

RESEARCH LETTER

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Non-febrile COVID-19 patients were common and often became critically ill: a retrospective multicenter cohort study

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To the Editor:

Recent cohort studies frequently reported low rate of fever in coronavirus disease 2019 (COVID-19) patients [1, 2], which was in sharp contrast with previous studies that reported >98% of patients presented fever on admission [3, 4]. Fever is a protective response for infections and an important criterion in the diagnosis of COVID-19. To understand the prevalence of fever in COVID-19 and its correlation with other symptoms and outcomes, we conducted a chart review of 252 hospitalized patients from 15 participating hospitals in Guangdong, Hubei, and Jiangxi provinces, China, from January 19 to March 6, 2020 (Table 1). Diagnosis of COVID-19 was based on positive severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) reverse transcription-PCR test. Our study was approved by the institutional review boards of the Sun Yat-sen University and the participating hospitals.

Demographic, clinical, laboratory, treatment, and outcome data were collected. The hospital course was reviewed for severity of disease. Critically ill patients were defined as those admitted to the ICU requiring mechanical ventilation or had a fraction of inspired oxygen (FiO₂) of at least 60% [5]. SPSS (Statistical Package for the Social Sciences) version 24.0 software (SPSS Inc.)

was used for Mann-Whitney *U*, chi-square, and the Fisher's exact test. All statistical tests were two sided, with *p* values of <0.05 considered to be statistically significant.

We found that, on admission, 197 (78%) patients had temperatures $\geq 37.3^\circ\text{C}$, 93 (37%) patients had temperatures $> 38^\circ\text{C}$, and 13 (5%) patients had temperatures $> 39^\circ\text{C}$ (Table 1). We then examined the differential symptoms and outcomes between febrile ($\geq 37.3^\circ\text{C}$) and non-febrile ($< 37.3^\circ\text{C}$) patients.

The most common symptoms on admission in both febrile and non-febrile patients were cough, poor appetite, and sputum production (Table 1). Smaller proportion of the non-febrile patients presented cough, poor appetite, and sputum production, compared to the febrile patients. In contrast, larger proportion of the non-febrile patients presented cephalalgia. The negative correlation between cephalalgia and fever is intriguing. Currently, there is no evidence for SARS-CoV-2 infection in brain tissue, although ACE2 expression in neuron was observed. Perhaps inflammatory cytokines from peripheral blood caused headache [6] in COVID-19. Cephalalgia may be a useful sign for the identification of non-febrile COVID-19, when epidemiological evidence for the infection exists.

No significant difference in any of the recorded comorbidities was observed between febrile and non-febrile patients.

Similar high proportions of febrile (157 [80%]) and non-febrile patients (43 [78%]) required oxygen supplementation (Table 1), indicating that respiratory system was the most affected system for both groups of patients.

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Table 1 Demographics and clinical characteristics of COVID-19 patients on admission

	Total (n = 252)	Febrile (n = 197)	Non-febrile (n = 55)	P value
Age, years				
≤ 29	26 (10%)	16 (8%)	10 (18%)	0.121
30–49	106 (42%)	85 (43%)	21 (38%)	
50–69	94 (37%)	73 (37%)	21 (38%)	
≥ 70	26 (10%)	23 (12%)	3 (5%)	
Sex				
Female	110 (44%)	82 (42%)	28 (51%)	0.231
Male	141 (56%)	114 (58%)	27 (49%)	
Temperature, °C				
< 37.3	55 (22%)	0	55 (100%)	< 0.001
37.3–38.0	104 (41%)	104 (53%)	0	
38.1–39	80 (32%)	80 (41%)	0	
39.1–41	13 (5%)	13 (7%)	0	
Signs and symptoms				
Cough	177 (70%)	145 (74%)	32 (58%)	0.027
Myalgia	42 (17%)	33 (17%)	9 (16%)	0.946
Cephalalgia	22 (9%)	12 (6%)	10 (18%)	0.005
Sputum	105 (42%)	92 (47%)	13 (24%)	0.002
Hemoptysis	4 (2%)	4 (2%)	0	0.579
Diarrhea	28 (11%)	23 (12%)	5 (9%)	0.590
Dyspnea	35 (14%)	28 (14%)	7 (13%)	0.768
Poor appetite	140 (56%)	117 (59%)	23 (42%)	0.020
Comorbidity				
Hypertension	48 (19%)	39 (20%)	9 (16%)	0.566
Diabetes	18 (7%)	14 (7%)	4 (7%)	1.000
Digestive tract disease	4 (2%)	2 (1%)	2 (4%)	0.444
Cardiovascular disease	10 (4%)	8 (4%)	2 (4%)	1.000
Cerebrovascular disease	3 (1%)	3 (2%)	0	1.000
Malignancy	4 (2%)	2 (1%)	2 (4%)	0.444
Liver disease	6 (2%)	3 (2%)	3 (5%)	0.234
Chronic lung disease	8 (3%)	5 (3%)	3 (5%)	0.512
Treatments and outcomes				
Oxygen supplementation	200 (79%)	157 (80%)	43 (78%)	0.806
Mechanical ventilation	10 (4%)	9 (5%)	1 (2%)	0.594
ECMO	4 (2%)	4 (2%)	0	0.579
Critically ill	52 (21%)	40 (20%)	12 (22%)	0.806
ARDS	21 (8%)	17 (9%)	4 (7%)	0.963
ICU admission	43 (17%)	34 (17%)	9 (16%)	0.876
Mortality	6 (2%)	6 (3%)	0	0.344

Data are median (IQR) or n (%). P values comparing febrile and non-febrile are from Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. Medical records of COVID-19 patients were accessed from Jingzhou Hospital of Traditional Chinese Medicine (61 cases), Jianli Hospital of Traditional Chinese Medicine (41 cases), Jingzhou Central Hospital (21 cases), Dongguan People's Hospital (14 cases), Jieyang People's Hospital (8 cases), Shangrao People's Hospital (12 cases), Shangrao No.2 People's Hospital (3 cases), Poyang People's Hospital (53 cases), Yugan People's Hospital (3 cases), Wuyuan People's Hospital (5 cases), Dexing People's Hospital (3 cases), Guangfeng People's Hospital (16 cases), Yushan People's Hospital (9 cases), Yanshan People's Hospital (2 cases), and Wannian People's Hospital (1 case).

ECMO extracorporeal membrane oxygenation, ARDS acute respiratory distress syndrome, ICU intensive care unit

Among these, 17 (9%) febrile and 4 (7%) non-febrile patients developed acute respiratory distress syndrome (ARDS). Forty-three (17%) febrile and 9 (16%) non-febrile patients were admitted to the ICU. Critical illness was similarly common in the febrile (40 patients [20%]) and non-febrile (12 patients [22%]) patients.

Fever promotes inflammatory reaction, which may help control viral infection leading to beneficial outcomes. However, fever-induced upregulation of the inflammatory cytokines such as IL-1, TNF, and IL-6 may contribute to cytokine storm that contributes to critical illness. These double-edged effects of fever may explain the absence of correlation between fever and the disease outcome.

Given the high proportion of non-febrile patients in COVID-19, and that 20% non-febrile patients became critically ill, heightened attention for this elusive group of patients may be required for a better containment of the pandemic. Our finding is a timely alarm for health care workers and general population that temperature monitoring alone does not identify many of the COVID-19 patients.

Abbreviations

ARDS: Acute respiratory distress syndrome; COVID-19: Coronavirus disease 2019; FiO₂: Fraction of inspired oxygen; SARS-CoV-2: Severe acute respiratory syndrome-related coronavirus-2

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Authors' contributions

LZ, RL, and PL conceived and designed this study. YL, NJ, SC, and LZ collected the data. All authors analyzed the data. YL, NJ, and LZ prepared the manuscript. All authors critically revised the manuscript and approved the final version.

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Availability of data and materials

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

Ethics approval and consent to participate

Our study was approved by the institutional review boards of the Sun Yat-sen University and the participating hospitals. The informed consent was waived because this chart review did not involve any patient tissue or interview.

Consent for publication

Not applicable.

Competing interests

All authors declare no competing interests.

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