Peer Review File
Article information: https://dx.doi.org/10.21037/jgo-24-559

Reviewer A

I read the manuscript JGO-24-559, entitled with "Fruquintinib in metastatic colorectal cancer: a multicenter real-world analysis on efficacy, safety, and predictive and prognostic factors."
The point of manuscript is original, and all TRAEs are already reported adverse events. It is supposed to be good tool to estimate prognosis by SMI as other chemotherapeutic agents.
Therefore, this manuscript is worth for publication.
I hope to read the manuscript by web, soon.

Reply: Thank you for your affirmation and recognition.

Reviewer B

1) First of all, my major concern is the development of OS prediction model but the authors did not report the accuracy of the two prediction models. Further, there is no external validation samples to provide validity data of the models. I suggest the authors to delete this part.

Reply 1): The OS prediction model is currently a preliminary conclusion, which brings inspiration and hints for subsequent validation, and will not be deleted for the time being after internal discussion by the authors.

2) Second, the title needs to indicate the clinical research design of this study, i.e., a retrospective cohort study. The authors need to consider whether the current sample size is sufficient to be a real-world study.

Reply 2): Data collection in patients treated with fruquintinib in this study has been approved in advance by the Ethics Committee. The date of the first ethical approval was December 12, 2019, and the first case was enrolled on January 31, 2020, which the investigators consider not to be a retrospective study.

3) Third, the abstract is not adequate. The background did not explain the clinical needs for real-world data. The methods need to describe the inclusion of subjects, the treatment administered, the assessment of baseline factors, follow up procedures, and prognosis and safety outcomes. The results need to report the HR and accurate P values of the identified factors. The current conclusion needs to be tone down since this is a retrospective study and the current patient sample differed from prior studies.

Reply 3):

We have modified our text as advised in the background "but real-world prognostic analyses have been seldom reported"(see Page 2, line 42).

The methods describe the inclusion of subjects, the treatment administered (advanced colorectal cancer who received fruquintinib, see Page 2, line 46),follow up procedures, and prognosis(focusing on progression-free survival, overall survival, and L3 skeletal muscle index,see Page 2, line 47-48).We added some data “including safety follow-up”(see Page 2, line 48). The assessment of baseline factors has been shown in Methods (see Page 4, line 116-118), we consider the baseline factors to be secondary and do not need to be included in the abstract.

About the results, We added the HR and accurate P values of the identified factors (see Page 2, line 55-57).

The conclusions have been stated to be based on available real-world results.

4) Fourth, the introduction is not adequate because the authors did not analyze the limitations of prior clinical studies on the efficacy and safety of fruquintinib for mCRC, analyze the needs for real-world data, as well as the needs for prognostic factors. The authors described the clinical question as “how to identify the specific patients who are able to achieve significant survival benefits from it” but the focus of this study is the efficacy and safety. This question is not adequate for the current study, further, the current data are not sufficiently answer this research question because the potential predictors are all clinical factors.

Reply 4): We have modified our text as advised in the introduction and Ref.9 (see Page 4, line 103-105, Page 11, line 349-351) .In this study, univariate analysis and multivariate analysis were used to identify independent prognostic factors after fruquintinib treatment, and to identify the beneficiary population through clinical characteristics.

5) Fifth, the methodology part is insufficient for assessing the methodology rigorousness. The authors need to report the clinical research design, sample size estimation, details of the baseline clinical factors, follow up procedures, and measure of prognosis and safety outcomes. The authors need to consider center-effect since this is a multicenter study. In statistics, please specify the process of the identification of prognostic factors.

Reply 5):

This study is a real-world study, the sample size has not been strictly calculated and required before the study, the study design is relatively simple, patients who meet the enrollment criteria are enrolled for observation, and the baseline clinical characteristics to be collected have been stated in the method.

We added the study design with "The patients who met the enrollment criteria to receive fruquintinib, either as a single agent or in combination, with monthly follow-up including adverse reaction recording, and efficacy assessment every 2 months and L3 skeletal muscle index (SMI) recorded until disease progression or intolerable adverse effects."(see Page 4, line 121-124)

In the statistics section, it is stated that “chi-square test was used for univariate analysis, factors influencing progression-free survival (PFS) and overall survival (OS) after primary screening,

followed by Cox regression for multivariate analysis, to find independent factors related to prediction and prognosis."(see Page 5, line 150-154)

6) Finally, please consider to review and cite several related papers: 1. Deng YY, Chen YW, Wang MX, Zhu PF, Pan SY, Jiang DY, Chen ZL, Yang L. Acute aortic dissection caused by fruquintinib for metastatic colorectal cancer—a case report and literature review. Transl Cancer Res 2023;12(1):177-185. doi: 10.21037/tcr-22-1872. 2. Li L, Wang T, Wu Z, Li Y, Ma H, Wang L, Lei S, Chen W. Fruquintinib in combination with sintilimab or TAS-102 as third-line or above treatment in patients with metastatic colorectal cancer: a real-world study. Transl Cancer Res 2023;12(11):3034-3044. doi: 10.21037/tcr-23-867. 3. Xu X, Yu Y, Liu M, Liang L, Liu T. Efficacy and safety of regorafenib and fruquintinib as third-line treatment for colorectal cancer: a narrative review. Transl Cancer Res 2022;11(1):276-287. doi: 10.21037/tcr-20-3539.

Reply 6): The first paper is a case report and therefore not cited; The second paper has been cited in Ref. 10(see Page 11, line 352-354); The third article is a review, in which the references have been indirectly cited.