

RESEARCH PAPER

Comparing associations between frailty and mortality in hospitalised older adults with or without COVID-19 infection: a retrospective observational study using electronic health records

RHIANNON K. OWEN¹, SIMON P. CONROY², NICHOLAS TAUB³, WILL JONES⁴, DANIELE BRYDEN⁵, MANISH PAREEK⁶, CHRISTINA FAULL¹, KEITH R. ABRAMS¹, DANIEL DAVIS⁷, JAY BANERJEE⁸

¹Health Sciences, University of Leicester, Leicester, Leicestershire, UK

²Department of Health Sciences, Centre for Medicine University of Leicester, University of Leicester School of Medicine, Leicester LE1 7HA, UK

³Department of Health Sciences, University of Leicester, Leicester LE1 6TP, UK

⁴Emergency Department, University Hospitals of Leicester NHS Trust, Leicester, UK

⁵Critical Care, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

⁶Cardiovascular Sciences, University of Leicester, Leicester, UK

⁷MRC Unit for Lifelong Health and Ageing, University College London, London WC1B 5JU, UK

⁸University Hospitals of Leicester NHS Trust, Leicester, UK

Address correspondence to: Simon P. Conroy, Department of Health Sciences, College of Life Sciences, George Davies Centre, University of Leicester, University Road, Leicester LE1 7RH, UK. Tel: (+44) (0)116 252 5992. Email: spc3@le.ac.uk

Abstract

Background: The aim of this study was to describe outcomes in hospitalised older people with different levels of frailty and COVID-19 infection.

Methods: We undertook a single-centre, retrospective cohort study examining COVID-19-related mortality using electronic health records, for older people (65 and over) with frailty, hospitalised with or without COVID-19 infection. Baseline covariates included demographics, early warning scores, Charlson Comorbidity Indices and frailty (Clinical Frailty Scale, CFS), linked to COVID-19 status.

Findings: We analysed outcomes on 1,071 patients with COVID-19 test results (285 (27%) were positive for COVID-19). The mean age at ED arrival was 79.7 and 49.4% were female. All-cause mortality (by 30 days) rose from 9 (not frail) to 33% (severely frail) in the COVID-negative cohort but was around 60% for all frailty categories in the COVID-positive cohort. In adjusted analyses, the hazard ratio for death in those with COVID-19 compared to those without COVID-19 was 7.3 (95% CI: 3.00, 18.0) with age, comorbidities and illness severity making small additional contributions.

Interpretation: In this study, frailty measured using the CFS appeared to make little incremental contribution to the hazard of dying in older people hospitalised with COVID-19 infection; illness severity and comorbidity had a modest association with the overall adjusted hazard of death, whereas confirmed COVID-19 infection dominated, with a sevenfold hazard for death.

Keywords: COVID-19, frailty, cohort study, older people

Key Points

- COVID-19 was associated with mortality rates of 60% in hospitalised older people.
- Illness severity and comorbidities, but not frailty, slightly increase the risk of dying from COVID-19.
- Frailty remains an important marker of prognosis in non-COVID-19 related scenarios.

Introduction

Coronavirus disease 2019 (COVID-19) is a viral illness that currently has no treatment, which impacts upon the course, duration or severity of the disease. In a proportion of individuals, COVID-19 leads to a severe inflammatory process and damage to the lungs [1]. Some patients develop respiratory failure and require critical care support, with the hope that the immune response settles and the individual's own organs recover.

The COVID-19 pandemic has forced countries across the world to consider decisions about escalation for critical care treatment, typically based upon clinicians' perceptions of who might benefit from organ support, such as invasive ventilation. Age has been a feature of such decision-making and has been shown to be an important marker of poor outcomes for people with COVID-19 [2–4]. The UK Intensive Care National Audit and Research Centre (ICNARC) produces weekly summaries of outcomes of patients admitted to critical care, with survival reported by age category. As of 26 June 2020, there have been 1,229 COVID-19-related deaths reported in critical care in those 70 years or over (60.5% mortality) compared to 2,250 deaths in those aged 50–69 (41.5% mortality). The ICNARC acknowledges that in the early phase of the pandemic, published figures for survival were biased towards those who recovered or died quickly and the true figures are not yet known as some individuals are still receiving critical care and hospital treatment. Nevertheless, age-based outcomes appear to be influencing decisions to offer critical care organ support, rather than looking at frailty in the older person as a marker of potential recovery and ability to benefit from treatment [5]. Frailty research seeks to stratify older people in terms of their risk of adverse outcomes based on their physiological reserve rather than chronological age [6]. In the non-COVID-19-related critical care context, Clinical Frailty Scale (CFS) scores ≥ 5 are associated with between 40 and 60% 30-day mortality after critical care, with much better outcomes seen in older people at lower levels of frailty [7–11]. The use of age-based cut-offs alone raises the possibility that some older people who might benefit from critical care may not be offered such treatment. In the UK, the National Institute for Health and Care Excellence (NICE) guidance NG 159, COVID-19 rapid guideline: critical care in adults advises using the CFS to guide clinical decision-making in older patients relating to discussions of critical care escalation [12].

The aim of this study was to describe mortality for older people with different levels of frailty, hospitalised with COVID-19 infection.

Methods

Study design and setting

We undertook a single-centre, retrospective cohort study measuring mortality captured on routine datasets, for hospitalised older people (65+) with frailty, with and without COVID-19 infection. The study took place at the Leicester Royal Infirmary (LRI), one of the largest single-site Emergency Departments (ED) in the UK. The catchment population is approximately 1.1 million people, of whom around 165,000 are 65 years or older. The ED has over 230,000 attendances a year, including around 48,000 in people aged 65+.

Data sources

The CFS is a 9-point scale representing different levels of frailty [13]; it is increasingly being used in the UK to assess frailty in the urgent care context [14]. The LRI ED has been implementing frailty identification since 2016, initially determining which validated frailty assessment tool was quickest and simplest to use [15] and then implementing CFS scoring using a structured programme including:

1. Internal validation of CFS use—clinical records were reviewed for evidence of frailty documentation and accuracy (inter-rater reliability kappa >0.8 [16]).
2. Interventions—education and training of all staff groups, individualised feedback and embedding the CFS into the electronic health record.
3. Continuous measurement—run charts (time-series analysis) were used to assess CFS use, and notes were reviewed for evidence that frailty identification was linking to elements of comprehensive geriatric assessment [17].

The CFS was recorded on the electronic health record (EHR) by the initial assessing clinician—typically a nurse or emergency physician. We linked EHR frailty scores to the Patient Administration System (PAS) using the hospital number (unique identifier); this allowed hospital processes and mortality to be captured at the individual patient level.

We captured COVID-19 status by linking to the microbiology laboratory using the hospital number. Samples for SARS-CoV-2 polymerase chain reaction (PCR) were sent to central Public Health England testing facilities from 23 January 2020 and from 13 March 2020 that were tested at the University Hospitals of Leicester—using real-time reverse transcription PCR targeting regions of the SARS-CoV-2 RNA genome.

Population

This study examined mortality in people aged 65 or older, who were admitted to hospital via the ED or died in the ED, with a COVID-19 test result following their first ED attendance between 29 February 2020 (pre-pandemic) and 16 April 2020.

For the purposes of this study, older people were assigned into six frailty categories reflecting the full spectrum of frailty rather than the dichotomous frail versus not frail approach used in previous critical care studies [7–11]:

- CFS 1–3: fit-managing well
- CFS 4–5: vulnerable/mild frailty
- CFS 6: moderate frailty
- CFS 7–8: severely to very severely frail
- CFS 9: terminally ill; life expectancy <6 months, but not otherwise evidently frail
- CFS not recorded: missing

We also reported outcomes using the CFS as a dichotomous predictor (CFS <5 versus ≥5), reflecting the NICE critical care guidance [12].

Clinical suspicion for testing was primarily based upon the prevailing Public Health England guidance at the time, which varied over the course of this study [18], but essentially included the following patient groups:

- Requiring admission to hospital (a hospital practitioner has decided that admission to hospital is required with an expectation that the patient will need to stay at least one night) and
- Have either clinical or radiological evidence of pneumonia or
- Acute respiratory distress syndrome or
- Influenza-like illness (fever ≥37.8°C and at least one of the following respiratory symptoms, which must be of acute onset: persistent cough (with or without sputum), hoarseness, nasal discharge or congestion, shortness of breath, sore throat, wheezing, sneezing)

Outcomes

Baseline data related to the index ED presentation only (the individual's first emergency presentation during the study period for which they received a COVID-19 test). Baseline data included age, sex, frailty (CFS), acuity (first recorded NHS Early Warning Score-2 at emergency presentation) [19], Charlson Comorbidity Index (CCI) [20] and COVID-19 status. Patient administration data contained a list of International Classification of Disease version 10 (ICD-10) codes (used for reimbursement) from which we calculated the CCI.

We tracked subsequent COVID-19 testing, hospital use and mortality (in and outside of hospital) up until 21 April 2020; the primary outcome was time to death (all-cause mortality). Deaths occurring outside of hospital were captured daily, generated from the NHS Spine (centralised national registry) as well as reports from community services (primary

care practitioners, social care etc.) and then updated in the Patient Administration System. Deaths in hospital were recorded by the ward clerks on discharge and validated by the hospital data quality team. Secondary outcomes included:

- Mortality at 30 days
- Admission to critical care
- Mortality in critical care

Critical care admissions were ascertained from the EHR; palliative care referrals and symptom management were not available.

Analyses

Baseline characteristics were reported using descriptive statistics. Mortality was described using survival analysis, displayed as Kaplan–Meier plots. Individuals alive at study end were censored on 21 April 2020. For individuals with readmissions, all preceding admissions were censored the day before subsequent readmission. A Cox proportional hazards model using robust standard errors to account for multiple observations (arising from readmissions) of the same individual was fitted. For subsequent admissions without further COVID-19 testing, a last test carried forward approach was implemented. The assumption of proportionality for Cox proportional hazards model was assessed for COVID-19 status and CFS categories. Neither of these variables were statistically significant, indicating that the proportionality assumption was not violated. Adjusted (based on clinical opinion and prognostically important variables for COVID-19-related outcomes [2–4]) and unadjusted hazard ratios were used to compare the rate of death for those with and without confirmed COVID-19, at different levels of CFS. We tested for an interaction between COVID-19 status and CFS. Statistical significance was assessed at the 5% significance level.

For secondary outcomes including mortality at 30 days, admission to critical care and mortality in critical care, descriptive statistics were calculated, as we anticipated that this exploratory study would not have adequate power to undertake modelling of the secondary outcomes.

Pre-planned sensitivity analysis.

We examined mortality outcomes before and after the implementation of the NICE guideline [12] being launched (25 March 2020) in a pre-planned sensitivity analysis. Adjusted hazard ratios were calculated adjusting for admissions pre and post the NICE guideline, together with the interaction between the implementation of the NICE guideline, different levels of CFS and COVID-19 status. Time-dependent effects associated with NICE guidelines were explored. To illustrate the impact of NICE guidelines on mortality outcomes, Kaplan–Meier plots and Lexis diagrams were produced for COVID-19-positive patients admitted pre- and post-NICE guideline launch.

All analyses were performed in Stata version 16. The Lexis diagram was produced using R version 3.6.1.

Table 1. Baseline characteristics of all eligible participants at their index emergency presentation, stratified by COVID-19 status

Variable	COVID-19 negative at index presentation (<i>n</i> = 786)	COVID-19 positive at index presentation (<i>n</i> = 285)
Mean age (SD)	80.1 (8.6)	78.8 (8.3)
Female sex	398 (50.6%)	131 (46.0%)
CFS 1–3	90 (11.5%)	49 (17.2%)
CFS 4–5	159 (20.2%)	70 (24.6%)
CFS 6	145 (18.5%)	38 (13.3%)
CFS 7–8	129 (16.4%)	41 (14.4%)
CFS 9	6 (0.8%)	0 (0%)
CFS < 5	185 (23.4%)	93 (32.6%)
CFS ≥ 5	344 (43.8%)	105 (36.8%)
CFS not recorded	257 (32.7%)	87 (30.5%)
Median early warning score (IQR)	4 (1–6)	4 (2–7)
Early warning score > 5	330 (42.6%)	143 (50.2%)
Median Charlson Comorbidity Index (IQR)	1 (0–2)	0 (0–1)

Governance

Guidance from the UK National Health Service Health Research Authority was that ethical approval was not required. The study was undertaken as a service evaluation, under the auspices of the University Hospitals of Leicester frailty strategy; governance approvals were granted by the hospital’s Clinical Audit and Service Evaluation department. All data was fully anonymised prior to transfer from the NHS to the University of Leicester for analysis. The sponsor (University Hospitals of Leicester) had no role in data collection, analysis, interpretation, writing of the manuscript and the decision to submit. RO, NT, SC and WJ had access to all of the data; all authors agreed upon the decision to submit the paper.

Results

We obtained data on 4,104 ED attendances in individuals aged 65+, giving rise to 2,713 hospital admissions or deaths in ED; of these, 1,123 had a COVID-19 test available (Figure 1) and re-admissions accounted for 52 of these presentations.

Baseline data at first ED presentation for eligible participants are summarised in Table 1. Of the participants with an index ED attendance admitted via (or dying in) the ED with a COVID-19 test available (*n* = 1,071), the mean age at ED arrival was 79.7 (SD 8.5, range 65–104), 49.4% were female; and 67.9% (727) had CFS scores recorded. Those with COVID-19 infection were slightly younger, less frail, had greater illness severity and marginally fewer comorbidities than those without COVID-19 infection.

Table 2 shows the short-term outcomes per admission (rather than at the individual patient level) by COVID-19 status for CFS and NICE CFS criteria; corresponding survival plots for 30-day mortality are provided in Figure 2 and Figure S1 (Supplementary data), respectively.

Increasing frailty appeared to be associated with greater mortality at 30 days in COVID-19-negative individuals;

however, this was not the case for COVID-19-positive individuals where 63.4 and 65.3% of hospitalised individuals died with CFS less than 5 and greater than or equal to 5, respectively (Table 2). Admission to critical care was higher in COVID-19-positive individuals with a CFS score < 5, compared with COVID-19-negative individuals (Table 2).

Table 3 shows the unadjusted and adjusted hazard ratios, adjusting for age, sex, acuity and comorbidities, for all-cause mortality. The unadjusted analysis suggests that those with COVID-19 had an eightfold higher hazard for death (HR: 8.16, 95% CI 3.34, 19.9) compared to those without COVID-19 having adjusted for frailty. Increasing CFS appeared to significantly increase the hazard for mortality in COVID-19-negative individuals. In COVID-19-positive individuals, the interaction between COVID-19 status and CFS suggests a sub-additive relationship, i.e. the hazard for death is less than the combination of the main effects of COVID-19 and CFS. In the adjusted model, the hazard for death was highest for those with COVID-19 (HR 7.34, 95% CI 3.00–17.95). CFS of 9 was the only CFS category that reached statistical significance in the adjusted analysis (HR 11.97, 95% CI 3.70–38.72), although this category describes individuals who are terminally ill rather than frail (Table 2). The point estimate for the interaction between COVID-19-positive and CFS suggested a sub-additive relationship, but this was not a statistically significant finding. The first NHS Early Warning Score (EWS) at presentation increased the hazard for death (HR 1.16, 95% CI 1.12–1.20) per unit increase in EWS. Each year increase in age was associated with a 3% increased hazard of mortality (HR 1.03, 95% CI 1.01–1.04), and each point increase in the Charlson Comorbidity Index was associated with a 9% (HR 1.09, 95% CI 1.03–1.15) increased hazard of death.

Figure 3 illustrates the overall hazard ratios and 95% confidence intervals of the adjusted model for COVID-19 status, sex and CFS score and the interaction between COVID-19 status and CFS score, having adjusted for age,

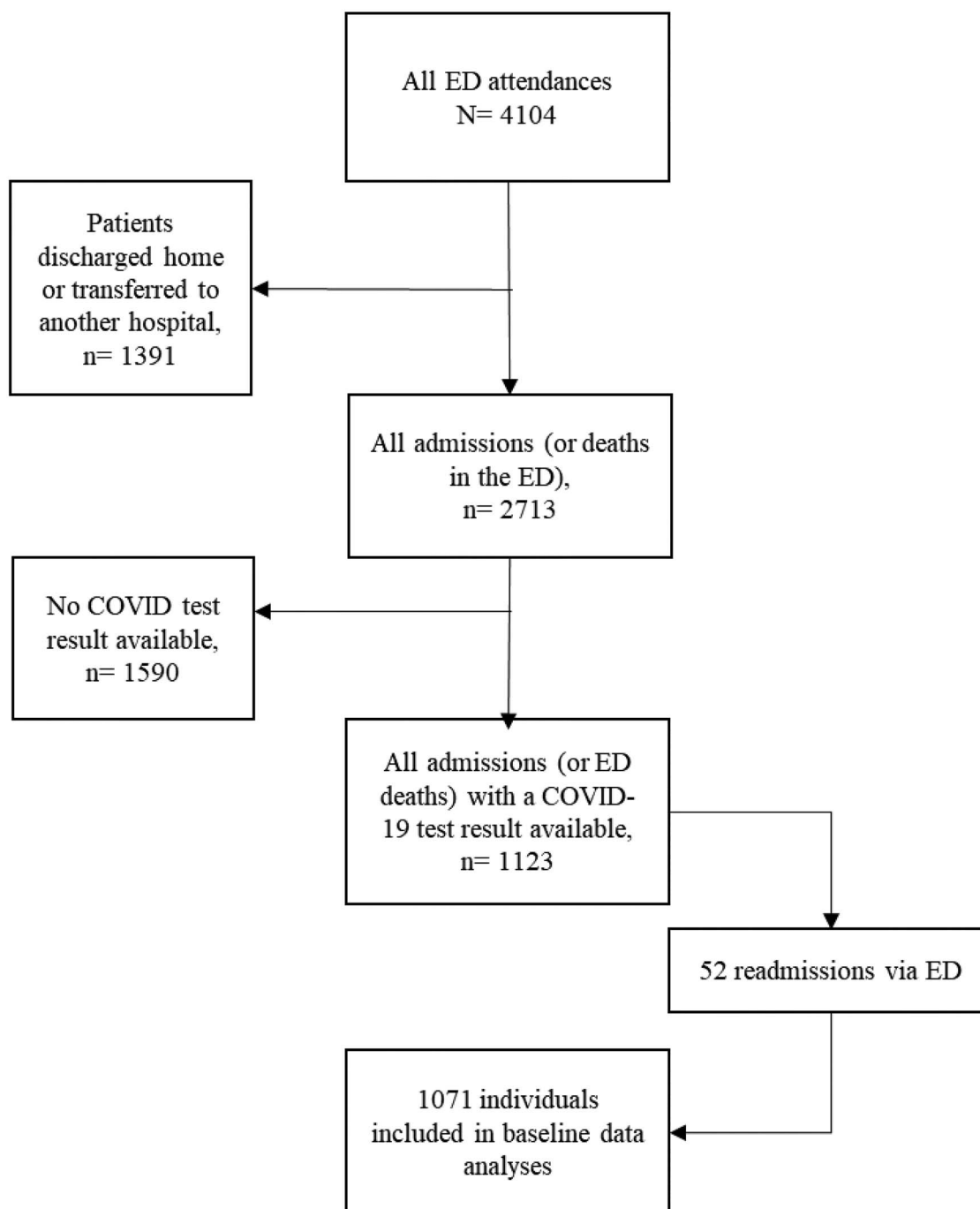


Figure 1. Study flow diagram.

first NHS early warning score and Charlson Comorbidity Index. The reference subgroup was COVID-19 negative, CFS score 1–3 and female. For COVID-19-negative subgroups, the hazard of mortality increases with increasing CFS scores. COVID-19-positive subgroups have a higher hazard of death compared to COVID-19-negative subgroups, but this does not appear to increase with increasing CFS score, with the exception of terminally ill subgroups (CFS score of 9).

Adjusting for NICE CFS criteria, COVID-19-positive status had an increased hazard of mortality (HR 4.78, 95%

CI 2.79–8.20). CFS ≥ 5 had an adjusted hazard ratio of 1.67 (95% CI: 0.98–2.83). Age, male sex, EWS and Charlson scores were all associated with relatively minor increases in mortality hazard in the adjusted model (Table S1, Supplementary data). There was a statistically significant interaction between COVID-19 status and CFS ≥ 5 , suggesting a sub-additive relationship between COVID-19 status and CFS score (HR 0.51, 95% CI 0.26–0.98).

There did not appear to be a difference in mortality outcomes following the introduction of NICE guidance (Table S2, Supplementary data). For COVID-19-positive

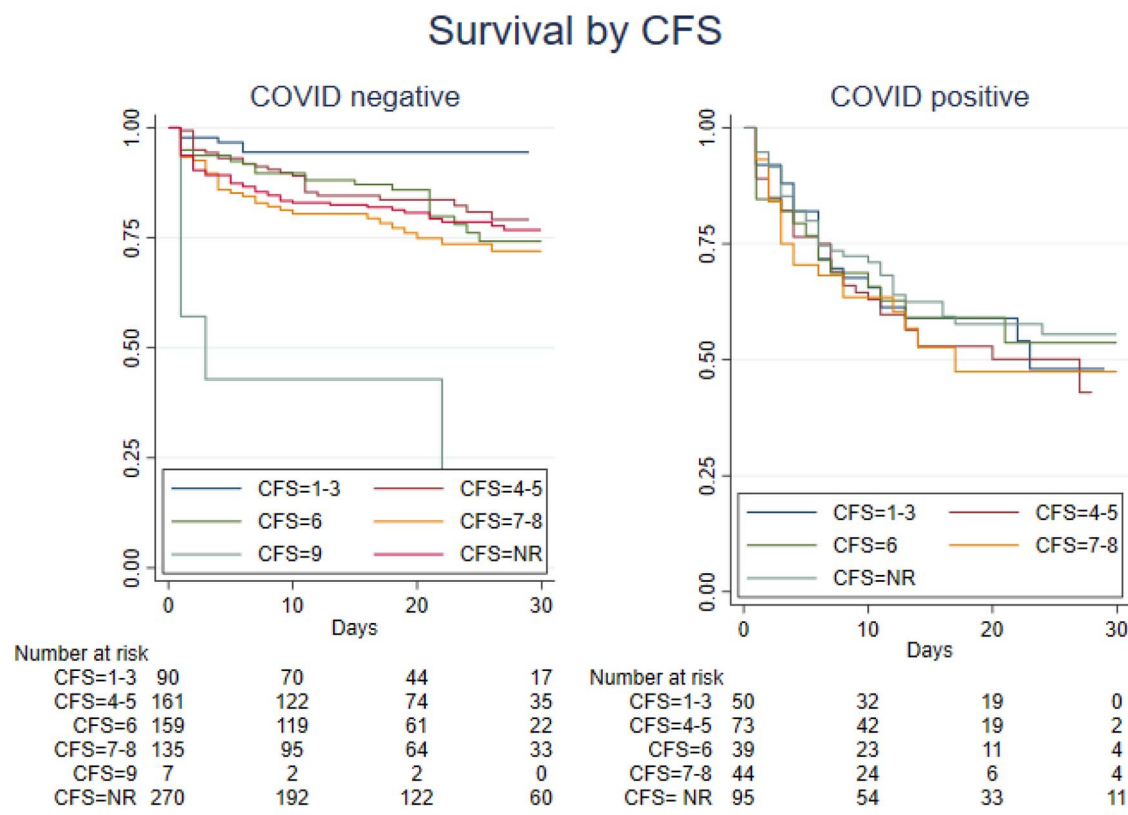


Figure 2. Kaplan–Meier plots showing time to all-cause deaths by CFS category.

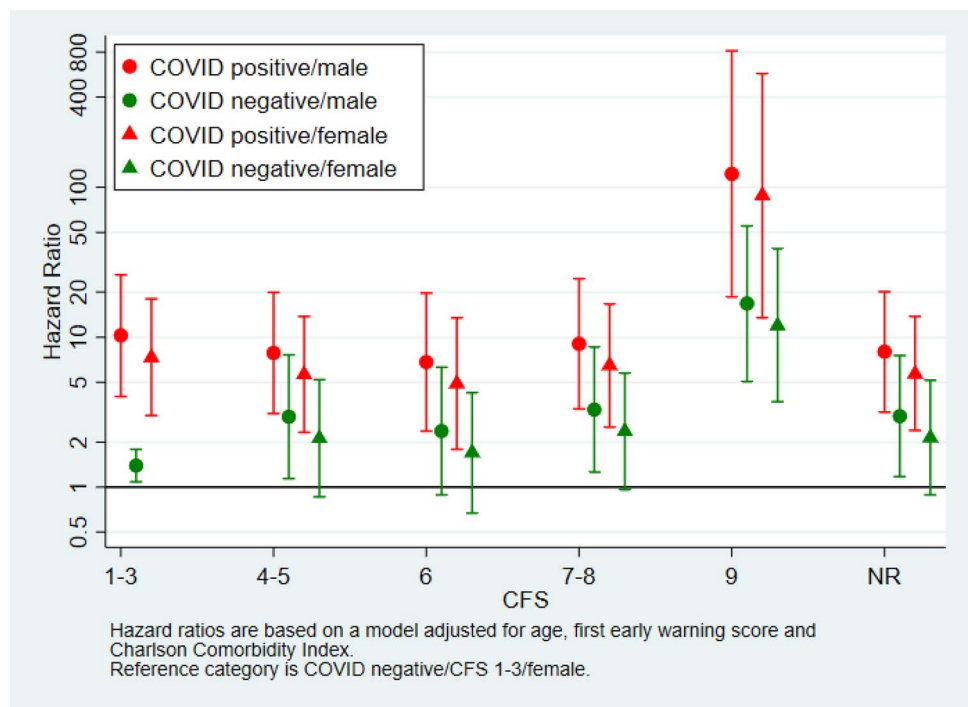


Figure 3. Adjusted hazard ratios for death, by different CFS categories

Table 2. Short-term outcomes for all admissions by COVID-19/frailty status

COVID-19-negative admissions (<i>n</i> = 822)			COVID-19-positive admissions (<i>n</i> = 301)				
CFS categories	Mortality by 30 days (all causes) (<i>n</i> , %) ^a	Admission to critical care (<i>n</i> , %) ^b	Mortality in critical care (<i>n</i> , %) ^c	CFS categories	Mortality by 30 days (all causes) (<i>n</i> , %) ^a	Admission to critical care (<i>n</i> , %) ^b	Mortality in critical care (<i>n</i> , %) ^c
CFS 1–3 (<i>n</i> = 90)	5 (8.9%)	1 (1.1%)	0 (0%)	CFS 1–3 (<i>n</i> = 50)	22 (61.1%)	9 (18.0%)	5 (55.6%)
CFS 4–5 (<i>n</i> = 161)	27 (24.2%)	2 (1.2%)	0 (0%)	CFS 4–5 (<i>n</i> = 73)	34 (62.4%)	4 (5.6%)	1 (25%)
CFS 6 (<i>n</i> = 159)	27 (26%)	0 (0%)	0 (0%)	CFS 6 (<i>n</i> = 39)	16 (54.2%)	0 (0%)	0 (0%)
CFS 7–8 (<i>n</i> = 135)	33 (32.8%)	0 (0%)	0 (0%)	CFS 7–8 (<i>n</i> = 44)	20 (58.8%)	0 (0%)	0 (0%)
CFS 9 (<i>n</i> = 7)	5 (84.5%)	0 (0%)	0 (0%)	CFS 9 (<i>n</i> = 0)	NA	NA	NA
CFS < 5 (<i>n</i> = 187)	18 (14.8%)	2 (1.1%)	0 (0%)	CFS < 5 (<i>n</i> = 96)	45 (63.4%)	12 (12.8%)	6 (50%)
CFS ≥ 5 (<i>n</i> = 365)	79 (30.8%)	1 (0.3%)	0 (0%)	CFS ≥ 5 (<i>n</i> = 110)	47 (65.3%)	1 (0.93%)	0 (0%)
CFS NR (<i>n</i> = 270)	54 (28.1%)	3 (1.1%)	2 (66.7%)	CFS NR (<i>n</i> = 95)	37 (51.8%)	4 (4.3%)	2 (50%)

^a Percentages calculated as actuarial percentages. ^b Denominator is those alive at discharge from ED. ^c Denominator is those admitted to critical care.

patients, the influence of NICE guidance on mortality outcomes is displayed using a Lexis diagram (Figure S2, Supplementary data) and Kaplan–Meier plots (Figure S1, Supplementary data), which showed no noticeable change in mortality outcomes pre- and post-launch of NICE guidance.

Discussion

Summary

This is one of the first studies to report outcomes for older people hospitalised during the COVID-19 pandemic, using prospectively measured grades of frailty. The most striking finding is that frailty, measured using the CFS, appears to make little incremental contribution to estimating hazard of dying. Illness severity measured using the NHS Early Warning Score had a modest contribution to the overall adjusted hazard for death, whereas confirmed COVID-19 infection dominated, with a sevenfold hazard. Although not statistically significant, the shape of the survival plot for the COVID-19-negative group resembled the expected distribution, with lower CFS categories associated with a reduced hazard for death. The observed interaction between the NICE guidance suggested CFS ≥ 5 category and COVID-19 suggests a sub-additive effect (HR 0.51), which could be related to a selection effect. For example, patients with a higher frailty score are more likely to be care home residents, in whom COVID-19 infection might be managed in the community [21]. This hypothesis is partly supported by the lower age, frailty and comorbidity seen in the COVID-19-positive group, suggesting the sickest and more frail might be managed in the community.

Frailty has been shown to be an important predictor of outcomes in hospitalised older people in a wide range of conditions [8,22,23] including sepsis (CFS ≥ 5 hazard for in-hospital death, adjusted odds ratio, 1.8) [24], and increasing frailty and illness severity have been shown to synergistically increase the risk of dying in acute hospital settings [25]. This suggests that there is something different about COVID-19 infection that makes it such a dominant influence over outcomes, over and above other well-established prognostic indicators (age, sex, comorbidities and frailty). Even in younger people, COVID-19 infection is reported to cause severe overwhelming conditions such as acute respiratory distress syndrome and multi-organ failure [1], thought to be mediated by a ‘cytokine storm’—the uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines and chemokines [26,27]. Older people with frailty are vulnerable to functional decline in the face of an ‘apparently innocuous insult’, such as a minor infection or medication side effect [28], so it is not surprising that their mortality is high with COVID-19. But the lack of discrimination by frailty state is somewhat surprising; *a priori* it could have been speculated that more robust older people (e.g. CFS 1–3) might be better able to withstand COVID-19 infection. The pathogenesis of frailty is thought to include elevated IL-6 levels, C-reactive protein

Table 3. Unadjusted and adjusted hazard ratios for all-cause mortality in hospitalised individuals with or without COVID-19

	Hazard ratio	95% confidence interval	P-value
Unadjusted model			
Main effects			
COVID-19 negative	Reference	Reference	Reference
COVID-19 positive	8.16	(3.34, 19.9)	<0.001
CFS 1–3	Reference	Reference	Reference
CFS 4–5	2.72	(1.13, 6.55)	0.025
CFS 6	2.78	(1.15, 6.73)	0.023
CFS 7–8	3.95	(1.65, 9.42)	0.002
CFS 9	19.97	(6.20, 64.33)	<0.001
CFS NR	3.26	(1.40, 7.58)	0.006
Interaction effects			
COVID-19 positive and CFS 4–5	0.41	(0.15, 1.14)	0.087
COVID-19 positive and CFS 6	0.35	(0.12, 1.04)	0.059
COVID-19 positive and CFS 7–8	0.31	(0.11, 0.86)	0.025
COVID-19 positive and CFS 9	NA	NA	NA
COVID-19 positive and CFS NR	0.27	(0.10, 0.72)	0.009
Adjusted model			
Main effects			
COVID-19 negative	Reference	Reference	Reference
COVID-19 positive	7.34	(3.00, 17.95)	<0.001
CFS 1–3	Reference	Reference	Reference
CFS 4–5	2.12	(0.86, 5.18)	0.101
CFS 6	1.69	(0.67, 4.28)	0.268
CFS 7–8	2.36	(0.96, 5.76)	0.060
CFS 9	11.97	(3.70, 38.72)	<0.001
CFS NR	2.14	(0.89, 5.13)	0.089
Female sex	Reference	Reference	Reference
Male sex	1.40	(1.09, 1.79)	0.009
Age	1.03	(1.01, 1.04)	0.001
First early warning score	1.16	(1.12, 1.20)	<0.001
Charlson Comorbidity Index	1.09	(1.03, 1.15)	0.004
Interaction effects			
COVID-19 positive and CFS 4–5	0.36	(0.13, 1.02)	0.054
COVID-19 positive and CFS 6	0.39	(0.13, 1.22)	0.107
COVID-19 positive and CFS 7–8	0.37	(0.13, 1.07)	0.067
COVID-19 positive and CFS 9	NA	NA	NA
COVID-19 positive and CFS NR	0.36	(0.14, 0.98)	0.045

and tumour necrosis factor- α [29], similar in some regards to the cytokine storm seen in COVID-19; it is possible that COVID-19 induces accelerated frailty—over days rather than years [30].

Strengths and limitations

This was a single-centre study and it is possible that local service configurations may have influenced outcomes. In particular it is likely that the more severely frail such as care home residents might not have been referred to hospital with possible COVID-19 infection but managed (palliatively) in the care home. However, the COVID-19-positive group included older people from across all frailty categories, allowing relative discrimination to be assessed. Although other authors report that frailty is associated with poorer outcomes in older people with COVID-19 [31], they studied a population which included those less than 65 years of age, did not adjust for illness severity and did not use the full range of the CFS, for example, reporting on those with

CFS scores 7–9, rather than individually as in our study. A separate study from London (not yet published) using similar methods to our paper reports strikingly similar findings [32], suggesting that our report is not an isolated phenomenon.

At the time of the study, universal COVID-19 screening was not in place, so the sample only reflects those in whom the assessing clinician thought there was a possibility of COVID-19 infection; decisions to test may have been influenced by frailty status and perceived outcomes. COVID-19 PCR has reported false-negative rates of between 2 and 29% (equating to sensitivity of 71–98%), based on negative PCR tests which were positive on repeat testing [33], so it is possible that some true COVID-19 cases were not identified using PCR and may appear in the COVID-19-negative group. This would have the effect of reducing precision, but the magnitude of the hazard ratio for mortality suggests this is not a major limitation.

Around one-third of older people did not have a CFS score at ED presentation; their outcomes are broadly similar to those with lower CFS scores—this is consistent with

non-COVID-19-related patterns of CFS scoring (seen in unpublished data from our hospital); again this could have reduced the precision of the study, though the magnitude of reported hazard ratios suggests this is not a major limitation. Inter-rater reliability for CFS categorisation during the study period was good (kappa 0.7).

Not only did we examine the influence of frailty in people with COVID-19, but we also took account of illness severity using the NHS Early Warning Scores and disease burden using the Charlson score; few previous studies of frailty in acute care settings have adjusted for illness severity. We were able to track the use of critical care services over calendar time, as it is possible that NICE guidance may have altered the threshold for using critical care during the study period. We explored the impact of NICE guidance in statistical analyses adjusting for admissions pre- and post-launch. There did not appear to be any significant difference in mortality outcomes pre- and post-launch of NICE guidance. The assumption that care may have changed during a hospital admission, which spanned the issuing of NICE guidance was assessed in a sensitivity analysis, but all results were robust to this assumption (Table S3, Supplementary data).

Implications

Clinicians might wish to exert caution in placing too much emphasis on the influence of frailty alone when discussing likely prognosis in older people with COVID-19 infection. Aside from those categorised as CFS 9 (terminally ill but NOT evidently frail), frailty appears not to predict survival outcomes. Illness severity is an important marker of risk within the COVID-19-positive cohort, and this might be the most important prognostic marker. However, a key consideration for clinicians, especially those working in critical care, is whether or not a given patient is likely to survive intensive care with an outcome that is acceptable to them. Critical care treatments are a traumatic intervention, and older people may not value survival as an absolute if it impacts significantly on the quality of their remaining years of life. An assessment of frailty may still have a useful role in helping clinicians in discussions with older people with COVID-19 that might benefit from critical care interventions, noting that overall survival is significantly reduced in the COVID-19 older age groups and those who do survive may do so with a significantly impaired change in functioning and increased frailty.

It would be useful to replicate this study in other settings, perhaps using other frailty measures, and to consider mechanistic studies to examine the notion of accelerated frailty due to COVID-19. Other important outcomes need to be described, especially functional ability and cognition.

If COVID-19 does result in accelerated frailty, there will be substantial implications for rehabilitation and recovery services—not just in older people but likely across all age groups. Similarly, the reported neurological manifestation of COVID-19, such as stroke and delirium [34], may lead to

accelerated cognitive ageing, with important implications for health and social care systems.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflicts of Interest: Professors Abrams, Conroy and Faull, Dr Pareek and Dr Owen report grants from National Institute for Health Research during the conduct of the study; Professor Abrams and Dr Owen report grants from MRC and HDR-UK; Professor Abrams reports grants from British Heart Foundation. Dr Owen is a member of the NICE Technology Appraisal Committee, and Professor Abrams and Dr Owen are members of the NICE Decision Support Unit (DSU), whilst Professor Abrams is also a member of the NICE Technical Support Unit (TSU). Professor Abrams and Dr Owen have served as paid consultants to the pharmaceutical industry, not in relation to this research. Professor Abrams is partner and director of Visible Analytics Limited, a healthcare consultancy company. Jay Banerjee is director of Jay Banerjee Consultancy Ltd, a healthcare training and consultancy company.

Declaration of Sources of Funding: There was no specific funding for this work, but M.P. is supported by the National Institute for Health Research (NIHR Post-Doctoral Fellowship, Dr Manish Pareek, PDF-2015-08-102). Professor Abrams is partially supported as a UK National Institute for Health Research (NIHR) Senior Investigator Emeritus (NF-SI-0512-10159). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

References

1. Huang C, Wang Y, Li X *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497–506.
2. Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. *J Med Virol* 2020; 92: 441–7.
3. Chen N, Zhou M, Dong X *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; 395: 507–13.
4. Porcheddu R, Serra C, Kelvin D, Kelvin N, Rubino S. Similarity in case fatality rates (CFR) of COVID-19/SARS-COV-2 in Italy and China. *J Infect Dev Ctries* 2020; 14: 125–8.
5. Intensive Care Society. Clinical Guidance: Assessing Whether COVID-19 Patients will Benefit from Critical Care, and an Objective Approach to Capacity Challenges, 2020. https://www.ics.ac.uk/ICS/ICS/Pdfs/COVID-19/ICS_Guidance_on_decision-making_under_pandemic_conditions.aspx (30 June 2020, date last accessed).
6. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. *Lancet* 2019; 394: 1376–86.

7. Darvall JN, Bellomo R, Paul E *et al.* Frailty in very old critically ill patients in Australia and New Zealand: a population-based cohort study. *Med J Aust* 2019; 211: 318–23.
8. Guidet B, de Lange DW, Boumendil A *et al.* The contribution of frailty, cognition, activity of daily life and comorbidities on outcome in acutely admitted patients over 80 years in European ICUs: the VIP2 study. *Intensive Care Med* 2020; 46: 57–69.
9. Langlais E, Nesseler N, Le Pabic E, Frasca D, Launey Y, Seguin P. Does the clinical frailty score improve the accuracy of the SOFA score in predicting hospital mortality in elderly critically ill patients? A prospective observational study. *J Crit Care* 2018; 46: 67–72.
10. Zeng A, Song X, Dong J *et al.* Mortality in relation to frailty in patients admitted to a specialized geriatric intensive care unit. *J Gerontol A Biol Sci Med Sci* 2015; 70: 1586–94.
11. Shears M, Takaoka A, Rochwerf B *et al.* Assessing frailty in the intensive care unit: a reliability and validity study. *J Crit Care* 2018; 45: 197–203.
12. National Institute for Clinical Excellence. COVID-19 Rapid Guideline: Critical Care in Adults. NICE Guideline, 2020; March 2020([NG159]).
13. Rockwood K, Song X, MacKnight C *et al.* A global clinical measure of fitness and frailty in elderly people. *Can Med Assoc J* 2005; 173: 489–95.
14. Improvement NHS. Ambulatory Emergency Care Guide: Same Day Acute Frailty Services, 2018.
15. Elliott A, Phelps K, Regen E, Conroy SP. Identifying frailty in the emergency department-feasibility study. *Age Ageing* 2017; 46: 840–5.
16. Aijaz F, Banerjee J, Conroy S. 59EMBEDDING the clinical frailty scale in the emergency department and its impact on patient care. *Age Ageing* 2018; 47: iii20–3.
17. Mitchell A, Tahir Q-U-A, Banerjee J. 032 clinical frailty score as a decision-making tool in the emergency department—a step towards better outcomes for older patients. *Emerg Med J* 2019; 36: 794–6.
18. Public Health England. COVID-19: Investigation and Initial Clinical Management of Possible Cases, 2020. <https://www.gov.uk/government/publications/wuhan-novel-coronavirus-initial-investigation-of-possible-cases/investigation-and-initial-clinical-management-of-possible-cases-of-wuhan-novel-coronavirus-wn-cov-infection> (24 March 2020, date last accessed).
19. Royal College of Physicians. National Early Warning Score (NEWS) 2. London: Royal College of Physicians, 2017.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–83.
21. British Geriatrics Society. COVID-19: Managing the COVID-19 Pandemic in Care Homes for Older People, London, 2020. <https://www.bgs.org.uk/resources/covid-19-managing-the-covid-19-pandemic-in-care-homes> (29 April 2020, date last accessed).
22. Hubbard RE, Peel NM, Samanta M, Gray LC, Mitnitski A, Rockwood K. Frailty status at admission to hospital predicts multiple adverse outcomes. *Age Ageing* 2017; 2017: 1–6.
23. Gilbert T, Neuburger J, Kraindler J *et al.* Development and validation of a hospital frailty risk score focusing on older people in acute care settings using electronic hospital records: an observational study. *Lancet* 2018; 391: 1775–82.
24. Zampieri FG, Iwashyna TJ, Viglianti EM *et al.* Association of frailty with short-term outcomes, organ support and resource use in critically ill patients. *Intensive Care Med* 2018; 44: 1512–20.
25. Romero-Ortuno R, Wallis S, Biram R, Keevil V. Clinical frailty adds to acute illness severity in predicting mortality in hospitalized older adults: an observational study. *Eur J Intern Med* 2016; 35: 24–34.
26. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. *J Pharm Anal* 2020; 10: 102–8.
27. McElvaney OJ, McEvoy N, McElvaney OF *et al.* Characterization of the inflammatory response to severe COVID-19 illness. *Am J Respir Crit Care Med* 2020.
28. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet (London, England)* 2013; 381: 752–62.
29. Chen X, Mao G, Leng SX. Frailty syndrome: an overview. *Clin Interv Aging* 2014; 9: 433–41.
30. Spiegelhalter D. How Much 'Normal' Risk Does COVID Represent? 2020. <https://medium.com/wintoncentre/how-much-normal-risk-does-covid-represent-4539118e1196> (26 April 2020, date last accessed).
31. Hewitt J, Carter B, Vilches-Moraga A *et al.* The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. *Lancet Public Health* 2020. (In Press).
32. Miles A, Webb TE, McLoughlin B *et al.* Outcomes from COVID-19 across the range of frailty: excess mortality in fitter older people. *medRxiv* 2020; 2020.05.22.20110486.
33. Watson J, Whiting PF, Brush JE. Interpreting a covid-19 test result. *BMJ* 2020; 369: m1808.
34. Mao L, Wang M, Chen S *et al.* Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan. China: A Retrospective Case Series Study.

Received 18 May 2020; editorial decision 14 July 2020