

# Clinical features and inpatient trajectories of older inpatients with COVID-19: a retrospective observational study.

**Christopher N Osuafor** (✉ [chrisosuafor@gmail.com](mailto:chrisosuafor@gmail.com))

Cambridge University Hospital NHS Foundation Trust <https://orcid.org/0000-0002-3537-6521>

**Catriona Davidson**

Medicine for the Elderly, Cambridge University Hospitals NHS Foundation Trust

**Alistair J Mackett**

Medicine for the Elderly, Cambridge University Hospitals NHS Foundation Trust

**Marie Goujon**

Medicine for the Elderly, Cambridge University Hospitals NHS Foundation Trust

**Lelane Van Der Poel**

Medicine for the Elderly, Cambridge University Hospitals NHS Foundation Trust

**Vince Taylor**

Cancer Research UK, Cambridge University Hospitals NHS Foundation Trust

**Jacobus Preller**

Acute and Internal Medicine, Cambridge University Hospitals NHS Foundation Trust

**Robert J B Goudie**

Medical Research Council Biostatistics Unit, University of Cambridge

**Victoria L Keevil**

Medicine for the Elderly, Cambridge University Hospitals NHS Foundation Trust

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## Research article

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## Abstract

**Background:** A comprehensive description of the clinical characteristics, inpatient trajectory and relationship with frailty of older inpatients admitted with COVID-19 is essential in the management of older adults during the COVID-19 pandemic. The aim of this study was to describe the clinical features and inpatient trajectory of older inpatients with confirmed COVID -19.

**Methods:** This was a retrospective observational study of hospitalised older adults. Subjects include unscheduled medical admissions of older inpatients to a University Hospital with laboratory and clinically confirmed COVID-19. The primary outcome was death during the inpatient stay or within 14 days of discharge after a maximum follow up time of 45 days. The characteristics of the cohort were described in detail as a whole and by frailty status.

**Results:** 214 patients were included in this study with a mean length of stay of 11 days (Range 6 to 18 days), of whom 140 (65.4%) patients were discharged and 74 (34.6%) patients died in hospital. 142 (66.4%) patients were frail with median Clinical Frailty Scale (CFS) score of 6. Frail patients were more likely to present with atypical symptoms including new or worsening confusion compared to non-frail patients (20.8% vs 45.1%,  $p < 0.001$ ) and were more likely to die in hospital or within 14 days of discharge (66% vs 16%,  $p = 0.001$ ). Older age, being male, presenting with high illness acuity and high frailty were all independently associated with higher risk of death and a dose response association between higher frailty and higher mortality was observed.

**Conclusions:** Older adult inpatients with COVID-19 infection are likely to present with atypical symptoms, experience delirium and have a high mortality, especially if they are also living with frailty. Clinicians should have a low threshold for testing for COVID-19 in older and frail patients presenting to hospital as an emergency during periods when there is community transmission of COVID-19 and, when diagnosed, this should prompt early advanced care planning with the patient and family.

## Background

In December 2019, doctors in China described a cluster of viral pneumonia cases secondary to a novel Coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The World Health Organisation named this emergent disease coronavirus disease 19, or 'COVID-19', and declared a pandemic on March 11, 2020 [2]. One of the main challenges of COVID-19 is the wide spectrum of clinical presentations, ranging from asymptomatic cases to mild upper respiratory tract illness with myalgia and fatigue [3, 4], severe viral pneumonia [1, 3, 4, 5], gastrointestinal symptoms [5, 6], neurological symptoms [7, 8], cardiovascular symptoms [9, 10] and other symptoms like loss of smell and taste [11, 12]. Atypical presentations [5] like delirium [13, 14], drowsiness [15], syncope [16] and fall [17] have also been described in older patients and our experience with other respiratory viral illnesses, such as seasonal Influenza, is that such illnesses often present without the typical fever and respiratory features in older adults [18, 19]. Indeed, many illness in older adults present atypically in the form of a Geriatric Syndrome such as delirium, falls or reduced physical functional ability [20, 21]. Understanding the spectrum of disease presentation is particularly important in COVID-19, given the necessity for prompt isolation of cases in order to prevent nosocomial spread and unnecessary exposure of health and social care staff.

Older adults are especially vulnerable to COVID-19 and experience high morbidity and mortality as a result of infection [22]. Age is independently linked with mortality [22, 23], but age alone does not adequately capture the robustness of older adults who are a heterogeneous group. Some live well into old age and do not experience the 'slowing up' and vulnerabilities associated with the onset of frailty whilst others do [24, 25]. Age alone is also not adequate to determine the likely effectiveness of treatment options and assess prognosis, as well as make decisions regarding healthcare resource allocation [26].

Over the past few decades, there has been an explosion of research into frailty and its operationalisation in the clinical setting. Assessment of frailty in older adults is now an important part of Comprehensive Geriatric Assessment and, therefore, it is necessary to understand the relationships between frailty and both the clinical presentations and outcomes of COVID-19. One study in patients over 80 years old showed mortality from COVID-19 was significantly higher in patients with frailty [23], another showed frailty was weakly associated with higher risk of mortality [27] while a third study found that frailty is not a good discriminator of prognosis in COVID-19 [28].

In this retrospective observational study, we aim to describe the range of clinical presentations of older patients ( $\geq 65$  years), admitted as an emergency to a University Hospital and diagnosed with COVID-19. We will comprehensively describe the characteristics of this patient group including their frailty and presence of dementia, delirium and multimorbidity. We will also describe their clinical trajectory from admission to discharge in terms of their hospital outcomes, primarily considering mortality during the inpatient admission or within the first 14 days after discharge.

## Methods

### Setting

This is a retrospective observational study conducted in a tertiary National Health Service (NHS) University Hospital in England.

### Sample

Any older adult ( $\geq 65$  years old) admitted as an emergency from March 1, 2020 to May 15, 2020 and diagnosed with COVID-19 infection was included. Diagnosis was confirmed either by clinical suspicion of probable COVID-19 infection and/or positive viral Polymerase Chain Reaction (PCR) for SARS-COV-2 viral RNA on nasopharyngeal swab.

**Patient characteristics:** The following information was retrieved by the clinical informatics team from the Electronic Health Record (EHR): age, sex, ethnicity, body mass index (BMI,  $\text{Kg}/\text{m}^2$ ), Clinical Frailty Scale (CFS) score [25], maximum National Early Warning Score 2 (NEWS2) [29] and vital signs (heart rate,

systolic blood pressure, respiratory rate and temperature) in the first 4 hours of admission, number of ward moves (excluding the Emergency Department or equivalent acute assessment area), PCR for SARS-COV-2 viral RNA results and laboratory tests on admission. Laboratory values were available from ED point-of-care tests and included C-reactive protein (CRP; mg/l), white cell count (WCC;  $10^9/l$ ) including lymphocyte and neutrophil counts, interleukin-6 (IL-6; pg/ml), creatinine ( $\mu\text{mol/l}$ ), high sensitivity troponin I (HsTNI; ng/L) and D-dimer (ng/ml).

In addition, the following information was manually extracted from the EHR: presenting symptoms including history of fever, cough, breathlessness, fatigue, myalgia, new or worsening confusion, fall, nausea and/or vomiting, diarrhoea, abdominal pain, loss of taste and/or smell, or non-specific illness; and also number of regular admission medications, multimorbidity (< 2, 2 or > 2 long term conditions), known dementia, admission from a care home (residential versus dual registered/nursing homes), functional status on admission and discharge (independently mobile, stick, frame or immobile), chest X-ray (CXR) on admission (British Society of Thoracic Imaging COVID-19 CXR Report Proforma) [30] and evidence of hospital acquired disease (identified if this was documented as the diagnosis by the treating team or if COVID-19 was diagnosed > 14 days after admission). Finally, whether the patient developed new or worsening confusion or was diagnosed with delirium during the admission episode was documented after searching the EHR using the terms "confusion" and "delirium". Patients were also retrospectively assigned a CFS score if this had not been completed by the treating team (102 [48%] patients). All CFS scores were verified by a consultant or specialist registrar in Geriatric Medicine.

For patients identified with hospital acquired COVID-19 disease, laboratory test results nearest to the first positive PCR for SARS-COV-2 viral RNA (within 12 hours), the maximum NEWS2 score and vital signs nearest to the first positive PCR for SARS-COV-2 viral RNA (within 4 hours) and presenting features prompting the treating team to consider a diagnosis of COVID-19 (including nearest CXR report) were used instead of results at hospital admission.

**Patient Outcomes:** Death during the inpatient stay or within 14 days of discharge was the primary outcome and was calculated using the dates of admission, discharge and death, with a maximum follow up time of 45 days for each patient. This was either 45 days from date of admission or from first positive swab in the case of hospital acquired disease. It was important to include deaths in the two weeks following discharge as well as inpatient death, since local preparations for the COVID-19 pandemic included facilitation of early discharge to community palliative care settings. Dates of both admission and discharge were used to calculate length of inpatient stay (LOS, days) and prolonged length of stay was defined as  $\text{LOS} \geq 10$  days. Readmission to hospital within 30 days of discharge and new institutionalisation were also available; all hospital outcomes were provided by the clinical informatics team.

**Statistical Analysis:** Descriptive characteristics were expressed as means (standard deviation, SD), medians (interquartile range, IQR) and percentages (frequency, % [n]). The characteristics of the cohort were described as a whole and by frailty status. Frail (CFS  $\geq 5$ ) and non-frail (CFS = < 4) patients were compared using t-test, Kruskal Wallis and Chi squared tests; and Venn diagrams were used to illustrate key differences. Cox proportional hazards regression further explored associations between frailty and mortality. Frailty was categorised as: CFS 1–4 "Non-Frail", CFS 5–6 "Mild to Moderate Frailty" and CFS 7–8 "Severe to Very Severe Frailty". Kaplan-Meier curves were explored to ensure that there was no violation of the proportional hazards assumption. Univariable and multivariable associations were explored after adjustment for age, sex, illness acuity and multimorbidity. These are important potential confounding variables and were available in our dataset. All analyses were performed using STATA (version 12).

## Results

There were 215 older inpatients eligible for this study and only one patient, who was terminally ill prior to developing COVID-19 and died on arrival to hospital, was excluded. Mean age was 80.3 years (range 65 to 103), 94 (43%) patients were women and 178 (83.2%) patients were White (Black: 1 [0.5%], Asian: 3 [1.4%]; Other: 1 [0.5%], missing ethnicity or not stated: 31[14.5%]). 213 (99.5%) patients had a PCR confirmed diagnosis while only 1 patient had a clinical diagnosis of COVID-19. Table 1 further details the characteristics and hospital outcomes of the cohort by level of frailty.

Table 1  
 Characteristics of the whole cohort and by frailty (CFS 1–4 'Non-Frail' versus CFS 5–8 'Frail')

Characteristic	All (N = 214)	Non-Frail (N = 72)	Frail (N = 142)	P
Age, years*	80.3 (8.3)	74.5 (6.0)	83.7 (7.6)	< 0.001
Sex, % (n) women	43.9 (94)	29.2 (21)	51.4 (73)	0.002
CFS#	6 (4, 7)	3 (2, 4)	6 (6, 7)	< 0.001
BMI, Kg/m <sup>2</sup> #	24.6 (21.2, 29.2)	26.5 (23.3, 31.2)	23.5 (20.1, 27.7)	0.0015
Known Dementia, % (n)	27.1 (58)	1.4 (1)	40.1 (57)	< 0.001
Admission from care home, % (n)	31.3 (67)	0 (0)	47.3 (67)	< 0.001
Pre-admission mobility, % (n)	39.3 (84)	84.7 (61)	16.2 (23)	< 0.001
Independent	15.0 (32)	9.7 (7)	17.6 (25)	
Stick	33.6 (72)	5.6 (4)	47.9 (68)	
Frame	12.2 (26)	0 (0)	18.3 (26)	
Immobile				
Symptoms, % (n)				
Fever	73.4 (157)	81.9 (59)	69.0 (98)	0.043
Cough	63.6 (136)	76.4 (55)	57.0 (81)	0.005
SOB	59.8 (128)	62.5 (45)	58.5 (83)	0.568
Fatigue	48.1 (103)	62.5 (45)	40.8 (58)	0.003
Myalgia	14.5(31)	26.4 (19)	8.5 (12)	< 0.001
Confusion	36.9 (79)	20.8 (15)	45.1 (64)	0.001
Fall	20.6 (44)	12.5 (9)	24.7 (35)	0.038
N&V	18.7 (40)	25.0 (18)	15.5 (22)	0.092
Diarrhoea	16.4 (35)	31.9 (23)	8.5 (12)	< 0.001
Abdominal pain	7.0 (15)	12.5 (9)	4.2 (6)	0.025
Taste/ smell	4.7 (10)	9.7 (7)	2.1 (3)	0.013
Non-specifically unwell	19.2 (41)	6.9 (5)	25.4 (36)	0.001
Multimorbidity, % (n)	7.5 (16)	16.7 (12)	2.8 (4)	< 0.001
<2 LTC	9.8 (21)	16.7 (12)	6.3 (9)	
2 LTC	82.7 (177)	66.7 (48)	90.8 (129)	
≥3 LTC				
Polypharmacy, % (n)	21.0 (45)	36.1 (26)	13.4 (19)	< 0.001
0–4 medications	51.9 (111)	45.8 (33)	54.9 (78)	
5–9 medications	27.1 (58)	18.1 (13)	31.7 (45)	
≥10 medications				
CXR on COVID-19 presentation % (n)	34.6 (74)	50.0 (36)	26.8 (38)	0.002
Classical/Probable COVID-19	17.8 (38)	19.4 (14)	16.9 (24)	
Indeterminate for COVID-19	18.7 (40)	9.7 (7)	23.2 (33)	
Non COVID-19 Features	28.5 (61)	20.8 (15)	32.3 (46)	
Normal				

\*values presented as mean with standard deviation; #values presented as median with interquartile range; \*\*excluding 8 patients who were swabbed in the community and 1 patient who never had a positive swab; \*\*\*N = 140 (those who died excluded); CFS: Clinical Frailty Scale; Non-frail = CFS1-4 and Frail = CFS5-8; BMI: body mass index (available for 63 non-frail and 130 frail patients); LTC: Long term condition(s); CXR: Chest X-ray; Interleukin-6 (available for 42 non-frail and 85 frail patients). Percentages may not add up to 100% due to missing data.

Characteristic	All (N = 214)	Non-Frail (N = 72)	Frail (N = 142)	P
Ward moves, % (n)	42.1 (90)	44.4 (32)	40.8 (58)	0.021
Up to 1	33.2 (71)	27.8 (20)	35.9 (51)	
2	15.4 (33)	12.5 (9)	16.9 (24)	
3	9.4 (20)	14.3 (11)	6.4 (9)	
4 or more				
Admission to High Care, % (n)	10.3 (22)	29.2 (21)	0.7 (1)	< 0.001
Hospital Acquired Disease, % (n)	9.8 (21)	11.1 (8)	9.2 (13)	0.649
Time to first positive swab**, days#	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.290
Acuity, % (n) yes	45.3 (97)	50.0 (36)	43.0 (61)	0.328
Low (NEWS2 < 5)	54.7 (117)	50.0 (36)	57.0 (81)	
High (NEWS2 ≥ 5)				
Vital signs, % (n)				
Fever > 38.0°C	28.5 (61)	29 (40.3)	32 (22.5)	0.007
Respiratory rate > 24 bpm	38.8 (83)	36.1 (26)	40.1 (57)	0.568
Systolic blood pressure ≤ 90 mmHg	3.3 (7)	0 (0)	4.9 (7)	0.060
Pulse > 130 bpm	5.1 (11)	5.6 (4)	4.9 (7)	0.845
Laboratory Values				
White blood cells, 10 <sup>9</sup> /L#	6.9 (5.0, 9.6)	6.3 (4.9, 8.6)	7.4 (5.1, 10.0)	0.094
Neutrophils, 10 <sup>9</sup> /L #	5.4 (3.7, 7.8)	4.8 (3.6, 7.2)	5.8 (3.8, 8.2)	0.19
Lymphocytes, 10 <sup>9</sup> /L #	0.67 (0.48, 1.01)	0.61 (0.46, 0.90)	0.67 (0.50, 1.04)	0.28
Creatinine# μmol/l	89.0 (71.1, 118.5)	87.5 (69.5, 111.0)	89.5 (71.6, 128.6)	0.32
C-Reactive Protein, % (n)	30.3 (65)	18.1 (13)	36.7 (52)	0.007
<40 mg/L	31.3 (67)	30.6 (22)	31.7 (45)	
40–100 mg/L	37.4 (80)	50.0 (36)	31.0 (44)	
>100 mg/L				
Interleukin-6, pg/mL #	19.6 (7.3, 50.8)	26.8 (9.6, 71.1)	17.6 (6.6, 39.2)	0.04
Troponin, % (n)	50.9 (109)	68.1 (49)	42.3 (60)	0.009
≤58.1 ng/L	23.8 (51)	16.7 (12)	27.5 (39)	
>58.1 ng/L				
D Dimer, % (n)	15.6 (35)	16.7 (12)	16.2 (23)	0.942
≤230 ng/mL	54.2 (116)	54.1 (39)	54.2 (77)	
>230 ng/mL				
Delirium or new confusion during admission at any point, % (n)	47.7 (102)	29.2 (21)	57.0 (81)	< 0.001

\*values presented as mean with standard deviation; #values presented as median with interquartile range; \*\*excluding 8 patients who were swabbed in the community and 1 patient who never had a positive swab; \*\*\*N = 140 (those who died excluded); CFS: Clinical Frailty Scale; Non-frail = CFS1-4 and Frail = CFS5-8; BMI: body mass index (available for 63 non-frail and 130 frail patients); LTC: Long term condition(s); CXR: Chest X-ray; Interleukin-6 (available for 42 non-frail and 85 frail patients). Percentages may not add up to 100% due to missing data.

Characteristic	All (N = 214)	Non-Frail (N = 72)	Frail (N = 142)	P
<b>Mobility at discharge***, % (n)</b>	35.0 (49)	75.4 (43)	7.2 (6)	< 0.001
Independent	5.7 (8)	3.5 (2)	7.2 (6)	
Stick	37.1 (52)	17.5 (10)	50.6 (42)	
Frame	20.0 (28)	0 (0)	33.7 (28)	
<b>Immobile</b>				
<b>Length of stay, days<sup>#</sup></b>	11 (6, 18)	8 (4, 17)	12 (7, 19)	0.08
<b>Hospital outcomes, % (n)</b>				
<b>Inpatient Death</b>	34.6 (74)	20.8 (15)	41.6 (59)	0.003
<b>Death as inpatient or within 14 days of discharge</b>	38.3 (82)	22.2 (16)	46.7 (66)	0.001
<b>Prolonged length of stay (&gt; 10 days)</b>	53.5 (114)	45.1 (32)	57.8 (82)	0.08
<b>New Institutionalisation***</b>	5.6 (12)	3.5 (2)	12.1 (10)	0.08
<b>Readmission***</b>	19.3 (27)	15.8 (9)	21.7 (18)	0.385
<b>Delayed transfer of care***</b>	46.4 (65)	26.3 (15)	60.2 (50)	< 0.001
*values presented as mean with standard deviation; <sup>#</sup> values presented as median with interquartile range; **excluding 8 patients who were swabbed in the community and 1 patient who never had a positive swab; ***N = 140 (those who died excluded); CFS: Clinical Frailty Scale; Non-frail = CFS1-4 and Frail = CFS5-8; BMI: body mass index (available for 63 non-frail and 130 frail patients); LTC: Long term condition(s); CXR: Chest X-ray; Interleukin-6 (available for 42 non-frail and 85 frail patients). Percentages may not add up to 100% due to missing data.				

Frail patients were significantly older and more likely to be women with lower BMI. They were also more likely to have dementia, multimorbidity, and polypharmacy and to be admitted from a care home. In terms of presenting symptoms, frail patients were less likely to complain of fever, cough, myalgia, fatigue, gastrointestinal symptoms or loss of taste and smell on presentation than non-frail patients but were more likely to have new or worsening confusion, a fall, or non-specific illness as part of their presenting features. These latter three features are common acute geriatric illness presentations and the differences in their prevalence between frail and non-frail patients is striking (Fig. 1).

Non-Frail: Clinical Frailty Score 1–4; Frail: Clinical Frailty Score 5–8; NOS: Non-specific illness.

There was no difference between frail and non-frail patients in terms of their illness acuity on presentation of COVID-19 infection. Laboratory markers were also similar, with the exception of CRP and IL-6, which were higher in non-frail patients (Table 1), and HsTNI, which was higher in frail patients. In terms of radiologic features, frail patients were more likely to have a normal CXR at the time of COVID-19 presentation compared to non-frail patients. Similar proportions of frail and non-frail patients acquired COVID-19 in hospital (Table 1).

In terms of inpatient trajectory, 57.0% of frail patients experienced new or worsening confusion, or received a diagnosis of delirium, during the admission episode compared to 29.2% of non-frail patients. Frail patients were also more likely to be immobile on discharge and remain in hospital after their clinically fit date. There were trends for longer lengths of inpatient stay, higher readmission and new institutionalisation amongst frail patients compared to non-frail patients, although differences were not significant.

In terms of mortality, patients who were frail were more likely to die during the inpatient episode or in the immediate two weeks following discharge (Table 1). A dose response association was observed between higher frailty categories and higher mortality (Fig. 2).

\*The time from COVID-19 presentation is defined as the number of days from either admission to hospital or time from first positive swab if hospital acquired disease. For those discharged alive, follow-up was extended for the first 14 days after discharge.

Associations between frailty and mortality were further explored using Cox (Proportional Hazards) regression (Table 2). The dose response association between higher frailty and higher mortality persisted after adjustment for age, sex, illness acuity and multimorbidity.

Table 2  
Cox Proportional Hazards Regression Analysis: relationships between age, sex, frailty, illness acuity, multimorbidity and death.

Characteristic	Univariable Analysis		Multivariable Analysis	
	HR	95% Confidence Interval	HR	95% Confidence Interval
Age, years	1.05	1.02, 1.07	1.04	1.01, 1.07
<b>Sex</b>				
Women	Ref		Ref	
Men	1.45	0.93, 2.27	2.05	1.28, 3.28
<b>CFS</b>				
1–4	Ref		Ref	
5–6	2.05	1.13, 3.71	1.82	0.91, 3.61
7–8	2.83	1.54, 5.21	2.53	1.24, 5.18
<b>Acuity, NEWS2</b>				
Low (< 5)	Ref		Ref	
High (≥ 5)	2.26	1.41, 3.62	2.31	1.43, 3.71
<b>Multimorbidity</b>				
0–1 LTC	Ref		Ref	
2 LTC	1.11	0.34, 3.68	0.89	0.26, 3.05
≥3 LTC	1.61	0.64, 4.05	0.96	0.36, 2.60
HR: Hazard Ratio; CFS: Clinical Frailty Scale; NEWS2: National Early Warning Score 2; LTC: long term condition(s). HRs adjusted for all co-variables in multivariable models.				

## Discussion

We have described the clinical features and inpatient trajectory of older inpatients with clinically confirmed COVID-19 admitted as an emergency to an NHS University Hospital in England. Our findings confirm the range of symptoms other than fever, cough and breathlessness which are common presenting features of COVID-19 infection in this population group. Furthermore, we found that presenting features differed by level of frailty, with frail patients much more likely to present with new or worsening confusion, falls and non-specific illness and less likely to present with fever and cough than non-frail older adults. This is in keeping with other studies [14, 31] and characterises the 'typical atypical' way in which older patients, particularly those living with frailty, often present with acute illness.

In particular, new or worsening confusion was present in 36.9% of all patients on admission rising to 45.1% of frail patients. In total 57.0% of frail patients experienced new or worsening confusion at some point during their admission episode, either formally diagnosed as delirium or noted as a symptom by the healthcare team caring for the patient. High prevalence of delirium associated with COVID-19 infection has been identified in other studies [28] yet local and national guidelines often fail to emphasise the importance of delirium as a potential indicator of COVID-19 illness [32]. Therefore, our findings on the prevalence of delirium and the range of other presenting features of COVID-19 in older adults, support recommendations which suggest lower thresholds for COVID-19 testing [5] in this population group during periods of significant community viral transmission.

Overall in hospital mortality was 34.6% which reflects the severity of the disease and the older age of our population and is similar to mortality reported in other studies [22–23]. Frail patients were more likely to die than non-frail patients and a dose response relationship was observed between frailty and mortality which persisted after adjustment for age, sex, illness acuity and multimorbidity. This finding has not been consistent across all recent reports, with some supporting our findings [22, 33] and others either equivocal [27] or failing to find an association [28]. Intuitively, we would expect to find an association between a clinical syndrome such as frailty, which is defined by the presence of low physiological reserve and 'vulnerability', and mortality from an acute severe viral illness such as COVID-19. Differing study results to date may reflect small sample sizes and it is likely that large multicentre studies or meta-analyses will be required to resolve this issue. Interestingly, results from the COPE study, which includes over 1500 patients with COVID-19 from several centres across the United Kingdom and Italy, support an association between higher frailty and higher mortality from COVID-19 [33].

There is considerable interest in understanding more about the pathogenesis of COVID-19 and pathways to mortality. We observed that 28.5% of our patient cohort had a normal CXR around the time of COVID-19 presentation and only 34.6% had classic or probable CXR features suggestive of the disease. This is similar to a study in 64 younger patients (mean age of 56 years) which showed 31% of them having normal baseline CXRs [34]. Therefore, since the initial CXR may be normal in COVID-19 [35], a negative result does not exclude COVID-19 illness and CXR results should only be used for clinical decision making in context of the clinical presentation [30]. We also note that this observation was exaggerated in frail patients, with only around 1 in 4 patients having classical or probable CXR changes on presentation compared to 1 in 2 older adults without frailty. This could reflect the underlying vulnerability of frail patients, who may be less able to compensate for the effects of COVID-19 illness and present before the radiological features of lung inflammation have developed. However, it could also indicate that the manifestations of the illness differ by level of frailty.

Other reports have suggested that there may be differences in the physiological response to COVID-19 infection by frailty status. For example, another cohort study found inflammatory responses blunted in frail patients presenting with COVID-19 compared to non-frail patients [28]. This is consistent with our findings in relation to CRP and IL-6 which were significantly higher in non-frail patients compared to frail patients; it is possible that frail older adults are not able to mount strong immune responses to COVID-19 infection due to immunosenescence [36]. Higher inflammatory responses to COVID-19 have been associated with severe disease and poorer outcomes [37], and dexamethasone, an immunosuppressant therapy, has been proven to reduce mortality in patients with COVID-19 requiring oxygen therapy or mechanical ventilation [38]. Therefore, if immune reactions differ in frail compared to non-frail older adults this may suggest the pathogenesis of COVID-19 differs by frailty and will have implications for the likely effectiveness of different treatments. It is also possible, as with the differences in CXR features, that frail patients are simply presenting earlier in their illness trajectory due to lower physiological reserve than non-frail patients and hence have lower levels of inflammatory markers on presentation. However, we also note that higher proportions of frail older adults in our cohort presented with raised HsTNI levels compared to non-frail older adults, and there was a non-significant trend for higher total white blood cell count driven by higher neutrophils. These findings hint at potential alternative pathological consequences of COVID-19 infection in older adults with frailty, with cardiac complications and bacterial superinfection perhaps more likely eventual causes of death than high levels of systemic inflammation.

Our data did not show a statistical difference in the LOS between frail and non-frail patients, unlike other studies [33], although there was a trend in this direction and frail patients were more likely to stay in hospital beyond their clinically fit date than non-frail patients. Delayed transfer of care has been previously observed in association with frailty and likely reflects difficulties in sourcing social care or accessing onward care facilities, such as inpatient rehabilitation centres and care homes [39]. Consistent with this, frail patients had lower mobility on discharge than non-frail patients and a higher proportion were discharged to a new institution, although this finding did not reach statistical significance. A limitation in our assessment of hospital outcomes other than mortality was the smaller sample size, after taking into account those who died during the inpatient episode.

Non-frail patients were more likely to be admitted to the high dependency unit or intensive care unit compared to frail patients (29% vs 0.7%,  $p < 0.001$ ). This suggests that in our centre, decisions regarding admissions to critical care were considered appropriately in our cohort in keeping with NICE guidelines [43]. It should be noted, however, decisions on access to critical care or mechanical ventilation for older adults overall should remain individualized and take into consideration patients' preference and goals of care [26].

Our study has some limitations. It is a single-centre, retrospective, observational study of inpatients in England, hence our results may not be generalisable to the whole population. For example, the older population in Cambridge is a highly homogenous demographic consisting mostly of individuals of White ethnicity. The impact of ethnicity on the morbidity and mortality of this disease has been widely reported [41, 42] but we were not able to add to this. The sample size was also relatively small, thus limiting the potential to detect differences between frail and non-frail patients, particularly with respect to secondary outcome measures such as hospital readmission, where the sample size was further reduced. Additionally, only routinely collected data were used and our definition of frailty and cognition were limited by the tools which are available locally at our centre. Furthermore, some patients were not assessed by their treating team for frailty, necessitating retrospective scoring. This was done by physicians experienced in frailty assessment using information about the patient documented in the EHR on admission by medical and therapy professionals. However, it is possible that retrospective scoring introduced bias, for example if the scorer was aware of the outcome status.

The absence of CFS in some of our patients, necessitating retrospective scoring, was partly due to the inclusion of patients 65 years and above in our study whereas routine frailty scoring in our centre is only mandated for patients aged 75 years and over. However, it may also suggest the unfamiliarity of some clinicians with this scoring system, though widespread. As a result of changes to workforce organisation in preparation for the pandemic, many clinicians who were not familiar with modern geriatric medicine practices were incorporated into acute medicine and general medicine rotas. Additionally, therapy teams such as our hospital's Early Intervention Team who routinely assess older patients on admission to hospital were temporarily re-deployed. Given the known associations of frailty with outcomes such as mortality, new institutionalisation and prolonged hospital stay in general medical patients [39], and the emerging evidence of the association of frailty with atypical presentations of COVID-19 and higher mortality following COVID-19 infection, the current pandemic is an opportunity for local educational and quality improvement work to increase awareness of frailty, its clinical assessment and implications for patient care [26].

The main strengths of our study are that it offers a detailed description of the clinical presentation, laboratory profile and inpatient trajectory of a cohort of hospitalised older adults with COVID-19 and includes a description of these patients by level of frailty. Data was retrieved digitally from the EHR or manually using a standardised data collection tool and missing data was limited. Also, the use of an EHR system in our hospital enabled clinicians to review patient medical records remotely and data was retrieved without the need for research staff to enter clinical areas which could increase the risk of infection.

## Conclusions

Older adult inpatients with COVID-19 infection are likely to present with atypical symptoms, develop delirium and have a high mortality, especially if they are also living with frailty. Clinicians should have a low threshold for testing for COVID-19 in older and frail patients presenting to hospital as an emergency during periods when there is community transmission of COVID-19. A diagnosis of COVID-19 in older, and especially in frail patients, should prompt early advanced care planning discussions with the patient and family.

## List Of Abbreviations

BMI: Body mass index.

CFS: Clinical Frailty Score.

COVID-19: Coronavirus Disease 19.

CRP: C-reactive protein.

CXR: Chest X-ray.

EHR: Electronic Health Record.

HsTNI: High sensitivity troponin I.

IL-6: Interleukin-6.

IQR: Interquartile range.

LOS: Length of inpatient stay.

NEWS2: National Early Warning Score 2.

NHS: National Health Service.

PCR: Polymerase Chain Reaction.

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

## Declarations

### Ethics approval and consent to participate

This study was formally approved by the West Midlands - Coventry and Warwickshire Research Ethics Committee (REC number 20/WM/0125, Protocol 1.1 Amendment, 1 24/04/2020). The data presented here were collected during routine clinical practice; there was no requirement for informed consent due to the nature of the study.

### Consent for publication

Not applicable.

### Availability of data and materials

The data that support the findings of this study are available from the corresponding author, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request subject to permission being obtained from Cambridge University Hospitals.

### Competing interests

There are no competing interests to declare for any of the authors.

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### Authors' Contributions

All authors listed were responsible for aspects of study design, data collection and analysis and writing of manuscript and meet criteria for authorship. CNO, RJBG, KP, LVDP and VLK conceived and initiated the project. VT led the clinical informatics team for auto-data extraction and RJBG processed the data to create a dataset for patients 65 years and over. CNO, CD, MG, AJM and VLK manually extracted the data from the EHR. CNO, AJM and VLK retrospectively assigned a CFS where this had not been done contemporaneously. VLK performed the final data analysis. CNO, AJM and VLK wrote the first draft of the manuscript. All authors contributed to interpreting the data and writing the final paper. All authors read and approved the final manuscript.

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#### Authors' information

#### Affiliations

**Department of Medicine for the Elderly, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.**

Christopher N Osuafor, Catriona Davidson, Alistair J Mackett, Marie Goujon, Lelane Van Der Poel and Victoria L Keevil.

**Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK.**

Christopher N Osuafor.

**Cancer Research UK, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.**

Vince Taylor.

**Department of Acute Internal Medicine and Intensive Care, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.**

Jacobus Preller.

**Medical Research Council Biostatistics Unit, University of Cambridge, UK.**

Robert J B Goudie.

**Department of Medicine, University of Cambridge, Cambridge, UK.**

Victoria L Keevil.

**Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK.**

Victoria L Keevil.

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## Figures

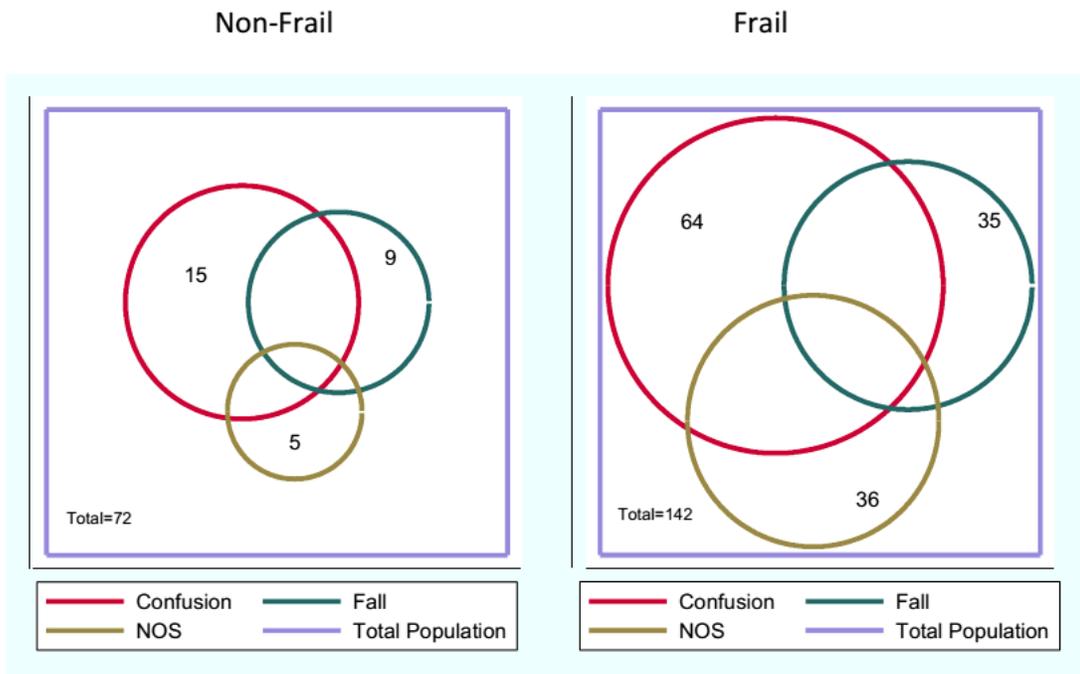
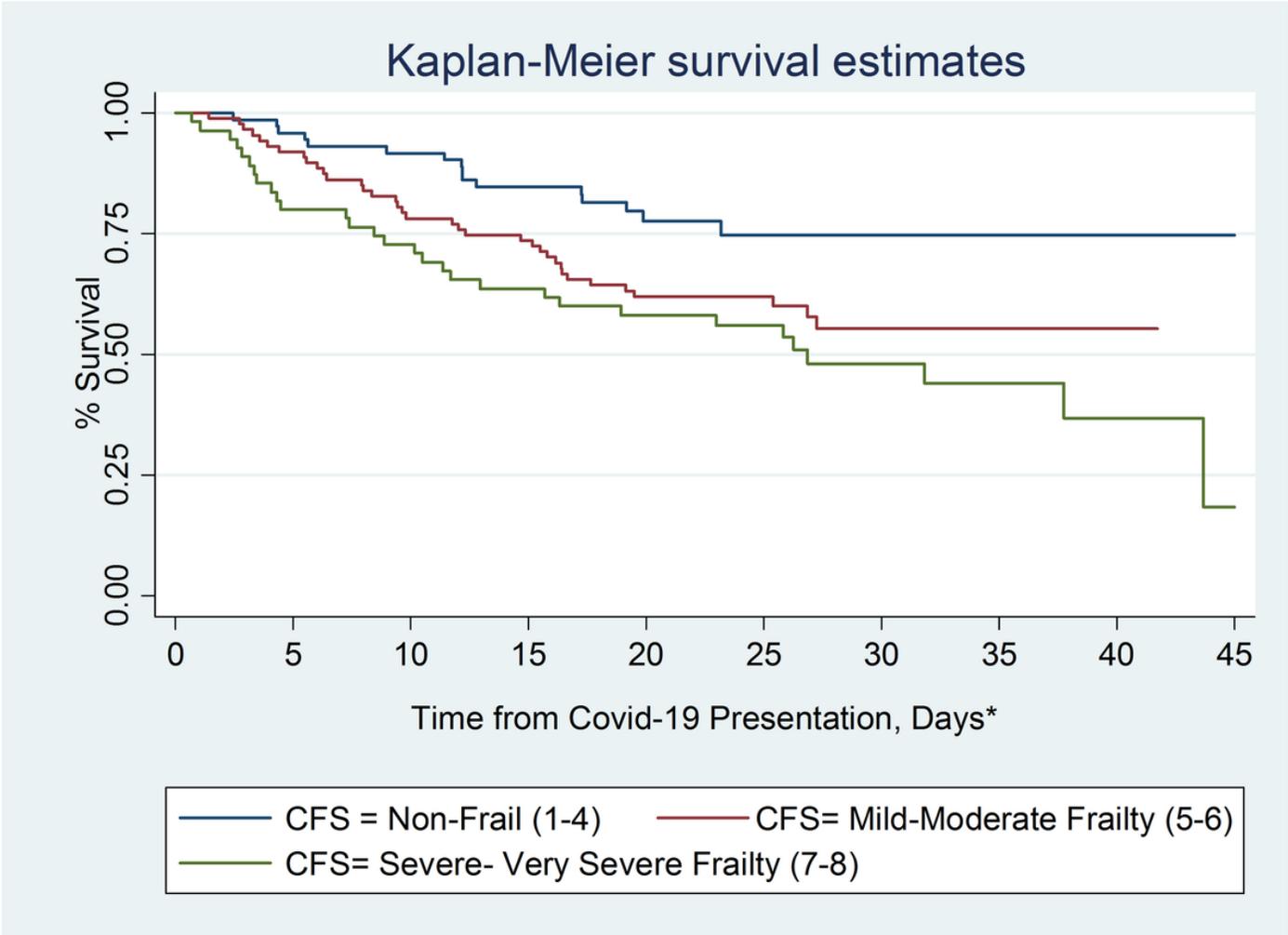


Figure 1

Venn Diagrams illustrating the prevalence of common geriatric illness by frailty with COVID-19 infection. Non-Frail: Clinical Frailty Score 1-4; Frail: Clinical Frailty Score 5-8; NOS: Non-specific illness.



**Figure 2**  
 Survival after presentation with COVID-19 infection by Clinical Frailty Scale (CFS) Score. \*The time from COVID-19 presentation is defined as the number of days from either admission to hospital or time from first positive swab if hospital acquired disease. For those discharged alive, follow-up was extended for the first 14 days after discharge.