ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2022 April 6; 10(10): 2976-3320

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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ABOUT COVER

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

PUBLICATION DATE

April 6, 2022

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2022 April 6; 10(10): 3047-3059

DOI: 10.12998/wjcc.v10.i10.3047

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Dose-response relationship between risk factors and incidence of COVID-19 in 325 hospitalized patients: A multicenter retrospective cohort study

Sheng-Chao Zhao, Xian-Qiang Yu, Xue-Feng Lai, Rui Duan, De-Liang Guo, Qian Zhu

Specialty type: Infectious Diseases

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Balaban DV, Romania; Kim KH, South Korea

Received: October 16, 2021
Peer-review started: October 16, 2021
First decision: November 17, 2021
Revised: December 13, 2021
Accepted: February 27, 2022
Article in press: February 27, 2022
Published online: April 6, 2022

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Abstract

BACKGROUND

The epidemiological and clinical characteristics of coronavirus disease 2019 (COVID-19) patients have been widely reported, but the assessment of dose-response relationships and risk factors for mortality and severe cases and clinical outcomes remain unclear.

AIM

To determine the dose-response relationship between risk factors and incidence of

COVID-19.

METHODS

In this retrospective, multicenter cohort study, we included patients with confirmed COVID-19 infection who had been discharged or had died by February 6, 2020. We used multivariable logistic regression and Cox proportional hazard models to determine the dose-response relationship between risk factors and incidence of COVID-19.

RESULTS

It clarified that increasing risk of in-hospital death were associated with older age (HR: 1.04, 95%CI: 1.01-1.09), higher lactate dehydrogenase [HR: 1.04, 95% confidence interval (CI): 1.01-1.10], C-reactive protein (HR: 1.10, 95%CI: 1.01-1.23), and procalcitonin (natural log-transformed HR: 1.88, 95%CI: 1.22-2.88), and D-dimer greater than 1 μg/mL at admission (natural log transformed HR: 1.63, 95%CI: 1.03-2.58) by multivariable regression. D-dimer and procalcitonin were logarithmically correlated with COVID-19 mortality risk, while there was a linear dose-response correlation between age, lactate dehydrogenase, D-dimer and procalcitonin, independent of established risk factors.

CONCLUSION

Higher lactate dehydrogenase, D-dimer, and procalcitonin levels were independently associated with a dose-response increased risk of COVID-19 mortality.

Key Words: Coronavirus disease 2019; Dose-response relationship; Risk factor; Prognosis; Incidence

Core Tip: This study showed that older age, higher lactate dehydrogenase and creatinine, and elevated procalcitonin and D-dimer at admission were risk factors for the mortality from coronavirus disease 2019 (COVID-19). These findings suggested that higher lactate dehydrogenase, D-dimer and procalcitonin levels were independently associated with a dose-response increased risk of COVID-19 incidence.

Citation: Zhao SC, Yu XQ, Lai XF, Duan R, Guo DL, Zhu Q. Dose-response relationship between risk factors and incidence of COVID-19 in 325 hospitalized patients: A multicenter retrospective cohort study. *World J Clin Cases* 2022; 10(10): 3047-3059

URL: https://www.wjgnet.com/2307-8960/full/v10/i10/3047.htm

DOI: https://dx.doi.org/10.12998/wjcc.v10.i10.3047

INTRODUCTION

In December 2019, many cases of unknown viral pneumonia were reported[1]. A novel coronavirus, capable of infecting humans, was detected in January 2020[2,3] and the disease caused was termed coronavirus disease 2019 (COVID-19) by WHO[2]. As of March 19, 2020 > 200000 Laboratory-confirmed cases had been documented globally[1,4-7]. With the increasing awareness of COVID-19 pneumonia, a variety of diagnostic protocols and guidelines have evolved to guide clinical practice[1,5,8-10].

Many patients in some case series which had been published, were hospitalized at the time of reporting. Studies in patients who were not discharged may have misclassified outcomes due to patients developing severe disease or dying during subsequent hospitalization. Consequently, It might be inaccurate and unreliable to estimate of risk factors for severe illness and death in these early case series. Furthermore, although several large studies have reported risk factors for mortality and severe disease in COVID-19 patients, studies that systematically explored the potential associations were limited. Thus, the association of risk factors with COVID-19 outcomes remained unknown.

Therefore, we detail all laboratory-confirmed COVID-19 patients admitted to two designated hospitals as of February 2020, along with clear clinical outcomes (death or discharge). The purpose of this study was to investigate risk factors for death in hospital and to clarify hospitalization characteristics of COVID-19 patients.

MATERIALS AND METHODS

This retrospective cohort study included two cohorts of adult inpatients (≥ 20 years old) from two designated hospitals. All patients who were diagnosed with COVID-19 according to the WHO interim guideline were screened[2], and those who died or were discharged by February 6, 2020 were included in the study. We extracted demographic, clinical, laboratory, treatment, and outcome data from the hospital electronic medical records using a standardized data collection form modified from the version of the WHO/International Severe Acute Respiratory and Emerging Infection Consortium. The primary endpoint was in-hospital death occurring beyond 24 h but within 28 d and composite severe cases referred to the admission to intensive care unit, intubation, or death during hospitalization. Patients, who had normalized temperature for over 3 days, relief of clinical symptoms, substantial improvement in the imaging of both lungs and throat-swab samples negative twice for at least 24h apart, were allowed to be discharged. All data were collected by two physicians, double-checked independently, and verified by a third researcher. The computed tomography (CT) demonstrations were described according to the internationally standard nomenclature defined by the Fleischner Society and peer-reviewed literature on viral pneumonia, using the terms including ground glass opacity (GGO), crazy-paving pattern, and consolidation[11,12]. A semi-quantitative scoring system was used to quantitatively estimate the pulmonary involvement of all these abnormalities on the basis of the area involved[13].

The total CT score was the sum of the individual lobar scores and ranged from 0 (no involvement) to 25 (maximum involvement). The distribution of lung abnormalities was recorded as predominantly subpleural (involving mainly the peripheral one-third of the lungs), random (without predilection for subpleural or central regions), or diffuse (continuous involvement without respect to lung segments) [14].

This study was approved by the Ethics of Committees of Zhongnan Hospital of Wuhan University, and in accordance with the Helsinki Declaration. Written informed consent was obtained from all patients before examination. The anonymous data was collected and analyzed to optimize clinical decision and treatment.

Statistical analysis

Continuous and categorical variables were presented as median and *n* (%), respectively. We used the Mann-Whitney *U* test, χ^2 test, or Fisher's exact test to compare differences between survivors and non-survivors where appropriate. To explore the risk factors associated with in-hospital death, multivariable logistic regression models and the Cox proportional hazards model was used to determine the independent factors, which were based on the variables selected by a univariate analysis. To generate the Receiver operating characteristic (ROC) curves, patients were classified as survivor or non-survivors and CT total score of different stages excluded patients who were lost to follow-up.

We compared patients' characteristics between the two hospitals and used a generalized linear model to adjust for possible differences in patients' characteristics and treatment between the two study centers. Statistical tests and *P* values were two-sided. Differences were considered significant with a value of $P < 0.05$. All statistical analyses were carried out using the SAS software (version 9.4), unless otherwise indicated. We assessed potential dose-response associations of incident COVID-19 mortality and severe cases risk by restricted cubic splines logistic and Cox regression using 3 knots at 25th, 50th, and 75th percentiles of the corresponding risk factors with the median value of the above risk factors as the reference group[15].

RESULTS

Patients

The basic characteristics of the patients are shown in Table 1. Medical workers accounted for 5.8% (19/325), and those who had a history of contact with wildlife accounted for 1.2%. The median incubation period was 6 d (interquartile range, 2-15 d). The median age was 45 years (interquartile range, 34-61 years). Female accounted for 57.8%. 77.5% of patients had fever on admission and 85.5% had fever during hospitalization. The second most common symptoms were cough (63.7%) and fatigue (48.0%), but nausea or vomiting (7.7%) and difficulty breathing (4.6%) were uncommon. In the total population, 21.2 % have at least one co-existing condition (*e.g.*, hypertension and diabetes).

At admission, the severity of COVID-19 was classified as not severe 265 cases and severe 60 cases. Patients with severe disease had a median age of 16 years older than those without severe disease, and any comorbidities were more common (66.7% *vs*26.4%), but exposure histories were similar.

Laboratory findings

On admission, lymphocytopenia, thrombocytopenia and leukopenia were present in 61.8%, 19.4% and 28.6%, respectively. Most patients (69.5%) had increased C-reactive protein (CRP) levels. Laboratory abnormalities, including lymphocytopenia and leukopenia, were more pronounced in critically ill patients than in non-critically ill patients (Table 2).

Table 1 Characteristics of the patient cohort

Characteristic	All patients (*n* = 325)	Survivornon-survivor (*n* = 308); (*n* = 17)		*P* value
Age				< 0.001[1]
Median (IQR)-yr	45.0 (34.0-61.0)	43.0 (33.0-61.0)	63.0 (57.0-76.0)	
Distribution-no./total no. (%)				
20-49 yr	178	178 (57.8)	0 (0.0)	
50-64 yr	91	80 (25.9)	11 (64.7)	
≥ 65 yr	56	50 (16.2)	6 (35.3)	
Male sex - no./total no. (%)	137 (42.2)	124 (40.3)	13 (76.5)	0.003[1]
Smoking history - no./total no. (%)	21 (6.5)	18 (5.8)	3 (17.7)	0.054
Exposure to source of transmission within past 14 days - no./total no.				0.035[1]
Yes	233 (71.7)	222 (4.9)	11 (66.8)	
No	92 (28.3)	86 (0.3)	6 (28.0)	
Median incubation period (IQR) - days	5.0 ± 4.0	5.0 ± 3.9	5.2 ± 3.5	0.862
Fever on admission				
Patients - no./total no. (%)	252 (77.5)	240 (77.9)	12 (70.6)	0.550
Median temperature (IQR) - °C				
Distribution of temperature - no./total no. (%)				0.603
< 37.3 °C	77 (23.7)	72 (22.2)	5 (1.5)	
37.3-38.0 °C	106 (32.6)	103 (31.7)	3 (0.9)	
38.1-39.0 °C	124 (38.2)	116 (35.7)	8 (2.5)	
> 39.0°C	18 (5.5)	17 (5.2)	1 (0.3)	
Symptoms - no. (%)				
Conjunctival congestion	1 (0.31)	1 (0.31)	0 (0.0)	1.000
Headache	52 (16)	51 (16.6)	1 (5.9)	0.243
Cough	207 (63.7)	199 (64.6)	8 (47.1)	0.143
Sputum production	81 (24.9)	76 (24.6)	5 (29.4)	0.660
Fatigue	156 (48)	145 (47.1)	11 (64.7)	0.157
Difficulty breathing	15 (4.6)	13 (4.2)	2 (11.8)	0.149
Shortness of breath	73 (22.5)	68 (22.1)	5 (29.4)	0.012[1]
Nausea or vomiting	25 (7.7)	21 (6.8)	4 (23.5)	0.012[1]
Diarrhea	28 (8.6)	27 (8.8)	1 (5.9)	0.680
Myalgia or arthralgia	92 (28.3)	88 (28.5)	4 (23.5)	0.630
Chills	55 (16.9)	54 (17.5)	1 (5.88)	0.212
Coexisting disorder - no. (%)				
Fatty liver	15 (4.6)	15 (4.9)	0 (0)	1.000
Chronic obstructive pulmonary disease	17 (5.2)	16 (5.2)	1 (5.9)	0.608
Diabetes	34 (10.5)	27 (8.77)	7 (41.2)	< 0.001[1]
Hypertension	69 (21.2)	58 (18.8)	11 (64.7)	< 0.001[1]
Coronary heart disease	9 (2.8)	6 (1.9)	3 (17.7)	< 0.001[1]
Cerebrovascular disease	18 (5.5)	14 (4.6)	4 (23.5)	0.010[1]
Hyperlipidemia	17 (5.2)	16 (5.2)	1 (5.8)	0.901
Hepatitis B infection	6 (1.9)	5 (1.6)	1 (5.9)	0.205

[1]Quantitative data were presented as mean ± SD (minimum-maximum), while the counting data were presented as count (percentage of the total).
IQR: Inter quartile range.

Radiologic findings

All patients underwent computed tomography scans at the time of admission, and 97.8% revealed abnormal results. The most common patterns on chest CT were GGO (61.1%) and bilateral patchy shadowing (84.7%). No CT abnormality was found in seven of 308 (2.2%) patients who survived and in none of 17 patients who died. GGO, crazy-paving pattern and consolidation were the most frequent CT findings in mild COVID-19 pneumonia (Supplementary Figure 1). Most patients (279/325), the total CT score increasedabout10 d after the onset of symptoms, and then gradually decreased (Table 3, Supplementary Figure 2). There were statistically significant differences between the bilateral lower lobe CT scores at stage 1 and the corresponding upper/middle lobe CT scores (left lower lobe *vs* left upper lobe: 1 ± 1 *vs* 0 ± 1, $P < 0.001$, $P = 0.004$) (Table 3). According to the degree of lung involvement and the quartile of patients 0-26 days after onset, there were six stages starting from the onset of symptoms (Table 4, Supplementary Figure 3). Overall, subpleural lesions were more common than changes in central lung disease. Bilateral lung involvement occurred in most patients during the course of the disease (Supplementary Figure 4). ROC curve analysis showed that the area under the curve (AUC) of stage 5 disease was higher than either of stage, and the combined AUC for stages 2 and 5 was highest among all stages (Figure 1).

Risk factors, dose-response relationship and ROC analysis

After univariate analysis, patients with diabetes or hypertension had a higher chance of death in hospital (Tables 1 and 2). Age, sex, leukocytosis, and elevated glucose level, lactate dehydrogenase (LDH), high-sensitivity C-reactive protein (CRP), D-dimer (DD), total cholesterol, triglyceride, creatinine, and procalcitonin (PCT) were associated with death or severe illness.

Older age [hazard ratio (HR):1.04, 95% confidence interval (CI): 1.01-1.09], higher LDH (HR: 1.04, 95% 95%CI:1.01-1.10), higher CRP (HR:1.10, 95%CI: 1.01-1.23), and elevated PCT ($\log_n$ transformed HR: 1.88, 95%CI: 1.22-2.88), and DD > 1 μg/mL at admission ($\log_n$ transformed HR: 1.63, 95%CI: 1.03-2.58) were associated with increasing odds of in-hospital death (Table 5). Furthermore, DD and PCT were log-linearly correlated with COVID-19 mortality risk, while there were linear dose-response correlations between age, LDH, DD and PCT. In particular, It was evident that the dose-response association of LDH and PCT occurred in severe patients (all P for overall association < 0.05). The dose-response relationship between LDH and PCT was more obvious in severe patients in the meantime (all P for interaction < 0.05) (Figure 2, Tables 5 and 6).

ROC curve analysis indicated that the combined AUC for age, sex, high-sensitivity CRP, DD, LDH and PCT (0.947) was higher than that of any one of these variables alone (Figure 1). These results show that combination of age, sex, high-sensitivity CRP, DD, LDH and PCT was more precise in predicting clinical outcome than single factors alone.

DISCUSSION

Consistent with most studies[1,2,16], we found that the clinical features of COVID-19 were similar to those of SARS. Fever, cough, gastrointestinal symptoms were rare[17]. Lymphocytopenia was common, a finding that was consistent with two recent reports[1,16]. We found that the fatality rate (5.2%) was lower than recently reported[1,16]. This may be due to differences in sample size and case inclusion criteria. Our findings were higher than the national official statistics, which showed a mortality rate of 3.9% among 81003 cases of COVID-19 as of March 13, 2020.

In this study, patients underwent multiple lung CT scans (≥ 3 times), providing reliable dynamic radiographic pattern data. During the first 2 wk, the number and severity of abnormal lesions on chest CT increased. Subsequently, there was a short plateau phase and a gradual decrease in abnormalities. There were six stages of lung involvement in patients who have recovered from COVID-19, which could be more accurately evaluate the time course of lung changes, compared with the previous 4 stages[18]. Combined profiling of stages 2 and 5provides a more precise clinical outcome prediction than conventional stages 1-4 classification[18], suggesting a novel valuable prognostic indicator for COVID-19 patients after antiviral therapy.

Our retrospective cohort study demonstrated several risk factors for death in patients who were hospitalized with COVID-19. Particularly, older age, LDH > 285 U/L, creatinine > 111 ng/mL, PCT > 0.05 ng/mL, and DD > 1 μg/mL on admission were associated with higher odds of in-hospital death. Previously, older age, DD > 1 μg/mL and sequential organ failure assessment (SOFA) score (including creatinine level) have been reported as important independent predictors of mortality in COVID-19[4], which is in accordance with our current study. The most plausible explanation included an age-dependent defect in T-cell and B-cell function and excess type 2 cytokines, which predispose to ischemia

Table 2 Laboratory findings of the patient cohort

Variable	All patients (*N* = 325)	Survivor non-survivor (*n* = 308); (*n* = 17)		*P* value
Laboratory findings				
White-cell count (10^9/L)	4.6 (3.3-6.0)	4.6 (3.29-5.9)	6.4 (3.6-7.4)	0.090
Red-cell count (10^{12}/L)	4.3 (4.1-4.7)	4.3 (4.1-4.7)	4.2 (4.0-4.6)	0.557
Hemoglobin (g/L)	131.0 (120.0-142.0)	131.0 (121.0-142.5)	130.0 (114.0-141.0)	0.360
Platelet count (10^9/L)	171.0 (134.0-202.0)	173.0 (136.0-204.5)	143.0 (119.0-155.0)	0.008[1]
Hematocrit (%)	39.4 (36.5-42.6)	39.4 (36.6-42.6)	40.0 (34.6-42.6)	0.530
Neutrophil percentage (%)	64.6 (56.8-75.5)	64.5 (56.4-75.2)	73.4 (67.3-81.8)	0.007[1]
Lymphocyte percentage (%)	26.5 ± 14.5	26.6 ± 12.3	18.6 (11.2-22.5)	0.008[1]
Monocyte percentage (%)	7.9 ± 3.5	8.1 ± 3.5	6.2 (3.4-6.9)	0.008[1]
Eosinophil percentage (%)	0.1 (0.0-0.6)	0.1 (0.0-0.55)	0.0 (0.0-0.8)	0.953
Basophil percentage (%)	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.946
Mean red blood cell volume (fL)	90.6 (87.5-93.6)	90.6 (87.6-93.6)	88.9 (85.7-93.1)	0.432
Mean hemoglobin content (pg)	30.0 (28.8-31.1)	30.0 (28.9-31.1)	29.4 (27.5-30.5)	0.209
Mean hemoglobin concentration (g/L)	330.0 (323.0-336.0)	330.0 (323.0-336.0)	324.0 (321.0-331.0)	0.029[1]
RBC distribution width standard deviation (%)	39.4 (36.7-41.2)	39.2 (36.5-41.2)	40.7 (37.5-42.8)	0.071
RBC distribution width-coefficient of variation (%)	12.7 (12.2-14.4)	12.7 (12.1-14.1)	13.3 (12.6-15.4)	0.116
Neutrophil count (10^9/L)	2.96 (1.92-4.05)	2.9 (1.9-4.0)	4.1 (2.7-4.9)	0.035[1]
Lymphocyte count (10^9/L)	1.13 ± 0.55	1.14 ± 0.55	0.89 ± 0.58	0.035[1]
Monocyte count (10^9/L)	0.34 (0.24-0.46)	0.3 (0.3-0.5)	0.3 (0.2-0.5)	0.828
Eosinophil count (10^9/L)	0.01 (0.0-0.02)	0.01 (0.0-0.02)	0.0 (0.0-0.06)	0.642
Basophil count (10^9/L)	0.01 (0.01-0.02)	0.01 (0.01-0.02)	0.01 (0.01-0.02)	0.060
Platelet distribution width (%)	12.5 (10.6-16.2)	12.5 (10.6-16.2)	15.1 (10.9-16.4)	0.452
Large platelet ratio (%)	11.1 (9.8-21.2)	11.1 (9.8-21.4)	10.0 (10.0-12.9)	0.405
Mean platelet volume (fL)	19.0 (10.0-28.7)	18.5 (9.9-27.9)	28.9 (18.8-32.4)	0.018[1]
Platelet hematocrit (%)	0.17 (0.14-0.20)	0.17 (0.14-0.20)	0.13 (0.13-0.16)	0.016[1]
Distribution of other findings-no./total no. (%)				
Systolic blood pressure (mmHg)	123.6 ± 13.6	123.0 ± 12.7	135.4 ± 21.0	0.022[1]
Diastolic blood pressure (mmHg)	76.4 ± 9.5	76.4 ± 9.3	76.2 ± 13.1	0.464
Blood glucose concentration (mmol/L)	6.4 ± 2.6	6.2 ± 2.3	9.1 ± 4.8	0.009[1]
Total cholesterol (mmol/L)	3.8 (3.2-4.5)	3.9 (3.3-4.5)	2.7 (2.6-3.3)	0.003[1]
Triglyceride (mmol/L)	1.1 (0.8-1.4)	1.1 (0.8-1.4)	0.9 (0.8-1.0)	0.455
High density lipoprotein (mmol/L)	1.1 (0.9-1.2)	1.1 (0.9-1.3)	0.97 (0.94-1.12)	0.354
Low density lipoprotein (mmol/L)	2.2 ± 0.7	2.2 ± 0.7	1.5 ± 0.6	0.002[1]
C-reactive protein (mg/dL)	1.3 (0.3-3.4)	1.3 (0.3-3.0)	5.9 (3.3-8.2)	< 0.001[1]
Lactate dehydrogenase (U/L)	178.5 (137.5-236.5)	173.0 (136.0-229.0)	275.0 (232.0-324.0)	< 0.001[1]
Aspartate aminotransferase (U/L)	22.2 (17.1-32.8)	21.7 (16.8-32.3)	31.2 (25.5-36.5)	0.019[1]
Alanine aminotransferase (U/L)	19.1 (12.8-32.6)	18.9 (12.7-33.2)	19.9 (15.5-29.7)	0.957
γ-Glutamyltransferase (U/L)	19.0 (12.6-38.2)	19.0 (12.4-38.0)	27.8 (16.9-69.0)	0.064
Blood urea nitrogen (mmol/L)	4.1 (3.2-5.3)	4.0 (3.2-5.0)	6.4 (5.3-11.1)	< 0.001[1]
Creatine kinase (ng/mL)	76.5 (45.0-140.0)	77.1 (45.0-138.0)	74.0 (61.0-203.0)	0.404
Creatinine (μmol/L)	63.9 (53.6-76.7)	63.0 (53.1-74.7)	83.7 (74.9-254.2)	< 0.001[1]

α-Hydroxybutyrate dehydrogenase (U/L)	137.5 (109.0-176.5)	135.0 (108.0-171.0)	208.0 (158.0-217.0)	0.001[1]
D-dimer (μg/mL)	0.4 (0.2-0.8)	0.4 (0.2-0.8)	1.1 (0.6-6.3)	< 0.001[1]
Procalcitonin (ng/mL)	0.05 (0.04-0.09)	0.05 (0.03-0.08)	0.3 (0.1-2.8)	< 0.001[1]
Brain Natriuretic peptide (pg/mL)	34.4 (13.0-128.0)	31.6 (12.0-108.0)	295.8 (177.0-406.1)	< 0.001[1]
Antihypertensive drugs				< 0.001[1]
Yes	57 (17.5)	47 (14.5)	10 (3.0)	
No	268 (82.5)	261 (80.3)	7 (2.2)	
Hypoglycemic drugs				< 0.001[1]
Yes	28 (8.6)	22 (6.8)	6 (1.8)	
No	297 (91.4)	286 (88)	11 (3.4)	
Lipid-lowering drugs				0.005[1]
Yes	14 (4.3)	11 (3.4)	3 (0.9)	
No	311 (95.7)	297 (91.4)	14 (4.3)	

[1]Indicated statistically significant values ($P < 0.05$). RBC: Red blood cell.

Table 3 The computed tomography score of the pulmonary involvement in four stages

	Stage-1 (*n* = 157)	Stage-2 (*n* = 194)	Stage-3 (*n* = 165)	Stage-4 (*n* = 211)	Stage-5 (*n* = 204)	Stage-6 (*n* = 137)	*P* value
Total CT score of the pulmonary involvement	2 ± 4 (0-18)	5 ± 5 (0-22)	7 ± 7 (0-22)	7 ± 7 (0-25)	5 ± 7 (0-24)	4 ± 6 (0-25)	< 0.0001[1]
Number of involved lobes	22 ± 2 (0-5)	3 ± 2 (1-5)	4 ± 2 (1-5)	3 ± 2 (1-5)	3 ± 2 (1-5)	4 ± 2 (1-5)	< 0.0001[1]
CT score in each lobe							< 0.0001[1]
Left upper lobe	0 ± 1 (0-3)	1 ± 2 (0-5)	1 ± 2 (0-5)	1 ± 2 (0-5)	1 ± 2 (0-4)	1 ± 1 (0-5)	
Left lower lobe	1 ± 1 (0-5)	1 ± 2 (0-5)	2 ± 2 (0-5)	2 ± 1 (0-5)	1 ± 2 (0-5)	1 ± 2 (0-5)	
Right upper lobe	0 ± 1 (0-3)	1 ± 2 (0-5)	1 ± 2 (0-5)	1 ± 2 (0-5)	1 ± 2 (0-5)	1 ± 2 (0-5)	
Right middle lobe	0 ± 1 (0-3)	1 ± 1 (0-5)	1 ± 2 (0-5)	1 ± 2 (0-5)	1 ± 1 (0-5)	0 ± 1 (0-5)	
Right lower lobe	1 ± 2 (0-12)	2 ± 1 (0-5)	2 ± 2 (0-5)	1 ± 2 (0-5)	1 ± 1 (0-5)	1 ± 1 (0-5)	

Quantitative data were presented as mean ± SD (minimum-maximum). Mann-Whitney *U* test showed significant difference between Stage-1 and Stage-2-6 ($P < 0.05$); Wilcoxon test showed significant difference between the left lower lobe and the left upper lobe ($P < 0.05$); Wilcoxon test showed significant difference between the right lower lobe and the right upper/middle lobe ($P < 0.05$).

[1]$P < 0.05$ by *t* test.

CT: Computed tomography.

and thrombosis, potentially leading to poor outcome[4,19-22]. SOFA score is a good diagnostic marker for renal function, and reflects the state and degree of multiorgan dysfunction[20,23]. In the current study, higher PCT and LDH levels were independently associated with prognosis of COVID-19. Additionally, we found that most patients had lower white blood cell count, and no bacterial pathogens were detected. Viral infections is one of the cause of sepsis syndrome, despite that bacterial infections are used to be the primary cause of sepsis, PCT, as an inflammatory indicator, could better stratify the degree of infection. The level of LDH is important in assessing the risk of cardiac and liver dysfunction, which has great significance for both patient isolation decision-making and guidance around the length of antiviral treatment. Effective antiviral therapy may improve the outcome of COVID-19 in spite of that we did not observe a reduction in viral shedding time after antiviral therapy in the current study. However, further research is needed to investigate the pathogenesis of sepsis in COVID-19.

We showed that CT stage is a powerful indicator in the evaluation of COVID-19 prognosis. We characterized specific factors-prognostic factors model (PFM), age, high-sensitivity CRP, DD, LDH and PCT as a valuable independent prognostic tool of COVID-19 from CT stage. Predictive value of PFM was comparable to that of CT stage. Thus, these results consistently point to the notion that high PFM and CT stage are pivotal factors in evaluating COVID-19, but further research is needed to investigate the prognostic value.

Table 4 Distribution and frequency of the major of lung lesions on computed tomography in different stages defined by the time of onset of symptoms

	Stage-1 (*n* = 157)	Stage-2 (*n* = 194)	Stage-3 (*n* = 165)	Stage-4 (*n* = 211)	Stage-5 (*n* = 204)	Stage-6 (*n* = 137)
Distribution of pulmonary lesions						
No lesion	12/157	1/194	0/165	1/211	2/204	0/137
Peripheral	60/157	18/194	55/165	105/211	88/204	66/137
Random	85/157	162/194	88/165	75/211	78/204	44/137
Diffuse	0/157	13/194	22/165	30/211	36/204	27/137
Involvement of the lesions						
No involvement	12/157	0/194	0/165	0/211	0/204	0/137
Single lobe	48/157	18/194	11/165	30/211	22/204	11/137
Bilateral multilobe						
GGO	96/157	180/194	154/165	180/211	176/204	121/137
None	24/157	0/194	22/165	30/211	47/204	49/137
Yes	133/157	194/194	143/165	181/211	157/204	88/137
Crazy-paving pattern						
None	120/157	104/194	110/165	180/211	183/204	126/137
Yes	36/157	90/194	55/165	31/211	121/204	11/137
Consolidation						
None	157/157	140/194	88/165	105/211	102/204	89/137
Yes	0/157	54/194	77/165	105/211	102/204	48/137
Fibrosis						
None	157/157	180/194	143/165	150/211	102/204	37/137
Yes	0/157	14/194	22/165	61/211	102/204	100/137

The counting data were presented as count (percentage of the total). GGO: Ground glass opacity.

Table 5 Associations of risk factors with incident mortality risk of coronavirus disease 2019

Variable	HR (95%CI)		*P* for overall association	*P* for nonlinear association
	Model 1	Model 2		
Age (*per* year increase)	1.06 (1.03, 1.10)	1.04 (1.01, 1.09)	0.080	0.805
CRP (*per* 1 mg/L increase)	1.15 (1.06, 1.24)	1.10 (1.01, 1.23)	0.062	0.715
DD (*per* 1 μg/mL increase of NLT	1.89 (1.34, 2.69)	1.63 (1.03, 2.58)	0.012	0.711
LDH (*per* 10 U/L increase)	1.06 (1.02, 1.09)	1.04 (1.01, 1.10)	0.080	0.805
Procalcitonin (*per* 1 ng/mL increase of NLT)	2.15 (1.59, 2.90)	1.88 (1.22, 2.88)	0.011	0.721

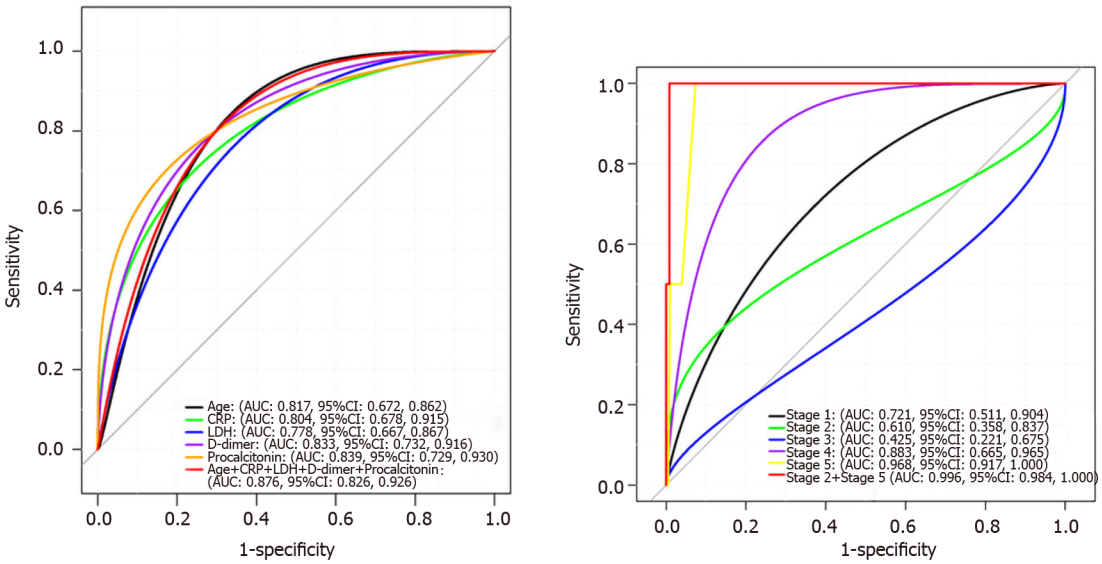
Hazard ratios are reported *per* 1-SD increase in loge D-dimer (DD) and Procalcitonin levels; 1-SD higher loge DD and Procalcitonin was approximately equivalent to 2-fold higher DD and Procalcitonin levels.
Model 1: adjusted age, sex.
Model 2: adjusted model 1 plus smoking status, history of hypertension, diabetes, cancers, cardiac disease, and chronic pulmonary disease, systolic blood pressure, fasting blood glucose, total cholesterol, triglyceride, white blood cell count, C-reactive protein, creatinine, DD, LDH, procalcitonin. CRP: C-reactive protein; DD: D-dimer; LDH: Lactate dehydrogenase; NLT: Natural log-transformation; CI: Confidence interval.

However, no published works were found about the dose-response relationship between mortality and severe illness in adult patients with COVID-19. In recent studies, the relationship of prognostic factors with risk of COVID-19 incidence has not been reported. Of note, we found that higher LDH, DD

Table 6 Associations of risk factors with severe cases incident risk of coronavirus disease 2019

Variable	OR (95%CI)		*P* for overall association	*P* for nonlinear association
	Model 1	Model 2		
Age (*per* year increase)	1.06 (1.04, 1.08)	1.04 (1.01, 1.07)	0.010	0.192
WBC (*per* 1 × 10^9/L increase)	1.27 (1.11, 1.46)	1.20 (1.01, 1.45)	0.003	0.046
FBG (*per* 1 mmol/L increase)	1.19 (1.07, 1.33)	1.15 (1.01, 1.32)	0.036	0.064
Total cholesterol (*per* 1 mmol/L increase)	1.43 (1.07, 1.91)	1.65 (1.09, 2.50)	0.028	0.260
LDH (*per* 10 U/L increase)	1.09 (1.05, 1.13)	1.06 (1.02, 1.10)	0.009	0.268
Procalcitonin (*per* 1 ng/mL increase of NLT)	2.26 (1.68, 3.05)	1.75 (1.16, 2.65)	0.007	0.099

Hazard ratios are reported *per* 1-SD increase in loge D-dimer (DD) and Procalcitonin levels; 1-SD higher loge DD and procalcitonin was approximately equivalent to 2-fold higher DD and Procalcitonin. Model 1: Adjusted age, sex. Model 2: Adjusted model 1 plus smoking status, history of hypertension, diabetes, cancers, cardiac disease, and chronic pulmonary disease, systolic blood pressure, fasting blood glucose, total cholesterol, triglyceride, white blood cell count, C-reactive protein, creatinine, DD, LDH, procalcitonin. LDH: Lactate dehydrogenase; NLT: Natural log-transformation. CI: Confidence interval.

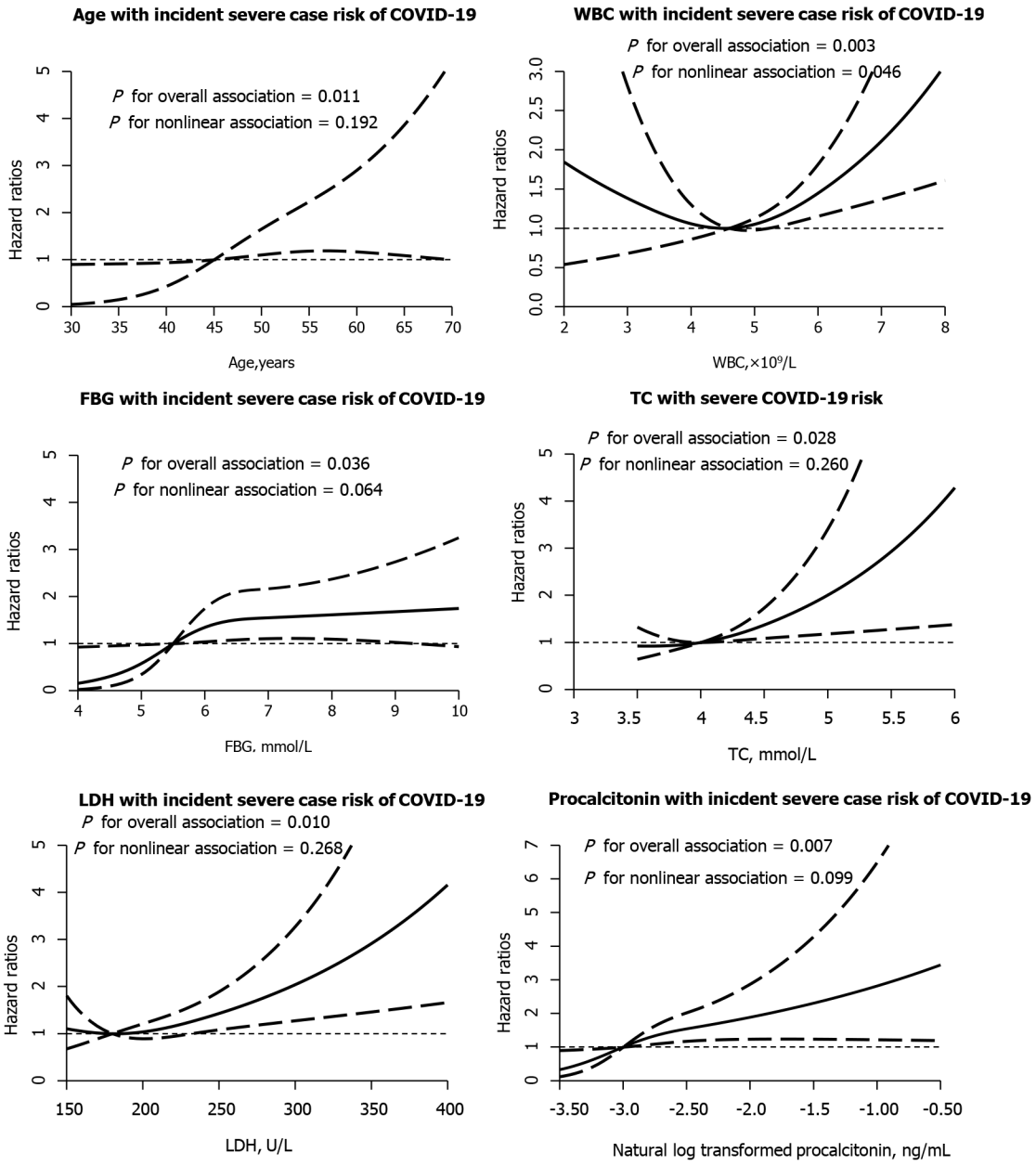


DOI: 10.12998/wjcc.v10.i10.3047

Figure 1 Receiver operating characteristic analysis of risk factors and computed tomography stages in coronavirus disease 2019 patients. CRP: C-reactive protein; AUC: Area under the curve; LDH:Lactate dehydrogenase.

and PCT levels were independently associated with a dose-response increased mortality risk in patients with COVID-19. Notably, the dose-response relationship between LDH and PCT levels and incidence of COVID-19 was seen in survivors and patients with severe illness. To our knowledge, this is the first study to demonstrate that the higher risk of COVID-19 incidence associated with LDH and PCT levels provides evidence of the dose-response relationship. Several potential mechanisms might explain the association between LDH, DD and PCT levels and COVID-19[4,19,20,22,23]. Although the underlying pathophysiological mechanisms are unclear, it is possible that the presence of COVID-19 risk factors could cover up the effect of LDH, DD and PCT on the risk of COVID-19 among high-risk persons and leave the pernicious effects prominent in relatively healthy adults. Further studies should be performed, which is the key for the development of specific inhibitors targeting COVID-19.

There are some limitations to our study. First, contact histories and laboratory testing records for some cases were incomplete. Second, we could only estimate the incubation period in patients who have recorded information. Uncertainty about the exact date (recall bias) might have inevitably influenced our assessment. Third, since our study did not include patients with mild illness who did not seek medical attention, the case fatality rate would likely have been lower in real-world situations. Meanwhile, during the beginning of the pandemic, we a little about COVID-19, so the treatment regimens have been improving. Also, due to limited medical resources, older patients and patients with serious symptoms may have been preferentially admitted, and this may have resulted in bias. Fourth,



DOI: 10.12998/wjcc.v10.i10.3047

Figure 2 Adjusted hazard ratios (solid lines) and 95% confidence interval (dashed lines) for coronavirus disease 2019 mortality from restricted cubic splines in a multivariate-adjusted Cox proportional hazard model. The model was adjusted for age, gender, smoking status, history of hypertension, diabetes, cancers, cardiac disease, and chronic pulmonary disease, systolic blood pressure, fasting blood glucose, total cholesterol, triglyceride, white blood cell count, CRP, creatinine, DD, LDH, procalcitonin. CRP: C-reactive protein; LDH: Lactate dehydrogenase; DD: D-dimer.

data generation was clinically driven and not systematic. Lastly, this was a retrospective study.

To our knowledge, this is the largest retrospective cohort study of COVID-19 patients who have experienced clear results and systematically explored almost all potential risk factors associated with mortality and severe illness. Six stages of lung involvement could be more accurately defined to evaluate the prognosis of COVID-19. The combination of PFM and six stages could provide the rationale for testing novel coronavirus management to improve outcomes. We found that older age, higher LDH and creatinine, and elevated PCT and DD at admission were risk factors for death of patients with COVID-19. These findings suggested that higher LDH, DD and PCT levels were independently associated with increased risk of COVID-19 incidence.

CONCLUSION

Higher LDH, DD and PCT levels were independently associated with a dose-response increased risk of COVID-19 mortality.

ARTICLE HIGHLIGHTS

Research background

Dose-response assessments and risk factors for mortality, severe cases and clinical outcomes for coronavirus disease 2019 (COVID-19) have not been well described.

Research motivation

To screen for dose-response relationships between risk factors and incidence of COVID-19.

Research objectives

To explore risk factors of in-hospital death and describe the clinical course of symptoms, viral shedding, and temporal changes of laboratory findings during hospitalization.

Research methods

This retrospective cohort study included two cohorts of adult inpatients from two designated hospitals. Multivariate logistic regression and Cox proportional risk models were used to determine the dose-response relationship between risk factors and the incidence of COVID-19.

Research results

D-dimer and procalcitonin were log-linear correlated with the risk of death from COVID-19, while there was a linear dose-response relationship between age, LDH, D-dimer and procalcitonin, independent of identified risk factors.

Research conclusions

High lactate dehydrogenase, D-dimer and procalcitonin levels were independently associated with an increased dose-response risk of death from COVID-19.

Research perspectives

This study provides ideas and basis for prospective observation of dose-response relationships between risk factors and incidence of COVID-19.

FOOTNOTES

Author contributions: Zhao SC and Yu XQ made equal contributions to the article; Yu XQ and Zhu Q had the idea for and designed the study and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; Zhao SC and Lai XF drafted the paper; Zhao J and Guo DL did the analysis, and all authors critically revised the manuscript for important intellectual content and gave final approval for the version to be published; all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Institutional review board statement: The study was reviewed and approved by the Zhongnan Hospital of Wuhan University Institutional Review Board

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: There has no conflict of interest of this study.

Data sharing statement: The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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S-Editor: Ma YJ
L-Editor: A
P-Editor: Ma YJ

REFERENCES

1 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

2 **Li Q**, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med* 2020; **382**: 1199-1207 [PMID: 31995857 DOI: 10.1056/NEJMoa2001316]

3 **Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]

4 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]

5 **Lv Z**, Cheng S, Le J, Huang J, Feng L, Zhang B, Li Y. Clinical characteristics and co-infections of 354 hospitalized patients with COVID-19 in Wuhan, China: a retrospective cohort study. *Microbes Infect* 2020; **22**: 195-199 [PMID: 32425649 DOI: 10.1016/j.micinf.2020.05.007]

6 **Khailany RA**, Safdar M, Ozaslan M. Genomic characterization of a novel SARS-CoV-2. *Gene Rep* 2020; **19**: 100682 [PMID: 32300673 DOI: 10.1016/j.genrep.2020.100682]

7 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

8 **Lau H**, Khosrawipour V, Kocbach P, Mikolajczyk A, Schubert J, Bania J, Khosrawipour T. The positive impact of lockdown in Wuhan on containing the COVID-19 outbreak in China. *J Travel Med* 2020; **27** [PMID: 32181488 DOI: 10.1093/jtm/taaa037]

9 **Wang J**, Qi H, Bao L, Li F, Shi Y; National Clinical Research Center for Child Health and Disorders and Pediatric Committee of Medical Association of Chinese People's Liberation Army. A contingency plan for the management of the 2019 novel coronavirus outbreak in neonatal intensive care units. *Lancet Child Adolesc Health* 2020; **4**: 258-259 [PMID: 32043976 DOI: 10.1016/S2352-4642(20)30040-7]

10 **Zhang J**, Zhou L, Yang Y, Peng W, Wang W, Chen X. Therapeutic and triage strategies for 2019 novel coronavirus disease in fever clinics. *Lancet Respir Med* 2020; **8**: e11-e12 [PMID: 32061335 DOI: 10.1016/S2213-2600(20)30071-0]

11 **Franquet T**. Imaging of pulmonary viral pneumonia. *Radiology* 2011; **260**: 18-39 [PMID: 21697307 DOI: 10.1148/radiol.11092149]

12 **Hansell DM**, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. *Radiology* 2008; **246**: 697-722 [PMID: 18195376 DOI: 10.1148/radiol.2462070712]

13 **Thomas M**, Price OJ, Hull JH. Pulmonary function and COVID-19. *Curr Opin Physiol* 2021; **21**: 29-35 [PMID: 33817453 DOI: 10.1016/j.cophys.2021.03.005]

14 **Wu X**, Dong D, Ma D. Thin-Section Computed Tomography Manifestations During Convalescence and Long-Term Follow-Up of Patients with Severe Acute Respiratory Syndrome (SARS). *Med Sci Monit* 2016; **22**: 2793-2799 [PMID: 27501327 DOI: 10.12659/msm.896985]

15 **Desquilbet L**, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. *Stat Med* 2010; **29**: 1037-1057 [PMID: 20087875 DOI: 10.1002/sim.3841]

16 **Guo CX**, He L, Yin JY, Meng XG, Tan W, Yang GP, Bo T, Liu JP, Lin XJ, Chen X. Epidemiological and clinical features of pediatric COVID-19. *BMC Med* 2020; **18**: 250 [PMID: 32762696 DOI: 10.1186/s12916-020-01719-2]

17 **Aishwarya M**, Singh M, Panda PK. Primary to tertiary COVID-19 transmission in a hospital - A cluster outbreak analysis. *J Family Med Prim Care* 2021; **10**: 1489-1492 [PMID: 34041199 DOI: 10.4103/jfmpc.jfmpc_2104_20]

18 **Duzgun SA**, Durhan G, Demirkazik FB, Akpinar MG, Ariyurek OM. COVID-19 pneumonia: the great radiological mimicker. *Insights Imaging* 2020; **11**: 118 [PMID: 33226521 DOI: 10.1186/s13244-020-00933-z]

19 **Opal SM**, Girard TD, Ely EW. The immunopathogenesis of sepsis in elderly patients. *Clin Infect Dis* 2005; **41** Suppl 7: S504-S512 [PMID: 16237654 DOI: 10.1086/432007]

20 **Armstrong BA**, Betzold RD, May AK. Sepsis and Septic Shock Strategies. *Surg Clin North Am* 2017; **97**: 1339-1379 [PMID: 29132513 DOI: 10.1016/j.suc.2017.07.003]

21 **Fountoulaki K**, Tsiodras S, Polyzogopoulou E, Olympios C, Parissis J. Beneficial Effects of Vaccination on Cardiovascular Events: Myocardial Infarction, Stroke, Heart Failure. *Cardiology* 2018; **141**: 98-106 [PMID: 30428464 DOI: 10.1159/000493572]

22 **Corrales-Medina VF**, Musher DM, Wells GA, Chirinos JA, Chen L, Fine MJ. Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. *Circulation* 2012; **125**: 773-781 [PMID: 22219349 DOI: 10.1161/CIRCULATIONAHA.111.040766]

23 **Wang H**, Kang X, Shi Y, Bai ZH, Lv JH, Sun JL, Pei HH. SOFA score is superior to APACHE-II score in predicting the prognosis of critically ill patients with acute kidney injury undergoing continuous renal replacement therapy. *Ren Fail* 2020; **42**: 638-645 [PMID: 32660294 DOI: 10.1080/0886022X.2020.1788581]

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