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ARTICLE

Symptoms at disease onset predict prognosis in COVID-19 disease

Aiyuan Zhou[a,b,c,d,e,*], Qing Song[f,*], Yating Peng[f], Xin Liao[g], Peng Huang[h], Wenlong Liu[i], Zhi Xiang[j], Qimi Liu[k], Mingyan Jiang[l], Xudong Xiang[m], Dingding Deng[n] and Ping Chen[f]

[a]Department of Respiratory Medicine, National Key Clinical Specialty, Branch of National Clinical Research Center for Respiratory Disease, Xiangya Hospital, Central South University, Changsha, Hunan, China; [b]Center of Respiratory Medicine, Xiangya Hospital, Central South University, Changsha, Hunan, China; [c]Clinical Research Center for Respiratory Diseases in Hunan Province, Changsha, Hunan, China; [d]Hunan Engineering Research Center for Intelligent Diagnosis and Treatment of Respiratory Disease, Changsha, Hunan, China; [e]National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Changsha, Hunan, P.R. China; [f]Department of Respiratory and Critical Medicine, the Second Xiangya Hospital, Central South University, Changsha, Hunan, China; [g]Department of Respiratory Medicine, Affiliated Shaoyang Central Hospital of University of South China, Shaoyang, Hunan, China; [h]Department of Respiratory Medicine, Zhuzhou Central Hospital, Zhuzhou, Hunan, China; [i]Department of Respiratory Medicine, Yueyang Second People's Hospital, Designated Hospital of Junshan District, Yueyang, Hunan, China; [j]Department of Respiratory Medicine, the First People's Hospital of Huaihua affiliated to University of South China, Huaihua, Hunan, China; [k]Department of Respiratory Medicine, the Second People's Hospital of Guilin, Guilin, Guangxi, China; [l]Department of Respiratory and Critical Medicine, Xiangtan Central Hospital, Xiangtan, Hunan, China; [m]Department of Emergency Medicine, Second Xiangya Hospital, Central South University, Changsha, Hunan, China; [n]Department of Respiratory Medicine, The first Attached Hospital of Shaoyang University, Shaoyang, Hunan, China

ABSTRACT

The main clinical manifestations of coronavirus disease 2019 (COVID-19) onset are respiratory symptoms, including cough, sputum, and dyspnea. However, a significant proportion of patients initially manifested non-respiratory symptoms, such as fever, myalgia, and diarrhea. Here, we compared the different characteristics and outcomes between the patients with respiratory symptoms and non-respiratory symptoms at illness onset. The patients admitted to the respiratory departments from eight hospitals in Hunan and Guangxi Province with nucleic acid-positive severe acute respiratory syndrome coronavirus (SARS-CoV-2) were recruited. Epidemiological information, clinical manifestations, laboratory findings, and radiological characteristics, treatment regimens, and outcomes data were recorded and analyzed. The median age of the recruited 541 subjects was 43 years (IQR, 33–55). Of the 541 subjects, 404 (74.5%) subjects had initial symptom that were respiratory, while 137 (25.5%) subjects had non-respiratory symptoms. Respiratory COVID-19 subjects had more secondary bacterial infections (8.7% vs 0.0%, $P < 0.001$), needed the intensive care unit more (9.7% vs 2.2%, $P = 0.005$), non-invasive ventilation more (7.2% vs 1.5%, $P = 0.004$), developed ARDS more (11.4% vs 2.2%, $P = 0.001$) and needed longer time to recover (18.5 vs 16.7 days, $P = 0.003$) compared to predominately non-respiratory COVID-19 subjects. The multivariate model showed that age (OR = 1.04, $P = 0.01$), dyspnea (OR = 4.91, $P < 0.001$) and secondary bacterial infection (OR = 19.8, $P < 0.001$) were independently associated with development of ARDS among COVID-19 patients. We identify COVID-19 subjects with dyspnea at disease onset who have a worse prognosis. We also demonstrate age and secondary bacterial infections to be independently associated with ARDS development in subjects with COVID-19.

ABBREVIATIONS: COVID-19: Coronavirus disease 2019; ARDS: acute respiratory distress syndrome; IQR: interquartile range; ICU: intensive care unit; CDC: Chinese Center for Disease Control and Prevention.

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KEYWORDS
COVID-19; SARS-CoV-2; ARDS; symptoms; outcome

1. Introduction

Starting December 2019, multiple cases of pneumonia of unknown etiology were reported in Wuhan, Hubei province, China [1]. The causative agent, a novel coronavirus, was subsequently identified (January 7th, 2020) by the Chinese Center for Disease Control and Prevention (CDC) and has been named Coronavirus disease 2019 (COVID-19).

So far, COVID-19 has claimed more cases and fatalities than severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV) [2,3]. This fact could be related to potentially more sources of viral transmission, including aerosolized droplets, direct contact and potentially fecal-oral transmission [4,5]. The lack of medical staff and personal

CONTACT Ping Chen pingchen0731@csu.edu.cn Department of Respiratory and Critical Care Medicine, Second Xiangya Hospital, Central South University, 139 Renmin Middle Road, Changsha, Hunan 410011, China; Dingding Deng dengdingding2008@126.com Department of Respiratory Medicine, First Affiliated People's Hospital of Shaoyang College, West Side of Dongfeng Pedestrian Street, Shuangqing District, Shaoyang, Hunan 422001, China
*These authors contributed equally to this study and share first authorship.

Table 1. Demographics, clinical variables and outcomes among COVID-19 subjects.

Variables	All (N = 541)	Respiratory[a] (N = 404)	Non-respiratory[b] (N = 137)	P[c]
Age (IQR)	43.0 (33.0–55.0)	45.0 (34.0–57.0)	38.0 (29.0–50.0)	<0.001
Gender: Female (%)	270 (49.9)	204 (50.5)	67 (48.9)	0.64
Body mass index (IQR)	23.3 (21.3–26.2)	23.4 (21.3–26.2)	23.1 (21.3–25.8)	0.55
Contact with confirmed cases (%)	417 (77.1)	301 (404)	116 (84.7)	0.05
Comorbidities, any (%)	173 (32.0)	144 (35.7)	29 (21.0)	0.002
Diabetes (%)	47 (8.7)	38 (9.4)	9 (6.5)	0.31
Hypertension (%)	77 (14.2)	67 (16.6)	10 (7.2)	0.007
Cardiovascular disease (%)	23 (4.3)	21 (5.2)	2 (1.5)	0.06
COPD (%)	10 (1.8)	10 (2.5)	0 (0.0)	0.06
Asthma (%)	13 (2.4)	11 (2.7)	2 (1.5)	0.40
Malignancy (%)	6 (1.1)	4 (1.0)	2 (1.5)	0.65
Disease severity at admission[d]	35/436/47/23	20/319/44/21	15/117/3/2	<0.001
Illness onset until hospitalization	4.0 (2.0–7.0)	5.0 (3.0–8.0)	4.0 (2.0–6.0)	0.16
Hospital days (IQR)	17 (14–21)	17 (12–24)	14 (11–20)	0.03
Day to recovery (IQR)	21 (16–28)	23 (17–28)	18 (14–25)	0.003
Clinical variables				
Therapy				
Antiviral therapy (%)[e]	541 (100)	403 (100)	138 (100)	1
Corticosteroids (%)	127 (23.5)	107 (26.5)	20 (14.6)	0.005
Antibiotics	244 (45.1)	194 (48.0)	50 (36.5)	0.02
Secondary bacterial infection (%)	36 (6.7)	35 (8.7)	1 (0.7)	<0.001
Support				
NIV (%)	31 (5.7)	30 (7.4)	1 (0.7)	0.004
IMV (%)	15 (2.8)	15 (3.7)	0 (0.0)	0.02
ECMO (%)	8 (1.5)	8 (2.0)	0 (0.0)	0.10
CRRT(%)	8 (1.5)	8 (2.0)	0 (0.0)	0.14
Outcomes				
ICU admission (%)	42 (7.8)	39 (9.7)	3 (2.2)	0.005
ARDS (%)	49 (9.1)	46 (11.4)	3 (2.2)	0.001
In-hospital mortality (%)	4 (0.4)	4 (0.5)	0 (0.0)	0.24
Laboratory findings				
White blood cell count (× 109/L)	4.6 (3.6–6.1)	4.7 (3.6–6.2)	4.6 (3.7–5.8)	0.53
Neutrophil count (× 109/L)	2.9 (2.2–4.1)	3.0 (2.1–4.2)	2.9 (2.3–3.8)	0.78
Lymphocyte count (× 109/L)	1.1 (0.8–1.6)	1.1 (0.8–1.6)	1.2 (0.9–1.6)	0.96
Hemoglobin (g/L)	133 (121–145)	132 (121–145)	134 (123–144)	0.68
Platelet count (× 109/L)	190 (146–247)	188 (146–246)	194 (147–248)	0.77
D-dimer (mg/L)	0.3 (0.2–0.6)	0.4 (0.2–0.6)	0.3 (0.15–0.53)	0.11
Albumin (g/L)	40.2 (36.2–43.7)	39.8 (35.6–43.4)	40.7 (37.7–44.4)	0.74
Globulin (g/L)	25.9 (23.2–28.6)	26.2 (22.9–29.0)	25.7 (23.3–28.1)	0.27
Creatine kinase (U/L)	68.7 (46.4–109.1)	69.5 (46.8–109.3)	65.8 (45.0–109.1)	0.34
Prothrombin time (s)	12.2 (11.1–12.9)	12.2 (11.1–12.9)	12.1 (11.1–12.8)	0.77
Alanine aminotransferase (IU/L)	21.0 (14.9–30.6)	21.0 (14.9–31.4)	21.0 (14.7–29.6)	0.32
Aspartate aminotransferase (IU/L)	24.0 (19.2–31.4)	24.5 (19.6–31.3)	23.4 (19.0–32.2)	0.41
Total bilirubin (umol/L)	12.0 (7.7–18.5)	12.0 (7.6–17.4)	12.0 (8.8–21.1)	0.13
Creatinine (umol/L)	62.7 (50.6–76.1)	63.0 (50.6–77.0)	59.5 (49.4–73.0)	0.16
Blood urea nitrogen (mmol/L)	4.1 (3.2–5.1)	4.1 (3.2–5.4)	4.1 (3.3–4.6)	0.29

COVID-19 = coronavirus disease 2019, COPD = chronic obstructive pulmonary disease, N = number of subjects, IQR = interquartile range, NIV = non-invasive ventilation, IMV = invasive mechanical ventilation, ECMO = extracorporeal membrane oxygenation, CRRT = Continuous Renal Replacement Therapies, ICU = intensive care unit, ARDS = acute respiratory distress syndrome. [a] Includes COVID-19 subjects with initial symptoms respiratory, [b] includes COVID-19 subjects with initial symptoms non-respiratory, [c] p value for statistical difference between respiratory COVID-19 subject and non-respiratory COVID-19 subjects, [d] severity of disease on admission (mild/moderate/severe/very severe). [e] includes abidol, lopinavir, ritonavir, interferon, [g] includes gamma globulin or thymosin. Continuous variables are presented as mean and standard deviation (if data were normally distributed) and median and interquartile range (if data were not normally distributed).

protective equipment may also have contributed to the high number of deaths. These various transmission sources are mirrored in the COVID-19 clinical syndrome, which includes some subjects with predominant respiratory symptoms at disease onset and others with more non-respiratory symptoms. In this study, we sought to explore baseline characteristics and outcomes in subjects with COVID-19 with particular attention to differences in symptoms at disease onset (respiratory versus non-respiratory). We also identify risk factors for the development of acute respiratory distress syndrome (ARDS).

2. Materials and methods

2.1. Study design and subjects

We performed a retrospective analysis of data collected from eight COVID-19 designated hospitals in Hunan and Guangxi Province, including the first Attached Hospital of Shaoyang University, the Affiliated Shaoyang Central Hospital of the University of South China, Zhuzhou Central Hospital, Yueyang Second People's Hospital, the First People's Hospital of Huaihua affiliated to the University of South China, the Second People's Hospital of Guilin, Xiangtan Central Hospital, and Loudi Central

Table 2. Frequencies of initial symptoms and signs of patients with COVID-19 infection.

Variables	All (N = 541)	Respiratory[a] (N = 404)	Non-respiratory[b] (N = 137)	P[c]
Respiratory only (%)	103 (19.0)	103 (25.5)	0 (0.0)	<0.001
Non-respiratory only (%)	137 (25.3)	0 (0.0)	137 (100)	<0.001
Combined (%)	301 (55.6)	301 (74.5)	0 (0.0)	<0.001
Initial symptom (respiratory)[e]				
Dry cough (%)	368 (68.0)	368 (91.1)	0 (0.0)	<0.001
Sputum production (%)	165 (30.5)	165 (40.8)	0 (0.0)	<0.001
Dyspnea (%)	89 (16.5)	89 (22.0)	0 (0.0)	<0.001
Runny nose (%)	3 (0.6)	3 (0.7)	0 (0.0)	0.31
Sore throat (%)	38 (7.0)	38 (9.4)	0 (0.0)	<0.001
Hemoptysis (%)	26 (4.8)	26 (6.4)	0 (0.0)	0.002
Chest tightness (%)	26 (4.8)	26 (6.4)	0 (0.0)	0.002
Nasal congestion (%)	15 (2.8)	15 (3.7)	0 (0.0)	0.02
Initial symptom (non-respiratory)[f]				
Fever (%)				
Fatigue (%)	179 (33.1)	128 (31.7)	51 (37.2)	0.25
Myalgia (%)	70 (12.9)	54 (13.4)	16 (11.7)	0.61
Diarrhea (%)	49 (9.1)	31(7.7)	18 (13.1)	0.05
Headache (%)	42 (7.8)	26 (6.4)	16 (11.7)	0.05
Palpitation (%)	3 (0.6)	3 (0.7)	0 (0.0)	0.31
Nausea (%)	32 (5.9)	25 (6.2)	7 (5.1)	0.64
Loss of smell/taste (%)	8 (1.5)	7 (1.7)	1 (0.7)	0.40

[a]Includes COVID-19 subjects with initial respiratory symptoms.
[b]includes COVID-19 subjects with initial non-respiratory symptoms.
[c]P value for statistical difference between respiratory COVID-19 subject and non-respiratory COVID-19 subjects.

Hospital. This research was approved by the local Ethics Committee (2020002). All hospitalized patients who tested positive for COVID-19 by real-time polymerase chain reaction between 1 January and 31 March 2020 were included. Asymptomatic subjects were excluded from the analysis. The asymptomatic subjects were those being tested positive due to intimate contact with confirmed cases.

We obtained baseline demographic, and clinical manifestations from a questionnaire designed by the CDC [6]. The treatment regimens and outcome data were collected from the electronic medical record. Respiratory symptoms at disease onset (termed 'respiratory COVID-19') were adjudicated to include patients who reported their first COVID-19 symptoms as respiratory (i.e. dry cough, sputum production, sneeze, nasal congestion, runny nose, sore throat, dyspnea, chest tightness, and hemoptysis). Similarly, predominantly non-respiratory symptoms at disease onset (termed 'non-respiratory COVID-19') were adjudicated to include patients who reported their first symptoms outside the respiratory system (i.e. fever, headache, fatigue, myalgia, diarrhea, palpitation, nausea, vomit, and loss of appetite). The initial symptoms or signs were defined as the first symptoms noticed by the patients. The date of disease onset was defined as the day when the first symptom was reported. For those asymptomatic patients, the date onset was specified as the day the positive nuclear acid was reported. The disease of severity was identified according to the diagnosis and treatment protocol for COVID-19 [6].

ARDS was defined according to the Berlin definition. Briefly, the ARDS was diagnosed based on hypoxemia, which is a ratio of PaO2 to fractional inspired oxygen concentration (FiO2) (PaO2/FiO2) ≤ 300 mmHg [7]. Secondary bacterial infection was diagnosed if the patients had clinical symptoms and signs. Briefly, if two or more of the following clinical features are present: temperature greater than 38°C or less than 36°C, leukopenia or leukocytosis, purulent tracheal secretions and decreased PaO2, and the absence of an alternative infective focus mandates that a chest radiograph be performed. Then if the radiograph shows alveolar infiltrates or an air bronchogram sign, or if the findings have worsened, it is recommended that the CPIS be calculated which is more than 6 scores. Or laboratory findings of nosocomial pneumonia or bacteremia not present on admission [8].

2.2. Statistical analysis

Means for continuous variables were compared by independent group t-tests or Mann-Whitney test. Proportions of categorical variables were compared using the chi-square test or Fisher's exact test. Adjusted multiple logistic regression models were performed to determine risk factors for ARDS development. All statistical analyses were performed using SPSS version 25.0 software. A value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Demographics, clinical variables, and outcomes among COVID-19 subjects

We recruited 541 cases in the final analysis. The median age of the recruited subjects was 43 years (IQR, 33–55). Of

Table 3. Differences in symptoms between patients who developed ARDS and non-ARDS.

Variables	ARDS (N = 49)	No-ARDS (N = 492)	P
Initial symptom (respiratory)			
Dry cough (%)	38 (7.8)	330 (67.1)	0.13
Sputum production (%)	18 (36.7)	147 (29.9)	0.32
Dyspnea (%)	31 (63.3)	58 (11.8)	<0.001
Runny nose (%)	0 (0)	3 (0.6)	0.58
Sore throat (%)	2 (4.1)	36 (7.3)	0.40
Hemoptysis (%)	5 (10.2)	21 (4.3)	0.06
Chest tightness (%)	5 (10.2)	21 (4.3)	0.06
Nasal congestion (%)	2 (4.1)	13 (2.6)	0.56
Initial symptom (non-respiratory)			
Fever (%)	46 (93.9)	356 (72.4)	0.001
Fatigue (%)	25 (51.0)	154 (31.3)	0.005
Myalgia (%)	4 (8.2)	66 (13.4)	0.30
Diarrhea (%)	6 (12.2)	43 (8.7)	0.42
Headache (%)	6 (12.2)	36 (7.3)	0.22
Palpitation (%)	0 (0)	3 (0.6)	0.58
Nausea (%)	5 (10.2)	27 (5.5)	0.18
Loss of smell/taste (%)	1 (2.0)	7 (1.4)	0.73

ARDS = acute respiratory distress syndrome.

Table 4. Univariate and stepwise multivariate analyses of risk factors for ARDS development.

	Univariate			Multivariate		
Variables	OR	95% CI	P	OR	95% CI	P
Age (years)	1.05	1.03–1.07	<0.001	1.04	1.01–1.06	0.01
Comorbidities	5.13	2.74–9.61	<0.001	1.18	0.50–2.78	0.71
Bacterial infection	50.2	21.7–116.0	<0.001	19.8	7.49–52.4	<0.001
Dry cough	1.70	0.85–3.40	0.01	0.96	0.40–2.33	0.93
Sputum production	1.36	0.74–2.51	0.32	-	-	-
Dyspnea	12.9	6.78–24.5	<0.001	4.91	2.21–10.9	<0.001
Chest tightness	2.55	0.92–7.09	0.07	-	-	-
Hemoptysis	2.55	0.92–7.09	0.07	-	-	-
Fever	5.86	1.79–19.2	0.003	3.76	1.01–14.0	0.05
Headache	1.78	0.71–4.43	0.23	-	-	-
Fatigue	2.27	1.26–4.11	0.007	1.67	0.77–3.63	0.20
Myalgia	0.57	0.20–1.65	0.30	-	-	-
Diarrhea	1.46	0.59–3.62	0.42	-	-	-

ARDS = acute respiratory distress syndrome, OR = odds ratio, CI = confidence interval.

the 541 subjects, 173 (32.0%) had one or more coexisting medical conditions. Hypertension (14.2%) and diabetes (8.7%) were the most common comorbidities. Respiratory COVID-19 subjects were more likely to be classified into the severe and very severe groups and had longer hospital days (17 vs 14, $P = 0.03$) relative to non-respiratory COVID-19 subjects. All the patients received antiviral therapy. Respiratory COVID-19 subjects received more corticosteroids (26.5 vs 14.6, $P = 0.005$) and antibiotics (48 vs 36.5, $P = 0.02$) compared to non-respiratory COVID-19 subjects. Respiratory COVID-19 subjects also had more secondary bacterial infections ($P < 0.001$), needed the intensive care unit more ($P = 0.005$), non-invasive ventilation more ($P = 0.004$), developed ARDS more ($P = 0.001$) and needed longer to recover ($P = 0.003$) compared to predominately non-respiratory COVID-19 subjects. No non-respiratory COVID-19 subject required advanced support, including invasive mechanical ventilation, extracorporeal membrane oxygenation, and continuous renal replacement therapies. There were no significant differences in laboratory findings between the two groups (Table 1).

3.2. Frequencies of initial symptoms and signs of patients with COVID-19 infection

Four hundred and four of the 541 (74.5%) subjects had an initial symptom that was respiratory, while 137 of the 541 (25.5%) subjects had non-respiratory symptoms. The most common respiratory symptom was dry cough (68.0%), followed by sputum production (30.5%) and dyspnea (16.5%), while the most common non-respiratory symptom was fever (74.3%) followed by fatigue (33.1%) and myalgia (12.9%) (Table 2).

3.3. Differences of symptoms between patients developed ARDS and no-ARDS

Compared with patients who did not develop ARDS, patients who developed ARDS had significantly higher percentage of dyspnea (63.3% vs 11.8%, $P < 0.001$), fever (93.9% vs 72.4%, $P = 0.001$) and fatigue (51% vs 31.3%, $P = 0.005$) (Table 3).

3.4. Risk factors for ARDS incidence

Forty-nine of 541 subjects in the cohort developed ARDS, most coming from the respiratory COVID-19 population. Univariate analysis showed several risk factors for developing ARDS, including age (odds ratio (OR) = 1.05, 95% confidence interval (CI) = 1.03–1.07, $P < 0.001$), comorbidities (OR = 5.13, 95% CI = 2.74–9.61, $P < 0.001$), secondary bacterial infection (OR = 50.2, 95% CI = 21.7–116.0, $P < 0.001$), dry cough (OR = 1.7, 95% CI = 0.85–3.40, $P = 0.01$), dyspnea (OR = 12.9, 95% CI = 6.78–24.5, $P = 0.01$), fever (OR = 5.86, 95% CI = 1.79–19.2, $P = 0.003$) and fatigue (OR = 2.27, 95% CI = 1.26–4.11, $P = 0.007$). The multivariate model showed that age (OR = 1.04, $P = 0.01$) dyspnea (OR = 4.91, $P < 0.001$) and secondary bacterial infection (OR = 19.8, $P < 0.001$) were independently associated with development of ARDS (Table 4).

4. Discussion

Our observation that relatively young patients (median age 38) with non-respiratory symptoms at COVID-19 disease onset have better outcomes may aid frontline healthcare workers caring for these patients. While COVID-19 disease is known to range from asymptomatic disease to ARDS/death, there is limited data to identify where patients will fall on this disease continuum. Here, we demonstrate a COVID-19 population (non-respiratory COVID-19) that utilized fewer hospital resources, required no advanced respiratory support, and had quicker recovery. As the previous studies showed, the most common symptoms were dry cough and fever [9,10].

Similarly, identifying patients (older patients), symptoms (dyspnea) at disease onset, and clinical developments (secondary bacterial infections) associated with ARDS development may help healthcare providers identify patients at the highest risk of clinical worsening. Here, our data demonstrate that subjects who reported dyspnea at disease onset were more likely to have worse outcomes. Interestingly, comorbidities, including diabetes and hypertension, were not associated with ARDS development but instead likely reflect the increased comorbidity burden associated with aging and were not a contributor to ARDS development itself. Rather, alterations in airway epithelium and dysregulated immune responses associated with aging are more likely causative [11].

Our study has strengths and limitations. The large, laboratory-confirmed, COVID-19 population (N = 541) from eight COVID-19 designed hospitals improves the generalizability of our observations to regions and hospital systems that designate hospitals to care for COVID-19 patients, but the mortality is not as high as reported for the COVID-19 patients, in China; the mortality is less than 1% except for Wuhan [12], which may due to the lack of medical staff and personal protective equipment in Wuhan at the early stage of the disease outbreak, and as such, the finding in this study may not apply to regions with severe outbreaks, such as New York and Lombardy. This is a retrospective study, and some rare symptoms might not have been noted, but the common symptoms of COVID-19 were all recorded in the questionnaire designed by CDC. Finally, we did not obtain microbiological information and for secondary bacterial infection definition, we referred to the standards as Rotstein et al. [8] reported. Because the management of patient specimens was very strict according to the official documents in China during the COVID-19 outbreak, ordinary laboratories were not allowed to conduct microbiological study for COVID-19 patients.

In conclusion, we identify COVID-19 subjects with dyspnea at disease onset who have a worse prognosis. We also demonstrate age and secondary bacterial infections to be independently associated with ARDS development in subjects with COVID-19.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Ethics approval

The research protocol was approved by the local Ethics (number: C2020002) and conducted in accordance with the Declaration of Helsinki and its amendments. Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

Availability of data and materials

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

AYZ, QS and YTP had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. PC and DDD supervised the whole study. The other authors helped to collect and analyze data.

ORCID

Yating Peng http://orcid.org/0000-0003-2345-4059

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