Review of: "Favipiravir for the Treatment of Coronavirus Disease 2019; a propensity score-matched cohort study"

Kazuhiro Itoh

Potential competing interests: The author(s) declared that no potential competing interests exist.

The authors conducted a retrospective analysis of COVID-19 patients, including those with severe disease and death, to determine the clinical improvement effect of favipiravir by propensity score matching. The reviewer considers that the statistical analysis is adequate, although the study is limited by the retrospective analysis. There is uniqueness regarding statistical analysis methods and outcomes. However, it is controversial whether the dose of favipiravir was appropriate for COVID-19. Several comments by the reviewer on this paper are listed below.

Major comments

1. The mechanism of favipiravir may be that it inhibits the RdRp of SARS-CoV-2. As variants of SARS-CoV-2 are arising continuously, the mechanism of RdRp inhibition may be expected to be effective for variants. The authors do not provide a description for the variants, but the reviewer suggests that these points can be added to the discussion.
2. Favipiravir has been reported by in vitro experiments to suppress inflammatory cytokine production stimulated and produced by host immune cells. In this study, have the authors obtained data on inflammatory cytokines, heat duration, etc.? If so, please provide them.
3. Multivariate analysis has shown that tocilizumab and systemic corticosteroid use are associated with clinical improvement. However, the authors stated in discussion that they had no effect on clinical improvement. From the results, the reviewer considers that tocilizumab and systemic corticosteroid use may be stronger prognostic factors than favipiravir.
4. Due to the retrospective analysis in this study, it is possible that other therapeutic agents besides favipiravir may have influenced the adverse events. QTc prolongation is not a commonly reported side effect of favipiravir itself. However, it is interesting to note that this was seen in a relatively large number of cases in the present study. How many milliseconds was the QTc prolongation seen in this study actually?
5. Table S1 compares the clinical improvements in patients not requiring oxygen support. Were these results adjusted by multivariate analysis? The reviewer is interested in the effect of favipiravir depending on the severity of COVID-19.

Minor comments

1. Table 1: Fisher's exact test is used for the statistical analysis on Nationality. However, the reviewer considered Pearson's chi-squared test to be appropriate because of the large number of groups to be compared.
2. Table 2: Which method was used for statistical analysis of clinical improvement within 28 days?
3. Table 3: Seems to be a stepwise method of variable selection. The reviewer suggests that factors with high risk be

employed in the multivariate analysis without reference to the P-value.