# Afebrile Patients with Severe Acute Respiratory Syndrome Coronavirus 2 Infection have a Longer Viral Positivity Duration: A Retrospective Analysis of 125 Patients

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**Research**

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# Abstract

**Background:** A pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is on-going. Clinical characters of afebrile cases infected with SARS-CoV-2 remain poorly understood and informations are limited on the duration of SARS-CoV-2 viral positivity.

**Methods:** We performed a single-center retrospective study of 125 patients with SARS-CoV-2 infection in Beijing Ditan Hospital, Capital Medical University from January 26 to March 15, 2020. Differences were compared among patients with/without fever. Risk factors for the duration of SARS-CoV-2 viral positivity were evaluated.

**Results:** A total of 125 patients with positive SARS-CoV-2 test were enrolled, including 38 afebrile patients and 87 febrile patients. On admission, a total of 35 (28%) patients had leukopenia, 41 (32.8%) had lymphopenia and 6 (4.8%) had thrombocytopenia. 73 patients (58.4%) had a loss of T lymphocytes and 96 patients (76.8%) had decreased CD4+T lymphocytes. Compared with febrile cases, afebrile patients had a significantly higher white blood cell count ($P = 0.001$), total lymphocytes ($P < 0.001$), platelet count ($P < 0.001$), T lymphocytes ($P = 0.013$) and CD8+ T lymphocytes ($P = 0.002$). The median SARS-CoV-2 viral positivity duration of these 125 patients was 14 days (IQR, 10-30 days) and for febrile and afebrile group were 12 days (IQR, 9-23 days) and 23 days (IQR, 11-30 days) respectively. Multivariate Cox regression results showed that the fever [hazard ratio (HR) = 0.497, $P = 0.006$], young age (HR = 0.965, $P = 0.018$), and higher count of platelet (HR = 4.555, $P = 0.034$) were the predominant risk factor for the SARS-CoV-2 viral positivity duration.

**Conclusion:** The SARS-CoV-2 virial positivity duration of the afebrile group was significantly longer than that in the febrile group. Fever, young age and a higher count of platelet were the independent protective factors for a shorter SARS-CoV-2 RNA positivity duration.


# Background

The infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a pandemic rapidly. On February 11, 2020, World Health Organization (WHO) officially named the disease of the novel coronavirus disease 2019 (COVID-19) [1]. At present, more than 7 million people worldwide have been diagnosed with the SARS-CoV-2 infection [2], which brought huge challenges and threats for both global health and economic development. Fever as the main clinical manifestation of SARS-CoV-2 infection is widely used in community and hospital emergency screening [3–5]. However, we found that afebrile patients of SARS-CoV-2 infection count for a certain part in the process of diagnosis and treatment. What’s more, the clinical characteristics and outcomes of these afebrile patients were rarely described until now. In this study, we did a retrospective study to compare the clinical characteristics and SARS-CoV-2 ribonucleic acid (RNA) positivity duration between afebrile and febrile patients with SARS-CoV-2 infection in Beijing Ditan Hospital. Besides, risk factors including clinical and laboratory data for the duration of SARS-CoV-2 RNA positivity were evaluated in 125 patients with SARS-CoV-2 infection.

## Methods

# Participants and data collection

From January 26, 2020 to March 15, 2020, a total of 176 patients were hospitalized and confirmed with SARS-CoV-2 infection in Beijing Ditan Hospital, Capital Medical University. On admission, 42 patients (23.9%) had no fever and 134 patients (76.1%) had fever. 51 patients were excluded, among whom 6 patients were less than 18 years old, 19 patients had taken NSAIDs before admission, 3 patients accompanied by autoimmune diseases and 23 patients with incomplete clinical data. At last, a total of 125 patients were enrolled in this study.

Confirmation of the SARS-CoV-2 infection was determined by real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) [6]. Specimens of the nasopharyngeal swab samples were collected every other day during hospitalization. SARS-CoV-2 RNA positivity duration time was calculated by an interval from the first day with SARS-CoV-2 RNA tested positive to the first day of SARS-CoV-2 returned to negative (at least consecutive two times of the RT-PCR negative results). Afebrile state was defined as an axillary temperature less than 37.3 ℃ until admission. The severity of illness (into mild vs. severe cases) at admission was assessed based on the latest guidelines of SARS-CoV-2 infection enacted by the Chinese Health and Health Council [7]. The following parameters were collected from electronic medical records: (1) General conditions: gender, age, symptoms, time from illness onset to hospital admission and severity of illness; (2) Chest CT findings within 24 hours after admission; (3) Laboratory characteristics: white blood cell, neutrophil, lymphocyte, monocyte, red blood cell, hemoglobin, platelet, fibrinogen, D-dimers, T lymphocyte, CD4 + T lymphocyte, CD8 + T lymphocyte, NK cell, B lymphocyte, albumin, lactic dehydrogenase, C-reactive protein, erythrocyte sedimentation rate, lactic acid, creatinine, sodium, potassium; (4) Clinical outcomes: duration of SARS-CoV-2 RNA positivity and length of hospital stay. The purpose of this study is to explore the characteristics of afebrile patients and observe the risk factors of viral RNA clearance within 30 days after illness onset.

# Statistical analysis

The statistical analysis was performed utilizing SPSS software (Version 19.0). Continuous variables were expressed as median with interquartile range (IQR) and compared by Mann-Whitney U test. Categorical variables were expressed as number (%) and compared by Chisquare ($\chi^2$) test or Fisher's exact test between groups. Cox regression proportional-hazards model was applied to assess the hazard ratio (HR) of each variable for the duration of SARS-CoV-2 viral positivity, and significant risk factors whose HR was further adjusted with covariate analysis. All statistical tests were two-sided and a $P < 0.05$ was considered statistically significant. Kaplan-Meier method with a Log-rank test was performed to evaluate the significance of the duration of SARS-CoV-2 viral positivity between afebrile and febrile group.

## Results

# The selection process of included patients

A total of 125 patients with confirmed SARS-CoV-2 infection were included in this study from January 26 to March 15, 2020 at Beijing Ditan Hospital, Capital Medical University, including 38 afebrile patients and 87 febrile patients. An overview of the selection process is presented in Fig. 1.

# Clinical characteristics of afebrile and febrile patients with SARS-CoV-2 infection at admission

Of the 87 febrile patients with SARS-CoV-2 infection, 45 (45/87, 51.7%) were male and 42 (42/87, 48.3%) were female, with a median age of 43 years (IQR, 33–60 years). Of the 38 afebrile patients with SARS-CoV-2 infection, 15 (15/38, 39.5%) were male and 23 (23/38, 60.5%) were female, with a median age of 39 years (IQR, 21–55 years). There were no differences in age and gender between the two groups. Myalgia ($P < 0.001$) and fatigue ($P = 0.004$) were more common in the febrile group than the afebrile group. There are no significant differences in respiratory symptoms including cough, sputum, shortness of breath, sore throat and rhinorrhea. What's more, the gastrointestinal symptoms like poor appetite ($P = 0.221$), nausea ($P = 0.102$) and diarrhea ($P = 0.355$) between two groups also had no significant differences. 11 patients (11/38, 29.0%) in the afebrile group showed normal chest CT on admission while 9 patients (9/87, 10.4%) in the febrile group showed normal chest CT on admission, the difference was statistically significant ($P = 0.009$). For overall patients, the median time from illness onset to hospital admission was 10 days (IQR, 6–13 days) and which had no significant difference between the two groups ($P = 0.659$). Besides, no significant difference was observed in the proportion of severe cases at admission ($P = 0.427$) (Table 1) .

Table 1
Comparision of demographic characteristics and clinical symptoms between febrile and afebrile patients infected with SARS-CoV-2

| | Total (N = 125) | Febrile (n = 87) | Afebrile (n = 38) | *P* Value |
|---|---|---|---|---|
| Sex (Male/Female) | 60/65 | 45/42 | 15/23 | 0.207 |
| Age, years | 43 (32–59) | 43 (33–60) | 39 (21–55) | 0.156 |
| Interval time from illness onset to hospital admission, days | 10 (6–13) | 8 (6 ~ 13) | 12 (6-14.25) | 0.659 |
| Severe cases at admission | 16 (12.8%) | 13 (14.9%) | 3 (7.9%) | 0.427 |
| Normal chest CT | 20 (16.0%) | 9 (10.4%) | 11 (29.0%) | 0.009 |
| Signs and symptoms | | | | |
| Dry cough | 74 (59.2%) | 56 (64.4%) | 18 (47.4%) | 0.075 |
| Expectoration | 40(32.0%) | 31 (35.6%) | 9 (23.7%) | 0.188 |
| Dyspnea | 20 (16%) | 17 (19.5%) | 3 (7.9%) | 0.102 |
| Myalgia | 34 (27.2%) | 33 (37.9%) | 1 (2.6%) | 0.000 |
| Sore throat | 21 (16.8%) | 16 (18.4%) | 5 (13.2%) | 0.472 |
| Runny nose | 10 (8.0%) | 5 (5.8%) | 5 (13.2%) | 0.295 |
| Anorexia | 12 (9.6%) | 10 (11.5%) | 2 (5.3%) | 0.221 |
| Fatigue | 50 (40.0%) | 42 (48.3%) | 8 (21.1%) | 0.004 |
| Headache | 20 (16.0%) | 17 (19.5%) | 3 (7.9%) | 0.102 |
| Diarrhea | 13 (10.4%) | 11 (12.6%) | 2 (5.3%) | 0.355 |
| Nausea | 20 (16.0%) | 17 (19.5%) | 3 (7.9%) | 0.102 |
| Asymptomatic | 8 (6.4%) | 0 (0%) | 8 (21.1%) | 0.000 |

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. CT: computed tomography. Data are median (IQR) or n/N (%), where N is the total number of patients with available data. *P* values comparing febrile and afebrile group from Mann-Whitney U test or Fisher's exact test. $P < 0.05$ was considered statistically significant.

The laboratory examination of the 125 patients is shown in Table 2. On admission, a total of 35 (28.0%) patients had leukopenia, 41 (32.8%) had lymphopenia and 6 (4.8%) had thrombocytopenia. 73 patients (58.4%) with SARS-CoV-2 infection in this study had a dramatic loss of T lymphocytes, while 55 patients (44.0%) had decreased CD8 + T lymphocytes and up to 96 patients (76.8%) had decreased CD4 + T lymphocytes. Compared with febrile cases, afebrile patients had a significantly higher white blood cells ($P = 0.001$), total lymphocytes ($P < 0.001$), platelet count ($P < 0.001$), T lymphocytes ($P = 0.013$) and CD8 +

T cells ($P = 0.002$). What's more, the plasma levels of C-reactive protein concentrations ($P < 0.001$) and sedimentation rate ($P = 0.023$) were lower significantly in afebrile patients than those in febrile patients. No significant differences were observed in CD4 + T lymphocytes ($P = 0 .113$), NK cells ($P = 0.637$) and B lymphocytes ($P = 0.620$) between two groups. As of April 20, 2020, a total of 123 patients were discharged from the hospital with a median hospitalization time of 22 days (IQR, 16–31 days). There was no statistical difference in length of hospital stay between two groups ($P = 0.930$).

Table 2
Comparision of laboratory characteristics and clinical outcomes between febrile and afebrile patients infected with SARS-CoV-2

| | Total (N = 125) | Febrile (n = 87) | Afebrile (n = 38) | P Value |
|---|---|---|---|---|
| Laboratory Indexes | | | | |
| White blood cell, $\times 10^9$/L | 4.78 (3.83–5.90) | 4.52 (3.58–5.63) | 5.43 (4.59–6.88) | 0.001 |
| 4 | 35 (28.0%) | 31 (35.6%) | 4 (10.5%) | 0.004 |
| 4 ~ 10 | 86 (68.8%) | 54 (62.1%) | 32 (84.2%) | 0.014 |
| 10 | 4 (3.2%) | 2 (2.3%) | 2 (5.3%) | 0.754 |
| Neutrophil count, × 109/L | 2.80 (2.05–4.05) | 2.80 (2.04–3.91) | 2.75 (2.09–4.37) | 0.856 |
| 2 | 27 (21.6%) | 19 (21.8%) | 8 (21.1%) | 0.922 |
| 2 ~ 8 | 95 (76.0%) | 67 (77.0%) | 28 (73.7%) | 0.689 |
| 8 | 3 (2.4%) | 1 (1.1%) | 2 (5.3%) | 0.219 |
| Lymphocyte count, $\times 10^9$/L | 1.23 (0.91–1.73) | 1.11 (0.84–1.38) | 1.90 (1.34–2.65) | 0.000 |
| 1 | 41 (32.8%) | 38 (43.7%) | 3 (7.9%) | 0.000 |
| ≥ 1 | 84 (67.2%) | 49 (56.3%) | 35 (92.1%) | .. |
| Monocyte count, $\times 10^9$/L | 0.30 (0.20–0.39) | 0.29 (0.20–0.37) | 0.34 (0.26–0.41) | 0.072 |
| 0.2 | 26 (20.8%) | 22 (25.3%) | 4 (10.5%) | 0.000 |
| ≥ 0.2 | 99 (79.2%) | 65 (74.7%) | 34 (89.5%) | … |
| Eosinophil count, $\times 10^9$/L | 0.02 (0.01–0.08) | 0.01 (0-0.04) | 0.07 (0.02–0.12) | 0.000 |
| Basophil count, $\times 10^9$/L | 0 (0-0.001) | 0 (0-0.01) | 0.01 (0.01–0.02) | 0.000 |
| Red blood cell count, $\times 10^{12}$/L | 4.59 (4.17–4.96) | 4.53 (4.12–4.85) | 4.77 (4.32–5.02) | 0.073 |
| Hemoglobin, g/L | 139 (129.0-147.8) | 138 (128.8–147.0) | 140.5 (130.8–150.0) | 0.279 |

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. RNA: ribonucleic acid. CT: computed tomography. Data are median (IQR) or n/N (%), where N is the total number of patients with available data. *P* values comparing febrile and afebrile group from Mann-Whitney U test or Fisher's exact test. $P < 0.05$ was considered statistically significant.

| | Total (N = 125) | Febrile (n = 87) | Afebrile (n = 38) | P Value |
|---|---|---|---|---|
| Platelet count, ×$10^9$/L | 206.5 (153.0-257.5) | 183.0 (147.8-228.8) | 249.0 (196.0-295.3) | 0.000 |
| 100 | 6 (4.8%) | 6 (6.9%) | 0 | 0.228 |
| 100 ~ 300 | 108 (86.4%) | 79 (90.8%) | 29 (76.3%) | 0.030 |
| 300 | 11 (8.8%) | 2 (2.3%) | 9 (23.7%) | 0.000 |
| Prothrombin time, s | 12.0 (11.2–12.5) | 12.1 (11.4–13.0) | 11.8 (11.0-12.2) | 0.059 |
| Fibrinogen, mg/dl | 273.5 (204.0-370.3) | 332.0 (226.3–386.0) | 229.0 (203.3-275.8) | 0.000 |
| D-dimer, mg/L | 0.31 (0.24–0.60) | 0.42 (0.26–0.66) | 0.25 (0.15–0.35) | 0.001 |
| Creatinine, μmol/L | 63.1 (50.9–77.6) | 62.0 (51.5–77.2) | 68.5 (48.98–79.5) | 0.847 |
| Creatine kinase, U/L | 72.9 (56.8-120.1) | 74.0 (58.9-135.8) | 70.2 (54.6-103.9) | 0.255 |
| Lactate dehydrogenase, U/L | 210.2 (179.9-301.4) | 239.1 (187.9-318.3) | 193.8 (173.3-239.7) | 0.014 |
| Alanine aminotransferase, U/L | 20.2(13.8–33.1) | 22.0 (16.5–34.0) | 16.3 (11.6–29.5) | 0.026 |
| ≤ 50 | 116 (92.8%) | 80 (92.0%) | 36 (94.7%) | 0.859 |
| 50 | 9 (7.2%) | 7 (8.0%) | 2 (5.3%) | … |
| T lymphocyte, cells/ul | 906.0 (606.5-1340.5) | 878.0 (527.0-1281.0) | 1128. 0 (774.5-1513.5) | 0.013 |
| 1027 | 73 (58.4%) | 56 (64.4%) | 17 (44.7%) | 0.041 |
| ≥ 1027 | 52 (41.6%) | 31 (35.6%) | 21 (55.3%) | … |
| CD8 + T lymphocyte, cells/ul | 358.0 (198.0-558.0) | 312.0 (161.0-450.0) | 454.5 (248.8–712.0) | 0.002 |
| 320 | 55 (44.0%) | 43 (49.4%) | 12 (31.6%) | 0.064 |
| ≥ 320 | 70 (56.0%) | 44 (50.6%) | 26 (68.4%) | … |
| CD4 + T lymphocyte, cells/ul | 534.0 (374.0-707.5) | 500.0 (359.0-676.0) | 588.0 (413.3-769.5) | 0.113 |

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. RNA: ribonucleic acid. CT: computed tomography. Data are median (IQR) or n/N (%), where N is the total number of patients with available data. *P* values comparing febrile and afebrile group from Mann-Whitney U test or Fisher's exact test. $P < 0.05$ was considered statistically significant.

| | Total (N = 125) | Febrile (n = 87) | Afebrile (n = 38) | P Value |
|---|---|---|---|---|
| 706 | 96 (76.8%) | 71 (81.6%) | 25 (65.8%) | 0.054 |
| ≥ 706 | 29 (23.2%) | 16 (18.4%) | 13 (34.2%) | … |
| NK cell, cells/ul | 171.0 (118.5–269.0) | 172.0 (119.0-245.0) | 160.5 (112.3-351.3) | 0.637 |
| 90 | 16 (12.8%) | 13 (14.9%) | 3 (7.9%) | 0.427 |
| ≥ 90 | 109 (87.2%) | 74 (85.1%) | 35 (92.1%) | … |
| B lymphocyte, cells/ul | 191.0 (131.5-250.5) | 192.0 (128.0-239.0) | 189.0 (143.5-283.8) | 0.620 |
| 90 | 4 (3.2%) | 3 (3.4%) | 1 (2.6%) | 1.000 |
| ≥ 90 | 121 (96.8%) | 84 (96.6%) | 37 (97.4%) | … |
| C-reactive protein, mg/L | 7.4 (1.1–31.4) | 14.1 (2.6–39.3) | 1.2 (0.5–5.7) | 0.000 |
| Erythrocyte sedimentation rate, mm/h | 18.0 (8.0-35.8) | 20.5 (11.8–47.3) | 14.0 (8.0-23.8) | 0.023 |
| Procalcitonin, ng/mL | 0.05 (0.05–0.08) | 0.05 (0.05–0.075) | 0.06 (0.05–0.17) | 0.241 |
| Lactic acid, mmol/L | 1.98 (1.49–2.25) | 1.90 (1.48–2.28) | 2.00 (1.51–2.25) | 0.680 |
| Clinical outcomes | | | | |
| Length of hospital stay, days | 22 (16–31) | 21 (16–31) | 23 (15–29) | 0.930 |
| Negative RNA in 30 days | 89 (71.2%) | 68 (78.2%) | 21 (55.3%) | 0.009 |
| RNA positivity duration, days | 14 (10–30) | 12 (9–23) | 23 (11–30) | 0.012 |

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. RNA: ribonucleic acid. CT: computed tomography. Data are median (IQR) or n/N (%), where N is the total number of patients with available data. *P* values comparing febrile and afebrile group from Mann-Whitney U test or Fisher's exact test. $P < 0.05$ was considered statistically significant.

# Risk factors related to the duration of SARS-CoV-2 viral positivity

The median SARS-CoV-2 viral positivity duration of these 125 patients was 14 days (IQR, 10–30 days) and for febrile and afebrile group were 12 days (IQR, 9–23 days) and 23 days (IQR, 11–30 days) respectively. The SARS-CoV-2 RNA positivity duration of the afebrile group was significantly longer than

that in the febrile group ($P = 0.012$) (Table 2). For the treatment of the 125 patients, 64 cases (51.2%) received interferon-α inhalation, 24 cases (19.2%) received oral lopinavir/ritonavir. 31 patients (24.8%) received lopinavir/ritonavir combined with interferon-α and 6 patients (4.8%) were treated with chloroquine combined with interferon-α (Table 3).

Table 3
The treatment of 125 patients infected with SARS-CoV-2

| Treatments | N (%) |
|---|---|
| Interferon-α | 64 (51.2) |
| Lopinavir/ritonavir | 24 (19.2) |
| Lopinavir/ritonavir combined with interferon-α | 31 (24.8) |
| Chloroquine combined with interferon-α | 6 (4.8) |

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Data are n/N (%), where N is the total number of patients with available data.

To observe the occurrence of viral RNA clearance within 30 days after illness onset, univariate Cox regression proportional hazards model was used to evaluate the clinical and laboratory parameters on admission and the results showed a significantly shorter SARS-CoV-2 viral positivity duration was related to younger (HR = 0.990, $P = 0.068$), fever (HR = 0.511, $P = 0.009$), higher count of platelet (HR = 4.309, $P = 0.041$) and not severe patient (HR = 0.549, $P = 0.038$). Multivariate Cox regression model showed fever (HR = 0.497, $P = 0.006$), young age (HR = 0.965, $P = 0.018$), and higher count of platelet (HR = 4.555, $P = 0.034$) were the predominant protective factors for a shorter SARS-CoV-2 RNA positivity duration (Table 4). Kaplan-Meier with Log-rank method was performed to evaluate the significance of fever to the SARS-CoV-2 viral positivity duration (Fig. 2).

Table 4
Univariate and stepwise multivariate Cox harzard analysis of risk factors for the duration of SARS-CoV-2 virus RNA detection

| Variables | Univariate analysi | | | *P* value | Stepwise multivariate analysis | | | *P* value |
|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | | | HR | 95% CI | | |
| Age | 0.990 | 0.979 | 1.001 | 0.068 | 0.965 | 0.947 | 0.985 | 0.018 |
| Gender | 1.271 | 0.800 | 1.851 | 0.358 | | | | |
| Time from illness onset to hospitalization | 0.998 | 0.944 | 1.055 | 0.938 | | | | |
| Fever or not | 0.511 | 0.310 | 0.844 | 0.009 | 0.497 | 0.301 | 0.821 | 0.006 |
| Duration of fever | 1.024 | 0.986 | 1.062 | 0.217 | | | | |
| White blood cell count | 0.823 | 0.523 | 1.296 | 0.400 | | | | |
| Neutrophil count | 0.718 | 0.439 | 1.173 | 0.186 | | | | |
| Lymphocyte count | 0.995 | 0.647 | 1.551 | 0.995 | | | | |
| Monocyte count | 0.713 | 0.436 | 1.164 | 0.176 | | | | |
| Eosinophil count | 0.823 | 0.542 | 1.251 | 0.363 | | | | |
| Basophil count | 0.993 | 0.979 | 1.007 | 0.306 | | | | |
| Platelet count | 4.309 | 1.059 | 17.530 | 0.041 | 4.555 | 1.119 | 18.543 | 0.034 |
| C-reactive protein | 1.105 | 0.723 | 1.686 | 0.645 | | | | |
| Lactic acid | 1.423 | 0.523 | 3.874 | 0.490 | | | | |
| T lymphocyte | 0.974 | 0.674 | 1.408 | 0.889 | | | | |
| CD8 + T lymphocyte | 1.112 | 0.731 | 1.692 | 0.621 | | | | |
| CD4 + T lymphocyte | 1.043 | 0.638 | 1.704 | 0.867 | | | | |
| NK + T lymphocyte | 0.714 | 0.422 | 1.209 | 0.210 | | | | |
| B lymphocyte | 0.867 | 0.351 | 2.140 | 0.756 | | | | |
| Prothrombin time | 0.982 | 0.602 | 1.604 | 0.943 | | | | |
| Fibrinogen | 0.999 | 0.997 | 1.001 | 0.573 | | | | |
| D-dimer | 0.309 | 0.047 | 2.029 | 0.221 | | | | |
| Urea | 0.997 | 0.991 | 1.002 | 0.259 | | | | |

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. HR, hazard ratio. CI, confidence interval.

| Variables | Univariate analysi | | | *P* value | Stepwise multivariate analysis | | *P* value |
|---|---|---|---|---|---|---|---|
| | HR | 95% CI | | | HR | 95% CI | |
| Alanine aminotransferase | 1.001 | 0.995 | 1.006 | 0.839 | | | |
| Albumin | 0.812 | 0.505 | 1.307 | 0.391 | | | |
| Lactate dehydrogenase | 0.999 | 0.996 | 1.002 | 0.488 | | | |
| Creatine kinase | 2.079 | 0.505 | 8.558 | 0.311 | | | |
| Creatinine | 0.996 | 0.998 | 1.004 | 0.302 | | | |
| Severe patients at admission | 0.549 | 0.312 | 0.829 | 0.038 | | | |
| Interferon-α monotherapy | 0.856 | 0.515 | 1.423 | 0.549 | | | |
| Lopinavir/ritonavir monotherapy | 0.694 | 0.438 | 1.097 | 0.118 | | | |
| Interferon-α combine lopinavir/ritonavir therapy | 0.852 | 0.495 | 1.466 | 0.563 | | | |
| Interferon-α combine chloroquine therapy | 2.064 | 0.652 | 6.537 | 0.218 | | | |
| Abnormal chest CT on admission | 0.965 | 0.545 | 1.708 | 0.901 | | | |

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. HR, hazard ratio. CI, confidence interval.

# Discussion

The WHO had defined COVID-19 as a pandemic on 11 March 202 [8], as a kind of coronavirus, the infectious number of SARS-CoV-2 were much higher than SARS-CoV in 2003 and MERS-CoV in 2012 [9, 10]. Temperature monitoring is currently widely used in community and hospital emergency settings as a major means of screening for SARS-CoV-2 infection, but a recent study has shown that the absence of fever in SARS-CoV-2 infection (42.8%) is much more frequent than that in SARS-CoV (1%) and MERS-CoV infection (2%) [9, 10]. Until now, reports on the clinical features of these non-febrile patients are rare. In this study, afebrile patients with SARS-CoV-2 infection in our hospital accounted for 23.9% (42/176) of the confirmed infection in the same period, which was lower than the previous studies [3, 11]. The different incidence rates may be explained by the different study populations, different definitions of fever, different data and methods of collection, and different prevalence among cities.

Fever is an evolutionarily conserved response of infection or injury and confers survival benefits during damage. When the pathogen enters the body, the first cells to detect foreign antigens are lymphocytes,

which produce cytokines, such as interleukins-1 beta and tumor necrosis factor-alpha, to stimulate other immune cells and begin phagocytosis of invading organisms [12, 13]. In the early stages of phagocytosis, endogenous pyrogens are released, causing fever by raising the hypothalamic temperature-setting point in the anterior hypothalamus. Fever, as a consequence of infection and inflammation, also reduces the activity of pathogens, providing a more appropriate working environment for macrophages, lymphocytes and other immune cells, and it is now thought to be a protective response that can accelerate tissue recovery [14]. Emerging evidence suggests that the increase in body temperature during fever is associated with the resolution of many infections and confers a survival advantage [15]. In addition, fever enhances immune surveillance by promoting lymphocyte trafficking to lymphoid organs and inflamed tissues during inflammation [15, 16]. That may explain the peripheral blood lymphocyte count in the febrile group was significantly lower than that in the afebrile group in our study. However, little is known about the regulation of lymphocyte by fever. In our study, the positive duration of SARS-CoV-2 RNA in febrile patients was significantly shorter than that in afebrile patients, and fever was markedly related to a shorter SARS-CoV-2 RNA positivity duration. Accordingly, we first propose that fever may play a protective role during the process of SARS-CoV-2 infection.

Our study also found that patients in the febrile group had significantly lower platelet counts than those in the non-febrile group. However, patients with a higher count of platelet have a shorter duration of SARS-CoV-2 virial positivity. Beyond the main function in hemostasis and blood coagulation, platelets are currently thought to be an important component of the inflammatory and immune response in the processes of viral infections [17]. It is susceptible to activation, damage, or degradation during severe infections or immune responses [18]. Thrombocytopenia was documented in 44.8% of the SARS patients on presentation which was higher than our results in patients infected with SARS-CoV-2 [19]. Suppression of bone marrow stromal cells, immune destruction, diffuse intravascular coagulation, platelet chemotaxis and peripheral migration, or phagocytosis by macrophages may be the potential mechanisms of the thrombocytopenia during viral infection [20]. Increasing evidence supports the idea that platelets play a role in host defense against infections. Like traditional innate immune cells, platelets are mobilized adaptively from the bone marrow in response to infection and inflammation, being the earliest and most abundant cells preset at vascular sites of inflammation and release a broad-ranging of immune mediators microparticles and exosomes that modulate innate and adaptive immune cells [21]. Evidences suggest that platelets could interact with viral pathogens directly [22, 23]. These functions are achieved through direct interaction with leukocytes, endothelial cells and via the release of soluble inflammatory mediators that enhance recruitment and activation of leukocytes [24, 25]. Besides, platelets also involve in phagocytosis by enhancing antigen presentation by antigen-presenting cells [26, 27]. The role of platelets in the clearance of virus was observed in respiratory syncytial virus infection by internalizing viral particles and by enhancing type I IFN production from peripheral blood mononuclear cells [28]. Studies had shown that patients with thrombocytopenia in infectious diseases had a higher disease activity [29]. We thus propose that low platelets induced immunodeficiency in SARS-CoV-2 infection in part explain the negative predictive value of low or declining platelet count in our study. Increasing the

understanding of immunoregulatory functions of platelets in viral infections will undoubtedly improve our knowledge on disease pathogenesis, clinical management, and therapeutic options.

In our study, leukopenia and lymphocytopenia occurred in 28.0% (35/125) and 32.8% (41/125) respectively. Lymphocytopenia was often detected in the infection of SARS-CoV [30], the exact mechanism is still being unclear. A study form Raymond SMW showed a significant decrease in white blood count and lymphocyte during the acute phase of SARS-CoV infection was found in 64% and 98% of patients respectively [31]. Compared with SARS-CoV, patients infected with MERS-CoV have a relatively low probability of leukopenia (14%) and lymphopenia (34%) [32]. Previous studies also showed that viral infections can lead to a down-regulation of lymphocyte subsets [33]. More than 80% of patients have a decrease in CD4 + T and CD8 + T lymphocyte counts during the acute phase of SARS-CoV infection [34, 35]. In a recent study by Fan Wang et al., significant decreases in lymphocytes and their subsets were also observed in patients with SARS-Cov-2 infection [36], suggesting that SARS-CoV-2 infection may have a similar immunologic response to SARS infection. Although coronavirus is not known to productively infect T lymphocytes, altered antigen-presenting cell function and impaired dendritic cell migration resulting in reduced priming of T lymphocytes likely contribute to a fewer number of T lymphocytes [37]. Despite extensive efforts, there is limited information available on the role of the antigen-specific T cell-mediated immune response to coronavirus including SARS-CoV-2.

Our study also finds that patients with young age were markedly related to a shorter duration of SARS-CoV-2 RNA positivity, which is consistent with recent studies of SRAS-CoV-2 infection [38, 39]. In most instances, children are more likely to develop a mild form of the infection. The specific mechanism remains unclear. Given the high plasticity of adaptive responses in children, particularly in their B lymphocyte compartment, could more efficiently clear the virus [40]. What’s more, angiotensin converting enzyme-2, as a receptor for SARS-CoV-2, has lung protective effects by limiting angiotensin-2 mediated pulmonary capillary leak and inflammation which is decreasing with age [41]. This could results in a better prognosis of patients with younger age.

Due to the sudden outbreak, the time of exposure to the patient's antigen and the onset of symptoms is relatively clear, we believe that this virus is the first infection in these patients, and the immune response is also the primary immune response. This study provided data on the relationship between fever and viral clearance time of SARS-CoV-2 infection, and the result shows that the SARS-CoV-2 RNA positivity duration was significantly longer than that of the febrile patients. Age and fever are independent risk factors for the duration of SARS-CoV-2 nucleic acid positivity. Our study is a retrospective study and performed in a single-center. A large-scale cohort study and a deeper look at inflammatory factors are needed to further elucidate the features of SARS-CoV-2 infection and achieve a better understanding of the interactions between the virus and host response.

# Conclusions

About a quarter of patients with SARS-CoV-2 infection did not experience fever before admission. Compared with febrile cases, afebrile patients were less likely to have myalgia and fatigue but more prone to develop asymptomatic and normal chest CT images. What's more, afebrile patients had a significantly higher white blood cell count, total lymphocytes, platelet count, T lymphocytes and CD8 + T lymphocytes. The SARS-CoV-2 virial positivity duration of the afebrile group was significantly longer than that in the febrile group. Fever, young age and a higher count of platelet were the independent protective factors for a shorter SARS-CoV-2 RNA positivity duration.

## Declarations

# Ethical Approval

This retrospective study was approved by the ethics committee of Beijing Ditan Hospital, Capital Medical University (No. 202000201). Written or oral informed consent was obtained from patients.

# Consent for publication

Not applicable

# Availability of data and materials

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

# Conflict of interest

We declare no conflict of interest.

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This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

# Authors' contributions

Study design: Rui Ding and Wen Xie. Data collection: Rugang Zhao, Ying Fan, Ligai Liu, Ying Cao, Cheng Cheng, JingJing Wang, Qi Wang, Yanbin Wang, Ting Zhang and Minghui LI. Data analysis: Rui Ding and Rugang Zhao. Writing: Rui Ding, Rugang Zhao and Wen Xie. All authors read and approved the final manuscript. Rui Ding and Rugang Zhao contributed equally to this work.

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# Figures

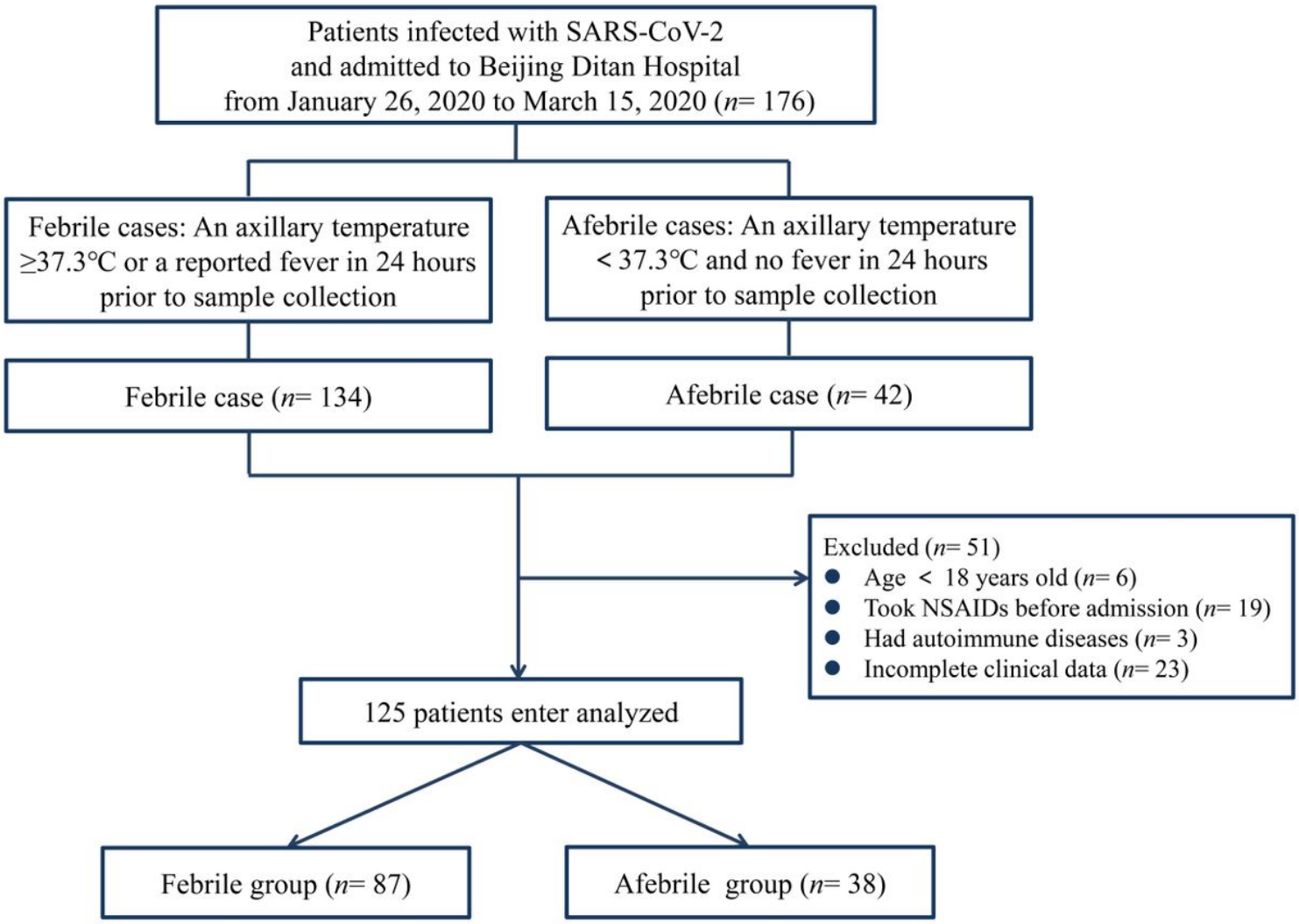
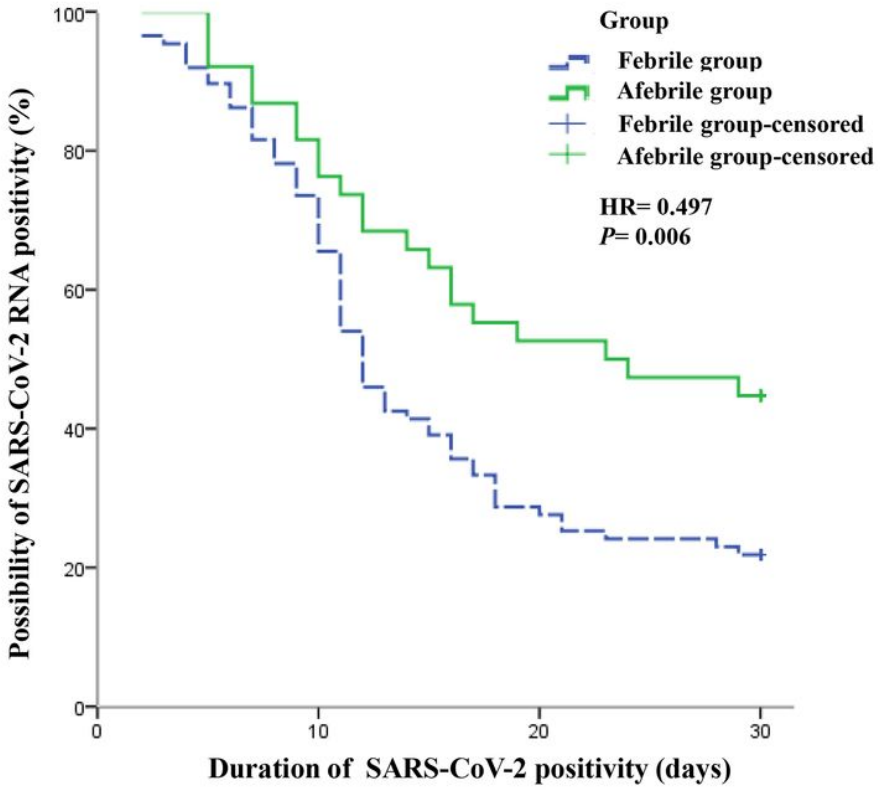



**Figure 1**

Title: The flow of patient enrollment. Legends: From January 26, 2020 to March 15, 2020, 176 patients were admitted to Beijing Ditan Hospital, Capital Medical University. 125 patients were enrolled into this study at last.




## Figure 2

Title: The survival between groups with and without fever. Legends: Kaplan-Meier method with Log-rank test was performed to evaluate the significance of fever for the duration of SARS-CoV-2 viral positivity (P = 0.006).