FLUOXETINE USE IS ASSOCIATED WITH IMPROVED SURVIVAL OF PATIENTS WITH COVID-19 PNEUMONIA: A RETROSPECTIVE CASE-CONTROL STUDY

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Background and purpose – We aimed to investigate the association between fluoxetine use and the survival of hospitalised coronavirus disease (COVID-19) pneumonia patients.
Methods – This retrospective case-control study used data extracted from the medical records of adult patients hospitalised with moderate or severe COVID-19 pneumonia at the Uzsoki Teaching Hospital of the Semmelweis University in Budapest, Hungary between 17 March and 22 April 2021. As a part of standard medical treatment, patients received anti-COVID-19 therapies as favipiravir, remdesivir, baricitinib or a combination of these drugs; and 110 of them received 20 mg fluoxetine capsules once daily as an adjuvant medication. Multivariable logistic regression was used to evaluate the association between fluoxetine use and mortality.
For excluding a fluoxetine-selection bias potentially influencing our results, we compared baseline prognostic markers in the two groups treated versus not treated with fluoxetine.
Results – Out of the 269 participants, 205 (76.2%) survived and 64 (23.8%) died between days 2 and 28 after hospitalisation. Greater age (OR [95% CI] 1.08 [1.05–1.11], p<0.001), radiographic severity based on chest X-ray (OR [95% CI] 2.03 [1.27–3.25], p=0.003) and higher score of shortened National Early Warning Score (sNEWS) (OR [95% CI] 1.20 [1.01-1.43], p=0.04) were associated with higher mortality. Fluoxetine use was associated with an important (70%) decrease of mortality (OR [95% CI] 0.33 [0.16–0.68], p=0.002) compared to the non-fluoxetine group. Age, gender, LDH, CRP, and D-dimer levels, sNEWS, Chest X-ray

A FLUOXETINT SZEDŐ COVID-19-PNEUMONIÁS BETEGEKNEK NAGYOBB A TÚLÉLÉSI ESÉLYE: RETROSPEKTÍV, ESET-KONTROLLOS VIZSGÁLAT
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Háttér és cél – Van-e összefüggés a fluoxetinszedés és a kórházban kezelt közepesen súlyos/súlyos COVID-19-pneumonia túlélése között?
Módszerek – A Semmelweis Egyetem Uzsoki Utcai Gyakorló Kórházában 2021. március 17. és április 22. között kezelt személyek orvosi dokumentációja alapján retrospektív eset-kontroll vizsgálatot végeztünk. A betegek a standard belgyógyászati kezelés mellett anti-COVID-19 kezelésben (favipiravir, remdesivir, baricitinib, vagy ezek kombinációi) részesültek. 110 fő ezenfelül napi 20 mg fluoxetint is kapott. A mortalitás és a fluoxetinszedés összefüggésének statisztikai elemzésére többváltozós logisztikus regressziót alkalmaztunk. Annak ellenőrzésére, hogy eredményeinket nem befolyásolhatta-e szelekciós hiba (fluoxetine selection bias), összehasonlítottuk a fluoxetinnel kezelt és nem kezelt két betegcsoport kórházi felvételi klinikai, radiológiai és laboratóriumi prognosztikai jellemzőit.
Eredmények – A 269 vizsgált személy közül 205-en (76,2%) maradtak életben, és 64-en (23,8%) hunytak el a felvételt követő 2. és 28. nap között. A fluoxetint szedő csoport mortalitása jelentősen, 70%-kal alacsonyabb – vagyis körülbelül harmadannyi – volt, mint a fluoxetint nem szedők mortalitása. Ez a hatás, függetlenül minden más, a mortalitást befolyásoló tényezőtől, statisztikailag szignifikáns volt (OR [95% CI] 0,33 [0,16–0,68], p = 0,002). Sem az életkor és a nem, sem a kórházi felvételi C-reaktív protein, LDH- és D-dimer-szint, sem a shortened National Early Warning Score pontszám és

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score did not show statistical difference between the fluoxetine and non-fluoxetine groups supporting the reliability of our finding.
Conclusion – Provisional to confirmation in randomised controlled studies, fluoxetine may be a potent treatment increasing the survival for COVID-19 pneumonia.

Keywords: *fluoxetine, COVID-19, SARS-CoV-2, pneumonia, survival, mortality*

a mellkasröntgen súlyossági pontszám, illetve az első 48 órában végzett mellkas-CT-vizsgálatok aránya nem mutatott statisztikai különbséget a fluoxetint szedő és fluoxetint nem szedő két csoport között, alátámasztva a vizsgálati eredmény validitását.
Következtetés – Amennyiben ezt az eredményt, a túlélés háromszorosára növekedését, randomizált, kontrollált vizsgálatok is megerősítik, a fluoxetin a COVID-19-pneumonia hatékony gyógyszere lehet.

Kulcsszavak: *fluoxetin, COVID-19, SARS-CoV-2, pneumonia, túlélés, mortalitás*

Since the emergence of the coronavirus disease (COVID-19) pandemic, several drugs have been used to improve patient outcomes worldwide; however, the current armamentarium against COVID-19 remains suboptimal. Repurposing clinically well-established drugs might constitute a time-sparing method for improving pharmacotherapy of COVID-19[1].

In spring 2021, the third COVID-19 wave culminated in Hungary, with a sad record of cases and deaths in that period[2]. A peak in mortality was experienced in the COVID-Centre of Uzsoki Hospital in Budapest, Hungary, too, severely distressing patients and medical teams. This extraordinary situation urged clinicians to induce new treatment strategies; e.g. introducing the antidepressant fluoxetine to the deeply worried and anxious COVID patients.

In one study, more than 40% of the population who were interviewed during the pandemic scored depressive or had anxiety symptoms[3]. Anxiety may compromise the immune system, which could result in an increased susceptibility to infection or increased disease severity[4]. This was evidenced in several medical conditions[5–7]. A meta-analysis revealed an association between mood disorders and increased COVID-19 mortality[8]. The anxiety levels of patients in the acute phase of COVID-19 pneumonia were found similar to those of patients with myocardial infarction[9]. Based on those data and facing the growing number of COVID-19 fatality hardly helped by antiviral medicines, the hospital team ventured contributing an anti-anxiety/antidepressive treatment to the standard antiviral medicines.

In medical emergencies, benzodiazepines are first-line anxiolytic drugs; however, at higher doses, they carry a risk of respiratory depression and may have an immune-compromising effect: a significant association was shown between benzodiazepine use and increased mortality of community-acquired pneumonia[10, 11]. Since selective serotonin reuptake inhibitors (SSRIs) are established drugs for the treatment of anxiety[12], they could suitably substitute benzodiazepines. The generally expected 2–3 weeks delay of SSRIs' clinical effect might limit their use, however, based on a meta-analysis, SSRIs can be effective by the end of the first week after treatment onset[13]. Therefore, the initiation of SSRI therapy soon after hospitalisation may help improving anxiety and mood within the likely period of hospital stay. Fluoxetine is considered the most effective anxiolytic SSRI drug[14] seeming therefore appropriate for treating anxiety and low mood in COVID-19 patients.

We aimed to assess the potential change of mortality associated to adjuvant fluoxetine treatment between days 2 and 24 after hospitalisation; analysing the data of those COVID-19 pneumonia patients receiving versus not receiving fluoxetine.

Patients and methods

To determine the potential impact of fluoxetine use on the mortality of COVID-19 patients, we reviewed the medical records and performed a retrospective analysis. The ethics committee of the hospital approved our study (Uzsoki Hospital IKEB No. 19-IK/2021).

PATIENTS

We reviewed the medical records of those patients more than 18-year-old who were admitted to the

COVID-Centre between 17 March and 22 April 2021, i.e. the culmination of the third wave of the pandemic. The inclusion criteria were the followings: Results of an antigen or polymerase chain reaction test that confirmed a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; Pneumonia indicated by chest X-ray or CT; Stay in the COVID-centre for longer than 48 hours; No prior anti-COVID-19 vaccination. The patients or their close family members (in critical cases) gave a general written informed consent.

TREATMENT

In the extraordinary circumstances of the pandemic, the clinical state of patients together with the changing availability of antiviral drugs, determined the treatment-choice. First, only favipiravir was accessible; whereas remdesivir could be administered just for a few critically ill patients. Later, due to its increasing availability, remdesivir became the main COVID-19 therapy, gradually contributed to by baricitinib, which was usually reserved for younger patients with severe COVID-19, due to its shortage.

The introduction of fluoxetine followed a similar pattern. Using or not using it, was initially the treating physicians' decision. Based on the favourable experiences - no clinically significant side-effects have occurred - it has become part of the local anti-COVID protocol. This real-world situation resulted in different anti-COVID-19 drug combinations, where remdesivir was combined with fluoxetine significantly more often than with the rest of the above mentioned drugs.

The anti-COVID-19 drug doses were the followings: Favipiravir: first and second dose, 1600 mg; third to tenth dose, 600 mg; Remdesivir: first dose 200 mg; second to fifth/tenth dose, 100 mg; Baricitinib: 4 mg once daily for 10 days. Fluoxetine was administered in 20 mg capsules once daily. Patient care was performed in accordance with standard medical guidelines, including dexamethasone and thrombosis-prophylaxis.

PROGNOSTIC FACTORS

Baseline routine blood investigations at admission included C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels for all patients and D-dimer concentrations in the majority of the study population.

Based on medical records, we retrospectively applied a shortened National Early Warning Score (sNEWS) for assessing the initial clinical prognosis of each patient. It included heart rate, systolic blood pressure, oxygen saturation, temperature, consciousness, need or no need of oxygen supply. Since respiration rate, which is part of the original NEWS[15, 16], was not systematically documented, we could not take it in account.

Based on the documentation, two of the authors (AH and ASZ) have postscored the after-admission chest X-rays of each patient (CX-score). The score ranged from 1 to 3 according to the documented radiographic severity (1 = mild, 2 = medium, 3 = severe). The fact that a thoracic CT scan was or was not performed in the first 48 hours of hospitalisation was also recorded.

STATISTICAL ANALYSIS

To describe the case (deceased) and control (survivor) groups, we provide descriptive statistics for all variables that were examined. Continuous variables were tested for normality of distribution using the Shapiro–Wilk test. To check the comparability of the two groups, the Mann–Whitney U tests were applied to evaluate the differences between the patient groups. Pearson chi-square and Fisher's exact tests were performed to assess the association between categorical variables. Continuous variables are expressed as median (IQR).

Congruent with the goals of the study, the primary response variable was defined as mortality between hospital days 2 and 28. To explore the associations between the primary response variable and explanatory variables for characterising survivors and deceased, all variables with a possible effect on mortality (i.e. prognostic factors) were entered into a multivariable logistic regression model.

We introduced age, LDH, CRP, D-dimer, sNEWS and CX-score as continuous variables, gender and medications as categorical variables. The adjusted risks are expressed as odds ratios (ORs) with 95% confidence intervals [CIs]). Due to the relatively small number of patients, the Box–Tidwell test was performed to test that the relationships between the continuous predictor and their logit is linear. Two models were built. In the first step, all variables were analysed; in the second, to build the model a backward stepwise variable selection was applied. Moreover, the area under the receiver operating characteristic curve (ROC-AUC) were calculated to measure the efficiency of the models in distinguishing between survivors and the deceased. Statistical significance was set at $p<0.05$. All statistical analyses were performed using IBM SPSS v23 (Armonk, New York, USA).

Table 1. *Patient characteristics and differences between survivors and deceased*

Baseline characteristics	All patients (n=269)	Survivors (n=205)	Deceased (n=64)	p-value
Age in years, median (IQR)	66.0 (52.5-74.5)	63.0 (50.0-72.0)	74.5 (66.25-80.00)	<0.001
Sex, male, n (%)	147 (54.6%)	114 (55.6%)	33 (51.6%)	0.569
Laboratory tests and clinical scores				
LDH IU/L median (IQR)	785.5 (624.5-1040.75)	772.0 (630.5-1031.5)	915.0 (585-1073.0)	0.308
CRP mg/L median (IQR)	108.9 (59.4-170.4)	106.5 (57.9-159.7)	137.0 (62.5-192.5)	0.035
D-dimer μg/L median (IQR)	0.47 (0.29-0.92)	0.41 (0.28-0.79)	0.61 (0.37-1.56)	0.002
sNEWS median (IQR)	5 (4-6)	5 (4-6)	6 (5-7)	<0.001
Chest CT performed n (%)	68 (25.3%)	54 (26.3%)	14 (21.9%)	0.514
CX-score median (IQR)	2 (1-2)	2 (1-2)	2 (1-3)	0.027
Therapy received, n (%)				
Favipiravir	124 (46.1%)	80 (39.0%)	44 (68.8%)	<0.001
Remdesivir	156 (58.0%)	133 (64.9%)	23 (35.9%)	<0.001
Baricitinib	44 (16.4%)	37 (18.0%)	7 (10.9%)	0.18
Fluoxetine	110 (40.9%)	95 (46.3%)	15 (23.4%)	0.001

CRP: C-reactive protein, CX: Chest X-ray, LDH: lactate dehydrogenase, sNEWS: shortened National Early Warning Score

Results

Out of 623 patients admitted during the study period, 269 (147 males [54.6%]; age, mean [range] 64.1 [19–96] years) were eligible for the study based on the inclusion criteria. A total of 205 patients survived (76.2%) and 64 patients died (23.8%) between days 2 and 28. None of the continuous variables (age, LDH, CRP, D-dimer, sNEWS and CX-score) were normally distributed in all subgroups (Shapiro Wilk $\min(p_{Survivors;}\ p_{Deceased})<0.009$ és $\min(p_{received\ fluoxetine;}\ p_{not\ received\ fluoxetine})<0.035$) therefore, the Mann–Whitney–Wilcoxon tests were applied.

We found significant intergroup differences in the age, CRP, and D-dimer, sNEWS, CX-score as well as in favipiravir, remdesivir, and fluoxetine use between the case and control groups **(Table 1)**. Fluoxetine was administered to 110 patients (40.9%). One patient developed severe hyponatraemia likely related to fluoxetine. Additional side effects possibly caused by fluoxetine included: increase in liver enzyme levels in one patient and confusion in another one. Fluoxetine was stopped in each case. Age, gender, LDH, CRP, and D-dimer levels, sNEWS, CX-score and the number of chest CT scans in the first 48 hours, did not show statistical difference between the fluoxetine and non-fluoxetine groups **(Table 2)**.

Table 2. *Characteristics of patients who did and did not receive fluoxetine*

Characteristics	Received fluoxetine (n=110)	Did not receive fluoxetine (n=159)	p-value
Age in years, median (IQR)	65.0 (51.0-73.25)	67.00 (53.0-75.0)	0.268
Sex, male, n (%)	58 (52.7%)	89 (56.0%)	0.596
Laboratory tests and clinical scores			
LDH IU/L median (IQR)	821 (638.3-1047.0)	765.0 (612.8-1030.0)	0.327
CRP mg/L median (IQR)	108.5 (56.6-174.0)	107.7 (60.1-164.5)	0.940
D-dimer μg/L median (IQR)	0.44 (0.3-0.87)	0.48 (0.3-0.93)	0.906
sNEWS median (IQR)	5 (3.5-6)	5 (4-6)	0.369
Chest CT performed n (%)	33 (30%)	35 (22%)	0.155
CX-score median (IQR)	2 (1-2)	2 (1-2)	0.349
Therapy received, n (%)			
Remdesivir	78 (70.9%)	78 (49.1%)	<0.001
Baricitinib	34 (30.9%)	10 (6.3%)	<0.001
Favipiravir	34 (30.9%)	90 (56.6%)	<0.001
Mortality in 2–28 days, n (%)	15 (13.6%)	49 (30.8%)	0.001

CRP: C-reactive protein, CX: Chest X-ray, LDH: lactate dehydrogenase, sNEWS: shortened National Early Warning Score

Table 3. *Odds ratios for mortality calculated in a binary logistics model that included all variables*

Characteristics	β	Wald	p-value	OR (95% CI)
Age (1 year)	0.09	16.58	<0.001	1.09 (1.05-1.14)
Sex (reference=male)	-0.17	0.19	0.66	0.85 (0.40-1.79)
Laboratory tests and clinical scores				
LDH IU/L	0.001	1.66	0.19	1.00 (0.999-1.002)
CRP mg/L	0.001	0.62	0.80	1.00 (0.996-1.006)
D-dimer μg/L	-0.002	0.0002	0.99	0.99 (0.77-1.28)
sNEWS	0.184	3.0	0.08	1.20 (0.98-1.48)
Chest CT performed	-0.27	0.28	0.59	0.76 (0.28-2.08)
CX-score	0.715	6.5	0.01	2.05 (1.18-3.55)
Medications				
FAV (reference=not receiving)	1.33	3.14	0.08	3.79 (0.87-16.55)
Remdesivir (reference= not receiving)	0.92	1.47	0.23	2.52 (0.57-11.12)
Baricitinib (reference=not receiving)	1.2	3.65	0.06	3.33 (0.97-11.42)
Fluoxetine (reference=not receiving)	-1.32	9.17	0.002	0.27 (0.11-0.63)

N=259 (discharged from hospital = 201; deceased = 58)
Likelihood ratio test: χ^2 = 76.26; df = 12; p<0.001
Nagelkerke R^2 = 0.39
ROC-AUC = 0.84 (95% CI 0.76–0.92)
CRP: C-reactive protein, CX: Chest X-ray, LDH: lactate dehydrogenase, ROC-AUC: area under the receiver operating characteristic curve, sNEWS: shortened National Early Warning Score

Table 4. *Odds ratios for mortality calculated in a binary logistics model that included only significant variables after backward stepwise variable selection*

Characteristics	β	Wald	p-value	OR (95% CI)
Age (1 year)	0.078	28.29	<0.001	1.08 (1.05-1.11)
Fluoxetine (reference=not receiving)	-1.11	8.92	0.002	0.33 (0.16-0.68)
CX-score	0.71	8.87	0.003	2.03 (1.27-3.25)
sNEWS	1.82	4.06	0.044	1.20 (1.01-1.43)

N=264 (discharged from hospital = 204; deceased = 60)
Likelihood ratio test: χ^2 = 65.254; df =4; p<0.001
Nagelkerke R^2 = 0.33
ROC-AUC = 0.81 (95% CI 0.75–0.87)
CRP: C-reactive protein, CX: Chest X-ray, ROC-AUC: area under the receiver operating characteristic curve, sNEWS: shortened National Early Warning Score

Only three variables showed a significant association with mortality: age, fluoxetine, and CX-score **(Table 3)**. Variables that were found to be significantly associated with mortality in the regression analysis using backward selection are presented in **Table 4**. The results of the Box–Tidwell test were acceptable for both of the continuous variables (age, p=0.99; sNEWS p=0.16).

Patients on fluoxetine therapy were 0.33 times (95% CI 0.16–0.68) less likely to die than those who had not received fluoxetine; i.e. the survival of patients in the fluoxetine group increased threefold. In addition, age increased the likelihood of death, wherein an increase of 1 year increased the OR by 8%. The increased likelihood of death was also associated with the sNEWS, one unit increase in sNEWS increased the OR by 1.2 (95% CI 1.01–1.43). The increased likelihood of death was also associated with the CX-score, one unit increase in the score increased the OR by 2.03 (95% CI 1.27–3.25).

The final model explained one-third of the variance (Nagelkerke R^2=0.33), and the distinguishing characteristics of the model were proven to be excellent (ROC-AUC=0.81 [95% CI 0.75–0.87]).

Discussion

We found that fluoxetine use associated with a reduction of mortality to one third in patients with COVID-19 pneumonia. This finding was independent from the effect of the frequently co-administered remdesivir **(Tables 2–4)**.

In our study, age was a risk factor significantly influencing mortality. In agreement with other studies[17, 18], the mortality risk increased by 8% with every 1-year increase in age. In accordance with the literature attributing strong prognostic value to sNEWS and CX-score in COVID-19, also we found them predictive for mortality[19, 20].

No quantitative psychology tests could be performed in the busy period with critically ill and severely dyspnoeic patients, but the team did not experience any clinically relevant increases of anxiety at the initiation of SSRI in this group, unlike in some reports of the literature[21]. Some of the published data suggest a risk of bleeding with fluoxetine[22], and in addition, COVID-19 patients received low-molecular-weight heparin (LMWH) for thrombosis-prophylaxis in the COVID-19-related hypercoagulable state. One study that evaluated combination therapy with LMWH and SSRI, did not detect an increased incidence of major bleeding[23]. We paid special attention to this risk, which has not occurred in our patients. Hyponatraemia is another concern[24, 25] and it developed in one patient who was treated with fluoxetine, thereby necessitating drug withdrawal.

We investigated the possibility of a fluoxetine-selection bias that could have influenced our results. In other words, we tried to exclude a deliberate or unwitting allocation of patients by the treating physician for fluoxetine treatment e.g. based on severity. We found no significant differences between the groups that were or were not treated with fluoxetine; marking similar prognoses at baseline and supporting the validity of our finding.

The striking improvement of survival in patients with COVID-19 pneumonia who were treated with fluoxetine is intriguing. This effect might have been related to a non-specific "psycho-immunologic" effect of fluoxetine; or to its immunomodulatory, anti-inflammatory and antiviral features; or potentially, to an additional unknown factor. Several studies in the literature suggest specific anti-COVID-19 and anti-inflammatory properties of the SSRIs fluoxetine and fluvoxamine[26–30]. Most of these data have been obtained from *in vitro* studies, which reveal multiple mechanisms of action: (1) modulation of the endolysosomal host-virus interface[31, 32], (2) modulation of the IL-6–mediated cytokine production[30, 33], (3) a sigma-1 receptor agonist profile resulting in an anti-inflammatory effect[34–36], (4) inhibition of lysosomal acid sphingomyelinase, and the resultant transformation of the biophysical properties of the plasma membrane to inhibit SARS-CoV-2 infection[37], and (5) modulation of the endocytic trafficking of the SARS-CoV-2 spike protein[38].

As Schloer notes, while the antiviral agent remdesivir acts directly on viral structures by interfering with the viral RNA-dependent RNA polymerase, fluoxetine targets the endolysosomal host–virus interface, i.e., the host factor in viral invasion. A host-directed drug might decrease the likelihood of drug resistance because profound changes would be required to allow viruses to replicate independently of essential host factors[39].

In a multicentre retrospective observational study, a significantly reduced risk of intubation and death was observed in hospitalised COVID-19 patients who were treated with the SSRI or SNRI antidepressants escitalopram, fluoxetine, paroxetine, venlafaxine, or mirtazapine[40]. In another study, an analysis of the medical billing data of approximately 739,000 COVID-19 patients revealed that patients who were treated with antipsychotic drugs carrying a sigma-1 receptor agonist profile needed mechanical ventilation half as often than those who were treated with the non-sigma-1 receptor agonist antipsychotic drugs[41]. Finally, a double-blind randomised trial found no clinical deterioration in 80 COVID-19 outpatients who received fluvoxamine, whereas 6 patients in the placebo arm (n=72) experienced clinical deterioration[42].

Fluoxetine was generally well tolerated by the COVID-19 patients of this study, possibly related also to its low dose used. The daily 20-mg fluoxetine used in this study, is the minimum effective antidepressant dose, far from the recommended peak dose (80mg). Higher doses might have an even stronger anti-COVID effect, too.

To our knowledge, this is the first inpatient clinical study exploring the impact of fluoxetine on the outcome of COVID-19 pneumonia, however, it has several limitations. The most important ones are the relatively small number of patients and the non-randomised, retrospective study design. We reassuringly corrected this aspect by comparing prognostic markers in the fluoxetine versus non-fluoxetine groups, showing similar prognoses. The single-centre design might have constituted another limitation, balanced by the large catchment area of the Uzsoki COVID department with a heterogeneous population of about three million people. The lack of proper psychiatric assessments, no anxiety or depression-scores taken, may be considered additional limitations.

Future research should clarify the mechanism of action of fluoxetine, its optimal dose, and a poten-

tially similar effect of other SSRIs in COVID-19. Another direction for research might be the possible role of psychiatric drugs, i.e., a "psycho-immunologic" treatment in severe infections.

Conclusion

Due to the retrospective and real-world nature of the study, the strong association found between fluoxetine therapy and survival requires further investigations. Provisional to confirmation in randomised controlled studies, fluoxetine may be a potent treatment for COVID-19 pneumonia. Fluoxetine's favourable profile – oral route, low cost, easy availability and safety – might make it especially suitable.

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