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Repeatability of Radiomics Studies in Colorectal Cancer: A Systematic Review

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Abstract

Purpose: Recently, radiomics has been widely used in colorectal cancer, but many variable factors affect the repeatability of radiomics research. This review aims to analyze the repeatability of radiomics studies in colorectal cancer and to evaluate the current status of radiomics in the field of colorectal cancer.

Methods: A total of 68 eligible studies was included in this review by searching from the PubMed and EmBase databases. Then each study in our review was evaluated using the Radiomics Quality Score (RQS). We analyzed the factors that may affect the repeatability in the radiomics workflow and discussed the repeatability of the included researches.

Results: A total of 68 articles was included in this review, of which only 2 (3%) articles controlled the influence of individual factors, just 2 (3%) articles considered the variability between scanners. In addition, the median score of RQS was 12(out of 36), range −7 to + 28.

Conclusions: The RQS score was moderately low, and most studies did not consider the repeatability of radiomics features, especially in terms of Intra-individual, scanners, and scanning parameters. In order to improve the generalization of the radiomics model, it is necessary to further control the variable factors of repeatability.

1. Introduction

Colorectal cancer (CRC) is one of the most common clinical malignant tumors. According to Global Cancer Statistics 2020, over 1.9 million new cases of colorectal cancer and about 935,000 deaths worldwide, ranking third and second in global cancer morbidity and mortality [1]. Overall survival (OS) with colorectal cancer has improved, with the emergence of neoadjuvant chemoradiotherapy (CRT) and immunotherapy[2], but personalized preoperative diagnosis, prognosis, and treatment options for colorectal cancer patients have so far remained challenging.

Tumors are composed of multiple subpopulations of cancer cells, the process of tumor growth, the same malignant tumor may exhibit temporal and spatial variation in different patients or different parts of the same patient[3], called tumor heterogeneity. At present, the biopsy is the most effective way to diagnose colorectal cancer. However, tissue biopsy only samples a certain part of the tumor, which cannot represent the whole tumor[4], so the information of tumor heterogeneity provided by tissue biopsy is limited. Medical images can analyze the overall situation of tumors at different time points, so it can provide incremental value for evaluating tumor heterogeneity[4]. However, traditional radiology usually relies on the naked eye to diagnose according to size and density. This qualitative method will miss many deep features[5]. In recent years, with the rapid development of image analysis methods and pattern recognition tools, the analysis of medical images has gradually developed from qualitative to quantitative analysis.

As a quantitative analysis tool, radiomics extracts features from medical images through high-throughput computing and applies them to personalized clinical decisions to improve the accuracy of diagnosis and prognosis [4]. In the past decade, radiomics has shown unique advantages in staging, grading, and predicting treatment response. Before applying the radiomics model to the clinical decision, it is necessary to ensure that the radiomics features are repeatable, the model can perform well in different populations, different scanners and different centers[5–8]. "Repeatability" refers to a feature that remains unchanged for more than one image in the same or nearly the same object[9]. It is an indicator of discrimination between different scanners or between different institutions[4, 8]. Radiomics obtains quantitative features from medical images through image acquisition, segmentation and feature extraction, in this process, there are many factors that affect the repeatability of features, such as intra-individual variation, differences between scanners, different scanning schemes, differences in segmentation and so on. Moreover, in the following process, feature reduction and modeling, the choice of methods also change the research results, so it is still challenging to obtain a repeatable and easily applicable radiomics model. In order to improve the generalization ability of the model and promote the clinical application of the research results, it is necessary to control the influence of the above variable factors. In the following, we propose several methods to reduce variation. At present, due to the lack of standardization in the field of radiomics, the results of many studies are not comparable and repeatable. The quality of researches in the field of colorectal cancer radiomics is uneven. It is necessary to evaluate the performance of radiomics as a tool for the diagnosis and prognosis of colorectal cancer. Therefore, this systematic review evaluates the repeatability and reporting quality of radiomics in colorectal cancer, and summarizes its current application.

2. Methods

2.1 Review Strategy

We conducted a systematic review according to the Preferred Reporting items for Systematic review and Meta-Analysis (PRISMA) checklist[10]. But the review was not registered before. Two reviewers used the following retrieval strategies on PubMed and EmBase databases for systematic search: ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "carcinoma"[All Fields]) OR "colorectal carcinoma" [All Fields] OR ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields])) AND ("radiomic"[All Fields] OR "radiomics"[All Fields]), the search deadline was March 2020.

Two reviewers included articles that met the following criteria: (1) articles published in full text retrieved on PubMed and EmBase databases, (2) articles related to radiomics in the field of colorectal cancer, (3) articles that used ultrasound (UA) and/or computed tomography (CT) and/or magnetic resonance imaging (MRI) and/or fluorodeoxyglucose positron emission tomography-computed tomography (FDG

PET-CT). The exclusion criteria were as follows: (1) non-original article (review, meta-analysis, case report, editorial and conference abstract), (2) the purposes of studies are about methodology or test-retest, (3) non-English language studies.

2.2 Study Extraction

Systematically recorded the following data from each included study: author, year, purpose, type, sample size, imaging modality, acquisition parameters, reconstruction parameters, pretreatment method, feature selection method, modeling method, segmentation method, number of features, verification method, performance index, and clinical utility.

2.3 Data synthesis

There are great differences in the methods used in the included studies, so we did not conduct a meta-analysis.

2.4 Quality Assessment

In addition,in order to evaluate the quality of these included studies, we introduced the RQS[4], RQS is a unique quality assessment tool in radiomics[11]. The score is composed of 16 parts, with a total score of 36. The higher the score, the better the quality of the article.

3. Results

According to the above retrieval strategies and standards, 218 articles were retrieved, and 68 articles were included in this study after all screening. The include and exclude flowchart is shown in Figure 1. The area under the curve (AUC) values of the included studies ranged from 0.71 to 0.95, implying a moderate to good predictive performance of the radiomics model. The key information of included studies is summarized in Additional Table 1.

From the four aspects of the number of articles, research tasks, research types, and RQS scores, we gave an overall overview of included articles, so as to analyze the current situation of the application of radiomics in colorectal cancer.

Figure 2 shows the published papers in the field of radiomics of colorectal cancer in recent years. From 2016 to now, the number of articles has increased year by year, with the fastest growth from 2017 to 2019, and its growth rate has slowed down by 2020. The overall trend showed that radiomics was in the stage of development in the field of colorectal cancer. So radiomics is a new field in recent years, and it still faces many challenges, such as the study of repeatability, model interpretability, over-fitting and so on.

In the field of colorectal cancer, radiology was mainly used for prognosis (51%), while few studies have carried out staging and grading (9%) (Figure 3A). The imaging methods studied can be roughly divided into CT, MRI, PET, PET-CT, UA, and the combination of the two imaging methods (Figure 3B). These

studies were mainly based on two imaging methods: CT (45%) and MRI (41%), while there were a few studies related to PET-CT (3%).

Prospective research may provide better clinical evidence for evidence-based medicine and make up for the shortcomings of retrospective research. However, the prospective study has a long follow-up time and many restrictions, so it is not easy to achieve. Most radiomics of colorectal cancer are based on retrospective data sets (94%), and only a few are prospective studies[12–15](6%).

Multicenter research can fully reflect the overall situation and evaluate the generalization ability of the model. Of all the studies, only 7[12, 16–21] (10%) conducted multicenter studies and 5[22–26] (7%) were dual-center studies.

3.1 RQS score

The included articles were scored by RQS, and the specific scores were shown in Additional Table 2. Its score ranges from-7 to 28 (- 19.44–77.78%), the median was 12 (33.33%), of which 13 studies scored less than 10%.

Figure 4 shows the score of each item in the RQS score, 66 studies (97%) reduced the dimension of features to reduce the risk of overfitting, 53 studies (78%) adopted multiple segmentation, and 65 studies reported the differentiation of the model. However, only 24 reported the calibration of the model. Low scores in the following six items (1) phantom studies (2) multiple time point (3) prospective studies (4) open science data (5) Cut-off analysis (6) cost-effectiveness analysis.

Figure 4. Completion rate of 68 studies in RQS.

Only two studies (3%) adopted test-retest reliability. Only five studies disclosed the code and data, but there were no studies that opened ROI-related data. Most studies used the best threshold method to select the threshold, only six (9%) studies used the median as the threshold. Four studies (6%) were prospective, and none of the studies conducted a cost-benefit analysis of the clinical application.

3.2 Repeatability

The repeatability of radiomics features is directly related to the accuracy of model[27]. And many factors in the workflow of radiomics will affect the repeatability of the radiomics features, Such as scanner[9, 27, 28], acquisition parameters[27, 29-33], pretreatment method[34, 35], segmentation method[36-39], inter/intra-observer variability [33, 34, 36], feature selection method [40], modeling method [40]. The factors and solutions that may affect repeatability in the radiomicsworkflow are shown in Figure 5.

Figure 5. Radiomics workflow and repeatability. Each step has associated factors which may influence the repeatability of the study. Although modelling affect reproducibility, there is still no solution.

3.2.1 Intra-individual repeatability

JE van Timmeren, et al. [41] scanned forty patients with rectal cancer twice with the same scanning scheme at 15-minute intervals, and used a consistent correlation coefficient (CCC) to assess the correlation between the features of the two scans, then 7 of 542 features had a CCC> 0.9, and 9 features had a CCC>0.85. Therefore, only some of the features are repeatable at different times for the same individual. The features with the highest repeatability were the “shape”, and the “wavelet” features appeared to be the least reproducible[41]. Certain features are sensitive to changes in organ motion or expansion or shrinkage of the target volume caused by physiological factors such as respiration, bowel peristalsis, cardiac and cardiac activity, so these features show low reproducibility[4]. However, a set of highly reproducible radiomic features can be obtained using the test-retest based on phantom or patients [42, 43].

However, only 2[44, 45] of the 68 articles carried out retest experiments. X Ma, et al. [44] set a base of intra-class correlation coefficient of 0.6 for the retest analysis, in order to ensure the robustness of the features. And J Wang, et al. [45] selected 40 patients with stage II rectal cancer and scanned twice using the same scanner and imaging protocol before treatment, and then used the Spearman correction coefficient to select repeatable features. Only these two studies considered and took measures to control for Intra-individual repeatability.

3.2.2 Acquisition parameters

There may be differences between different scanners. D Mackin, et al. [28]used phantom to compare the radiomics features obtained from four CT scanners: GE, Philips, Siemens, and Toshiba, and found differences between scanners. Then R Berenguer, et al. [27] used two phantom models (the pelvic phantom and the phantom of different materials) to detect the feature differences of intra-CT analysis(differences between different CT acquisition parameters) and inter-CT analysis(differences between five different scanners), showing that only 71 out of 177 features were reproducible. And using hierarchical cluster analysis, the 10 most representative features were selected, including "60 Percentile", “Global Median”, “Global Minimum”, “Kurtosis”, “Mass”, “Volume”, “Roundness”, “Surface Area Density”, “4-Inverse Difference Normalized” and “4-Auto Correlation”. In addition, R Berenguer, et al. [27] reported that the impact of different scanners could be reduced by standardizing the acquisition parameters.

Of the 31 CT-based imaging studies, except for 5 [25, 45–48] that did not provide scanner parameters, the other studies neither used consistent scanning parameters nor assessed the impact of scanner differences on feature repeatability. Therefore, it could not be ruled out that scanner differences do not affect the results of these studies. Among the 28 studies based on MRI, SP Shayesteh, et al. [49] considered the influence of scanner and scanning parameters on feature repeatability and tried to use image preprocessing (noise reduction, intensity normalization and discretization) to reduce the difference. In the PET-CT based research, J Kang, et al. [50] reduced the SUV measurement difference between the two scanners to less than 10 percent through regular standardization and quality assurance.

L He, et al. [32] demonstrated that acquisition parameters (slice thickness, convolution kernel and enhancement) had affects on the diagnostic performance of radiomics, and that radiomics features

constructed based on thin-slice (1.25 mm) have better performance in differential diagnosis than features based on thick-slice (5 mm). The reason for the better performance of thin-slice may be the introduction of larger partial volume artifacts in thick-slice. Similarly, L Lu, et al. [31] demonstrated there exist differences in the values of radiomics feature extracted from CT images with different slice thicknesses and reconstruction methods. And Features associated with tumor size, border morphology, low-order density statistics, and coarse texture were more sensitive to variations in acquisition parameters. Subsequently, a more rigorous experiment [30] showed that 63 of the 213 features were affected by voxels, but 42 features were significantly improved, and 21 features changed greatly after resampling. Therefore, for the image data with different slice thicknesses, the resampling may effectively reduce the influence of layer thickness on the repeatability of the study. Of the 68 studies, 9 [16, 21, 23, 51–56] (13%) reduced the effect of slice thickness by resampling.

3.2.3 Segmentation

Accurate and efficient segmentation of regions of interest is helpful to extract robust quantitative imaging features[9]. The segmentation method can be roughly divided into manual, semi-automatic, and automatic segmentation. Manual segmentation is usually regarded as the gold standard, but it has two problems. According to statistics, it took an average of 18 minutes to delineate the region of interest of a tumor. Therefore, it is unlikely to be implemented in the clinic[36]. Second, there were great subjective differences among the observers, which may affect the repeatability of the target area[57, 58]. Existing studies [36–38, 59, 60] proved that semi-automatic segmentation had better stability and higher efficiency than manual segmentation (the average segmentation time was reduced by 4 minutes). Although automatic segmentation based on deep learning may further improve the accuracy of segmentation[39],automatic segmentation is not yet mature and needs further research before it can be used in the clinic. Of the 68 studies, 13 [12, 26, 61–71](19%) used semi-automatic segmentation, 3 [52, 72, 73](4%) used automatic segmentation. Except for 12 [21, 25, 44, 45, 49, 53, 74–79] studies which did not describe the segmentation methods used, the remaining 40[13–20, 22–24, 46–48, 50, 51, 54–56, 80–100]studies adopted the manual segmentation method.

Manual and semi-automatic segmentation may cause deviation between features and real values because of the variability of the segmentation process [101]. Variability includes subjective differences among multiple observers (inter-observer variation) and subjective differences of the same person at different times (intra-observer variation), so it is necessary to use multi-person segmentation or multiple methods to reduce deviation[4]. Of all the articles, 15 did not use multiple segmentation. 19 of the other articles did not analyze the differences between observers or segmentation methods and did not rule out unstable features. Only 34 articles evaluated the variation, but the evaluation indicators were not consistent: 24 articles evaluated by intraclass correlation coefficient(ICC), 3 articles[16, 20, 21]used Dice similarity Coefficient and/or Jaccard similarity coefficient, 1 article [83] used Bland-Altman plots as evaluation parameter, 1 article[45] used Spearman correlation coefficient, 1 article [73] used automatic segmentation which repeatability was verified,and 4 articles [12, 48, 52, 54] did not describe the evaluation index. In a word, most studies (71%) use ICC to evaluate variability, while I Fotina, et al. [102]

preferred to use Jaccard similarity coefficient, conformal number, or generalized conformability index to evaluate inter-observer variability.

3.2.4 Feature selection

Radiomics studies always extract a large number of features, whereas the number of samples is often very small, so it is easy to cause dimension disaster so that the model is over-fitted and lacks generalization ability[8, 103]. To ensure that the model has statistical significance and clinical significance, and reduce the false positive rate,A Chalkidou, et al. [103] proposed the following measures: (1) repeatability of features (2) cross-correlation analysis (3) inclusion of clinically important features (4) at least 10-15 patients with each feature (5) external verification.

The main purpose of feature selection is (1) to select repeatable features between different institutions, (2) to remove redundant features (highly related features between features), and (3) to select features that are strongly related to the result variables. Feature selection can effectively reduce the number of features, but different methods need to be selected according to the needs of the research[104]. In all the studies, the Least Absolute Shrinkage and Selection operator (LASSO) (46%) was the most commonly used feature selection method, followed by correlation analysis (33%). The feature selection method is not unique, it needs to be adjusted according to the number of features and sample size[8]. The most suitable method should be selected by comparing a variety of methods.

The sample size of all studies ranged from 15 to 701, with a median of 111, and 78% of the studies had a sample size of 0-200. To assess the adequacy of the sample size in the study, MA Babyak [105] suggested that at least 10-15 patients were needed for each feature. Based on this standard, 17 (25%) of the included studies did not meet the above conditions except 5 studies[73, 74, 79, 98, 106], which did not establish a model and 4 studies[26, 46, 78, 87] that did not indicate the characteristic quantity(Figure 6).

Figure 6. Sample size of included studies. Adequate sample means the ratio of the sample size to the feature number of the study is more than 10, inadequate sample means the ratio is less than 10, unclear means the study did not establish a model or did not specify the number of features.

3.2.5 Modelling methodology

C Parmar, et al. [40] evaluated the performance and stability of 12 classification methods in predicting overall survival, which showed that random forest classification had the highest prediction performance and stability. However, it is not clear which statistical method or machine learning method is better. The model generated by the simple modeling method is easy to explain, and the complex model improves the performance but needs further verification [107].

3.2.6 Evaluation

The generalization ability of the model can be evaluated by using the verification data. According to the principle of confirmatory analysis, independent data sets are needed to verify the results of the training

set[108]. Only 51 articles (75%) used independent dataset validation, including 5[22–26] articles using dual-center validation sets and 7[12, 16–21] articles using multicenter validation sets.

3.3 How to increase repeatability

3.3.1 Standardization protocol

Standardizing the radiomics process is the most reliable way to increase repeatability[7]. So Image Biomarker Standardization Initiative (IBSI) [109]standardizes the definition, naming, and software. The Quantitative Imaging Network (QIN) [110] project initiated by NIC (National Cancer Institute) has also promoted the standardization of imaging methods and imaging protocols. In addition, the Quantitative Imaging Biomarkers Alliance (QIBA) [111] organization sponsored by, Radiological Society of North America (RSNA) has developed a standardized quantitative imaging document "Profiles" to promote clinical trials and practices of quantitative imaging markers. At present, only 4[26, 53, 54, 61] (6%) of the radiomics studies of colorectal cancer comply with the IBSI standard.

3.3.2 Test-retest reliability

Before a unified standard is formed, test-retest reliability tests can be taken to increase the repeatability of the study. The same scanner and the same patient were scanned twice at an interval of 15 minutes to determine the characteristics with high repeatability[112]. Moreover, JE van Timmeren, et al. [41] indicated that appropriate test-retest reliability should be carried out in each step. Also, the effects of hardware, acquisition, reconstruction, tumor segmentation, and feature extraction should be strictly controlled. However, only 2 articles[44, 45] (3%) conducted test-retest reliability.

3.3.3 Phantom

For retrospective data that did not use the same scanning scheme, phantom could remove unstable features due to differences in scanner, scanning, and reconstruction parameters[4]. However, none of the included studies used phantom to analyze its repeatability.

3.3.4 Post-processing

With the continuous emergence of new features, the efficiency of test-retest reliability research and phantom research becomes lower[35]. The following post-processing methods can also reduce the variability of features.

Resampling and normalization: Some studies[29, 30, 113]showed that resampling could effectively improve the feature variation caused by voxel differences. However, resampling alone might not improve the variations of all features, and features need to be normalized according to voxel size[30]. Among the 68 studies, resampling was used in 9 articles [16, 21, 23, 51–56] (13%). In other studies, normalization was used to reduce the influence of different gray ranges or the effects of low frequency and intensity inhomogeneity. Normalization also has some disadvantages, such as introducing noise, blurring the

image, and causing the loss of image details [114]. However, these shortcomings of normalization would be avoided by using ComBat.

ComBat: Previously, genomics has been affected by batch effects, that is, systematic technical biases introduced by samples in different batches of processing and measurement that are not related to biological status[115]. WE Johnson, et al. [116] developed and validated a method to deal with the "batch effect"-ComBat. In radiomics, the impact of different scanners or scanning schemes is similar to that of batches. Studies[117–119] showed that ComBat could reduce the feature differences caused by different scanners or scanning schemes, and retain the feature differences formed by biological variation. Although ComBat is practical, convenient and fast, it will be affected by the distribution of validated data sets[35], and it cannot be directly applied to imaging data[120]. So Y Li, et al. [35] developed a normalization method based on deep learning, which may effectively avoid the above problems.

4. Discussion

The results of radiomics need to be applied to different environments and people, and the repeatability of the evaluation model is helpful to judge its generalizability and clinical application value. So this review analyzed the details of the methods provided in each study to discuss the repeatability of 68 radiomics studies on colorectal cancer and evaluated the quality of studies by RQS. Although the included studies demonstrated the excellent predictive performance (AUC=0.71~0.95) of radiomics in colorectal cancer, most studies did not take into account the repeatability of radiomics features, especially in terms of Intra-individual repeatability, repeatability between scanners, and repeatability of scanning parameters.

Since 2016, the number of colorectal cancer radiomics has increased year by year, but the median RQS score was 12 (33.33%), indicating that radiomics was an immature new technology in the field of colorectal cancer. Three of the four items with the lowest scores in RQS are related to repeatability, including phantom studies, multiple time point and open science data. The same phantom is scanned with the same scanning scheme in different scanners, and the radiomics features independent of the scanner are obtained [4]. Of all the studies reviewed, only J Kang, et al. [50] used phantom and regular standardization for quality control to keep differences in measurements of the standardized uptake value (SUV) between the two scanners below 10%. P Lambin, et al. [4] explained that the purpose of multiple time point is to eliminate the radiomics features that strongly depend on the organ movement or the expansion or shrinkage of the target volume, and the retest-test can be used to detect unstable features, thus reducing the influence of intra-individual variability [42, 43], but only 2[44, 45] (3%) of all studies used the test-retest. Through the retest test, X Ma, et al. [44] removed the unstable radiomics features whose intra-class correlation coefficient is less than 0.6. J Wang, et al. [45] selected the most repeatable radiomics features based on the test-retest data of 40 patients with rectal cancer. Although the subjects of the retest test may be the patient or the phantom[121, 122], the retest study of the patient may increase unnecessary radiation damage. In addition, JE van Timmeren, et al. [41]believes that extensive retest-test experiments can provide a stable set of imaging features, and emphasizes that retest-test studies should be carried out in each scenario, not only in intra-individual variability, but also in scan acquisition and

reconstruction settings, tumor segmentation and feature extraction. Open science data includes opening scanning information, opening segmentations of ROIs, opening source code and opening feature extraction methods (including formulas)[4], but only five studies disclosed the code and data, there were no studies that opened ROI-related data. The open science data is beneficial for other researchers to reproduce the research results (independent researchers use the same technology and different data to repeat the research results and independently verify the results) and promote the application of the research model in clinical practice[4–6].

The standardization of scanning parameters, acquisition parameters and reconstruction parameters could effectively reduce variability, because there are many variable factors and a wide variety of diseases in radiology[5, 6], there is no global standard at present. In addition to standardization, the influence of scanning parameters can be reduced by using the same scanning scheme, unstable features may be removed by retest tests[121], resampling might be used to control the influence of slicer thickness[30], and the "batch effect" could be reduced by combat method[117–119]. Of the 68 studies, 9 (13%) adopted resampling and 1 (1%) adopted combat methods to control variability. In order to balance the deviation of imaging features from four institutions, Z Liu, et al. [19] normalized the data of each organization, adopted combat methods to control the deviation of radiomic features, and weighted the radiomics features with inverse probability of treatment weighting (IPTW) to eliminate the covariant effect among the four cohorts.

With regard to the method of image segmentation, it is proved that semi-automatic segmentation is more efficient than manual segmentation, has less variation between observers, and is more mature than automatic segmentation[36–38, 59, 60]. Of all the studies, 40 (59%) were segmented manually, and only 13 (19%) were segmented semi-automatically. For inter-observer variability, only 34 (44%) studies took into account inter-observer variability and excluded instability. Even though the Jaccard index, Cn and CIgen may be better as evaluation parameters [102], 24 studies were evaluated by ICC.

According to the Harrell criterion[123], the sample size should be more than 10 times the number of variables, and feature selection can reduce redundant features and reduce the risk of model over-fitting[8, 103]. But 17 studies (25%) have the possibility of over-fitting even though feature selection has been carried out. Such as, in the study of C Yang, et al. [76], random forest was used to measure the Gini importance of parameters, and finally 10 important parameters were included in the model. But the study included only 89 patients, there was still a risk of over-fitting according to the Harrell criteria. [124]recommends that at least 50 patients be included in radiomics studies, but there are 9 of all reviewed articles have a sample size of less than 50. Too small sample size will seriously affect the quality of the article and reduce the credibility of the research results[125].

In addition to the repeatability of the study, it is also important to avoid overly optimistic results. In many studies, the combination of optimal cut-off method and multiple hypothesis testing may increase type I errors[103], while the multiple hypothesis test correction (Holm Bonferroni or Benjamin-Hochberg pair) is

helpful to reduce class I errors[6]. Therefore, only 11 (14%) of the studies were corrected by multiple hypothesis testing.

The main limitation of this review is that there are great differences in the methods used in the included studies, so we did not conduct a meta-analysis. In addition, some related studies may not be retrieved, such as some grey literature. In this paper, only RQS is used to evaluate the quality of the article, whereas RQS is not the only and perfect evaluation method, and other methods (such as QUADAS-2 or TRIPOD) should be used later.

According to the review of 68 literatures, the key problem in radiomics studies is the lack of repeatability, and the standardization of radiomics processes can help to compare or replicate existing studies[7]. But at present, it is difficult to form global standardization[7], so the repeatability of research can be improved through the open science data[4], retest-test research[121] and post-processing. Before radiomics is applied to the clinic, it is not only necessary to conduct a reliable prospective study with large samples, but also to verify the existing models, preferably independently with multicenter data. Based on the existing literature, some studies[22, 26, 52, 53, 83, 98, 100] use DNA microarrays to directly sequence genes, and then use radiomics to predict sequencing results, combining genomics and radiomics. However, it is noteworthy that there are no studies on the combination of liquid biopsy and radiomics. Studies have shown that the combination of liquid biopsy and imaging can play an early warning role in patients prone to recurrence and metastasis [126]. In the future, it may be possible to add biomarkers from other disciplines to the imaging model. T Cheng and X Zhan [127] proposed that a pattern consisting of three or more biomarkers could improve the accuracy and specificity of tumor prediction, diagnosis and prognosis, that is, pattern recognition[127]. Multi-time imaging may be more helpful to observe the changing process of treatment response and obtain more data. Delta radiomics is to quote the time component in the study, that is, to use the image data of multiple time points for radiomics analysis. This method is expected to improve the diagnosis, prognosis prediction and treatment response evaluation [4]. At present, only 7 studies have used multi-time point imaging, and the purpose of these was to predict the response to treatment. Since 95% of the studies are retrospective, more prospective studies with large samples and multiple centers are needed in the future to promote the development of imaging in the field of colorectal cancer. Cost-effectiveness analysis from an economic point of view is necessary for the clinical application of colorectal cancer imaging in the future[4], while there is no related analysis in any study at present.

5. Conclusion

Although existing studies showed that radiomics is helpful to the personalized treatment of patients in the field of colorectal cancer, there are still many challenges that remain to be solved. According to the RQS score, the quality of included studies was moderately low. Moreover, we found that the main reason for the low RQS score was the lack of repeatability, most studies did not eliminate the influence of scanners, imaging parameters, and other factors. Therefore, these studies of lower quality and lack of repeatability mean that the results are not universal. In order to improve the clinical use of colorectal

cancer radiomics, it is necessary to take measures to control repeatability. For example, carried out appropriate test-retest reliability in each step of radiomics or reduced the influence of variable factors by post-processing. In the future, larger sample and multicenter prospective high-quality studies are needed. In addition, and future researches should focus on building a more stable and repeatable model.

Abbreviations

AUC
Area Under the Curve
CRC
Colorectal cancer
CRT
Chemoradiotherapy
CT
Computed Tomography
IBSI
Image Biomarker Standardization Initiative
ICC
Intraclass Correlation Coefficient
LASSO
Least Absolute Shrinkage and Selection operator
MRI
Magnetic Resonance Imaging
PET-CT
fluorodeoxyglucose Positron Emission Tomography-Computed Tomography
PRISMA
Preferred Reporting items for Systematic review and Meta-Analysis
QIBA
Quantitative Imaging Biomarkers Alliance
QIN
Quantitative Imaging Network
RQS
Radiomics Quality Score
RSNA
Radiological Society of North America
SUV
Standardized Uptake Value
UA
Ultrasound

Declarations

- **Ethics approval and consent to participate**

Not applicable.

- **Consent to publish**

Not applicable.

- **Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

- **Competing interests**

The authors declare that they have no competing interests.

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Not applicable.

- **Authors Contributions**

YL and XQW contributed equally to the work. YL and XQW contributed to study design and wrote the study protocol. XF and YL performed the literature search. YL and XQW performed data collection and data interpretation and drafted the manuscript. XF, YL and GLF reviewed and critically revised the manuscript. YD were responsible for study supervision. All authors have read and approved the manuscript.

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Figures

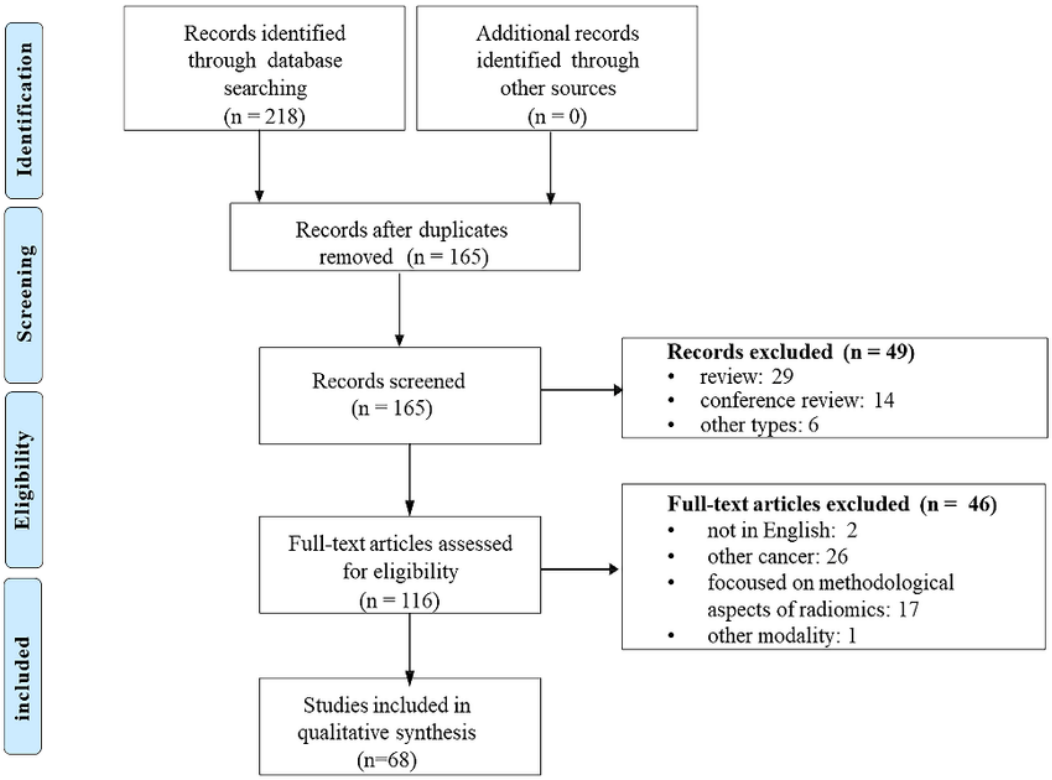

Figure 1

Include and exclude flowchart.

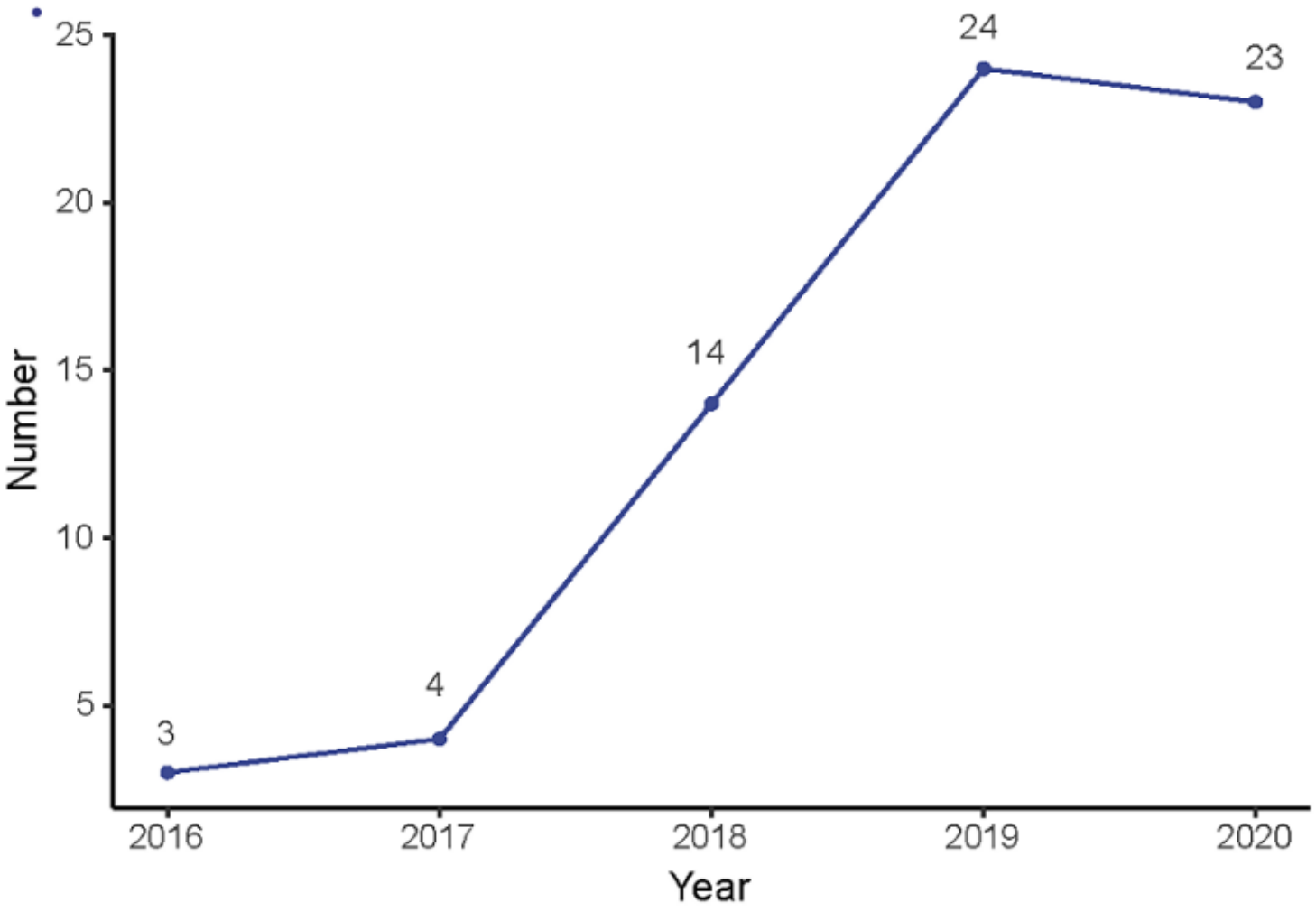

Figure 2

Published frequency of radiomics studies on colorectal cancer from 2016 to March 2021.

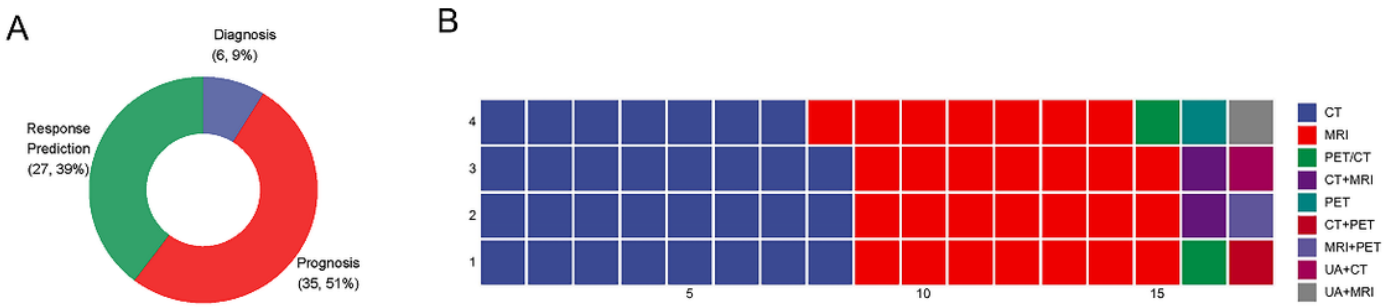

Figure 3

General situation of radiomics research purpose and imaging mode of colorectal cancer. A, Pie chart of the research purpose of studies; B, waffle plot of imaging mode of studies.

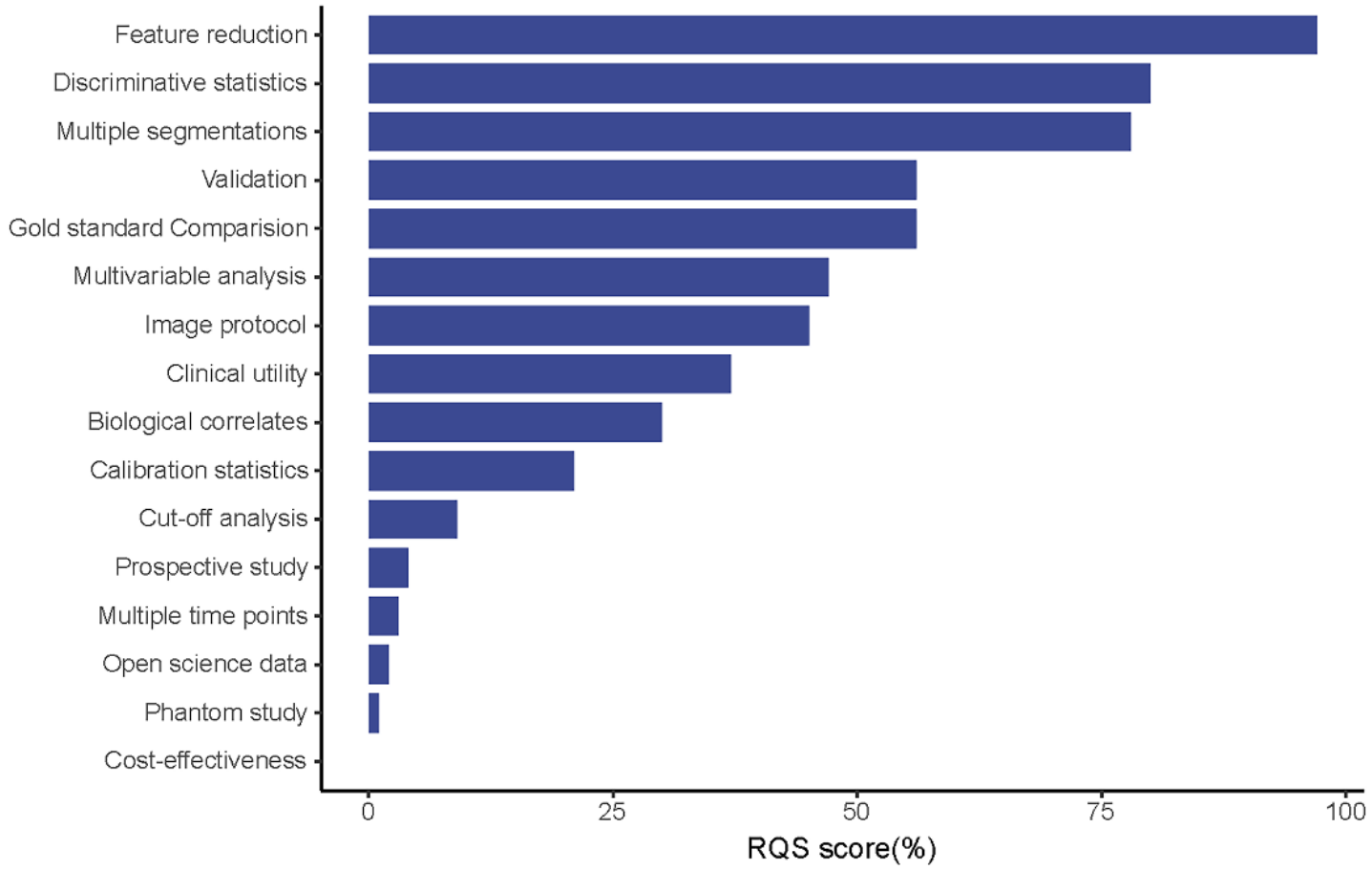

Figure 4

Completion rate of 68 studies in RQS.

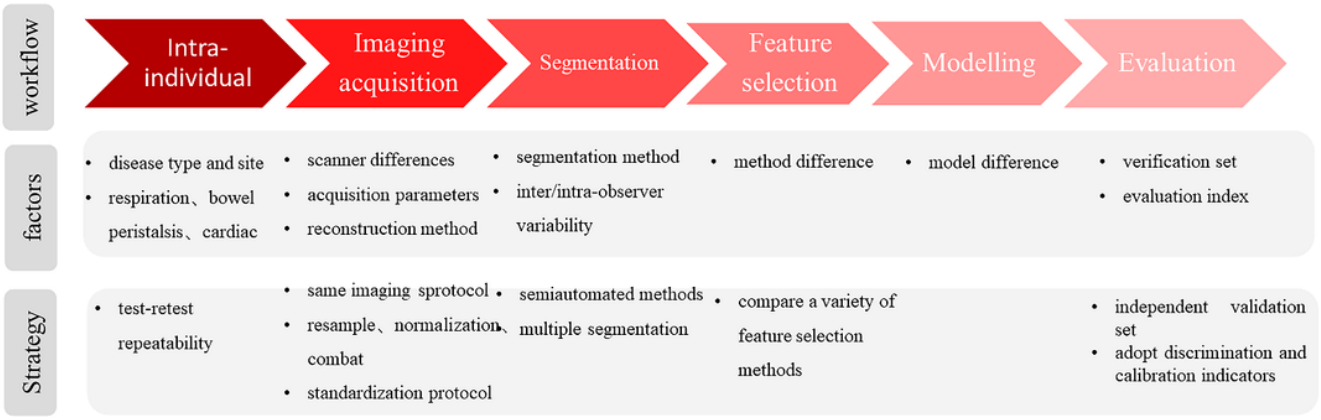

Figure 5

Radiomics workflow and repeatability. Each step has associated factors which may influence the repeatability of the study. Although modelling affect reproducibility, there is still no solution.

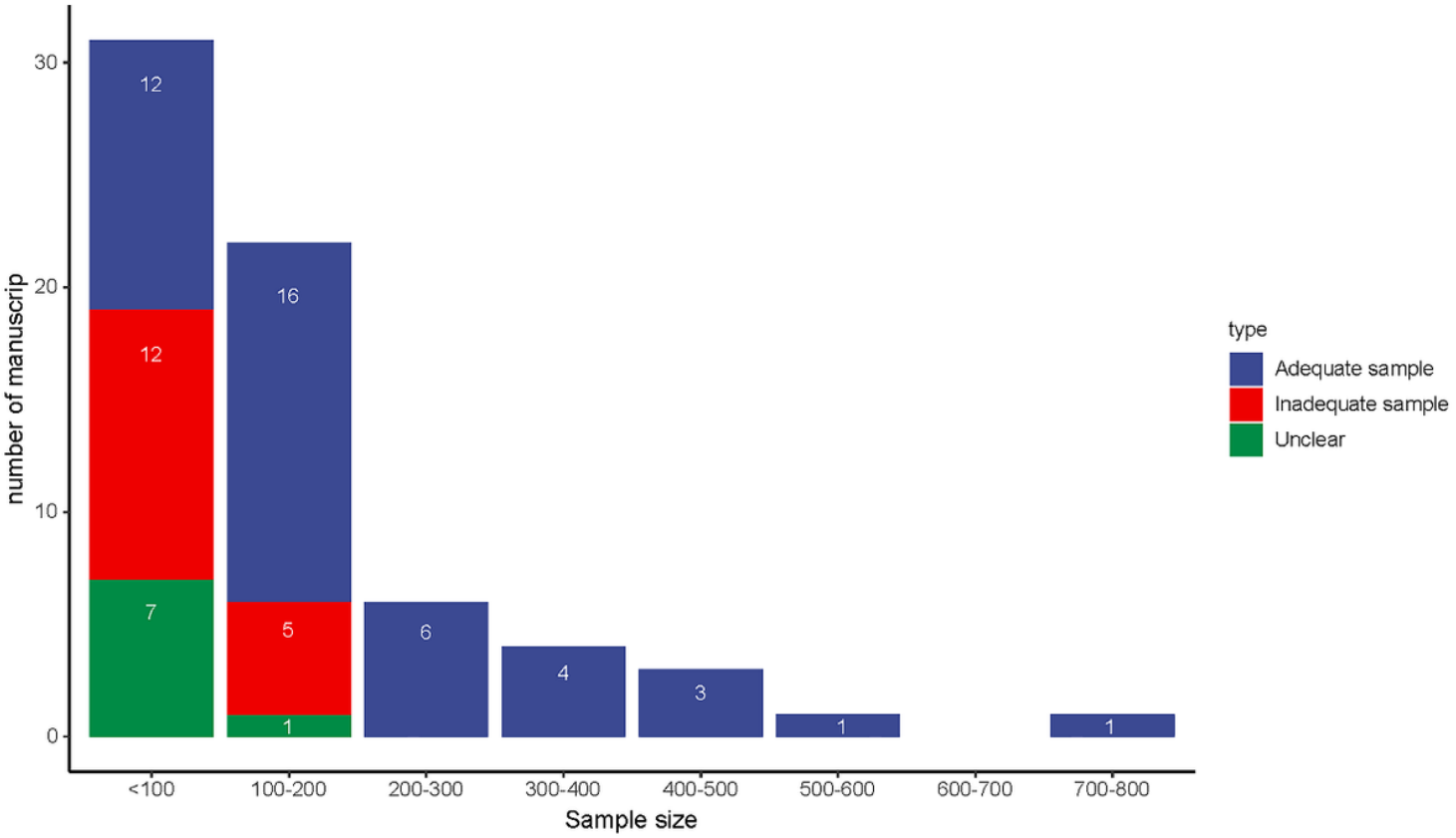

Figure 6

Sample size of included studies. Adequate sample means the ratio of the sample size to the feature number of the study is more than 10, inadequate sample means the ratio is less than 10, unclear means the study did not establish a model or did not specify the number of features.

Supplementary Files

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- ESM1.docx
- ESM2.docx
- PRISMA2020checklist.docx