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Mortality 30 and 90 days after hospitalisation for COVID-19: prognostic factors on admission to hospital

Stephen A. Murphy*, Fatima Khalil, Mohammad Fayaz, Louise Robinson and Natalie M. Cummings

Department of Respiratory Medicine, University Hospital of North Durham, Durham, United Kingdom

Summary points

- Severe acute respiratory syndrome (SARS-CoV-2) infection causes substantial mortality
- Prognostic factors on hospitalisation for SARS-CoV-2 were investigated
- Mortality was 30.8% at 30 days increasing to 34% at 90 days
- Risk factors: Age, male-sex, smoking, comorbidity, frailty, chest x-ray changes and raised CRP

Abstract

***Introduction*:** Severe acute respiratory syndrome (SARS-CoV-2) infection causes substantial mortality in hospitalised patients. The purpose of this study was to investigate mortality and identify prognostic factors from the data collected on hospital admission.

***Methods*:** This was a retrospective cohort study of patients hospitalised with clinically suspected and/or laboratory confirmed SARS-CoV-2 infection. The primary outcome was mortality 30 and 90 days after admission. Risk factors for death were identified by multivariable logistic regression.

***Results*:** Three hundred and thirty-four patients were included; 93.4% of patients had positive SARS-CoV-2 RT-PCR swab; median (IQR) age 75 (63–84) years, male 54.2%, smoking (≥ 5 CPD/ ≥5 pack years) 37.1%, obesity 24.8% and frailty 42%. Mortality was 30.8% at 30 days after admission and 34% at 90 days after admission. Mortality was greatest in older patients (age >65 years; 36.7 vs. 16.5%; $P < 0.001$), particularly older males (age >65 years; male 42.5 vs. female 30%; $P = 0.046$); smoking (41.1 vs. 24.8%; $P = 0.003$); younger smokers (age ≤ 65 years; 35.3 vs. non-smoker 6.5%; $P < 0.001$); with chronic kidney disease (CKD: 50 vs. 27.8%; $P = 0.003$), chronic neurological disease (43.8 vs. 27.2%; $P = 0.007$), COPD (41.3 vs. 28.8%; $P = 0.048$), cardiac disease (40.7 vs. 25.1%; $P = 0.003$), frailty (44.3 vs. 21%; $P < 0.001$), and with chest x-ray changes of COVID-19 (39 vs. 13.2%; $P < 0.001$). Mortality was associated with raised C-reactive protein (CRP) and lymphopaenia on admission. Independent predictors of mortality were (adjusted OR; 95% CI): age (1.05; 1.02–1.08), smoking (2.08; 1.19–3.63); CKD (2.32; 1.09–4.92), chronic neurological disease (2.27; 1.17–4.40), frailty (1.92; 1.047–3.53); chest x-ray changes of COVID-19 (4.31; 2.12–8.79) and Log-CRP (3.21; 1.43–7.22); ROC analysis AUC *0.811 (0.765–0.852)*.

***Conclusion*:** Mortality for patients hospitalised with SARS-CoV-2 infection is high (>30%) with greatest risk in older-age males with chronic disease and frailty. A history of moderate–heavy smoking is a major risk factor, particularly in younger patients (≤ 65 years). Chest x-ray changes of COVID-19 and raised CRP are clinically valuable prognostic indicators.

Keywords: *hospitalisation*; *mortality*; *prognostic factors*; *SARS-CoV-2*; *smoking*

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The clinical characteristics of patients admitted to hospital with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been described extensively [1–5]. Mortality rates have varied from as low as 5% in China to more than 40% in Europe [1, 5, 6]. Some of these reports were published before all patient outcomes were known but disparities are partly attributable to demographic differences, particularly patient age with a 20-year variance between those hospitalised in China and Europe [1, 5, 6].

Increased age is a consistent risk factor for mortality from COVID-19 in all populations but the significance

of other demographic variables is less clear; smoking was a risk factor in some studies, seemed protective or had no effect in others and was not included in many [7–10]. The significance associated with obesity varies with a gradient of risk for hospitalisation and critical care related to BMI in the United States and increased mortality in some UK studies but contradictory findings elsewhere [3, 5, 7, 10–13].

Chronic diseases, particularly cardiovascular, chronic lung and kidney disease, are associated with critical illness and mortality in many studies. Hypertension and diabetes mellitus have also been linked with increased risk, particularly in China and the United States [2–7, 14].

In addition to demographic and clinical factors, several biomarkers for disease severity and outcome have been identified; the presence of lymphopaenia and raised CRP are most widely reported [3, 6, 13, 14–18].

The purpose of this study was to investigate the mortality 30 and 90 days after hospitalisation in patients with clinically suspected and laboratory confirmed SARS-CoV-2 during the first wave of the pandemic and to identify prognostic factors from demographic, clinical and laboratory data collected during routine clinical-practice.

Materials and methods

Study design and participants

The study was performed at the University Hospital of North Durham, a 520-bed district general hospital serving about 350,000 residents in the city of Durham and former mining villages of County Durham with a majority (96.6%) indigenous white British population. It was a single-centre, retrospective cohort study of adult patients hospitalised from February 2020 with a discharge diagnosis of COVID-19. Patients admitted for other reasons that developed COVID-19 in hospital were included. Patients were tested for SARS-CoV-2 by real-time reverse-transcription polymerase chain reaction (RT-PCR) on a nasopharyngeal swab. All patients with clinical features of an acute viral illness and a positive RT-PCR test were included in the study. It was anticipated that about 25% of patients with COVID-19 would have a false-negative test (sensitivity 70%) [19]. Patients with a discharge diagnosis of COVID-19 but negative RT-PCR were included if pretest test probability of COVID-19 was considered >90% (post-test probability of disease after single negative test 74%). Follow-up of the cohort was censored 1 September 2020.

Data collection

Data extracted from the patients' clinical records included age and gender; smoking history was obtained by comprehensive review of all available hospital records, and smoking status was defined as moderate/heavy smoker (current regular smoker of ≥ 5 cigarettes per day [cpd]; or documented evidence of historic smoking ≥ 5 pack years), non/light-smoker (never smoked, current smoker <5 cpd and/or <5 pack years), unknown (no smoking history in records, unable to quantify); obesity (physician described and/or record of body mass index ≥30 kg/m^2); residence (residential/nursing-home/sheltered or warden controlled); professional home carers; chronic disease groups; cardiac disease (atrial fibrillation, ischaemic heart disease, cardiac failure, valvular heart disease); chronic kidney disease (CKD; estimated GFR <30 ml/min); chronic neurological disease (cerebrovascular disease, Parkinson's disease, other neurodegenerative diseases, multiple sclerosis and any brain injury); chronic lung disease (COPD and non-asthmatic chronic lung conditions); and other chronic conditions.

The primary clinical diagnoses were COVID-19 (community or hospital acquired) if symptoms of lower respiratory infection with chest x-ray changes compatible with COVID-19; lower respiratory tract infection (LRTI with normal/unchanged chest x-ray); and other (no respiratory symptoms and normal/unchanged chest x-ray). The presence of frailty (physician described and/or Rockwood clinical frailty score [CFS] ≥ 6) was recorded [20]; Laboratory tests include lymphocyte count and C-reactive protein (CRP). Chest x-rays were reviewed and categorised as normal/pre-existing abnormality and new-changes consistent with COVID-19.

Ethics

This study was a retrospective review of data obtained for routine clinical care and service evaluation for patients admitted to hospital with COVID-19. The study was approved by the hospital research and innovation department. Formal ethics approval was therefore not considered necessary [21].

Analysis and statistics

The distribution of continuous variables was tested for normality by the Kolmogorov–Smirnov test. Continuous variables with a non-normal distribution are expressed as median and interquartile range (IQR), and categorical variables are expressed as percentages. Variables were compared using non-parametric methods (*Mann-Whitney test)* for continuous variables and χ^2 for categorical data. Cut-off values for lymphocyte count and CRP were obtained from comparison of outcomes between deciles and by probit regression with logarithmic transformation. Collinearity between predictor variables was assessed by Pearson's *phi coefficient*. The association(s) between variables on admission and mortality 30-days after admission was evaluated by univariate and multivariable logistic regression. Subgroup analysis of 90-day survival was performed for age range, sex and smoking history by the Kaplan–Meier method with hazard ratios (HRs).

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Statistical analyses were made using MedCalc® Statistical Software version 19.5.3.

Results

Three hundred and thirty-four patients were included in the study; 312 (93.4%) patients had a positive SARS-CoV-2 RT-PCR swab. A further 22 cases (6.6%) with a negative RT-PCR result were included. Fifty-two (15.6%) cases were due to hospital acquired infection.

Table 1 shows the distribution of demographic variables. The median age was 75 (63–84) years; more than 70% were over 65 years of age and 54.2% were male. A quarter (25.4%) lived in a residential care facility, and 20.6% of those living at home had professional carers. The prevalence of smoking (≥ 5 CPD/ ≥ 5 pack years) was 37.1% (20% in the under 50s and 41.7% for age 76–85 years). Obesity was present in 24.8% overall but more frequent (49.5%) in patients ≤ 65 years.

Chronic disease was common with a median of three comorbid condition per patient (Table 2). Cardiac disease and hypertension were most frequent. Chronic neurological disease was present in 22% (67% cerebrovascular disease) and 16.2% of patients had some form of dementia. COPD was present in 19% overall and 25% of those that died but asthma was infrequent (8%). Chronic kidney disease (CKD) affected 13.8% overall and 22.3% of non-survivors.

Clinical and laboratory variables are shown in Table 3. Frailty was common and more frequent in those with

Table 1. Demographic characteristics of patients

Demographic	Total (*n* = 334)	Alive (*n* = 231)	Died (30 days)‡ (*n* = 103)	*P*
Age (IQR) years	75 (63–84)	72 (61–82)	81 (73–87)	*<0.0001*
Male	181/334 (54.2%)	119/231 (51.5%)	62/103 (60.2%)	*0.14*
Residential care	85/334 (25.4%)	43/231 (18.6%)	42/103 (40.8%)	*<0.0001*
Home carers	51/248 (20.6%)	35/187 (18.7%)	16/61 (26.2%)	*0.2*
Smoker[ƒ]	124/334 (37.1%)	73/231 (31.6%)	51/103 (49.5%)	*0.001*
Smoking unknown	29/334 (8.7%)	18/231 (7.8%)	11/103 (10.6%)	
Obesity (total)	83/334 (24.8%)	69/231 (29.8%)	14/103 (13.5%)	*0.0015*
Obese (> 65 years)	35/237 (14.4%)*	28/150 (18.7%)	7/87 (8%)	*0.026*
Obese (≤ 65 years)	48/97 (49.5%)*	41/81 (50.6%)	7/16 (43.7%)	*0.6*

‡Died within 30 days of admission.
*$P < 0.001$.
[ƒ]Current/ex-smoker (≥ 5 pack years or ≥ 5 cpd).

Table 2. Prevalence of chronic disease

Comorbidity	Total (*n* = 334)	Alive (*n* = 231)	Died‡ (*n* = 103)	*P*
No. chronic conditions (median [IQR])	3 (2–3)	2 (1–3)	3 (2–4)	0.009
Cardiac disease	123/334 (36.8%)	73/231 (31.6%)	59/103 (48.5%)	0.003
Hypertension	99/334 (29.6%)	67/231 (29.1%)	32/103 (30%)	0.7
Diabetes	85/334 (25.4%)	58/231 (25%)	27/103 (26.2%)	0.8
Chronic neurological disease[§]	73/334 (22%)	41/231 (17.8%)	32/103 (31.1%)	0.006
Chronic lung disease[*]	71/334 (21.3%)	44/231 (19%)	27/103 (26.2%)	0.14
COPD	63/334 (19%)	37/231 (16%)	26/103 (25%)	0.046
Cerebrovascular disease	49/333 (14%)	28/230 (12.2%)	21/103 (20.4%)	0.051
Chronic kidney disease	46/334 (13.8%)	23/231 (10%)	23/103 (22.3%)	0.0025
Dementia	54/334 (16.2%)	33/231 (14.3%)	21/103 (20%)	0.16
Malignancy	34/334 (10.2%)	26/231 (11.3%)	8/103 (7.8%)	0.33
Asthma	28/334 (8.4%)	25/231 (10.8%)	3/103 (2.9%)	0.016
Alcohol excess	14/334 (2.2%)	11/231 (4.8%)	3/103 (2.9%)	0.43

‡Died within 30 days of admission.
[*]COPD (chronic obstructive pulmonary disease) and other non-asthma chronic lung diseases.
[§]includes cerebrovascular disease.

Table 3. Clinical characteristics and laboratory variables on admission

Clinical feature	Total (n = 334)	Alive (n = 231)	Died* (n = 103)	P
Frailty[f]	140 (42%)	78 (33.8%)	62 (60.2%)	< 0.0001
CXR** changes of COVID-19	228 (68.2%)	139 (60.4%)	89 (86.4%)	*< 0.0001*
CXR changes (male)[¶]	138/181 (76.2%)	81/119 (68.1%)	57/62 (91.9%)	*<0.001*
CXR changes (female)[¶]	90/153 (58.8%)	58/112 (51.8%)	32/41 (78%)	*0.003*
COVID-19-CAP[§]	208 (62.3%)	130 (56.3%)	78 (75.7%)	*0.015*
COVID-19-HAP[§]	19 (5.7%)	8 (3.5%)	11 (10.7%)	*0.001*
LRTI[§]	55 (16.5%)	50 (21.6%)	5 (4.9%)	*0.002*
No acute respiratory disease	52 (15.6%)	43 (18.6%)	9 (8.7%)	*0.018*
Biomarkers				
Lymphocyte count (IQR) x 10^9/l (admission)	0.9 (0.6–1.2)	0.9 (0.6–1.3)	0.8 (0.6–1.05)	0.011
Lymphopaenia (< 1.0 x 10^9/l; admission)	186/328 (56.7 %)	123/228(53.9 %)	63/100 (63 %)	0.12
Lymphopaenia (Male)[†]	112/177 (63.3 %)	70/117 (59.8%)	42/60 (70%)	0.18
Lymphopaenia (Female)[†]	74/151 (49 %)	53/111 (47.7%)	21/40 (52.5%)	0.6
Lymphocytes ≤ 0.8 x 10^9/l (admission)	157/328 (47.9 %)	99/228 (43.4 %)	58/100 (58 %)	*0.015*
Lymphocytes (IQR) x 10^9/l (lowest value)	0.7 (0.5–1.0)	0.75 (0.5–1.1)	0.6 (0.4–0.8)	0.0015
CRP (IQR) mg/l (admission)	97 (50–172)	87 (41.2–152)	124 (74–194)	*0.0012*
CRP (IQR) mg/l (highest value)	149 (79–245)	133 (63–228)	198 (105–280)	*<0.001*
CRP ≤ 50 mg/l (admission)	81/331 (24.8%)	65/228 (28.5%)	16/103 (15.5%)	*0.011*
CRP ≤ 50 mg/l (Male)[‡]	35/178 (19.7%)	25/116 (21.6%)	10/62 (16.1%)	*0.38*
CRP ≤ 50 mg/l (female)[‡]	47/152 (30.9%)	41/111 (36.9%)	6/41 (14.6%)	*0.008*
CRP > 100 mg/l (admission)	161/331 (48.6%)	98/231 (42.4%)	63/103 (61.1%)	*0.002*
CRP > 100 mg/l (Male)[$]	95/178 (53.4%)	56/116 (48.3%)	39/62 (62.9%)	*0.06*
CRP > 100 mg/l (Female)[$]	67/153 (43.8%)	42/112 (37.5%)	25/41 (61%)	*0.009*

* Died within 30 days of admission; [f] Physician described frailty or CFS ≥ 6; **CXR chest x-ray; [§]CAP community acquired pneumonia, [§]HAP hospital-acquired pneumonia, [§]LRTI lower respiratory tract infection. Male v Female [¶]p<0.001; [†]p=0.009; [‡]p=0.018; [$]$p$=0.08.

hospital acquired SARS-CoV-2 infection (57.7 vs. 39%; P = 0.012). Frail patients were older (median [IQR]: 83 [76–88] vs. 69 [59–78] years; P < 0.001) and had more chronic conditions (median [IQR]: 3 [2–4] vs. 2 [1–3]; P < 0.001). Most (84.6%) patients had pneumonia or a LRTI.

The distributions of lymphocyte count and CRP values were wide (Fig. 1). More than half (56.7 %) of patients were lymphopaenic which was more pronounced in non-survivors and worsened after admission in 52.9% of patients, particularly those that died (63.6 vs. 48.2%; P = 0.01).

The admission CRP was raised in 97.6% of patients and increased further in 62.4% (survivors 60 vs. 67%) with good correlation between admission and peak CRP values (r^2 = 0.61; P < 0.001). Admission and peak CRP were higher in non-survivors but there was no difference in the incremental change in CRP. The chest x-ray was abnormal with changes compatible with COVID-19 in more than two-thirds of cases (died 86.4 vs. 60.4%; P < 0.001)

There was no gender difference for age, smoking or comorbidity, and frailty but males were more likely to be lymphopaenic (63.3% v 49% P =0.009) had higher CRP levels (median (IQR) 107.5 (62–184) v 83.5 (45–167) mg/l P = 0.03) and chest x-ray changes of COVID-19 (76.2 vs. 58.8%; P < 0.001).

Thirty-five patients (10.5%) were admitted to the intensive care unit (ICU) with marked disparity by age (≤65 years 29.9 vs. 2.5%; P < 0.001). Obese patients were more likely to be admitted to ICU (25 vs. 5.4%; P < 0.001), particularly patients ≤65 years (41.7 vs. 18.4%; P = 0.012).

Mortality was 30.8% at 30 days after hospitalisation increasing to 34% at 90 days after hospitalisation. Mortality increased with age, and there was a trend to poorer survival in males overall with significantly worse survival in older men (Tables 4 and 5; Fig. 2). Mortality was higher amongst patients admitted from a residential care/supported living facility. Smoking was associated with a poorer survival, particularly in younger patients (Fig. 2). Obesity was associated with lower mortality in older patients. The risk of death was greatest with CKD, chronic neurological disease, COPD, cardiac disease and cumulative comorbidity.

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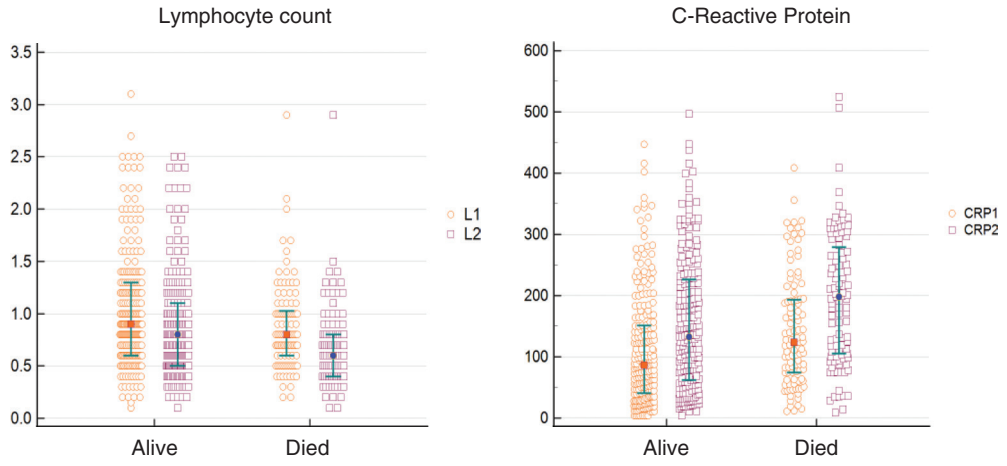

Fig. 1. Distribution of lymphocyte count and C-reactive protein levels. Lymphocyte × 10^9 cells/l (L1, lymphocyte count on admission; L2, minimum lymphocyte count). Error bars median and IQR; CRP, C-reactive protein mg/l (CRP1, level on admission; CRP2, highest level).

Table 4. Univariate analysis of demographic characteristics and 30-day mortality

	Mortality %			
Variable	Present	Absent	OR (95% CI)	*P*
Age (years)			1.05 (1.03–1.07)	<0.001
Age > 65 years	87/237 (36.7%)	16/97 (16.5%)	2.94 (1.61–5.55)	<0.001
Sex = Male	62/181 (34.6%)	41/153 (27.2%)	1.42 (0.88–2.27)	0.144
Sex = Male (>65 years)	54/127 (42.5%)	33/110 (30%)	1.7 (1.0073–2.95)	0.047
Obesity (total)	14/83 (16.8%)	89/251 (35.5%)	0.37 (0.19–0.69)	<0.001
Obese (> 65 years)	7/35 (20%)	80/202 (39.6%)	0.38 (0.16–0.91)	0.03
Obese (≤ 65 years)	7/48 (14.6%)	9/49 (18.4%)	0.76 (0.26–2.23)	0.6
Smoker*	51/124 (41.1%)	52/210 (24.8%)	2.12 (1.32–3.41)	0.003
Smoking unknown[§]	11/29 (38.3%)	41/181 (22.7%)	2.08 (0.91–4.77)	0.08
Care home	42/85 (49.5%)	61/249 (24.4%)	3.0 (1.8–5.0)	<0.001
Home carers	16/51 (31.4%)	45/197 (22.8%)	1.54 (0.78–3.04)	0.2

*Current/ex-smoker (≥ 5 CPD/ ≥ 5 pack years) versus non/light-smokers/unknown status.
[§]compared with non-smokers.

Mortality rate was doubled by frailty and trebled with chest x-ray changes of COVID-19. Lymphopaenia and raised CRP were both associated with increased mortality. Mortality was higher if lymphocyte count fell after admission (36.4 vs. 23.4%; $P = 0.01$). A CRP level >100 mg/l almost doubled the mortality risk compared to the CRP level <50 mg/l. Males were more likely to have a peak CRP > 100 mg/l (72.1 vs. 61.2%; $P = 0.036$), and females were more likely to have CRP ≤ 50 mg/l (30.9 vs. 19.7%; $P = 0.018$). Logarithm of CRP (admission or peak value) had a highly significant association with mortality.

Variables were included in a multivariable logistic regression analysis if $P < 0.15$ on univariate analysis. The final models are shown in Table 6. Sex, COPD, cardiac disease, cumulative comorbidity and lymphopaenia were not independent predictors of mortality due to multicollinearity with other predictor variables; Pearson's *phi* coefficients for sex (chest x-ray changes 0.186, lymphopaenia 0.129 and log CRP 0.125); COPD (smoking 0.61); cardiac disease (age 0.349 and frailty 0.23); cumulative comorbidity (age 0.249, cardiac disease 0.459, CKD 0.30 and frailty 0.218).

Discussion

This study describes the outcomes of the first cohort of patients admitted to the University Hospital of North Durham with SARS-CoV-2 infection. The 30-day

Table 5. Univariate analysis of comorbidity/clinical variables and 30-day mortality

Variable	Mortality %		OR (95% CI)	*p*
	Present	Absent		
Comorbidity†			1.30 (1.07–1.58)	0.008
Cardiac disease	50/123 (40.7%)	53/211 (25.1%)	2.04 (1.27–3.28)	0.003
Chronic neurological	32/73 (43.8%)	71/261 (27.2%)	2.09 (1.22–3.57)	0.007
CKD‡	23/46 (50%)	80/288 (27.8%)	2.6 (1.38–4.9)	0.003
COPD	26/63 (41.3%)	77/271 (28.8%)	1.77 (1.004–3.12)	0.048
Chronic lung	27/71 (38%)	76/263 (29.4%)	1.51 (0.87–2.61)	0.14
Diabetes	27/85 (31.8%)	76/249 (30.5%)	1.06 (0.62–1.80)	0.8
Hypertension	32/99 (32.3%)	71/235 (30.2%)	1.10 (0.66–1.82)	0.70
Malignancy	8/34 (23.5%)	94/298 (31.8%)	0.66 (0.29–1.53)	0.34
Dementia	21/54 (38.9%)	83/281 (29.5%)	1.51 (0.83–2.77)	0.17
Asthma	3/28 (10.7%)	100/306 (32.9%)	0.24 (0.072–0.83)	0.02
CXR** changes of COVID-19	89/228 (39%)	14/106 (13.2%)	4.21 (2.56–7.84)	<0.001
Frailty	62/140 (44.3%)	41/194 (21%)	2.96 (1.84–4.8)	<0.001
Hospital-acquired SARS-CoV-2	21/52 (40.4%)	82/282 (29.1)	1.65 (0.89–3.04)	0.10
CRP* mg/l			1.004 (1.001–1.006)	0.005
Log-C-reactive protein (CRP) (admission)			3.07 (1.62–5.82)	<0.001
Log-CRP (peak)			3.64 (1.75–7.56)	<0.001
*CRP ≤ 50 mg/l	16/81 (19.8%)	87/250 (34.5%)	0.46 (0.25–0.84)	0.012
*CRP > 100 mg/l	63/161 (39.1%)	40/170 (23.5%)	2.08 (1.29–3.36)	0.0024
Lymphocytes × 10^9/l *			0.85 (0.6–1.2)	0.36
*Lymph ≤ 0.8 × 10^9/l	58/157 (36.9%)	42/171 (24.6%)	1.79 (1.12–2.89)	0.015
L2 < L1$	63/173 (36.4%)	36/154 (23.4%)	1.87 (1.15–3.04)	0.01

†OR for each additional condition; ‡CKD chronic kidney disease, COPD chronic obstructive pulmonary disease; §CAP Community acquired pneumonia, HAP hospital-acquired pneumonia, **CXR chest x-ray, *Admission value, $ L1 Lymphocyte count on admission, L2 minimum lymphocyte count.

mortality (30.8%) rate was comparable to other UK and European studies but higher than in the United States and China where hospitalised patients were younger [1–6, 12, 13, 18]. The risk of death increased incrementally with age as observed elsewhere [3–5]. There was a male predominance as reported by others, and survival was significantly worse in older men but sex was not an independent predictor of mortality due to collinearity with variables associated with disease severity (chest x-ray changes, lymphopaenia and CRP), but there was no gender difference for other risk factors. Speculation as to why men may be more susceptible to SARS-CoV-2 embraces biological (immune system, ACE 2 receptor expression) and behavioural differences including attitude towards the COVID-19 pandemic [22].

We found a strong association of mortality with smoking not universally observed by others. Smoking prevalence reflects historical UK smoking rates; 70% in men and 50% in women in the 1970s [23]. Differences between studies is likely due to variation in completeness of smoking record; many had smoking rates much less than the general population others omitted data on smoking [5, 7]. Our search of available records identified past smoking often absent from contemporary clinical notes, or patients were misclassified (as smokers or vice-versa). Furthermore, as cumulative tobacco consumption outweighs current smoking habit, grouping light smokers with non-smokers seems apposite. In a large UK study, current smoking was not a mortality risk after adjusting for comorbidity but past smoking was (OR 1.19; 1.14–1.24) [10].

Meta-analyses confirm an association between disease severity/inpatient mortality and past-smoking history rather than current smoking [24, 25]. As in this study, Mesas et al. found smoking-related risk to be greater in younger patients (≤ 60 y OR 2.78; 1.43–5.39 v 1.2; 1.04–1.41). In older patients, smoking as an independent risk factor is offset due to clustering of smoking-related diseases with increased age [25]. The greater risk from COVID-19 in smokers is not unexpected; smoking increases severity of respiratory infections [26]. Many former smokers may have unrecognised smoking-related lung damage increasing susceptibility to respiratory infection [27].

We observed a higher frequency of obesity in younger patients (≤ 65 years) than in the general population (49.5 vs. 35%) but less for older patients (>65 years 14.4

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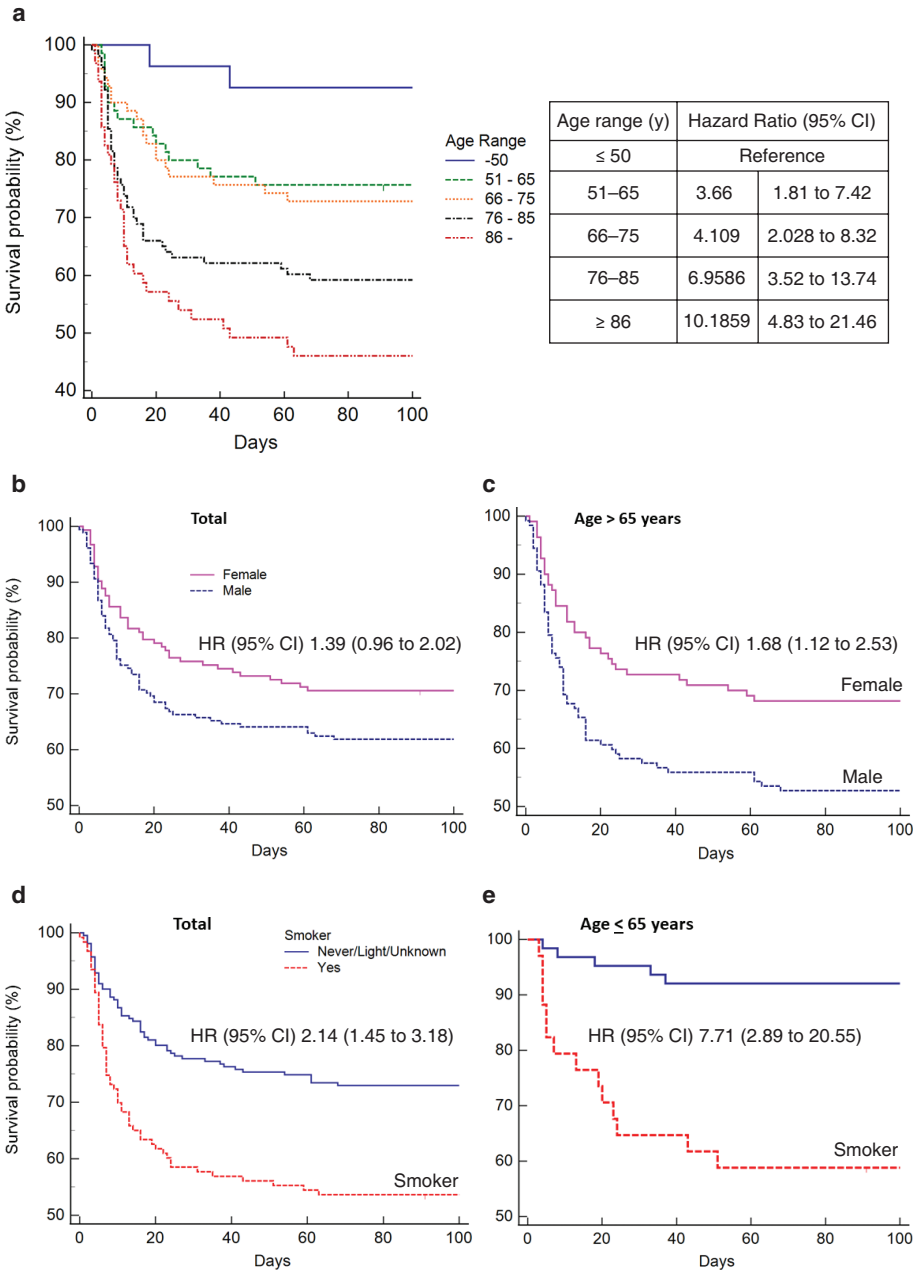

Age range (y)	Hazard Ratio (95% CI)	
≤ 50	Reference	
51–65	3.66	1.81 to 7.42
66–75	4.109	2.028 to 8.32
76–85	6.9586	3.52 to 13.74
≥ 86	10.1859	4.83 to 21.46

Fig. 2. Kaplan–Meier analysis of 90-day survival by age, sex and smoking. (a) Age range; Hazard ratio (HR 95% CI); (b) Sex (total); (c) Sex for age > 65 years; (d) Smoking-total; (e) Smoking for age ≤ 65 years.

vs. 32%). This contrasts with an obesity rate of only 10.5% in the ISARIC study that is unrepresentative of community prevalence [5, 28]. Our findings concur with reports that obesity increases the risk of hospitalisation and of ICCU admission [3, 13, 29]. But we did not see increased mortality with obesity. Similarly, the study by Petrilli had a high prevalence of obesity (35.3%) but no mortality risk [3], whereas the findings of two Italian studies differed. In the Giacomelli study, the obesity rate was only 16.3% but associated with higher mortality (aHR 3.04, 1.42−6.49), whereas Ciceria reported more obesity (22.9%) but no association with mortality (HR for BMI 0.96; 0.90–1.02) [12, 13]. Obesity appeared protective in older patients in our study; this resembles the effect of obesity in severe COPD and community-acquired pneumonia [30–32]. The cohort effect of chronic disease in older patients is likely to be a factor. This concurs with the meta-analysis by Mesas that suggests obesity is a prominent prognostic factor only in patients with fewer comorbidities [25].

Table 6. Multivariable logistic regression of 30-day mortality

Variable	Model 1			Model 2		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (years)	1.05	1.02–1.079	0.0005	1.05	1.02–1.08	0.0002
Smoker (>5 pack years)	2.59	1.26–5.31	0.009	2.08	1.19–3.63	0.009
Chronic neurological disease	2.33	1.20–4.53	0.0125	2.27	1.17–4.40	0.014
Cardiac disease	1.56	0.87–2.81	0.130			
COPD*	0.71	0.30–1.65	0.429			
Chronic kidney disease	2.24	1.05–4.80	0.036	2.32	1.09–4.92	0.028
Frailty	1.82	0.98–3.36	0.055	1.92	1.047–3.53	0.014
CXR** changes of COVID-19	4.34	2.12–8.87	0.0001	4.31	2.12–8.79	0.0001
Log-CRP on admission	3.42	1.50–7.78	0.003	3.21	1.43–7.22	0.0046
Nagelkerke R^2	*0.3509*			*0.3415*		
AUC (95% CI)	*0.814 (0.768–0.855)*			*0.811 (0.765–0.852)*		
Correctly classified	*75.76%*			*76.67%*		

*COPD chronic obstructive pulmonary disease; **CXR chest x-ray.

Most patients had multiple chronic conditions; the frequency of hypertension mirrors community prevalence but diabetes was more common (25.4% all ages vs. UK prevalence of 10% for age <65 years and 15% for age >65 years) [33]. This corresponds with many studies in which diabetes is a risk factor for hospital admission but as reported by others neither diabetes or hypertension was associated with increased inpatient mortality [5, 6]. Cumulative comorbidity count, cardiac disease and COPD were not independently predictive of mortality due to collinearity with age, smoking and frailty. Chronic kidney disease was particularly high risk as observed in many previous reports [3, 5–7, 13]. Chronic neurological disease was twice as common in this study (22%) as in the ISARIC study (11%) but equivalent to other studies. Variance between studies is due to differences in conditions included but there is consensus that chronic neurological disease is an independent predictor of hospital mortality [5, 34].

For simplification, we limited the clinical variables to the primary diagnosis, presence of frailty and chest x-ray changes. The clinical frailty scale (CFS) is included in the hospital admission document but the score was often not recorded; patients were commonly described as being frail, and frailty was often a reason for ceiling of care or do not attempt resuscitation decisions. Physician-described frailty was accepted as synonymous with moderate frailty (CFS score of ≥ 6). Frailty was common and associated with increased age and greater comorbidity. The finding that frailty was more frequent with hospital-acquired SARS-CoV-2 infection has been observed previously [35]. As in other studies, frailty was associated with worse survival independent of age [36–38]. In the recently published multicentre COMET study of patients hospitalised with COVID-19, frailty (CFS 6–9) was less frequent than in the present study (20 vs. 42%) but more than half of the patients were excluded due to no CFS score [38]. Hospital mortality was higher for frail patients of all ages (36.9% v 10.3%; OR adjusted for age and comorbidity 2·71; 2·04–3.60) but excluded patients were older with more comorbidities suggesting that our inclusion of physician-described frailty in lieu of a CFS score maybe more representative [38]. Frailty is a readily identifiable clinical finding that transcends diagnoses [20, 39] and given its association with high mortality is a key determinant of the level of care for patients hospitalised with SARS-CoV-2 infection [36–41].

This study shows that evidence of pneumonitis is the most important prognostic factor in patients hospitalised with SARS-Cov-2 infection. The absence of respiratory symptoms and/or chest x-ray changes of COVID-19 is evidently predictive of survival. Others have shown that radiographic evidence and extent of pneumonitis are of prognostic importance [1,4,12,13,16, 42, 43]. Some of these are based upon CT scans only [1, 4], and many larger studies did not include radiological findings as a variable [3, 5, 18, 44].

Multiple putative biomarkers of disease severity in COVID-19 have been identified. We included only lymphocyte count and CRP as they are measured routinely in all acute hospital admissions. Lymphopaenia on admission and/or a fall in lymphocyte count is a risk factor for mortality but we did not find it sufficiently discriminating or significant on multivariable regression. Many studies have shown the prognostic value of CRP on hospital admission with COVID-19 [3, 6, 13, 17, 18]. Both CRP on admission and its logarithm remained significant on multivariable analysis but model fit was superior with the latter. A threshold CRP ≤ 50 mg/l may identify patients with a good prognosis, whilst CRP > 100 mg/l is associated

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with almost doubling of mortality risk. Petrilli reported increased mortality proportional to CRP level with HRs >3.5 for all abnormal CRP levels [3]. Similarly, Giacomelli described higher mortality related to incremental rise in CRP (aHR 1.17, 95% CI 1.02−1.35 per 50 mg/L) [13].

In summary, this study confirms the high mortality rate for patients hospitalised with SARS-CoV-2 infection with greatest risk in older-age males with chronic disease and frailty. A history of moderate-heavy smoking is a major risk factor, particularly in patients aged 65 years and younger. Chest x-ray changes of COVID-19 and raised CRP are clinically valuable prognostic indicators.

Limitations of this study include the following: due to its retrospective design, several clinical variables and biomarkers were not available in many patients and therefore not included. Frailty was based upon subjective physician assessment rather than the CFS in many cases and we did not report the scores that were available. Furthermore, as a single centre study and lack of ethnic diversity of our patient population, the generalisability of our findings may be limited.

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***Stephen A. Murphy**
Department of Respiratory Medicine
University Hospital of North Durham
North Rd, Durham DH1 5TW, UK
Email: Stephen.murphy13@nhs.net

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