assessment

Two authors (XMZ and XHX) employed quality bias assessment using the Newcastle–Ottawa Scale (NOS), widely applied for observational studies. The total point ranged from 0-9 point, with the more point, the high quality of study. There are three categories for the level of quality, low (0-4), moderate (5-7) and high (>7).

Statistical analysis

The effect size of the association between frailty and mortality was extracted by two independent authors (JJ and JC) with Microsoft Excel, and analyzed by STATA. The heterogeneity between the different studies was presented by I^2 and was detected by Cochran's Q test. The standard for the category of heterogeneity was defined as $I^2 > 50\%$ for significant $I^2 < 50\%$ for insignificant. A random model was used to calculate and pooled the effect size of hazard ratio (HR) with a 95%CI between frailty and mortality because of different populations, study design, and various frailty assessment scales. In addition, subgroup analysis was also performed, based on population, study design, and frailty assessment scale. Publication bias and sensitivity analysis were conducted by funnel plots.

Results And Study Characteristics

We found 253 relevant articles from three databases, PubMed (116), Embase (128), and Cochrane Library (9). After using Endnote software to delete the duplications, 175 articles remained. At this stage, two authors checked the titles and abstracts to identify closely relevant studies, with 28 assessed for eligibility. Consequently, after checking the full text, there were 11 studies included for quantitative analysis in terms of the pre-defined inclusion criteria. Detailed information on the reasons for exclusion is presented in Figure 1.

There are 11 studies for quantifying the relation between frailty and mortality, with a of 22,105 patients with COVID-19. Overall, a majority of the studies that were included studies only focused on older adults. The study design in five studies was prospective cohort studies[8, 12, 18-20], while the others were all retrospective cohort studies[9, 11, 13, 15-17]. There was a variety of countries, ranging from the U.S. to European countries, with 2 in UAS[11, 16], four in the UK[8, 13, 15, 20], 1 in Turkey[19], 1 in France[17], 1 in Spain[9], 1 in Sweden[12], and 1 in the UK and Italy[18]. Of these, ten study settings were in hospital[8, 9, 11-13, 15, 17-20] and one was in a nursing home[16]. The prevalence of frailty ranged from 11.00% to 71.3%, producing the pooled results was 51% (95%CI:42%-60%)(SFigure1). The majority of outcomes was in-hospital mortality, with only one study reporting 30-day mortality. The largest sample size was in Turkey[19] with 18,234, and the smallest was in France[17] with 94 patients. Among all of the included studies, seven studies used clinical frailty scale as an assessment tool for frailty[8, 9, 12, 13, 15, 18, 20], one for hospital frailty risk score[19], one for frailty index[16], one for palliative performance scale[11] and one for frail non-disabled questionnaire[17]. (shown in Table 1)

Meta-analysis of the effects of frailty on mortality

There are 11 studies for meta-analysis, with the results showing pooled HR value of 2.27 (95%CI:1.79-2.89) among frail patients, compared with COVID-19 patients without frailty, indicating that frailty can be an independent predictor for mortality among patients with COVID-19 (Figure2)

Subgroup analysis

Five studies were prospective cohort, and the others were retrospective cohort studies, thus, we performed subgroup analysis based on study design. The results indicated a statistically significant association between frailty and mortality in both of these groups (cohort study versus retrospective cohort study: HR=2.23, 1.81-2.75 versus HR=2.44, 1.20-4.96)(SFigure2). We also performed subgroup analysis based on geographic region, due to the different prevalence levels of COVID-19 worldwide. The results found the associations in the U.S.A. were higher than in European countries(SFigure3), with both suggesting that patients with frailty have an incremental greater risk of mortality than non-frail COVID-19 patients.

SubGroup analysis was based on different populations.

A majority of studies focused on hospitalized patients, with only one study reported among nursing home residents. Older nursing home residents infected with COVID-19 coexisting with frailty had a 2.95-fold risk of mortality, compared to non-frail patients. (HR=2.95, 95%CI:1.19-7.32). Meanwhile, hospitalized

patients also had similar results. (HR=2.24,95%CI:1.74-2.89)(Figur3).

Subgroup analysis was based on different frailty assessment scales.

A majority of studies included the CFS frailty assessment scale, and the results showed that frail patients with COVID-19 presented an increased risk of mortality when using CFS tool to assess frailty syndrome (HR=2.41,95%CI:1.60-3.62). Other frailty assessment instruments included the Frailty index (HR=2.95,95%CI:1.19-7.32), hospital frailty risk score (HR=1.96,95%CI:1.72-2.15) and palliative performance scale (HR=2.89, 95%CI:1.42-5.87), which all indicated similar results, with the exception of the Frail non-disabled questionnaire (HR=1.15,95%CI:0.22-5.99),showed in Figure4.

Quality assessment

A majority of studies had more than a seven-point score, and one study had six points according to the criterion of the Newcastle–Ottawa Scale. (Table 2)

Sensitivity analysis and potential publication bias

Begg's test was used for publication bias and the results showed no potential bias ($p=0.512$) (SFigure4). We also conducted a sensitivity analysis, and the results indicated our study was stable and robust (SFigure5).

Discussion

In this study, we found that COVID-19 patients with frailty have a 2.27-fold greater risk of mortality than those without frailty, independent of study design, country, and setting, indicating that frailty could be a prognostic factor for clinicians to predict mortality, and also support the use of frailty assessment to stratify high-risk hospitalized patients to provided appropriate medical care. This is the first meta-analysis with a large sample size, to the best of our knowledge, to explore the association between frailty and mortality among patients with COVID-19. Given the ongoing COVID-19 pandemic, a larger number of deceased patients and an overwhelmed health care system, frailty screening could help clinicians establish a comprehensive prognostic tool for predicting mortality in patients with COVID-19 and early intervention for improving frail syndrome to reduce mortality rates.

There is a great number of studies that pooled the prevalence of frailty among different populations that resided in nursing home residents[21] or community-dwelling older adults[22] with the figures of 52.3% (95% CI:37.9%-66.5%) and 17.4% (95% CI 14.4% -20.7%), respectively. Our study found that the prevalence of frailty in patients with COVID-19 was similar to nursing home residents, but for both groups, was higher than in community-dwelling older adults. This is not an exceptional finding, because the median or average age in the studies we included is more than 70 years old. Aging was a risk factor increased prevalence of frailty[23]. The oldest people (>70years old) were reported as the most vulnerable population for SARS-CoV-2 infection, especially older residents of nursing homes. In addition, different frailty assessment tools and comorbidities were also factors that produced variations in prevalence.

Frailty as a predictor for mortality has widely been applied in different populations: community-dwelling older adults[24], nursing home residents[25], critically ill patients[26] and oncology patients[27], with HR values ranging from 1.8 to 3.39. A great number of evidence-based systematic reviews and meta-analyses found that frailty could be a predictive factor for adverse outcomes including mortality[25], hospitalization[28], and readmission[29], which means that screening for frailty is very important in a clinical setting.

Although the mechanism between frailty and mortality has been described by previous studies, this association was not completely explained, because of the involvement of complicated multiple factors. Several reasons may account for this. First, frail patients mean a more vulnerable condition characterized by various observable deficits, such as reduced physiologic reserve, chronic undernutrition and cognitive impairment, increasing the likelihood of an adverse outcome when patients are exposed to major negative Stressors including COVID-19, or surgery operation. Second, frailty involving the process of complex chronic inflammation, pro-inflammatory cytokines, such as C-reactive protein, tumor necrosis factor (TNF)- α , and Interleukin (IL) or interleukin-6, exacerbating the risk of morality when patients contracted COVID-19[30]. A previous study reported that pro-inflammatory cytokines were enormously aggravated in patients with COVID-19[31]. Pro-inflammatory cytokines related to frailty and COVID-19 bring about an inflammatory storm in COVID-19patients, progressing to the development of lung injury and later ARDS, intensifying the risk of mortality[14]. Third, older adults infected with SARS-CoV-2 have a high possibility of developing severe status, requiring intensive medical care such as invasive ventilation, more drugs, and even extracorporeal circulation support. Frail older people are often unable to endure these invasive treatments or medical side effects, resulting in a greater likelihood of death during treatment. A previous meta-analysis showed that critically ill patients with frailty have a 1.71-fold risk of mortality. Thus, patients with both frailty and COVID-19 can develop a vicious circle of impairment.

Our subgroup analysis, based on the frailty assessment tool, showed that frailty can be an independent predictor for mortality risk when using HFS, frailty index, clinical frailty scale (CFS) and Palliative performance scale, with the exception of the Frail non-disabled questionnaire. Given the human-to-human transmission of COVID-19, being simple, less time-consuming and accurate were the key points when clinicians consider to use frailty instruments, especially for patients with a critical illness whose care requires more energy and time. CFS was considered as a most common and useful frailty assessment tool for a clinical setting, because there are only five patient domains that need to be assessed [32], whereas other tools need to be evaluated on many different aspects, such as the Frailty index including using 35 items[33]. Additionally, our study also confirmed that frail patients assessed by CFS have an increased risk of morality compared to those without frailty. Recently, National Institute for Clinical Excellence (NICE) published a guideline that recommends CFS as an assessment tool to evaluate frailty in patients with COVID-19[34]. Other subgroup analyses based on different designs and countries also showed similar results, meaning the association between frailty and mortality in patients with COVID-19 is reliable and stable.

Our subgroup analysis shows that the association between frailty and mortality still existed in different settings, both in hospitalized patients and nursing home residents, and the pooled HR for nursing home residents(HR=2.95,95%CI:1.19-7.32) was higher than for hospitalized patients(HR=2.24,95%CI:1.74-

2.89). It is estimated that 2 in 5 US deaths from COVID-19 happened in long-term care facilities or nursing homes. The main reason why nursing home residents were the most vulnerable group for COVID-19 is those patients often suffered many comorbidities such as heart disease, diabetes and kidney disease, which was reported as fact risk of mortality[35]. In fact, COVID-19 patients need to be treated at designed hospital at first in case of contracting other non-covid-19 patients. Given the surging number of COVID-19 patients in the U.S. and Europe, hospitals were overwhelmed by COVID-19 patients and medical staff were enduring huge pressures. Government authorities and policymakers required most nursing home residents to remain in their facility. Whereas, preventing COVID-19 transmission in nursing homes is very challenging but important.

Our systematic review and meta-analysis have some strengths and limitations. To the best of our knowledge, this is the first systematic review and meta-analysis study including 21,890 participants, to explore the association between frailty and mortality in patients with COVID-19, using comprehensive analysis methods. Our study may help answer the question of whether frailty could be a stratified tool for COVID-19 patients, and our results indicate that frailty is an independent predictor of mortality. However, there are also some limitations, and we need to remain cautious about the conclusions. First, there was only one study of nursing home residents, requiring more studies to confirm the impact of frailty on mortality in nursing home residents, guiding policymakers to better manage this valued, high risk group. Second, the numbers for some important frailty assessment tools, such as frailty index or HFR, were limited, influencing the subgroup analysis results based on the frailty assessment tool. Most studies did not provide the adjusted model for the HR value of frailty on mortality; therefore, the pooled HR might be an overestimate. Third, some important studies considered frailty score as a continuous variable, which was excluded.

Conclusion

This systematic review and meta-analysis, which summarizes the evidence of the impact of frailty on mortality in COVID-19 patients, shows that COVID-19 patients with frailty have a 2.15-fold incremental risk of mortality, compared with non-frail patients with COVID-19, and this association was independent of country, study design and setting.

Overall, assessment of frailty can help clinicians stratify the category risk of older patients with COVID-19 for the sake of helping clinical healthcare workers manage and balance the benefits and risk for patients. Thus, multi-dimensional and effective medical care or intervention are required for this group, with the aim of reducing mortality rates.

Abbreviations

COVID-19: Coronavirus disease 2019; CFS: clinical frailty scale; NOS: Newcastle–Ottawa Scale; HR: hazard ratio; CI: Confidence interval.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

All authors approved and obtained by all the authors

Availability of data and materials

All the data can obtain from internet database

Competing interests

The author(s) declare no competing interests.

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Authors' contributions

Xinjuan Wu and Xiao-hua Xie were responsible for the concept and design. Tao Xu analyzed and interpreted the data; and Xiao-Ming Zhang helped design the study and drafted the initial manuscript. Jing Jiao and Jing Cao conducted data acquisition. Xiao-peng Huo and Chen Zhu were responsible for screening and selecting the articles. Xiao-Ming Zhang and Xiao-Hua Xie extracted all of the raw data and were responsible for assessing the quality of bias. All authors have read and approved the manuscript.

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Tables

Table1: Summary of Included Studies on frailty associated with Mortality among patients with Covid-19

Author	Design	Country	Male%	Setting	Prevalence of frailty	Sample size	Age/years	Sarcopenia Criteria	Outcome assessed
Kundi 2020	PCS	Turkey	46.6%	Hospital	67.40%	18234	74.1(7.4)	HFRS	In-hospital mortality
Hagg 2020	PCS	Sweden	48%	Hospital	44.10%	250	81.01 (8.56)	CFS	in-hospital mortality
Aw 2020	PCS	UK	54%	Hospital	70.70%	677	81.1(8.1)	CFS	In-hospital mortality
Hewitt 2020	PCS	UK and Italy	58%	Hospital	51.25%	1564	74(64-83)	CFS	In-hospital mortality
Shi 2020	RCS	USA	44.10%	Nursing home	71.30%	139	85.0(9.3)	Frailty index	In-hospital mortality
Maguire 2020	RCS	UK	55.30%	Hospital	37.70%	224	older than 20 years	CFS	30-day mortality
Siles 2020	RCS	Spain	57%	Hospital	35.15%	128	84 (75, 89)	CFS	In-hospital mortality
Steinmeyer 2020	RCS	France	45.00%	Hospital	11.00%	94	85.5 ± 7.5	FNDQ	In-hospital mortality
Owen 2020	RCS	UK	54.00%	Hospital	53.30%	206	78.8 (8.3)	CFS	In-hospital mortality
Fiorentino 2020	RCS	USA	NA	Hospital	64.10%	374	NA	Palliative Performance Scale	In-hospital mortality
Chinnadurai 2020	PCS	UK	61.9%	Hospital	51.20%	215	74 (60–82)	CFS	In-hospital mortality

RCS: Retrospective cohort study; PCS: prospective cohort study; FNDQ: Frail Non-Disabled questionnaire; HFRS: Hospital Frailty Risk Score

Table 2 Result of the Newcastle-Ottawa scale quality assessment

Author/years	Selection (4)				Comparability	Outcome			Quality
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	(2)	(3)	Assessment of outcome	Was follow-up long enough for outcome to occur	Adequacy of follow up of cohorts
Kundi 2020	1	1	1	1	2	1	1	1	9
Hagg 2020	1	1	1	1	2	1	0	1	8
Aw 2020	1	1	1	1	2	1	0	1	8
Hewitt 2020	1	1	1	1	2	1	1	1	9
Shi 2020	1	1	1	1	2	1	0	1	8
Maguire 2020	1	1	1	1	1	1	0	1	7
Siles 2020	1	1	1	1	1	1	0	1	7
Steinmeyer 2020	1	1	1	1	0	1	0	1	6
Owen 2020	1	1	1	1	2	1	0	1	8
Fiorentino 2020	1	1	1	1	1	1	0	1	7
Chinnadurai 2020	1	1	1	1	2	1	0	1	8

Figures

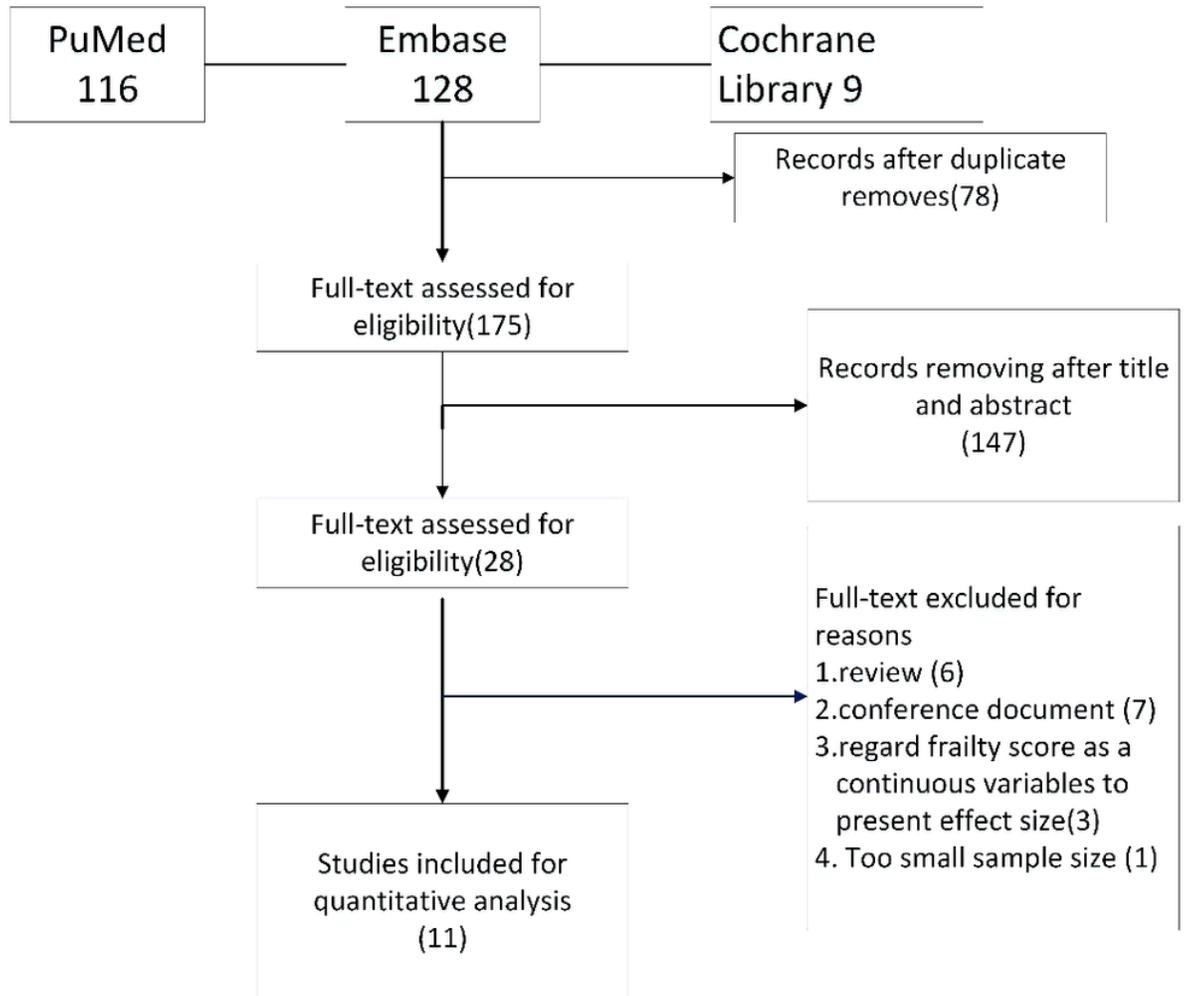


Figure 1

The flowchart of research screening.

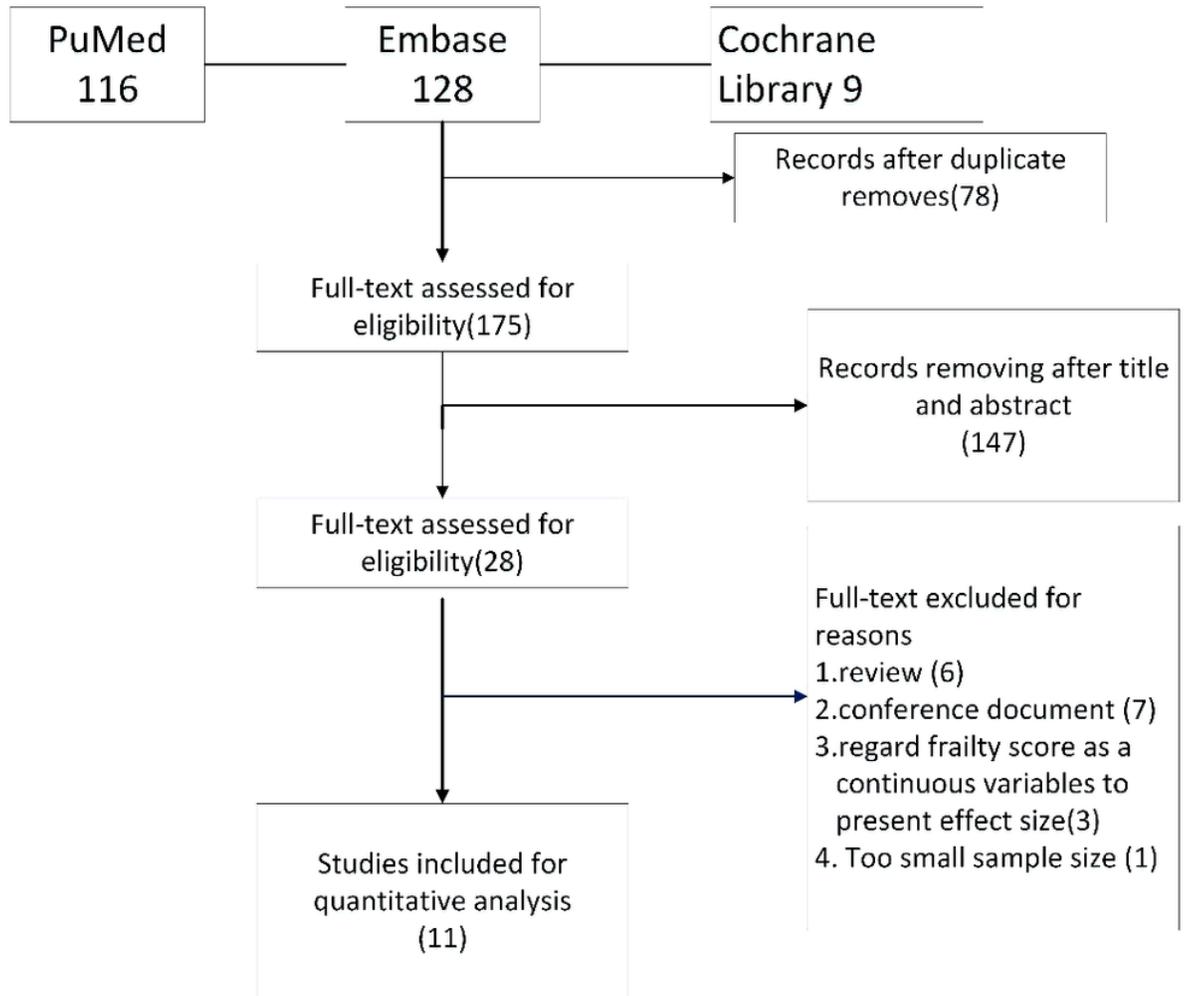


Figure 1

The flowchart of research screening.

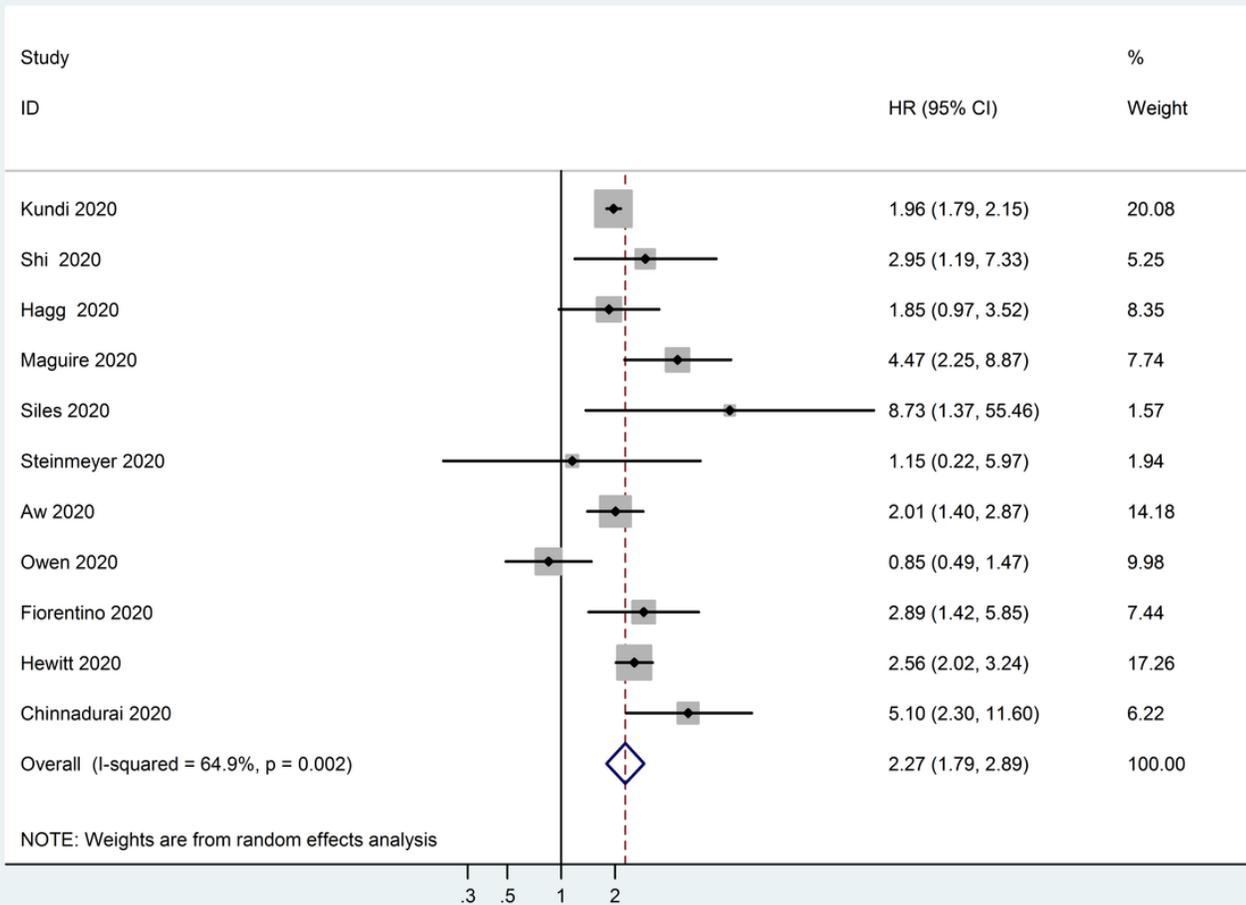


Figure 2

Meta-analysis of the effects of frailty on mortality among patients with COVID-19.

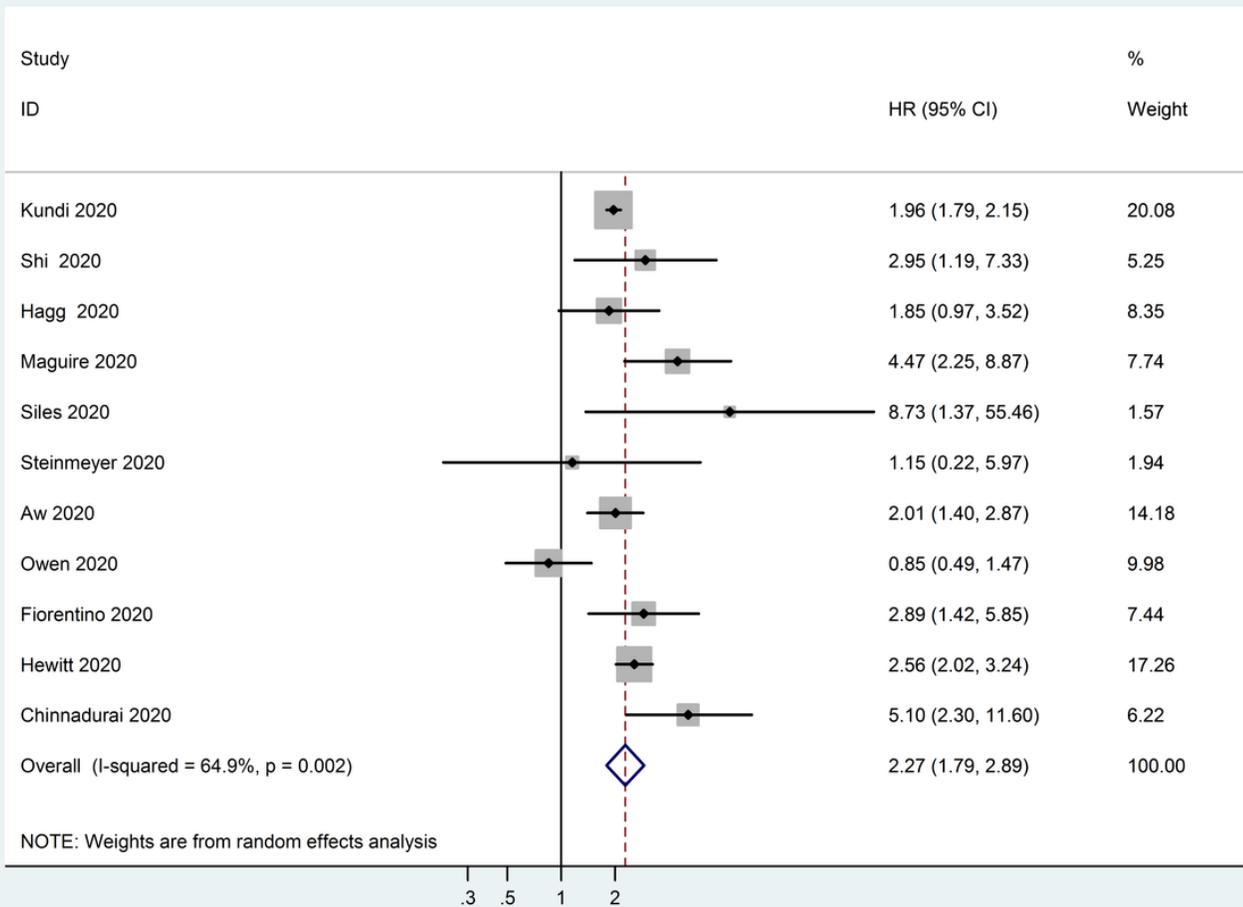


Figure 2

Meta-analysis of the effects of frailty on mortality among patients with COVID-19.

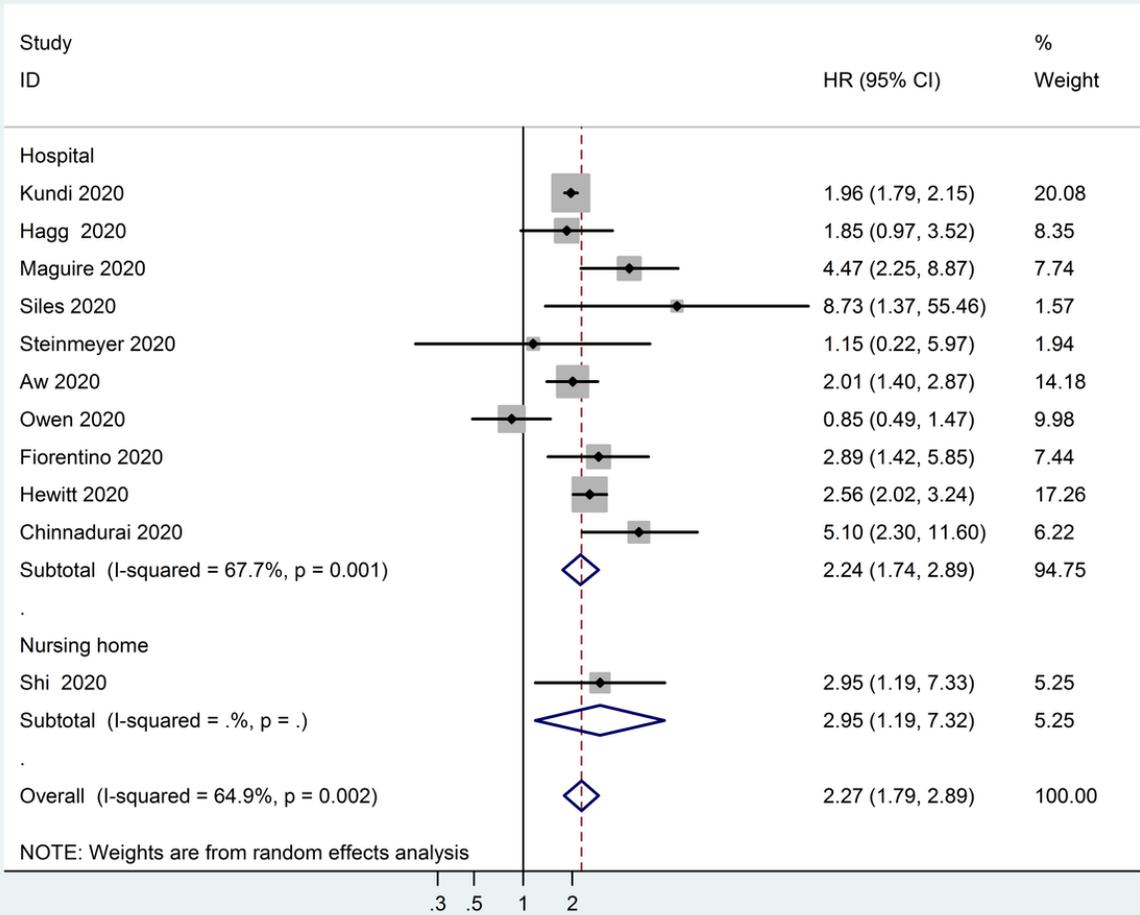


Figure 3

Meta-analysis of the effects of frailty on mortality based on different populations among patients with COVID-19.

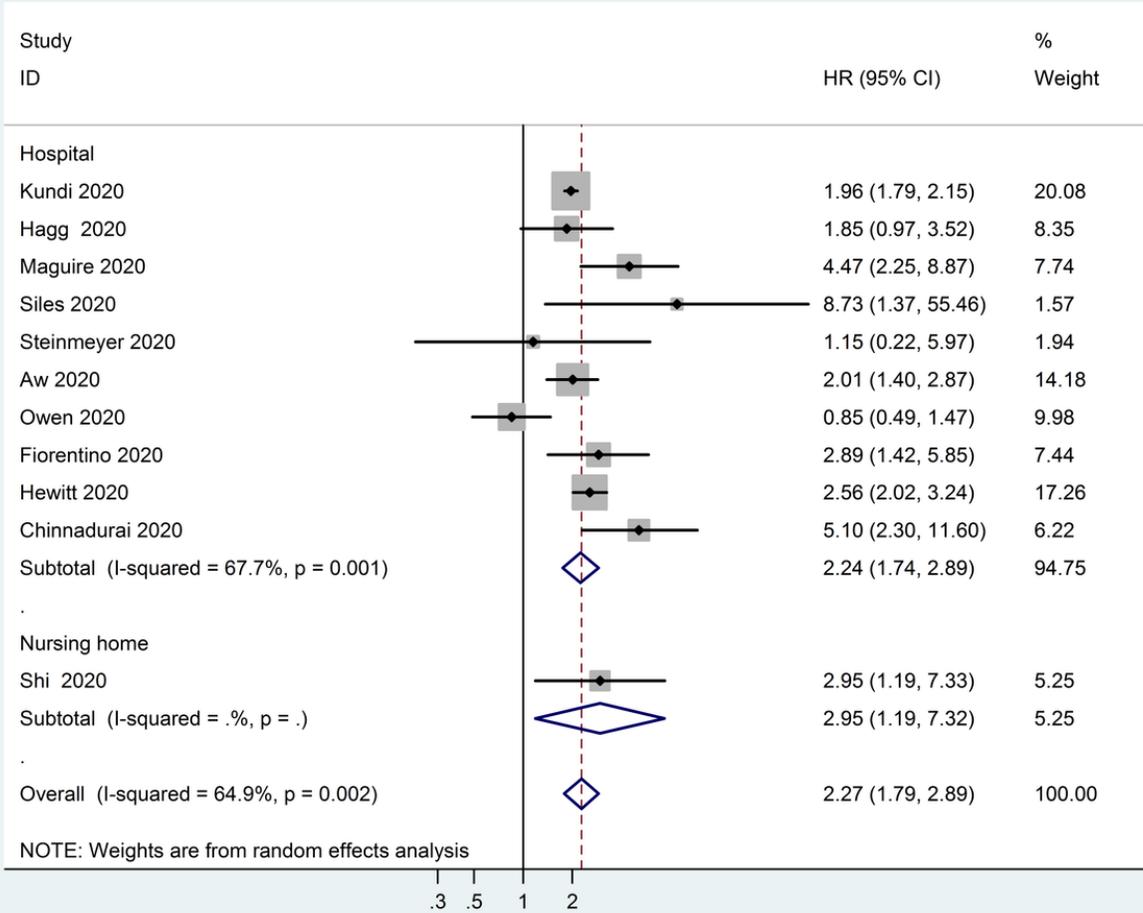


Figure 3

Meta-analysis of the effects of frailty on mortality based on different populations among patients with COVID-19.

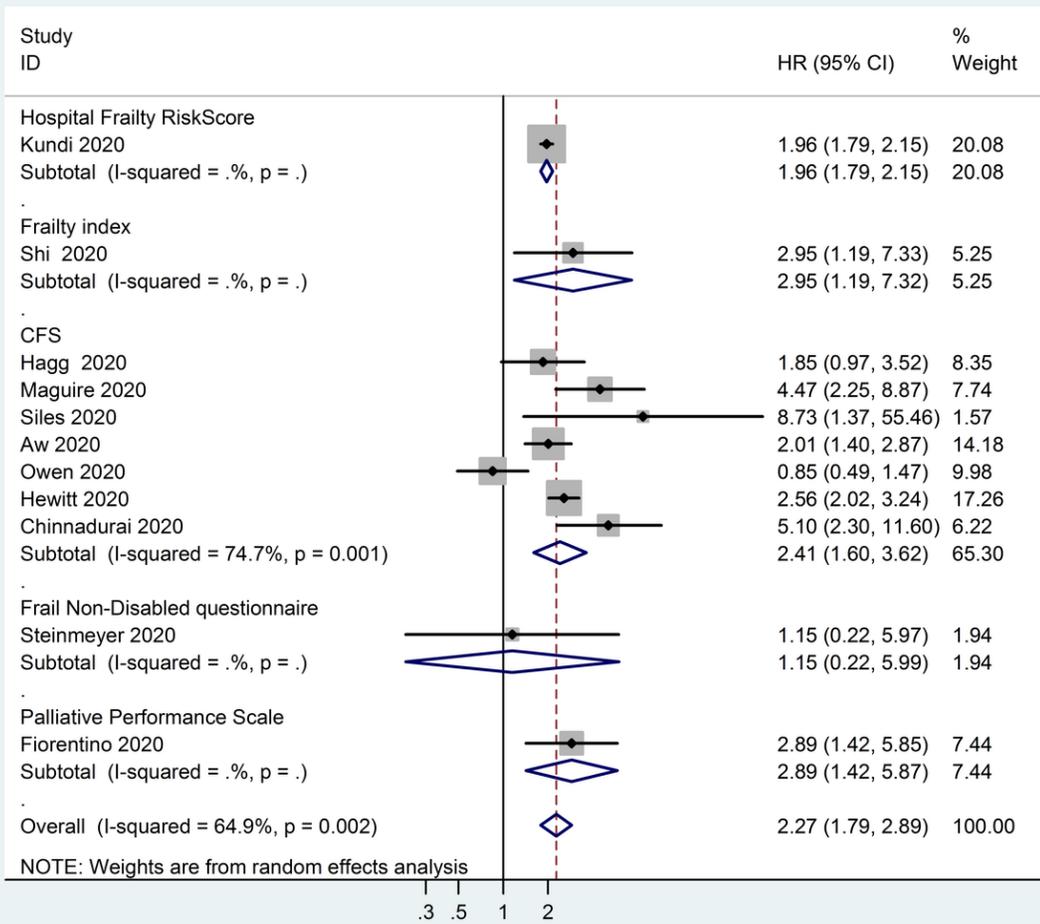


Figure 4

Meta-analysis of the effects of frailty on mortality based on different frailty assessment scales among patients with COVID-19.

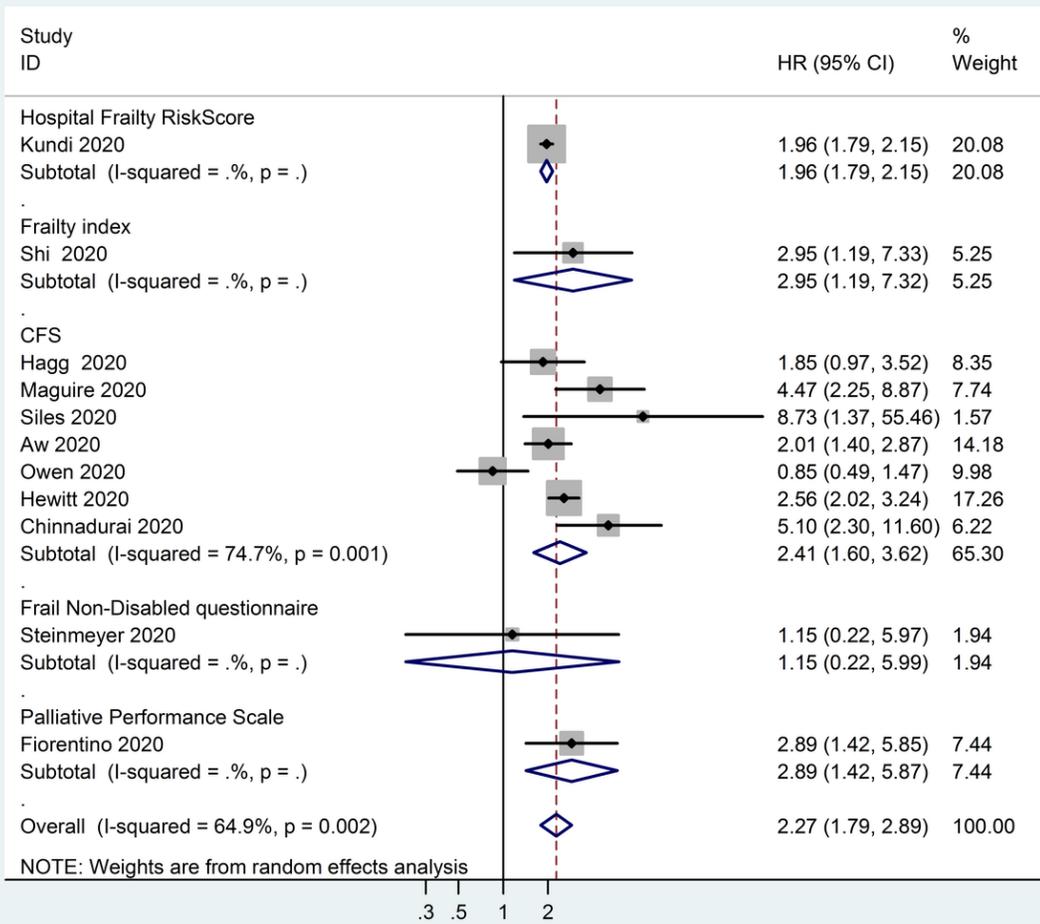


Figure 4

Meta-analysis of the effects of frailty on mortality based on different frailty assessment scales among patients with COVID-19.

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