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# Sleep Medicine

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# Original Article

# Symptomless multi-variable apnea prediction index assesses adverse outcomes in patients with Corona Virus Disease 2019



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### ABSTRACT

*Purpose*: To explore the relationship between symptomless multi-Variable apnea prediction (sMVAP) index and adverse outcomes of patients with Corona Virus Disease 2019 (COVID-19).

Methods: According to the sMVAP quartiles, we divided all patients into four groups. The clinical electronic medical records, nursing records, laboratory findings, and radiological examinations for all patients with laboratory confirmed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection were reviewed. Cox proportional hazard ratio (HR) models were used to determine the risk factors associated with in hospital death.

Results: A total of 97 patients were included in this study. The "Quartile 4" group 's ICU transfer rate was significantly higher than the "Quartile 1" group. Coronary heart disease, high d-dimer and sMVAP at admission were associated with increased odds of death.

Conclusions: Using the sMVAP index for obstructive sleep apnea hypopnea syndrome (OSAHS) risk assessment, and then predicting the adverse outcomes of COVID-19 patients, is an effective method. Therefore, the use of sMVAP index for OSAHS screening for inpatients with COVID-19 should be vigorously promoted, and high-risk patients should be effectively managed.

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# 1. Introduction

The outbreak of COVID-19 has lasted for more than half a year and has been steadily spreading at the global level, World Health Organization (WHO) had called it pandemic. During the epidemic, due to cross-infection issues, PSG has not been widely used in patients with COVID-19, which makes the impact of OSAHS on patients with COVID-19 unknown. At the same time, due to the lack of sufficient attention to OSAHS, many patients were not collected for OSAHS-related clinical manifestations such as neck circumference, snoring, and daytime sleepiness, Therefore, it is difficult to use the

# 2. Methods

# 2.1. Study design and participants

This single-center, retrospective, observational study was done at Wuhan Union Hospital (Wuhan, China). We retrospectively analyzed patients from Jan 29, 2020, to Mar 23, 2020, who had been diagnosed with COVID-19, according to WHO interim guidance [4]. Laboratory confirmation of SARS-CoV-2 infection was performed by the local health authority.

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STOP-Bang questionnaire [1] and NoSAS questionnaire [2] to perform OSAHS screening for COVID-19 patients. The sMVAP index has proved to be an effective tool for screening OSAHS [3], including only parameters such as gender, age and body mass index (BMI). This study explored the relationship between sMVAP index and adverse outcomes of patients with COVID-19, trying to reveal the effect of OSAHS on COVID-19.

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The Ethics Commission of the First Affiliated Hospital of Guangzhou Medical University approved this study (IRB:202051). Written informed consent was waived due to the rapid emergence of this infectious disease.

### 2.2. Data collection

We reviewed clinical electronic medical records, nursing records, laboratory findings, and radiological examinations for all patients with laboratory confirmed SARS-CoV-2 infection. The admission data of these patients were collected.

### 2.3. Outcomes

The primary outcome was the mortality from hospital admission to the cut off date. The cut-off date was set to the date of the last patient's outcome (death or discharge from hospital). In this study, the cut-off date was May, 2, 2020. Secondary outcome was the rate of any stay in ICU. Sepsis and septic shock were defined according to the 2016 Third International Consensus Definition for Sepsis and Septic Shock [5]. Secondary infection was diagnosed when patients showed clinical symptoms or signs of pneumonia or bacteremia and a positive culture of a new pathogen was obtained from lower respiratory tract specimens (qualified sputum, endotracheal aspirate, or bronchoalveolar lavage fluid) or blood samples after admission [5]. Acute kidney injury was diagnosed according to the KDIGO clinical practice guidelines [6] and acute respiratory distress syndrome (ARDS) was diagnosed according to the Berlin Definition [7]. The illness severity of COVID-19 was defined according to the Chinese management guideline for COVID-19 (version 7.0) [8].

# 2.4. Statistical analysis

The purpose of this study is to explore the relationship between sMVAP and adverse outcomes in patients with COVID-19. There were, therefore, no formal hypotheses being implemented to drive the sample size calculation and we included the maximum number of patients who met the inclusion criteria.

The sMVAP index is calculated as:  $sMVAP = e^X/(1 + e^X)$ , where "e" is natural constant (Its value is about 2.718281828459) and  $X = -10.784 + 0.203 \times (BMI) + 0.043 \times (Age) + 1.004 \times (Gender:$ 0 = female, 1 = male) [3]. The sMVAP ranges from 0 to 1, with higher values indicating higher OSAHS risk. To provide clinicallyrelevant interpretations, we based analyses on sMVAP quartiles (patients were divided into four groups). We expressed descriptive data as mean (SD) or median (IQR) for continuous variables and number (%) for categorical variables. We assessed differences between different groups using one-way ANOVA or kruskal-wallis H test depending on parametric or nonparametric data for continuous variables and Fisher's exact test for categorical variables. Cox proportional HR models were used to determine HRs and 95% CIs between individual factors on mortality. Previous studies have shown blood levels of d-dimer and history of coronary heart disease associated with adverse clinical outcomes in patients with COVID-19 [17,18]. Some laboratory findings, including alanine aminotransferase (ALT), lactate dehydrogenase, high-sensitivity cardiac troponin I, and d-dimer, might be unavailable in emergency circumstances. Therefore, we chose d-dimer, coronary heart disease, and sMVAP index as the three variables for our multivariable Cox proportional HR models. Survival curves were developed using the Kaplan-Meier method with log-rank test. Time to events (death) were defined as the time from hospital admission to events. Since the P value of the log-rank test between the four groups was >0.05, we only performed survival analysis on the "Quartile 1" and "Quartile 4" group.

Tests were two-sided with significance set at  $\alpha$  less than 0.05. The SPSS 24.0 software (IBM SPSS) was applied for all analyses.

#### 3. Results

A total of 97 patients were included in this study (Fig. 1). The average age of all patients was 58 years (IQR 42.5–67.0), with 78.7% males (Table 1), 36.1% of patients had hypertension, while 15.5% of patients had Diabetes. 77.3% of patients had bilateral infiltrates on chest x-ray. The most common symptoms were cough (72.2%), fatigue (42.3%) and fatigue (23.7%). About four-fifths of patients (78.4%) were general disease status on admission, whereas 17.5% of patients should transfer to Intensive care unit (ICU) and required invasive mechanical ventilation, 58 (59.8%) patients received antibiotics and 84 (86.6%) received antivirals (Table 2), 73 (75.3%) patients were treated with high-flow nasal cannula, three (3.1%) with extracorporeal membrane oxygenation (ECMO), eight (8.2%) patients were treated with continuous renal replacement therapy (CRRT). The proportion of patients in the "Quartile 4" group using invasive mechanical ventilation was significantly higher than that in the "Quartile 1" group. There was no significant difference in the proportion of non-invasive mechanical ventilation (NIMV) between groups.

There were 82 patients (84.5%) discharged before the cut-off date. Although the mortality of the "Quartile 4" group is almost eight times that of the "Quartile 1" group, there was no significant difference in mortality between groups. The "Quartile 4" group 's ICU transfer rate was significantly higher than the "Quartile 1" group. The median time of hospital length of stay was 22 days (IQR 15–34.5) and there was no significant difference in that between groups. The most common complications was secondary infection (10.3%), acute kidney failure (8.2%) and respiratory failure (8.2%) (Table 2).

In univariable analysis, odds of in-hospital death was higher in "Quartile 4" group (Table 3). Old age, male sex, coronary heart disease, lactate dehydrogenase, high-sensitive cardiac troponin I, prothrombin time and d-dimer were also associated with death (Table 3). In the multivariable Cox proportional HR models, we found that coronary heart disease, high d-dimer and sMVAP at admission were associated with increased odds of death (Table 3). For the primary outcome, among 97 patients with SARS-CoV-2 infection, 15 (15.5%) patients had died before the cut-off date, and the mean duration from hospital admission to death was 67.8 days (IQR 54.7–81.0) in "Quartile 4" group (Fig. 2).

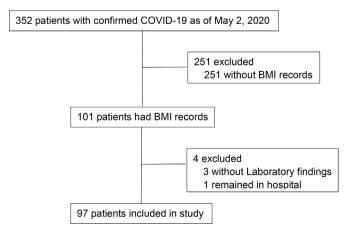


Fig. 1. Study flow diagram.

Table 1 Demographic, clinical, laboratory, and radiographic findings of patients on admission.

	Overall $(n = 97)$	sMVAP quartile					
		Quartile 1 (n = 24)	Quartile 2 (n = 25)	Quartile 3 (n = 26)	Quartile 4 (n = 22)	P value	
Demographics and clinic	al characteristics						
Age, years	58.0 (42.5–67.0)	40.0 (30.0-50.5)	57.4 (13.9) <sup>a</sup>	61.3 (12.5) <sup>b</sup>	62.8 (14.2) <sup>c</sup>	< 0.001	
Sex	` ,	,	. ,	` '	` ,		
Male	43 (44.3%)	1 (4.2%)	7 (28%)	17 (65.4%) <sup>b,d</sup>	18 (81.8%) <sup>c,e</sup>		
Female	54 (55.7%)	23 (95.8%)	18 (72%)	9 (34.6%)	4 (18.2%)	< 0.001	
BMI, kg/m <sup>2</sup>	24.1 (3.5)	22.3 (2.6)	23.1 (3.2)	24.2 (2.9)	26.9 (3.7) <sup>c,e,f</sup>	< 0.001	
sMVAP	0.05 (0.03-0.09)	0.01 (0.01)	0.03 (0.01) <sup>a</sup>	0.07 (0.06–0.08) <sup>b,d</sup>	0.12 (0.11–0.18) <sup>c,e,f</sup>	< 0.001	
Chronic medical illness	0.05 (0.05 0.05)	0.01 (0.01)	0.05 (0.01)	0.07 (0.00 0.00)	0.12 (0.11 0.10)	10.001	
Hypertension	35 (36.1%)	4 (16.7%)	7 (28%)	15 (57.7%) <sup>b</sup>	9 (40.9%)	0.018	
Coronary heart	7 (7.2%)	3 (12.5%)	2 (8%)	2 (7.7%)	0	0.478	
disease	7 (7.270)	3 (12.5%)	2 (8/8)	2 (7.775)	· ·	0.170	
Cerebrovascular	2 (2.1%)	1 (4.2%)	0	0	1 (4.5%)	0.357	
disease	2 (2.1%)	1 (1.270)	0	· ·	1 (1.5%)	0.557	
Diabetes	15 (15.5%)	1 (4.2%)	4 (16%)	5 (19.2%)	5 (22.7%)	0.289	
Chronic obstructive	2 (2.1%)	1 (4.2%)	1 (4%)	0	0	0.726	
	2 (2.1%)	1 (4.2%)	1 (4%)	U	U	0.720	
lung disease	2 (2 1%)	0	2 (8%)	0	1 (4 59/)	0.201	
Chronic liver disease	3 (3.1%)	0	2 (8%)	0	1 (4.5%)	0.261	
Carcinoma	6 (6.2%)	1 (4.2%)	2 (8%)	2 (7.7%)	1 (4.5%)	1	
Current smoker	9 (9.3%)	0	2 (8%)	3 (11.5%)	4 (18.2%)	0.175	
Respiratory rate >24	17 (17.5%)	2 (8.3%)	5 (20%)	7 (26.9%)	3 (13.6%)	0.357	
breaths per min							
Pulse ≥125 beats per	2 (2.1%)	0	1 (4%)	0	1 (4.5%)	0.475	
min							
Fever (temperature	17 (17.5%)	2 (8.3%)	4 (16%)	6 (23.1%)	5 (22.7%)	0.489	
≥37.3 °C)							
Cough	70 (72.2%)	11 (45.8%)	20 (80%)	21 (80.8%)	18 (81.8%)	0.012	
Sputum	29 (29.9%)	4 (16.7%)	9 (36%)	9 (34.6%)	7 (31.8%)	0.430	
Myalgia	17 (17.5%)	2 (8.3%)	4 (16%)	6 (23.1%)	5 (22.7%)	0.489	
Fatigue	41 (42.3%)	9 (37.5%)	12 (48%)	10 (38.5%)	10 (45.5%)	0.848	
Nausea or vomiting	10 (10.3%)	4 (16.7%)	2 (8%)	2 (7.7%)	2 (9.1%)	0.772	
Pharyngalgia	4 (4.1%)	2 (8.3%)	2 (8%)	0	0	0.274	
Headache	3 (3.1%)	0	1 (4%)	2 (7.7%)	0	0.615	
Dyspnea	23 (23.7%)	2 (8.3%)	7 (28%)	7 (26.9%)	7 (31.8%)	0.227	
Nasal discharge	3 (3.1%)	1 (4.2%)	2 (8%)	0	0	0.454	
General malaise	9 (9.3%)	1 (4.2%)	2 (8%)	2 (7.7%)	4 (18.2%)	0.453	
Disease severity status	9 (9.3%)	1 (4.2%)	2 (8%)	2 (7.7%)	4 (18.2%)	0.433	
Mild	1 (19/)	1 (4 3%)	0	0	0	0.474	
	1 (1%)	1 (4.2%)					
General	76 (78.4%)	21 (87.5%)	20 (80%)	22 (84.6%)	13 (59.1%)	0.113	
Severe	3 (3.1%)	1 (4.2%)	1 (4%)	1 (3.8%)	0	1	
Critical	17 (17.5%)	1 (4.2%)	4 (16%)	3 (11.5%)	9 (40.9%) <sup>c</sup>	0.012	
Laboratory findings							
White blood cell	6.0 (4.5-7.8)	6.4 (4.0-7.9)	5.8 (4.0-7.2)	5.8 (4.7–7.9)	5.9 (4.9–9.5)	0.700	
count, × 10° per L							
Lymphocyte	1.3 (0.8–1.8)	1.3 (0.6)	1.5 (0.9–2.2)	1.2 (0.6)	1.2 (0.5)	0.497	
count, × 10° per L							
Hemoglobin, g/dL	126 (114-135)	118.5 (105.0-127.5)	123.8 (15.9)	132.5 (12.1) <sup>b</sup>	125.5 (24.5)	0.006	
Platelet count, × 10° per	199.0 (158.5-257.5)	209.0 (174.3-269.3)	194.2 (88.5)	204.0 (157.3-251.5)	193.5 (145.0-334.5)	0.606	
L							
Albumin, g/L	33.3 (7.0)	34.3 (8.8)	35.3 (7.2)	32.3 (5.3)	31.3 (5.9)	0.181	
ALT, U/L	30.0 (20.0-48.5)	24.5 (13.0-31.5)	34.1 (17.5)	35 (23-56)	31.0 (23.0-49.3)	0.071	
Lactate dehydrogenase,	204.0 (163.5-356.0)	185.5 (140.8-243.3)	208.8 (156.5-380.0)	200.5 (169.8-371.8)	259.5 (195.8–433.3) <sup>c</sup>	0.023	
U/L	,	,	,	,	,		
Creatinine, µmol/l	60.6 (51.9-77.8)	49.9 (42.3-56.6)	57.3 (52.9-73.9) <sup>a</sup>	71.0 (16.1) <sup>b</sup>	76.9 (22.9) <sup>c</sup>	< 0.001	
CRP, mg/L	5.7 (1.0–39.5)	3.8 (0.7–19.2)	16.3 (2.9–42.7)	4.1 (0.5–36.6)	16.3 (2.8–87.7)	0.166	
High-sensitive cardiac	3.2 (1.7–21.7)	1.8 (0.6–7.0)	1.8 (0.6–26.0)	7.7 (2.3–18.0)	11.7 (2.8–35.3)	0.031	
troponin I, ng/mL	3.2 (1.1 21.1)	1.0 (0.0 7.0)	1.0 (0.0 20.0)	1.1 (2.3 10.0)	11.7 (2.0 '33.3)	0.031	
Prothrombin time, s	12.9 (12.2-13.8)	127 (121_122)	13 1 (12 3_13 5)	13 1 (12 2-14 2)	13.0 (12.0-13.9)	0.410	
	12.3 (12.2-13.0)	12.7 (12.1–13.2)	13.1 (12.3–13.5)	13.1 (12.2–14.2)	13.0 (12.0-13.9)	0.410	
D-dimer, μg/L	40 (50 5%)	15 (62 5%)	12 (52%)	12 (50%)	0 (20 49/)		
≤0.5	49 (50.5%)	15 (62.5%)	13 (52%)	13 (50%)	8 (36.4%)	0.0.0=	
>0.5	48 (49.5%)	9 (37.5%)	12 (48%)	13 (50%)	14 (63.6%)	0.367	
Procalcitonin, ng/mL	0.1 (0-0.2)	0.1 (0-0.1)	0.1 (0-0.2)	0.1 (0.1–0.1)	0.1 (0.1–0.2)	0.438	
BNP, pg/mL	49.6 (23.8–113.1)	33.8 (21.3–180.0)	69.5 (56.6)	49.6 (13.1–120.0)	64.9 (42.7–118.1)	0.831	
Imaging features							
Bilateral pulmonary	75 (77.3%)	16 (66.7%)	23 (92%)	18 (69.2%)	18 (81.8%)	0.108	
infiltration							

Data are mean (SD), median (IQR) or n (%). BMI, body mass index; sMVAP, symptomless multi-variable apnea prediction; ALT, alanine aminotransferase; CRP, c-reactive protein; BNP, brain natriuretic peptide.

orden; BNP, brain natriuretic peptide.

a Compared with the "Quartile 2" group, P value of the "Quartile 1" was  $\le 0.05$ .

b Compared with the "Quartile 3" group, P value of the "Quartile 1" was  $\le 0.05$ .

c Compared with the "Quartile 4" group, P value of the "Quartile 1" was  $\le 0.05$ .

d Compared with the "Quartile 2" group, P value of the "Quartile 3" was  $\le 0.05$ .

e Compared with the "Quartile 2" group, P value of the "Quartile 4" was  $\le 0.05$ .

f Compared with the "Quartile 3" group, P value of the "Quartile 4" was  $\le 0.05$ .

Table 2
Treatments and outcomes

	Overall (n = 97)	sMVAP quartile				
		Quartile 1 (n = 24)	Quartile 2 (n = 25)	Quartile 3 (n = 26)	Quartile 4 (n = 22)	
Treatments						
Antibiotics	58 (59.8%)	18 (75%)	14 (56%)	14 (53.8%)	12 (54.5%)	0.378
Antiviral treatment	84 (86.6%)	17 (70.8%)	21 (84%)	26 (100%) <sup>b</sup>	20 (90.9%)	0.013
Corticosteroids	36 (37.1%)	5 (20.8%)	7 (28%)	11 (42.3%)	13 (59.1%) <sup>c</sup>	0.037
Intravenous immunoglobin	22 (22.7%)	4 (16.7%)	5 (20%)	6 (23.1%)	7 (31.8%)	0.684
High-flow nasal	73 (75.3%)	14 (58.3%)	23 (92%) <sup>a</sup>	21 (80.8%)	15 (68.2%)	0.037
cannula oxygen						
therapy						
Invasive	17 (17.5%)	1 (4.2%)	4 (16%)	3 (11.5%)	9 (40.9%) <sup>c</sup>	0.012
mechanical ventilation	, ,	, ,	, ,	, ,	,	
Non-invasive	9 (9.3%)	0	3 (12%)	2 (7.7%)	4 (18.2%)	0.167
mechanical	` ,		, ,	` ,	, ,	
ventilation						
ECMO	3 (3.1%)	0	1 (4%)	0	2 (9.1%)	0.134
CRRT	8 (8.2%)	0	2 (8%)	1 (3.8%)	5 (22.7%)	0.032
Prognosis	,		( )	(/		
Discharge from hospital	82 (84.5%)	23 (95.8)	21 (84%)	23 (88.5%)	15 (68.2%)	0.084
Death	15 (15.5%)	1 (4.2%)	4 (16%)	3 (11.5%)	7 (31.8%)	0.084
Outcome						
Any stay in ICU	17 (17.5%)	1 (4.2%)	4 (16%)	3 (11.5%)	9 (40.9%) <sup>c</sup>	0.012
Hospital length of	22.0 (15.0-34.5)	24.7 (10.3)	16 (12-30)	25.7 (11.8)	28.2 (12.4)	0.132
stay, days	,	` ,	, ,	` ,	` ,	
Complications						
Septic shock	4 (4.1%)	0	0	0	4 (18.2%)	0.002
Secondary infection	10 (10.3%)	0	3 (12%)	0	7 (31.8%) <sup>c</sup>	< 0.001
Acute kidney	8 (8.2%)	0	3 (12%)	1 (3.8%)	4 (18.2%)	0.091
failure	` ,		, ,	` ,	, ,	
DIC	2 (2.1%)	0	1 (4%)	0	1 (4.5%)	0.475
pneumothorax	1 (1%)	0	0 `	0	1 (4.5%)	0.227
Stress ulcer	2 (2.1%)	1 (4.2%)	1 (4%)	0	0	0.726
ARDS	4 (4.1%)	0	1 (4%)	1 (3.8%)	2 (9.1%)	0.453
Respiratory failure	8 (8.2%)	0	3 (12%)	2 (7.7%)	3 (13.6%)	0.299
Heart failure	1 (1%)	0	0	0	1 (4.5%)	0.227
Sepsis	1 (1%)	0	0	0	1 (4.5%)	0.227
Acidosis	2 (2.1%)	0	0	0	2 (9.1%)	0.050
Viral myocarditis	3 (3.1%)	0	1 (4%)	2 (7.7%)	0	0.615
Hypoproteinemia	2 (2.1%)	0	1 (4%)	1 (3.8%)	0	1
Coagulopathy	1 (1%)	1 (4.2%)	0	0	0	0.474

Data are mean (SD), median (IQR) or n (%). sMVAP, symptomless multi-variable apnea prediction. ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; ICU, intensive care unit; DIC, disseminated intravascular coagulation; ARDS, acute respiratory distress syndrome.

# 4. Discussion

This retrospective cohort study identified the relationship between OSAHS risk and the mortality and ICU transfer rate in patients in Wuhan who were hospitalised with COVID-19. In particular, coronary heart disease, d-dimer levels greater than  $0.5~\mu g/L$ , and higher sMVAP on admission were associated with higher odds of in-hospital death. Additionally, elevated ICU transfer rate and the incidence of complications were more commonly seen in higher sMVAP patients. To our knowledge, this is the first study to explore the association between sMVAP index and COVID-19.

During the COVID-19 pandemic, considering that SARS-CoV-2 was highly contagious, sleep monitoring for inpatients was inconvenient to carry out. A multi-center study from Europe pointed out that the number of polysomnography in Lab fell by more than 70% during the pandemic [9]. The Canadian Chest Association also recommends that patients should not be tested for sleep disordered breathing during the pandemic unless a clinician determines that a case is "extremely urgent" [10]. At the same time, despite the lack of

clinical trials, based on the pathophysiology of OSAHS, some scholars believe that OSAHS could lead to increased risk of COVID-19 infection and severity [11-13]. We have noticed that there are two small sample studies showing that 21%-28.6% of critically ill COVID-19 patients were accompanied by OSAHS on admission [14,15]. Although the above studies did not analyze the impact of OSAHS on the prognosis of critically ill COVID-19 patients, one of the studies pointed out that patients with coexisting conditions were at risk for severe disease and poor outcomes after ICU admission [14], which indirectly reflects the negative impact of OSAHS on the progress of COVID-19. At this time, it is particularly important to choose a simple and accurate OSAHS screening tool, such as STOP-Bang questionnaire and NoSAS questionnaire. However, in the early stage of the epidemic in Wuhan, in the face of a large number of patients, medical staff may have no time to pay attention to the patients' OSAHS history, such as snoring and sleepiness, and they also have no time to measure patients' neck and abdominal circumference. Therefore, we cannot use the above questionnaires to assess patients' OSAHS risk.

<sup>&</sup>lt;sup>a</sup> Compared with the "Quartile 2" group, P value of the "Quartile 1" was ≤0,05.

<sup>&</sup>lt;sup>b</sup> Compared with the "Quartile 3" group, P value of the "Quartile 1" was  $\leq$ 0,05.

 $<sup>^{\</sup>rm c}$  Compared with the "Quartile 4" group, P value of the "Quartile 1" was  $\leq\!0,\!05.$ 

**Table 3**Risk factors associated with in-hospital death.

	Univariable HR (95% CI)	p value	Multivariable HR (95% CI)	P value
Demographics and clinical chara	acteristics			,
Age, years				
<65	1 (ref)	_	_	_
≥65	3.35 (1.19-9.43)	0.022	_	_
Male sex (vs	5.62 (1.59–19.93)	0.008	_	_
female)	, , ,			
BMI, kg/m <sup>2</sup>				
<28	1 (ref)		_	_
≥28	0.80 (0.18–3.52)	0.762	_	_
Current smoker (vs	3.20 (0.88–11.64)	0.078	_	_
nonsmoker)	3.20 (0.00 1.101)	0.070		
Comorbidity	1.39 (0.49-3.90)	0.534	_	_
present (vs not	1.55 (0.15 5.50)	0.55 1		
present)				
Chronic	5.09 (0.67-38.91)	0.117	_	_
obstructive	3.03 (0.07-36.31)	0.117		
pulmonary				
disease	2.57 (1.01, 12.00)	0.040	15 40 (2.00, 76.02)	0.001
Coronary heart	3.57 (1.01–12.68)	0.049	15.40 (3.09–76.92)	0.001
disease	1.45 (0.41, 5.14)	0.565		
Diabetes	1.45 (0.41–5.14)	0.565		
Hypertension	2.13 (0.77–5.88)	0.143		
Laboratory findings				
White blood cell count, × 10° per				
<4	0.34 (0.04-2.70)	0.309	_	_
4-10	1 (ref)		_	_
>10	2.65 (0.89-7.90)	0.082	_	_
Lymphocyte	1.09 (0.99-1.19)	0.075		
count, × 10° per				
L				
Platelet count, $\times$ 10° per L				
<100	3.54 (0.99-12.70)	0.052	_	_
100-300	1 (ref)	_	_	_
>300	0.40 (0.05-3.10)	0.380	_	_
ALT, U/L				
≤40	1 (ref)	_	_	_
>40	2.12 (0.77-5.85)	0.146	_	_
Lactate dehydrogenase, U/L				
≤245	1 (ref)	_	_	_
>245	29.78 (3.91-226.74)	0.001	_	_
High-sensitive cardiac troponin I,				
≤28	1 (ref)	_	_	_
>28	4.07 (1.31–12.64)	0.015	_	_
Prothrombin time, s	(			
≤16	1 (ref)	_	_	_
>16	15.04 (4.11–55.02)	< 0.001	_	_
D-dimer, μg/L	13.04 (4.11 33.02)	<b>\0.001</b>		
≤0.5	1 (ref)	_	1 (ref)	_
>0.5	3.44 (1.09–10.79)	0.035	4.47 (1.22–16.35)	0.024
	3.44 (1.09-10.79)	0.033	4.47 (1.22–10.33)	0.024
Procalcitonin, ng/mL	1 (ref)			
≤0.5 > 0.5	` ,	0.400	_	_
>0.5	2.03 (0.27–15.40)	0.496	_	_
Others				
sMVAP	1 ( 6		1 ( 6	
Quartile 1	1 (ref)	_	1 (ref)	_
Quartile 2	4.19 (0.47–37.45)	0.200	6.52 (0.68–62.13)	0.103
Quartile 3	2.96 (0.31-28.50)	0.347	4.82 (0.46-50.38)	0.189
Quartile 4	8.83 (1.09-71.80)	0.042	17.11 (1.70-172.65)	0.016

CI, confidence interval; HR, hazard ratio; BMI, body mass index; sMVAP, symptomless multi-variable apnea prediction; ALT, alanine aminotransferase.

Previous studies reported that old age, male sex and obesity are independent risk factors for COVID-19 mortality [16—18]. Although the above indicators are also risk factors for OSAHS, it is relatively one-sided to use one or two alone to evaluate the risk of OSAHS. The sMVAP index proves to be a practical OSAHS screening tool [3], including parameters such as age, gender, and BMI that only need to be extracted from the patient's electronic medical record. In this current study, the increased D-dimer and history of coronary heart disease were associated with poor prognosis, reflecting the direct

effect of patients' coagulation function and cardiac dysfunction on mortality, consistent with previous reports [19,20].

This study has several limitations. First, due to the specificity of SARS-CoV-2, none of the patients underwent PSG test, so the efficacy of SMVAP index in screening OSAHS could not be evaluated. Secondly, since this study is a retrospective study, we cannot collect this information of sequential organ failure assessment (SOFA) score and acute physiology and chronic health evaluation II (APACHE II) score.

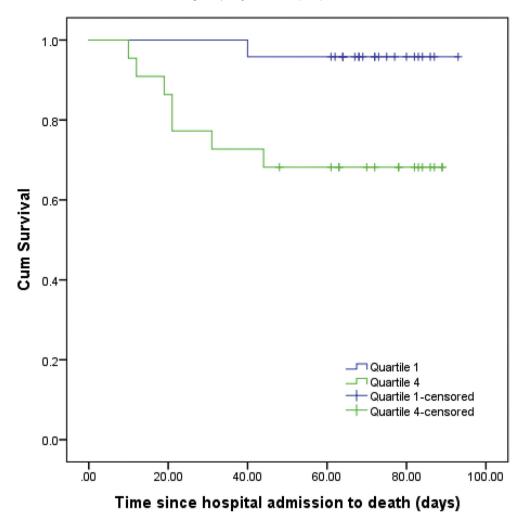


Fig. 2. Survival of patients with COVID-19.

# 5. Conclusions

In conclusion, this study confirms that using the sMVAP index for OSAHS risk assessment, and then predicting the adverse outcomes of COVID-19 patients, is an effective method. Therefore, the use of sMVAP index for OSAHS screening for inpatients with COVID-19 should be vigorously promoted, and high-risk patients should be effectively managed.

# **Disclosure statement**

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# **CRediT authorship contribution statement**

Sun Zhang: Methodology, Software, Writing - original draft. Yuanda Xu: Conceptualization, Methodology. Jieying Li: Methodology, Software. Kang Wu: Formal analysis. Tao Wang: Formal analysis. Xiaofen Su: Investigation. Qian Han: Methodology. Yin Xi: Investigation, Resources. Yong Gao: Resources. Hongbo Wang: Data curation. Yu Hu: Resources. Chunli Liu: Visualization, Conceptualization. Pixin Ran: Supervision. Nuofu Zhang: Writing review & editing. Nanshan Zhong: Project administration.

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# **Abbreviations list**

COVID-19 Corona Virus Disease 2019

SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus 2

WHO World Health Organization

PSG polysomnography

OSAHS obstructive sleep apnea hypopnea syndrome sMVAP symptomless multi-variable apnea prediction

BMI body mass index

IRB institutional review board ALT alanine aminotransferase AST aspartate aminotransferase

CRP c-reactive protein
BNP brain natriuretic peptide

DIC disseminated intravascular coagulation ARDS acute respiratory distress syndrome

DVT deep venous thrombosis

ECMO extracorporeal membrane oxygenation
CRRT continuous renal replacement therapy
IMV invasive mechanical ventilation
NIMV non-invasive mechanical ventilation

ICH intensive care unit

SOFA sequential organ failure assessment

APACHE II acute physiology and chronic health evaluation II

standard deviation SD IOR interquartile range CI confidence interval

HR hazard ratio

# **Conflict of interest**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2020.08.031.

### References

- [1] Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology 2008;108(5):812-21.
- Marti-Soler H, Hirotsu C, Marques-Vidal P, et al. The NoSAS score for screening of sleep-disordered breathing: a derivation and validation study. Lancet Respir Med 2016;4(9):742-8.
- Lyons MM, Keenan BT, Li J, et al. Symptomless multi-variable apnea prediction index assesses obstructive sleep apnea risk and adverse outcomes in elective surgery. Sleep 2017;40(3).
- [4] WHO. Clinical management of COVID-19. May 27, 2020. https://www.who. int/publications-detail/clinical-management-of-severe-acute-respiratory infection-when-novel-coronavirus-(ncov)-infection-is-suspected.
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
- Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120:c179-84.

- [7] Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition, JAMA 2012;307:2526-33.
- [8] National Health Commission of the People's Republic of China, Chinese management guideline for COVID-19 (version 7.0). Mar 3 2020. in Chinese), http://www.nhc.gov.cn/yzygj/s7653p/202003/ 46c9294a7dfe4cef80dc7f5912eb1989/files/ ce3e6945832a438eaae415350a8ce964. pdf. [Accessed 3 March 2020].
- [9] Grote L, McNicholas WT, Hedner J, et al. Sleep apnoea management in Europe during the COVID-19 pandemic: data from the European sleep apnoea database (ESADA). Eur Respir J 2020;55(6).
- [10] Avas NT. Fraser KL. Giannouli E. et al. Key highlights from the Canadian thoracic society's position statement on optimizing the management of sleep disordered breathing during the COVID-19 pandemic. Chest 2020.
- [11] Tufik S, Gozal D, Ishikura IA, et al. Does obstructive sleep apnea lead to increased risk of COVID-19 infection and severity? J Clin Sleep Med 2020:16(8):1425-6.
- [12] Salles C, Mascarenhas Barbosa H. COVID-19 and obstructive sleep apnea. J Clin Sleep Med 2020. https://doi.org/10.5664/jcsm.8606
- McSharry D, Malhotra A. Potential influences of obstructive sleep apnea and obesity on COVID-19 severity. J Clin Sleep Med 2020, https://doi.org/10.5664/ icsm 8538
- [14] Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the seattle region - case series. N Engl J Med 2020;382(21):2012–22.
  [15] Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill
- patients with COVID-19 in Washington state. JAMA 2020.
- [16] Yu C, Lei Q, Li W, et al. Clinical characteristics, associated factors, and predicting COVID-19 mortality risk: a retrospective study in wuhan, China. Am J Prev Med 2020;59(2):168-75.
- Sattar N, McInnes IB, McMurray J. Obesity a risk factor for severe COVID-19 infection: multiple potential mechanisms. Circulation 2020;142(1):4-6.
- [18] Lighter J, Phillips M, Hochman S, et al. Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission. Clin Infect Dis 2020:71(15):896-7.
- [19] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020:395(10229):1054-62.
- [20] Barman HA, Atici A, Sahin I, et al. Prognostic significance of cardiac injury in COVID-19 patients with and without coronary artery disease. Coron Artery Dis 2020. https://doi.org/10.1097/MCA.000000000000014.