What is the relationship between validated frailty scores and mortality for adults with COVID-19 in acute hospital care? A systematic review.

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Abstract

Background & aim

The COVID-19 pandemic has had a disproportionate impact upon older people; the frailty construct has been used to assess risk of poor outcomes in many settings. The aim of this systematic review was to quantify the association between frailty and COVID-19 in relation to mortality in hospitalised patients.

Methods

Medline, Embase and the grey literature were searched for papers from inception to 10th September 2020. Screening (and grading) was undertaken by two reviewers according to pre-defined inclusion and exclusion criteria. Met-analysis was not possible so the result were summarised narratively.

Results

2276 papers were screened resulting in 16 being included in the review. All studies were from Europe, mostly the UK; the median sample size was 308.5, mean age of participants 78.7 and 42% were female. 15/16 used the Clinical Frailty Scale; reported mortality ranged from 19 to 65%. Most, but not all studies showed an association between increasing frailty and a greater risk of dying. Two studies indicated a sub-additive relationship between frailty, COVID-19 and death, and one study showed no increase in dying.

Conclusions

This review showed that whilst many studies have shown an association between an increased risk of COVID-19 related death with increasing frailty, other studies demonstrate a more nuanced understanding of frailty and outcomes in COVID-19 is needed. Clinicians should exert caution in placing too much emphasis on the influence of frailty alone when discussing likely prognosis in older people with COVID-19 infection.

Keywords

COVID-19; frailty, hospital related mortality, systematic review

Key points

Frailty is being used to assess the risk of dying from COVID-19

Researchers should ensure that frailty scales are used as designed when planning and reporting future research.

Emerging studies demonstrate a complex relationship between frailty and COVID-19 related deaths

Clinicians should exert caution in placing too much emphasis on the influence of frailty in older people with COVID-19

Introduction

The COVID-19 pandemic has had a disproportionate impact upon older people. An emerging feature of the clinical response has been to use the frailty construct to estimate likely outcomes or direct treatment escalation planning [1, 2]. Frailty is a state of increased vulnerability to poor resolution of homeostasis after a stressor event, which increases the risk of adverse outcomes, including delirium, disability and death [3-5].

Where frailty has previously been studied in the critical care context, lower levels of frailty have been associated with better outcomes[6-10]. This data may have informed the decision by the National Institute of Clinical Excellence to encourage the use of the Clinical Frailty Scores when considering critical care escalation in older people with COVID-19 [2]. At the time of the NICE guidance being issued, there had been no studies validating such an approach in the context of COVID-19. Since, there have been a number of studies assessing outcomes from COVID-19 in older people using various frailty scales.

The aim of this review was to synthesise emerging findings by quantifying the association between frailty and COVID-19 in relation to mortality in hospitalised patients.

Methods

The full systematic review protocol has been published elsewhere (PROSPERO ID: CRD42020200445)[6].

Search strategies

Medline, Embase and Web of Science databases were searched with exploded MeSH headings and relevant keywords, restricted to English language. Databases were searched from inception to 10th September 2020, and references were managed using Endnote software. The reference lists of included full-texts were hand-searched for additional papers. Indicative search terms are displayed below; these were modified accordingly for each database.

“Frail*”

AND

COVID-19 (("COVID-19" OR "COVID-2019" OR "severe acute respiratory syndrome coronavirus 2" OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" OR "SARS-CoV-2" OR "2019nCoV" OR (Wuhan AND coronavirus))

Grey literature was accessed by searching: Open Grey, medRxiv, bioRxiv.

Inclusion Criteria

- Studies published from inception to 10th September 2020.
- Original peer-reviewed articles, pre-prints, conference proceedings and letters to the editor reporting primary data, in any language.
- Studies reporting mortality as related to frailty in individuals diagnosed with COVID-19 in acute hospital settings.
- Frailty identified using a recognised frailty instrument.
- Participants with a positive diagnosis of COVID-19 (RNA positive or specialist clinical opinion).
- Participants aged 18 years or older.

Exclusion Criteria

- Studies not involving humans
- Articles not reporting primary data
- Studies in which COVID-19 is self-diagnosed

Study Quality Assessment

Two independent reviewers (TDC and KW) assessed the included study quality using the Newcastle-Ottawa Quality Assessment Scale (NOS). The NOS scale uses a 'star system' assess the validity of studies in the domains of the selection and comparability of cohorts, and the ascertainment of either the exposure or outcome of interest. This gives rise to quality ratings:

- **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

Data Extraction

Two reviewers (TDC and KW) identified and exported articles identified by the search strategy into EndNote reference software; duplicates were deleted. Independent title and abstract screens were conducted by TDC and KW identifying articles for full-text extraction. Full-text screening was used to identify a final list of included studies. Relevant data were extracted by two independent researchers (JB and TDC) from the included studies into a pre-established extraction form.

Analysis

A meta-analysis was planned but the heterogeneity in study designs and reporting made this impossible. However, summary statistics for age were combined, after converting medians/IQRs into means and standard deviations using Wan's method [7]. Mortality and CFS relationships were summarised narratively.

Ethics and funding

No ethical approval was required for this work.

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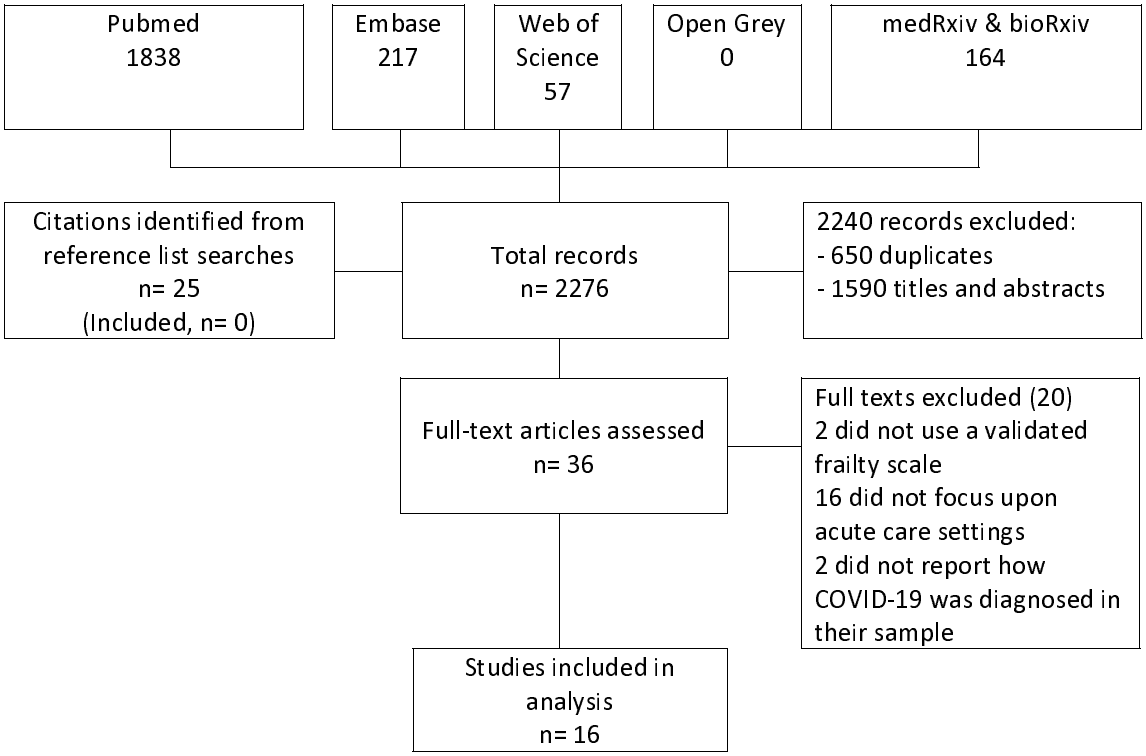
Results

The initial searches identified 2276 records of which 650 were duplicates, leaving 1626 papers for review. After scrutinising the titles and abstracts against the eligibility criteria, 36 papers were retained for full-text review, which led to 16 papers being included for data abstraction (Figure 1).

Figure 1 Study selection



The summary characteristics are shown in Table 1.

Eleven of the sixteen studies were from the UK, and all studies reported findings from acute hospitals (secondary care), with Crespo *et al* [8] reporting specifically on renal transplant recipients and Doglietto on surgical patients [9]; all the other studies reported outcomes for acute medical care. All studies described outcomes in people with clinically and PCR confirmed COVID-19, with the exception of Miles (contemporaneous matched controls), Owen and Aw (clinical and PCR positive versus clinically positive only) and Doglietto (historical matched controls). The overall quality of the studies was fair-good on the Newcastle-Ottawa Quality Assessment Scale.

The median sample size was 308.5 (IQR 94.5-666.5); the largest study reported on almost 2000 participants from England (Apea [10]). Overall the mean age of included participants was 78.7 years (95% CI 74.2-83.2) and 41.8% were female. Where reported, the majority of studies reflected white participants, although Apea had a majority of non-white participants. Frailty was assessed using the Clinical Frailty Score (CFS) in 15 studies, with using Fried's frailty phenotype. COVID-19 infection was confirmed using clinical features and a positive PCR in all studies though Hewitt and Owen [11] also included people with clinical diagnoses.

Table 1 Summary characteristics of retained studies examining frailty and COVID-19 related outcomes

Author	Country	Setting	Sample size	Age; mean (SD)	Proportion female	Proportion White	Frailty measure	COVID diagnosis	NOS grading
Apea	UK	Five acute hospitals	1996	62.2 (17.4)	39%	35%	CFS	PCR	6
Aw	UK	Acute hospital	677	81.1 (8.1)	46%	81%	CFS	PCR	6
Baker	UK	Acute hospital	316	72.7 (17.1)	45%	96%	CFS	PCR	6
Brill	UK	Acute hospital	410	81.1 (8.1)	65%	60%	CFS	PCR	4
Cobos-Siles	Spain	Acute hospital	656	82.7 (10.5)	43%	Not stated	CFS	PCR	6
Crespo	Spain	Renal transplant cohort, acute hospital	16	59.7 (12.6)	6%	Not stated	Fried	PCR	4
De Smet	Belgium	General hospital	81	70.3 (20.1)	59%	Not stated	CFS	PCR	6
Doglietto	Italy	Patients with COVID undergoing surgery	41	82.7 (10.5)	56%	Not stated	CFS	PCR	4
Frost	UK	Seven acute hospitals	749	85.3 (6.8)	32%	Not stated	CFS	PCR	6
Hewitt	Italy/UK	11 acute hospitals (10 England, 1 Italy)	1564	76.0 (5.2)	42%	Not stated	CFS	PCR/clinical	6
Hoek	Netherlands	Multi-centre - solid organ transplant recipients	23	60.7 (15.0)	22%	61%	CFS	PCR	4
Knights	UK	General hospital	108	69.3 (16.3)	39%	76%	CFS	PCR	4
Miles	UK	Acute hospital	217	59	38%	Not stated	CFS	PCR	6
Owen	UK	Acute hospital	301	68.7 (15.6)	44%	Not stated	CFS	PCR/clinical	6
Rawle	UK	Acute hospital	134	80.0 (6.8)	46%	76%	CFS	PCR	4
Thompson	UK	Acute hospital	470	78.8 (8.3)	46%	83%	CFS	PCR	6

Table 2 Descriptions of mortality outcomes

Author	Frailty measure used	Overall cohort mortality	Follow up (days)	Associations of frailty with mortality
Mortality reported using hazard ratios (95% CI)				
Apea [10]	CFS	28.7%	30	Covariates in adjusted analysis: age, sex, ethnicity, smoking, BMI, and IMD CFS 1-2: reference category CF 3-4: 1.61 (0.82-3.16) CFS 5-6: 1.84 (0.93-3.64) CSF 8-9: 3.25 (1.49-7.06)
Aw [12]	CFS	40.0%	34	Covariates in adjusted analysis: age, sex, ethnicity, IMD, previous hospital admissions in 2019 and NEWS-2 CFS 1-3: reference category CFS 4 1.30 (0.76–2.21) CFS 5 1.19 (0.70–2.03) CFS 6 2.13 (1.34–3.38) CFS 7–9 1.79 (1.12–2.88) Sensitivity analyses: association between frailty and mortality was similar when cases were confined to RT-PCR positive cases.
Hewitt [13]	CFS	27.2%	28	Covariates in adjusted analysis: age, sex, smoking, C-reactive protein, diabetes, coronary artery disease, hypertension, renal function CFS 1-2: reference category CFS 3-4: 1.55 (1.00–2.41) CFS 5-6: 1.83 (1.15–2.91) CFS 7–9: 2.39 (1.50–3.81)
Miles [14]	CFS	51.2%	60	Covariates used in the adjusted analysis included age, sex, ethnicity, IMD For each 1 point increase in the CFS score, the hazard ratio for death was 1.88 (1.37-2.59) The different associations with frailty according to COVID-19 status was confirmed by demonstrating an interaction term (HR 0.51, 95% CI 0.37 to 0.71)
Owen [11]	CFS	42.9%	30	Covariates in adjusted analysis: age, sex, acuity and comorbidities. Compares results in those with PCR confirmed COVID-19 only.

				CFS 1-3: reference CFS 4-5: 2.12 (0.86-5.18) CFS 6: 1.69 (0.67- 4.28) CFS 7-8: 2.36 (0.96- 5.76) CFS 9: 11.97 (3.70- 38.72) CFS Not Recorded 2.14 (0.89-5.13) In COVID-19 positive individuals, the interaction between COVID-19 status and CFS suggests a sub-additive relationship.
Mortality reported using risk ratios				
Cobos-Siles [15]	CFS	19.5%	33	Comparing mild to very severely frail older people, the odds ratio for death was 8.73 (95% CI 1.37–55.46)
De Smet [16]	CFS	23.5%	48	Covariates included in adjusted analysis: age, LDH, RT-PCR For each 1-point increase in CFS, the odds of being dead at follow up increased by 1.75 (5% CI 1.1-3.4)
Rawle [17]	CFS	64.9%		The risk of death was associated with an odds ratio of 2.68 (96% CI 1.26,-6.49) for each 1 point increase in CFS.
Thompson [18]	CFS	36.0%	30	Median CFS was significantly higher in non-survivors (6 IQR 4-7 vs. 3 IQR 2-5 for survivors. In the multivariate analysis adjusting for age, hypertension, cancer, CRP, platelet count, acute kidney injury and >50% total lung field infiltrates, frailty was not a significant predictor.
Other comparisons using CFS				
Baker [19]	CFS	25.6%	28	Patients who died without ventilatory support had a median (IQR) CFS score of 7 (6 – 7).
Brill [20]	CFS	42.2%	28	People aged 80+ that died were more frail (median (IQR) CFS 6 (5, 7) vs. 5 (4, 6), p= 0.002
Crespo [8]	Fried	50.0%	14	Mortality if Fried >0 was 5/7 (62.5%)
Doglietto [9]	CFS	19.5%		No data on CFS associated mortality (used as a case-mix adjuster)
Frost [21]	CFS	40.1%	30	Univariate difference in CFS score (median and IQR): at 72-hours: 3 (2-6) alive versus 6 (4-7) deceased at 30-days: 3(2-5) versus alive 5 (3-6) deceased
Hoek [22]	CFS	21.7%		Mean CFS was 5.8 in those that died
Knights [23]	CFS	31.5%	30	Median CFS was higher in patients over 65 who died (5, IQR 4–6) than in survivors (3.5, IQR 2–5) p<0.01).

Mortality was reported variably across the different studies, ranging from 19 to 65%; a descriptive summary is shown in Table 2. It was not possible to undertake a meta-analysis as the study designs, populations included and frailty reporting was too variable (I^2 heterogeneity 94.7%).

Five studies (Apea, Aw, Hewitt, Miles, Owen) reported adjusted hazard ratios for CFS vs. mortality; the reference category was either CFS 1-2 or CFS 1-3 and CFS categories varied across studies – some combining CFS scores, others preserving the scale as 1-9. All showed an increase in mortality risk of between 1.3-3.25 per increase in CFS category, although Owen *et al* found a hazard ratio of almost 12 in those with a CFS score of 9.

Five studies that reported the association of frailty with mortality in older people with clinically and PCR confirmed COVID-19 infection showed a linear increase in the risk of dying increased across frailty strata (Apea, Aw, De Smet, Hewitt, Rawle). Two studies included some form of control groups that permitted testing for interactions between frailty, COVID status and mortality. Miles and Owen both found an interaction between frailty and PCR testing that attenuated the expected mortality associated with increasing frailty. Only Thompson *et al* found that frailty was not a significant predictor in an adjusted analysis. Other studies measured frailty dichotomously, but also found an increased risk of dying from COVID-19 if frailty was present (Cobos-Siles, Crespo). Five studies reported that frailty was more common in older people who had died of COVID-19 (Baker, Brill, Frost, Hoek, Knights, Thompson).

Discussion

Summary

This systematic review identified 16 studies assessing the influence of frailty on COVID-19 related mortality in hospitalised patients. The overall quality of the studies was reasonable, but the more robust studies showed that in older people hospitalised with COVID-19 infection that frailty (measured using the Clinical Frailty Scale) is a predictor of mortality. However, this was not consistent across all cohorts, with some showing a more complex interaction between frailty and COVID-19 status: two studies with contemporaneous non-COVID controls, found a sub-additive interaction with frailty i.e. that the mortality seen in severely frail older people was not as high as expected and excess mortality in those relatively fitter. This may relate to a selection effect, as policy and practice during the pandemic emphasised avoiding hospitalisation in many settings. For example, hospitalisation and treatment escalation plans may have altered over the course of the pandemic and impacted on observed mortality. Patients with higher frailty scores are more likely to represent care-home residents, in whom COVID-19 infection might be managed in the community [24]. Less frail patients may have had more aggressive treatment than those with increased levels of frailty (e.g. steroids, non-invasive ventilation) and this practice may have changed over time and varied between centres. Our findings suggest a more nuanced understanding of frailty and outcomes in COVID-19 is needed.

Strengths and weakness

This review was methodologically robust according to the Quality of Reporting of Meta-analyses (QUOROM) and PRISMA reporting guidelines. It is possible that in this new field, emerging studies not yet published may have been missed, although we searched pre-print collections in an effort to minimise this risk. The British Geriatrics Society has agreed to host a live update of this review so that future studies can be incorporated into the analysis [INSERT www once available]. Whilst the individual papers included in the review were of fair-good quality, frailty (its operationalisation and reported cut-points) and mortality were reported variably across the studies, making meta-analysis impossible and comparisons difficult.

All of the studies were from Europe - mostly the UK - which may limit generalisability to other health systems. We focused upon studies reporting outcomes for hospitalised patients, so we cannot make any

comment about COVID-19 related risk in the wider population, in particular in care homes or population samples.

We did not examine other risk scores designed to predict outcomes from COVID-19, such as those looking at comorbidities or biomarkers [21, 25-27], as these are separate constructs from frailty. In clinical practice, both physiological risk scores and frailty risk scores would be used together to inform prognostication, and future work might compare the relative merits of combined risk scoring.

We focused upon mortality, but outcomes such as function, cognition or quality of life are equally, if not more important, especially for older people [28]. However, in this relatively early stage of the COVID-19 pandemic, we anticipated that there would be very few studies reporting such outcomes, though this will be an important area upon which to focus in the future.

Relationship to existing literature

The CFS appears to perform similarly to other predictors of mortality in the context of COVID-19, such as the Palliative Performance Scale[26], but perhaps less well than the 4C Mortality Score, developed and validated specifically in COVID-19 cohorts [27].

Whilst mortality in hospital may be related to frailty, wider determinants of health have an important impact upon country specific survival rates. Paradoxically, 1% decrease in pre-existing all-cause mortality is associated with a 4.1% increase in the COVID-19 death rate in those ≥60 years of age, thought to be related to an unhealthy survivor effect i.e. longevity at the price of dependency and increased susceptibility to COVID-19 (e.g. care home populations) [29]. This unhealthy survivor effect may in part explain the findings of Owen and Miles of the sub-additive effect found when taking account of frailty and COVID testing interactions.

Implications for research

Larger, more robust studies examining the relationship between COVID-19 and frailty are needed to resolve the limitations of the existing papers. Future studies should preserve the integrity of frailty scales so that comparisons can be made across studies[30], and should take account of the apparent interaction between frailty and COVID-19 testing [11, 14].

Implications for clinical practice

Clinicians should exert caution in placing too much emphasis on the influence of frailty alone when discussing likely prognosis in older people with COVID-19 infection. No tool should be used in isolation, though frailty scores can form part of a more holistic assessment to inform a shared decision making discussion. Frailty can be useful in identifying the risk of complications such as delirium - increasingly being recognised as a high risk scenario [31-33] – and further frailty or deconditioning [34]. Updated clinical guidance on frailty and COVID, as well as other resources are available here: https://www.criticalcarenice.org.uk/ and the British Geriatrics Society will maintain a live web-repository of COVID and frailty studies [HERE].

Appendix 1 Grading of papers using the NOS scale

	Selection of cohorts				parability of coh	Outcome			Total
author	Representativen	Selection of the r	Ascertainment of	Demonstration th	Comparability of	Assessment of o	Was follow up lo	Adequacy of follow up of cohorts	
apea	n/a	n/a	*	n/a	**	*	*	*	6
aw	n/a	n/a	*	n/a	**	*	*	*	6
baker	n/a	n/a	*	n/a	**	*	*	*	6
bellelli	n/a	n/a	*	n/a	**	*	*	*	6
brill	n/a	n/a	*	n/a		*	*	* (40 of 450 lost)	4
cobos-siles	n/a	n/a	*	n/a	**	*	*	*	6
crespo	n/a	n/a	*	n/a		*	*	*	4
de smet	n/a	n/a	*	n/a	**	*	*	*	6
doglietto	n/a	n/a	*	n/a		*	*	*	4
fiorentino	n/a	n/a	*	n/a	**	*	*	*	6
frost	n/a	n/a	*	n/a	**	*	*	* (81 of 850 miss	6
hewitt	n/a	n/a	*	n/a	**	*	*	* (64 of 1564 mis	6
hoek	n/a	n/a	*	n/a		*	*	*	4
knights	n/a	n/a	*	n/a		*	*	*	4
koduri	n/a	n/a	*	n/a	**	*	*	*	6
miles	n/a	n/a	*	n/a	**	*	*	*	6
owen	n/a	n/a	*	n/a	**	*	*	*	6
philipose	n/a	n/a	*	n/a	**	*	*	*	6
rawle	n/a	n/a	*	n/a	**	*	*	*	4
thompson	n/a	n/a	*	n/a	**	*	*	*	6

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