PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Analyzing Eleven Years of Incidence Trends, Clinicopathological Characteristics, and Forecasts of Colorectal Cancer in Young and Old Patients: A Retrospective Cross-Sectional Study in An Indonesian National Referral Hospital.
AUTHORS	Rahadiani, Nur; Habiburrahman, Muhammad; Abdullah, Murdani; Jeo, Wifanto Saditya; Stephanie, Marini; Handjari, Diah Rini; Krisnuhoni, Ening

VERSION 1 – REVIEW

REVIEWER	Suriawinata, Arief Dartmouth College Geisel School of Medicine
REVIEW RETURNED	27-Feb-2022

GENERAL COMMENTS	Rahadiani et al presented an 11-year retrospective histopathologic study on colorectal cancer (CRC) from an Indonesian national referral hospital. The study addressed the lack of retrospective studies in Southeast Asian population. It revealed a rather unique and unexpected increasing trend of early onset CRC's in Indonesia. The result of the study may potentially shape CRC screening/surveillance and improve public health policy and funding in Indonesia. This manuscript would benefit from reducing long connecting sentences and revising the use of subordinating conjunctions throughout to improve comprehension. Previous studies' result and description should be in past tense. Be consistent with the use of terms (and their definitions), such as age group and ethnic group – "young patients" vs "younger patients" vs "younger populations"; "old patients" vs "elderly patients", "young onset" vs "early onset" vs "under the age of 50", "tumor" vs "neoplasm" etc. Page 11 line 15-19. Rework sentences to show direct comparison between APC of this study vs WHO, e.g. xx% vs xx% Page 9 line 8. Clarify findings in Romanian study. Page 13 line 12. Clarify "unavoidable risk of several biases" Figure 1. Increase brightness and contrast of histologic pictures. Figure 2 and 3. Image size of the graphs was too small or the resolution was too low.

	Clarify and translate findings (J-shaped, S-shaped, S-curve) in the second paragraph of trend analysis of CRC section. The conclusion of the abstract and manuscript should be synchronized.

REVIEWER	Deloumeaux, Jacqueline Université des Antilles et de la Guyane
REVIEW RETURNED	04-Mar-2022

GENERAL COMMENTS	In the abstract, some abbreviations are not properly introduced in the abstract CRC at first citation (CRC) others are not at all (LNR1) . This study is limited to the referral hospital and used data for patients with completed medical records. Comments/questions: - First, it would have useful to know how many patients were excluded from the study and what data were missing using a flow chart. - Second if analyzing cases with complete records is acceptable to better describe clinical and histological characteristics of CRC, it is not to estimate five-year trends. Even if some medical data were missing; these cases could have been used to estimate the trends of CRC over years. Assessing such trends only with cases with complete data is inaccurate. Were the patients with missing data older, younger? - A rapid view of CRC cancers on the IARC sites, shows than more than 17000 cases are diagnosed each year. How representative of the overall cases is the sample studied? Some data on the overall incidence of CRC cancers in Indonesia would help situate the study in the context of the general population of Indonesia Results While it is said in the method section than the patients came form the Dr Cipto hospital, the authors mention patients in “these centers” and in our “center” in the result section. - Which centers is it about? How were these centers selected? Can this point be clarified? The presentation of table 1 is quite unusual with entries difficult to read. The choice of the presentation of age both as a class and a quantitative variable in the same table does not seem pertinent. Mean ages could be given in the text. The same comment applies for the tumor size in table 1 and for adequacy of dissected nodes in table 2. Figures 1 to 3 should be displayed on a wider scale for a better visualization. As mentioned above, the exhaustiveness of the CRC cases included in the study for this trend analysis is not given. Moreover, the assumption of a similar pattern of missing data in the young and old is not even discussed. This point needs to be detailed in the method section and mentioned in the discussion. Discussion The first part of the discussion (from 1.1 to 1.9) needs to be synthetized, to focus on the case analyses based on age group which is the stated objective of the manuscript.

VERSION 1 – AUTHOR RESPONSE

#Reviewer Number 1
Arief Suriawinata, Dartmouth College Geisel School of Medicine

General Comments: Rahadiani et al. presented an 11-year retrospective histopathologic study on colorectal cancer (CRC) from an Indonesian national referral hospital. The study addressed the lack of retrospective studies in Southeast Asian population. It revealed a rather unique and unexpected increasing trend of early onset CRC's in Indonesia. The result of the study may potentially shape CRC screening/surveillance and improve public health policy and funding in Indonesia.

Author's Responses: Thank you for your generous comment and suggestions to improve our paper. We appreciate the details you shared about areas we can improve upon—this insight will help us significantly improve our paper. The changes and modifications addressing the suggestion from reviewer 1 will be highlighted in blue.

Table 2. Summary of revision based on Comments from Reviewer 1

No.	Suggestions	Response from the Author
1.	This manuscript would benefit from reducing long connecting sentences and revising the use of subordinating conjunctions throughout to improve comprehension. Previous studies' result and description should be in past tense.	Thank you for your recommendation. To increase comprehension, we tried removing long connecting sentences and modifying the use of subordinating conjunctions throughout. The results and description of prior investigations have been fixed and made in the past tense. Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 261-607, p8-16
2.	Be consistent with the use of terms (and their definitions), such as age group and ethnic group – "young patients" vs "younger patients" vs "younger populations"; "old patients" vs "elderly patients", "young onset" vs "early onset" vs "under the age of 50", "tumor" vs "neoplasm" etc.	Thank you for your detailed feedback. First, we write those terms to make several variations in writing one term; thus, we search for all possible synonyms. However, we agree with your suggestion for being consistent with one term. Thus, we restructured all inconsistent terms according to the contextual meaning. The changes have been made for the entire manuscript. Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 116, p3; line 151, p4; Line 236-238 p6, Line 382 p11, and all entire manuscript text.
3.	Page 11 line 15-19. Rework sentences to show direct comparison between APC of this study vs WHO, e.g. xx% vs xx%	Thank you for your suggestion. We have revised all writing about the comparison between APC and other numbers when comparing to other previous studies. Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 298-300, p9
4.	Page 9 line 8. Clarify findings in Romanian study.	Thank you for pointing this out.

		We are sorry for the incomplete sentence written in the text. We want to write," However, instead of being among young patients, only one patient with signet-ring cell carcinoma was found in the Romanian study, and that patient was > 50 years." Our findings contradict those of the Romanian study, which identified a case of signet-ring cell carcinoma in an 'old patient' in their cohort; in comparison, we identified the same histological subtypes of colorectal cancer in a 'young patient.' Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 521-523, p15
5.	Page 13 line 12. Clarify "unavoidable risk of several biases"	Thank you for pointing this out. Due to ambiguity, we have deleted this sentence but replaced those with several more straightforward explanations. We want to express that the increasing proportion of young patients in our population may well be influenced by the demographic profile of the Indonesian population, which had a high proportion of people aged 50 in 2019. (213,984,600 of 268,074,600; percentage: 79.82 percent).[44] Moreover, The introduction of national health insurance in the middle of the study period (2014) made access to healthcare more accessible, increasing people's concern for their health, and logically this will make the number of patients diagnosed with CRC higher than expected in other countries. However, further research should be conducted regarding the impact of the new national health insurance scheme on the increasing trend of CRC. Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 279-281, p9
6.	Figure 1. Increase brightness and contrast of histologic pictures.	Thank you for pointing this out. We have corroborated your suggestion by increasing the brightness and contrast of histologic pictures. Current details of this picture are 300 dpi, TIFF format, dimension of 2225 x 1504 pixels, bit depth 24, compression LZW, and resolution unit 2. Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 259, p8 (Figure 5)
7.	Figure 2 and 3. Image size of the graphs was too small or the resolution was too low.	Thank you for pointing this out. We have corroborated your suggestion by modifying the figure and giving attention to image size and resolution. We have made the size of the image and resolution to be: - Figure 1 (study flow diagram for data collection and selection process): 600 dpi, TIFF format, dimension of 3756 x 5250 pixels, bit depth 24, compression LZW, and resolution unit 2.

		- Figure 2 (trend analysis of CRC cases based on tumor locations and side involvement): 600 dpi, TIFF format, dimension of 3805 x 5082 pixels, bit depth 24, compression LZW, and resolution unit 2. - Figure 3 (tumor subsites specific trend analysis on colon cancer): 600 dpi, TIFF format, dimension of 4016 x 2699 pixels, bit depth 24, compression LZW, and resolution unit 2. - Figure 4 (forecasting of CRC cases based on tumor locations and side involvement): 600 dpi, TIFF format, dimension of 3868 x 5246 pixels, bit depth 24, compression LZW, and resolution unit 2. - Figure 5 (histopathological features of colorectal cancer resection specimen): 300 dpi, TIFF format, dimension of 2225 x 1504 pixels, bit depth 24, compression LZW, and resolution unit 2. During the revision, we ensure the format has fitted journal guidelines. However, please contact us if there is still an error in the format after this modification and uploading the revised figure or if there are further requirements we should fulfill. Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 109 p4 (Figure 1), Line 206 p6 (Figure 2), Line 213 p6 (Figure 3), Line 226 p6 (Figure 4), and Line 259 p8 (Figure 5)
8.	Clarify and translate findings (J-shaped, S-shaped, S-curve) in the second paragraph of trend analysis of CRC section.	Thank you for pointing this out. We have made the shape of the forecasting model clear and tried to interpret the clinical implication, although very few current studies about forecasting cancer incidence and few papers have been found to address the trend model's shape specifically and in detail. - The linear model means the cases increase gradually over time linear at a constant rate. - The quadratic curve model is a forecasting method that develops a non-linear relationship between time and the response variable. It is a particular case of the polynomial regression model in which the independent variable is nothing but the time index or some other equally spaced sequence of numbers. Their value of accuracy parameters shows that the quadratic trend model forecasts more accurately for time series than the other models where the trend is polynomial. This accuracy is because the quadratic trend model resembles a polynomial regression model that accurately captures the polynomial data trend.[6] - An exponential growth curve has a J-shape, which refers to a growth whose rate is proportional to the size of the population over a specific period. Exponential growth curve modeling is a regression-based method for analyzing longitudinal data (i.e., tracking the same sample at different points in time), suited to the projection of trends in one disease entity like CRC into a different period. The advantage of growth curve modeling over other methods is that this technique permits the testing of several types

		of trajectories until the one with the best fit to the data is found and an output far more precise than other statistical means. This increased precision is achieved by controlling the variance across several single trajectories while calculating the trajectory representing the whole bundle best.[7,8] Exponential growth is characterized by growing slowly at first and continues at some point by accelerating growth rate. This equation describes the growth with a constant doubling time. The exponential growth curve is the fastest growth over S-curve, quadratic, and linear. This pattern causes an explosion of the cases relatively more than the S-curve, which causes a relatively constant population growth rate. - The sigmoid-shaped (S-shaped) curve trend model refers to a case growth whose rate decreases with the increasing number of individuals. It is a forecasting method that develops a sigmoid relationship between time and the response variable.[6] S-curve trend is a particular case of the logistic regression model in which the independent variable is nothing but the time index or some other equally spaced sequence of numbers. An S-shaped curve is symmetric around the inflection point, which means that the case increases initially rapidly, followed by a slower rate after the inflection point than the rate postulated by a curve. The cases following this pattern will be slow growth initially, then explosion faster, and at their upper limit will be gradually steady. However, this can lead to potential under- and over-estimation of the actual disease risk at the lower and upper tails.[104] The S-curve trend model performmost accurately for a time series that follows a logistic.[6] Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 412 p 12
9.	The conclusion of the abstract and manuscript should be synchronized.	Thank you for pointing this out. We have synchronized the conclusion of the abstract and manuscript. The editorial will be: In abstract: Conclusions: Epidemiological trends and forecasting of CRC cases in Indonesian patients showed an enormous increase, notably for colon cancer, with a particularly concerning trend in young patients. Additionally, young patients exhibited particular clinicopathological characteristics that contributed to the disease's severity. In manuscript: Conclusion: This study aimed to assess clinical trends in CRC over 11 years based on tumor locations and side involvement, forecast the future incidence of CRC for ten years, and analyze the clinicopathological profile of CRC among the Indonesian population in a single center. Epidemiological trends and forecasting of CRC cases in Indonesian patients showed an enormous increase, notably for colon cancer, with a particularly concerning trend in young patients. Additionally, young patients exhibited particular

		clinicopathological characteristics that contributed to the disease's severity. Forecasts for the next ten years using fit-model regression analysis found a significantly high number of CRC burdens in the future, particularly in the colon, following linear, quadratic, exponential, or S-shaped population growth models with a higher number of patients to be diagnosed compared to the current period, except for rectal cancer cases, which are stable and declining. Young patients have distinct and more worrisome clinicopathological features in tumor location, subsites, histological subtypes, adequacy of dissected node, and PNI impacting disease aggressiveness and prognosis. Multidisciplinary policies encompassing specialized screening protocols, extensive educational efforts, and lifestyle adjustments are required immediately to address this perplexing problem. Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 41-43, p1 and Line 608-619, p17.

#Reviewer Number 2
Dr. Jacqueline Deloumeaux, Université des Antilles et de la Guyane

General Comments: The authors provide a very detailed clinical and histopathological description of 11 years of colorectal cancers in the national referral hospital of Indonesia distinguishing young patients below 50 to older ones. Overall, the manuscript is well written but is far too dense and not of easy reading. The presentation of tables 1 and 2 are quite unusual as well and not intuitive. The figures should be in larger format for a better visualization. This manuscript presents detailed and informative data on CRC in e referral center in Indonesia. Even if extrapolation should be careful considering the sample size of the study, the lack of some essential information on the global health situation of CRC in the country, this study should be considered for publication after addressing the comments.

Author's Responses: We thank the reviewer for their constructive comments and suggestions, and we discuss these in the sequence below. The changes and modifications addressing the suggestion from reviewer 2 will be highlighted in yellow.

Table 3. Summary of revision based on Comments from Reviewer 2

No.	Suggestions	Response from the Author
1.	Overall, the manuscript is well written but is far too dense and not of easy reading. The presentation of tables 1 and 2 are quite unusual as well and not intuitive. The figures should be in larger format for a better visualization.	Thank you for your feedback. Regarding this issue, we have made our text more concise and tried to ensure the flow of reading is more straightforward. We also edited the table and added one table for variables with mean values to separate them from tables 1 and 2, which we hope would make the layout more intuitive. We have also fixed the format of the figure. There has been an error in submitting the figure, and we hope that by re-uploading new figures which have been fixed, the size and resolution of this issue will be clear. Hopefully, the new figures published have met your criteria. Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view

		mode): Line 109 p4 (Figure 1), Line 206 p6 (Figure 2), Line 213 p6 (Figure 3), Line 226 p6 (Figure 4), and Line 259 p8 (Figure 5)
2.	Abstract In the abstract, some abbreviations are not properly introduced in the abstract CRC at first citation (CRC) others are not at all (LNR1) .	Thank you for your feedback. We have added the abstract to make it clear in reading, specifically for CRC and LNR in the first place where they were introduced. The M0 was replaced with no distant metastasis. Meanwhile, pT3 and pN0 were preserved since it was a common abbreviation. Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 23, 28, 38, and 39, p5
3.	Methods This study is limited to the referral hospital and used data for patients with completed medical records. First, it would have useful to know how many patients were excluded from the study and what data were missing using a flow chart.	We agree, and we thank the reviewer for asking about this matter. We have followed your suggestion. In this study, we have excluded 374 of 1,958 enrolled cases. The details flow on how we select the cases until complete data were analyzed have been put in the main text as shown below in Figure 1. Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 104-109, p3
4.	Methods Second if analyzing cases with complete records is	We thank the reviewer for their support on this matter. We have made a new analysis that included all 1,584 eligible patients to be analyzed in trend analysis and case forecasting.

	acceptable to better describe clinical and histological characteristics of CRC, it is not to estimate five-year trends. Even if some medical data were missing; these cases could have been used to estimate the trends of CRC over years. Assessing such trends only with cases with complete data is inaccurate. Were the patients with missing data older, younger?	We agree and thank you for your criticism that assessing trends only with cases with complete data is inaccurate. At first, we thought we were better off only including complete data within the study. However, after restructuring the paper, we propose including all eligible patients based on exclusion and inclusion criteria proportionally according to what data can still be retrieved. We also added the trend and forecasting by side involvement and the analysis of trend by subsites because we thought sharing these findings was essential to support discussion about the findings. Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 143-148, p3-4 and Line 104-109, p3
5.	Methods A rapid view of CRC cancers on the IARC sites, shows than more than 17000 cases are diagnosed each year. How representative of the overall cases is the sample studied? Some data on the overall incidence of CRC cancers in Indonesia would help situate the study in the context of the general population of Indonesia	We appreciate the time you have committed to providing detailed and constructive feedback. Reflecting on data from the International Agency for Research on Cancer (IARC) sites, it was confirmed that the incidence of colon cancer and rectal cancer predicted in 2020 was 17,368 and 16,059 cases per year.[10] This figure of 17,000 was obtained from the national cancer registry managed by the Ministry of Health, which compiled data from several hospitals throughout the country. In Indonesia, the health system is carried out in stages where certain CRC cases can only be handled at a certain level of health services so that not all CRC cases are referred to a national referral hospital, such as our hospital. Hence, the number of cases was similar to what was reported in IARC. Meanwhile, our study collected CRC case archives from national referral hospitals for cancer for an extended period and became the first report related to trend analysis and forecasting. We think its coverage could represent CRC epidemiology on a regional scale since primary data regarding cancer cases in Indonesia is spread across hospital-based cancer registry data. It is challenging to connect and link data from multiple centers to extract it for a similar study. Our hospital is one of two national referral hospitals for cancer, and it is the largest national referral hospital, with the capacity to be the final entry point for complex cases referred from other referral hospitals. It is important to note that the system for pathological diagnostics in Indonesia has not yet been integrated, so cancer data is still kept in hospitals, not population-based, as one has been published in other developed countries. Also, our institution has experience in publishing hospital-based cancer registry data in a journal.[9] Thus, we recognize our shortcomings and that our sample may not fully represent the entire country, but it is still valuable data collected from a wide range of patients, geographical origins, and periods. Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 589-593, p16
6.	Results	Thank you for asking about this issue.

	While it is said in the method section than the patients came form the Dr Cipto hospital, the authors mention patients in “these centers” and in our “center” in the result section. - Which centers is it about? How were these centers selected? Can this point be clarified?	We admitted that we were mistaken in writing the sentence. We were supposed to write “this center” since this study was only obtained from a single health center, Dr. Cipto Mangunkusumo Hospital. This has been amended Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 187, p5
7.	Results The presentation of table 1 is quite unusual with entries difficult to read. The choice of the presentation of age both as a class and a quantitative variable in the same table does not seem pertinent. Mean ages could be given in the text. The same comment applies for the tumor size in table 1 and for adequacy of dissected nodes in table 2.	We agree, and we thank the reviewer for their support on this matter. We proposed putting the numeric (quantitative) variables in a specific table, i.e., the new Table 3, since we want to compare it between two age groups. Those parameters included: ● CRC cases per year ● Colon cancer cases per year ● Rectal cancer cases per year ● Right-sided CRC cases per year ● Left-sided CRC cases per year ● Age (years old) ● Tumor size (cm) ● Smallest tumor size (cm) ● Largest tumor size (cm) ● Total count of positive lymph nodes (LNs) ● Total count of dissected LNs ● Positive LNs ● Dissected LNs ● Lymph node ratio (LNR) Meanwhile, specific age groups per decade have been put in the text of the result section. Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 179-183 p4 and Line 248, p8
8.	Results Figures 1 to 3 should be displayed on a wider scale for a better visualization.	Thank you so much for your prompt feedback. We have met with your suggestion by modifying the visualization of figures as such: Figure 2

		Figure 3 Figure 4

		Figure 5 Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 109 p4 (Figure 1), Line 206 p6 (Figure 2), Line 213 p6 (Figure 3), Line 226 p6 (Figure 4), and Line 259 p8 (Figure 5)
9.	Results As mentioned above, the exhaustiveness of the CRC cases included in the study for this trend analysis is not given. Moreover, the	Thank you for your detailed feedback. We understand your concern about the exhaustiveness of the CRC cases included in the study and your question regarding how the pattern of incomplete data was not included in the trend analysis. We have tried to open our database again and make the recruitment flow for the sample clearer to address this issue (Figure 1). By including all the eligible patients

	assumption of a similar pattern of missing data in the young and old is not even discussed. This point needs to be detailed in the method section and mentioned in the discussion.	and no incomplete data left behind from the analysis, we believe that our results have adequately given the actual and accurate trends regarding CRC epidemiology in Indonesia. In the method section, we emphasize the selection process, and we think we do not need to explain the pattern of missing data in the young and old groups since all the data has been analyzed except for the pathological analysis, which only included resected specimens with complete data. We could not include all the resected specimens since there are roadblocks to completing the process, such as medical record retention, slide staining deterioration, and missing pathological slides. Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 178, p5
10.	Discussion The first part of the discussion (from 1.1 to 1.9) needs to be synthesized to focus on the case analyses based on age group, which is the stated objective of the manuscript.	We truly appreciate your thoughts. Thank you for asking about this matter. We have restructured the writing of this manuscript as a whole from the first page to the end page. In the first part of the discussion, we also synthesized more focus on young-age CRC to highlight why it mattered. We also highlighted the implication of young patients in this disease entity. We included trend analysis and forecasting earlier in the discussion to explain the study's aims. Then, as a secondary outcome, we discussed distinct features related to clinicopathological characteristics between two patient age groups. This knowledge will enlighten us about what makes these two age groups different. Instead of focusing only on trend analysis and forecasting, we also discussed clinicopathological features to picture the pathological data of CRC in the Indonesian patients, which were as a whole scarce, and we also holistically compared young and old patients. Several studies have been published in Indonesia but did not explain the trend analysis, forecasting, or clinicopathological analysis of young and old patients. Those studies are: a study focused on the molecular profile of Indonesian CRC patients,[10] a study highlighting the genomic profile of Indonesian CRC patients,[11] a study focused on genetic risk factors of CRC among multiethnic Indonesian populations,[12] one hospital-based study with few samples, only involving a shorter period, and focused on only microscopic type, sex, age, and anatomical location,[13] and one retrospective study only discussing clinical data on young CRC patients,[14] Therefore in this study we would like to fill the knowledge gap and need of data about histopathological profile to be more complete, comprehensive, and holistic. We also went straight to the point of discussion related to pathological profiles and highlighted the difference between CRC in the young and old populations, which had significant differences and implied a tendency to be different. Current position of revision in the new version of the manuscript clear without track changes (or with track changes but no markup view mode): Line 279-279, p9 and Line 491, p14.

We also made additional changes regarding the revision process of our manuscript, including:

1. Reformating the abstract.

2. Restructuring the method and explaining specific steps in doing trend and forecasting analysis.
3. Make more clear inclusion and exclusion criteria in the method section.
4. Revise, modify and edit the study parameters in the method section.
5. Adding more explanation regarding the statistical analysis.
6. Adding a STROBE checklist.
7. Adding the flowchart of the study selection process for the sample.
8. Editing the results and restructuring the order of figures and tables.
9. Adding a new Table 3 to accommodate the quantitative parameters, adding analysis regarding side involvement, comparison between young and age on-trend and forecasting analysis, and adding a figure related to the trend analysis of CRC subsites (caecum to sigmoid).
10. Revised the discussion and clarified the flow of data and discussion presentation.
11. Correcting grammatical errors.
12. Adding potential biases at the end of paragraph (before conclusion) and giving how to tackle them.
13. Adding several supplementary files, including:

- Supplementary File 1. Checklist

Description: STROBE checklist for a cross-sectional study

- Supplementary File 2. Trend Analysis of All Patients

Description: Detail analysis of annual incidence trend of colorectal cancer using Joinpoint regression analysis among young patients based on tumor location and tumor side involvement

- Supplementary File 3. Trend Analysis of Young Patients

Description: Detail analysis of annual incidence trend of colorectal cancer using Joinpoint regression analysis among young patients based on tumor location and tumor side involvement

- Supplementary File 4. Trend Analysis of Old Patients

Description: Detail analysis of annual incidence trend of colorectal cancer using Joinpoint regression analysis among old patients based on tumor location and tumor side involvement

- Supplementary File 5. Forecasting Analysis of All Patients

Description: Detail analysis for forecasting future ten-years incidence of colorectal cancer using the best-fitted curve model obtained from regression analysis among all patients based on tumor location and tumor side involvement

- Supplementary File 6. Forecasting Analysis of Young Patients

Description: Detail analysis for forecasting future ten-years incidence of colorectal cancer using the best-fitted curve model obtained from regression analysis among young patients based on tumor location and tumor side involvement

- Supplementary File 7. Forecasting Analysis of Old Patients

Description: Detail analysis for forecasting future ten-years incidence of colorectal cancer using the best-fitted curve model obtained from regression analysis among old patients based on tumor location and tumor side involvement

- Supplementary Table 1. Summary of Forecasted Cases 2020-2029

Description: Summary of a best-fitted model, predicted case equation, and number of forecasting cases during the period between 2020 and 2029

13. Editing the contributorship, the final version is:

- Conceptualization: Nur Rahadiani
- Data curation: Nur Rahadiani, Marini Stephanie, Diah Rini Handjari, Ening Krisnuhoni, Murdani Abdullah, Wifanto Saditya Jeo
- Formal Analysis: Nur Rahadiani, Muhammad Habiburrahman
- Funding Acquisition: Nur Rahadiani
- Investigation: Nur Rahadiani, Muhammad Habiburrahman
- Methodology: Nur Rahadiani, Muhammad Habiburrahman
- Project Administration: Nur Rahadiani

- Resources: Nur Rahadiani, Marini Stephanie, Diah Rini Handjari, Ening Krisnuhoni
- Software: Muhammad Habiburrahman
- Supervision: Nur Rahadiani, Ening Krisnuhoni, Murdani Abdullah, Wifanto Saditya Jeo
- Validation: Nur Rahadiani, Marini Stephanie, Diah Rini Handjari, Ening Krisnuhoni, Murdani Abdullah, Wifanto Saditya Jeo
- Visualization: Muhammad Habiburrahman
- Writing – original draft preparation: Nur Rahadiani, Muhammad Habiburrahman
- Writing – review & editing: Nur Rahadiani, Muhammad Habiburrahman, Marini Stephanie, Diah Rini Handjari, Ening Krisnuhoni, Murdani Abdullah, Wifanto Saditya Jeo

That is all the changes we have made. Because there are many revisions in our manuscript, which resulted in quite a lot of changes in the reference citation arrangement and improvement in grammar, hence, to prevent missed data, we ask the reviewer and editor to use this latest version of our Word document for the following publication process. We also have proofread for any grammatical and wording issues in the revision process. Please use the Track Changes feature inherent to your word processing software to view revised sentences and phrases.
We hope that this revised manuscript will meet your requirements and be granted the opportunity to be published in BMJ Open.

Thank you

Sincerely,
Nur Rahadiani, MD, Ph.D.
Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia and
Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

References:
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