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Real-world Efficacy of Ensitrelvir in Hospitalized Patients with COVID-19 in Japan: A Retrospective Observational Study

Ryohei Yoshida

yryohei@asahikawa-med.ac.jp

Yoshida Hospital

Takaaki Sasaki

Asahikawa Medical University

Yoshinobu Ohsaki

Yoshida Hospital

Research Article

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Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic necessitates continuously evaluating antiviral treatments, especially for high-risk groups, including older individuals. This study aimed to compare the efficacy of three antiviral drugs, including remdesivir, molnupiravir, and ensitrelvir, in hospitalized patients, focusing on outcomes such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antigen levels, hospitalization duration, and fever resolution.

Methods: This retrospective observational study was conducted at Yoshida Hospital, Asahikawa city, Japan, enrolling 154 patients who received antiviral treatment upon COVID-19 diagnosis from July 1, 2022 to September 15, 2023. The diagnosis was confirmed by proprietary antigen tests or loop-mediated isothermal amplification assays. Patients who received treatment outside the hospital or with consistently negative antigen results were excluded. Drug administration was determined by attending physicians, considering oral administration challenges and renal dysfunction. The data were statistically analyzed using an unpaired two-tailed Student's t-test and one-way analysis of variance complemented by the Tukey post-hoc test for detailed group comparisons.

Results: No significant differences were observed in the initial antigen levels among the treatment groups. By day 10, the ensitrelvir group showed lower antigen levels than did the other groups, but not significantly. The ensitrelvir group had a higher antigen-negative conversion rate and a significantly shorter hospital stay than did the molnupiravir group. However, no significant differences were noted in the fever resolution time among the groups.

Conclusion: This study suggests the potential benefits of ensitrelvir in reducing antigen levels and hospitalization duration. However, the overall efficacy of the antiviral agents for symptomatic relief appears similar. These findings underscore the need for further research to optimize COVID-19 management by considering personalized treatment approaches and long-term outcomes.

Background

The novel coronavirus classification in Japan has shifted from Category 2 to Category 5 under the Infectious Disease Control Law as of May 2023. This classification signifies the persistent necessity to address treatments for coronavirus infections. On November 6, 2020, our hospital experienced a precipitous spread of the coronavirus disease 2019 (COVID-19) cluster following the onset of fever in one inpatient and one nurse. This escalation required support from the Disaster Medical Assistance Team to reach a conclusion. The cluster incident that unfolded in November 2020 resulted in a large-scale outbreak, encompassing 136 inpatients and 77 staff members, totaling 213 affected individuals. Consequently, our hospital has maintained a rigorous and prudent approach to managing coronavirus infections, focusing on the inpatient cohort and drawing on lessons learned during the significant outbreak.

The development of vaccines against COVID-19 has contributed significantly to the prevention of the disease and mitigation of its severity [1, 2]. However, multiple factors, including advanced age, diabetes, and hypertension, reportedly contribute to an increased risk of severe disease [3–5]. Therefore, treatments, including those involving antiviral medications, play a critical role in clinical management.

Several antiviral drugs, including remdesivir, molnupiravir, nirmatrelvir/ritonavir, and ensitrelovir, are available for clinical use in Japan. Elderly individuals and nursing home residents continue to be at an elevated risk of requiring hospitalization or experiencing severe illnesses due to COVID-19. Consequently, the selection of suitable antiviral medications after hospitalization is critical. Several studies have assessed the efficacy of various antiviral drugs when treating COVID-19 [6, 7]. However, research comparing the effectiveness of distinct antiviral medications, including ensitrelvir, in hospitalized patients is scarce. Using real-world data, we aimed to compare the efficacy of three different drugs administered after hospitalization in patients who tested positive for COVID-19 and required hospitalization at our institution.

Methods

Study design

This retrospective observational study enrolled 154 patients who received antiviral treatment upon admission to Yoshida Hospital, Asahikawa city, Japan from July 1, 2022 to September 15, 2023. Positive COVID-19 diagnoses were confirmed using the institution's proprietary antigen test or the loop-mediated isothermal amplification (LAMP) assay. Patients who tested positive via LAMP but consistently displayed negative SARS-CoV-2 antigen results were excluded from the analysis. A negative result was an antigen level of < 1.0 pg/ml. The patient cohort comprised 89 women and 68 men. The average age was notably high, at 83.7 (range 53–104) years, because of the large number of patients admitted to our hospital from chronic care facilities and nursing homes. Patients were excluded if they tested positive for COVID-19 antigens and received treatment outside our facility. The attending physician determined the choice of drugs administered. Remdesivir is frequently prescribed to patients for whom oral consumption is challenging. Contraindications and renal dysfunction were considered when prescribing the medications.

Statistical analyses

Statistical significance was assessed using an unpaired two-tailed Student’s t-test and one-way analysis of variance, followed by the Tukey post-hoc test. A p-value of < 0.05 was considered statistically significant. Asterisks indicate significance, with * indicating $p < 0.05$ and ** representing $p < 0.005$. Columns represent means ± standard errors of the mean (SEMs). GraphPad Prism7 was used for all statistical analyses.

Results

Verification of SARS-CoV-2-antigen levels

We conducted a comparative analysis to validate the antigen levels of hospitalized patients when they were administered various drugs (Table 1). Upon quantitatively assessing the SARS-CoV-2 antigen levels at admission, no discernible differences in antigen concentrations across the treatment (remdesivir [17007 ± 1599 pg/ml], molnupiravir [14291 ± 2315 pg/ml], and ensitrelvir [19996 ± 2808 pg/ml]) groups were noted (Fig. 1a).

Table 1
Background characteristics of patients

	Remdesivir	Molnupiravir	Ensitrelvir
Variables	(N = 85)	(N = 44)	(N = 25)
Age at admission, years			
50s	1 (1.2)	0 (0)	1 (4)
60s	3 (3.5)	4 (9.1)	3 (12)
70s	12 (14.1)	11 (25)	7 (28)
80s	33 (38.8)	22 (50)	10 (40)
90s	33 (38.8)	7 (15.9)	4 (16)
100s	3 (3.5)	0 (0)	0 (0)
Sex			
Male	29 (34.1)	25 (56.8)	11 (44)
Female	55 (64.7)	19 (43.2)	14 (56)
Underlying condition			
Cardiovascular diseases (including hypertension)	53 (62.3)	33 (75)	17 (68)
diabetes mellitus	30 (35.3)	18 (40.9)	10 (40)
Dyslipidemia	22 (25.9)	6 (13.6)	4 (16)
Chronic kidney disease	20 (23.5)	24 (54.5)	2 (8)
Chronic liver disease	0 (0)	2 (4.5)	2 (8)
COPD	7 (8.2)	1 (2.3)	4 (16)
Cancer	13 (15.3)	11 (25)	3 (12)
Dementia	39 (45.9)	10 (22.7)	6 (24)
Depression/Schizophrenia	3 (3.5)	3 (6.8)	0 (0)
Stroke	12 (14.1)	8 (18.2)	7 (28)
Body mass index, kg/m^2			
< 25	81 (95.3)	40 (90.9)	22 (88)
25–29	3 (3.5)	3 (6.8)	2 (8)
≥ 30	1 (1.2)	1 (2.3)	1 (4)

	Remdesivir	Molnupiravir	Ensitrelvir
Hospitalization in the past year			
Yes	35 (41.2)	29 (65.9)	15 (60)
No	50 (58.8)	15 (34.1)	10 (40)
Vaccination history			
No vaccination	5 (5.9)	1 (2.3)	1 (4)
Yes	59 (69.4)	36 (81.8)	22 (88)
1 time	1 (1.2)	1 (2.3)	1 (4)
2 times	7 (8.2)	1 (2.3)	1 (4)
More than 3 times	51 (60)	34 (77.3)	20 (80)
Unknown	21 (24.7)	7 (15.9)	2 (8)

Upon evaluating the antigen levels on day 10 of treatment, we observed no significant difference between the remdesivir (3383 ± 770.7 pg/ml) and molnupiravir (2587 ± 884.4 pg/ml) groups ($p = 0.5240$). The antigen levels in the ensitrelvir (701.3 ± 436.8 pg/ml) group were lower than those in the other groups. Nevertheless, the differences were not significant between the ensitrelvir and molnupiravir groups ($p = 0.1275$) and the ensitrelvir and remdesivir groups ($p = 0.0662$) (Fig. 1b). Subsequently, we assessed the drug-specific SARS-CoV-2 antigen-negative conversion rate after 10 days of treatment. The ensitrelvir group had a rate of 40% (10/25), surpassing the rates of 20% (17/85) and 4.54% (2/44) in the remdesivir and molnupiravir groups, respectively (Fig. 1c). To elucidate the nuanced changes in the antigen levels corresponding to the use of each drug, we tracked level alterations upon admission and on day 10 of treatment. Our findings indicated that the antigen levels surged despite therapeutic intervention. Nonetheless, the antigen resurgence rates were 8% (2/25), 22.3% (19/85), and 20.4% (9/44) in the ensitrelvir, remdesivir, and molnupiravir groups, respectively, underscoring the distinctions across the drug treatments (Fig. 2).

Verification of hospitalization days

In our subsequent analysis of hospitalization duration among the various drug groups, no significant differences were observed between the remdesivir (12.11 ± 0.369 days) and molnupiravir (12.7 ± 0.354 days) groups ($p = 0.2982$) or the remdesivir and ensitrelvir (11.04 ± 0.212 days) groups ($p = 0.1264$). However, the ensitrelvir group demonstrated a significantly shorter hospital stay than did the molnupiravir group ($p = 0.0013$) (Fig. 3a). Temporal changes in the antigen levels, as depicted in Fig. 2, indicated differential antigen escalation rates across various drug treatments. Based on the antigen data, we classified patients on day 10 after treatment, relative to their admission day, into two distinct categories: the down group ($n = 124$), with decreased levels, and up group ($n = 30$), with increased levels. The ensuing

analysis revealed an average hospital stay of 11.57 days in the down group, compared with 14.3 days in the up group. This difference was significant, suggesting that patients in the up group tended to have longer hospitalizations than did those in the down group ($p < 0.0001$) (Fig. 3b).

Time for COVID-19 fever improvement

During the investigation of fever alleviation related to COVID-19, patient groups were evaluated based on the drugs they received. Upon admission, 78.8% (67/85), 80.4% (37/46), and 68% (17/25) of patients in the remdesivir, molnupiravir, and ensitrelvir groups, respectively, presented with a fever exceeding 37°C. However, analyses of the mean duration required for the fever decrease below 37°C within 5 days after admission revealed no significant differences between the groups (mean ± SEM days: 3.493 ± 0.1784, 3.432 ± 0.1958, and 2.882 ± 0.3417 in the remdesivir, molnupiravir, and ensitrelvir groups, respectively) (Fig. 4).

Discussion

This study compared the effectiveness of remdesivir, molnupiravir, and ensitrelvir in managing hospitalized patients with COVID-19, focusing on key outcomes, including SARS-CoV-2 antigen levels, hospitalization duration, and fever resolution.

Several mechanisms are currently being explored as therapeutic options for the development of antiviral agents against COVID-19. Within the scope of this study, two drugs, remdesivir and molnupiravir, function as RNA-dependent RNA polymerase (RdRp) inhibitors. Ensitrelvir is categorized as a SARS-CoV-2 main protease (Mpro) inhibitor [8]. Remdesivir, a nucleotide analog prodrug, exhibits broad-spectrum antiviral activity [9, 10]. This drug undergoes intracellular migration to synthesize its active metabolite, remdesivir triphosphate [11]. The active form of the drug impedes viral replication via a mechanism known as delayed-chain termination [12]. Molnupiravir acts as an RdRp inhibitor and is an oral prodrug of β-d-N4-hydroxycytidine. This drug operates through a mechanism termed lethal mutagenesis or “error catastrophe” [13, 14]. This process involves the accumulation of lethal mismatched nucleobases in the viral RNA genome [15], causing the proliferation of non-infectious viral particles, thereby inhibiting viral replication. Mpro, also known as 3C-like protease, is a cysteine protease that plays a pivotal role in the intracellular propagation phase of SARS-CoV-2 [16]. This protease is unique to viruses and has no human homolog, making it an ideal target for antiviral intervention. Inhibiting Mpro proteolytic activity prevents the maturation of crucial viral enzymes, including NSP12 and NSP16, consequently impeding viral replication. Thus, inhibitors targeting Mpro function act as effective antiviral agents [17, 18]. Ensitrelvir has been developed as a small-molecule compound targeting Mpro, demonstrating efficacy in cell culture studies by inhibiting many SARS-CoV-2 variants [19, 20]. All three drugs are currently employed in clinical settings and exhibit unique characteristics when used as antiviral medications [21–23]. Notably, oral antivirals medications are significantly advantageous as they can be self-administered to patients, enhancing the ease of treatment accessibility. This attribute is particularly beneficial for pandemic

management as oral antiviral medications may play an increasingly important role in curbing the virus spread [24].

Our findings demonstrated no significant differences in the initial antigen levels across the three treatment groups. However, the ensitrelvir group exhibited lower antigen levels on day 10 of treatment, although this difference was not statistically significant when compared with results in the remdesivir and molnupiravir groups. This trend aligns with that reported in earlier studies suggesting the potential efficacy of entsitrelvir in reducing viral load but emphasizes the need for larger trials to obtain conclusive evidence [25, 26]. Interestingly, the ensitrelvir group had a higher antigen-negative conversion rate (40%) than did the remdesivir (20%) and molnupiravir (4.54%) groups, indicating more rapid viral clearance with ensitrelvir. This finding merits further investigation, particularly regarding its potential impact on transmission dynamics.

Our analysis revealed a statistically significantly shorter hospital stay in patients treated with ensitrelvir than in those treated with molnupiravir. This finding is crucial because shorter hospital stays can reduce healthcare burdens, especially during pandemic peaks. However, the few significant differences with remdesivir suggest that factors other than antiviral efficacy, including patient demographics and comorbidities, may influence hospitalization duration [27, 28]. Furthermore, the study found no significant difference in the time taken to achieve fever resolution between groups. This observation suggests that while antiviral medications may influence the viral load, their impact on symptomatic relief, including fever, may not be as pronounced. This finding is consistent with the understanding that antiviral medications primarily reduce viral replication rather than directly alleviating symptoms.

These results have important clinical implications. Although ensitrelvir demonstrated promise in reducing the antigen levels and hospitalization duration, its role in clinical management requires further exploration. Additionally, the few significant differences in fever resolution across groups suggest that symptom management should be addressed with supportive care alongside antiviral therapy.

The limitations of this study include the relatively small sample size and absence of long-term follow-up data. Future research should focus on larger, diverse populations and assess long-term outcomes, including the post-acute sequelae of COVID-19.

Conclusion

While our study suggests the advantages of ensitrelvir regarding antigen clearance and reduced hospitalization duration, the overall effectiveness of these antiviral agents is similar, especially in terms of symptomatic relief. This finding underscores the need for personalized treatment approaches and further research to optimize COVID-19 management strategies.

Abbreviations

COVID-19: Coronavirus Disease 2019

LAMP: Loop-mediated Isothermal Amplification

Mpro: Main Protease

RdRp: RNA-dependent RNA Polymerase

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

SEM: Standard Error of the Mean

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Yoshida Hospital (approval no. 20230809003) and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all study patients using the opt-out method.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Author contributions

RY analyzed the data and was a major contributor in writing the manuscript. TS contributed to the manuscript by reviewing and editing the content and also played a supervisory role in the overall project. YO was responsible for the conceptualization of the project and managed the project administration.

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Not applicable.

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Figures

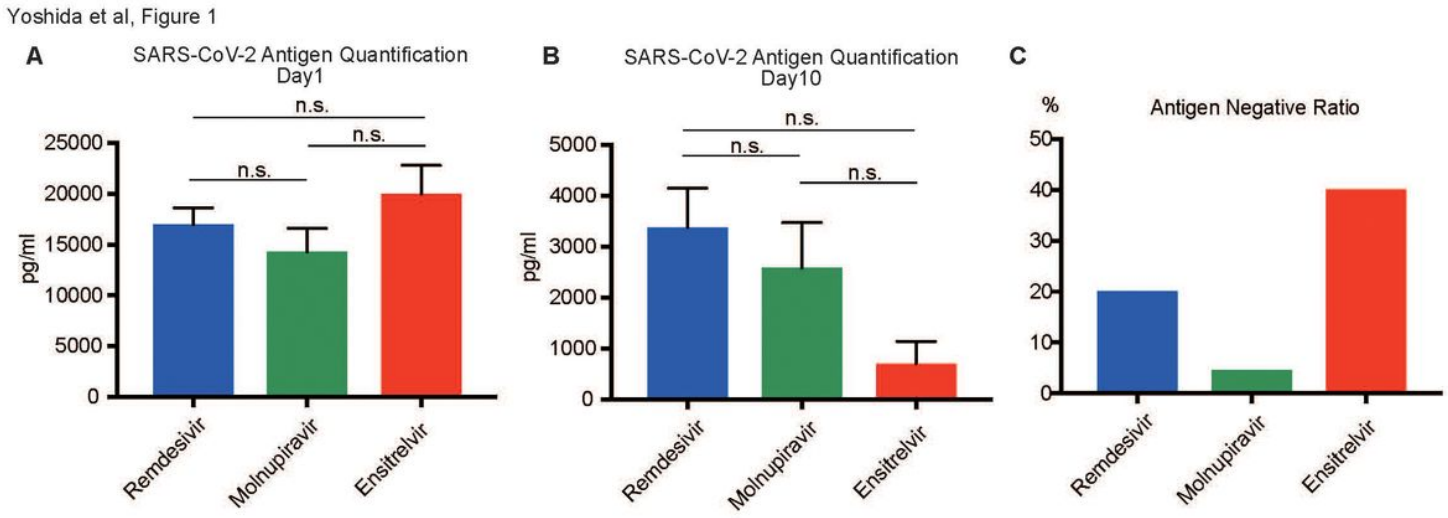

Figure 1

Comparison of SARS-CoV-2 antigens.

(a) Antigen levels on day 1 of hospitalization. (b) Antigen levels on day 10 after each antiviral treatment. (c) Antigen negative ratio for each antiviral treatment.

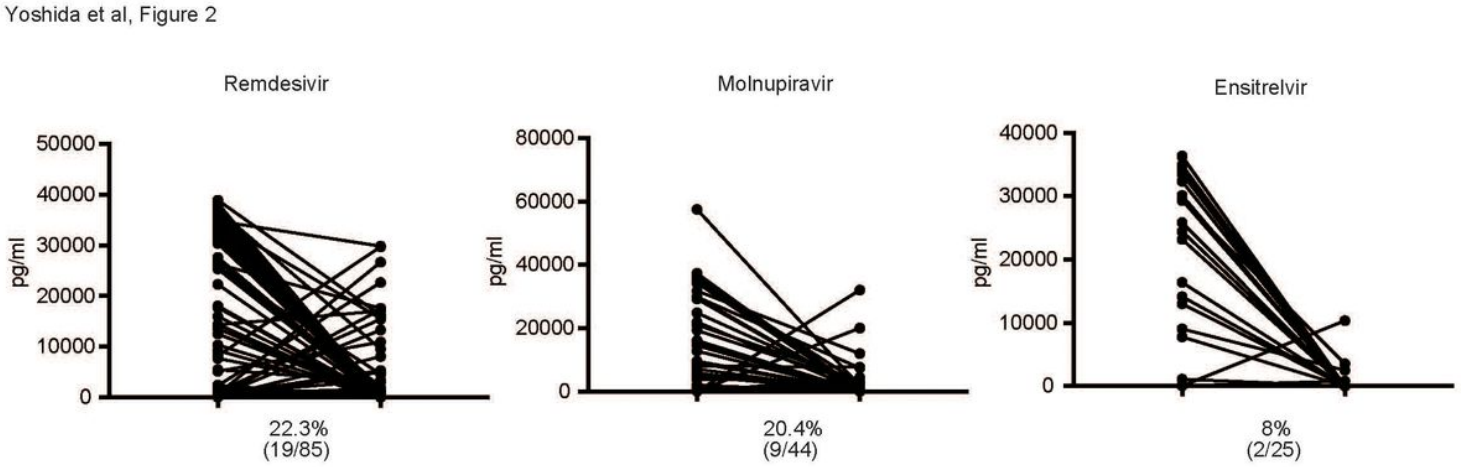

Figure 2

Comparison of day 1 and 10 antigen resurgence rates among individuals for each antiviral treatment.

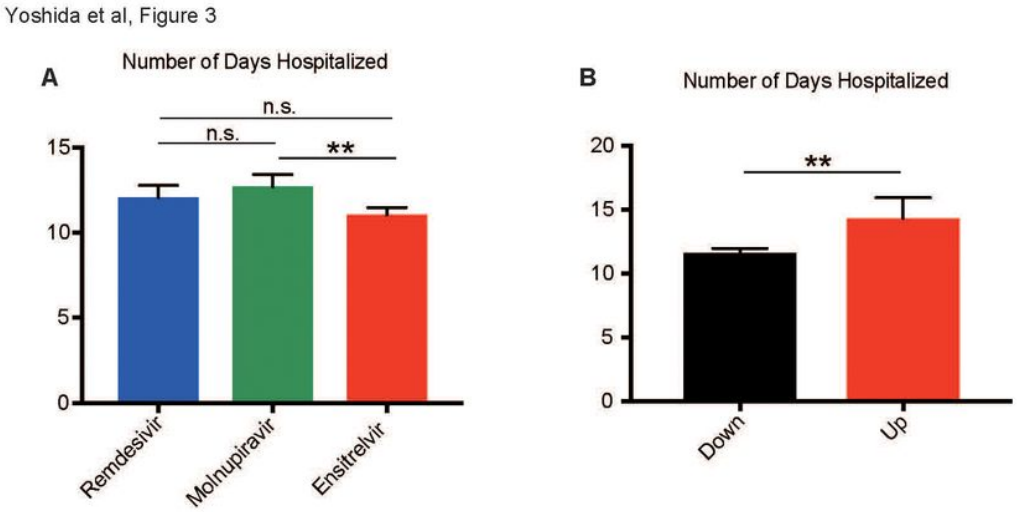

Figure 3

Comparison of hospitalization days.

(a) Hospitalization days for each antiviral treatment. (b) Comparison of hospitalization days between the up-group (Up) and down-group antigens (Down) based on Figure 2.

Yoshida et al, Figure 4

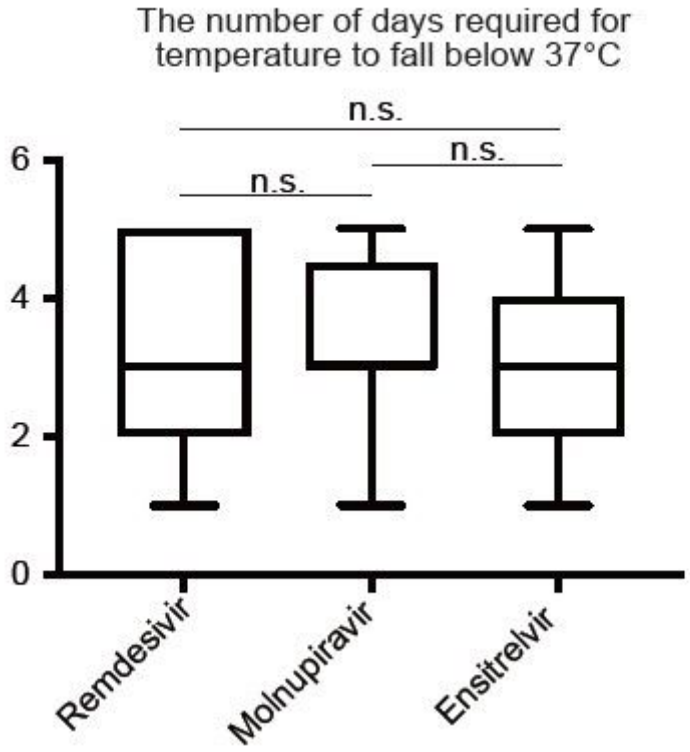

Figure 4

Duration before an admission temperature of >37 °C decreased to <37 °C with antiviral treatments.