Received: 12 November 2021 | Accepted: 19 November 2021

DOI: 10.1111/bcp.15166

LETTER TO THE EDITOR

Fluvoxamine for COVID-19 ICU patients?

To the Editor,

I read with interest a recent report on the use of fluvoxamine in COVID-19 patients needing admission to an intensive care unit (ICU).[1] I believe that the suggested (huge) effect of fluvoxamine (40% reduction in instantaneous risk of death) deserves some attention. The authors report[1] on a cohort ($n = 51$) of patients who, upon ICU admission, were treated with fluvoxamine added to the standard of care (SoC) (3×100 mg/day/15 days, then 2×50 mg/day/7 days), and were compared to a cohort ($n = 51$) of SoC-only patients. The cohorts were said to be matched.[1] Based on data,[1] it appears that the patients were matched exactly in respect to gender and COVID-19 vaccination status, and, seemingly, on a rather narrow age-caliper, but

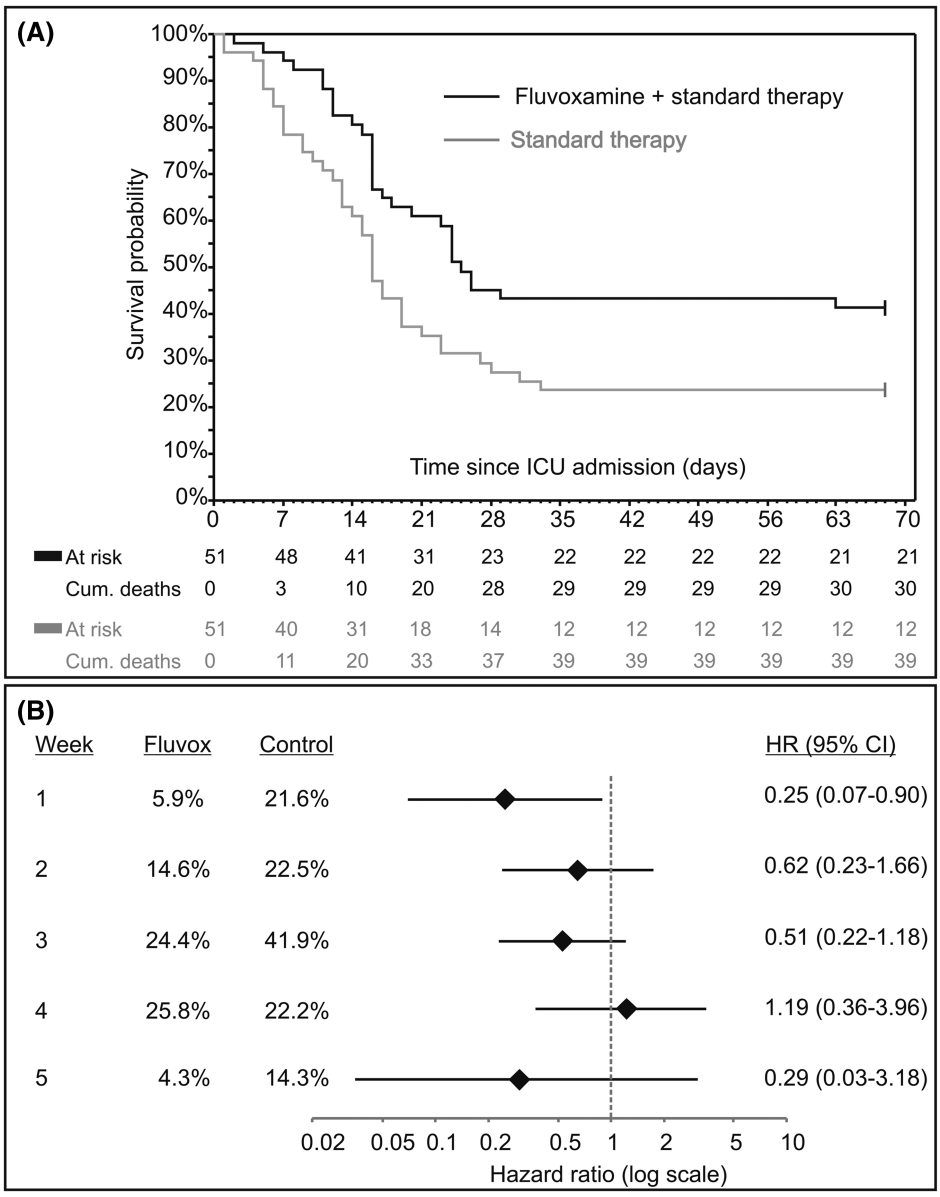

FIGURE 1 Summary of re-analysis of survival data published in Čalušić et al.[1] (A) Reconstructed curves of Kaplan–Meier product-limit estimates. Data[1] were read using a digitizing software, and were re-analyzed and curves were drawn using JMP 13 software (SAS Institute Inc., Cary, NC). Ticks at the end of curves indicate censorings. ICU—intensive care unit. In respect to the reported curves (Figure 2 in Čalušić et al.[1]), the present one only differ in graduation of the *y* axis, and the fact that the *x* axis points-out day 7, 14, and so on, illustrative of 7-day intervals (days). (B) Estimated probabilities of death during weeks 1 to 5 by treatment (Fluvox—fluvoxamine) and period-specific hazard ratios (HR) with confidence intervals. A complementary log–log model was fitted to reconstituted data using SAS 9.4 for Windows (SAS Inc., Cary, NC)

the matching method was not reported[1]; not reported was also a measure of matching adequacy—standardized difference (*d*), a preferred method of balance assessment (adequate if $d < 0.1$) since independent of the sample size.[2] Based on data,[1] for example, the *fluvoxamine – SoC d* regarding body mass index was −0.30 (−0.31 in women, −0.29 in men); $d = -0.122$ regarding history of diabetes; $d = -0.350$ regarding history of treated hypertension; $d = -0.11$ regarding on-admission APACHE score—all suggesting a nontrivial imbalance between the cohorts (lower values in the fluvoxamine cohort). The authors provide Kaplan–Meier survival curves but without the numbers at risk.[1] "Ticks" indicating censoring (discharged from ICU alive) are confined to the end of the curves (Figure 2 in Čalušić et al.[1]). Since cut-off point of follow-up was not stated,[1] this could mean that survivors were (a) discharged only at day 68 or (b) were followed-up to day 68 (out of the ICU). If so, this is in contrast with the study flow diagram.[1] If, on the other hand, patients were discharged alive consecutively over time (e.g., at days 2 and 5), then "at risk" numbers at any time later than 4–5 weeks were likely very low. Be it as it may, data could be read from the graphs and curves reconstructed (Figure 1A): (i) the first marked difference between the treated and controls occurs during the first week– 3 patients died in the former and 11 died in the latter cohort (Figure 1A). This difference (3 vs. 11) did not change over the entire later period [difference in cumulative deaths was 9 (30/51 in treated vs. 39/51 in controls)]. This would indicate a very rapid-onset (and subsequently "lost") effect of fluvoxamine, which does not seem pharmacologically plausible. The assumed fluvoxamine mechanisms[1] are not of the immediate-onset type; with a 3 × 100 mg/day dosing, elimination half-life is likely to extend well beyond 30 h resulting in steady-state only after 7–10 days.[3] Combined with the baseline between-group imbalance, this indicates that the initial separation of the curves—preserved throughout the subsequent period—was likely not attributable to fluvoxamine; (ii) after day 35, numbers at risk were low and there was only one additional death (1 treated patient, day 63) (Figure 1A). Under such circumstances (and particularly if patients were actually discharged consecutively over time), accounting for the entire curve is likely misleading[4]; (iii) the curves (Figure 1A) indicate a possibility that hazard ratio varied over time. As generated in a Cox proportional hazard model (as done here[1]), it is an average of values over time[5]; it is also inherently prone to selection bias and its interpretation is not straightforward.[5] This holds for randomized and particularly for nonrandomized settings.[5] Reconstructed data (Figure 1A) were used to fit a complementary log–log model taking into account the first 35 days: the method treats time as a more "coarsely" measured variable, in intervals of identical length (7-day intervals) and provides period-specific (for weeks 1–5) hazard ratios,[6] which is likely a preferable option.[5] Figure 1B depicts estimated probabilities of death and HRs: it is only during week 1 that the hazard appeared lower in treated – a period during which fluvoxamine most likely had no effect. Authors also fitted a multivariable Cox model[1] to substantiate the fluvoxamine effect. With a total of 15 independents and 102 subjects, the model was likely overfitted and susceptible to bias arising from over (unnecessary)-adjustments.[7] But more importantly, it included adjustment for renal replacement therapy (RRT), which was actually one of the outcomes. Inadequacy of adjustments for post-exposure outcomes as if they were baseline covariates has been extensively elaborated[8] and almost inevitably results in a considerable bias.[8] Such adjustments require implementation of marginal structural models or some of the *g-estimation* methods.[9] Finally (Table 3 in Čalušić et al.[1]), fluvoxamine-treated patients experienced more acute renal failure (37.3% vs. 25.5%), RRT (41.2% vs. 11.8%) and inotropic support (25.5% vs. 11.8%) and were not "superior" to controls regarding mechanically assisted respiration, vasopressor use, infections or thromboembolism. It appears counterintuitive that fluvoxamine had no beneficial effect on these ominous post-baseline developments, and yet conveyed such a marked survival benefit.

Overall, despite the reasonable plausibility of possible molecular effects of fluvoxamine and some previous clinical experience in milder COVID-19 patients,[1] the reported mortality difference between the two cohorts is more likely bias arising from design and analysis than evidence supporting a causal effect of fluvoxamine.

CONFLICT OF INTEREST

The author has no conflict of interest to declare.

Vladimir Trkulja

Department of Pharmacology, Zagreb University School of Medicine, Zagreb, Croatia

Correspondence
Vladimir Trkulja, Department of Pharmacology, Zagreb University School of Medicine, Šalata 11, Zagreb, Croatia.
Email: vladimir.trkulja@mef.hr

ORCID

Vladimir Trkulja https://orcid.org/0000-0002-0968-1194

REFERENCES

1. Čalušić M, Marčec R, Lukša L, et al. Safety and efficacy of fluvoxamine in COVID-19 ICU patients: an open label, prospective cohort trial with matched controls. *Br J Clin Pharmacol*. 2021. doi: 10.1111/bcp.15126
2. Stuart EA. Matching methods for causal inference: a review and a look forward. *Stat Sci*. 2010;25(1):1-21.
3. Hiemke C, Hartter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther*. 2000;85(1):11-28.
4. Machin D, Cheung YB, Parmar MKB (Eds). *Survival Analysis: A Practical Approach*. 2nd ed. Chichester, West Sussex: John Wiley & Sons Ltd; 2006:38.
5. Hernan MA. The hazards of hazard ratios. *Epidemiology*. 2010;21(1):13-15.
6. Prentice RL, Gloecker LA. Regression analysis of grouped survival data with application to breast cancer data. *Biometrics*. 1978;34(1):57-67.
7. Schisterman EF, Core SF, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiological studies. *Epidemiology*. 2009;20(4):488-495.
8. Greenland S. Quantifying biases in causal models: classical confounding vs collider-stratification bias. *Epidemiology*. 2003;14(4):300-306.
9. Hernan MA, Robins JM (Eds). *Causal Inference: What If*. 1st ed. CRC Press LLC; 2019.