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Frailty and mortality associations in patients with COVID-19: a systematic review and meta-analysis

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Key words
COVID-19, frailty, hospital-related mortality, systematic review, meta-analysis, older people.

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Abstract

Background: Observational data during the pandemic have demonstrated mixed associations between frailty and mortality.
Aim: To examine associations between frailty and short-term mortality in patients hospitalised with coronavirus disease 2019 (COVID-19).
Methods: In this systematic review and meta-analysis, we searched PubMed, Embase and the COVID-19 living systematic review from 1 December 2019 to 15 July 2021. Studies reporting mortality and frailty scores in hospitalised patients with COVID-19 (age ≥18 years) were included. Data on patient demographics, short-term mortality (in hospital or within 30 days), intensive care unit (ICU) admission and need for invasive mechanical ventilation (IMV) were extracted. The quality of studies was assessed using the Newcastle−Ottawa Scale.
Results: Twenty-five studies reporting 34 628 patients were included. Overall, 26.2% ($n = 9061$) died. Patients who died were older (76.7 ± 9.6 vs 69.2 ± 13.4), more likely male (risk ratio (RR) = 1.08; 95% confidence interval (CI): 1.06–1.11) and had more comorbidities. Fifty-eight percent of patients were frail. Adjusting for age, there was no difference in short-term mortality between frail and non-frail patients (RR = 1.04; 95% CI: 0.84–1.28). The non-frail patients were commonly admitted to ICU (27.2% (4256/15639) vs 29.1% (3567/12274); $P = 0.011$) and had a higher mortality risk (RR = 1.63; 95% CI: 1.30–2.03) than frail patients. Among patients receiving IMV, there was no difference in mortality between frail and non-frail (RR = 1.62; 95% CI 0.93–2.77).
Conclusion: This systematic review did not demonstrate an independent association between frailty status and short-term mortality in patients with COVID-19. Patients with frailty were less commonly admitted to ICU and non-frail patients were more likely to receive IMV and had higher mortality risk. This finding may be related to allocation decisions for patients with frailty amidst the pandemic.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The clinical spectrum ranges widely from asymptomatic to severe respiratory failure, multi-organ failure and death.[1,2] Older age, male sex, obesity and

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pre-existing health conditions such as diabetes and hypertension have all been identified as risk factors for poor outcomes.[3–5] There is some evidence for a disproportionate effect on older people with frailty.[6] High degree of frailty and cumulative comorbidities have been associated with higher mortality rates in patients with COVID-19.[7] It may be that patients with frailty have a poor immune response to SARS-CoV-2, leading to higher short-term mortality, slower recovery and further functional decline in patients.[8]

With healthcare resources worldwide overstretched and scarce intensive care resources, frailty is being used in clinical decision-making for patients with COVID-19 in some settings. Early evidence on the impact of frailty demonstrated mixed results with some studies demonstrating an association of frailty and mortality,[9–11] while others did not.[12,13] A few systematic reviews have demonstrated a prognostic effect of frailty in patients with COVID-19.[14–16] Many observational studies have been published recently in patients with COVID-19 comparing patient characteristics and outcomes among survivors and non-survivors.[7,9–11,13,17–36] Several studies used frailty as one of the predictors of mortality. No studies have pooled and analysed the results examining the association between frailty and mortality, adjusting for important confounders such as age. Therefore, we aimed to evaluate the association of frailty and age with all-cause short-term mortality and intensive care unit (ICU) pertinent outcomes, such as ICU admission and the need for invasive mechanical ventilation (IMV), in patients hospitalised with COVID-19.

Methods

The protocol was registered with PROSPERO (CRD42021233599). The study was conducted in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement.[37]

Eligibility criteria

We included studies reporting on consecutive adult hospitalised patients with COVID-19 with a documented frailty assessment (regardless of the frailty measure used) reporting on survivors and non-survivors. The studies were excluded if frailty assessment was not reported.

Frailty

People who are susceptible to poorer outcomes, beyond the risk explained by their age or comorbidities, is defined as frailty. There are two accepted paradigms of frailty: phenotypic construct,[38] and deficit accumulation model.[39] The phenotype construct is based on a cluster of signs and symptoms such as self-reported exhaustion, slowed performance (by walking speed), weakness (by grip strength), unintentional weight loss (4.5 kg in the past year) and low physical activity.[38] In contrast, the deficit accumulation model is quantified based on the number rather than the nature of health problems,[39,40] along with biochemical and physiological impairments. An overlap exists between the two constructs,[38,39] their sum contributing to a risk state.[41]

Frailty tools

Frailty was measured by four tools in the included studies: the clinical frailty scale (CFS),[39] the hospital frailty risk scale (HFRS),[42] the frailty index (FI)[43] and the Frail Non-Disabled survey (FIND).[44]

Search strategy, information sources, study selection and data extraction

Two authors (ZL, SA) independently searched the publicly available COVID-19 living systematic review,[45] which is updated daily to provide a dynamic database of research papers related to COVID-19 that are indexed by PubMed, EMBASE, MedRxiv and BioRxiv. This has been validated in previously published COVID-19-related research.[46] The last was conducted on 16 July 2021. Studies were extracted between 1 December 2019 and 15 July 2021, using the search terms 'frail' and 'frailty' within the title and the abstract. These terms were combined with the Boolean operator 'OR'. Pre-print and non-English articles were included. The bibliography of each study was analysed to identify studies that may have been missed during the literature search. Although we mainly focussed on older frail patients, we included all adult patients aged ≥18 years as some younger people can be frail.[47] In the case of overlapping patient data across two or more studies in our primary meta-analysis, we included the larger study. Data were collected independently by two reviewers (HB, SA) using a prespecified data extraction form; any conflicts were resolved by consensus or by a third reviewer (AS). Corresponding authors were contacted for additional information where data were incomplete. Data collection covered study characteristics (study design, study period, sample size and country where the study was conducted), patient demographics, frailty status, frailty tools used, need for IMV, in hospital mortality and hospital length of stay (LOS). These were independently extracted, tabulated and verified by the two reviewers (HB, SA).

Quality assessment and risk of bias in individual studies

The quality of studies was assessed using the Newcastle−Ottawa Scale (NOS) tool[48] by two independent reviewers (HB, SA) using the same set of decision rules. Any discrepancies were resolved by a third author (AS). Publication bias was examined using the symmetry of funnel plots and Egger regression test.[49] To account for the heterogeneity, sensitivity analysis was performed based on study quality for all outcomes.

Definitions

Short-term mortality was defined as all-cause in hospital mortality or death within 30 days of hospitalisation.[6]

Study outcomes

The primary aim was to examine associations of frailty status and short-term mortality. The primary outcome was to evaluate the pooled mortality among hospitalised frail and non-frail patients with COVID-19. In addition, secondary outcomes included mortality among patients who required ICU admission or ventilatory supports.

Post hoc analyses

Outcomes were compared between the type of frailty measure (CFS vs others). A further *post hoc* analysis to evaluate the primary outcome based on studies that used CFS as a frailty measure. For this meta-analysis, we stratified patients as CFS 1–3, CFS-4, CFS-5, CFS-6 and CFS 7–9.

Data collection and analysis

Statistical analyses were performed using the statistical software package Stata-Version 16 (StataCorp., College Station, TX, USA). Mean (standard deviation (SD)) was used for numerical data and proportion for categorical data. Where median (interquartile range) was reported, the mean (SD) was derived using an estimation formula.[50] Age stratification was performed based on the mean age of the individual study population. Five studies[9,30,32,34,36] that reported on longer-term outcomes were censored at 30 days to reflect the short-term mortality. We reported standardised mean difference (MD) with 95% confidence intervals (CI) for physiological parameters and event rates using a random-effects model to account for both within-study and between-study variances.[51] The results were presented in Forest plots as a log risk ratio (RR). For convenience, we also reported the anti-log RR by calculating the RR using the = EXP(value) function in Microsoft Excel (MS Office 365). Heterogeneity was tested using the χ^2 test on Cochran Q statistic, which was calculated using H and I^2 indices. The I^2 index estimates the percentage of total variation across studies that were based on true between-study differences rather than on chance. Conventionally, I^2 values of 0–25% indicate low heterogeneity, 26–75% indicate moderate heterogeneity and 76–100% indicate substantial heterogeneity.[52] For the *post hoc* analysis, we used CFS 1–3 as the control group and compared these patients against those with CFS scores of 4, 5, 6 and 7–9 to assess their respective RR of short-term mortality. A P-value <0.05 was considered statistically significant.

Results

A total of 914 studies was extracted from the living systematic review. Eighty-seven full-text articles were assessed for eligibility. Twenty-five studies[7,9–11,13,17–20,22–36] across 19 countries (Belgium, Brazil, Cyprus, Egypt, France, Greece, Iraq, Italy, Libya, The Netherlands, Poland, Saudi Arabia, Spain, Sudan, Sweden, Switzerland, Turkey, UK and the USA) reporting on 34 628 patients with COVID-19 with frailty assessments, from the early phase of the pandemic, were included in the qualitative and quantitative analysis. Study population sizes were variable, ranging between 23 and 18 234 patients (Supporting Information Fig. S1). Most of the studies were from the UK ($n = 14$).[7,9–11,13,18,19,23,24,26,30,33,35,36] All studies reported findings from acute care hospitals, one study specifically on transplant patients[22] and another study from a COVID-19-specific hospital.[27] Five studies[20,24,27,30,31] provided additional data to enable further analysis. Based on the NOS, four studies were of good quality,[30,33–35] 12 studies were of fair quality[9,11,18,19,21,26,27,29,31,32,36] and the remaining nine were of poor quality.[7,10,13,17,20,22,24,25,28] The CFS was the most common frailty measure. Most studies included all consecutive patients with no specified exclusion criteria. One study randomly selected patients from a list of all patients with confirmed COVID-19 who were discharged from the hospital during the period.[29] One study excluded nosocomial COVID-19 cases.[30] Only one large study reported on missing data and those who were still alive in the hospital at the end of the study period.[31] Table 1 illustrates the characteristics and descriptions of the included studies.

Survivor versus non-survivor demographics

Overall mortality and demographic predictors

Table 2 summarises the study features and the characteristics of patients with COVID-19, comparing survivors

Table 1 Summary characteristics and descriptions for the included studies that investigated frailty and COVID-19-related mortality

Author, country	Setting	Study type	Study period (DD/MM/YY)	Sample size, proportion male (%)	Age, mean (SD) (years)	Proportion Caucasian (%)	Frailty measure; proportion frail (%)	COVID-19 diagnosis	Comments	NOS grading
Aliberti,[1] Brazil	COVID-19 special hospital	Retrospective cohort study	30/03/20 to 7/07/20	1830 (57)	66 (11)	N/R	CFS†; 25	RT-PCR	Although patients were followed up at 6 months, only 30-day follow up was included in this study	7 (fair)
Apea,[2] UK	Acute hospitals (5 in UK)	Prospective Cohort study	1/01/20 to 13/05/20	1996 (60.6)	63.4 (18.3)	35.2	HFRS; 47.9	RT-PCR	The primary outcome was 30-day mortality from time of first hospital admission with COVID-19 diagnosis	8 (good)
Aw,[3] UK	Acute hospital	Cohort study	8/03/20 to 30/04/20	677 (61)	62.2 (17.4)	35	CFS; 71.3	RT-PCR	The follow-up period was the time between admission and death, discharge or 28 days Censored at 28 days from hospitalisation	6 (fair)
Baker,[4] UK	Acute hospital	Retrospective cohort study	8/01/20 to 12/04/20	316 (55)	72.7 (17.1)	96	CFS; N/R	RT-PCR	Censored at 28 days from hospitalisation	6 (poor)
Bellelli,[5] Italy	General hospital	Cohort study	27/02/20 to 7/04/20	105 (68.6)	N/R	N/R	FI; N/R	RT-PCR	Follow up at 48 days	6 (poor)
Brill,[6] UK	Acute hospital	Retrospective cohort study	9/03/20 to 6/04/20	410 (35)	81.1 (8.1)	60	CFS; N/R	RT-PCR	Censored at 28 days from hospitalisation	6 (fair)
Chinnadurai,[7] UK	Acute hospital	Cohort study	23/03/20 to 30/04/20	215 (62)	72.0 (16.4)	87	CFS; 51.2	RT-PCR	Censored at 14 days from hospitalisation	7 (fair)
Davis,[8] UK	Acute hospital	Retrospective cohort study	18/03/20 to 20/04/20	222 (33)	82 (range 56–99)	N/R	CFS; 75	RT-PCR	Reported 30-day mortality post hospitalisation	6 (poor)
De Smet,[9] Belgium	General hospital	Retrospective cohort study	12/03/20 to 30/04/20	81 (41)	70.3 (20.1)	N/R	CFS; 79.5	RT-PCR	–	6 (poor)
Dres,[10] France, Switzerland Belgium	ICU	Prospective cohort study	25/02/20 to 04/05/20	1199 (73)	74.7 (4.4)	N/R	CFS; 9	RT-PCR	Follow up at 28 days Mortality was 60% at 90 days	8 (good)
Fagard,[11] Belgium	Acute hospital	Retrospective cohort study	16/03/20 to 16/05/20	105 (52.4)	81.7 (8.3)	N/R	CFS; 59	RT-PCR	In hospital mortality	7 (fair)

Table 1 *Continued*

Author, country	Setting	Study type	Study period (DD/MM/YY)	Sample size, proportion male (%)	Age, mean (SD) (years)	Proportion Caucasian (%)	Frailty measure; proportion frail (%)	COVID-19 diagnosis	Comments	NOS grading
Hendra,[12] UK	Acute hospital with four satellite dialysis units	Retrospective cohort study	11/03/20 to 10/05/20	148 (56.8)	64.1 (14.6)	32.4	CFS	RT-PCR	Follow up censored on 26 May 2020	8 (good)
Hewitt,[13] Italy/UK	Acute hospital (UK 10, Italy 1)	Cohort study	27/02/20 to 30/04/20	1564 (58)	76.0 (5.2)	N/R	CFS; 35	RT-PCR/ clinical	Patients still in hospital at follow-up point were censored for the time-to-mortality analysis. Censored at 28 days from hospitalisation	7 (fair)
Hoek,[14] Netherlands	Acute hospital	Cohort study	27/02/20 to 30/04/20	23 (78)	60.7 (15.0)	61	CFS; ~22	RT-PCR	Reported on in hospital mortality	4 (poor)
Knights,[15] UK	General hospital	Retrospective cohort study	01/03/20 to 31/03/20	108 (61)	69.3 (16.3)	76	CFS; N/R	RT-PCR	In hospital deaths included patients discharged for palliative care either at home or a local palliative care inpatient unit	7 (fair)
Koduri,[16] UK	Acute hospital	Retrospective cohort study	20/02/20 to 07/05/20	500 (60)		87.6	CFS; 42.9	RT-PCR	–	6 (poor)
Kokosz-Bargiel,[17] Poland	Acute hospital and ICU	Retrospective cohort study	10/03/20 to 10/06/20	67 (32 ICU) (69)	62.4 (10.4)	N/R	CFS; 55	RT-PCR	–	5 (poor)
Kundi,[18] Turkey	All acute hospitals in Turkey	Retrospective cohort study	11/03/20 to 22/06/20	18 234 (46.6)	74.1 (7.4)	N/R	HFRS; 67.4	RT-PCR	In hospital all-cause mortality	7 (fair)
Maguire,[19] UK	General hospital	Retrospective cohort study	17/03/20 to 01/05/20	224 (55)	Most >70	93.3	CFS; 46	RT-PCR/ clinical	Censored at 30 days from hospitalisation	7 (fair)
Marengoni,[20] Italy	COVID-19 special hospital	Retrospective cohort study	08/03/20 to 14/04/20	165 (61)	69.3 (14.5)	N/R	CFS; 15.2	RT-PCR/ clinical	To death or discharge. Maximum 40 days	7 (fair)
Osuafor,[21] UK	Acute hospital	Retrospective cohort study	01/03/20 to 15/05/20	214 (55.1)	80.7 (8.9)	83.2	CFS; 66.4	RT-PCR	Follow up at 45 days	7 (fair)

Table 1 *Continued*

Author, country	Setting	Study type	Study period (DD/MM/YY)	Sample size, proportion male (%)	Age, mean (SD) (years)	Proportion Caucasian (%)	Frailty measure; proportion frail (%)	COVID-19 diagnosis	Comments	NOS grading
Owen,[22] UK	Acute hospital	Retrospective observational study	23/01/20 to 13/03/20	301 (56)	68.7 (15.6)	N/R	CFS; 43.8	RT-PCR/ clinical	The primary outcome was time to death (all-cause mortality). Deaths occurring outside the hospital were captured daily Censored at 30 days of hospitalisation	6 (poor)
Steinmeyer,[23] France	Acute hospital	Retrospective cohort study	13/03/20 to 04/05/20	94 (45)	85.5 (7.5)	N/R	FIND 76.6 dependent 10.6 frail	RT-PCR	Patients were followed up from hospital admission to hospital discharge or death	5 (poor)
Tehrani,[24] Sweden	Acute hospital	Retrospective cohort study	05/03/20 to 28/04/20	255 (59)	66.0 (17.0)	N/R	CFS; 50	RT-PCR	Follow up at 60 days	7 (fair)
Welch,[25] UK, USA, Italy Libya, Egypt, Iraq, Saudi Arabia, Spain, Greece, Sudan, Turkey, Cyprus	55 acute hospitals	Cohort study	01/02/20 to 31/05/20	5711 (55.1)	71.7 (18.8)	N/R	CFS; 42.8	RT-PCR	Censored at 30 days from hospitalisation	8 (good)

†Only five patients had a CFS score of 9.

CFS, clinical frailty score; FI, frailty index; FIND, frail non-disabled survey; HFRS, hospital risk frailty score; ICU, intensive care unit; NOS, Newcastle–Ottawa Quality Assessment Score; N/R, not reported; RT-PCR, reverse transcription–polymerase chain reaction.

NOS study quality.

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

and non-survivors. The pooled mortality was 26.2% (range 13.3–56%). The mean (SD) age was 73.0 (±11.5) years; the patients who died were older (76.7 ± 9.6 vs 69.2 ± 13.4; MD = 7.4 years; 95% CI 4.0–10.8; $P < 0.001$; $I^2 = 99.2\%$) and mortality increased with age (Fig. S2). Over half the patients were male (52%; 17 768/34 141; range 33% to 78%; 22 studies[7,9–11,17–24,26–35]). Male patients, compared with female patients, had higher short-term mortality risk (RR = 1.08; 95% CI 1.06–1.11; Fig. S3). Although the heterogeneity was minimal ($I^2 = 23\%$), the Egger regression test suggested publication bias ($P = 0.038$). The sensitivity analysis adjusting for study quality demonstrated consistently higher mortality in male patients in higher quality studies. There was no difference in mortality by ethnicity (Caucasian vs Others: 52% vs 48%; $n = 6056$; 10 studies[9,10,18,19,23,24,26,32,33,35]). Patients with acute kidney injury (11 studies[7,10,11,18–20,25,26,28–30]; 48.1% vs 24.1%) and delirium (six studies[7,20,24,26,28,30]; 26.8% vs 16.6%) were more likely to die. The treatment limitation documentation was only reported in five studies[10,17,20,23,29] (34%; 286/840), most (84.1%) with treatment limitations died.

Comorbidities

Table 3 summarises the comorbidities comparing survivors and non-survivors. Mortality was higher among patients with dementia,[7,10,17,20,21,23,26–30,33] (RR = 1.39; 95% CI 1.22–1.58), chronic kidney disease[10,17,19–22,25,26,29,31,33–35] (RR = 1.23; 95% CI 1.12–1.35), heart failure[7,13,19,22,25–31,35,53] (RR = 1.22; 95% CI 1.08–1.36), diabetes mellitus[10,11,17–21,24,25,27–35] (RR = 1.11; 95% CI 1.05–1.07), hypertension[7,10,11,17–21,23–29,31–35] (RR = 1.13; 95% CI 1.07–1.19) and cerebrovascular accident[17,19,20,23–25,29,31,33] (RR = 1.28; 95% CI 1.07–1.39). Chronic respiratory disease and obesity (body mass index ≥30 kg/m^2) was not associated with mortality. Patients who died were more likely to have acute kidney injury (11 studies[7,10,11,18–20,25,26,28–30]; 48.1% vs 24.1%; $P < 0.0001$) and delirium (six studies[7,20,24,26,28,30]; 26.8% vs 16.6%; $P < 0.0001$).

Primary outcome for short-term mortality based on frailty status

Association of frailty with mortality adjusting for covariates

Of patients with COVID-19, 57.9% were classified as frail (18 936/32 687). Eight studies reported mortality over time using hazard ratios,[9,11,13,19,27,30,32,34] six studies report mortality risk as odds ratio[17,20,21,24,27,31] whilst another seven studies[7,10,18,22,23,25,36] using other descriptions all demonstrated an association between increased mortality risk with increasing levels of frailty (Table S1). Four studies[26,28,33,35] reported no association between frailty and mortality. Despite the higher univariate pooled mortality amongst patients with frailty (30.6% vs 19.4%) when compared with non-frail patients, there was no independent increased risk of dying (RR = 1.27; 95% CI 0.97–1.42) when compared with non-frail patients when adjusting for age and other covariates (Fig. 1). Although there was high heterogeneity ($I^2 = 98.9\%$), Egger test suggested no publication bias ($P = 0.32$). The sensitivity analysis adjusting for study quality showed patients with frailty were more likely to die if the studies were of fair quality (RR = 1.43; 95% CI: 1.30–1.58), but no difference in good or poor qualities studies (Fig. S4).

Secondary ICU-specific outcome comparing among survivors and non-survivors

ICU admission

Of all patients hospitalised with COVID-19, 26% were admitted to the ICU (8317/32 028; 19 studies[9,10,13,18–20,22–25,27–35]). More than half the patients admitted to ICU died (52.7%), but the pooled analysis demonstrated that no increased risk of death among patients admitted to the ICU (RR 0.94; 95% CI 0.78–1.15; Fig. 2A). Despite the high heterogeneity ($I^2 = 96.3\%$), Egger test suggested no publication bias ($P = 0.95$). The sensitivity analysis based on study quality demonstrated similar observations (Fig. S5). We found that patients with frailty were commonly admitted to ICU (27.2%; 4256/15 639). Based on 11 studies,[9,13,20,22,24,25,30–34] a higher proportion of non-frail patients were admitted to the ICU compared with patients with frailty (29.1% (3567/12 274) vs 27.2% (4256/15 639); $P = 0.011$) and non-frail patients had higher mortality risk compared with patients with frailty (RR = 1.63; 95% CI: 1.30–2.03; Fig. 2B).

Invasive mechanical ventilation

A majority of patients admitted to ICU required IMV (76.9%; 5850/7602; 14 studies[10,18,19,22–25,27,29,31–34,36]). The patients who received IMV were at higher risk of dying if they were older: patients aged between 70 and 79 years (13 studies[10,18,19,22–25,27,29,32–35]; RR = 1.39; 95% CI 1.26–1.54) or ≥80 years (RR = 2.18; 95% CI 1.28–3.71; Fig. 2C). Despite the high heterogeneity ($I^2 = 94.2\%$), there was no publication bias (Egger test $P = 0.78$). The sensitivity analyses based on the study quality were consistent (Fig. S6). The patients with

Table 2 Patient demographics among survivors and non-survivors

	Overall, % (95% CI) (*n*/*N*)	Survivors, % (95% CI) (*n*/*N*)	Non-survivors, % (95% CI) (*n*/*N*)
Total patients with documented frailty†	34 628	25 567 (73.8%)	9061 (26.2%)
Female, % (*n*) [22 studies]	48 (47.4–48.5%) (16 373/34 141)	80.2 (79.6–80.9%) (13 139/16 373)	19.8 (19.1–20.4%) (3234/16 373)
Age, mean (SD) (years) [20 studies]	73.0 (±11.5)	69.2 (±13.4)	76.7 (±9.6)
Patient residence prior to hospitalisation, % (*n*) [13 studies]			
Nursing home resident	15.5 (14.8–16.3%) (1369/8832)	12.2 (11.4–13.0%) (735/6027)	22.7 (21.2–24.3%) (634/2795)
Own home	63.0 (62.0–64.0%) (5564/8832)	66.2 (65.0–67.4%) (3992/6027)	56.2 (54.4–58.1%) (1572/2795)
Residential care/other‡	15.0 (14.3–15.8%) (1325/8832)	14.9 (14.0–15.9%) (899/6027)	20.3 (18.9–21.8%) (568/2795)
Ethnicity, % (*n*) [9 studies]			
Caucasian	59.3 (58.0–60.5%) (3612/6094)	64.5 (62.9–66.0%) (2288/3549)	52.0 (50.1–54.0%) (1324/2545)
Other	40.7 (39.5–42.0%) (2482/6094)	35.5 (34.0–37.1%) (1261/3549)	48.0 (46.0–49.9%) (1221/2545)
Frailty data, % (*n*) [20 studies]			
Total non-frail†	42.1 (41.5–42.6%) (13 751/32 687)	80.6 (80.0–81.3%) (11 089/13 751)	19.4 (18.7–20.0%) (2662/13 751)
Total frail†	57.9 (57.4–58.5%) (18 936/32 687)	69.4 (68.7–70.0%) (13 137/18 936)	30.6 (30.0–31.3%) (5799/18 936)
Comorbidities, % (*n*)			
Charlson comorbidity index <2 [4 studies]	45.5 (42.2–48.9%) (388/852)	56.6 (52.4–60.7%) (305/539)	26.5 (21.9–31.6%) (83/313)
Charlson comorbidity index >2 [4 studies]	54.5 (51.1–57.8%) (464/852)	43.4 (39.3–47.6%) (234/539)	73.5 (68.4–78.1%) (230/313)
Acute kidney injury [11 studies]	31.1 (30.1–32.0%) (2837/9134)	24.1 (23.0–25.1%) (1560/6483)	48.2 (46.3–50.1%) (1277/2651)
Delirium [6 studies]	17.0 (16.2–17.8%) (1472/8662)	15.7 (14.8–16.7%) (870/5526)	19.2 (17.8–20.6%) (602/3136)
Hospital-specific data			
Hospital LOS, mean (SD) (days) [14 studies]	9.8 (±8.4)	11.0 (±9.4)	9.9 (±7.6)
Goals of care documentation, % (*n*) [5 studies]	34.0 (30.9–37.3%) (286/840)	13.3 (10.7–16.2%) (79/594)	84.1 (79.2–88.3%) (207/246)
ICU-specific data, % (*n*)			
ICU admission [19 studies]	26.0 (25.5–26.5%) (8317/32 028)	47.3 (46.2–48.4%) (3932/8317)	52.7 (51.6–53.8%) (4385/8317)
Non-frail [11 studies]	29.1 (28.3–29.9%) (3567/12 274)§	56.2 (54.5–57.8%) (2004/3567)§	43.8 (42.2–45.5%) (1563/3567)§
Frail [11 studies]	27.2 (26.5–27.9%) (4256/15 639)§	39.7 (38.2–41.2%) (1690/4256)§	60.3 (58.8–61.8%) (2566/4256)§
Invasive mechanical ventilation [14 studies]	76.9 (76.0–77.9%) (5850/7602)	35.3 (34.1–36.5%) (2066/5850)	64.7 (63.5–65.9%) (3784/5850)
Non-frail [7 studies]	75.5 (73.6–77.4%) (1499/1985)	39.4¶ (36.1–42.7%) (326/828)	56.3¶ (52.9–59.6%) (466/828)
Frail [7 studies]	68.8 (67.3–70.2%) (2790/4057)	29.0†† (24.6–34.3%) (98/335)	71.0†† (66.0–75.7%) (238/335)

†Comparison between frail and non-frail requiring ICU admission also *P*-value of <0.0001.

‡Based on three studies that had granular data. *P*-value 0.024 for both survivors and non-survivors when compared between frail and non-frail requiring mechanical ventilation.

§Frailty measure:17 studies CFS; one study each from FI, FIND and HFRS.

¶Other and missing data.

††Binomial 95% confidence interval (CI) (alpha 0.05).

CFS, clinical frailty scale; HFRS, hospital frailty risk scale; ICU, intensive care unit; LOS, length of stay; SD, standard deviation.

frailty were less likely to receive IMV (68.8% (2790/4057) vs 75.5% (1499/1985); $P = 0.026$) and demonstrated no increased mortality risk compared with non-frail patients (RR = 1.62; 95% CI 0.93–2.77; Fig. 2D).

Post hoc analysis

The CFS was the most common frailty screening tool, used in 21 studies.[7,9–11,13,17–27,29,30,32,34–36] The other measures included were FI,[17] HFRS[31,33] and FiND.[28] The outcomes were similar comparing CFS and the other frailty screening tools (Fig. S7). When we analysed the studies that used CFS as a frailty screening tool, compared to CFS 1–3 (control group), the CFS scores of 4, 5, 6 and 7–9 had higher RR of short-term mortality; however, it was not significantly different between CFS 4 and CFS 7–9 (Figs. 3, S8).

Discussion

Key findings

This systematic review and meta-analysis evaluated studies that compared survivors and non-survivors predominantly among older patients with COVID-19 who

Table 3 Comorbidities among survivors and non-survivors, along with risk ratio (including log-transformed)

Comorbidities	No. studies	Mortality for patients with each comorbidity, % (*n*/*N*)	Mortality for patients without each comorbidity, % (*n*/*N*)	Log of risk ratio (95% CI)	Risk ratio (95% CI)	I^2
Dementia	12	44.8 (657/1466)	28.6 (2496/8735)	**0.33** (0.20, 0.46)	**1.39** (1.22, 1.58)	70.7%
Chronic kidney disease	13	39.2 (1041/2658)	20.6 (4358/21 131)	**0.21** (0.11, 0.30)	**1.23** (1.12, 1.35)	55.9%
Smoking	6	35.6 (580/1628)	32.6 (1186/3635)	**0.07** (0.02, 0.12)	**1.07** (1.02, 1.13)	6.4%
Heart failure	8	32.6 (956/2931)	16.4 (2685/16 398)	**0.28** (0.11, 0.46)	**1.22** (1.08, 1.36)	72.7%
Cardiovascular disease	19	29.7 (3627/12 214)	21.5 (4323/20 153)	**0.25** (0.18, 0.33)	**1.28** (1.07, 1.54)	89.2%
Cerebrovascular accident	9	29.4 (1172/3990)	20.2 (3714/18 409)	**0.25** (0.07, 0.43)	**1.28** (1.20, 1.39)	83.3%
Hypertension	20	24.3 (4733/19 461)	22.2 (1635/7358)	**0.12** (0.07, 0.17)	**1.13** (1.07, 1.19)	76.4%
Diabetes mellitus	21	27.6 (3054/11 084)	24.2 (5197/21 461)	**0.10** (0.05, 0.14)	**1.11** (1.05, 1.15)	62.5%
Chronic respiratory disease[†]	20	24.6 (2347/9528)	21.5 (3888/18 121)	0.04 (0.03, 0.07)	1.02 (0.97, 1.07)	64.3%
Obesity	9	26.7 (556/2079)	31.9 (2402/7528)	0.06 (−0.12, 0.012)	0.94 (0.89, 1.01)	49.2%

[†]Respiratory diseases include a composite of asthma, chronic obstructive pulmonary disease and pulmonary fibrosis. Bold values are statistically significant.

had frailty assessments. We identified five key messages. First, the patients who died were likely to be older, of the male sex, and more likely to have specific comorbidities (dementia, chronic kidney disease, cardiovascular disease, heart failure, diabetes mellitus and previous stroke). Second, there was no increased mortality risk among patients with frailty compared with non-frail patients, after adjusting for age and other covariates. Third, non-frail patients were more commonly admitted to ICU and, once in the ICU, had a higher risk of short-term mortality. Fourth, approximately 75% of patients with frailty were not admitted to ICU, suggesting a more stringent triaging for ICU admission for such patients. Fifth, patients with frailty admitted to ICU were less likely to receive IMV when compared with non-frail patients, and their short-term mortality risk was similar to non-frail patients receiving IMV.

Relation to previous studies

Almost 60% of patients included in our review were identified as frail. The prevalence of frailty in our cohort of patients requiring ICU (57.9%) was comparable with pre-COVID-19 pandemic studies of 30–59%.[54–57] The pooled mortality in patients with frailty (30.6%) was higher than previously reported in hospitalised patients without COVID-19.[57,58] A recent prospective cohort study before the COVID-19 pandemic identified that frailty on admission was associated with a higher risk of death (15.8%) at 30 days, independent of the pneumonia severity in older adults hospitalised with non-COVID-19 pneumonia.[58]

The relationship between frailty and ICU admission or IMV is likely to be complex, as ICU admission and IMV for patients with frailty may be preferentially avoided by patients, their families, or clinicians, while increased vulnerability to illness may increase the need for organ support and ICU resource use.[57] Our study observed that more than a quarter of frail older patients were admitted to ICU. A retrospective study of Australian and New Zealand adult ICU patients aged ≥65 years admitted with pneumonia before the COVD-19 pandemic found that although the patients with frailty were twice as likely to die in the ICU and hospital (12% vs 6%), the adjusted increased risk of death was only observed in those with severe and very severe frailty.[57] Contrastingly, we demonstrated significantly higher mortality rates in those admitted to ICU. The quality of care and patient outcomes may have been compromised in many jurisdictions due to resource constraints and overwhelming caseloads, with several studies demonstrating an association of higher mortality with a higher hospital or regional COVID-19 caseloads, regardless of whether the patients were frail or not,[59] during the peak of the pandemic. Furthermore, our study identified that non-frail patients were more commonly admitted to ICU and more likely to die.

A recent study found that patients with frailty were less likely to receive IMV in the ICU and more commonly received non-invasive ventilatory support.[57] Similarly, we observed that patients with frailty were less likely to receive IMV compared with non-frail patients. The survival proportions in our review were somewhat lower than a recent systematic review that had a

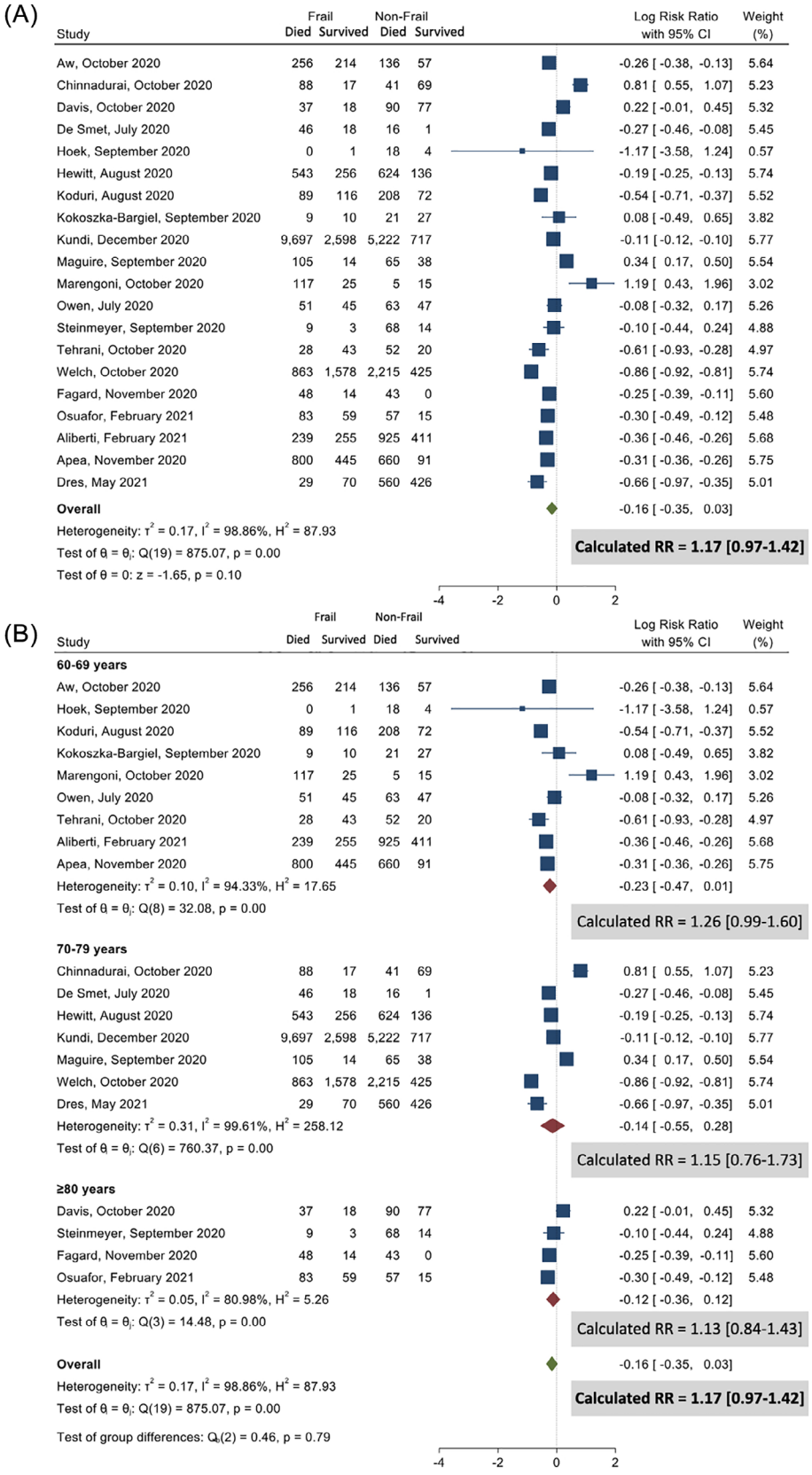
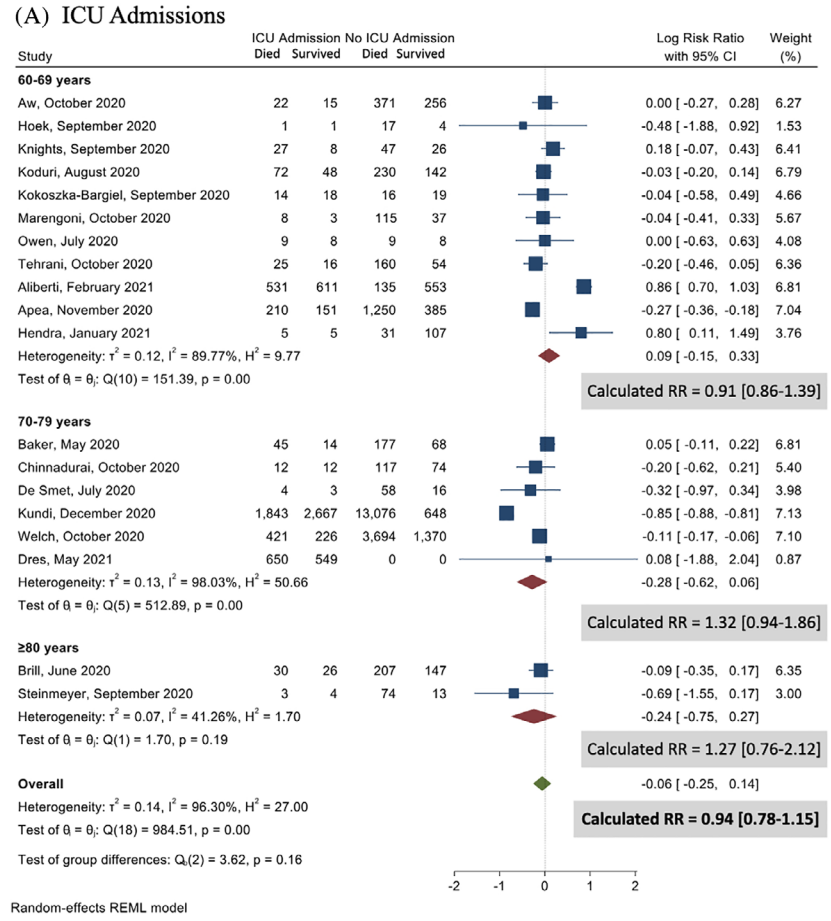


Figure 1 Non-survivors among frail and non-frail patients. (A) All studies and (B) age stratified.



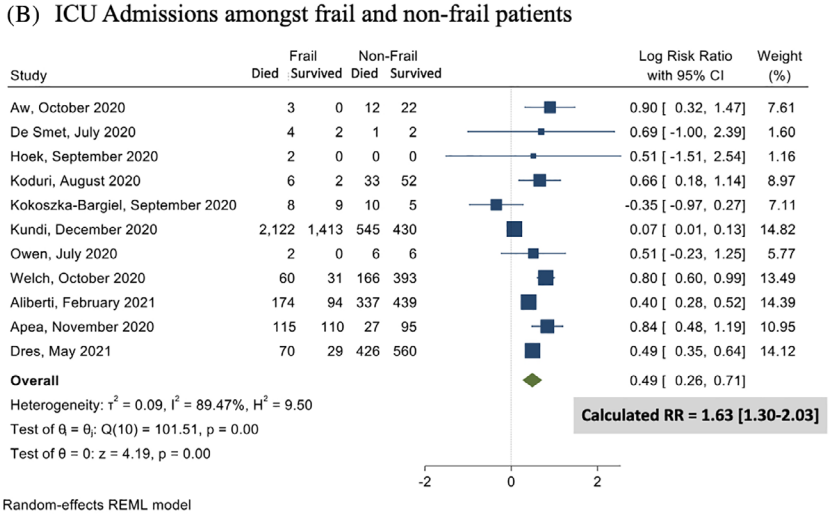
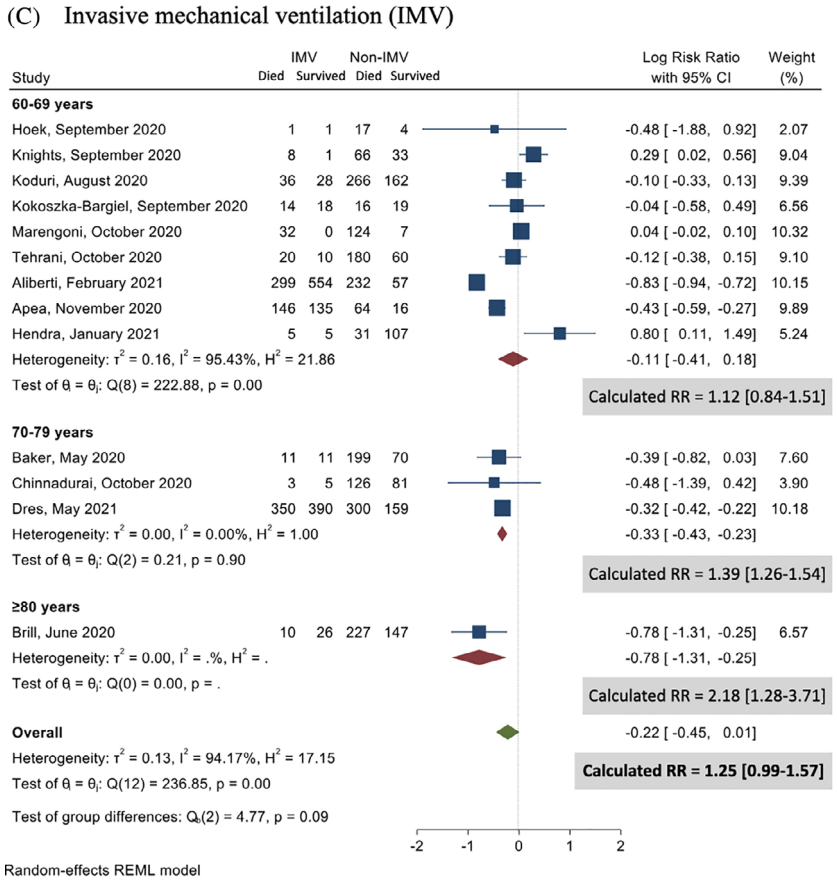


Figure 2 Intensive care unit therapy among survivors and non-survivors. (A) Age group for patients admitted to intensive care unit (ICU); (B) ICU admissions among frail and non-frail patients; (C) patients who required invasive mechanical ventilation (IMV); and (D) invasive mechanical ventilation (IMV) among frail and non-frail patients.

reported case fatality rate of 45% in patients with COVID-19 who needed IMV.[60] We also observed that there was no mortality risk difference between frail and non-frail patients who needed IMV. This might suggest the ICU triaging process and being selective in offering potentially life-saving organ supports, more commonly



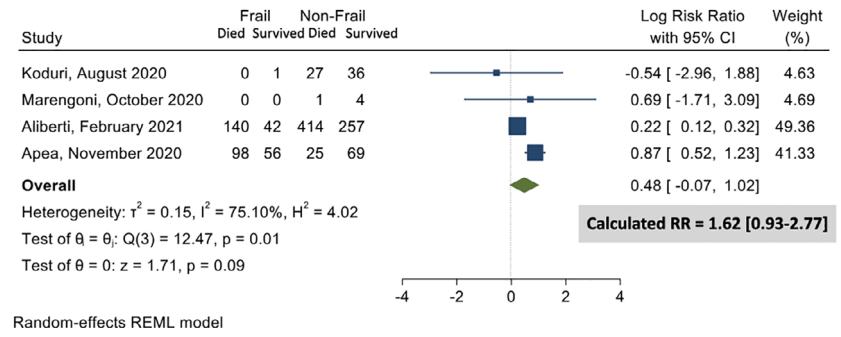


Figure 2 (Continued)

for patients with frailty, by withholding or withdrawing life-sustaining treatments outside ICU among the patients with severe frailty.[56] This could have influenced our results, but we would not expect this to mitigate an association between frailty and hospital survival. In addition, the National Institute for Health and Care Excellence (NICE triage guidelines)[61] could have influenced a lower priority for ICU admission to patients with severe frailty.

Frailty is an important predictive factor for adverse outcomes, including mortality,[62] hospitalisations,[63] and readmission.[64] In addition, older age (>60 years), presence of frailty, multiorgan failure and need for IMV were identified as clinical predictors of mortality in patients with COVID-19.[65] A recent systematic review and meta-analysis recommended that frailty screening should be performed early to stratify high-risk groups.[16] Our absence of an independent association between frailty

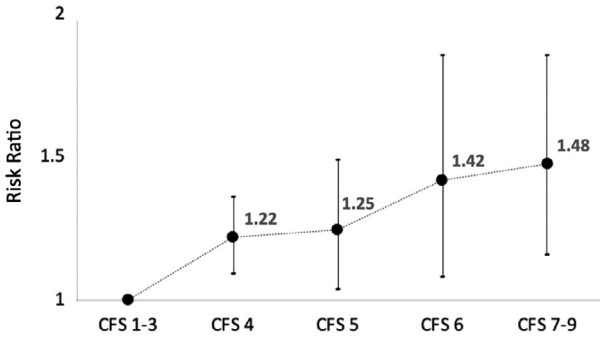


Figure 3 Sensitivity analysis using only clinical frailty scale (CFS): risk associated with increased frailty: CFS 1–3 (reference) with increasing CFS scores.

and short-term mortality may be due to the limitations in the available data, but our findings suggest additional studies are needed before we can propose that frailty be an important predictor of outcome.

Frailty assessments in patients with COVID-19 should not be used in isolation but might be considered as part of an integrated patient-centred assessment along with other factors such as age, comorbidities, disease severity and the availability of medical interventions.[11] Despite vaccinations and public health measures to mitigate this pandemic, COVID-19 might continue to impact severely frail older and vulnerable patients. Therefore, we must ensure that these frail older adults receive goal-concordant care, which may avoid burdensome treatment.[66]

With a plethora of tools available to measure frailty, there are significant variations amongst each measurement tool with feasibility, validity and predictive ability,[67] as different tools or scores identify different subsets of the population as frail.[68] In this systematic review, we included studies that measured frailty using four different tools. Although the most common frailty screening tool used was CFS, it is likely that the pooled data may have been skewed due to the large study that used the HFRS. While the concept of a single unified measurement tool that would enhance adaptability and ease of use seems logical or tempting, this may not be pragmatic. This is because it is unclear if one triage tool is superior to another in a particular setting and some authors advocate for different validated standardised tools for different clinical settings.[69,70] However, we demonstrated no differences in the outcomes based on the sensitivity analysis comparing CFS with other frailty measures grouped together. Although the comprehensive geriatric assessment is generally considered the gold standard,[71] it is impractical for quantifying frailty status in patients with COVID-19. Furthermore, frailty is considered as a continuous measure; however, due to limitations in data and reporting, and because four different frailty tools were used, we had to resort to a dichotomous measure. This classification may have influenced the overall results. However, when we only analysed patients with the CFS score, we observed that the patients with the CFS score ≥4 had a higher risk of short-term mortality.

Limitations

There are several limitations to this systematic review. First, a few included studies had very small numbers of patients. Second, multiple studies may have covered similar patient cohorts. However, each study's period, hospital, and location were considered in the final inclusion of studies to minimise overlap in patient cohorts. Third, the overall heterogeneity was high (I^2 >90%), which may limit the validity of the conclusion from pooled results. Although we performed a sensitivity analysis, the heterogeneity could not be minimised. This is most likely due to the case mix and the variable prevalence of older adults within included populations. Fourth, treatment limitations were not reported in many studies, and even where documented, there was no clear demarcation between frail and non-frail patients. Fifth, a large proportion of patients (n = 18 234) were from one study,[31] that used the administrative HFRS that did not assess the frailty status just before the admission. However, we did sensitivity analysis on patients by including one the CFS demonstrated differences in patients admitted to ICU or those requiring IMV. Finally, limitations of the NOS in terms of inter-rater reliability and external validation should be acknowledged.[72]

Conclusion

This systematic review did not demonstrate an association between frailty status and short-term mortality risk independent of patient age for patients with COVID-19. Approximately 75% of patients with frailty were not admitted to ICU. Moreover, patients with frailty were less likely to receive IMV compared with non-frail patients. Coupled together, these two findings might indicate that frailty was one of the factors used by intensivists to screen patients for ICU admission and/or appropriate limitations of treatment. These in turn might at least in part be related to the prudent selection of patients with frailty amidst the pandemic. There may be important unmeasured confounders, given the observational nature of included studies and that care provided in the context of the pandemic and the lack of data on advance care planning reported by most studies. Future

studies should focus on using standardised frailty assessments with appropriate predictor variables including age, gender, and comorbidities. Our findings reinforce the need for an objective, reproducible measurement of frailty.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Figure S1 PRISMA flowchart of study inclusions and exclusions.
Figure S2 Standardised mean difference in age and age-stratified raw outcomes between survivors and non-survivors.
Figure S3 Age-stratified gender difference amongst survivors and non-survivors.
Figure S4 Frail versus non-frail patients.
Figure S5 ICU Admission: survivor versus non-survivor analysis.
Figure S6 Invasive Mechanical Ventilation (IMV).
Figure S7 *Post Hoc* Analysis CFS versus other frailty measures.
Figure S8 *Post hoc* sensitivity analysis using only CFS: Risk associated with increased frailty: CFS 1–3 (reference) with increasing CFS scores.
Table S1 Summary characteristics and descriptions for the included studies that investigated frailty and COVID-19-related mortality.