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RESEARCH PAPER

Clinical frailty score as an independent predictor of outcome in COVID-19 hospitalised patients

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Key summary points

Aim To explore potential predictive variables associated with outcomes using baseline clinical parameters in 500 hospitalised COVID-19 patients.

Findings Older age, clinical frailty score and C-reactive protein are independent predictors of mortality.

Message Integrated frailty and age-based risk stratification are essential to allow for early intervention to improve patient outcomes.

Abstract

Purpose of the study We explored potential predictive variables associated with outcomes using baseline clinical parameters of 500 hospitalised patients with COVID -19 in a single centre, UK.

Methods Retrospective study collecting demographic and clinical characteristics of patients admitted at Southend University Hospital from 20th February to 7th May 2020.

Results The mean age of the cohort admitted to hospital with Covid-19 was 69.4 and 58% were over 70. Comorbidities were more frequently observed in non-survivors, whose mean Clinical Frailty Scale was significantly higher (5 vs 3) than survivors, $p < 0.001$. In addition, mean C-reactive protein was significantly higher.

Conclusion Older and frailer patients with high inflammatory markers were at risk of poor outcomes. Integrated frailty and age-based risk stratification is essential, in addition to monitoring saturation /FiO2 ratio (SFR) and inflammatory markers throughout the disease course to allow for early intervention to improve patient outcomes. A frailty-based risk-stratification approach, rather than age may prove more valuable when considering interventions in patients with multiple comorbidities.

Keywords COVID-19 · Epidemiological characteristics · Sars-Cov-2 · Prognostic factors

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Introduction

The coronavirus disease 19 (COVID-19) pandemic is one of the worst infectious disease outbreaks of recent times; with the first wave in the UK, we have encountered 312,000 confirmed cases and 44,819 fatalities [1]. COVID-19 is characterized by a highly variable course. While most patients experience only mild symptoms, a relevant proportion of patients develop severe disease progression up to respiratory failure. Several factors and mechanisms are proposed to influence COVID-19 pathogenesis. The most notable risk factor is age, followed by co-morbidities, including diabetes, obesity, cardiovascular and cerebrovascular diseases [2–5].

The mortality rate is variable; this is because of differences in the population demographics, the method used to register COVID-19, and the health services [6]. A recent report showed that mortality rate was 5.6% for China and 15.2% outside of China [7]. Belgium has relatively high case fatality rates (16.34%), followed by France (15.65%), UK (14.21%), Italy (14.15%), Hungary (13.07%), Netherlands (12.91%), Sweden (12.21%) and USA (5.95%). The mortality excess has been primarily seen in the age group of ≥ 65 years globally with higher case fatality rates in older patients with comorbidities [8,9]

In most studies, older age and co-morbidities have consistently shown to be associated with poor outcomes and aging process is known to increase frailty. In addition, there is substantial evidence that frailty is associated with worse outcomes in both medical and surgical patients, prolonged length of stay, increased care needs on discharge and mortality [10, 11]. Thus, it is very likely that frailty, together with comorbidities, may have contributed to the high mortality from COVID-19 among older people. Only few studies have evaluated Clinical Frailty Score (CFS) in COVID -19 [12, 13].

Therefore, our specific aim was to assess if CFS, was an independent predictor which has not been extensively described in existing literature as an efficient tool for assessing frailty, since this may be significant in determining outcomes for older patients. We hope that by adding to this growing body of evidence, we can assist early intervention in these patients to prevent rapid clinical deterioration and offer medications that have shown evidence in improving outcomes [14, 15].

Methodology

In this retrospective study, 500 patients with proven RT—PCR assay of nasopharyngeal swab positive and/or high likelihood of SARS COVID-19 infection with clinical and radiographic evidence who were admitted to Southend University Hospital from 20th February to 7th May 2020 were enrolled.

Collected demographic and disease characteristics included age, sex, ethnicity, clinical signs and symptoms at presentation and baseline observations. Laboratory findings included full blood count, neutrophil to lymphocyte ratio (NLR), C-reactive protein (CRP) and renal function, as well as ferritin, D-dimer, lactate dehydrogenase (LDH) and troponin, where available.

Patients' oxygen saturations (SpO_2) and supplementary oxygen (FiO_2) were recorded. SpO_2 to FiO_2 ratio (SFR) was calculated. The SFR has previously been shown to have a promising role to predict ITU admission [16]. Rice et al. were able to describe a relation between PaO2/FiO2 and SFR. An SFR of 235 and 315 corresponded to PaO2/FiO2 of 200 and 300 with a sensitivity of 85% and 91%; and specificity of 85% and 91%, respectively [17]. Bilan et al. also were able to demonstrate the reliability of SFR for the diagnosis of moderate Acute Respiratory Distress Syndrome, in substitute of the PaO2/FiO2. They demonstrate that an SFR of 181 and 235, predict a PaO2/FiO2 of 200 and 300, respectively [18].

Imaging results comprised chest radiography (CXR) abnormality and computed tomographic (CT) imaging. CXR findings were separated into three groups. Group 1 had no abnormalities, group 2 had classic changes including consolidation, pulmonary infiltrates, crazy paving pattern and ground glass opacities and in group 3 there were extensive changes of Ground glass opacities or multifocal consolidation. CT scan of the chest was done in selected patients with severe hypoxemia and to rule any other cause.

Comorbidity was defined as the presence of the conditions or history of these conditions and was extracted from electronic database. Several studies have shown that most common comorbidities including pulmonary disease, diabetes, hypertension, coronary artery disease, cerebrovascular disease, cancer and chronic renal disease were risk factors and we also evaluated these in our cohort.

The research team also collected data on degree of frailty; using the Rockwood Clinical Frailty Scale (CFS) [19] on all patients, outcomes, total length of stay and need for mechanical ventilation. CFS was documented by the clerking doctor (COVID proforma, supplementary1). Estimated CFS scores were calculated retrospectively from documentation taken no later than the first 24 h of admission, including clerking, past medical history, social history, previous discharge letters and any aspect of functional status.

We analysed the demographic, clinical, laboratory and imaging features of 500 patients with COVID-19 to determine potential biomarkers that may affect the prognosis of these patients.

Statistical analysis

The baseline characteristics of all enrolled patients in survivor and non-survivor groups were summarized and compared by applying Student's *t* test, the Chi-square test, and the Mann–Whitney *U* test as appropriate. We did not calculate sample size prior to conducting our study. However, based on a rule of thumb, we achieved a minimum required sample size for the development of the model based on the need for 10–15 non-survived patients per risk factor [20].

Quantitative data were described by mean (standard deviation) and median (minimum–maximum). Categorical variables were summarized by frequency and percent. Bivariate analysis using Independent sample *t*-test, Mann–Whitney test as well as Pearson's Chi-square test compared different demographic and clinical parameters between survivors and non-survivors. Statistically significant and clinically relevant predictors were fitted in multivariate stepwise backward logistic regression analysis. Variables initially included were age, gender, CFS, Comorbidities > 2, NLR, CRP, creatinine, Respiratory rate, CPAP, SFR, Total Length of stay and interaction CPAP*CFS. Model selection was judged by goodness of the fit using Likelihood Ratio Test as well as pseusoR [2]. Model cross-validation was performed by randomly splitting the sample into development and test sets (ratio 3:1). The prognostic ability of the model was determined by calculating the accuracy of model's predicted probability as well as the area under the receiver operating characteristics curve (AUROC) on the test set. Statistical analysis was performed using IBM SPSS statistics program and R software packages "caTools", "lmtest", "caret", "ROCR" and "ggplot2". All statistical tests were two-sided and judged at 0.05 significance level.

Results

A total of 592 with suspected or confirmed COVID-19 were recorded during the study period, of these 500 patients with complete data set were included in the analysis. The demographic and clinical parameters of the cohort, Survivors and Non-survivors are shown in Table 1.

462 patients had positive RT—PCR nasopharyngeal swab and 38 had negative swab results. Mean age of the cohort was 69 years, 300 were Male (60%) and 200 (40%) were female patients. Cough and dyspnoea were the most common presentation with equal representation 294(60.2%) followed by fever 247(49.5%), GIT symptoms 98(19.9%), falls 65(13%) and confusion 47(9.4%). Falls and confusion were common in older patients. 80(16%) patients with CFS over 4 had dementia. Majority of the cohort was Caucasian, 438(87.6%) and age > 70 were 291 (58.9%). Older patients tended to present atypically, with features such as falls, confusion, decreased consciousness, poor oral intake, dizziness, general deterioration, lethargy, drowsiness and reduced mobility, Table 2.

Of the 500 patients 193(38.6%) died. There was male preponderance among non-survivors 128(66.3%) and were much older (77.4 vs 64.5 years, $P < 0.001$) and presented with more comorbidities, including diabetes (65 [33.7%] vs. 63 [20.6%], $P = 0.001$ and cardiovascular disease (95 [49.2%] vs. 83 [27.1%], $P < 0.001$). The proportion of deaths with PaO_2/FiO_2 less than 336 (mean) was statistically significantly ($p < 0.001$). As per ARDS criteria, non-survivors had lower SFR < 315, $p < 0.001$. Non-survivors were more tachypnoeic (respiratory rate > 24) $p < 0.001$.

Clinical Frailty Scale: Mean CFS was 4, however compared to survivors of COVID- 19, non-survivors had significantly higher CFS (3 vs 5, $p < 0.001$). A number of laboratory parameters showed significant differences among survivors and non-survivors, Table 3. Mean CRP was significantly higher 150 vs 90, $p < 0.001$ in non-survivors, as well as neutrophil count 7.84, $p < 0.001$, urea 12.71, $p < 0.001$ and creatinine 136, $p = 0.001$.CXR abnormalities were observed more in non-survivors and supplemental oxygen requirement was higher in non-survivors 181(93.8%) as compared to survivors 165(53.9%), $p < 0.001$.

There appeared to be a low incidence of superadded or co-existing bacteraemia in our patients, with most of the organisms identified from the 44 positive blood cultures being those typically associated with commensals or contamination, it was not possible to determine if any of these were nosocomial infections. The most common pathogens identified were Staphylococcus aureus, epidermidis, Staphylococcus hominis, see supplementary 2. The COVID proforma at our hospital suggested the prescription of doxycycline and co-amoxiclav for patients who required admission, 85% of our cohort received antibiotics. However, some also received Co-trimoxazole (22%) and Clarithromycin (17%) as first course. Subsequently 29% required change in antibiotics for suspected secondary bacterial infection which were Tazocin (36%), Gentamicin (16%), Meropenem (22%) or Vancomycin (8%).

There were no statistical differences on length of stay, need for mechanical ventilation or symptoms between the two groups.

Predictors for mortality, multivariate analysis

Variables that were significantly associated with the outcome from univariate analysis were also entered into multivariate logistic regression models. Next, we examined various clinical parameters in the multivariate logistic regression models to identify if these were independent predictors for mortality. Age in both models was a continuous variable.

Table 1 Demographics and baseline characteristics of the cohort

Variables	Total 500	Survivors 307	Non-Survivors 193	Sig*
Male (*n*, %)	300 (60)	172 (56)	128 (66.3)	*p* 0.02
Female	200 (40)	135 (44)	65 (33.7)	
Age in Years mean (SD)	69.39 (17.2)	64.5 (18.3)	77.4 (11.6)	$p < 0.001$
Median (min–max)	73 (19–100)	68 (19–100)	78 (37–99)	
IQR	(59–83)	(52–80)	(70.5–87)	
< 40	36 (7.2)	35 (11.4)	1 (0.5)	
40–70	173 (34.6)	131 (42.7)	42 (21.8)	$p < 0.001$
70–80	132 (26.4)	67 (21.8)	60 (33.7)	
> 80	159 (31.8)	74 (24.1)	85 (44)	
Ethnicity Asian (*n*, %)	31 (6.2%)	24 (7.8%)	7 (3.6%)	*p* 0.25
Black-African	21 (4.2%)	12 (3.9%)	9 (4.7%)	
Caucasian	438 (87.6%)	264 (60%)	174 (40%)	
Other	10 (2%)	7 (70%)	3 (30%)	
Comorbidities, (*n*,%) < 2	282 (56.4)	203 (66.1)	79 (40.9)	$p < 0.001$
> 2	218 (43.6)	104 (33.9)	114 (59.1)	
Diabetes Mellitus	128 (25.7)	63 (20.6%)	65 (33.7%)	*p* 0.001
Hypertension	188 (37.8)	108 (35.3)	80 (41.7)	*p* 0.15
Cardiovascular disease	178 (35.7)	83 (27.1)	95 (49.2)	$P < 0.001$
Cerebrovascular disease	44 (8.8)	28 (9.2)	16 (8.3)	*p* 0.74
Respiratory disease	148 (29.7)	100 (32.7)	48 (24.9)	*p* 0.06
Other	281 (56%)	151 (49.3)	132 (68.4)	$p < 0.001$
CFS, median (min–max)	4 (1–9)	3 (1–9)	5 (1–9)	$p < 0.001$
Respiratory rate/min > 24/min (*n*, %)	271 (54.2)	140 (45.6%)	131 (67.9)	$p < 0.001$
Heart rate/min, > 100/min, (*n*, %)	175 (35)	100 (32.6)	74 (38.9)	*P* 0.15
SFR, mean (SD)	383.5 (106.8)	413.0 (76.6)	336.8 (129.1)	$p < 0.001$
SFR < 235	52 (10.4)	12 (3.9)	40 (20.7)	
SFR(235–315)(ARDS)	181 (10.2)	21 (6.8)	30 (15.5)	$p < 0.001$
SFR ≥ 315(acute lung injury)	397 (79.4)	274 (89.3)	123 (63.7)	
Cough(*n*, %)	294 (60.2)	186 (62)	108 (57.4)	*p* 0.32
SOB	294 (60.2)	177 (59)	117 (62.2)	*p* 0.45
Sore throat	32 (6.5)	23 (7.6)	9 (4.8)	*p* 0.21
GI	98 (19.9)	67 (22.2)	31 (16.3)	*p* 0.11
Fever	247 (49.5)	158 (51.6)	89 (46.1)	*p* 0.23
Lethargy	52 (10.4)	32 (10.5)	20 (10.4)	*p* 0.98
Falls	65 (13)	37 (12.1)	28 (14.5)	*p* 0.44
Myalgia	20 (4)	15 (4.9)	5 (2.6)	*p* 0.20
Confusion	47 (9.4)	24 (7.8)	23 (11.9)	*p* 0.13

CFS Clinical Frailty Scale, *SFR* SpO_2 to FiO_2 ratio, *ARDS* acute respiratory distress syndrome, *SOB* shortness of breath, *GI* gastrointestinal symptoms

ǂComorbidities of interest have been selected. SFR is categorised by American European consensus

*Results ≤ 0.05 are significant, *IQR* interquartile range

In the stepwise logistic regression models, the following were independent risk factors for mortality in model 1, age adjusted OR 1.035 (95% CI 1.012–1.058), NLR adjusted OR 1.021 (95% CI 1.00–1.04), CFS adjusted OR 1.132 (95% CI 1.13–1.53) and CRP adjusted OR 1.006 (95% CI 1.003–1.009), (Table 4). Again, in model 2, age and CFS score were strong risk factors. Interestingly gender did not reach the statistical significance for mortality. Similarly, creatinine, SFR and CXR abnormalities did not reach statistical significance but had a trend towards increased mortality (Table 4).

Table 2 Most common symptoms depending on the level of clinical frailty scale

	Clinical frailty scale < 3, *n* (%)	Clinical frailty scale > 4, *n* (%)
Cough	156 (31)	137 (28)
Dyspnoea	143 (29)	150 (30)
Fever	133 (27)	113 (23)
GIT	59 (12)	38 (7.6)
Falls	10 (2)	54 (11)
Confusion	4 (0.8)	42 (8.4)
Chest pain	22 (4.4)	8 (1.6)
Headache	22 (4.4)	4 (0.8)
Decreased consciousness	2 (0.4)	10 (2)
Poor oral intake	11 (2.2)	6 (1.2)
Dizziness	2 (0.4)	6 (1.2)
Sore throat	22 (4.4)	9 (1.8)
Lethargy	25 (5)	26 (5.2)
Myalgia	20 (4)	2 (0.4)
Reduced mobility	0	12 (2.4)

Discussion

This retrospective study identified several risk factors for poor outcomes in hospitalised adults with COVID-19.

The striking observation was the high mortality rate in our cohort, 38% compared to the national average of 33% [21]. One plausible explanation is that a large proportion of population in Southend are retired and older, 19% over 65 years of age compared to national average of 17.5% as per the office of the national statistics.

The second key finding was older age with greater frailty scores. There are very few studies which evaluated clinical frailty in patients in COVID -19. Similar to our study, an Italian group assessed frailty, which demonstrated increased in-hospital mortality, ICU admissions, independent of age and sex [22]. Another study showed that CFS, but not age, remained independently associated with mortality [23]. Three other studies demonstrated higher in-patient mortality in older and frail patients [12, 24, 25]. Furthermore, a recent meta-analysis showed that each 1-point increase in CFS was associated with 12% increase in mortality in a linear fashion [26].

Frailty describes the state that results from the physiological decline resulting from natural ageing and co-morbidities, encompassing parameters such as decreasing muscle mass and strength, declining exercise tolerance and inability to provide self-care: there may also be accompanying changes in metabolism and immune system response and there is an increased vulnerability to decompensation after a stressor such as COVID. Frailty should be considered in risk assessment models in future studies and clinical trials to assess interventions and meaningful outcomes.

There is substantial literature emphasizing the importance of geriatric medicine toward frailty prevention and clinical criteria to rapidly identify those with frailty or pre-frailty [27, 28]. Frailty, rather than simply chronological age, is considered to make patients vulnerable to decompensation and hard to recover loss of physiological reserve. This was clearly reflected in the recent COVID -19 pandemic, particularly in countries such as Italy.

In a prospective study of older patients with community acquired pneumonia, nursing home residency was an independent risk factor for viral pneumonia, which highlights the role of frailty in institutionalised populations [29] and is associated with worse outcomes in hospitalized older patients [30, 31]. The UK NICE guidelines suggest that CFS can be used as part of a holistic assessment in appropriate patients to support clinical decision-making regarding management including ceiling of care decisions. However, empirical evidence supporting the use of frailty instruments to predict treatment outcomes and triage accordingly is lacking [32].

Thirdly, our results confirmed that comorbidities, in particular cardiovascular disease and diabetes were strongly associated with negative outcomes. This is consistent with recent meta-analysis, from CDC China [33]. Similarly, another study of 5700 hospitalised patients with COVID-19 in the New York City area, the most common comorbidities were hypertension (57%), obesity (42%), and diabetes (34%) [34]. Other studies have reported that hypertension increases the risk odds for death in patients with COVID-19 [35, 36]; however, our study did not find hypertension to be statistically significant. While hypertension does appear to be associated with more severe disease and increased mortality, there is no strong evidence to indicate increased susceptibility of patients with hypertension to COVID-19 [37]. The mechanisms of this possible relationship and their clinical relevance have been reviewed in a recent statement of the European Society of Hypertension. The putative relationship between hypertension and COVID-19 may relate to the role of ACE 2(angiotensin-converting enzyme) [37]. Diabetes, lung disease, and obesity are now well-recognised major predictors of poor clinical outcomes in many clinical scenarios. These aspects emphasize the importance of the need for multidisciplinary assessment and treatment, including cardiovascular risk evaluation and therapy, during the course of COVID-19 to reduce mortality.

Data show European mortality is generally higher in older patients compared to earlier reports from China. Age was observed as an independent predictor of mortality in our cohort, which was consistent with the large prospective UK ISARIC study of hospitalised patients [21] and Chinese data

Table 3 Baseline clinical parameters and Laboratory studies at presentation

Variables	Total	Survivors	Non-survivors	Sig*
CRP mg/L, mean (SD)	114.19 (91.26)	90.64 (82.18)	150.27 (93)	$P < 0.001$
Lymphocyte 10^9/L, mean (SD)	1.37 (4.56)	1.35 (3.8)	1.39 (5.5)	P 0.93
Neutrophil 10^9/L, mean (SD)	6.88 (4.8)	6.29 (4.3)	7.84 (5.42)	$P < 0.001$
NLR, mean (SD)	12.56 (24.5)	10.62 (27.86)	15.65 (17.72)	p 0.03
Urea mmol/L, mean (SD)	9.88 (8.92)	8.06 (7.98)	12.71 (9.58)	$P < 0.001$
Creatinine umol/L, mean (SD)	114 .65 (107.8)	100.89 (93.31)	136.05 (124.40)	P 0.001
Chest X-Ray, *n* (%)Not done	28 (5.6%)			
Normal	140 (29.7)	103 (36)	37 (19.9)	
Moderate changes	317 (67.2)	177 (61.9)	140 (75.3)	$P < 0.001$
Severe changes	15 (3.2)	6 (2.1)	9 (4.8)	
CT Scan Not done, *n* (%)	397 (79.4%)			
Covid changes	103 (20.6%)			
Blood cultures, *n* (%)				p 0.65
Gram positive	34 (6.8%)	16 (11.2)	18 (14.8)	
Gram negative	10 (2.0%)	6 (4.2)	4 (3.3)	
No growth	221 (83.4)	121 (84.6)	100 (82)	
Not done	235 (47)			
Oxygen requirement, n (%)	346 (69.3)	165 (53.9)	181 (93.8)	$P < 0.001$
CPAP	56 (11.2%)	36 (11.7)	20 (10.4)	p 0.64
Mechanical ventilation	64 (12.8%)	36 (11.7)	28 (14.5)	p 0.37
Length of stay, mean (SD)	9.33 (12.17)	9.51 (14.01)	9.05 (8.5)	p 0.68
Total IMV days, mean (SD)	14.5 (12.31)	17.62 (14)	10.60 (8.55)	p 0.02
SFR, mean (SD)	383.65 (106.81)	413.08 (76.68)	336.82 (129.19)	$P < 0.001$
Baseline Fio2, mean (SD)	0.46 (4.19)	0.54 (5.53)	0.35 (0.23)	p 0.62
Baseline S02, mean (SD)	91.92 (8.61)	93.29 (8.08)	89.75 (9)	$P < 0.001$
Respiratory rate, mean (SD)	25.75 (8.29)	24.29 (7.44)	28.07 (9.03)	$P < 0.001$

*Results ≤ 0.05 are significant by either independent sample t test, Mann–Whitney test for CFS and Chi-square test for categorical variables

CRP C-reactive protein, *NLR* Neutrophil Lymphocyte ratio, *CXR* chest X-Ray, *CXR 1* Normal, *CXR 2* Classic/Moderate, *CXR 3* severe COVID changes, *CT* computer tomography, *CPAP* continuous positive airway pressure, *IMV* invasive mechanical ventilation, *SFR* SPO2 to FiO2 ratio, *FiO2* fraction of inspired oxygen, *S02* saturation of oxygen

[38–40]. In Italian studies, case fatality rates ranged from 35.5 to 52.5% in patients aged over 70 years with COVID infection [41–44]. In the USA, older patients aged ≥ 65 years accounted for higher deaths, with the highest incidence of severe outcomes in patients aged ≥ 85 years [45]. Why the disease is particularly dangerous in older people is not yet known and poorly understood at the molecular level. It is clear, however, that advanced age alone is by far the most significant risk factor, independent of underlying comorbidities [46, 47]. An abundance of recent data describing the pathology and molecular changes in COVID-19 patients points to both immunosenescence and inflammaging as major drivers of the high mortality rates in older patients.

In contrast to the literature, male sex was not associated with increased mortality in our study. Large studies from China, Europe and Italy established that males were more susceptible to COVID-19-related complications, representing between 50 and 82% of the hospitalized patients with COVID -19 [5, 8, 48, 49].

Within our cohort, increased baseline CRP, creatinine and NLR were associated with poorer prognosis. The most consistent prognostic markers in COVID-19 across the different studies were elevated levels of CRP, LDH, lymphopenia and neutrophil-to-lymphocyte ratio (NLR), and these appear to stratify patients into higher risk of complications [50–52]. Intriguingly, elevated levels of C-reactive protein appear to be unique to COVID-19 patients when compared to other viral infections. Other consistently reported markers in non-survivors are increased procalcitonin (PCT) and IL-6 levels [53].

Table 4 Multivariate logistic regression analysis for assessing independent predictors for mortality

	Sig	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Model 1			
Age	0.002*	1.05 (1.03–1.06)	1.035 (1.012–1.058)
Neutrophil to lymphocyte ratio(NLR)	0.024*	1.04 (1.02–1.06)	1.021 (1.00–1.04)
CFS	< 0.001*	1.45 (1.30–1.62)	1.132 (1.13–1.53)
CRP	< 0.001*	1.006 (1.004–1.009)	1.006 (1.003–1.009)
Creatinine	0.070	1.004 (1.001–1.008)	1.002 (0.999–1.005)
SFR	< 0.001*	0.993 (0.990–0.995)	0.995 (0.993–0.998)
Constant	< 0.001*		0.020 (0–0.01)
Model 2			
Age	< 0.001*	1.05 (1.03–1.06)	1.038 (1.013–1.063)
Male gender	0.113		1.583 (0.896–2.797)
Neutrophil to lymphocyte ratio(NLR)	0.050	1.04 (1.02–1.06)	1.019 (0.999–1.039)
CFS	< 0.001*	1.45 (1.30–1.62)	1.356 (1.145–1.606)
CRP	< 0.001*	1.006 (1.004–1.009)	1.006 (1.002–1.009)
Creatinine	0.121	1.004 (1.001–1.008)	1.002 (0.999–1.005)
SFR	0.094	0.993 (0.990–0.995)	0.997 (0.994–1)
LOS	0.038	0.997 (0.979–1.015)	0.971 (0.946–0.998)
Supp Oxygen (Yes)	< 0.001*	12.25 (5.94–25.25)	7.66 (3.24–18.10)
CXR	0.059	1.73 (1.22–2.46)	1.585 (0.981–2.56)
Constant			0 (0–0.01)

Model1: Variables initially included: Age, gender, CFS, Comorbidities > 2, Neutrophil to lymphocyte ratio(NLR)

CRP, creatinine, RR, CPAP, SFR, Total LOS, interaction CPAP*CFS

Model2: Variables initially included were the same as model 1 + Supp 02 and CXR.pseusoR$^2_{model1}$ = 25.2%, pseusoR$^2_{model2}$ = 32.6% which mean Sup 02 as a significant predictor could explain additional 7.4% of variance in mortality outcome

Model1 cross validation accuracy on test set = 78.3%, AUROC = 0.842.Model2 cross validation accuracy on test set = 78.1%, AUROC = 0.871

Limitations

The findings of this study are derived from hospitalised cases which might have introduced a bias in disease severity and fatality. We did not collect more details on pre-existing comorbidities and severity. The data collection is limited to what is documented in the electronic patient database whether there may be errors both with patient and clinician recall. Our single centre findings may not be generalizable. Routine tests such as LDH, Ferritin, D-Dimer and Troponin were not carried out on all patients, even with the introduction of an agreed COVID investigation panel part way through the period of interest.

Conclusion

In this large retrospective study, we found that older age, comorbidities, frailty and elevated CRP at admission were significant risk factors for poor outcomes in patients with COVID-19. Our findings add to the emerging reports quantifying the relationship between frailty and mortality in COVID-19.

Now, more than ever, a holistic approach to patients with comorbidities is required, and rapid solutions to support this must be identified and implemented with urgency. Older patients are particularly susceptible to adverse clinical outcomes in COVID-19 infection and assessment and treatment is challenging. Long-stay residential care homes and hospitals need to urgently design adequate health care plans for older patients. Our results strengthen the NICE guidance on the Clinical Frailty Scale, to assist decision-making regarding hospitalization. We suggest integrating the frailty assessment in all COVID-19 patients at hospital admission, which can help clinicians in their decision-making processes. However, shared decision-making is always warranted with respect to personal wishes and preferences of the patient. Given the economic and resource constraints, shifting hospice and palliative care resources to the community was a key message in a recent review to inform practice in the pandemic [54].

A frailty-based risk-stratification approach, rather than age may prove more valuable when considering

interventions in patients with multiple comorbidities. The planning strategies perhaps should include awareness, tools to facilitate communication with healthcare professionals, improved access to institutional health communication and better access to local and social support activities. In addition, standardising investigations to allow early risk stratification, and inform good quality decision-making at the front door would be key to identifying the most appropriate location for, and level of care that an individual patient should receive ideally this approach should be supported by early involvement of clinicians with sufficient experience to make those decisions. In light of the patient demographics, an ideal scenario would involve geriatricians being heavily involved in planning and delivering these services.

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Declarations

Conflict of interest Dr. GK, SG, MD, VW, FH, ID and YA have nothing to disclose.

Ethical approval This study was conducted in accordance with the Institutional review board and approved by the Southend University Hospital NHS Foundation Trust and granted a waiver due to its retrospective observational design.

Competing interests All authors had no competing interests.

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