Symptoms at disease onset predict prognosis in COVID-19 disease

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Research

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Abstract

Background: 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 extra-respiratory symptoms, such as fever, myalgia and diarrhea. Here we compared the different characteristics and outcomes between the patients with respiratory symptoms and extra-respiratory symptoms at illness onset.

Methods: The patients admitted to the respiratory departments from eight hospitals out of Wuhan with nucleic acid-positive of 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.

Results: 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 extra-respiratory symptoms. Respiratory COVID-19 subjects 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 extra-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.

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

Background

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). As of April 22th, 2020, over 2.5 million human infections with COVID-19 have been confirmed worldwide with over 180,000 reported deaths[2].

So far, COVID-19 has claimed more cases and fatalities than severe acute respiratory syndrome coronavirus (SARS-CoV)[3] and and middle east respiratory syndrome coronavirus (MERS-CoV) [4]did. This fact could be related to potentially more sources of viral transmission, including aerosolized droplets, direct contact [5]and potentially fecal–oral transmission [6]. The

lack of medical staff and personal protective equipment may also contribute to the high number of deaths. These various transmission sources are mirrored in the COVID-19 clinical syndrome, which includes some subjects with predominate respiratory symptoms at disease onset and others with more

extra-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 extra-respiratory). We also identify risk factors for development of acute respiratory distress syndrome (ARDS).

Methods

We performed a retrospective analysis of data collected from eight COVID-19 designated hospitals out of Wuhan. 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 January 1st and March 31th, 2020 were included. Asymptomatic subjects were excluded in 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[7]. The treatment regimens and outcome data were collected from the electronic medical record. Respiratory symptoms at disease onset (termed “respiratory COVID-19”) was 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, hemoptysis). Similarly, predominantly extra-respiratory symptoms at disease onset (termed “extra-respiratory COVID-19”) was 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.[7]

ARDS was defined according to the Berlin definition [8]. Secondary bacterial infection was diagnosed if the patients had clinical symptoms, signs or laboratory findings of nosocomial pneumonia or bacteremia not present on admission [9].

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 $\chi 2$ test or Fisher 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. P value of < 0.05 was considered statistically significant.

Results

Demographics, clinical variables and outcomes among COVID-19 subjects

We identified 594 hospitalized subjects infected by COVID-19, 53 asymptomatic patients were excluded. 541 cases were recruited in the final analysis. The median age of the recruited subjects was 43 years (IQR, 33–55). Of 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 severe and very severe group and had longer hospital days (17 vs 14, $p = 0.03$) relative to extra-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 extra-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 extra-respiratory COVID-19 subjects. No extra-respiratory COVID-19 subject required advanced support, including invasive mechanical ventilation, extracorporeal membrane oxygenation, and continuous renal replacement therapies. There were no significant differences of laboratory findings between the two groups. (Table 1)

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

Variable	All	Respiratory[a]	Extra-respiratory[b]	p[c]
N	**541**	**404**	**137**	
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
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

Variable	All	Respiratory[a]	Extra-respiratory[b]	p[c]
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)	3.3.3–4.6)	0.29

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

404 of the 541 (74.5%) subjects had initial symptom that were respiratory, while 137 of the 541 (25.5%) subjects had extra-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 extra-respiratory symptom was fever (74.3%), and followed by fatigue (33.1%) and myalgia (12.9%). (Table 2).

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

Variable	All	Respiratory[a]	Extra-respiratory[b]	p[c]
Respiratory only (%)	103 (19.0)	103 (25.5)	0 (0.0)	< 0.001
Extra-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 (extra-respiratory) [f]				
Fever (%)	402 (74.3)	288(71.3)	114(83.2)	0.006
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

[a] Includes COVID-19 subjects with initial symptoms respiratory, [b] includes COVID-19 subjects with initial symptoms extra-respiratory

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

Compared with patients who didn't develop to 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).

Table 3
Differences of symptoms between patients developed ARDS and no- ARDS.

Variable	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 (extra-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

Risk factors for ARDS incidence.

49 of 541 subjects in the cohort developed ARDS, most coming from the respiratory COVID-19 population. Univariate analysis showed several factors are 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).

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

Variable	Univariate			Multivariate		
	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.						

Discussion

Our observation that relatively young patients (median age 38) with extra-respiratory symptoms at COVID-19 disease onset have better outcomes may aide 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 (extra-respiratory COVID-19) that utilized less 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[10, 11].

Similarly, identifying patients (older patients), symptoms (dyspnea) at disease onset and clinical developments (secondary bacterial infections) associated with ARDS development may help health care providers identify patients at highest risk of clinical worsening. Here our data demonstrates subjects who

reported dyspnea at disease onset are more likely to have worse outcomes. Interestingly, comorbidities, including diabetes and hypertension, were not associated with ARDS development but instead likely reflect the increase comorbidity burden associated with aging and not a contributor to ARDS development itself. Rather, alterations in airway epithelium and dysregulated immune responses associated with aging are more likely causative [12].

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 of the COVID-19 patients, in China, the mortality is less than 1% except Wuhan[13], this may due to the lack of medical staff and personal protective equipment in Wuhan at the early stage of the disease outbreak, 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, some rare symptoms may have not been noted, but the common symptoms of COVID-19 were all recorded in the questionnaire designed by CDC.

Conclusion

We identify COVID-19 subjects with dyspnea at disease onset have 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.

Declarations

Ethics approval

The research protocol was approved by the local Ethics Committee of the First Affiliated People's Hospital of Shaoyang College (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.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Conflict of Interest Disclosures:

None of the authors have a conflict of interest that could affect this manuscript.

Author contributions:

Dr Aiyuan Zhou and Yating Peng had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr Aiyuan Zhou, and Yating Peng contributed equally to this article and share first authorship. Dr Ping Chen designed supervised the whole study. The other authors helped to collect and analyze data. The first version manuscript was drafted by Aiyuan Zhou and Yating Peng. The others made Critical revision of the manuscript.

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References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020, 395:497-506.
2. Johns Hopkins Coronavirus Resource Center. [cited 2020 Apr 18]; Available from: https://coronavirus.jhu.edu/map.htmlhttps://coronavirus.jhu.edu/map.html.
3. Zhong NS, Zheng BJ, Li YM, Poon, Xie ZH, Chan KH, Li PH, Tan SY, Chang Q, Xie JP, et al: Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. Lancet 2003, 362:1353-1358.
4. Anderson LJ, Baric RS: Emerging human coronaviruses–disease potential and preparedness. N Engl J Med 2012, 367:1850-1852.
5. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, et al: Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med 2020, 382:1199-1207.
6. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural A, et al: First Case of 2019 Novel Coronavirus in the United States. N Engl J Med 2020, 382:929-936.
7. National Health Commission of China. New coronavirus pneumonia prevention and control program (5th edn). Feb 22, 2020.http://www.gov.cn/zhengce/zhengceku/2020-02/22/content_5482010.htm.

8. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS: Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012, 307:2526-2533.
9. Rotstein C, Evans G, Born A, Grossman R, Light RB, Magder S, McTaggart B, Weiss K, Zhanel GG: Clinical practice guidelines for hospital-acquired pneumonia and ventilator-associated pneumonia in adults. Can J Infect Dis Med Microbiol 2008, 19:19-53.
10. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, et al: Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020, 395:507-513.
11. Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, Li P, Zhou Y, Lin YF, Duan Q, et al: Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. J Infect 2020.
12. Cho SJ, Stout-Delgado HW: Aging and Lung Disease. Annu Rev Physiol 2020, 82:433-459.
13. Lian J, Jin X, Hao S, Cai H, Zhang S, Zheng L, Jia H, Hu J, Gao J, Zhang Y, et al: Analysis of Epidemiological and Clinical features in older patients with Corona Virus Disease 2019 (COVID-19) out of Wuhan. Clin Infect Dis 2020.

Highlights

1. Respiratory COVID-19 subjects had more secondary bacterial infections, needed more intensive care unit care, more ventilation support and developed ARDS more compared to predominately extra-respiratory COVID-19 subjects.
2. Dyspnea at disease onset is an independently factor for developing ARDS among COVID-19 subjects.
3. Age and secondary bacterial infections are independently associated with ARDS development in subjects with COVID-19.