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RESEARCH ARTICLE

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Multiple organ injury on admission predicts in-hospital mortality in patients with COVID-19

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Abstract

Multiorgan injury has been implicated in patients with coronavirus disease 2019 (COVID-19). We aim to assess the impact of organ injury (OI) on prognosis according to the number of affected organs at admission. This is a retrospective cohort study of patients with confirmed COVID-19 in Wuhan Third Hospital & Tongren Hospital of Wuhan University from February 17 to March 22, 2020. We classified the patients according to the presence and number of damaged organs (heart, liver, and kidney). The percentage of patients with no, one, two, or three organs affected was 59.75%, 30.46%, 8.07%, and 1.72%, respectively. With the increasing number of OI, there is a tendency of gradual increase regarding the white blood cell counts, neutrophil counts, levels of C-reactive protein (CRP), lactate dehydrogenase, D-dimer, and fibrinogen as well as the incidence of most complications. In a Cox regression model, individuals with OI, old age, and an abnormal level of CRP were at a higher risk of death compared with those without. Patients with three organ injuries had the highest mortality rate (57.9%; hazard ratio [HR] with 95% confidence interval [CI] vs. patients without OI: 22.31 [10.42–47.77], those with two [23.6%; HR = 8.68, 95% CI = 4.58–16.48], one [8.6%; HR = 3.1, 95% CI = 1.7–5.7], or no OI [2.6%]; $p < .001$). The increasing number of OI was associated with a high risk of mortality in COVID-19 infection.

KEYWORDS
COVID-19, mortality, organ injury, risk factor, SARS-CoV-2

1 | INTRODUCTION

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to the outbreak of coronavirus disease 2019 (COVID-19) globally. At present, this pandemic has resulted in over 24,299,923 individuals affected and over 827,730 fatalities inflicted in more than 200 countries.[1]

Although the presence of respiratory tract infection and subsequent pulmonary compromise are the principal features, extrapulmonary organ injury (OI), including heart, kidney, and liver injury,

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frequently arise after viral infection and during the exacerbation of COVID-19.[2–4] Acute respiratory distress syndrome (ARDS), multiple organ dysfunction, and even death are commonly manifested in severe cases.[5] Remarkably, individuals with OI tend to be associated with poorer outcomes. For example, several studies proposed that cardiac injury was significantly associated with fatal outcome of COVID-19 based on the levels of high-sensitivity troponin I (hs-TNI), which supports the notion of the cardiac implications of COVID-19 highlighted by the American College of Cardiology clinical bulletin.[6] Similarly, emerging evidence demonstrates the prevalence of kidney injury among patients with a severe condition, particularly in the intensive care unit (ICU) setting, and suggests the potential of it as an adverse prognostic factor concerning overall survival. However, it remains uncertain whether liver injury affects the mortality of COVID-19 patients,[4,5] although it occurred more commonly in patients who had severe COVID-19 than mild ones.[7] According to the recent reports, the incidence of liver injury was uncovered as high as 58.06% or 78% in the deceased.[5,8]

Given the multifactorial cascade of events in patients with COVID-19, multiple organ systems are involved and will become prognostic of outcomes related to COVID-19. However, to date, clinical consequences of organ damage were usually studied placing a single organ dysfunction in isolation.[2,3,9] No investigation reported whether multiple OI had a relation with the ominous outcomes and to what extent it affects the mortality of COVID-19 patients. In clinical practice, various organs may be affected and can be utilized as a critical prognosticator in the decision-making of therapeutic strategy. We aimed to explore the association between OI and mortality according to the number of affected organs (heart, liver, and kidney) in patients with COVID-19.

2 | METHODS

2.1 | Study participants

From February 17 to March 22, 2020, consecutive patients with highly suspecting COVID-19 were admitted to Wuhan Third Hospital & Tongren Hospital of Wuhan University. According to clinical criteria for "Diagnosis and Treatment Scheme of New Coronavirus Infected Pneumonia" (trial version 6) released by the National Health Commission of China,[10] we employed patients with laboratory-confirmed COVID-19. Cases were excluded if the core data were missing.

2.2 | Data collection

We collected data on demographic characteristics (age and sex), clinical data (symptoms and signs, comorbidities, laboratory findings, treatments, and outcomes) by medical records management system on admission. In light of the guidelines for diagnosis and management of COVID-19 released by the National Health Commission of China,[10] patients were divided into four types according to the disease severity, including mild, moderate, severe, and critical conditions. Cardiac biomarkers, liver function, and kidney function indexes measured within 24 h after admission were collected. The major indicators included high-sensitivity cardiac troponin I (hs-cTNI), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glutamyl transpeptidase (GGT), and serum creatinine (Scr). The enrolled patients were categorized according to the numbers of damaged organs, including the heart, liver, and kidney. One, two, three, or none of the organic injuries were listed, respectively. The cardiac injury was defined as serum levels of hs-cTNI above the 99th percentile upper limit of the reference range.[11] Patients were considered liver injury as any parameter more than the upper limit of the standard value of ALT, AST, ALP, and GGT.[12–14] Acute kidney injury was defined as an increase in serum creatinine by 0.3 mg/dl within 48 h according to the kidney disease improving global outcomes (KDIGO) criteria.[15]

2.3 | Outcome

The endpoint of this study was the incidence of survival or death in patients with COVID-19. The criterion of successful treatment and hospital discharge was comprised of clinical symptoms and signs resolved, laboratory indexes and chest radiography substantially improved, and two consecutive negative results by reverse transcription-polymerase chain reaction assay for COVID-19 at least 24 h apart.

2.4 | Statistics

The descriptive data were expressed as mean with standard deviation for continuous variables. Abnormally distributed variables were expressed as median with interquartile range (IQR). The categorical variables are expressed as numbers and proportions. All continuous variables were compared by analysis of variance (Kruskal–Wallis test) or *t*-test, and categorical variables were analyzed for the study outcome by using the $\chi 2$ test or Fisher exact test, as appropriate. Survival curves were plotted by the Kaplan–Meier method and compared between groups using the log-rank test. The risk for OI and mortality was estimated with the univariable or multivariate Cox regression models and presented as hazard ratios (HRs) with 95% confidence interval (95% CI). A $p < .05$ was considered a statistically significant difference. All statistical analyses were performed with software SPSS (version 25.0) in this study.

3 | RESULTS

3.1 | Patients characteristics on admission

Figure 1 shows a flowchart of study participants. In brief, 2569 patients were screened initially in admission records from January 17 to March 22, 2020. We excluded 840 patients that were not

confirmed, 201 patients without available or duplicated medical records, and 425 patients lacking key indexes of OI. Finally, we enrolled 1103 cases for the final analysis.

The median age of these patients was 63 years (IQR, 51–71 years). Males accounted for 48.6% of all patients. No evidence of OI was shown in 59.7% of patients, while damage of one, two, or three organs on admission was found in 30.5%, 8.1%, and 1.7% of the total, respectively. We observed a gradient of age change along with the number of injured organs, resulting in the highest median level in those with three OI (median [IQR] age, 70 (63–79), $p < .001$). The percentage of male patients with triple, double, and single OI was higher than those without OI (63.2% vs. 69.7% vs. 56.5% vs. 41.3%, respectively).

At admission, only 4 (0.4%) patients were classified as being mild COVID-19 condition, while 786 (71.3%), 174 (15.8%), and 139 (12.6%) were classified as moderate, severe, and critical, respectively. The number of OI was significantly associated with disease severity. Patients with three, two, or one organ involvement were more likely to develop a critical illness than those without OI (36.8% vs. 24.7% vs. 15.5% vs. 8.8%, $p < .001$). The severe and critical ill condition was more commonly seen in triple or double OI compared to individuals with single or no OI (42.1% vs. 22.5% vs. 13.4% vs. 15.3%, $p = .005$).

No difference was found in the clinical signs and symptoms across groups. Out of the total patients, hypertension (43.7% of patients), diabetes (13.6% of patients), and chronic heart disease (CHD; 11.8% of patients) were among the ranking prevalent comorbidities. Digestive system diseases, chronic obstructive pulmonary diseases (COPD), tumor, liver cirrhosis, hyperlipemia, and cerebrovascular diseases were relatively rare in our investigation. CHD was more common in patients with three, two, or one organ affected compared with those without OI (26.3% vs. 24.7% vs.10.6% vs. 9.8%, $p < .001$), which is similar to the trend observed in individuals with chronic kidney diseases (CKD; 26.3% vs. 22.5% vs. 8.6% vs. 3.2%, $p < .001$). The details of patient characteristics are presented in Table 1.

3.2 | Laboratory examination and radiographic findings on admission

The laboratory examination and radiologic findings are presented in Table 2. With the increasing number of OI, peripheral blood test revealed a tendency of gradual increase of the white blood cell counts, neutrophil counts, and levels of C-reactive protein (CRP),

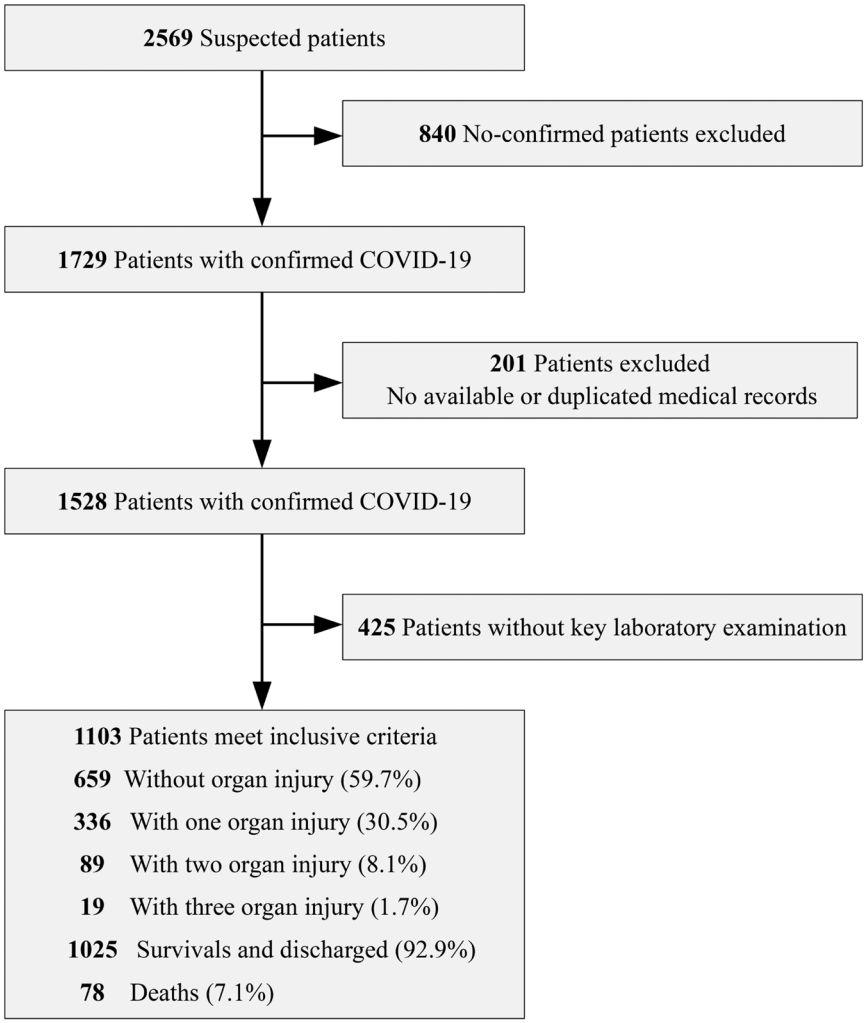


FIGURE 1 Flowchart of study participants

TABLE 1 Baseline clinical characteristics of 1103 patients with COVID-19

Characteristics	Patients, *N* (%)					
	Total (*n* = 1103)	Without OI (*n* = 659)	With one OI (*n* = 336)	With two OI (*n* = 89)	With three OI (*n* = 19)	*p*[a]
Age, median (IQR), years	63 (51–71)	62 (50–70)	63 (52–72)	66 (57–75)	70 (63–79)	<.001
Male	536 (48.6)	272 (41.3)	190 (56.5)	62 (69.7)	12 (63.2)	<.001
Clinical classification						
Mild	4 (0.4)	4 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	.541
Moderate	786 (71.3)	496 (75.3)	239 (71.1)	47 (52.8)	4 (21.1)	<.001
Severe	174 (15.8)	101 (15.3)	45 (13.4)	20 (22.5)	8 (42.1)	0.005
Critical	139 (12.6)	58 (8.8)	52 (15.5)	22 (24.7)	7 (36.8)	<.001
Smoking	360 (32.6)	171 (25.9)	142 (42.3)	40 (44.9)	7 (36.8)	<.001
Signs and symptoms at admission						
Fever	741 (67.2)	433 (65.7)	236 (70.2)	62 (69.7)	10 (52.6)	.168
Cough	709 (64.3)	406 (61.6)	229 (68.2)	62 (69.7)	12 (63.2)	.146
Fatigue	359 (32.5)	212 (32.2)	117 (34.8)	22 (24.7)	8 (42.1)	.210
Chest pain	284 (25.7)	175 (26.6)	89 (26.5)	18 (20.2)	2 (10.5)	.246
Shortness of breath	275 (24.9)	159 (24.1)	93 (27.7)	18 (20.2)	5 (26.3)	.381
Sputum production	211 (19.1)	132 (20.0)	57 (17.0)	19 (21.3)	3 (15.8)	.669
Diarrhea	93 (8.4)	56 (8.5)	24 (7.1)	12 (13.5)	1 (5.3)	.317
Sore throat	79 (7.2)	49 (7.4)	21 (6.3)	8 (9.0)	1 (5.3)	.836
Chills	75 (6.8)	50 (7.6)	19 (537)	4 (4.5)	2 (10.5)	.444
Headache	71 (6.4)	41 (6.2)	23 (6.8)	7 (7.9)	0 (0.0)	.726
Muscle ache	69 (6.3)	37 (5.6)	24 (7.1)	7 (7.9)	1 (5.3)	.624
Rhinorrhea	33 (3.0)	18 (2.7)	11 (3.3)	4 (4.5)	0 (0.0)	.678
Comorbidities						
Hypertension	482 (43.7)	294 (44.6)	141 (42.0)	41 (46.1)	6 (31.6)	.579
Diabetes	150 (13.6)	90 (13.7)	41 (12.2)	13 (14.6)	6 (31.6)	.140
CHD	130 (11.8)	70 (10.6)	33 (9.8)	22 (24.7)	5 (26.3)	<.001
Digestive system diseases	111 (10.1)	71 (10.8)	32 (9.5)	6 (6.7)	2 (10.5)	.680
Chronic kidney diseases	75 (6.8)	21 (3.2)	29 (8.6)	20 (22.5)	5 (26.3)	<.001
COPD	30 (2.7)	14 (2.1)	12 (3.6)	3 (3.4)	1 (5.3)	.283
Tumor	30 (2.7)	17 (2.6)	10 (3.0)	3 (3.4)	0 (0.0)	.866
Hyperlipemia	27 (2.4)	15 (2.3)	10 (3.0)	2 (2.2)	0 (0.0)	.869
Cerebrovascular diseases	21 (1.9)	13 (2.0)	8 (2.4)	0 (0.0)	0 (0.0)	.417
Chronic liver diseases	22 (2.0)	15 (2.3)	6 (1.8)	1 (1.1)	0 (0.0)	.892

Abbreviations: CHD, chronic heart disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; OI, organ injury.

[a]Statistical difference between groups with different number of injured organs. *P* values among groups are from the $\chi 2$ test or Fisher exact test.

lactate dehydrogenase (LDH), D-dimer, and fibrinogen (FIB) (both $p < .001$). In contrast, lymphocyte counts changed in the opposite direction ($p < .001$). Notably, our data demonstrated remarkably higher levels of hs-cTNI, creatinine kinase–myocardial band, brain natriuretic peptide, creatine kinase, ALP, total bilirubin, Scr, and blood urea nitrogen in patients with three or two OI than that in other groups. The increased level of procalcitonin (PCT) was more frequent in patients with OI versus those without ($p < .001$). Patients with three or two OI manifested more obvious abnormal coagulation function than others, including platelet, prothrombin time (PT), activated partial thromboplastin time, international normalized ratio, PT-% activity, FIB, and D-dimer (all $p < .001$).

No significant difference was found in the proportion of unilateral and bilateral pneumonia, ground-glass opacity, and pleural thickening across groups. However, patients were more likely to have pulmonary consolidation and pleural effusion if they had three or two OI as compared with other groups.

3.3 | Complications and clinical outcome

During hospitalization, the overall incidence of complications was 35.4%. The frequency of most complications showed a gradual, significant increase according to the number of organs affected,

TABLE 2 Baseline laboratory and radiographic findings of 1103 patients with COVID-19

Characteristics	Median (IQR) Total (*n* = 1103)	Without OI (*n* = 659)	With one OI (*n* = 336)	With two OI (*n* = 89)	With three OI (*n* = 19)	*p*[a]
Complete blood cell count, $\times 10^9$/L						
White blood cell	5.2 (4.1–6.8)	5.0 (4.0–6.3)	5.4 (4.1–7.0)	6.3 (4.7–9.0)	8.2 (4.8–11.6)	<.001
Neutrophil	3.36 (2.43–4.79)	3.08 (2.30–4.15)	3.66 (2.59–5.12)	4.95 (3.16–7.29)	7.13 (3.70–10.59)	<.001
Lymphocyte	1.16 (0.81–1.64)	1.26 (0.90–1.72)	1.04 (0.78–1.52)	0.81 (0.53–1.22)	0.71 (0.39–0.98)	<.001
Cardiac biomarkers						
Hs-cTNI, ng/L	2 (0–11)	0 (0–8)	4 (0–13)	79 (21–185)	257 (93–552)	<.001
CK–MB, IU/L	10 (8–14)	10 (7–13)	10 (8–16)	13 (9–19)	22 (11–32)	<.001
BNP, pg/ml	29.7 (12.2–75.8)	24.9 (11.0–50.3)	30.6 (11.9–72.1)	140.5 (47.4–780.5)	389.3 (82.5–995.9)	<.001
LDH, IU/L	203 (160–280)	182 (151–227)	240 (179–343)	288 (218–406)	483 (277–648)	<.001
CK, IU/L	72 (46–126)	67 (45–102)	80 (45–152)	118 (58–285)	148 (54–395)	<.001
Liver biomarkers						
ALT, IU/L	24 (15–37)	20 (14–27)	43 (25–63)	27 (15–46)	59 (39–89)	<.001
AST, IU/L	26 (20–37)	23 (18–29)	38 (27–56)	33 (20–51)	80 (46–142)	<.001
γ-GGT, IU/L	22 (15–40)	18 (13–26)	42 (22–71)	29 (15–67)	73 (36–111)	
ALP, IU/L	61 (50–76)	58 (49–69)	66 (52–88)	73 (58–100)	139 (62–184)	<.001
TBil, μmol/L	9.1 (6.8–12.5)	9 (6.8–11.9)	9.2 (6.9–12.8)	9.8 (6.2–15.2)	14 (9.6–19.8)	.024
Kidney biomarkers						
Scr, μmol/L	64.4 (52.1–81.5)	60.2 (50.2–72.6)	68.7 (54.2–83.5)	130.2 (92.2–781.8)	180.8 (110.8–557.5)	<.001
BUN, mmol/L	4.4 (3.4–5.8)	4 (3.3–5.1)	4.7 (3.6–6.1)	10.1 (6.4–20.4)	14.9 (11.1–27.2)	<.001
Electrolytes						
Potassium	4.00 (3.67–4.39)	4.00 (3.66–4.30)	4.00 (3.61–4.40)	4.30 (3.78–4.80)	4.50 (4.11–5.00)	<.001
Calcium	2.15 (2.06–2.25)	2.16 (2.08–2.26)	2.13 (2.04–2.23)	2.12 (1.99–2.24)	2.12 (1.95–2.29)	.002
Sodium	142 (139–144)	142 (139–145)	142 (138–144)	141.0 (136.0–144.5)	139.0 (137.0–143.0)	.001
Lactic acid	2.88 (2.36–3.49)	2.84 (2.40–3.46)	2.91 (2.34–3.50)	2.70 (2.10–3.36)	3.20 (2.00–3.71)	.378
Blood lipids						
HDL, mmol/L	0.98 (0.81–1.20)	1.04 (0.85–1.27)	0.92 (0.75–1.09)	0.92 (0.73–1.09)	0.70 (0.50–0.83)	<.001
LDL, mmol/L	2.39 (1.91–2.89)	2.41 (1.96–2.92)	2.39 (1.88–2.88)	2.17 (1.68–2.81)	2.14 (1.38–2.82)	.034
TCH, mmol/L	4.05 (3.43–4.74)	4.14 (3.52–4.82)	3.99 (3.40–4.66)	3.80 (3.02–4.63)	3.45 (2.47–4.32)	.001
TG, mmol/L	1.24 (0.95–1.71)	1.16 (0.90–1.62)	1.33 (1.02–1.77)	1.38 (1.07–1.91)	1.60 (1.24–2.16)	<.001
Inflammatory markers						
IgA, g/L	2.5 (1.9–3.3)	2.4 (1.8–3.2)	2.6 (2.0–3.4)	2.9 (2.1–3.6)	2.5 (2.1–3.3)	.022
CRP, mg/L	10.7 (1.6–48.5)	5.3 (1.0–27.4)	21.0 (3.5–75.7)	40.5 (9.8–138.9)	139.2 (32.6–200.0)	<.001
PCT, ng/mL, patients, *N* (%)						
≤0.05	782 (71.9)	557 (84.5)	206 (61.3)	17 (19.1)	2 (10.5)	<.001
>0.05	321 (29.1)	102 (15.5)	130 (38.7)	72 (80.9)	17 (89.5)	
Coagulation profiles						
PLT, $\times 10^9$/L	196 (152–253)	200 (157–253)	200 (159–262)	157 (118–228)	154 (120–201)	<.001
PT, s	11.6 (11.1–12.3)	11.6 (11.1–12.1)	11.6 (11.2–12.2)	12.2 (11.5–12.9)	13.2 (12.1–14.5)	<.001
APTT, s	29.5 (26.2–33.1)	29.0 (26.0–32.2)	29.6 (26.3–33.9)	32.5 (28.0–38.8)	34.2 (28.7–40.6)	<.001
INR	1.0 (1.0–1.1)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.1–1.1)	1.1 (1.0–1.3)	<.001
PT-% activity	96.2 (79.2–111.3)	98.3 (81.4–111.3)	95.6 (79.3–108.1)	83.6 (71.9–99.0)	70.0 (56.3–88.5)	<.001
FIB, g/L	3.66 (2.92–4.59)	3.46 (2.78–4.25)	3.98 (3.14–4.97)	4.28 (3.19–5.39)	4.57 (3.49–5.29)	<.001
D-dimer, mg/L	0.60 (0.34–1.35)	0.52 (0.31–0.99)	0.68 (0.42–1.63)	1.53 (0.57–4.27)	3.64 (0.94–6.96)	<.001
Imaging features, patients, *N* (%)						
Pneumonia						
Bilateral	1001 (90.8)	586 (88.9)	313 (93.2)	84 (94.4)	18 (94.7)	.216
Unilateral	87 (7.9)	61 (9.3)	21 (6.3)	4 (4.5)	1 (5.3)	

TABLE 2 (Continued)

Characteristics	Median (IQR) Total (*n* = 1103)	Without OI (*n* = 659)	With one OI (*n* = 336)	With two OI (*n* = 89)	With three OI (*n* = 19)	*p*[a]
Ground-glass opacity	686 (62.2)	401 (60.8)	214 (63.7)	58 (65.2)	14 (68.4)	.556
Pleural thickening	208 (18.9)	119 (18.1)	65 (19.3)	18 (20.2)	7 (36.8)	.226
Pleural effusion	119 (10.8)	41 (6.2)	41 (12.2)	29 (32.6)	10 (52.6)	<.001
Consolidation	91 (8.3)	43 (6.5)	29 (8.6)	14 (15.7)	5 (26.3)	.001

Note: SI conversion factors: to convert hs-cTNI to ng/ml, multiply by 0.001.

Abbreviations: γ-GGT, γ-glutamyl transpeptidase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CK, creatine kinase; CK–MB, creatinine kinase–myocardial band; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; FIB, fibrinogen; HDL, high-density lipoprotein; Hs-cTNI, high-sensitivity cardiac troponin I; IgA, immunoglobulin A; INR, international normalized ratio; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; PCT, procalcitonin; PLT, platelet; PT, prothrombin time; Scr, serum creatinine; TBil, total bilirubin; TCH, total cholesterol; TG, triglyceride.

[a]Statistical difference between four groups with different number of injured organs. *P* values among groups are from the $\chi 2$ test, Fisher exact test, or ANOVA (Kruskal–Wallis test).

including ARDS, electrolyte disturbance, hypoproteinemia, coagulation disorders, and multiple organ dysfunction syndromes. Eventually, 1025 patients were fully recovered and were discharged, and 78 died in the hospital with a mortality rate of 7.1%. The details of the complications and treatments are presented in Table 3.

3.4 | OI and mortality

The detailed distribution of the population and type of injured organs in different organs-injured groups are shown in Table 4. The mortality rate was elevated unceasingly with more organs affected. Patients with OI had a higher mortality rate (57.9% vs. 23.6% vs. 8.8% vs. 2.6%, $p < .001$) and risk of mortality (HR = 22.31 vs. 8.68 vs. 3.1 vs. 1, $p < .001$) compared with patients with no OI as shown in Figure 2 (for three, two, one, and no OI, respectively).

The rate and risk of mortality were of no significant difference among the different types of two OI groups (Figure 3). By contrast, in the context of single OI, patients with cardiac affection had a higher rate (29% vs. 8.51% vs. 6.2%, $p = .002$) and risk of mortality (HR = 6.01 vs. 1.35 vs. 1, $p = .001$) compared with those with only liver or kidney affected (Figure 4).

After adjusting for age, sex, comorbidities, CRP, and D-dimer in multivariable-adjusted Cox proportional hazard regression model, the number of OI as well as age and CRP appeared to be predictors of high risk for death during durations from admission to endpoint (HR = 2.03, 95% CI = 1.56–2.63; Table 5).

4 | DISCUSSION

The primary findings of this investigation were the following: (i) OI was typical in SARS-CoV-2 infection. Nearly 40.3% of the total patients had organ injuries regarding the heart, liver, and kidney. (ii) COVID-19 patients with OI were associated with poorer clinical outcomes. There was a significantly graded relationship between the number of affected organs and all-cause mortality. Our findings provided objective evidence to take into account the amount of OI in the comprehensive risk assessment of prognosis among patients with COVID-19 on admission.

Clinical studies suggested SARS-CoV-2 infection was associated with heart, kidney, and liver injury, which could serve as possible risk factors for increased disease severity.[16,17] However, in previous investigations, OI was usually evaluated in isolation. Various organs might be affected at the same time or one after the other in disease progression, which could identify a specific clinical-pathological profile and maybe an indicator of a more severe course of COVID-19. Herein, we found a progressive association between the number of injured organs and the mortality rate. COVID-19 patients with one, two, and three organs affected had 3, 8, and 22 times higher risk of mortality than those with none, respectively. This finding indicates the potential clinical utility of comprehensive evaluation of multiple OI (heart, kidney, and liver) for better characterization of those who may poorly respond to conventional therapy.

In our cohort, the overall mortality rate (7.1%) was higher than that reported in other studies,[6] but comparable to the mortality rate in a large cohort study with populations from Europe, Asia, and North America.[18] Through analyzing the potential risk factors for death, we found that older age coupled with CRP and OI served as coeffects on the risk for death. It is important to note that senior age was associated with the progression of ARDS and eventual death among COVID-19 patients.[19] Herein we identified that elderly with chronic comorbidities were more likely to develop multiple OI. However, these patients often presented atypical signs and symptoms, which often led to delayed diagnosis and treatment. Indeed, these patients are at higher risk of COVID-19, hospital admission, intensive care unit admission, and in-hospital death than young adults. Hence, attention should be paid to monitoring organ function in this subpopulation. It is reasonable to focus predominantly on those with evidence of multiorgan injury, which would provide effective triage for the treatment and management of individual patients.

TABLE 3 Complications and clinical outcome of 1103 patients with COVID-19

Characteristics	Patients, *N* (%) Total (*n* = 1103)	Without OI (*n* = 659)	With one OI (*n* = 336)	With two OI (*n* = 89)	With three OI (*n* = 19)	*p*[a]
Treatment						
Antiviral treatment	980 (88.8)	591 (89.7)	298 (88.7)	73 (82.0)	18 (94.7)	.177
Antibiotic treatment	837 (75.9)	505 (76.6)	248 (73.8)	71 (79.8)	13 (68.4)	.487
ACEI/ARB therapy	369 (33.5)	230 (34.9)	98 (29.2)	37 (41.6)	4 (21.1)	.064
β-blocker therapy	240 (21.8)	135 (20.5)	77 (22.9)	24 (27.0)	4 (21.1)	.49
Oxygen inhalation	93 (8.4)	27 (4.1)	38 (11.3)	21 (23.6)	7 (36.8)	<.001
Noninvasive ventilation	29 (2.6)	8 (1.2)	9 (2.7)	9 (10.1)	3 (15.8)	<.001
Invasive ventilation	15 (1.4)	3 (0.5)	5 (1.5)	5 (5.6)	2 (10.5)	<.001
Complications						
ARDS	105 (9.5)	29 (4.4)	44 (13.1)	23 (25.8)	9 (47.4)	<.001
Electrolyte disturbance	82 (7.4)	27 (4.1)	30 (8.9)	17 (19.1)	8 (42.1)	<.001
Hypoproteinemia	76 (6.9)	30 (4.6)	30 (8.9)	12 (13.5)	4 (21.1)	<.001
Anemia	63 (5.7)	13 (2.0)	21 (6.3)	25 (28.1)	4 (21.1)	<.001
Hyperlipemia	45 (4.1)	24 (3.6)	17 (5.1)	3 (3.4)	1 (5.3)	.588
Coagulation disorders	15 (1.4)	3 (0.5)	7 (2.1)	4 (4.5)	1 (5.3)	.002
MODS	22 (2.0)	3 (0.5)	7 (2.1)	7 (7.9)	5 (26.3)	<.001
Clinical outcome						
Discharged	1025 (93.0)	642 (97.4)	307 (91.4)	68 (76.4)	8 (42.1)	<.001
Died	78 (7.1)	17 (2.6)	29 (8.6)	21 (23.6)	11 (57.9)	

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; MODS, multiple organ dysfunction syndromes; OI, organ injury.

[a]Statistical difference between four groups with different number of injured organs. *P* values among groups are from the $\chi 2$ test or Fisher exact test.

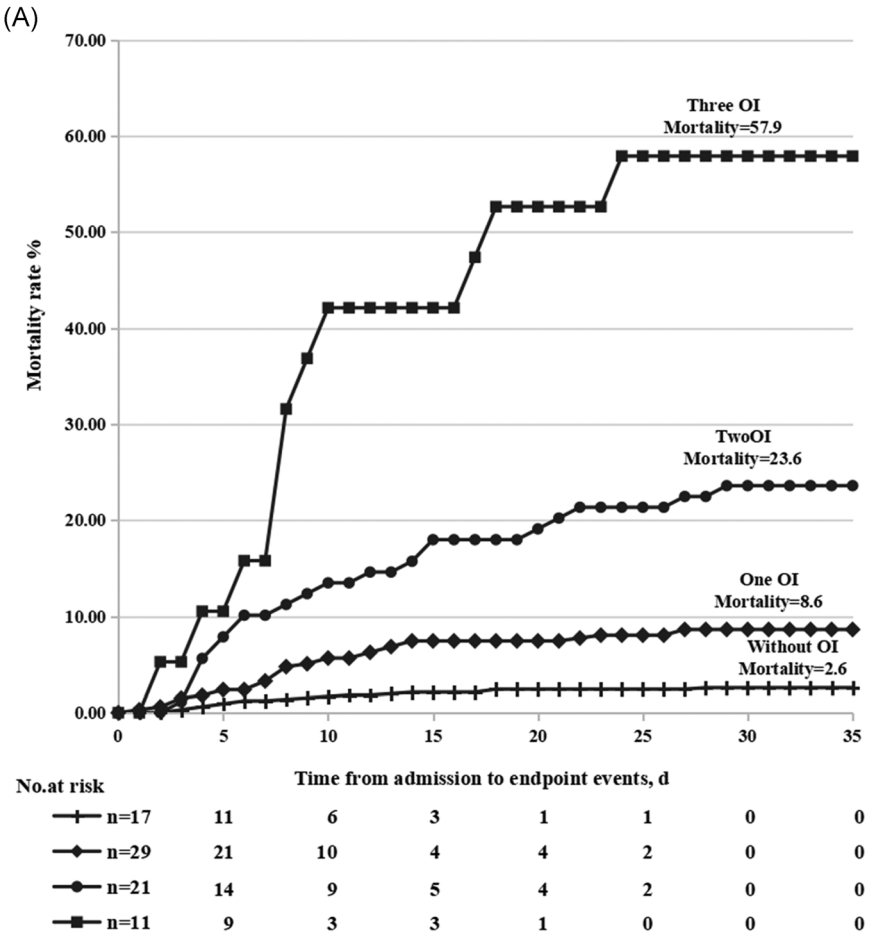
OI occurred most frequently after viral infection and during the exacerbation of COVID-19.[20] Recent clinical findings and post-mortem, biopsies indicated that the infection could potentially damage the heart, kidney, and liver. Although the underlying mechanism remains nebulous, several modes probably contribute to this action. First, SARS-CoV-2-induced cytokines or mediators may exert indirect effects on myocardial, renal, and hepatic tissues.[3,21–23] The immune-mediated damage can be evidenced by several inflammatory biomarkers significantly elevated in severe COVID-19 patients.[23] In our study, we observed a gradient in the levels of CRP, D-dimer, and PCT with the number increase of OI, leading to a high elevation of these biomarkers in patients with all three organs affected. This further reinforces the view that accumulated systematic inflammation is associated with the end-organ injury.[24] This phenomenon also has therapeutic implications, as anti-inflammatory treatments should be appropriately implemented to prevent subsequent OI with poor prognosis in patients with COVID-19.[25,26]

TABLE 4 The details of the number of patients and the type of injured organs in different organs-injured groups

Groups	Injured organs	Patients, *N* (%) Total	Died
Without OI (*n* = 659)	–	659 (59.7)	17 (2.6)
With one OI (*n* = 336)	Cardiac injury	31 (2.8)	9 (29.0)
	Liver injury	258 (23.4)	16 (6.2)
	Kidney injury	47 (4.3)	4 (8.5)
With two OI (*n* = 89)	Cardiac and liver injury	25 (2.3)	8 (32.0)
	Cardiac and kidney injury	37 (3.4)	8 (21.6)
	Kidney and liver injury	27 (2.4)	5 (18.5)
With three OI (*n* = 19)	–	19 (1.7)	11 (57.9)

Abbreviation: OI, organ injury.

Second, patients with pre-existing underlying diseases may be more susceptible to OI from SARS-CoV-2 or drugs.[27–29] The current results showed that patients with three or two OI had a higher percentage of CHD and CKD than those with one or none. This suggested a critical role of CHD and CKD in the development of multiorgan injury and eventual mortality, thus supporting the notion that chronic conditions were strongly associated with an increased risk of developing severe COVID-19.[30,31] However, no correlation was established between chronic liver diseases and OI, which was inconsistent with the earlier statement that COVID-19 patients with coinfection of hepatitis B virus, nonalcoholic fatty liver disease, and



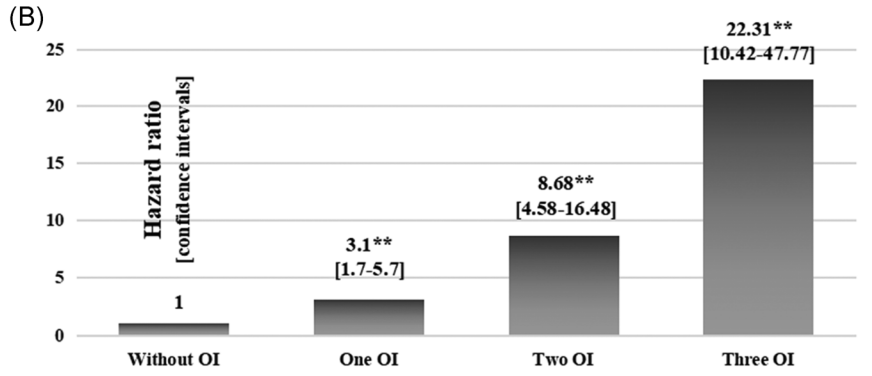


FIGURE 2 The association between the number of OI and mortality in patients with COVID-19. (A) Kaplan–Meier curves of the mortality rate of patients with COVID-19 divided according to the number of OI, $p < .001$ across groups. (B) Graded relationship between the number of injured organs and the risk of mortality using univariate Cox analysis. $^{**}p < .001$ versus patients without OI. COVID-19, coronavirus disease 2019; OI, organ injury

autoimmune hepatitis patients were more prone to develop hepatic damage with more adverse outcomes.[32] This heterogeneity may have been attributed to the small sample size in our study. Moreover, unlike the observation of spherical virus-like particles characteristic of SARS-CoV-2 in renal tubular epithelium and cardiomyocytes, no evidence of definitive viral particles was identified in the liver,[33] providing a rationale that the liver may not be the primary target of direct infection and cell destruction by SARS-CoV-2.

Patients with elevated liver or kidney enzymes on admission had considerably higher odds of progressing to severe COVID-19,[34] which was probably due to a history of using antipyretics and multiple antiviral drugs in a subset of patients.[35] In particular, when it came to the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACEI/ARB), no difference was established between individuals with and without OI. This finding suggests that the use of ACEI/ARB would not trigger or aggravate OI during SARS-CoV-2 infection, which complies with the current guidelines and societal recommendations for treating COVID-19.[36] However, given that taking ACEI/ARB exerts a favorable effect on renal or cardiac injury in non-COVID-19 patients,[37] in-depth studies for the comprehensive evaluation of ACEI/ARB on OI are warranted.

Overall, individuals with numerous organ injuries were thought to be the consequence of complex interplay among the direct cytotoxicity induced by viral replication, an indirect insult from the

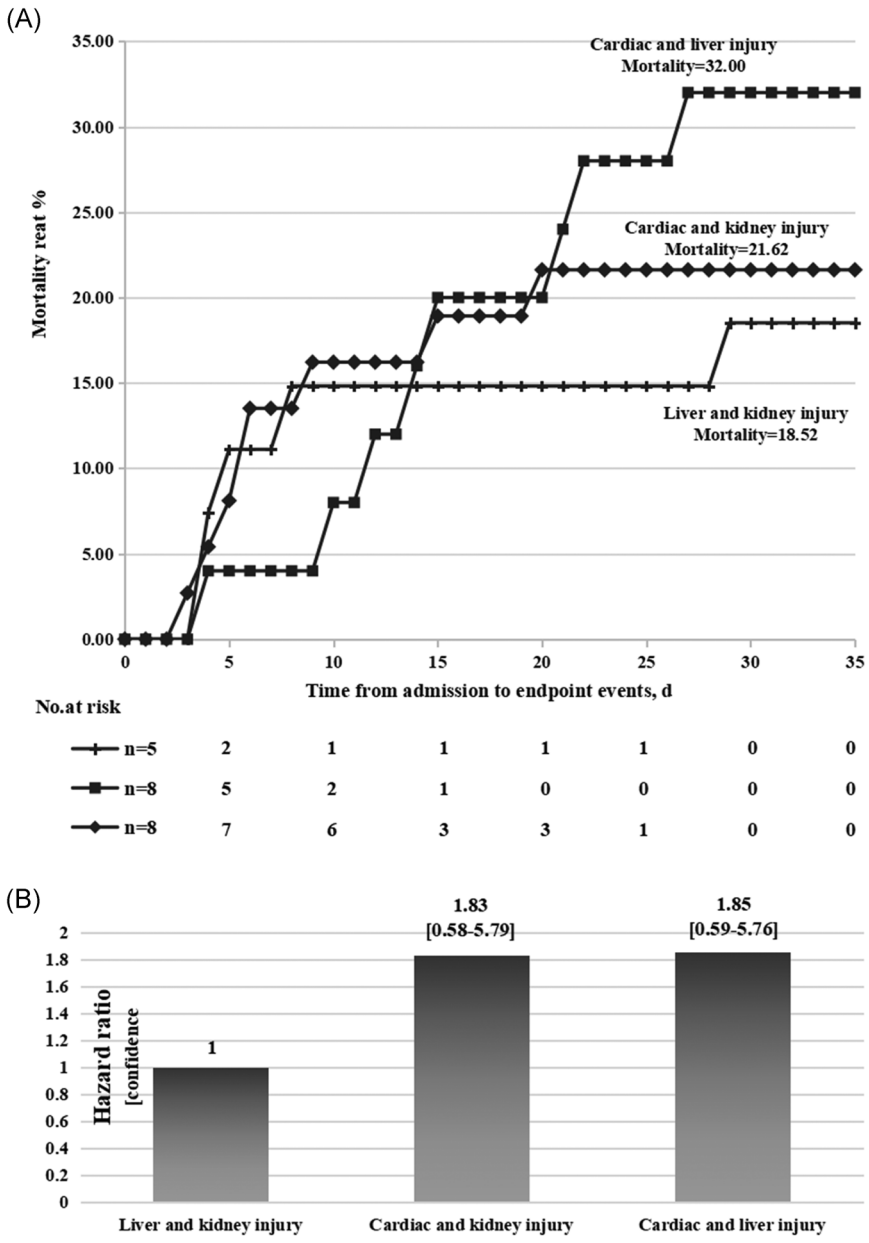


FIGURE 3 The association between the coexistence of two OI and mortality in patients with COVID-19. (A) Kaplan–Meier curves of the mortality rate of patients divided according to different types of two OI, $p = .514$ across groups. (B) Graded relationship between the different types of two OI and risk of mortality using univariate Cox analysis, both $p > .05$ versus patients with liver and kidney injury. COVID-19, coronavirus disease 2019; OI, organ injury

systemic cytokines or mediators, drug-induced injuries, and vulnerability of organs with chronic conditions, or a combination of all the above. The presence and increasing number of OI, mainly two or three OI, substantially reflected the extreme danger of poor outcomes in COVID-19 patients. Interestingly, the single cardiac injury had a higher mortality risk than those with only kidney or liver implicated. This may be due to an increased risk of myocardial infarction, heart failure, and arrhythmia caused by the virus.[38] Furthermore, cardiac injury may bring a great challenge to the cardiopulmonary function, aggravating congestion, and hypoperfusion of vital organs, thus seriously affecting the prognosis of patients.[16,17] However, the risk of mortality was comparable between different types of two OI groups, demonstrating that the number, instead of the type of affected organs, would be a better prognostic indicator in patients with combined OI. Because individuals, especially those with >1 OI, were at a very high risk of mortality, early diagnosis, and management for these subpopulations would be of great importance in the clinic.

The predictive function of OI in this study is different from existing risk prediction systems, such as the Acute Physiology And Chronic Health Evaluation-III and Sequential Organ Failure Assessment scores, which principally aim at critically ill patients hospitalized in ICU and not accounting for several commonly accepted risk factors (e.g., cardiac injury).[39] As is known, the applicability of any prognostic model tends to reduce following its development when encountering global public health emergencies, changes in medical practice and adjustments in the provision of health care, and even case-mix over time.[39,40] Our method, based on the number of OI defined by laboratory indices that are readily available, estimated patient outcomes in an effective and agile

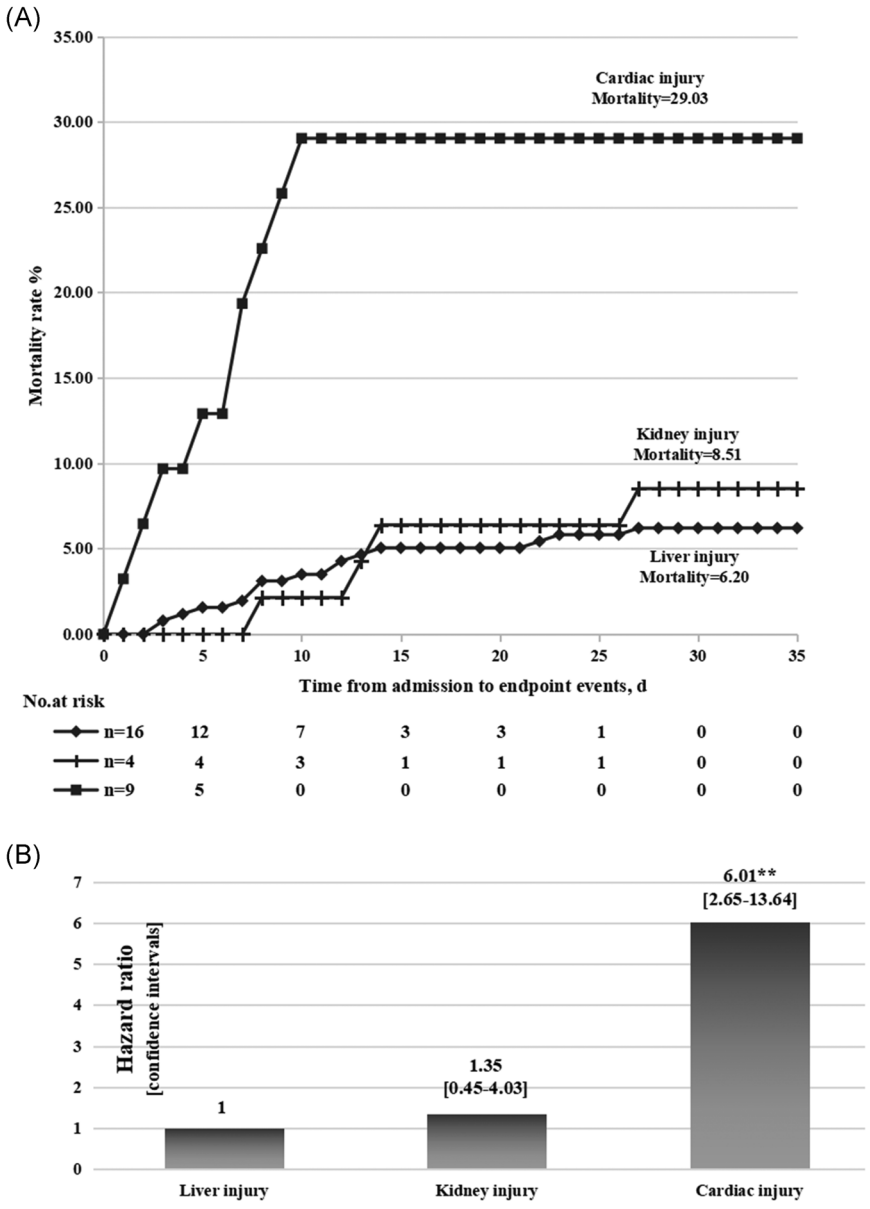


FIGURE 4 The association between single OI and mortality in patients with COVID-19. (A) Kaplan–Meier curves of the mortality rate of patients with COVID-19 divided according to the type of single OI, $p = .001$ across groups. (B) Graded relationship between single OI and risk of mortality using univariate Cox analysis. $^{**}p < .001$ versus patients without liver injury. COVID-19, coronavirus disease 2019; OI, organ injury

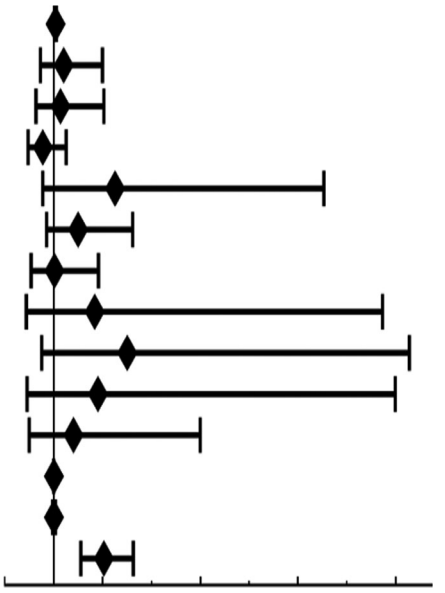
manner. This may be an essential and prescient step toward improving prognosis because it helps clinicians to identify entirely different individuals without apparent abnormalities in vital signs and life-sustaining treatments at the early stage of disease progression, instead of during the period of deterioration.

Some limitations should be addressed in our study. First, the primary target of SARS-CoV-2 is the lungs. We focused on cardiac, liver, and renal injury using arbitrary definitions, mainly due to the lack of well-validated biomarkers to quantify the damage of the lungs and other organs, and we applied a generally accepted algorithm used in previous studies about COVID-19. However, some comorbidities may be present in chronically ill patients leading to minor elevation of AST or ALT, falsely increasing the prevalence of those with liver dysfunction, which may possibly lead to an overestimation of the number of the OI patient to some extent. Second, given it was a single-center and retrospective observational study with small sample size, subject selection bias could not be avoided, and the nature of this study might compromise the conclusion. The results might not represent the overall features of the general population with COVID-19. Therefore, further multicentered and retrospective studies are needed to verify the validity of this conclusion in the future. Third, dynamic changes in serum biomarkers, which reflected organ damage during the hospital stay, had not been systematically analyzed. Hence, our data should be viewed only in the context of the presence of OI at admission. Large-scale cohort studies should be prospectively validated for a thorough evaluation of multiple affected organs as a reliable prognosticator.

In conclusion, we first demonstrated a graded relationship between the number of OI and mortality in SARS-CoV-2 infection. Clinicians must assess OI as a whole rather than in isolation in hospitalized COVID-19 patients.

TABLE 5 Multivariate Cox regression analysis on the risk factors associated with mortality in patients with COVID-19

Factors	HR	95% CI		*p*	Hazard ratio[a]
		Lower limit	Upper limit		
Age, years	1.04	1.02	1.06	<.001	
Male	1.21	0.73	2.00	.461	
Diabetes	1.14	0.64	2.03	.669	
Hypertension	0.78	0.48	1.26	.309	
COPD	2.26	0.78	6.53	.134	
CHD	1.50	0.86	2.62	.153	
CKD	1.02	0.54	1.92	.946	
CLD	1.84	0.44	7.73	.408	
CVD	2.51	0.76	8.28	.131	
Hyperlipemia	1.91	0.46	7.99	.375	
Tumor	1.41	0.50	4.00	.518	
CRP	1.01	1.00	1.01	<.001	
D-dimer	1.01	0.98	1.04	.537	
No. of injured organs, 0/1/2/3	2.03	1.56	2.63	<.001	



Abbreviations: CHD, chronic heart diseases; CI, confidence interval; CKD, chronic kidney diseases; CLD, chronic liver diseases; COPD, chronic obstructive pulmonary diseases; COVID-19, coronavirus disease 2019; CVD, cerebrovascular diseases; CRP, C-reactive protein; HR, hazard ratio.
[a]*Y* intersects the *X*-axis at *X* = 1, and the interval between the two points at *X*-axis is 2.5.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Jie Yan, Xisheng Yan, and Dongsheng Li designed the study and take responsibility for the integrity of the data and the accuracy of the data analysis. He Yan, Shanshan Lu, Liangpei Chen, and Yufang Wang contributed to patient recruitment, data collection, data analysis, data interpretation, literature searches, and writing of the manuscript. Shanshan Lu, Jie Yan, and Qiaomei Liu had roles in patient management, data collection, data analysis, and data interpretation. All authors reviewed and approved the final version of the manuscript. He Yan, Shanshan Lu, and Liangpei Chen are co-first authors, the order in which they were listed was determined by workload.

ETHICS APPROVAL

This study was performed according to the Declaration of Helsinki principles. The protocol was approved by the National Health Commission of China and the Research Ethics Commission of Wuhan Third Hospital & Tongren Hospital of Wuhan University (KY2020-047). Written informed consent was exempted owing to the rapid emergence of this infectious disease.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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