Effect of early oseltamivir on COVID-19-suspected outpatients without hypoxia.

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Research Article

Abstract

Background

Since December 2019, COVID-19 (corona virus disease 2019) outbreaks has occurred in China and many countries around the world. We evaluate the effectiveness of oseltamivir on COVID-19-suspected outpatients without hypoxia.

Methods

We studied 13 COVID-19-suspected medical staffs and their cohabitation families without hypoxia, who came to our adult fever clinic from March to May 2020. All patients received antiviral therapy (oseltamivir) and antibacterial therapy together.

Results

Most of the infected patients were female (8 [62%]); less than half had diabetes (one [8%]) and hypertension (three [23%]). Median age was 45 years (IQR 26−53). Oseltamivir administration made the temperature fall within 24 hours in part (8 [62%]). Clinical data were compared between patients receiving early treatment (ET) with oseltamivir, initiated within 24 hours, and patients administered late treatment (LT), initiated after this time point. Duration of fever was shorter in the ET group than in the LT group (33 ± 24 versus 94 ± 38 hours; $p < 0.01$). The time from fever onset to treatment initiation correlated with duration of fever ($r = 0.74$; $p < 0.01$) and the time from peak to decline ($r = 0.55$; $p < 0.05$).

Conclusions

Our findings suggest that early oseltamivir administration may lower the duration of fever in COVID-19-suspected outpatients without hypoxia when it is used in combination with antibacterial therapy.

Background

In late December 2019, an outbreak of an emerging disease (COVID-19) due to SARS-CoV-2 started in Wuhan, China and rapidly spread in China and outside.[1, 2] The Hokkaido Governor declared a state of emergency on February 28th 2020, and we started to avoid going out. The WHO declared the epidemic of COVID-19 as a pandemic on March 12th 2020.[3] Prime Minister declared a state of emergency on April 16th 2020 in Japan.

According to a recent Chinese study, about 80% of patients present with mild disease and the overall case-fatality rate is about 2.3% but reaches 8.0% in patients aged 70 to79 years and 14.8% in those aged > 80 years.[4] However, there is probably an important number of asymptomatic carriers in the population.

And a part of mild disease will change to severe, later. Thus, there is an urgent need for an effective treatment to treat symptomatic patients but also to decrease the duration of virus carriage in order to limit the transmission in the community.

Unfortunately, there are no vaccines approved for COVID-19. Several drugs such as chloroquine, remdesivir, and favipiravir are currently undergoing clinical studies to test their efficacy and safety in the treatment of COVID-19.[5, 6] A study has revealed that antivirals to treat influenza (umifenovir, known as arbidol) can effectively inhibit SARS-CoV-2 infection *in vitro*.[7] Oseltamivir has been most widely used for influenza, with > 65 million treatment courses prescribed worldwide. Oseltamivir was also used as an anti-MERS-CoV therapy *in Korea* and an anti-SARS-CoV2 therapy *in China*.[8, 9]

We, thus, test the hypothesis that oseltamivir administration may lower the duration of symptoms, such as fever in COVID-19-suspected outpatients.

Methods

Study Design and Participants

Twenty one medical staffs and their cohabitation families with medication in our fever clinic, from March 1, 2020, to May 14, 2020 were prospectively enrolled in the study if they fulfilled five primary criteria: i) age≧20 years, ii) peak temperature (≧37.5℃), iii) one or more respiratory symptoms; iv) a nose swab for influenza A and B was negative, v) peripheral capillary oxygen saturation (SpO2)≧93% (Fig. 1). Seven with low grade fever (peak temperature<37.5℃) were excluded. One patient with hypoxia was excluded. Thus, the study population consisted of 13 patients without low grade fever and hypoxia.

Eligible participants to receive oseltamivir 75 mg were given orally twice a day for 5 days.

Case Definition and Variable Measurement

A COVID-19-suspected case was defined as an individual who had an influenza-like illness, as shown by peak temperature≧37.5℃, 1 or more respiratory symptoms (cough, sputum, or sore throat), and a nose swab for influenza was negative.

Oseltamivir therapy was considered early treatment (ET) if the patients received treatment within 24 hours of the onset of fever (≧37.0℃) and late treatment (LT) if the antiviral therapy commenced 24 hours after onset of fever.

Duration of fever was defined as the time from the onset of fever (≧37.0℃) to the decline of fever (<37.0℃). Time from fever onset to treatment initiation was defined as the interval between onset of fever and the initial administration of oseltamivir. Time from onset to peak was defined as the interval between onset of fever and peak of fever. Time from peak to decline was defined as the interval between peak of fever and decline of fever. Last, given practical considerations, participants were asked to record data on a diary card twice or more daily in this study.

Breastfeeding and pregnant patients were excluded based on their declaration and pregnancy test results when required. Influenza antigen tests were performed immediately after sample collection (ImmunoAce Flu, Tauns Co.).[10]

Statistical Analysis

Data are expressed as mean ± standard deviation or percentages of patients. Differences were compared by Wilcoxon non-parametric test for Gaussian variable. The ratio between baseline and after medication was compared by χ^2 test. $p < 0.05$ was considered significant for all tests.

Results

Patients Characteristics

We enrolled 13 patients meeting the inclusion criteria in this study that had at least seven days of follow-up at the time of the present analysis. The baseline characteristics of the whole population are shown in Table 1. Overall, 8 patients were female (62%), with a mean age of 42 years. Median age was 45 years (IQR 26–53). All participants were negative with a local diagnostic test for influenza, of which 13 (100%) were using rapid antigen assays. Less than half had underlying diseases (5 [38%]), including diabetes (one [8%]) and hypertension (three [23%]). Any patient did not have cardiovascular disease, lung disease, chronic kidney disease, and cancer. The influenza was not spreading during the study in Sapporo and the almost all number of Influenza patient reports per fixed point of the coverage period was 1.00 or more, although the number was 1.61 only in the period from 9 March 2020 to 15 March 2020.

Effect of Oseltamivir

A total of 13 patients received oseltamivir. Among oseltamivir-treated patients, all patients also received antibacterial agents: levofloxacin (500mg on day1 followed by 500mg per day, the next six days), garenoxacin (400mg on day1 followed by 400mg per day, the next six days), or amoxicillin/ clavulanic acid (750mg on day1 followed by 750mg per day, the next six days), considering the possibility of bacterial coinfection.

The symptoms of baseline and after oseltamivir treatment are shown in Table 2. Common symptoms at onset of illness were fever (13 [100%]), myalgia or fatigue (10 [77%]), sore throat (10 [77%]), and cough (9 [69%]); less common symptoms were chills (5 [38%] of 13), headache (4 [31%]), diarrhea (4 [31%]), and sputum production (2 [15%]). Any patients did not have olfactory and taste disorders. The proportion of patients with upper respiratory symptoms was 77% and that of patients with lower respiratory symptoms was 69%.

All patients received oseltamivir, which made the temperature fall to normal(<37.0°C) within 24 hours (8 [62%] of 13 patients) and 48 hours (11 [85%]) in part. The fever disappeared in all patients at 4 days after the initial administration of oseltamivir. We let 11 medical staffs wear a mask and come back, because their symptoms disappeared at 7 days. One of these 11 medical staffs had a recurrence of the fever, but

the chest computed tomography (CT) did not show pneumonia. Two medical staffs took a day off over 1 week, because one had diarrhea and appetite loss, and another had a constant cough. Their chest CT did not also show pneumonia.

The study was divided into two groups if the patients received treatment at 24 hours of the fever onset: 7 patients (54 %) received oseltamivir within 24 hours of the onset of fever (early treatment: ET) and 6 after 24 hours (late treatment: LT). Each 2 patients received acetaminophen in the ET and the LT groups. Some patients' fever has gone within 24 hours (4 [57%] versus 4 [67%], p=NS) and 48 hours (6 [88%] versus 5 [83%], p=NS) after the initial administration in the ET and the LT groups. The two groups were comparable in terms of peak temperature, duration of fever, the time from onset to peak, and the time from peak to decline. Duration of fever were significantly shorter in the ET group than in the LT group (33±24 versus 94±38 hours; P<0.01)(Fig. 2A). The time from peak to decline tended to be shorter in ET than LT (26±27 versus 70±50 hours; p=0.07)(Fig. 2C). The time from onset to peak was significantly shorter in ET than LT (7±9 versus 24±16 hours; p<0.05)(Fig. 2B). A comparison of peak temperature showed no significant difference between the ET and the LT groups (38.0±0.6 versus 38.0±0.9°C; p=0.88).

Interaction between Duration of Fever and Time from Fever Onset to Treatment Initiation

Univariate regression analysis confirmed the time from fever onset to treatment initiation positively correlated with the duration of fever (r=0.740, p<0.01)(Fig. 3A). Likewise, the significant relationship was observed between the time from fever onset to treatment initiation and the time from peak to decline (r=0.554, p<0.05)(Fig. 3B). The time from onset to peak tended to correlate with the time from fever onset to treatment initiation (r=0.532, p<0.10). The peak temperature did not correlate with the time from fever onset to treatment initiation (r=0.009, p=NS).

Discussion

Oseltamivir were not effective enough as empirical treatment in COVID-19-infection with dyspnea or hypoxia in Wuhan.[9] COVID-19-pneumonia may be resistant at the beginning of treatment. We need to begin treatment before COVID-19-pneumonia appears. Oseltamivir was licensed for use within 48 hours of onset of symptoms, in influenza patients. Early initiation of oseltamivir after onset of symptoms increases its therapeutic effects, though even those who initiated therapy at 36 hours after onset of illness were noted to have a 25% reduction in duration of influenza.[11] Therefore I early gave oseltamivir to COVID-19-suspected outpatients without hypoxia.

Fever was the most common manifestation of COVID-19 followed by respiratory symptoms.[9] In a disease such as influenza that typically resolves within 3–4 days, using twice-daily assessments may be insensitive to detect rapid improvement. But COVID-19 sometimes differs from influenza in longer duration of fever. All patients in this study received oseltamivir within 4 days after fever onset. In more than half patients, their fever has gone within 24 hours after the initial administration. It has shown that early oseltamivir administration can reduce the duration of fever and the time from peak to decline in COVID-19-

suspected outpatients without hypoxia when it is used in combination with antibacterial therapy. The presence of fever may select for a population with more likely to benefit from oseltamivir.

Our study has some limitations, however in the current context, we believe that our results should be shared with the scientific community. First, the number of patients is too small to draw the definite conclusions. Further studies are clearly needed. Second, there was no control group for patients without use of oseltamivir, therefore, it is difficult to directly compare the duration of fever in patients with and without use of oseltamivir. Third, the population was lack of coronavirus tests because we cannot inspect coronavirus of patients without pneumonia or close contact with a SARS-CoV-2 patient in Japan. Fourth, a definitive diagnosis of influenza requires a PCR-based method in general. Therefore, this study may have included patients with influenza like illness or other respiratory diseases. We obtained influenza diagnosis information based on use of rapid diagnosis kits by medical institutions, therefore, we believe the diagnosis information was reliable.

Despite some methodological limitations, the main conclusion was that early administration of antiviral treatment with oseltamivir was key to a favorable outcome for COVID-19-suspected outpatients without hypoxia. Delay in antiviral administration has an appreciable effect on resource utilization by increasing length of fever and result in the continuous infection. Medical staffs place in a high risk situation. Early oseltamivir administration may prevent COVID-19-infected pneumonia and let medical staff come back as soon as possible.

Conclusions

Despite some methodological limitations, the main conclusion was that administration of antiviral treatment with neuraminidase inhibitors within 24 hours of fever onset was associated with a favorable outcome. Delay in antiviral administration has an appreciable effect on resource utilization by increasing length of fever and result in the continuous infection.

Abbreviations

BMI: body mass index. SpO2: peripheral capillary oxygen saturation. BCG: Bacille de Calmette et Guérin.

Declarations

Acknowledgments

We thank all of the staff members and their cohabitation families of the Sapporo Suzuki Hospital who agreed to participate in this study; we thank the president and all the doctors and nurses who cared for these patients; we thank all the technical and paramedical staffs of the hospitalization units for their support in this difficult context.

Authors' contributions

Not applicable.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

The study was approved by the institutional ethical committee and the procedures were in accordance with institutional guidelines. Informed consent was obtained from each study patient.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Patient characteristics

Variables	n=13
Age, years	42±16
Sex	
Female, n(%)	8 (62%)
BMI (kg/m^2)	22±3
SpO2 (%)	98±1
Smoking, n(%)	6 (46%)
Influenza Vaccine, n(%)	6 (46%)
BCG, n(%)	12 (92%)
Basic disease	
Hypertension, n(%)	3 (23%)
Diabetes mellitus, n(%)	1 (8%)
Dyslipidemia, n(%)	3 (23%)
Medications	
Oseltamivir, n(%)	13 (100%)
Levofloxacin, n(%)	11 (85%)
Garenoxacin, n(%)	1 (8%)
Amoxicillin/clavulanic acid, n(%)	1 (8%)
Acetaminophen, n(%)	4 (31%)
Probiotics (MIYA-BM), n(%)	2 (15%)

BMI: body mass index. SpO2: peripheral capillary

oxygen saturation. BCG: Bacille de Calmette et Guérin.

Table 2 COVID-19-suspected signs and symptoms of baseline and after oseltamivir treatment

	Baseline	7days	P value
Fever, n(%)	13 (100%)	0 (0%)	<0.001
Myalgia or fatigue, n(%)	10 (77%)	1 (8%)	<0.001
Sore throat, n(%)	10 (77%)	2 (15%)	<0.001
Cough, n(%)	9 (69%)	1 (8%)	<0.001
Chills, n(%)	5 (38%)	0 (0%)	<0.05
Headache, n(%)	4 (31%)	0 (0%)	<0.05
Diarrhea, n(%)	4 (31%)	1 (8%)	0.08
Sputum production, n(%)	2 (15%)	2 (15%)	1.00
Dyspnea, n(%)	1 (8%)	0 (0%)	0.34
Nausea or vomit, n(%)	1 (8%)	0 (0%)	0.34
Appetite loss, n(%)	1 (8%)	1 (8%)	1.00

Figures

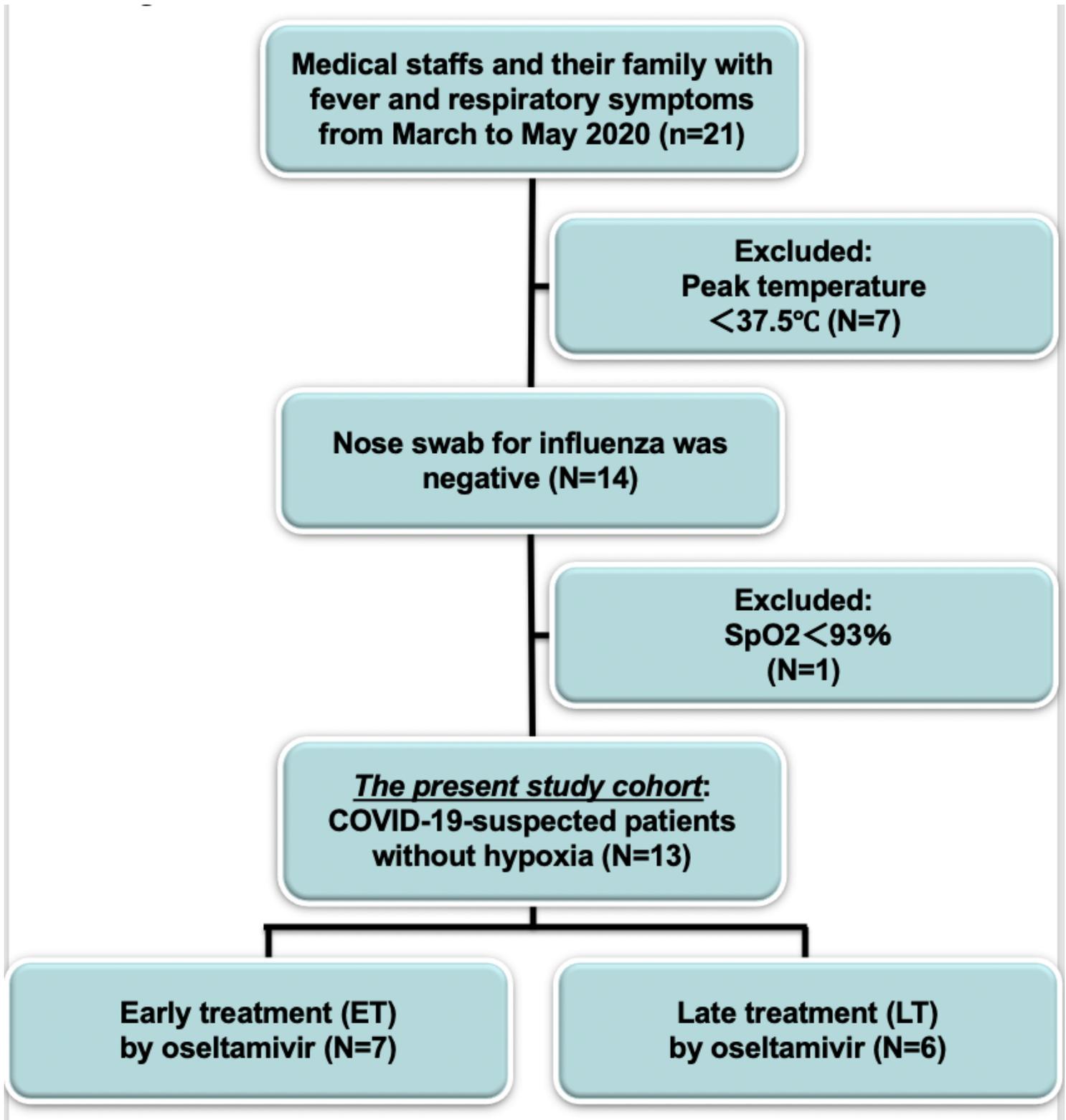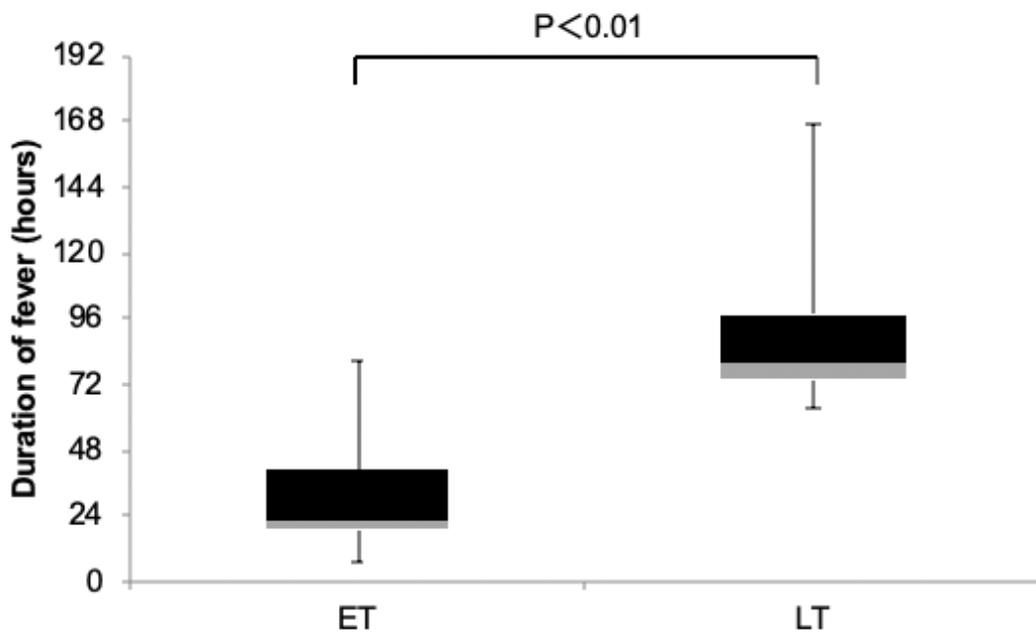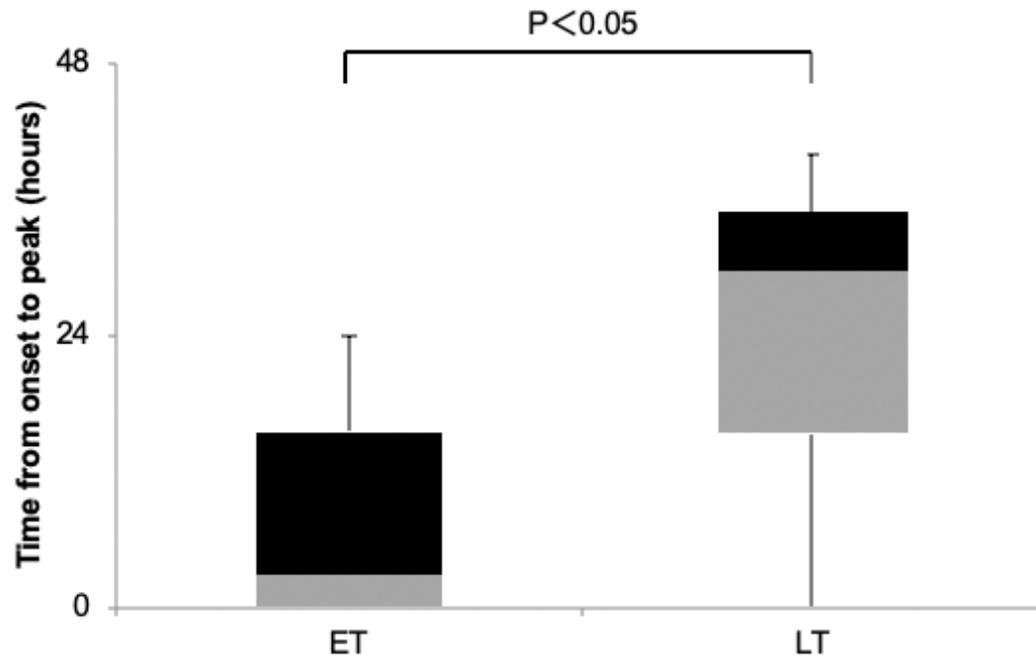**Figure 1**

Flow chart of the COVID-19-suspected outpatients study cohort. SpO2: peripheral capillary oxygen saturation

A

Duration of fever (hours): 192, 168, 144, 120, 96, 72, 48, 24, 0

P<0.01

ET   LT

B

Time from onset to peak (hours): 48, 24, 0

P<0.05

ET   LT
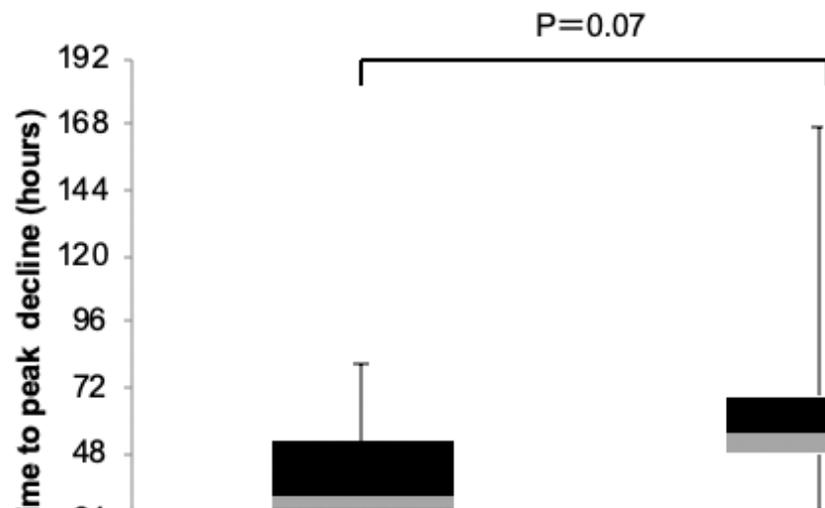
C

Time to peak decline (hours): 192, 168, 144, 120, 96, 72, 48
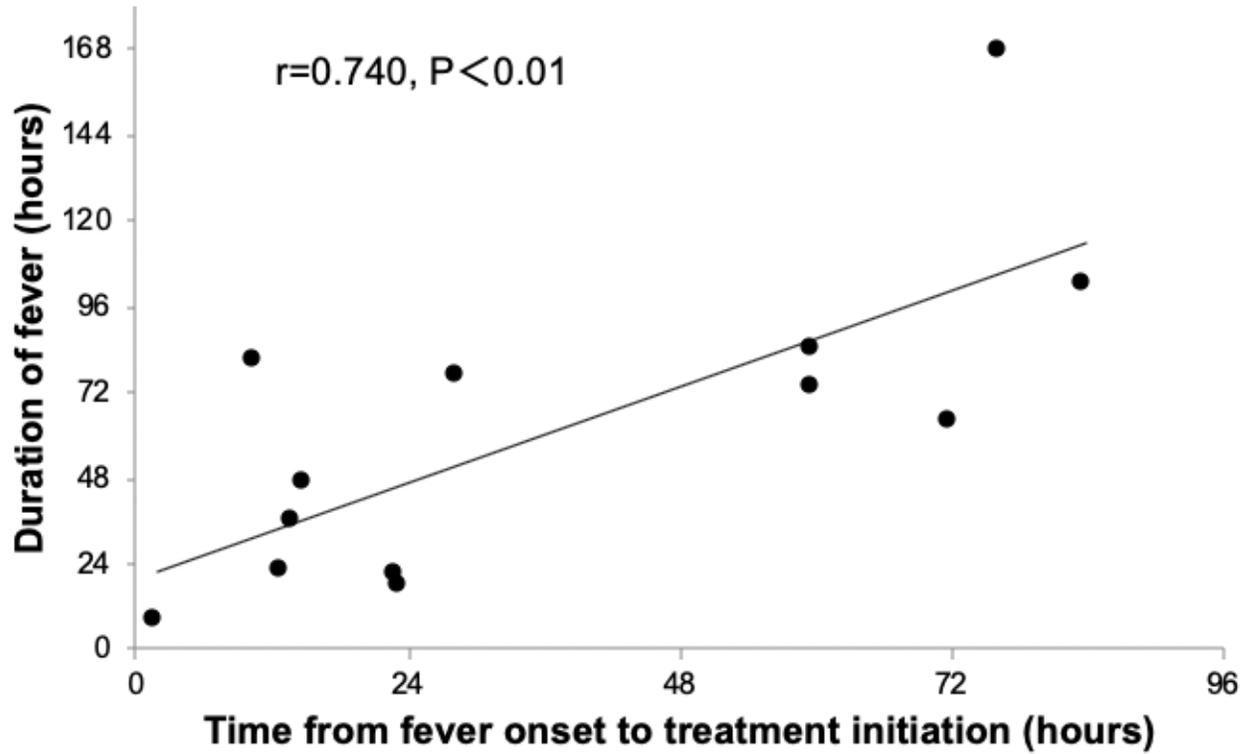
P=0.07

Figure 2

Comparison of ET (n=7) versus LT (n=6). (A) Duration of fever, (B) Time from onset to peak, (C) Time from peak to decline. ET: patients receiving early treatment with oseltamivir, initiated within 24 hours. LT: patients receiving late treatment with oseltamivir, initiated after 24 hours.
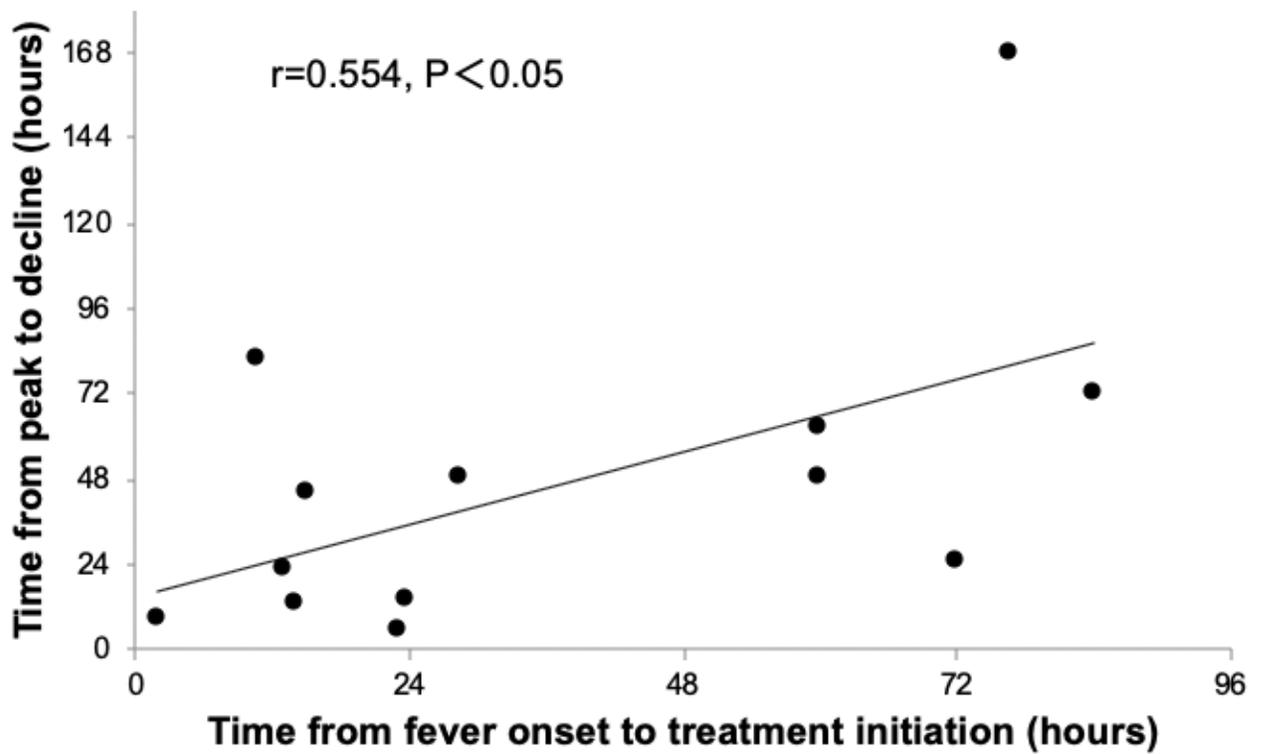
A

B

Figure 3

Correlation between time from fever onset to treatment initiation and duration of fever (A) or time from peak to decline (B)