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ORIGINAL RESEARCH

The Association Between Alveolar–Arterial Oxygen Tension Difference and the Severity of COVID-19 in Patients

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) emerged as a global pandemic and resulted in a significantly high death toll. Therefore, there is an urgent need to find a potential biomarker related to the disease severity that can facilitate early-stage intervention.

Methods: In the present study, we collected 242 laboratory-confirmed COVID-19-infected patients. The patients were grouped according to the alveolar to arterial oxygen tension difference ($P_{A\text{-}a}O_2$) value of COVID-19 infection after admission.

Results: Among the 242 laboratory-confirmed COVID-19- infected patients, 155 (64.05%) had an abnormal $P_{A\text{-}a}O_2$ value on admission. Compared with the normal $P_{A\text{-}a}O_2$ group, the median age of the abnormal $P_{A\text{-}a}O_2$ group was significantly older ($p = 0.032$). Symptoms such as fever, cough, and shortness of breath were more obvious in the abnormal $P_{A\text{-}a}O_2$ group. The proportion of severe events in the abnormal $P_{A\text{-}a}O_2$ group was higher than the normal $P_{A\text{-}a}O_2$ group (10.34% vs. 23.23%, $p = 0.013$). The abnormal $P_{A\text{-}a}O_2$ group had a higher possibility of developing severe events compared with the normal $P_{A\text{-}a}O_2$ group (HR 2.622, 95% CI 1.197–5.744, $p = 0.016$). After adjusting for age and common comorbidities (hypertension and cardiovascular disease), the abnormal $P_{A\text{-}a}O_2$ group still exhibited significantly elevated risks of developing severe events than the normal $P_{A\text{-}a}O_2$ group (HR 2.986, 95% CI 1.220–7.309, $p = 0.017$). Additionally, the abnormal $P_{A\text{-}a}O_2$ group had more serious inflammation/coagulopathy/fibrinolysis parameters than the normal $P_{A\text{-}a}O_2$ group.

Conclusion: Abnormal $P_{A\text{-}a}O_2$ value was found to be common in COVID-19 patients, was strongly related to severe event development, and could be a potential biomarker for the prognosis of COVID-19 patients.

This study was retrospectively registered in The Institutional Ethics Board of The Second Xiangya Hospital of Central South University (No. 2020001). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. The study was completed in accordance with the declaration of Helsinki.

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Key Summary Points

- Abnormal PA-aO2 values are common in COVID-19 patients and are strongly associated with the occurrence of severe events.
- Abnormal PA-aO2 group had more serious inflammation/coagulopathy/fibrinolysis parameters than the normal PA-aO2 group.
- The PA-aO2 value might be a potential biomarker for the prognosis of COVID-19 patients.

INTRODUCTION

Over the past 3 years, the global pandemic of Severe Acute Respiratory Syndrome Coronavirus 2, referred to as Coronavirus Disease 2019 (COVID-19), has been, and continues to be, a significant threat to human health [1–3]. First observed in Wuhan, China, in December 2019, the disease has caused significant economic losses and had considerably negative impacts, especially in terms of the death toll [4]. According to recent reports, 500 million have been diagnosed with COVID-19 and over 5 million have died, with the numbers continuing to rise [5]. As such, there is an urgent need to find biomarkers of disease severity and prognosis, which can facilitate early-stage intervention and ultimately save lives.

In clinical practice, the alveolar to arterial oxygen tension difference ($P_{A\text{-}a}O_2$) is used to evaluate the gas exchange function of the lungs [6], to aid in the decision of therapy [7], to measure the effect of therapy [8], and to predict the outcome in different patient groups [9]. Previous studies had reported that $P_{A\text{-}a}O_2$ value combined with low-dose chest computed tomography (CT) scan could serve as a rapid tool to select mild COVID-19 in need for hospitalization [10], and other studies had also indicated that the $P_{A\text{-}a}O_2$ value may be used as a early marker to predict severe pneumonia [11–13]. Certain COVID-19 patients display hypoxemia and dyspnea with unclear incidences of abnormal $P_{A\text{-}a}O_2$ value, and there is an apparent association with severe events of COVID-19.

Thus, in the present study, to better understand the potential effects of $P_{A\text{-}a}O_2$ value on COVID-19 patients, we present the clinical features of COVID-19 patients with or without abnormal $P_{A\text{-}a}O_2$ value, and analyze the association between abnormal $P_{A\text{-}a}O_2$ value and the results of COVID-19 patients.

METHODS

Research Design and Participants

The present study was a retrospective cohort study, in which 242 laboratory-confirmed COVID-19-infected patients were included. All patients were hospitalized in the Public Health Treatment Center of Changsha, China, from April 15 to June 1, 2022.

Based on the results of blood gas examination within the first day after hospitalization, and according to the formula ($P_{A\text{-}a}O_2 = FiO_2$ (Barometric pressure−vapor pressure of water)−($PaCO_2$/0.8)−PaO_2, (with 0.8 representing the respiratory quotient), the actual $P_{A\text{-}a}O_2$ value of each patient [6]. According to the formula ($P_{A\text{-}a}O_2 = age/4 + 4$), the theoretical PA-$aO_2$ value of each patient was calculated. If the calculated actual value was greater than the theoretical value, then the patient would be assigned into the abnormal PA-aO_2 group; otherwise, the patient would be assigned into the normal $P_{A\text{-}a}O_2$ group.

A severe event developed when a patient exhibited the following: (1) rate of respiration ≥ 30/min; (2) oxygen saturation ≤ 93%; (3) $PaO_2/FiO_2 \leq 300$ mmHg; (4) progress of lung lesions over 50% within 24–48 h; (5) mechanical ventilation was provided; (6) shock; and (7) admission to intensive care unit.

The laboratory findings of each patient were recorded every 3 days within the first 15 days after admission, with every 3 days being one period. There were five periods as follows: T0 (D0–D2), T1 (D3–D5), T2 (D6–D8), T3 (D9–D11), and T4 (D12–D14).

Statements of Ethics

Retrospectively registered in The Institutional Ethics Board of The Second Xiangya Hospital of Central South University (No. 2020001). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. The study was completed in accordance with the declaration of Helsinki.

Data Gathering

In the present study, the data gathered from the e-medical records were explored. The following information was examined and extracted: demographic information and chronic comorbidities at the first time of hospitalization, clinical symptoms, results, and related laboratory coefficients at various time periods, such as coagulation, liver function, routine blood examinations, renal function, and inflammatory coefficients. All the records were independently verified and collected by two authors.

Statistical Analysis

The Mann–Whitney-test was used to analyze the data, and the median and IQR were reported. The differences of the categorical variables were compared using the χ^2-test or Fisher's exact-test. Univariate and multivariate analyses were conducted using the Cox regression model to determine the relationship between the abnormal $P_{A\text{-}a}O_2$ group and severe events with the hazard ratio (HR) and 95% confidence interval (95% CI) observed. The univariate and multivariate analyses included baseline variables with significant differences between the abnormal $P_{A\text{-}a}O_2$ group and the normal $P_{A\text{-}a}O_2$ group. IBM SPSS v.26 software was adopted to perform all the analyses.

RESULTS

In the present study, 242 patients with laboratory-confirmed COVID-19 were recruited. Among the patients, 155 (64.05%) had abnormal $P_{A\text{-}a}O_2$ value and 87 (35.95%) had normal $P_{A\text{-}a}O_2$ value on admission.

Among the 155 patients with abnormal $P_{A\text{-}a}O_2$ value, the median age was 47 years old (IQR 36–61 years old), which was significantly higher than that of the normal PA-aO2 group of 41 years old (IQR 29–58 years, $p = 0.032$). Further, the patients in the abnormal $P_{A\text{-}a}O_2$ group were more likely to have symptoms of fever, cough, and shortness of breath than those in the normal $P_{A\text{-}a}O_2$ group (80.00% vs. 65.2%, $p = 0.013$; 50.32% vs. 33.33%, $p = 0.011$; and 39.35% vs. 24.14%, $p = 0.016$) (Table 1). In addition, the clinical outcomes of COVID-19 patients with normal $P_{A\text{-}a}O_2$ value and abnormal $P_{A\text{-}a}O_2$ value were analyzed, and the proportion of severe events in the abnormal $P_{A\text{-}a}O_2$ group was found to be higher than in the normal $P_{A\text{-}a}O_2$ group (23.23% vs. 10.34%, $p = 0.013$) (Table 2).

Moreover, patients with abnormal $P_{A\text{-}a}O_2$ values were more likely to develop severe events compared with patients with normal $P_{A\text{-}a}O_2$ value (HR 2.622, 95% CI 1.197–5.744, $p = 0.016$). After the modification for age and common comorbidities (hypertension and cardiovascular disease), patients with abnormal $P_{A\text{-}a}O_2$ value still displayed significantly increased risks of developing severe events than patients with normal $P_{A\text{-}a}O_2$ value (HR 2.986, 95% CI 1.220–7.309, $p = 0.017$) (Table 3).

The abnormal $P_{A\text{-}a}O_2$ value group was significantly older than the normal $P_{A\text{-}a}O_2$ group ($p = 0.032$), which may suggest that age was one of the factors responsible for the above change except for the $P_{A\text{-}a}O_2$ value. We then compared the baseline characteristics and clinic parameters of the abnormal $P_{A\text{-}a}O_2$ value group and the normal $P_{A\text{-}a}O_2$ group with COVID-19 matched according to age, and only found that the virus shedding time and the length of hospital stay

Table 1 Baseline characteristics of COVID-19 patients with normal $P_{A\text{-}a}O_2$ and abnormal $P_{A\text{-}a}O_2$

	Non-group ($n = 87$)	Group ($n = 155$)	All patients ($n = 242$)	p value
Gender (male/female)	44 (50.57)	75 (48.39)	119 (49.17)	0.744
Age (years), M (IQR)	41 (29, 58)	47 (36, 61)	45 (34, 59.25)	0.032*
Smoking (*n*, %)	8 (9.20)	11 (7.10)	19 (7.85)	0.560
Alcohol (*n*, %)	5 (5.75)	5 (3.23)	10 (4.13)	0.344
Symptoms				
Fever (*n*, %)	57 (65.52)	124 (80.00)	181 (74.79)	0.013*
Fatigue (*n*, %)	29 (33.33)	78 (50.32)	107 (44.21)	0.011*
Cough (*n*, %)	65 (74.71)	130 (83.87)	195 (80.58)	0.084
Shortness of breath	21 (24.14)	61 (39.35)	82 (33.88)	0.016*
Expectoration (*n*, %)	39 (44.83)	69 (44.52)	108 (44.63)	0.963
Hemoptysis (*n*, %)	2 (2.30)	5 (3.23)	7 (2.89)	0.680
Pharyngalgia (*n*, %)	13 (14.94)	21 (13.55)	34 (14.05)	0.680
Vomiting (*n*, %)	11 (12.64)	15 (9.68)	26 (10.74)	0.475
Diarrhea (*n*, %)	20 (22.99)	35 (22.58)	55 (22.73)	0.942
Abdominal pain (*n*, %)	6 (6.90)	4 (2.58)	10 (4.13)	0.106
Nausea (*n*, %)	10 (11.49)	20 (12.90)	30 (12.40)	0.750
Anorexia (*n*, %)	40 (45.98)	77 (49.68)	117 (48.35)	0.580
Myalgia (*n*, %)	8 (9.20)	16 (10.32)	24 (0.99)	0.778
Chill (*n*, %)	11 (12.64)	18 (11.61)	29 (11.98)	0.813
Dizziness (*n*, %)	12 (13.79)	17 (10.97)	29 (11.98)	0.516
Headache (*n*, %)	11 (12.64)	20 (12.90)	31 (12.81)	0.954
Comorbidities				
Hypertension (*n*, %)	10 (11.49)	26 (16.77)	36 (14.88)	0.268
Cardiovascular (*n*, %)	6 (6.90)	3 (1.94)	9 (3.72)	0.074
Diabetes (*n*, %)	7 (8.05)	8 (5.16)	15 (6.20)	0.372

PA-aO$_2$ alveolo–arterial oxygen tension difference
*$p < 0.05$

was longer ($p = 0.042$, $p = 0.016$) in the abnormal $P_{A\text{-}a}O_2$ value group (Table S1). Additionally, we also examined the association of $P_{A\text{-}a}O_2$ value and disease severity in a multivariate logistic regression model after matching with age, and it still showed that the $P_{A\text{-}a}O_2$ value increased the risk of serious events (Table S2). Collectively, these results further proved our findings.

Subsequently, the dynamic processes and the differences between the abnormal $P_{A\text{-}a}O_2$ group and the normal $P_{A\text{-}a}O_2$ group were investigated in terms of the related laboratory coefficients. There were different trends of inflammatory biomarkers in the abnormal $P_{A\text{-}a}O_2$ group. The white

Table 2 Outcomes of COVID-19 patients with normal $P_{A\text{-}a}O_2$ and abnormal $P_{A\text{-}a}O2$

	Normal $P_{A\text{-}a}O_2$ ($n = 87$)	Abnormal $P_{A\text{-}a}O_2$ ($n = 155$)	All patients ($n = 242$)	*p* value
Severe event (*n*, %)	9 (10.34)	36 (23.23)	45 (18.60)	0.013[a]
Noninvasive ventilator (*n*, %)	0 (0.00)	4 (2.58)	4 (1.65)	1.000
Invasive ventilator (*n*, %)	1 (1.15)	2 (1.29)	3 (1.24)	0.476
Mortality (*n*, %)	1 (1.15)	1 (0.65)	2 (0.83)	1.000
Virus shedding time (days, IQR)	17 (13, 23.25)	19 (13, 26)	18 (13, 25)	0.226
Length of hospital stay (days, IQR)	15 (11, 22.25)	16 (12, 25.25)	16 (11.25, 25)	0.122

IQR interquartile range
[a]Indicates a significant difference

blood cell (WBC) count exhibited an increasing tendency from T0 to T4, the C-reactive protein (CRP) level displayed a declining trend from T1 to T4, while the erythrocyte sedimentation rate (ESR) peaked at T2 and T3. In terms of coagulation indicators, platelets (PLTs) increased from T0 to T4, but activated partial thromboplastin time (APTT) decreased from T0 to T4. Prothrombin time (PT) declined from T0 to T3, but slightly increased in T4, and Fibrinogen (Fib) had two peaks in T0 and T1 (Table 4).

When comparing the differences between the abnormal $P_{A\text{-}a}O_2$ group and the normal $P_{A\text{-}a}O_2$ group in terms of relevant laboratory parameters, the following findings were made: the WBC count and PLTs were significantly higher in T3 and T4 in the abnormal $P_{A\text{-}a}O_2$ group; CRP and Fib were significantly higher in T0 and T1 in the abnormal $P_{A\text{-}a}O_2$ group; ESR was significantly higher in T0–T2 in the abnormal $P_{A\text{-}a}O_2$ group; D dimer (D–D) was significantly higher in T2 and T3 in the abnormal $P_{A\text{-}a}O_2$ group; lymphocytes (Lys) were significantly lower in T1 in the abnormal $P_{A\text{-}a}O_2$ group; regarding two direct indicators of liver function, alanine aminotranspherase (ALT) was significantly higher in T0 in the abnormal $P_{A\text{-}a}O_2$ group, and aspartate aminotransferase (AST) exhibited no significant differences during the study period; regarding indirect indicators, albumin (ALB) was significantly lower in T1 and T2 in the abnormal $P_{A\text{-}a}O_2$ group, and the total bilirubin (TBil) also exhibited no significant differences during the study period; regarding indicators of kidney function, serum creatinine (Cr) was significantly lower in T2 in the abnormal $P_{A\text{-}a}O_2$ group and urea nitrogen (BUN) exhibited no significant differences during the study period (Table 4).

DISCUSSION

In the present study, 242 laboratory-confirmed COVID-19-infected patients were recruited, and the clinical data were evaluated. Among those recruited, 155 (64.05%) patients had abnormal $P_{A\text{-}a}O_2$ value on admission and the abnormal $P_{A\text{-}a}O_2$ was related to subsequent severe events. Meanwhile, the data revealed a link between abnormal $P_{A\text{-}a}O_2$ value and several significant markers of inflammation/coagulopathy/fibrinolysis, especially for the early-stage inflammation parameters.

First, the demographic features, clinical symptoms, and results of the abnormal $P_{A\text{-}a}O_2$ group and the normal $P_{A\text{-}a}O_2$ group were compared. The median age of the abnormal $P_{A\text{-}a}O_2$ group was higher than the normal $P_{A\text{-}a}O_2$ group. At the same time, more severe events and more clinical symptoms, such as fever, fatigue, and shortness of breath, were found in the abnormal $P_{A\text{-}a}O_2$ group. As reported in previous studies, the $P_{A\text{-}a}O_2$ value is used to evaluate the gas exchange

Table 3 Association of $P_{A\text{-}a}O_2$ and disease severity in the Logistic regression model

Variables	Univariate logistic regression analysis							Multivariate logistic regression analysis						
	B	SE	Wald	*p*	Exp (B)	95% CI		*B*	SE	Wald	*p*	Exp (B)	95% CI	
						Lower	Upper						Lower	Upper
PA-aO_2	0.964	0.400	5.803	0.016	2.622	1.197	5.744	1.094	0.457	5.738	0.017	2.986	1.220	7.309
Gender	0.425	0.334	1.624	0.203	1.530	0.729	2.681	NA	NA	NA	NA	NA	NA	NA
Age	0.044	0.011	15.793	< 0.001	1.045	1.023	1.068	0.031	0.012	6.062	0.014	1.031	1.006	1.056
Hypertension	1.433	0.392	13.392	< 0.001	4.190	1.945	9.027	0.759	0.444	2.923	0.087	2.136	0.895	5.099
Cardiovascular disease	1.791	0.693	6.725	0.010	6.031	1.551	23.456	1.489	0.795	3.510	0.061	4.433	0.934	21.052
Diabetes	0.501	0.609	0.676	0.411	1.650	0.500	5.440	NA	NA	NA	NA	NA	NA	NA
Smoking	− 0.708	0.767	0.854	0.355	0.492	0.110	2.213	NA	NA	NA	NA	NA	NA	NA
Alcohol	0.662	0.711	0.868	0.352	1.939	0.481	7.809	NA	NA	NA	NA	NA	NA	NA

NA not available

[a]Difference significant

Table 4 Laboratory parameters of COVID-19 patients with normal $P_{A\text{-}a}O_2$ and abnormal $P_{A\text{-}a}O_2$ in different time points after admission

	T0 (D0–D2)		T1 (D3–D5)		T2 (D6–D8)		T3 (D9–D11)		T4 (D12–D14)	
	Normal $P_{A\text{-}a}O_2$	Abnormal $P_{A\text{-}a}O_2$	Normal $P_{A\text{-}a}O_2$	Abnormal $P_{A\text{-}a}O_2$	Normal $P_{A\text{-}a}O_2$	Abnormal $P_{A\text{-}a}O_2$	Normal $P_{A\text{-}a}O_2$	Abnormal $P_{A\text{-}a}O_2$	Normal $P_{A\text{-}a}O_2$	Abnormal $P_{A\text{-}a}O_2$
WBC	4.7 (3.3, 5.8)	4.6 (3.7, 5.9)	5.2 (3.8, 7.0)	5.5 (4.1, 7.8)	5.7 (4.5, 6.6)	6.2 (4.6, 8.2)	5.8 (4.8, 7.4)[a]	6.5 (5.4, 9.0)	6.3 (5.2, 7.8)[a]	7.2 (6.1, 10.2)
HGB	131 (120, 141)	130 (119, 141)	132 (118, 143)	130 (119, 143)	130 (118, 141)	127 (115, 142)	123 (113, 139)	124 (114, 136)	128 (115, 137)	126 (114, 137)
PLT	172 (143, 227)	170 (139, 230)	200 (152, 263)	211 (147, 269)	218 (178, 272)	233 (180, 313)	219 (174, 284)[a]	263 (203, 312)	227 (180, 279)[a]	269 (204, 330)
Lys	1.2 (0.9, 1.8)	1.11 (0.8, 1.5)	1.3 (0.9, 1.7)[a]	1.1 (0.7, 1.6)	1.37 (1.0, 1.8)	1.2 (0.8, 1.7)	1.4 (1.0, 1.7)	1.4 (1.1, 1.8)	1.5 (1.2, 1.8)	1.4 (1.1, 1.9)
CRP	7.7 (2.0, 22.1)[a]	17.2 (6.8, 36.4)	9.1 (4, 21.6)[a]	17.6 (8.3, 37.0)	5.8 (2.4, 12.7)	8.4 (3.7, 21.7)	3.8 (2.0, 7.4)	5.5 (2.2, 11.6)	3.1 (1.3, 5.5)[a]	5.0 (2.1, 11.4)
ESR	25 (11, 51)[a]	42 (23, 72)	43 (17, 69)[a]	59 (33, 78)	51 (23, 78)[a]	66 (37, 89)	53 (28, 77)	74 (41, 85)	43 (12, 77)	55 (26, 88)
PT	11.9 (11.2, 12.4)	11.8 (11.2, 12.5)	11.3 (10.9, 12.0)	11.4 (10.8, 12.2)	10.8 (10.4, 11.3)	10.8 (10.5, 11.5)	10.9 (10.3, 11.2)	10.7 (10.3, 11.3)	10.8 (10.5, 11.4)	10.8 (10.3, 11.5)
APTT	32.4 (29.9, 35.1)	32.7 (30.7, 35.0)	31.8 (23.0, 34.1)	31.7 (29.7, 34.5)	31.9 (30.0, 33.8)	31.2 (28, 2.3)	31.0 (27.6, 33.1)	30.1 (27.2, 32.9)	32.4 (28.8, 34.6)	29.9 (26.4, 33.0)
Fib	3.4 (2.7, 3.9)[a]	3.7 (3.1, 4.5)	3.6 (2.9, 4.1)[a]	3.9 (3.2, 4.6)	3.4 (2.8, 3.9)	3.6 (3.0, 4.3)	3.1 (2.7, 3.6)	3.3 (2.8, 3.9)	2.9 (2.5, 3.3)	3.2 (2.7, 3.6)
D-D	0.2 (0.1, 0.5)	0.3 (0.1, 0.6)	0.2 (0.1, 0.4)	0.3 (0.1, 0.6)	0.2 (0.1, 0.3)[a]	0.2 (0.1, 0.6)	0.1 (0.1, 0.5)[a]	0.2 (0.1, 0.7)	0.2 (0.1, 0.5)	0.3 (0.1, 1.1)
ALT	17.1 (13.1, 23.4)[a]	20.0 (14.3, 28.4)	17.1 (12.8, 24.2)	19.3 (15.0, 26.7)	18.2 (14.0, 34.0)	22.4 (15.6, 34.8)	27.1 (15.6, 49.5)	27.7 (16.2, 44.4)	25.4 (16.0, 48.2)	30.0 (19.7, 63.1)
AST	21.6 (17.9, 27.9)	25.3 (21.4, 32.9)	20.7 (17.1, 26.4)	22.4 (17.5, 29.0)	22.2 (17.6, 30.0)	23.5 (18.1, 29.6)	23.6 (16.8, 31.4)	23.3 (18.6, 31.7)	26 (18.6, 34.0)	26.0 (20.0, 34.3)
Tbil	10.1 (8.1, 14.5)	11.5 (8.8, 16.4)	12.1 (9.4, 22.3)	14.2 (9.4, 20.0)	9.6 (6.8, 12.3)	10.8 (8.0, 14.0)	9.0 (7.1, 12.2)	9.3 (7.0, 12.9)	8.4 (6.8, 12.9)	10.3 (8.2, 14.0)

Table 4 continued

	T0 (D0–D2)		T1 (D3–D5)		T2 (D6–D8)		T3 (D9–D11)		T4 (D12–D14)	
	Normal $P_{A-a}O_2$	Abnormal $P_{A-a}O_2$	Normal $P_{A-a}O_2$	Abnormal $P_{A-a}O_2$	Normal $P_{A-a}O_2$	Abnormal $P_{A-a}O_2$	Normal $P_{A-a}O_2$	Abnormal $P_{A-a}O_2$	Normal $P_{A-a}O_2$	Abnormal $P_{A-a}O_2$
ALB	38.7 (35.9, 42.3)	38.1 (35.2, 40.5)	39.2 (36.0, 42.4)[a]	37.3 (33.7, 40.6)	39.1 (36.2, 42.4)[a]	37.5 (32.9, 40.9)	38.9 (34.3, 42.5)	37.7 (33.2, 41.5)	41.5 (38.6, 44.6)[a]	38.1 (33.7, 41.9)
Cr	51.1 (40.0, 68.1)	51.3 (41.3, 61.9)	55.8 (42.8, 73.2)	55.1 (43.3, 64.7)	64.3 (48.0, 75.6)[a]	50.4 (41.4, 62.4)	53.3 (46.1, 65.5)	57.1 (46.1, 70.8)	56.9 (47.2, 75.6)	54.1 (45.0, 63.7)
BUN	4.2 (3.6, 5.1)	4.4 (3.2, 5.5)	4.5 (3.6, 5.3)	5.0 (3.9, 6.6)	4.8 (4.0, 5.9)	4.9 (4.0, 6.5)	5.1 (4.2, 60.4)	5.4 (4.6, 6.5)	5.4 (4.4, 6.3)	5.3 (4.7, 6.7)

WBC white blood cell, *HGB* hemoglobin, *PLT* platelet, *Lys* lymphocytes, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *Fib* fibrinogen, *D-D* D dimer, *ALT* alanine aminotranspherase, *AST* aspartate aminotransferase, *TBil* total bilirubin, *ALB* albumin, *Cr* serum creatinine, *BUN* urea nitrogen

[a]Difference significant

function of the lungs [6], and an abnormal $P_{A-a}O_2$ value indicates deficient pulmonary oxygenation [14]. Similarly, a number of studies have indicated that severe events generally occur in older patients [15, 16]. Moreover, COVID-19 always affects the lung tissue, and can impair the oxygen exchange to the blood of patients [17]. Previous studies have also reported that $P_{A-a}O_2$ value may serve as an early marker to predict severe pneumonia, which was consistent with our findings [10–12]. Such findings can explain the present results in which abnormal $P_{A-a}O_2$ was related to severe events. Therefore, an assumption could be made that, for patients not displaying obvious hypoxemia in the early stage of the disease, those with abnormal $P_{A-a}O_2$ may already be suffering with compensatory hyperventilation and may deteriorate further. Hence, COVID-19 patients with abnormal $P_{A-a}O_2$ value should be adequately monitored, even when there are no signs of hypoxemia. Additionally, according to recent studies, COVID-19 death is generally caused by a severe case of the disease [18]. However, in the present study, there were only 2 deaths. Therefore, no relationship analysis on abnormal $P_{A-a}O_2$ and mortality could be performed, but the rate of developing severe events and the $P_{A-a}O_2$ value were significantly related according to the present research. Additionally, an observational prospective study has reported that the $P_{A-a}O_2$ value could be used to predict survival though with limited samples [13]. Hence, an assumption can be made that abnormal $P_{A-a}O_2$ value on admission may also be a potential predictive element for death, but such an assumption needs to be verified with a larger sample of studies.

Further findings have reported that the inflammation/coagulopathy/fibrinolysis parameters in the abnormal $P_{A-a}O_2$ group, such as C-reactive protein, erythrocyte sedimentation rate, fibrinogen, WBC count, and D–D were higher, while PLTs, alanine aminotranspherase, and albumin were lower compared with the normal $P_{A-a}O_2$ group. Of the parameters, the increase in WBC count and the decrease in PLTs could be regarded as hematologic biomarkers in COVID-19 patients [19, 20]. The increases in C-reactive protein and erythrocyte sedimentation rate could be regarded as inflammatory

biomarkers prior to indications of critical findings with CT in COVID-19 patients [20, 21]. In respect of coagulation biomarkers, there was an increase in D–D as one of two biomarkers (the other biomarker being prothrombin time) with severe systemic disease in COVID-19 patients [20, 22, 23]. These findings indicate that abnormal $P_{A\text{-}a}O2$ values might contribute to a stronger inflammation/coagulopathy/fibrinolysis response in COVID-19 patients. However, the underlying mechanisms that account for this phenomenon remain unknown. Further studies will be performed by our group to determine which pathway dominates. Collectively, the present results show that the $P_{A\text{-}a}O_2$ value was associated with hematologic parameters, biochemical parameters, inflammatory parameters, coagulation parameters, and severe events, thereby demonstrating that the $P_{A\text{-}a}O_2$ value may be a novel potential biomarker for severe COVID-19 in patients.

Notably, the present research has several limitations. Due to the study being retrospective, there is less evidence than in prospective and interventional studies. Additionally, only a brief description of the predictive value of abnormal $P_{A\text{-}a}O_2$ on severe events in patients with COVID-19 has been provided, while the association between abnormal $P_{A\text{-}a}O_2$ value and death could not be explored due to the limited sample size.

CONCLUSION

An abnormal $P_{A\text{-}a}O_2$ value has been found to be common in COVID-19 patients, is highly related to severe event development, and could be a potential biomarker for the prognosis of COVID-19 patients.

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Author Contributions. Yanjun Zhong and Jinxiu Li developed the study design and conducted the analyses. Canbin Xie interpreted the results, reviewed the study design, and performed the statistical analyses. Jiayi Deng and FanglinLi acquired patient demographic and clinical data. Min Xu, Chenfang Wu, Bo Yu and GuobaoWu participated in interpreting the clinical results and reviewed the manuscript. Da Tang wrote and revised the manuscript. All authors have read and approved the final version.

Disclosures. Canbin Xie, Jiayi Deng, Fanglin Li, Chenfang Wu, Min Xu , Bo Yu , Guobao Wu, Yanjun Zhong, Da Tang and Jinxiu Li declares no conflict of interest.

Compliance with Ethics Guidelines. The studies involving human participants were reviewed and approved by The Institutional Ethics Board of The Second Xiangya Hospital of Central South University (No. 2020001). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. The study was completed in accordance with the declaration of Helsinki.

Data Availability. The datasets presented in this article are not readily available because they need permission from local health and disease control authorities. Requests to access the datasets should be directed to zhongyanjun@csu.edu.cn.

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