Title page

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

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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 26th June 2020, there have been 1229 COVID-19-related deaths reported in critical care in those 70 years or over (60.5% mortality) compared to 2250 deaths in those aged 50-69 (41.5% mortality). 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 40-60% 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 Clinical Frailty Scale (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 23rd January 2020, and from 13th March 2020 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 Emergency Department (ED) or died in the ED, with a COVID-19 test result following their first ED attendance between 29th February 2020 (pre-pandemic) and 16th 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 vs. 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 vs. ≥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 21st 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 21st 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 (25th 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.

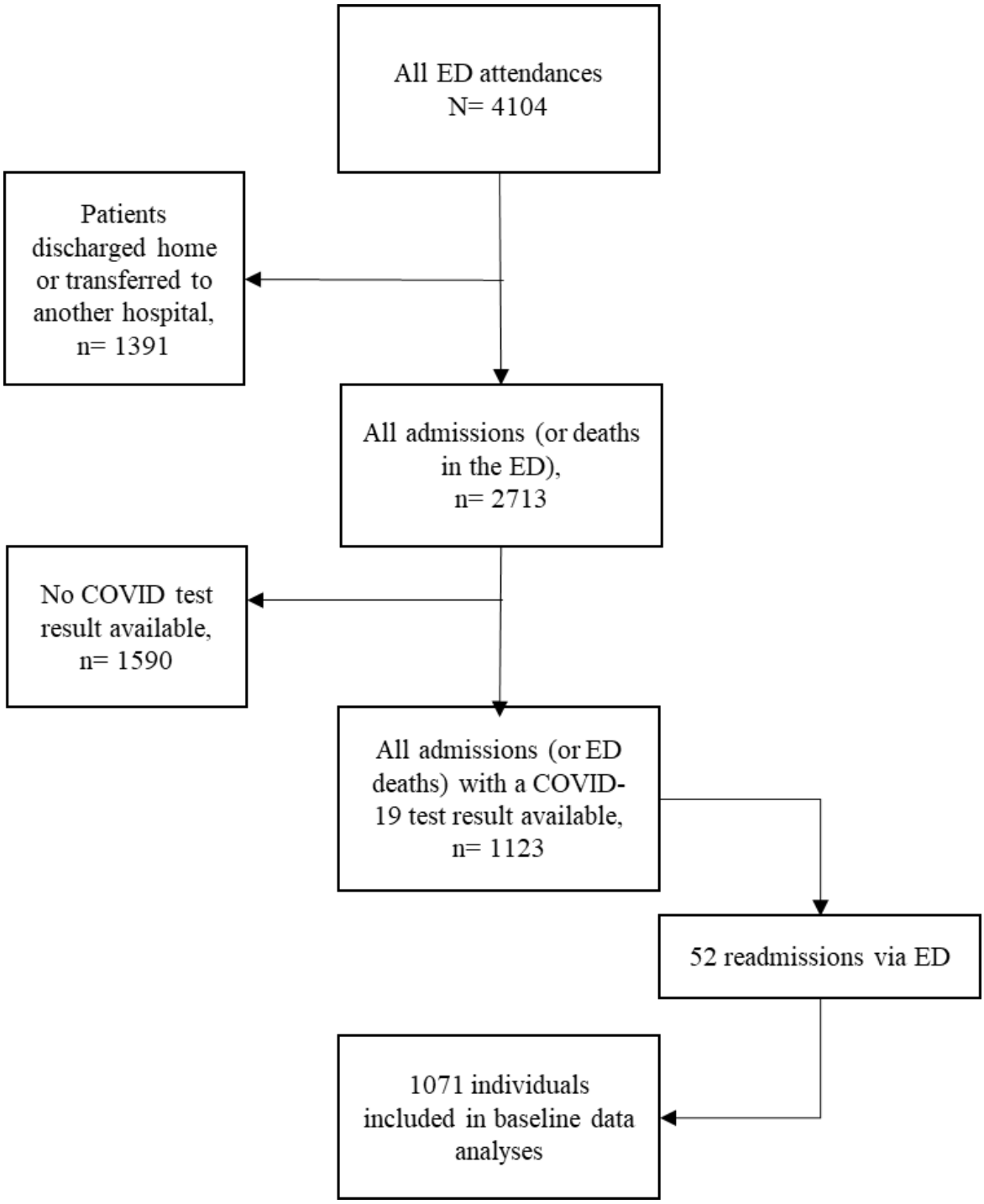
Governance and funding

Guidance from the United Kingdom 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. There was no specific funding for this work. 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 4104 ED attendances in individuals aged 65+, giving rise to 2713 hospital admissions or deaths in ED; of these, 1123 had a COVID-19 test available (Figure 1) and re-admissions accounted for 52 of these presentations.

Figure 1 Study flow diagram



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=1071), 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 1 Baseline characteristics of all eligible participants at their index emergency presentation, stratified by COVID-19 status

Variable		**COVID-19 negative at index presentation (n=786)**	**COVID-19 positive at index presentation (n=285)**
Mean age (SD)	..	80.1 (8.6)	78.8 (8.3)
Female sex	.	398 (50.6%)	131 (46.0%)
Clinical Frailty Scale 1-3	.	90 (11.5%)	49 (17.2%)
Clinical Frailty Scale 4-5	.	159 (20.2%)	70 (24.6%)
Clinical Frailty Scale 6	.	145 (18.5%)	38 (13.3%)
Clinical Frailty Scale 7-8	.	129 (16.4%)	41 (14.4%)
Clinical Frailty Scale 9	.	6 (0.8%)	0 (0%)
Clinical Frailty Scale < 5	.	185 (23.4%)	93 (32.6%)
Clinical Frailty Scale ≥ 5	.	344 (43.8%)	105 (36.8%)
Clinical Frailty Scale 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)

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 material) respectively.

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

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

[1]Percentages calculated as actuarial percentages; [2]Denominator is those alive at discharge from ED; [3]Denominator is those admitted to critical care.

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).

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

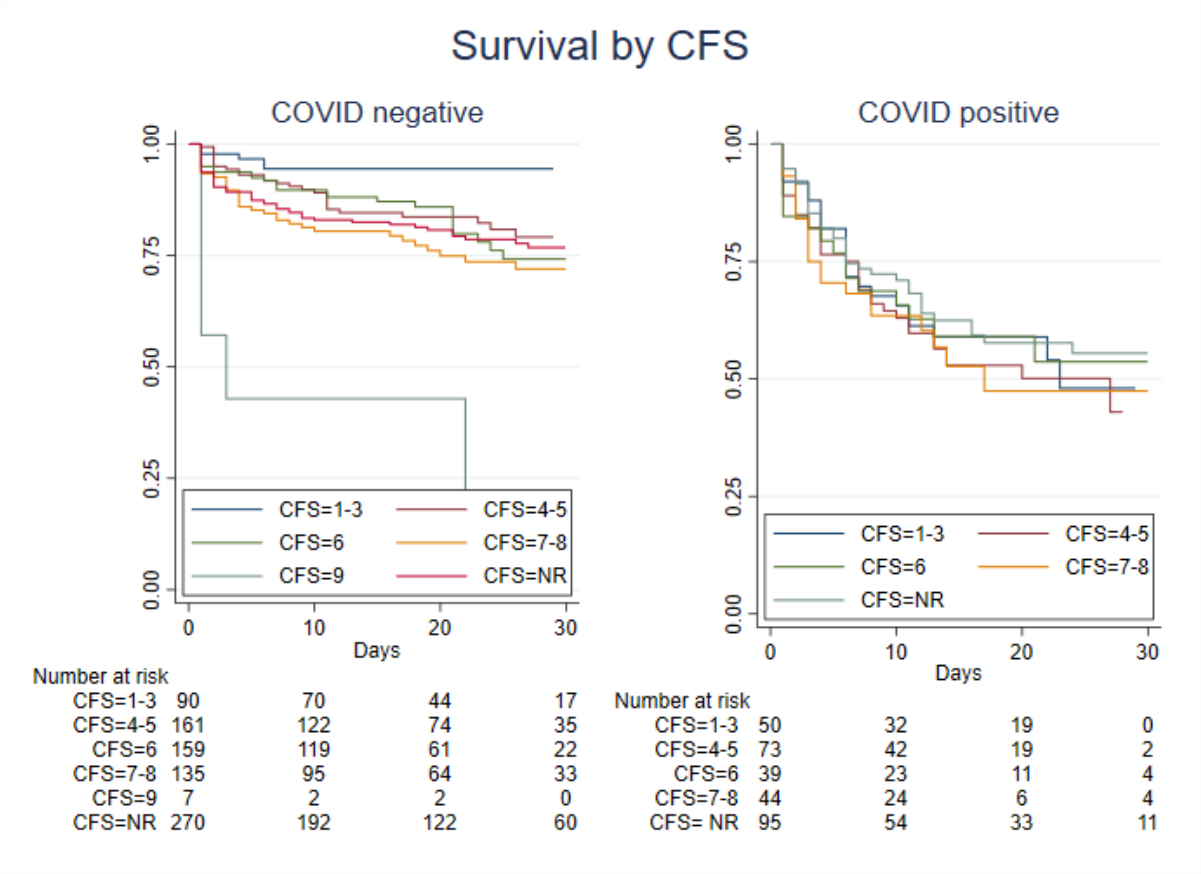


Table 3 shows the unadjusted and adjusted hazard ratios, adjusting for age, sex, acuity and comorbidities, for all-cause mortality. The unadjusted analysis suggests that those with COVID-19 had an eight-fold higher hazard for death (HR: 8.16, 95% CI 3.34, 19.9) compared to those without COVID-19 having 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, 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).

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

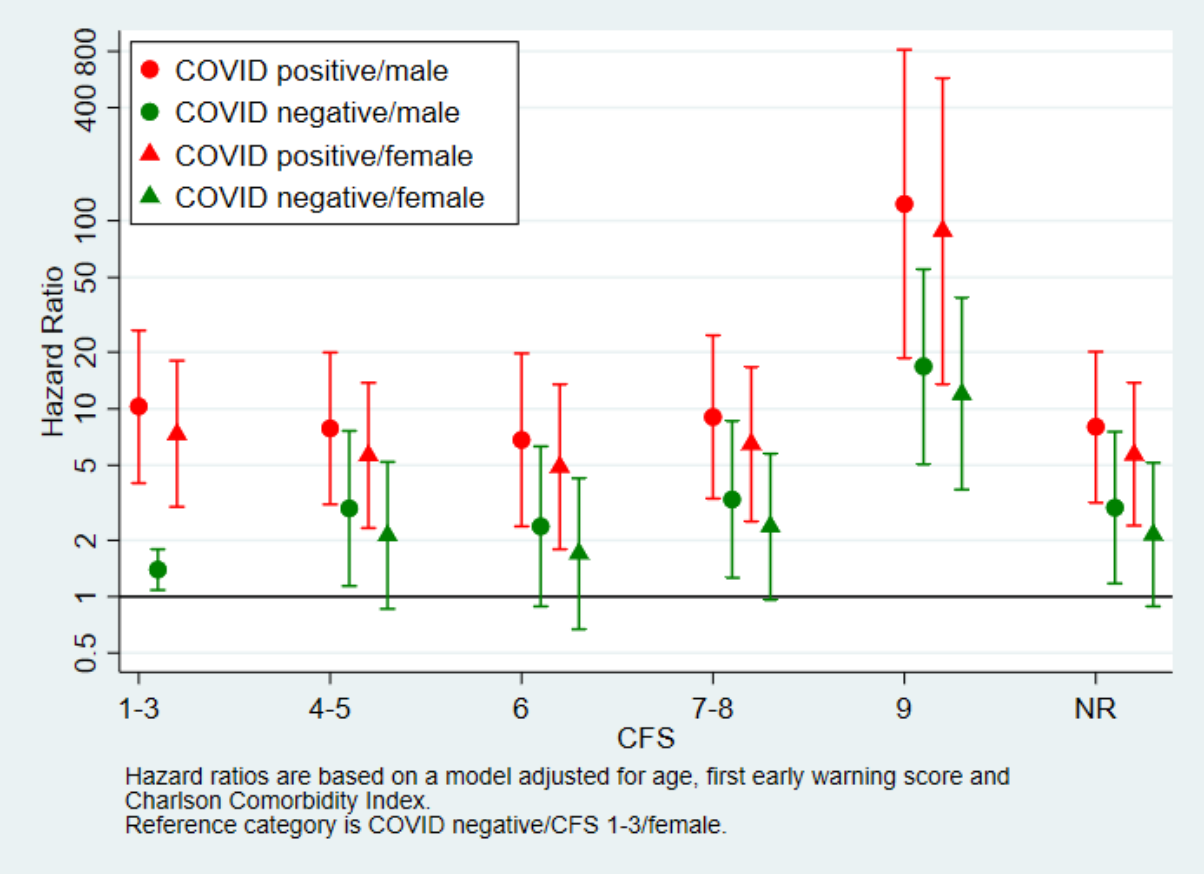


Table 3 Unadjusted and adjusted hazard ratios for all-cause mortality in hospitalised individuals with or without COVID-19

Unadjusted model	**Hazard Ratio**	**95% Confidence Interval**	**p-value**
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 & CFS 4-5	0.41	(0.15, 1.14)	0.087
COVID-19 positive & CFS 6	0.35	(0.12, 1.04)	0.059
COVID-19 positive & CFS 7-8	0.31	(0.11,0.86)	0.025
COVID-19 positive & CFS 9	NA	NA	NA
COVID-19 positive & 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 & CFS 4-5	0.36	(0.13, 1.02)	0.054
COVID-19 positive & CFS 6	0.39	(0.13, 1.22)	0.107
COVID-19 positive & CFS 7-8	0.37	(0.13, 1.07)	0.067
COVID-19 positive & CFS 9	NA	NA	NA
COVID-19 positive & CFS NR	0.36	(0.14, 0.98)	0.045

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 patients the influence of NICE guidance on mortality outcomes is displayed using a Lexis diagram (Figure S2, supplementary material) and Kaplan-Meier plots (Figure S1, supplementary material), 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 Clinical Frailty Scale, 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 seven-fold 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 potential selection effect. For example, patients with a higher frailty score are more likely to represent 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 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 & 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 the 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 suggest 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.

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Contributions

Contributor		Contribution				
		Conception and design	Acquisition of data	Analysis and interpretation of data	Critical revision of manuscript	Final approval of manuscript
R	Owen	✓		✓	✓	✓
S	Conroy	✓	✓	✓	✓	✓
N	Taub	✓		✓	✓	✓
W	Jones	✓	✓		✓	✓
D	Bryden	✓		✓	✓	✓
M	Pareek	✓			✓	✓
C	Faull	✓		✓	✓	✓
K	Abrams			✓	✓	✓
D	Davis			✓	✓	✓
J	Banerjee	✓	✓	✓	✓	✓

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Supplementary data

Table S1: Adjusted hazard ratios for all-cause mortality by NICE CFS categories

Adjusted model	Hazard Ratio	95% Confidence Interval	p-value
Main effects			
COVID-19 negative	Reference	Reference	Reference
COVID-19 positive	4.78	(2.79, 8.20)	<0.001
CFS <5	Reference	Reference	Reference
CFS ≥5	1.67	(0.98, 2.83)	0.058
CFS NR	1.57	(0.90, 2.75)	0.111
Female sex	Reference	Reference	Reference
Male sex	1.39	(1.08, 1.78)	0.010
Age	1.02	(1.01, 1.04)	0.004
First early warning score	1.16	(1.12, 1.20)	<0.001
Charlson Comorbidity Index	1.09	(1.03, 1.16)	0.002
Interaction effects			
COVID-19 positive & CFS ≥5	0.51	(0.26, 0.98)	0.044
COVID-19 positive & CFS NR	0.56	(0.28, 1.10)	0.092

Figure S1 Survival by NICE CFS categories

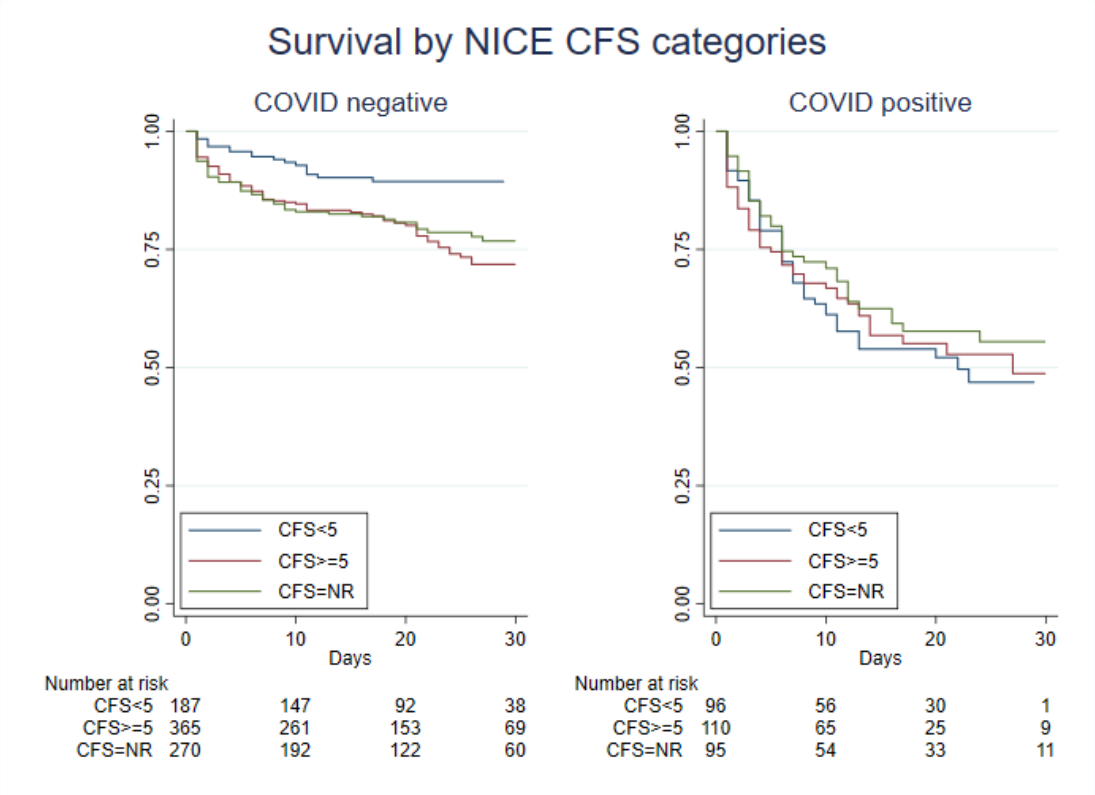

Table S2: Results adjusting for pre and post NICE guidance

Adjusted model	Hazard Ratio	95% Confidence Interval	p-value
Main effects			
COVID-19 negative	Reference	Reference	Reference
COVID-19 positive	6.01	(2.29, 15.79)	<0.001
CFS <5	Reference	Reference	Reference
CFS ≥5	1.75	(0.75, 4.10)	0.197
CFS NR	1.57	(0.65, 3.81)	0.315
Admitted pre NICE guideline	Reference	Reference	Reference
Admitted post NICE guideline	1.14	(0.44, 2.97)	0.791
Female sex	Reference	Reference	Reference
Male sex	1.39	(1.08, 1.79)	0.009
Age	1.02	(1.01, 1.04)	0.003
First early warning score	1.15	(1.11, 1.20)	<0.001
Charlson Comorbidity Index	1.11	(1.05, 1.17)	<0.001
Interaction effects			
COVID-19 positive & CFS ≥5	0.26	(0.07, 0.95)	0.042
COVID-19 positive & CFS NR	0.35	(0.10, 1.18)	0.091
COVID-19 positive & Admitted post NICE guideline	0.75	(0.23, 2.42)	0.635
CFS ≥5 & Admitted post NICE guideline	0.91	(0.32, 2.60)	0.864
CFS NR & Admitted post NICE guideline	1.03	(0.34, 3.15)	0.953
COVID-19 positive & CFS ≥5 & Admitted post NICE guideline	2.31	(0.51, 10.49)	0.277
COVID-19 positive & CFS NR & Admitted post NICE guideline	1.77	(0.40, 7.76)	0.448

Figure S2 Lexis diagram illustrating date of admission and outcomes for COVID-19 positive patients by NICE CFS categories

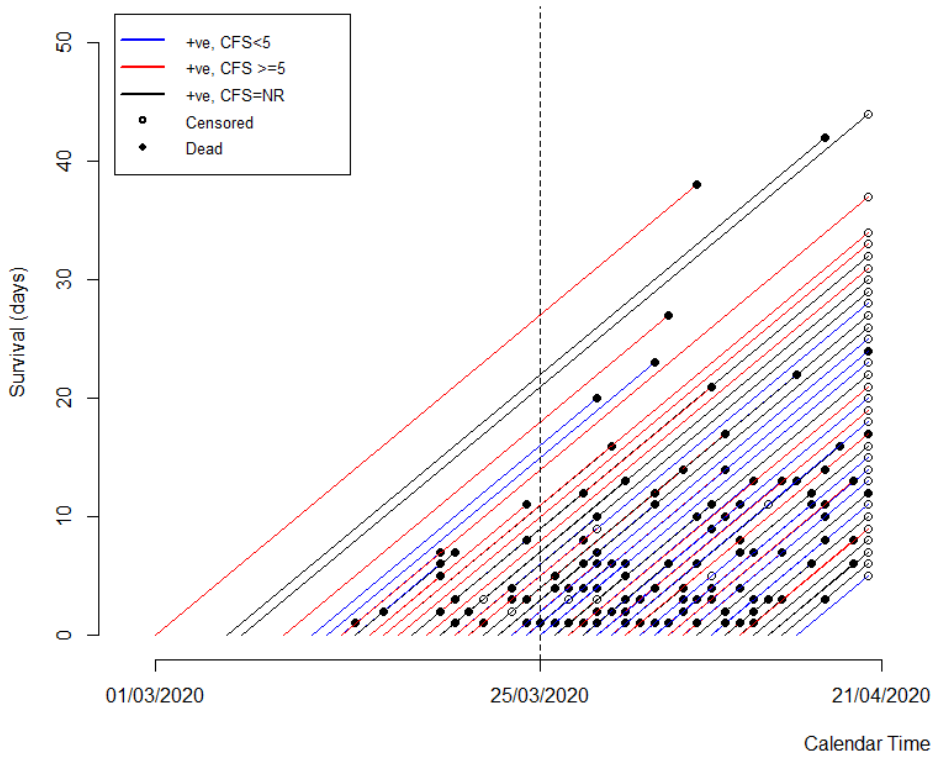

Figure S1: Survival of COVID-19 patients by NICE CFS categories pre and post-NICE guidance

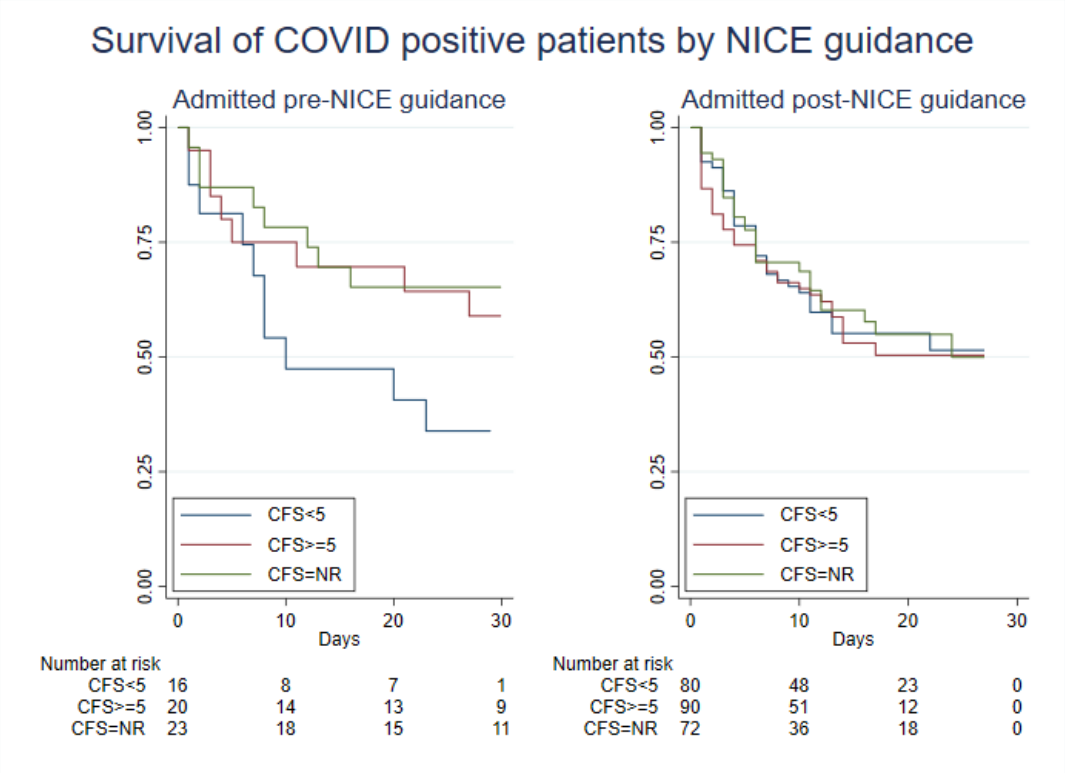

Table S3: Results adjusting for pre and post NICE guidance assuming time-dependent effects

Adjusted model	Hazard Ratio	95% Confidence Interval	p-value
Main effects			
COVID-19 negative	Reference	Reference	Reference
COVID-19 positive	3.83	(1.97, 7.46)	<0.001
CFS <5	Reference	Reference	Reference
CFS ≥5	1.49	(0.77, 2.85)	0.230
CFS NR	1.67	(0.84, 3.30)	0.140
Female sex	Reference	Reference	Reference
Male sex	1.40	(1.09, 1.80)	0.008
Age	1.02	(1.01, 1.04)	0.005
First early warning score	1.16	(1.12, 1.20)	<0.001
Charlson Index	1.09	(1.03, 1.16)	0.003
Interaction effects			
COVID-19 positive & CFS ≥5	0.64	(0.28, 1.46)	0.289
COVID-19 positive & CFS NR	0.51	(0.22, 1.17)	0.112
Time dependent effects			
Main effects			
Pre NICE guideline	Reference	Reference	Reference
Post NICE guideline	1.00	(0.93, 1.08)	1.00
Interaction effects			
COVID-19 positive & Post NICE guideline	1.03	(0.97, 1.10)	0.325
CFS ≥5 & Post NICE guideline	1.02	(0.97, 1.07)	0.517
CFS NR & Post NICE guideline	0.99	(0.94, 1.05)	0.796
COVID-19 positive & CFS ≥5 & Post NICE guideline	0.97	(0.90, 1.05)	0.401
COVID-19 positive & CFS NR & Post NICE guideline	1.01	(0.94, 1.10)	0.774

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