

Original Article



Fluvoxamine Treatment of Patients with Symptomatic COVID-19 in a Community Treatment Center: A Preliminary Result of Randomized Controlled Trial

OPEN ACCESS

Received: Dec 21, 2021

Accepted: Feb 19, 2022

Published online: Mar 3, 2022

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ABSTRACT

Background: This study aimed to evaluate whether fluvoxamine reduces clinical deterioration in adult patients with mild to moderate coronavirus disease 2019 (COVID-19), and to identify risk factors for clinical deterioration in patients admitted to a community treatment center (CTC).

Materials and Methods: A randomized, placebo-controlled trial was conducted in a CTC, in Seoul, Korea from January 15, 2021, to February 19, 2021. Symptomatic adult patients with positive results of severe acute respiratory syndrome coronavirus 2 real time-polymerase chain reaction within 3 days of randomization were assigned at random to receive 100 mg of fluvoxamine or placebo twice daily for 10 days. The primary outcome was clinical deterioration defined by any of the following criteria: oxygen requirement to keep oxygen saturation over 94.0%, aggravation of pneumonia with dyspnea, or World Health Organization clinical progression scale 4 or greater.


Results: Of 52 randomized participants [median (interquartile range) age, 53.5 (43.3 - 60.0) years; 31 (60.0%) men], 44 (85.0%) completed the trial. Clinical deterioration occurred in 2 of 26 patients in each group ($P>0.99$). There were no serious adverse events in either group. Clinical deterioration occurred in 15 (6.0%) of 271 patients admitted to the CTC, and all of them were transferred to a hospital. In multivariate analysis, age between 55 and 64, fever and pneumonia at admission were independent risk factors for clinical deterioration.

Conclusion: In this study of adult patients with symptomatic COVID-19 who were admitted to the CTC, there was no significant differences in clinical deterioration between patients treated with fluvoxamine and placebo (ClinicalTrials.gov Identifier: NCT04711863).

Keywords: COVID-19; Fluvoxamine; SARS-CoV-2; Community treatment center; Risk factor

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Funding

This study was supported by a grant (grant number: 2021L0042) from the Asan Institute for Life Sciences, Asan Medical Center, Seoul, Korea.

Conflict of Interest

SOL and SHC are editorial board of Infect Chemother; however, they did not involve in the peer reviewer selection, evaluation, and decision process of this article. Otherwise, no potential conflicts of interest relevant to this article was reported.

Author Contributions

Conceptualization: HS, SB, YPC. Data curation: HS, SP, HC. Formal analysis: HS. Funding acquisition: YPC. Methodology: HS, SB, HK, YPC. Software: HS. Supervision: HS, KYS, MJK, JJ, SHK, SOL, SHC, YSK. Writing – original draft: HS. Writing – review & editing: YPC.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has caused massive morbidity and mortality and increased health care burdens since 2019 [1, 2]. In the absence of a therapeutic agent, early studies focused on decreasing mortality in severely ill, hospitalized patients [3-5]. However, the spectrum of COVID-19 includes more than 80% of mild disease [6, 7], and preventing progression to severe illness in patients with mild to moderate COVID-19 might reduce the mortality and health care burden. In a previous study, Lenze et al. reported the results of a fully remote randomized trial indicating that fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), reduced clinical deterioration in outpatients with acute COVID-19 compared to placebo [8]. Fluvoxamine activates sigma-1 receptors, which function as endoplasmic reticulum chaperones [9], and reduce cytokine production [10], and previous studies suggested that severe COVID-19 is associated with increased plasma cytokine levels [11, 12].

In Korea, after the first wave focused on Daegu and Gyeongbuk area between January 2020 and April 2020 with maximum daily incidence of 800, local outbreaks moved to Seoul and Gyeonggi region, and the daily incidence grew rapidly to 1,200, especially during the winter season from November 2020 [13, 14]. Therefore, community treatment centers (CTC) were set up in each region to monitor and provide supportive care and isolation for patients with mild to moderate COVID-19 who did not require hospitalization and had minor or no underlying medical conditions [15, 16]. We aimed to evaluate whether fluvoxamine would reduce clinical deterioration in adult patients with mild to moderate COVID-19 and identify risk factors for clinical deterioration in patients admitted to a CTC.

MATERIALS AND METHODS

1. Study design

This was a single-blind, randomized, placebo-controlled trial that compared fluvoxamine with placebo in adult patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who were admitted to a CTC, in Seoul, Korea. The CTC, previously a dormitory building for the University of Seoul, was a temporary facility operated by Asan Medical Center between January 1, 2021 and February 19, 2021 to monitor and provide supportive care for asymptomatic to moderate COVID-19 patients who did not require hospitalization. Patients were enrolled from January 15, 2021 to February 8, 2021. The 30-day post-randomization follow-up assessment by phone calls was completed on March 20, 2021.

Every patient admitted to the CTC was provided with an oxygen saturation monitor, an automated blood pressure monitor, and a thermometer. Patients were usually admitted within 24 hours of diagnosis of COVID-19 and were discharged after 10 days from initial diagnosis if they had been afebrile for at least 24 hours without antipyretics, and their symptoms were improving. All data were collected on electronic medical records linked to self-report smartphone apps. Participants were recruited via phone calls by physicians on day 1 of admission to the CTC, informing them of eligibility and instructions for the study. The study medication was delivered at the patients' doors without contact with the patients. The study was performed contactless. However, in the case of clinical deterioration physicians examined the patients with appropriate personal protective equipment and decided whether to transfer the patients to a general hospital.

2. Ethics and regulatory issues

The study was approved by the Institutional Review Board of Asan Medical Center (IRB No: 20210109) and the Ministry of Food and Drug Safety (MFDS), and was conducted in compliance with the Declaration of Helsinki [17], the Good Clinical Practice guidelines, and local regulatory requirements. All participants provided written informed consent. The trial protocol and statistical analysis plan are shown in **Supplementary document 1**.

3. Participants

This study included adult patients over 18 with SARS-CoV-2 infection laboratory-confirmed by real time-polymerase chain reaction (RT-PCR). Patients who had symptoms consistent with COVID-19 with onset less than 7 days after randomization and had positive RT-PCR results within 3 days of randomization were enrolled (**Fig. 1**). Exclusion criteria included patients with severe medical comorbidities such as severe underlying lung disease, chronic liver disease, congestive heart failure (New York Heart Association class III or IV), chronic

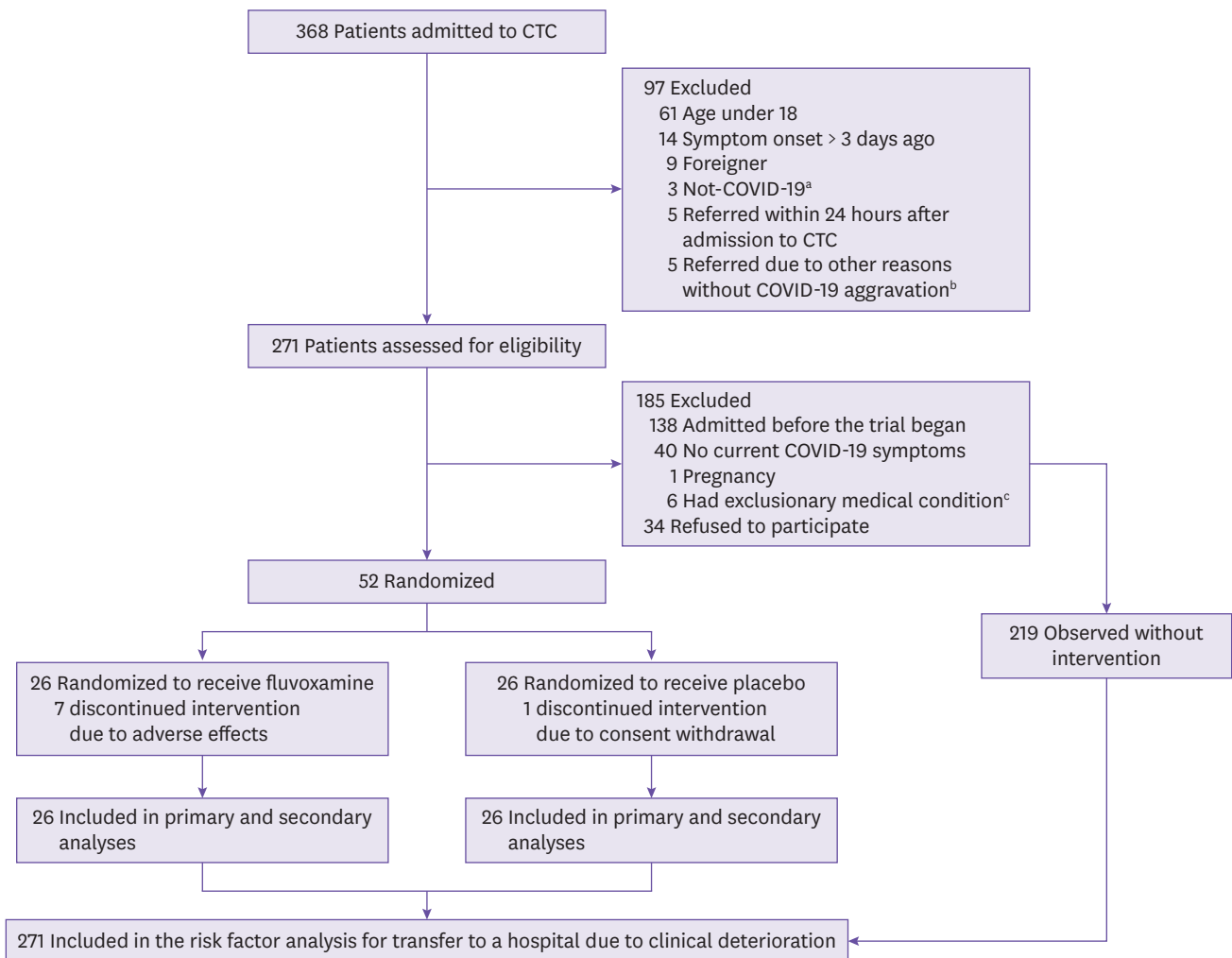


Figure 1. Enrollment and patient flow.

^aOf the three patients, one gave a false positive SARS-CoV-2 positive result followed by repeated negative results, and the remaining two patients with negative SARS-CoV-2 results were admitted to the CTC to take care of their children with COVID-19.

^bOf the five patients, two were referred to a hospital because of poor oral intake, one was referred due to a burn wound, and one due to claustrophobia.

^cOf the six patients, two had chronic liver disease, three had psychiatric diseases, and one had a cognitive disorder.

CTC, community treatment center; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

kidney disease, or those who were immunocompromised. Patients who were referred to a hospital within 24 hours after admission to the CTC with evidence of the primary endpoint at the time of randomization, or those who were referred to a hospital for other reasons without aggravation of COVID-19, were also excluded from the analysis. Foreigners were also excluded because they were unable to provide self-reports written in Korean. Additional details are provided in **Supplementary document 1** trial protocol.

4. Study procedures

Participants were randomized 1:1 to fluvoxamine or a matching placebo group and blinded to their group assignment. Randomization was stratified by age (18 - 44, 45 - 54, 55 - 64, and ≥ 65 years) to reflect the age distribution of ascending risk of severe symptoms requiring hospitalization [18]. Participants were randomized to fluvoxamine (Dumirox, JW Pharmaceutical, Korea) or placebo in a 1:1 ratio using alternating block sizes of 4. Participants received a dose of 50 mg of fluvoxamine or placebo (ursodeoxycholate) on day 1, then an increased dose of 100 mg twice daily, as tolerated, until discharge from the CTC (about 10 days). Dosing reduction was allowed for tolerability reasons. After discharge from the CTC, participants in the fluvoxamine group received a 1-day open-label course of 50 mg of fluvoxamine twice daily to taper out. Chest X-ray was performed on the admission date and repeated according to the physician's judgment in cases of clinical deterioration.

5. Primary and secondary endpoints

The primary endpoint was clinical deterioration defined by any of the following: (1) decrease in oxygen saturation ($<94.0\%$) in room air [19]; (2) supplemental oxygen required in order to maintain an oxygen saturation of 94% or more; (3) aggravation of pneumonia with dyspnea and increased infiltrate on chest X-ray, or minute respiratory rate over 25; (4) WHO clinical progression scale 4 or greater [20]. Secondary endpoints included all the categories of clinical deterioration described above as primary endpoints, and days to clinical deterioration.

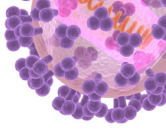
The primary and secondary endpoints were evaluated from participants' self-reported responses in twice-daily surveys and vital signs using smartphone apps. Patients who were unable to self-report were contacted via phone or video call by research staff, who reported daily symptoms and vital signs. Adverse events were assessed daily after randomization through self-reports or phone calls. On day 30 after discharge from the CTC, a follow-up phone call was made to identify any post-trial observational events such as visits to emergency rooms or hospitalization.

6. Analysis of risk factors for clinical deterioration

We performed a multivariate analysis to identify risk factors for clinical deterioration based on all the patients admitted to the CTC. We included in the risk factor analysis not only patients who were enrolled in the trial but also those who were observed without intervention (**Fig. 1**).

7. Statistical analysis

While the incidence of COVID-19 was increasing sharply, a study reported a rate of transfer from CTC to hospital of up to 10.0% [21]. Therefore, we calculated statistical power based on a 10.0% clinical progression rate in the placebo group, and a reduction of 75.0% in the risk of clinical deterioration in the fluvoxamine group. With a type I error of 0.05, a total sample size of 324 participants was required (162 in each group) to have 80.0% statistical power. The target enrollment was 406 patients over 2 months allowing for a 20.0% loss to follow-up.



The primary and secondary efficacy analyses were evaluated in a modified intention-to-treat population, defined as all patients who underwent randomization and received either fluvoxamine or placebo at least once and whose clinical outcome data were collected before discharge. The safety population included all patients who underwent randomization and received either fluvoxamine or placebo at least once. The primary analysis involved comparing the proportion of events in the fluvoxamine and placebo groups. Patients were censored on the day when they met the primary outcomes or were discharged and finished their self-reports. The Student *t*-test or Mann-Whitney *U* test was used to compare differences between continuous variables, and the Pearson's chi-square test or Fisher's exact test was used for the corresponding categorical variables for secondary efficacy analysis and analysis of adverse events. To identify risk factors for clinical deterioration in patients admitted to the CTC, all significant variables in the univariate analysis, and other variables of clinical importance, were included in a multiple logistic regression model. A two-tailed *P* value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software, version 21.0 (SPSS Inc., Chicago, IL, USA).

8. Early trial termination

After starting enrollment for the trial on January 15, 2021, weekly confirmed cases of COVID-19 in Korea decreased from 5,413 in January to 2,630 in February [22]. The Korean Government therefore decided to operate the CTC for the winter season only, and closed it on February 19, 2021. Since admission was allowed up to February 8, 2021, we only enrolled a total of 52 patients during the study period, and the trial was terminated on February 19, 2021.

RESULTS

1. Baseline characteristics of the enrolled patients

During the trial period from January 15, 2021 to February 8, 2021, 230 patients were admitted to the CTC, of whom 97 (42.2%) were excluded, 133 (57.8%) were assessed for eligibility, and 52 (22.6%) were randomly assigned to receive either fluvoxamine or placebo (Fig. 1). Demographic and clinical characteristics were well balanced between the two groups (Table 1). The median age of the patients was 53.5 years (interquartile range, 43.3 - 60.0), and 31 (59.6%) patients were male. Overall, 21 (40.4%) patients had one or more preexisting medical conditions. The proportion of patients with pneumonia at admission did not differ between the groups [5 (19.2%) for fluvoxamine *vs.* 3 (11.5%) for placebo, *P* = 0.70]. Forty-four patients (84.6%) completed the trial while 2 (7.7%) patients in the fluvoxamine group, and 1 (3.8%) in the placebo group had a 50.0% dose reduction.

2. Efficacy of fluvoxamine *vs.* placebo

Seven patients (26.9%) in the fluvoxamine group discontinued participation due to adverse events including drowsiness (7.7%), diarrhea (3.8%), nausea (3.8%), headache (3.8%), and others (7.7%) while one patient (3.8%) in the placebo group discontinued participation due to withdrawal of consent. Clinical deterioration occurred in 2 (7.7%) of 26 patients in each group (*P* > 0.99) (Table 2). Kaplan–Meier survival curve estimates over time for clinical deterioration did not differ significantly between the two groups (*P* = 0.97) (Fig. 2), and none of the outcomes in Table 2 differed significantly between the treatment groups. Days to clinical deterioration were also not significantly different (mean of 6.5 for fluvoxamine *vs.* 7.5 for placebo, *P* = 0.30). The results were consistent when analyzed in the per-protocol population who completed the trial (Supplementary Table 1). Of 19 patients in the

Table 1. Baseline characteristics of symptomatic patients enrolled in the study

Characteristic	Fluvoxamine no. (%)	Placebo no. (%)
	n = 26	n = 26
Age (yr), median (IQR)	54.0 (44.0 - 60.3)	51.5 (42.0 - 59.3)
<45	6 (23.1)	7 (26.9)
45 - 54	8 (30.8)	8 (30.8)
55 - 64	12 (46.2)	10 (38.5)
Male	18 (69.2)	13 (50.0)
Days from PCR confirmation to enrollment, median (IQR)	1 (0 - 1)	1 (0 - 1)
Preexisting medical condition	11 (42.3)	10 (38.5)
Asthma	0 (0.0)	0 (0.0)
Chronic lung disease	2 (7.7)	0 (0.0)
Diabetes mellitus	3 (11.5)	1 (3.8)
Hypertension	8 (30.8)	6 (23.1)
Heart disease	0 (0.0)	0 (0.0)
Hyperlipidemia	4 (15.4)	4 (15.4)
Chronic liver disease	0 (0.0)	0 (0.0)
Chronic kidney disease	0 (0.0)	0 (0.0)
Hyperthyroidism	0 (0.0)	1 (3.8)
Malignancy, current	0 (0.0)	0 (0.0)
Depression	0 (0.0)	0 (0.0)
Other psychiatric disease	0 (0.0)	0 (0.0)
BMI over 25	13 (50.0)	12 (54.5)
Current smoker	2 (7.7)	0 (0.0)
Symptom at admission		
Fever	4 (15.4)	5 (19.2)
Chill	7 (26.9)	11 (42.3)
Cough	19 (73.1)	13 (50.0)
Sputum	13 (50.0)	15 (57.7)
Sore throat	15 (57.7)	14 (53.8)
Rhinorrhea	7 (26.9)	6 (23.1)
Myalgia	15 (57.7)	8 (30.8)
Fatigue	14 (53.8)	11 (42.3)
Headache	14 (53.8)	10 (38.5)
Dyspnea	4 (15.4)	4 (15.4)
Chest pain	6 (23.1)	0 (0.0)
Loss of taste	6 (23.1)	8 (30.8)
Loss of sense of smell	5 (19.2)	5 (19.2)
Loss of appetite	10 (38.5)	10 (38.5)
Nausea	3 (11.5)	1 (3.8)
Vomiting	0 (0.0)	1 (3.8)
Diarrhea	4 (15.4)	3 (11.5)
Pneumonia at admission	5 (19.2)	3 (11.5)
Unilateral infiltration	2 (7.7)	1 (3.8)
Bilateral infiltration	3 (11.5)	2 (7.7)
SpO ₂ at admission, median (IQR) (%)	97 (96.0 - 97.0)	96 (96.0 - 97.0)
Temperature at admission, median (IQR) (°C)	36.3 (36.1 - 36.7)	36.3 (36.1 - 36.8)

Data are presented as number of patients (with the corresponding percentage shown in parentheses), unless otherwise specified.

IQR, interquartile range; PCR, polymerase chain reaction; BMI, body mass index; SpO₂, saturation of oxygen at room air.

fluvoxamine group, one (5.3%) progressed to clinical deterioration compared with 2 (8.0%) out of 25 patients in the placebo group ($P > 0.99$).

3. Adverse events of fluvoxamine

Adverse events are shown in Table 3. Of these events, 10 were considered by the researchers to be related to fluvoxamine, and one to be related to placebo. There was no serious adverse event in either group, and the types of event did not differ significantly between the two groups.

Table 2. Primary and secondary outcomes

Outcome	Fluvoxamine no. (%) n = 26	Placebo no. (%) n = 26	Absolute difference (95 % CI) ^a	P-value
Primary end point				
Clinical deterioration	2 (7.7)	2 (7.7)	0 (-17.37 - 17.37)	>0.99
Secondary end point				
Decrease in O ₂ saturation (SpO ₂ <94%) but not requiring oxygen therapy	1 (3.8)	0 (0.0)	3.8 (-9.45 - 18.83)	>0.99
Requirement of oxygen therapy to maintain SpO ₂ ≥94%	1 (3.8)	1 (3.8)	0 (-15.35 - 15.35)	>0.99
WHO Clinical Progression Scale ≥4	2 (7.7)	2 (7.7)	0 (-17.37 - 17.37)	>0.99
Days to clinical deterioration, mean ± standard deviation	6.5 ± 0.7	7.5 ± 3.5	0.39 (-0.35 - 1.12)	0.30
30-day post-trial events ^b	0/22	0/24		

Data are presented as number of patients (with the corresponding percentage shown in parentheses), unless otherwise specified.

^aFor outcomes reported as No. (%), the absolute difference is a difference in proportions.

^bPost-trial events include visits to an emergency room or hospitalization after discharge from the community treatment center. Four patients who were transferred to a hospital were excluded from 30-day post-trial observation, and two patients in the fluvoxamine group were lost to follow-up.

CI, confidence interval; O₂, oxygen; SpO₂, saturation of oxygen at room air; WHO, World Health Organization.

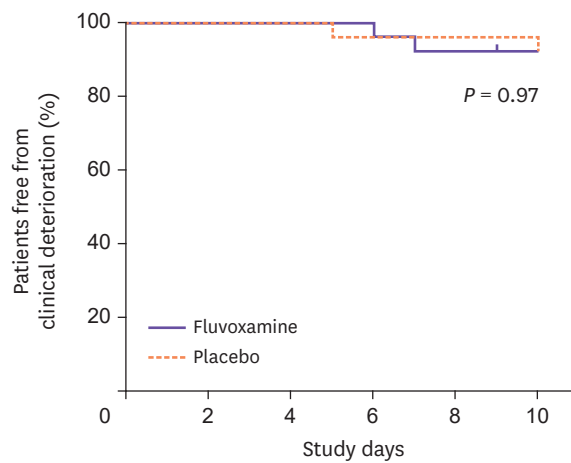


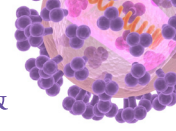
Figure 2. Time to clinical deterioration in the fluvoxamine and placebo groups (log-rank test). The median observation time for both groups were 10 days (interquartile range, 10 - 10 days). Study 0 indicates the day of randomization.

Table 3. Adverse events

Event	Fluvoxamine no. (%) n = 26	Placebo no. (%) n = 26	P-value
Loss of appetite	18 (69.2)	16 (61.5)	0.56
Headache	16 (61.5)	15 (57.7)	0.78
Myalgia	13 (50.0)	11 (42.3)	0.58
Mania	12 (46.2)	10 (38.5)	0.58
Dyspepsia	10 (38.5)	10 (38.5)	>0.99
Diarrhea	9 (34.6)	8 (30.8)	0.77
Insomnia	9 (34.6)	7 (26.9)	0.55
Nausea	6 (23.1)	8 (30.8)	0.53
Constipation	6 (23.1)	7 (26.9)	0.75
Abdominal pain	3 (11.5)	4 (15.4)	>0.99
Vomiting	3 (11.5)	2 (7.7)	>0.99
Drowsiness	3 (11.5)	1 (3.8)	0.61
Rash	4 (15.4)	0 (0.0)	0.11
Dry mouth	1 (3.8)	2 (7.7)	>0.99
Palpitations	1 (3.8)	2 (7.7)	>0.99
Agitation	1 (3.8)	0 (0.0)	>0.99
Others ^a	2 (7.7)	0 (0.0)	
Serious adverse event	0 (0.0)	0 (0.0)	

Data are presented as number of patients (with the corresponding percentage shown in parentheses), unless otherwise specified.

^aOf the two patients, one had desquamation of the sole of the foot, and the other had a nail color change. IQR, interquartile range.



4. Outcomes and risk factors for clinical deterioration in the total set of patients admitted to the CTC

Clinical deterioration occurred in 15 (5.5%) of the 271 patients admitted to the CTC from January 1, 2021 to February 19, 2021, and all of them were transferred to a hospital (**Supplementary Table 2**). Patients who showed clinical deterioration were more likely to be elderly ($P < 0.001$), have dyspnea at admission to CTC ($P = 0.048$), and have pneumonia at admission ($P = 0.02$). Age, fever, dyspnea, pneumonia at admission, and diabetes mellitus were included in a logistic regression model to identify independent risk factors for clinical deterioration (**Supplementary Table 3**). In the multivariate analysis, age between 55 and 64 [adjusted odds ratio (aOR), 14.35; 95% confidence interval (CI), 2.75 - 74.96; $P = 0.002$], fever at admission (aOR, 4.20; 95% CI, 1.29 - 13.65; $P = 0.02$) and pneumonia at admission (aOR 3.47; 95% CI, 1.08 - 11.10; $P = 0.04$) were independent risk factors for clinical deterioration.

DISCUSSION

In this study, fluvoxamine was not associated with a reduction in clinical deterioration in adult patients with mild to moderate COVID-19 who were admitted to the CTC. There are a few studies which reported a clinical benefit of fluvoxamine in outpatients with COVID-19 [8, 23]. Lenze et al. reported that, in a randomized clinical trial, outpatients with COVID-19 treated with fluvoxamine suffered no clinical deterioration (0/80), whereas 8% (6/72) of the patients in the placebo group suffered progression [8]. Seftel et al. reported the result of a prospective cohort study in which no hospitalization occurred in the fluvoxamine group (0/65), whereas 12.5% (6/48) of the patients in the observation group were hospitalized [23]. The difference of our study compared to the previous ones is that due to the suspension of the community treatment center earlier than scheduled, the number of patients was too limited to demonstrate efficacy. However, due to the characteristics of CTCs, which provide supportive care and isolation with close observation of the patients, the subjects' physical conditions were more accurately evaluated compared to outpatient centered observational clinical studies.

Furthermore, based on the 11 patients (5.0%) with clinical deterioration among the 219 CTC patients who were not enrolled in the randomized trial, the intended trial numbers would have provided insufficient primary endpoint events to demonstrate the primary efficacy in the fluvoxamine group. Since the incidence and severity of COVID-19 in Korea decreased rapidly, and the transfer rate from the CTC to a hospital due to clinical deterioration was lower than anticipated, the study was underpowered and further enrollment would have been unable to reveal a difference between the two groups. Since a few studies do suggest that some CNS drugs including fluvoxamine are effective in patients with COVID-19 [9, 11], further randomized controlled trials are needed to provide supporting evidence for fluvoxamine use. Recent study by Mills, *et al.* demonstrated that fluvoxamine treatment for high-risk outpatients reduced the rate of hospitalization compared to placebo by relative risk 0.68 [24]. They included patients from community health facilities with at least one criterion for high-risk comorbidity. In contrast, our study included patients from community treatment center which were established for outpatients with minimum comorbidities, and over half of the participant in our study had no underlying diseases. Therefore, our results implies that routine fluvoxamine treatment for every outpatient may not be useful, and selecting high risk group among outpatients is needed to ensure the effect of fluvoxamine treatment.

In our study, age between 55 and 64 was an independent risk factor for clinical deterioration in patients with mild to moderate COVID-19 in the CTC. Age is a well-known risk factor for progression to severe COVID-19 [25, 26], and our results are in line with a previous study reporting age as a risk factor for transfer to hospital from CTC [27]. We stratified the risk of deterioration by age, and patients aged 55 to 64 had the highest adjusted odds ratio. This was not anticipated by the researchers, who expected patients over 65 years to have the highest odds ratio. Undurraga et al. reported that fatality risk increased significantly from age 50 when they adjusted risk by age group and gender [28]. Though the risk of progression in patients over 65 cannot be overlooked due to the small number of cases in our study, our results suggest that clinicians should be aware of the risk of progression in patients between 55 and 64 with mild to moderate COVID-19.

Although fever, and pneumonia at admission to CTC were independent risk factors for progression in our study, none of the patients with clinical deterioration had fever at the time of transfer to a hospital. These results suggest that fever and pneumonia at admission should be considered meaningful for predicting clinical deterioration in patients with mild to moderated COVID-19 who are admitted to a CTC.

This trial has several limitations. First, the number of patients enrolled did not meet the intended minimum number of subjects, so post-hoc power was very low to give statistical significance. Second, it was conducted in a single center, so, there is a potential for selection bias and confounders, and the results need to be interpreted cautiously. Third, we did not include any laboratory data except for the initial confirmation of SARS-CoV-2 by RT-PCR. Further studies including viral kinetics and inflammatory markers could be helpful in identifying any clinical benefit of fluvoxamine. Finally, patients in this study had minor comorbidities, so it would be inappropriate to underestimate the potential of fluvoxamine in patients with underlying diseases. Further research including adequate number of patients with various comorbidities is needed.

In conclusion, this randomized, single-blind, placebo-controlled trial did not show that fluvoxamine was effective in preventing patients with mild to moderate COVID-19 from clinical deterioration. However, due to its small sample size, larger randomized trials are needed.

ACKNOWLEDGEMENTS

We are grateful to the healthcare workers in the University of Seoul community treatment center for COVID-19. We also thank Sun Hwa Park for her help in data curation.

SUPPLEMENTARY MATERIALS

Supplementary document 1

Trial protocol.

[Click here to view](#)

Supplementary Table 1

Primary and secondary outcomes in the per-protocol analysis

[Click here to view](#)

Supplementary Table 2

Baseline and clinical characteristics of patients admitted to CTC according to the outcome

[Click here to view](#)

Supplementary Table 3

Results of analyses of risk factors for transfer to hospital due to clinical deterioration

[Click here to view](#)

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