Study Protocol Systematic Review

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Clinicopathological significance of Ki67 expression in colorectal cancer

A protocol of systematic review and meta-analysis

Jing Li, MM[a], Zhi-ye Liu, MB[b], Hai-bo Yu, MM[c], Qing Xue, Undergraduate[d], Wen-jie He, MB[e], Hai-tao Yu, MB[f,*]

Abstract

Background: This study will investigate the diagnostic accuracy of Ki67 expression in colorectal cancer (CC).

Methods: A comprehensive search in electronic bibliographic databases (MEDLINE, EMBASE, Cochrane Library, Web of Science, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure) will be performed from inception to the February 29, 2020 with no restrictions to the language and publication status. Two authors will examine the collected studies, extract essential data, and appraise study quality separately. If possible, we will estimate receiver operating characteristic (ROC), sensitivity and specificity by utilizing bivariate random effects and hierarchical summary ROC models.

Results: This study will summarize present evidence to explore the diagnostic accuracy of Ki67 expression in CC.

Conclusion: The findings of this study will clarify the diagnostic accuracy of Ki67 expression in CC.

Systematic review registration: INPLASY202030009.

Abbreviations: CC = colorectal cancer, CIs = confidence intervals, ROC = receiver operating characteristic.

Keywords: accuracy, colorectal cancer, Ki67 expression, sensitivity, specificity

1. Introduction

Colorectal cancer (CC) is one of the most lethal cancers and prevalent malignant tumors globally.[1–4] It has been reported that about 1.8 million new patients increased, and 881,000 patients were dead in 2018.[5–8] It contributes approximately 10% new cases and mortality.[2] Previous studies have reported that its 5-year survival rate is about 64%.[9] However, the 5-year survival rate of metastatic CC is only 12%.[2,9] Thus, it is very important to diagnose CC at early stage.

Previous studies have found that Ki67 expression may help to diagnose CC, although there are still inconsistent results.[10–18] In addition, no systematic review has been explored to address this topic. Thus, this study will systematically assess the diagnostic accuracy of Ki67 expression in patients with CC.

2. Methods

2.1. Objective

This study aims to investigate the diagnostic accuracy of Ki67 expression in CC.

2.2. Study registration

This study has been registered on INPLASY (202030009). It has been organized following the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol statement.[19]

2.3. Eligibility criteria

2.3.1. Types of studies. All case-controlled studies (CCSs) that explored the diagnostic accuracy of Ki67 expression in CC will be included. We will not apply restrictions to the basis of language of publications.

2.3.2. Types of participants. We will include CCSs that compare Ki67 expression between CC participants with CC tissues and normal adjacent tissues. We will not employ any restrictions to the age, sex, race, and CC severity.

JL and Z-yL have contributed equally to this study.

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

The authors have no conflicts of interest to disclose.

[a] *Department of Physiology, Jiamusi University School of Basic Medical Sciences,* [b] *Department of Chemotherapy and Radiotherapy,* [c] *Department of Cardiology,* [d] *Clinical Medicine of Class 7 in Grade 2016, Jiamusi University,* [e] *Department of Outpatient,* [f] *Department of Anorect, First Affiliated Hospital of Jiamusi University, Jiamusi, China.*

[*] *Correspondence: Hai-tao Yu, Department of Anorect, First Affiliated Hospital of Jiamusi University, No.348 Dexiang Street, Jiamusi, 154002, China (e-mail: 18645468692@163.com).*

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2.3.3. Type of index test. Index test: We will include studies that specify the index test utilized Ki67 expression to diagnose potential patients with CC.

Reference test: Any patients with histological-proven CC will be included.

2.3.4. Types of outcome measurements. Primary outcomes are sensitivity and specificity. Secondary outcomes are positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio.

2.4. Data sources and search strategy

2.4.1. Electronic searches. A comprehensive search for associated articles in electronic bibliographic databases (MEDLINE, EMBASE, Cochrane Library, Web of Science, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure) will be carried out from inception to the February 29, 2020. There will be no language and publication status restrictions. We will build search strategy sample for Cochrane Library (Table 1), and we will adapt similar search strategies for other databases.

2.4.2. Other resources. We will check and obtain potential studies from clinical trial registry, conference abstracts, and reference lists of relevant reviews.

2.5. Data collection and analysis

2.5.1. Selection of studies. All searched citations will be imported into EndNote 7.0 software: organization, Clarivate Analytics; city, Philadelphia; country, USA to eliminate all duplicates. Tiles/abstracts of potential studies will be scanned to exclude all irrelevant literatures. The remaining articles will be identified against all inclusion criteria. Any disagreements between 2 authors will be resolved by a third author through discussion. The process of study selection will be summarized in a flow diagram.

2.5.2. Data collection and management. After study selection, 2 authors will independently collect information from all eligible studies. Any differences will be solved by a third author with consultation. We will extract following information: first author, year of publication, country, sample size, age, sex, CC severity, index test, reference test, outcomes, results, conclusions, and conflict of interest.

2.5.3. Dealing with missing data. Any unclear or missing data will be tried to obtain from original study authors. If we can not request it, we will analyze reachable data using intention-to-treat analysis.

2.6. Methodological quality assessment

Two authors will independently appraise methodological quality using Quality Assessment of Diagnostic Accuracy Studies tool.[20] We will assess it through 4 aspects. Any different conflicts will be settled by a third experienced author through consultation.

2.7. Statistical analysis

2.7.1. Data synthesis. RevMan V.5.3 software and Stata V.12.0 software will be employed to carry out statistical analysis. We will estimate outcome values as descriptive statistics and 95% confidence intervals. I^2 statistic will be utilized to check heterogeneity across eligible studies. $I^2 \leq 50\%$ implies homogeneity, and we will use a fixed-effects model. On the other hand, $I^2 > 50\%$ reveals discrete heterogeneity, and we will exert a random-effects model. We will estimate values of outcome data using 2×2 tables. Additionally, we will estimate a descriptive forest plot and a summary receiver operating characteristic plot. If there is homogeneity among included studies, we will perform a meta-analysis. If there is obvious heterogeneity, we will scrutinize its sources using a subgroup analysis and bivariate random-effects regression approach.

2.7.2. Subgroup analysis. Whenever necessary, we will investigate sources of apparent heterogeneity based on the differences in study characteristics, study quality, and outcomes.

2.7.3. Sensitivity analysis. Whenever necessary, we will examine the stability of study results by eliminating low quality studies.

2.7.4. Reporting bias. If possible, we will perform a funnel plot and Egger regression test to investigate the reporting bias when >10 studies are included.[21]

2.8. Ethics and dissemination

This study will not collect individual patient data, thus, we will not need ethic approval. We will publish this study on a peer-reviewed journal.

3. Discussion

Several studies have reported that Ki67 expression may help to diagnose CC. However, no consistent conclusions have been reached and no study has systematically investigated the diagnostic accuracy of Ki67 expression in patients with CC. Thus, this study will firstly explore the diagnostic accuracy of Ki67 expression in CC. The findings of this study may provide

Table 1

Search strategy for Cochrane Library.

Number	Search terms
1	MeSH descriptor: (colorectal neoplasms) explode all trees
2	((colorectal neoplasms*) or (colorectal cancer*) or (bowel cancer*) or (colon cancer*) or (rectal cancer*) or (rectum cancer*) or (large intestine cancer*)):ti, ab, kw
3	Or 1-2
4	(Ki67) explode all trees
5	MeSH descriptor: (gene expression) explode all trees
6	Or 4–5
7	(case-controlled studies) explode all trees
8	((case controlled study*) or (case-controlled*) or (trial*) or (control*) or (controlled trials *)):ti, ab, kw
9	Or 7–8
10	3 and 6 and 9

evidence to determine whether Ki67 expression is helpful in diagnose CC.

Author contributions

Conceptualization: Jing Li, Zhi-ye Liu, Hai-bo Yu, Qing Xue, Wen-jie He, Hai-tao Yu.
Data curation: Jing Li, Zhi-ye Liu, Wen-jie He, Hai-tao Yu.
Formal analysis: Jing Li, Hai-bo Yu, Qing Xue, Wen-jie He.
Funding acquisition: Hai-tao Yu.
Investigation: Zhi-ye Liu.
Methodology: Jing Li, Zhi-ye Liu, Hai-bo Yu, Qing Xue, Wen-jie He.
Project administration: Hai-tao Yu.
Resources: Jing Li, Zhi-ye Liu, Hai-bo Yu, Qing Xue, Wen-jie He.
Software: Jing Li, Zhi-ye Liu, Hai-bo Yu, Qing Xue, Wen-jie He.
Supervision: Hai-tao Yu.
Validation: Zhi-ye Liu, Hai-bo Yu, Qing Xue.
Visualization: Jing Li, Hai-bo Yu, Wen-jie He, Hai-tao Yu.
Writing – original draft: Jing Li, Zhi-ye Liu, Hai-bo Yu, Qing Xue, Wen-jie He, Hai-tao Yu.
Writing – review & editing: Jing Li, Zhi-ye Liu, Hai-tao Yu.

References

[1] Lombardi N, Bettiol A, Crescioli G, et al. Association between anthraquinone laxatives and colorectal cancer: protocol for a systematic review and meta-analysis. Syst Rev 2020;9:19.
[2] Dekker E, Tanis PJ, Vleugels JLA, et al. Colorectal cancer. Lancet 2019;394:1467–80.
[3] Kim BH, Kim JM, Kang GH, et al. Standardized pathology report for colorectal cancer, 2nd edition. J Pathol Transl Med 2020;54:1–9.
[4] Goodwin BC, Ireland MJ, March S, et al. Strategies for increasing participation in mail-out colorectal cancer screening programs: a systematic review and meta-analysis. Syst Rev 2019;8:257.
[5] Plumb AA, Obaro A, Fanshawe T, et al. Prevalence and risk factors for post-investigation colorectal cancer ("interval cancer") after computed tomographic colonography: protocol for a systematic review. Syst Rev 2017;6:36.
[6] Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Prz Gastroenterol 2019;14:89–103.
[7] Mattiuzzi C, Sanchis-Gomar F, Lippi G. Concise update on colorectal cancer epidemiology. Ann Transl Med 2019;7:609.
[8] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
[9] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7–34.
[10] Melling N, Kowitz CM, Simon R, et al. High Ki67 expression is an independent good prognostic marker in colorectal cancer. J Clin Pathol 2016;69:209–14.
[11] Aladhraei M, Kassem Al-Thobhani A, Poungvarin N, et al. Association of XPO1 overexpression with NF-κB and Ki67 in colorectal cancer. Asian Pac J Cancer Prev 2019;20:3747–54.
[12] Yang Y, Li J, Jin L, et al. Independent correlation between Ki67 index and circulating tumor cells in the diagnosis of colorectal cancer. Anticancer Res 2017;37:4693–700.
[13] Li W, Zhang G, Wang HL, et al. Analysis of expression of cyclin E, p27kip1 and Ki67 protein in colorectal cancer tissues and its value for diagnosis, treatment and prognosis of disease. Eur Rev Med Pharmacol Sci 2016;20:4874–9.
[14] Li P, Xiao ZT, Braciak TA, et al. Association between Ki67 index and clinicopathological features in colorectal cancer. Oncol Res Treat 2016;39:696–702.
[15] Ma YL, Peng JY, Zhang P, et al. Immunohistochemical analysis revealed CD34 and Ki67 protein expression as significant prognostic factors in colorectal cancer. Med Oncol 2010;27:304–9.
[16] Padilla D, Cubo T, Villarejo P, et al. Molecular profile of node-negative colorectal cancer of poor prognosis using immunohistochemical determination of p53, ki67, VEGF, and metalloproteinase-9. Rev Esp Enferm Dig 2007;99:424–5.
[17] Forones NM, Oshima C, Nanogaki S, et al. Determination of proliferative activity using Ki67 and expression of p53 in colorectal cancer. Arq Gastroenterol 1999;36:122–6.
[18] Berenzi A, Benetti A, Bertalot G, et al. Ki67 immunohistochemical evaluation in colorectal cancer and normal colonic mucosa. Possible clinical applications. Pathologica 1992;84:155–63.
[19] Shamseer L, Moher D, Clarke M, et al. PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;349:g7647.
[20] Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.
[21] Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005;58:882–93.