Answer to Reviewers Comments

Dear Editor and Reviewers, thank you for your valuable comments and inquiries regarding our manuscript. Please find below our point-by-point response to the issues raised in the peer review report.

Name of Journal: World Journal of Clinical Cases
Manuscript Type: ORIGINAL ARTICLE

Retrospective Study

Colorectal cancer patients in a tertiary hospital in Indonesia: Prevalence of the younger population and associated factors

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We have revised the manuscript in accordance to the suggestions made by reviewers, and addressed the issues point-by-point, as can be found below.

Reviewer 05469117

1. On page 7, 2nd paragraph, "as it has been widely reported that these patients display more aggressive tumor biology and molecular and pathological features. [13,14] " Can it be described in detail?
   It was reported that colorectal cancer (CRC) in young patients were associated with poorly differentiated tumor, more advanced stage at diagnosis, and more aggressive tumor as shown by larger tumor size, higher frequency of metastases and lymphovascular invasion.
2. On page12, "no difference between the two age groups was observed for suspicion of FAP, parental history, or other family history of CRC." Can you explain the criteria of FAP?

FAP is suspected when the patients showed multiple colorectal adenomatous polyps (>100) or had family history of FAP.

3. As we all know, adenocarcinoma is the most common type of gastrointestinal tumor, followed by NEN. Is this pathological classification suitable (Table 2 Histopathological features of early-onset and late-onset CRC)?
   Thank you for the question. As for the histopathological classification, we followed the WHO histologic classification of malignant primary tumor consisting of epithelial tumor (adenocarcinoma), nonepithelial and carcinoid tumors.
4. Some citations lack punctuation, such as citations 11 and 41.
   Thank you for your comment. We have corrected the referencing style in our citations.

Reviewer 04232981

1. Spacing, punctuation marks, grammar, and spelling errors should be reviewed wholly.
   Thank you for the comments. We have reviewed and submitted the manuscript to an English editing service for further proof-reading service.
2. English is poor. The authors need to improve their writing style. In addition, the whole manuscript needs to be checked by native English speakers.
   The manuscript had been checked by a native English editing service recommended by BPG before the first submission. However, thank you for your suggestion. We have tried to improve our writing style and re-submitted the revised manuscript to another English editing service for a second proof-read.
3. The abstract section is well, but need to add a focus point to the abstract section. The background (abstract) is lengthy. In the abstract section, rewrite the sentence: "Early-onset CRC cases were more likely to be underweight (34.6% vs. 20.0%, $P < 0.001$) and suspected of suffering from hereditary nonpolyposis colorectal cancer (HNPCC) (9.3% vs. 4.1%, $P < 0.05$); both of these variables were significantly higher than among the late-onset CRC

cases". This is a complex sentence. I found some sentences like this. Need to make those lucid and clear.

Thank you for your comment and suggestion. We have re-written the sentence in the abstract section to deliver the message more clearly.

4. Introduction section look well.

   Thank you for your compliment.

5. Originality of the work should be improved by the author (either in the conclusion or introduction section).

   Thank you for the advice. We have added a point regarding the originality of the work in our conclusion.

6. State the objective/aim of the research clearly in the last paragraph of the introduction section.

   We have added more details regarding the aim of our research in the last sentence of the introduction section.

7. Try to remove I, we, our throughput the manuscript.

   Thank you for the comment. We have replaced these words to more appropriate ones.

8. Patient selection and data collection should be fragment into two headings.

   Thank you, we have divided the patient selection and data collection into two subheadings.

9. Criteria's for patients selection need to define preciously. How did the authors validate the number of patients?

   We identified patients who underwent colonoscopy examination with diagnosis of CRC based on histopathological findings from medical records. We used consecutive sampling for patients selection. Sample size was calculated using following formula:

$$n = \frac{Z^2 P (1 - P)}{d^2}$$

$$n = \frac{1.96^2 \times 0{,}39 (1 - 0{,}39)}{0.05^2}$$

$n = 365.56$ → Minimum of 366 samples

10. Statistical analysis section need more precise information (whether mean or SD or SEM etc.).

    Thank you for your advice. The results were presented in proportion frequency and its percentage.

11. Results section looks poor. Need to divide into subtitles. Results description written haphazardly. Need to maintain a logical flow.

    We have divided the result section into several subtitles and put it according to the categorical order based on the tables.

12. In the discussion, many concepts already reported in the introduction are repeated, so it is better to avoid unnecessary repetitions.

    Thank you for the suggestion.

13. Tables presentation is well-defined.

    Thank you.

14. Conclusion has to be improved by including more points (personal recommendation, limitation, etc.).

    Thank you, we have added more points regarding our study limitation and further recommendations.

Reviewer 06086481

1. The authors shown that most patients with early-onset CRC were male, had left-sided tumors, histopathologically displayed adenocarcinoma, presented with abdominal pain. Clinical data regarding the characteristics and risk factors for early-onset CRC in Indonesia are lacking and this report is the first to determine them.

   Thank you for the review. Yes, our study is the first to determine the current condition of early-onset CRC in Indonesia.

2. The limitation is to conduct in a single tertiary health center with a retrospective cross-sectional study design.

   Yes, our limitation is that a single tertiary center based study may not be representative enough for the general population.

3. I think that this paper is interested in colorectal surgeons and oncologists. Before the final decision, the authors should revise several places so that the message of this paper more clearly. I believe that the process would make the manuscript more attractive.

   Thank you for the review and comments. We have revised the manuscript and hope that the message can be delivered more clearly.

Reviewer 06097460

1. The main finding of the study is that EACRC constituted 41.4% of the cases in the hospital from 2008 to 2019. In 2020 in the US, based on a yearly increase in early-onset cases, EACRC was projected to constitute 10-12% of CRC cases. 41.4% vs 10-12% is a staggering difference. If the rate of EACRC in Indonesia is truly 41% than Indonesia has a national emergency on tis hands. I suspect however that this result is instead the product of faulty methodology, as well as the inherent biases of a retrospective single-center study. For example, table 1 shows there were 114 cases of CRC from 2008-2013 and 381 from 2014 to 2019. It is unclear to me how a single center can have > 3 times as many colorectal cancer cases in 2 consecutive 5 years periods. As stated in the methods, records with incomplete medical information were excluded and I suspect these were mostly late-onset CRC, which inflated their EACRC numbers. Of note, the authors make no effort to explain their 41.4% result in their discussion. I feel very strongly that this manuscript should not be published until this result is explained in the text or the data table shared. This is the kind of result that gets picked up by lay media and misinterpreted and diminishes public confidence in science.

   Thank you for your comments. We agree that our data showed much higher rate of early-onset CRC patients than other reports. However, we have mentioned in our article that as it is a retrospective single center study conducted in a tertiary hospital, our findings may not be representative to the whole general population and thus we recommend further multi-center or population-based studies involving larger sample size to better assess the

clinical demographics and determine the population at risk for early-onset CRC in Indonesia.

2. The authors in their discussion misinterpret and overstate many of their findings. For example, they state there was an increase in EACRC between the 2 five year periods when the numbers are 41.2% and 41.5%.
   We stated that there is only a slight increase of early-onset CRC cases between the two periods, but it is not a significant increase.