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Risk factors for death in 1859 subjects with COVID-19

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Abstract

We studied 1859 subjects with confirmed COVID-19 from seven centers in Wuhan 1651 of whom recovered and 208 died. We interrogated diverse covariates for correlations with risk of death from COVID-19. In multi-variable Cox regression analyses increased hazards of in-hospital death were associated with several admission covariates: (1) older age (HR = 1.04; 95% Confidence Interval [CI], 1.03, 1.06 *per* year increase; $P < 0.001$); (2) smoking (HR = 1.84 [1.17, 2.92]; $P = 0.009$); (3) admission temperature *per* °C increase (HR = 1.32 [1.07, 1.64]; $P = 0.009$); (4) Log_{10} neutrophil-to-lymphocyte ratio (NLR; HR = 3.30 [2.10, 5.19]; $P < 0.001$); (5) platelets *per* 10 E + 9/L decrease (HR = 0.996 [0.994, 0.998]; $P = 0.001$); (6) activated partial thromboplastin (aPTT) *per* second increase (HR = 1.04 [1.02, 1.05]; $P < 0.001$); (7) Log_{10} D-dimer *per* mg/l increase (HR = 3.00 [2.17, 4.16]; $P < 0.001$); and (8) Log_{10} serum creatinine *per* μmol/L increase (HR = 4.55 [2.72, 7.62]; $P < 0.001$). In piecewise linear regression analyses Log_{10}NLR the interval from ≥0.4 to ≤1.0 was significantly associated with an increased risk of death. Our data identify covariates associated with risk of in hospital death in persons with COVID-19.

Introduction

The SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) pandemic has caused many deaths from coronavirus disease 2019 (COVID-19) [1–8]. The outbreak began in December 2019 in Wuhan city, Hubei province, China [9–16]. There are several studies or risk factors for death from COVID-19 but most have relatively few subjects and come from 1 or 2 centers [17–26]. We analyzed prognostic covariates for death in 1859 subjects with confirmed COVID-19 from 7 centers in Wuhan city from January 20 to April 4, 2020. Curiously, we found COVID-19 progressed similarly until day 10 after admission but progressed more slowly in the cohort of subjects who died compared with those recovering, possibly because of therapy interventions [27, 28]. Subjects who died had a greater frequency of comorbidities before COVID-19 and complications after developing COVID-19. We were able to show a

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correlation between likelihood of death and several hematological and other laboratory covariates at diagnosis.

Methods

Subjects

From 20 January to 4 April 2020, all consecutive patients ≥18 years were enrolled from Union Hospital (main part, Union West Hospital and Union Tumor Hospital), Wuhan Central Hospital, General Hospital of Central Theater Command, PLA, Wuhan Third Hospital and Wuhan Jin-Yin-Tan Hospital. These hospitals were reconstructed and designated as COVID-19 treatment centers. Between February 4 and February 18, 2020 persons with clinical symptoms and a lung computed tomography (CT) scan consistent with COVID-19 were diagnosed as having COVID-19 without confirmation of SARS-CoV-2-infection by quantitative reverse transcript polymerase chain reaction (qRT-PCR). After hospitalization subjects were tested by qRT-PCR to confirm the diagnosis and monitor their course. Beginning 4 March, 2020, anti-SARS-CoV-2 IgM and/or IgG antibodies were assayed at Union Hospital and Wuhan Central Hospital by the centers to confirm the diagnosis and to evaluate suspected cases of COVID-19 which were qRT-PCR-negative [29]. Subjects in whom we could not confirm SARS-CoV-2-infection by a qRT-PCR, IgM/IgG assay, or either were excluded from the study. Subjects recovering from COVID-19 were discharged and transferred to designated hotels, Fangcang shelter hospitals [30] or Leishenshan Hospital for 2–4 weeks of isolation or further care if needed. The study was approved by the Ethics Committees of Union Hospital (2020-0095) and of Wuhan Central Hospital (2020-007). Written and orally informed consent from subjects was waived by the Ethics Committees.

Data collection

We obtained epidemiological, demographic, clinical, laboratory, radiological, therapy, and outcomes data from electronic medical records using a standardized data collection form. Therapies included antibiotics, anti-viral therapy, corticosteroids, and supportive care including supplemental oxygen, mechanical ventilation (with and without intubation), and extracorporeal membrane oxygenation (ECMO). Data were independently entered and cross validated by two physicians (WH and JY). A third researcher (QL) adjudicated discordances. Missing data were retrieved from the relevant hospital.

SARS-CoV-2 testing and laboratory covariants

Methods for diagnosis of SARS-CoV-2-infection by qRT-PCR are described [24]. Before January 11, 2020 testing was done by a few institutions such as the Chinese Center for Disease Control and Prevention. Beginning January 11, 2020, qRT-PCR testing was done at local Centres for Disease Control and Prevention and from January 27, 2020 in the study hospitals. Beginning March 4, 2020 IgM/IgG antibodies to SARS-CoV-2 were tested at Union Hospital and after March 5, 2020 in Wuhan Central Hospital. Nasopharyngeal swab specimens were obtained every other day if there was clinical improvement judged by clinical signs and symptoms and lung CT scan. Subjects recovering were discharged after ≥2 negative qRT-PCR tests >24 h apart. Studies on admission included a CBC and differential, biochemistry panel, coagulation profile, and tests of inflammation including C-reactive protein (CRP), procalcitonin, lactate dehydrogenase (LDH), and ferritin. All subjects had a lung CT scan.

Definitions

Exposure history was defined as exposure to persons with confirmed SARS-CoV-2-infection or visiting the Huanan Wholesale Seafood Market, possible origin site of the SARS-CoV-2 epidemic in Wuhan city. Smoking history was defined as current or former smoker (stopping >5 years ago) with exposure of ≥20 cigarettes per day for ≥1 year (1 pack year). Fever was defined as temperature ≥37.3 °C. Diagnosis of bacterial infection required ≥1 positive culture or a positive antigen detection test. Acute kidney injury, acute respiratory distress syndrome (ARDS), and acute cardiac injury were diagnosed according to guidelines or as reported [24, 31, 32]. Liver damage was defined as more than 2x upper limit of normal. Severity of COVID-19 was classified as; (1) mild; (2) moderate; (3) severe; or (4) critical according to the Chinese management guideline for COVID-19 (version 7) [29, 33]. Recovery was defined as complete resolution of clinical signs and symptoms, normalization of the lung CT scan (if abnormal) and ≥2 negative qRT-PCR tests for SARS-CoV-2. Subjects dying of unrelated causes were excluded from analyses of COVID-19-related deaths. Invasive and noninvasive mechanical ventilations were defined as mechanical ventilation with and without intubation.

Statistical analysis

Demographics and clinical covariates were presented using descriptive statistics with frequencies (percentage) for discrete variables and median (IQR) and range for continuous variables. Medians were compared using independent group

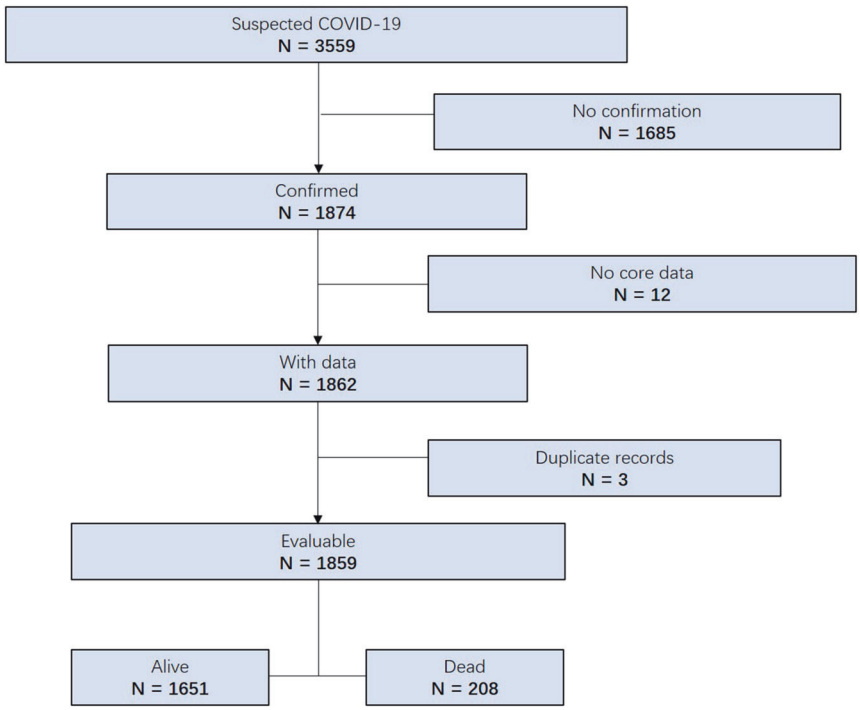

Fig. 1 Study flow diagram.

t test and Mann–Whitney test for normally and abnormally distributed data. Proportions for categorical variables were compared by χ^2 test. Missing data were ignored without multiple imputations. Covariates considered for correlations with death included age, sex, occupation, signs and symptoms, laboratory and radiological findings, smoking history, comorbidities including arterio-sclerotic cardio-vascular disease (ASCVD), arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), cancer, ARDS, infection, septic shock, acute renal failure, myocardial infarction, liver injury, gastro-intestinal bleeding, disseminated vascular coagulation, and multiple organ failure. Neutrophil-to-lymphocyte ratio (NLR), D-dimer and serum creatine (Scr) were $\log_{10}$ transformed before the analyses because of non-normal distributions. Uni- and multi-variable Cox regression models were used to evaluate associations of covariants with risk of death. R version 3.5.2 was used for statistical analyses. For unadjusted comparisons, a two-sided alpha of <0.05 was considered significant. Analyses were not adjusted for multiple comparisons.

Results

Admission clinical covariates

From January 20 to April 4, 2020, 3559 subjects who died or had been discharged with clinical- or qRT-PCR-confirmed COVID-19 [34, 35] were enrolled. As shown in Fig. 1, 1859 subjects were included for analysis, with SARS-CoV-2-infection confirmed in 1790 subjects by qRT-PCR and by antibody testing in 69. Of the 1859 subjects, 208 died (11%), 157 (8%) recovered and discharged but remained hospitalized in other units for 2–4 weeks of recovery-related care, and 1494 (80%) discharged and transferred to COVID-19 designated hotels or Fangcang shelter hospitals [30] for 2–4 weeks of isolation.

Median age was 59 years (Interquartile Range [IQR] 45–68 years; Table 1). 806 (43%) were 60–79 years and 122 (7%) >80 years. 934 subjects were male (50%). 111 (6%) were current or former smokers, 71 (5%), health care provider, and 14 (1%), with pregnancy or puerperium. In total, 4 subjects were exposed at Huanan Seafood Wholesale Market and 78 (4%) had close contact with persons with confirmed SARS-CoV-2 infection. 579 (31%) had hypertension, 268 (14%), ASCVD, 262 (14%), diabetes, 98 (5%), gastro-intestinal disease, 69 (4%), cancer and 61 (3%), COPD. Most common signs and symptoms included fever ($n = 1448$, 78%), shortness of breath ($n = 716$, 39%), dry ($n = 619$, 43%) or wet cough ($n = 715$, 39%), fatigue ($n = 695$, 37%), chills ($n = 281$, 19%) and myalgia ($n = 315$, 17%). Bilateral pneumonia ($n = 1570$, 88%) and Ground-glass opacity ($n = 1331$, 75%) were two most findings in lung CT scan. 34 (2%) subjects had mild, 1170 (63%), moderate, 453 (24%), severe and 202 (11%) critical COVID-19.

Table 1 Demographic and clinical covariates.

	Total $n = 1859$	Alive $n = 1651$ (89)	Died $n = 208$ (11)	P value
Age, median (IQR), years	59 (45, 68)	57 (43, 66)	70 (63, 78)	<0.001
Age distribution				<0.001
<40 years	342 (18)	337 (20)	5 (2)	
40–59 years	589 (32)	556 (34)	33 (16)	
60–79 years	806 (43)	681 (41)	125 (60)	
≥80 years	122 (7)	77 (5)	45 (22)	
Female sex	925 (50)	870 (53)	55 (26)	<0.001
Smoking history	111 (6)	86 (5)	25 (13)	<0.001
Former smoker	66 (4)	54 (3)	12 (6)	
Current smoker	45 (2)	32 (2)	13 (7)	
Health care provider	71 (5)	69 (6)	2 (1)	0.008
Pregnancy/Puerperium	14 (1)	14 (1)	0 (0)	0.394
Exposure history				0.005
Huanan Seafood Market	4 (0.2)	1 (0.1)	3 (1)	
Close contact with patients	78 (4)	72 (4)	6 (3)	
Comorbidity				
ASCVD	268 (14)	205 (12)	63 (30)	<0.001
Hypertension	579 (31)	475 (29)	104 (50)	<0.001
Diabetes	262 (14)	203 (12)	59 (28)	<0.001
COPD	61 (3)	49 (3)	12 (6)	0.039
Cancer	69 (4)	52 (3)	17 (8)	<0.001
Chronic kidney disease	45 (2)	25 (2)	20 (10)	<0.001
Gastro-intestinal disease	98 (5)	82 (5)	16 (8)	0.097
Auto-immune disease	10 (1)	9 (1)	1 (1)	0.999
Psychiatric disorders	7 (0.5)	6 (0.5)	1 (1)	0.586
Signs and symptoms				
Fever[a]	1448 (78)	1274 (77)	174 (84)	0.025
Temperature (°C)[b]	36.6 (36.4, 37.0)	36.6 (36.4, 37.0)	36.8 (36.5, 37.5)	<0.001
Shortness of breath	716 (39)	572 (35)	144 (70)	<0.001
Dry cough	619 (43)	554 (43)	65 (38)	0.205
Wet cough	715 (39)	609 (37)	106 (51)	<0.001
Fatigue	695 (37)	595 (36)	100 (48)	<0.001
Nausea or vomiting	124 (9)	114 (9)	10 (6)	0.186
Diarrhea	243 (13)	213 (13)	30 (14)	0.522
Chills	281 (19)	236 (18)	45 (26)	0.015
Rhinorrhea	33 (2)	30 (2)	3 (1)	0.999
Myalgia	315(17)	282 (17)	33 (16)	0.681
Headache	107 (6)	101 (6)	6 (3)	0.061
Radiological features				
Bilateral pneumonia	1570 (88)	1402 (87)	168 (96)	<0.001
Consolidation	326 (18)	266 (17)	60 (35)	<0.001
Ground-glass opacity	1331 (75)	1213 (76)	118 (69)	0.042
Patchy shadows	736 (41)	664 (41)	72 (42)	0.81
COVID-19 stage				<0.001
Mild	34 (2)	34 (2)	0 (0)	
Moderate	1170 (63)	1162 (70)	8 (4)	
Severe	453 (24)	427 (26)	26 (13)	
Critical	202 (11)	28 (2)	174 (84)	

Data are median (IQR) or n (%).

ASCVD atherosclerotic cardio- and cerebro-vascular disease, *COPD* chronic obstructive pulmonary disease.

[a]≥1 temperature ≥37.3 °C from onset of symptoms to admission.

[b]Admission temperature.

Comparison of survivors and nonsurvivors by clinical covariates

Subjects who died were older (medians 70 versus 57 years; $P < 0.001$, Table 1), more likely male (74% *versus* 47%; $P < 0.001$), more likely smokers (13% versus 5%; $P < 0.001$) and less likely health care providers (1% versus 6%, $P = 0.008$). More subjects who died were exposure at the Huanan Seafood Wholesale Market (1% *versus* 0.1%, $P = 0.005$). Nonsurvivors more likely to have comorbidities of hypertension (50% versus 29%; $P < 0.001$), ASCVD (30% versus 12%; $P < 0.001$), diabetes (28% versus 12%; $P < 0.001$), COPD (6% versus 3%; $P = 0.039$), cancer (8% versus 3%; $P < 0.001$) and kidney failure (10% versus 2%; $P < 0.001$). Fever from illness onset to admission (84% versus 77%; $P = 0.025$), shortness of breath (70% versus 35%; $P < 0.001$), wet cough (51% versus 37%; $P < 0.001$), fatigue (48% versus 36%; $P < 0.001$), chills (26% versus 18%; $P = 0.015$), bilateral pneumonia (96% versus 87%; $P < 0.001$) and lung consolidation on CT scan (35% versus 17%; $P < 0.001$) were more common in subjects who died. Paradoxically, survivors were more likely to have ground-glass lung opacity on lung CT scan (76% versus 69%; $P = 0.042$). Subjects who died were more likely to have critical COVID-19 on admission (84% versus 2%; $P < 0.001$) and less likely to have moderate severity (4% versus 70%; $P < 0.001$).

Comparison of survivors and nonsurvivors by laboratory covariates

There were significant differences in admission laboratory covariates between survivors and nonsurvivors (Table 2). Subjects who died had higher median neutrophils (7×10 E + 9/L [IQR 4–10×10 E + 9/L] versus 3 $\times 10$ E + 9/L [IQR 2–4×10 E + 9/L]; $P < 0.001$), lower median lymphocytes (0.6×10 E + 9/L [IQR 0.4–0.9×10 E + 9/L] *versus* median 1.2×10 E + 9/L [IQR 0.9–1.6×10 E + 9/L]; $P < 0.001$), lower median platelets (163×10 E + 9/L [IQR 113–223×10 E + 9/L] versus 207 10 E + 9/L [IQR 161–268×10 E + 9/L]; $P < 0.001$) and higher median neutrophil-to-lymphocyte ratios (NLR; 11 [IQR 6–20] versus 3 [IQR 2–4]; $P < 0.001$). Nonsurvivors had lower median proportions of CD3-positive cells (60% [IQR 52–70%] *versus* 72% [IQR 63–79%]; $P < 0.001$), median proportions of CD8-positive cells (16% [IQR 11–20%] versus 24% [IQR 18–30%]; $P < 0.001$), median proportions of NK-cells (8% [IQR 3–12%] versus 10%, [IQR 6–17%]; $P = 0.011$), and higher proportions of B-lymphocyte (15% [IQR 9–28%] versus 12% [IQR 9–17%]; $P = 0.033$) and higher median CD4/CD8 ratios (3 [IQR 2–4] versus 2 [IQR 1–3]; $P < 0.001$) compared with survivors.

Subjects who died had longer median aPTT (37 s [IQR 31–42 s] versus 34 s [IQR 30–38 s]; $P < 0.001$) and higher median concentrations of fibrinogen (4.3 g/L [IQR 3.2–5.1 g/L] versus 3.7 g/L [IQR 2.9–4.6 g/L]; $P < 0.001$) and median D-dimer concentrations (2.5 mg/L [IQR 0.7–8 mg/L] versus 0.4 mg/L [IQR 0.2–0.8 mg/L]; $P < 0.001$).

Subjects who died also had higher median hCRP concentrations (10 mg/L [IQR 10–80 mg/L] versus 3 mg/L [IQR 1–10 mg/L]; $P < 0.001$), median procalcitonin concentrations (0.3 ng/ml [IQR 0.1–0.6 ng/mL] versus 0.05 ng/ml [IQR 0.04–0.1 ng/mL]; $P < 0.001$), median LDH activities (412 U/L [IQR 306–561 U/L] versus 201 U/L [IQR 165–261 U/L]; $P < 0.001$), median ferritin concentrations (1579 ng/mL [IQR 1206-2000 ng/mL] versus 470 ng/mL [IQR 197–940 ng/mL]; $P < 0.001$), median IL-6 concentrations (79 pg/mL [IQR 23–525 pg/mL] versus 9 pg/mL [IQR 4–32 pg/mL]; $P < 0.001$), median IL-10 concentrations (10 pg/mL [IQR 5–22 pg/mL] versus 4 pg/mL[IQR 3–5 pg/mL]; $P < 0.001$) and lower median TNF-α concentrations (2.7 pg/mL [IQR 1.9–3.6 pg/mL] versus 3.5 pg/mL [IQR 2.3–5.6 pg/mL]; $P = 0.009$).

Subjects who died also had higher median activities of alanine aminotransferase (ALT; 58 U/L [IQR 30–139 U/L] versus 36 U/L [IQR 21–63 U/L]; $P < 0.001$), aspartate aminotransferase (AST; 64 U/L [IQR 40–140 U/L] versus 30 U/L [IQR 22–44 U/L]; $P < 0.001$), creatine kinase (262 U/L [IQR 135–636 U/L] versus 81 U/L [IQR 52–135 U/L]; $P < 0.001$) and median concentrations of total bilirubin (24 μmol/L [IQR 15–36 μmol/L] versus 13 μmol/L [IQR 10–18 μmol/L]; $P < 0.001$), b-type natriuretic peptide (BNP; 467 pg/ml [IQR 121–1467 pg/ml] versus 47 pg/ml, [IQR 15–140 pg/ml]; $P < 0.001$), myoglobin (576 ng/ml [IQR 175–1013 ng/ml] versus 30 ng/ml [IQR 21–51 ng/ml]; $P < 0.001$) and troponin I (161 ng/L [IQR 46–712 ng/L] versus 3 ng/L [IQR 1–8 ng/L]; $P < 0.001$), blood urea nitrogen (BUN; 15 mmol/L [IQR 9–27 mmol/L] versus 5 mmol/L [IQR 4–6 mmol/L]; $P < 0.001$) and Scr (108 μmol/L [IQR 76–256 μmol/L] versus 69 μmol/L [IQR 58–81 μmol/L]; $P < 0.001$).

Complications and treatments for survivors and non-survivors

Subjects who died were more likely to have complications (207 [99.5%] versus 1039 [63%]; $P < 0.001$) including ARDS (174 [84%] versus 53 [3%]; $P < 0.001$), bacterial infection (180 [87%] versus 383 [23%]; $P < 0.001$) and liver damage (102 [50%] versus 354 [22%]; $P < 0.001$; Table 3). Nonsurvivors also had higher incidence of heart injury (130 [63%] versus 99 [6%]; $P < 0.001$), multiple organ failure (126 [61%] versus 3 [0.2%]; $P < 0.001$), acute kidney injury (82 [39%] versus 17 [1%]; $P < 0.001$), septic shock (63 [37%] versus 1 [0.1%]; $P < 0.001$), abnormal coagulation parameters (47

Table 2 Laboratory covariates on admission.

Covariates (normal range)	*N*	Total	Alive	Died	*P* value
CBC					
Neutrophils ×10E + 9/L (1.8–6.3)	1816	3 (2, 5)	3 (2, 4)	7 (4, 10)	<0.001
Lymphocytes ×10 E + 9/L (1.1–3.2)	1847	1.0 (0.8, 1.6)	1.2 (0.9, 1.6)	0.6 (0.4, 0.9)	<0.001
Monocytes ×10 E + 9/L (0.1–0.6)	1805	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)	0.3 (0.2, 0.5)	<0.001
Hemoglobin, g/L (115–150)	1433	128 (117, 139)	128 (117, 139)	129 (117, 140)	0.539
Platelets ×10 E + 9/L (125–350)	1814	203 (155, 264)	207 (161, 268)	163 (113, 223)	<0.001
NLR	1814	3 (2, 5)	3 (2, 4)	11 (6, 20)	<0.001
Inflammation covariates					
hCRP, mg/L (<4)	995	4 (1, 10)	3 (1, 10)	10 (10, 80)	<0.001
Procalcitonin, ng/ml (< 0.5)	1643	0.06 (0.05, 0.1)	0.05 (0.04, 0.1)	0.3 (0.1, 0.6)	<0.001
LDH, U/L (109–245)	1729	212 (170, 292)	201 (165, 261)	412 (306, 561)	<0.001
Ferritin, ng/ml (4.6–204)	308	567 (246, 1218)	470 (197, 940)	1579 (1206, 2000)	<0.001
Coagulation covariates					
aPTT, s (28–43.5)	1356	34 (30, 38)	34 (30, 38)	37 (31, 42)	<0.001
Fibrinogen, g/L (2–4)	1323	3.7 (2.9, 4.6)	3.7 (2.9, 4.6)	4.3 (3.2, 5.1)	<0.001
D-dimer, mg/L (<0.5)	1602	0.4 (0.2, 1.1)	0.4 (0.2, 0.8)	2.5 (0.7, 8)	<0.001
Biochemical covariates					
ALT, U/L (5–35)	1832	38 (22, 67)	36 (21, 63)	58 (30, 139)	<0.001
AST, U/L (8–40)	1830	32 (22, 49)	30 (22, 44)	64 (40, 140)	<0.001
Total bilirubin, μmol/L (5.1–19)	1586	14 (10, 19)	13 (10, 18)	24 (15, 36)	<0.001
Creatine kinase, U/L (26–140)	1493	88 (54, 165)	81 (52, 135)	262 (135, 636)	<0.001
BNP, pg/ml (< 100)	838	61 (18, 242)	47 (15, 140)	467 (121, 1467)	<0.001
Myoglobin, ng/ml (<140)	972	35 (21, 73)	30 (21, 51)	576 (175, 1013)	<0.001
Troponin I, ng/L (<26.2)	1083	4 (1, 14)	3 (1, 8)	161 (46, 712)	<0.001
BUN, mmol/L (2.9–8.2)	1815	5 (4, 7)	5 (4, 6)	15 (9, 27)	<0.001
Scr, μmol/L (44–106)	1813	71 (59, 85)	69 (58, 81)	108 (76, 256)	<0.001
Lymphocyte subsets					
CD3+, (58–84%)	759	71 (62, 78)	72 (63, 79)	60 (52, 70)	<0.001
CD4+, (25–51%)	759	41 (32, 48)	41 (33, 48)	37 (28, 46)	0.094
CD8+, (14–39%)	759	23 (17, 30)	24 (18, 30)	16 (11, 20)	<0.001
NK cell, (3–30%)	561	10 (6, 16)	10 (6, 17)	8 (3, 12)	0.011
B lymphocyte, (4–18%)	561	13 (9, 18)	12 (9, 17)	15 (9, 28)	0.033
CD4 + /CD8 + Ratio (0.41–2.72)	755	2 (1, 3)	2 (1, 3)	3 (2, 4)	<0.001
Cytokines					
IL-4, pg/ml (0.1–3.2)	505	3 (2, 4)	3 (2, 4)	2 (2, 3)	0.21
IL-6, pg/ml (0.1–2.9)	857	10 (4, 42)	9 (4, 32)	79 (23, 525)	<0.001
IL-10, pg/ml (0.1–5)	505	4 (3, 6)	4 (3, 5)	10 (5, 22)	<0.001
TNF-α, pg/ml (0.1–23)	505	3.3 (2.2, 5.4)	3.5 (2.3, 5.6)	2.7 (1.9, 3.6)	0.009
IFN-γ, pg/ml (0.1–18)	505	3.1 (2.0, 4.1)	3.1 (2.0, 4.1)	2.7 (1.8, 4.2)	0.313

Data are median (IQR).

NLR neutrophil-to-lymphocyte ratio, *hCRP* high-sensitivity c-reactive protein, *LDH* lactate dehydrogenase, *aPTT* activated partial thromboplastin time, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BNP* B-type natriuretic peptide, *BUN* blood urea nitrogen, *Scr* serum creatinine, *IL* interleukin, *TNF* tumor necrosis factor, *IFN* interferon.

[23%] versus 2 [0.1%]; $P < 0.001$) and gastro-intestinal bleeding (29 [14%] versus 5 [0.3%]; $P < 0.001$).

Also, subjects who died were more likely to receive antibiotics (203 [98%] versus 1356 [84%]; $P < 0.001$), antifungal drugs (39 [20%] versus 32 [2%]; $P < 0.001$), lopinavir and ritonavir (59 [35%] versus 280 [22%]; $P < 0.001$), corticosteroids (165 [80%] versus 588 [36%]; $P < 0.001$), intravenous immunoglobin (IVIG; 105 [52%] versus 401 [26%]; $P < 0.001$), high-flow nasal cannula oxygen therapy (152 [89%] versus 81 [6%]; $P < 0.001$),

Table 3 Complications and therapy.

	Total $n = 1859$	Alive $n = 1651$ (89)	Died $n = 208$ (11)	P value
Complications				
ARDS	227 (12)	53 (3)	174 (84)	<0.001
Bacterial infections	563 (30)	383 (23)	180 (87)	<0.001
Septic shock	64 (4)	1 (0.1)	63 (37)	<0.001
Acute kidney injury	99 (5)	17 (1)	82 (39)	<0.001
Cardiac injury	229 (12)	99 (6)	130 (63)	<0.001
Abnormal LFT	456 (25)	354 (22)	102 (50)	<0.001
Gastro-intestinal bleeding	34 (2)	5 (0.3)	29 (14)	<0.001
Coagulopathy	49 (3)	2 (0.1)	47 (23)	<0.001
Multiple organ failure	129 (7)	3 (0.2)	126 (61)	<0.001
Therapy				
Antibiotics	1559 (85)	1356 (84)	203 (98)	<0.001
Antifungal drugs	71 (4)	32 (2)	39 (20)	<0.001
Oseltamivir	757 (41)	688 (42)	69 (33)	0.021
Umifenovir	1386 (75)	1226 (74)	160 (77)	0.351
Lopinavir/Ritonavir	339 (23)	280 (22)	59 (35)	<0.001
Interferon	387 (21)	344 (21)	43 (21)	0.957
Corticosteroids	753 (41)	588 (36)	165 (80)	<0.001
IVIG	506 (29)	401 (26)	105 (52)	<0.001
High-flow nasal cannula oxygen therapy	233 (16)	81 (6)	152 (89)	<0.001
Noninvasive mechanical ventilation	145 (8)	27 (2)	118 (57)	<0.001
Invasive mechanical ventilation	85 (5)	12 (1)	73 (35)	<0.001
ECMO	4 (0.2)	1 (0.1)	3 (1)	0.005
CRRT	23 (2)	4 (0.3)	19 (11)	<0.001
Outcomes				
ICU admission	106 (6)	36 (2)	70 (34)	<0.001
Time from illness onset to ICU admission, median (IQR), days	14 (10, 20)	14 (10, 21)	14 (10, 20)	0.962
ICU length of stay, median (IQR), days	10 (4, 17)	10 (5, 18)	10 (4, 16)	0.676
Time from illness onset to repeated negative SARS-CoV-2 tests, median (IQR), days	22 (17, 28)	22 (17, 28)	21 (15, 27)	0.284
Time from illness onset to admission, median (IQR), days	10 (7, 15)	10 (7, 16)	9 (6, 12)	<0.001
Time from illness onset to progression, median (IQR), days	10 (7, 15)	10 (6, 14)	12 (9, 18)	<0.001
Time from illness onset to outcome, median (IQR), days	30 (23, 37)	31 (24, 38)	21 (14, 28)	<0.001
Time from diagnosis to outcome, median (IQR), days	19 (13, 27)	20 (14, 28)	11 (5, 17)	<0.001
Time from admission to outcome, median (IQR), days	18 (12, 23)	18 (14, 23)	10 (6, 19)	<0.001

LFT liver function test, *ARDS* acute respiratory distress syndrome, *IVIG* intravenous immunoglobin, *ECMO* extra-corporeal membrane oxygenation, *CRRT* continuous renal replacement therapy, *ICU* intensive care unit.

noninvasive mechanical ventilation (118 [57%] versus 27 [2%]; $P < 0.001$), invasive mechanical ventilation (73 [35%] versus 12 [1%]; $P < 0.001$), ECMO (3 [1%] versus 1 [0.1%]; $P = 0.005$) and continuous renal replacement therapy (CRRT) (19 [11%] versus 4 [0.3%]; $P < 0.001$).

Nonsurvivors had briefer median intervals from onset of symptoms to admission (9 d [IQR 6–12 d] versus 10 d [IQR 7–16 d]; $P < 0.001$) and median intervals from onset of symptoms to death or discharge (21 d [IQR 14–28] versus 31 d [IQR 24–38 d]; $P < 0.001$), and from admission to death or discharge (10 d [IQR] 6–19 d versus 18 d [IQR 14–23 d]; $P < 0.001$) but longer median intervals from onset of symptoms to progression (median 12 d [IQR 9–18 d] versus 10 d [QR 6–14 d]; $P < 0.001$). There were no differences between survivors and nonsurvivors in median intervals from symptoms onset to ICU admission (14 d [IQR 10–20 d] versus 14 d [IQR 10–21 d]; $P = 0.962$) or median intervals to negative SARS-CoV-2 testing (21 d [IQR 15–27 d] versus 22 d [IQR 17–28 d]; $P = 0.284$). In

Table 4 Risk factors for death.

	Uni-variable HR (95% CI)	*P* value	Multivariable HR (95% CI)	*P* value
Clinical covariates				
Age, years	1.07 (1.06–1.08)	<0.001	1.04 (1.03–1.06)	<0.001
Female sex (vs male)	0.35 (0.26–0.48)	<0.001	..	..
Smoking history (vs nonsmoking)	2.43 (1.59–3.73)	<0.001	1.84 (1.17–2.92)	0.009
Health care provider (vs non health care provider)	0.24 (0.06–0.96)	0.044	..	..
Comorbidity (Yes/No)				
ASCVD	2.56 (1.90–3.45)	<0.001	..	..
Diabetes	2.47 (1.82–3.34)	<0.001	..	..
Hypertension	2.21 (1.68–2.90)	<0.001	..	..
Cancer	2.59 (1.58–4.26)	<0.001	..	..
Symptoms and complications (Y/N)				
Dyspnea	6.26 (4.76–8.24)	<0.001	..	..
Wet cough	1.63 (1.24–2.14)	0.001	..	..
ARDS	54.21 (37.13–79.14)	<0.001	..	..
Bacterial infections	18.36 (12.16–27.72)	<0.001	..	..
Temperature at admission (°C)	1.50 (1.28–1.75)	<0.001	1.32 (1.07–1.64)	0.009
Laboratory covariates				
Neutrophils ×10E + 9/L	1.23 (1.20–1.26)	<0.001	..	..
Lymphocytes x10E + 9/L	0.07 (0.05–0.10)	<0.001	..	..
Log_{10} NLR	1.06 (1.06–1.07)	<0.001	3.30 (2.10–5.19)	<0.001
Platelets x10E + 9/L	0.99 (0.99–1.00)	<0.001	0.996 (0.994–0.998)	0.001
hCRP, mg/L	1.02 (1.02–1.02)	<0.001	..	..
Procalcitonin, ng/ml	1.23 (1.18–1.28)	<0.001	..	..
LDH, U/L	1.00 (1.00–1.00)	<0.001	..	..
Ferritin, ng/ml	1.00 (1.00–1.00)	<0.001	..	..
aPTT, s	1.06 (1.04–1.08)	<0.001	1.04 (1.02–1.05)	<0.001
Log_{10} D-dimer, mg/L	1.09 (1.08–1.11)	<0.001	3.00 (2.17–4.16)	<0.001
Total bilirubin, μmol/L	1.03 (1.03–1.04)	<0.001	..	..
Creatine kinase, U/L	1.00 (1.00–1.00)	<0.001	..	..
Troponin I, ng/L	1.00 (1.00–1.00)	<0.001	..	..
BUN, mmol/L	1.06 (1.05–1.07)	<0.001	..	..
Log_{10} Scr, μmol/L	1.00 (1.00–1.00)	<0.001	4.55 (2.72–7.62)	<0.001
IL-6	1.00 (1.00–1.00)	<0.001	..	..
IL-10	1.00 (1.00–1.00)	0.004	..	..
CD3-positive, %	0.95 (0.93–0.97)	<0.001	..	..
CD8-positive, %	0.91 (0.88–0.94)	<0.001	..	..
CD4/CD8 ratio	1.27 (1.18–1.37)	<0.001	..	..

CI confidence interval, *ASCVD* atherosclerotic cardio- and cerebro-vascular disease, *ARDS* acute respiratory distress syndrome, *NLR* neutrophil-to-lymphocyte ratio, *hCRP* high-sensitive c-reactive protein, *LDH* lactate dehydrogenase, *aPTT* activated partial thromboplastin time, *BUN* blood urea nitrogen, *Scr* serum creatinine.

total, 178 of the 208 subjects who died (86%) had a positive qRT-PCR test until death.

Risk factors for death

In total, 33 covariants had significant associations with risk of death in uni-variable analyses, 8 of which remained significant in multi-variable analyses including age (HR = 1.04 [1.03, 1.06]; $P < 0.001$), smoking history (HR = 1.84 [1.17, 2.92]; $P = 0.009$), temperature value (°C) at admission (HR = 1.32 [1.07–1.64]; $P = 0.009$), log_{10} NLR (HR = 3.30 [2.10, 5.19]; $P < 0.001$), admission platelet concentration (HR = 0.996; [0.994–0.998]; $P = 0.001$), aPTT on admission (HR = 1.04 [1.02, 1.05]; $P < 0.001$), Log_{10}

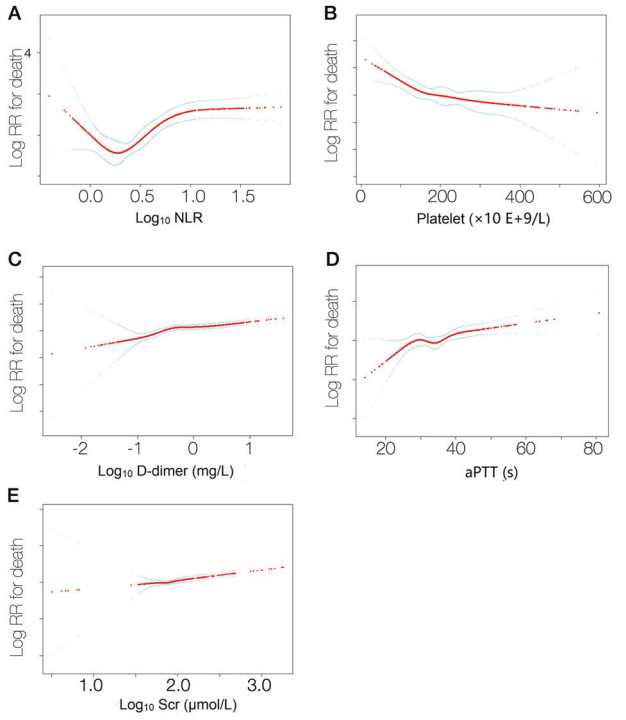

Fig. 2 The linear relationship between admission covariants and risk of death. (**a**) log10NLR, (**b**) platelet (x 10 E+9/L), (**c**) log10D-dimer (mg/L), (**d**) aPTT (s) and (**e**) log10Scr (μmol/L).

D-dimer (HR = 3.00 [2.17, 4.16]; $P < 0.001$), and Log_{10} Cr (HR = 4.55 [2.72, 7.62]; $P < 0.001$; Table 4).

We further showed the linear relationship between these covariants except age, smoking history, and temperature at admission and risk of death (Fig. 2). Based on the steep curve of Log_{10} NLR we conducted a further piecewise linear regression analysis of NLR and death. The results indicate a Log_{10} NLR value of ≥0.4 to ≤1.0 is significantly associated with risk of death (Table 5).

Discussion

We identified eight hospital admission covariates which are independent risk factors for death in almost 2000 persons with COVID-19 including older age, smoking history, higher body temperature (°C), and levels of D-dimer, aPTT, Scr, platelet, and NLR on admission. Several are reported by others; however, we were unable to confirm other risk factors reported in smaller datasets [15, 18–21, 23, 24, 26, 36].

We identified Log_{10} NLR as an independent risk factor for death with an HR = 14.1 (3.2, 61.2) with Log_{10} values ≥0.4 to ≤1.0 but not otherwise (Table 5). Although higher neutrophil and lower lymphocyte concentrations and higher NLR were previously reported [23, 26, 36–38], Log_{10}NLR has not.

Table 5 Piecewise linear regression analysis of the effect of Neutrophil-to-lymphocyte ratio (NLR) on risk of death.

	Hazard ratio (95% CI)	*P* value
Log_{10} NLR	3.30 (2.10–5.19)	<0.001
Log_{10} NLR < 0.4	0.44 (0.02–10.09)	0.608
Log_{10} NLR ≥ 0.4, ≤ 1.0	14.06 (3.23–61.21)	<0.001
Log_{10} NLR > 1.0	0.49 (0.17–1.44)	0.195

There are important limitations to our study. First, not all covariates were available in all subjects including body mass index and SOFA score (a factor for death identified by logistic regression analysis) [24]. Also, BNP and TNI were reported in different units and were therefore not included for multi-variable Cox regression analyses. Second, at the data lock 65 (1.8%) subjects remained hospitalized and are excluded from our analyses. Third, some covariates such as bacterial coinfection and BUN could not be accurately analysed and interpreted together with other covariants for interactions. Our conclusions although based on a large dataset require confirmation. Nevertheless, they may be useful in predicting outcomes in persons with COVID-19.

Data availability

All data generated or analyzed are included in this typescript including supplement.

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Author contributions YH and QL designed the study. LeC, JY, WH, LCh, GY, FD, WC, YC, JY, LC, DW, QR, LL, QL, WR, FG, HW, and ZC collected the data. All authors had full access to the data, were involved in data interpretation and vouch for the accuracy of the analyses. QL, LeC, and RPG prepared the typescript which all authors approved final approval and supported the decision to submit for publication.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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