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SYSTEMATIC REVIEWS

Nomograms for colorectal cancer: A systematic review

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Abstract

AIM: To assist in the selection of suitable nomograms for obtaining desired predictions in daily clinical practice.

METHODS: We conducted electronic searches for journal articles on colorectal cancer (CRC)-associated nomograms using the search terms colon/rectal/colorectal/nomogram. Of 174 articles initially found, we retrieved 28 studies in which a nomogram for CRC was developed.

RESULTS: We discuss the currently available CRC-associated nomograms, including those that predict the oncological prognosis, the short-term outcome of treatments, such as surgery or neoadjuvant chemoradiotherapy, and the future development of CRC. Developing nomograms always presents a dilemma. On the one hand, the desire to cover as wide a patient range as possible tends to produce nomograms that are too complex and yet have C-indexes that are not sufficiently high. Conversely, confining the target patients might impair the clinical applicability of constructed nomograms.

CONCLUSION: The information provided in this review should be of use in selecting a nomogram suitable for obtaining desired predictions in daily clinical practice.

Key words: Colon; Rectum; Nomograms; Prognosis; Cancer

Core tip: In this review, we discuss currently available colorectal cancer (CRC)-associated nomograms, including those that predict the oncological prognosis, the short-term outcome of treatments, such as surgery or neoadjuvant chemoradiotherapy, and the future development of CRC. This review aims to assist in the selection of suitable nomograms for obtaining desired predictions in daily clinical practice.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies in Asia as well as in most Western countries[1]. A number of studies have suggested scoring or stratifying the risk associated with CRC, as represented by the American Joint Committee on Cancer TNM classifications[2-4]. A nomogram is a graphic calculating scale designed to provide the likelihood of the occurrence of a specific event. In clinical practice, a nomogram is typically used to predict the probability of a particular outcome as related to a disease. The clinical use of nomograms extends as far back as 1928 when nomograms were first used by Lawrence Henderson[5]. In recent years, a number of nomograms concerning the treatment of cancers, including prostate cancers[6], gastric cancers[7], and CRCs, have been reported because of their user friendly interface and strong statistical ability to predict individualized outcome.

In this systematic review, we discuss the currently available CRC-related nomograms, including those that predict the prognosis, the short-term outcome of treatments, such as surgery or neoadjuvant chem-oradiotherapy (CRT), and CRC prevalence.

MATERIALS AND METHODS

Evidence acquisition

We used PubMed to perform electronic searches for publications on CRC-associated nomograms. Our search included all English language entries from inception until February 2015 and incorporated the following keywords: nomogram/colon/rectal/colorectal in all fields. Only human studies were eligible for inclusion; case reports, editorials, letters, commentaries, and nomograms that were not published in print were excluded. Studies that only validated previously published nomograms without describing the development of new nomograms were also excluded. The initial search resulted in 174 publications. After title and abstract screening, 41 studies remained, and 28 were finally selected for the present review after full text screening (Figure 1).

RESULTS

Assessment of the predictive quality of nomograms

Before applying published nomograms to clinical practice, understanding the reliability of the predictions as well as the limitations of each nomogram is essential. First, the targeted patient characteristics and predicted outcomes should be noted. The targeted cancer location and the TNM stage varies among nomograms, and inputting data into a nomogram that was not developed pursuant to a particular patient's disease type might result in misreporting the probabilities. In Tables 1, 2, 3 and 4[8-42], we tabulated nomograms according to patient backgrounds for which the nomograms were developed as well as the intended outcomes with the aim of assisting clinical doctors in selecting the appropriate nomogram for their particular needs.

Second, the concordance index (C-index) is important. The C-index represents the ability of a model to reliably predict whether individuals more likely to experience the intended result and is equivalent to the area under the receiver-operator characteristic curve if there are no censored cases. A value of 0.5 indicates no predictive discrimination, whereas a value of 1.0 indicates perfect separation of patients with different outcomes. C-indexes of most nomograms ranged from 0.7 to 0.8, and those below 0.7 were regarded to have a relatively low prediction ability. Third, whether the validation of the nomogram was disclosed or not is also essential. Because the outcome of a treatment varies substantially between institutions, results from a single institution tend to be

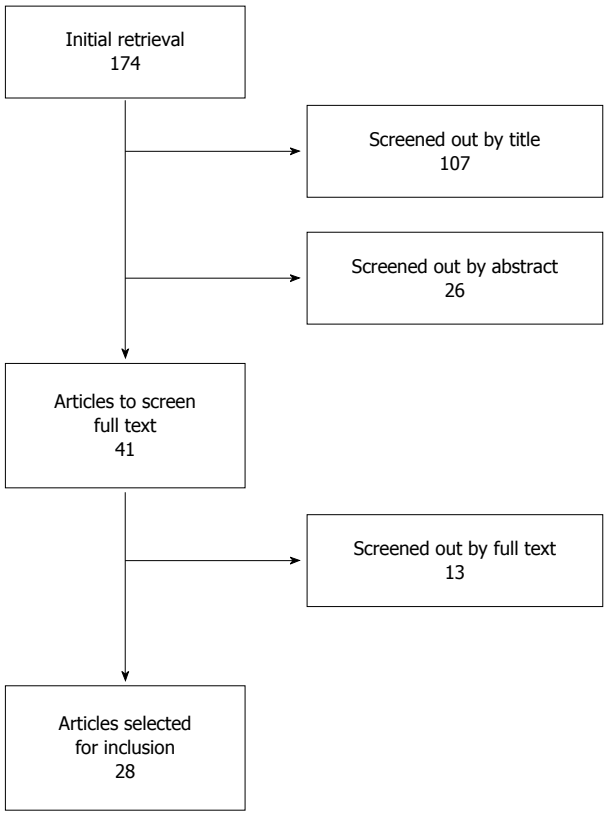

Figure 1 Flow chart of the study selection process.

Table 1 Nomograms predicting stage Ⅰ-Ⅲ colorectal cancer oncological prognosis

Ref.	Year	Cancer location	Targeted patients	Predicted outcome	Number of patients	C-index	Validation	Calibration	Variables	Comments
Weiser *et al*[8]	2008	Colon	Stage Ⅰ-Ⅲ	RFS	1320	0.77	Absent	Present	Age, CEA, No. of positive and negative nodes, pT, adjuvant chemotherapy, cancer location, differentiation, lymphovascular invasion, perineural invasion	
Segelman *et al*[9]	2014	Colorectal	Stage Ⅰ-Ⅲ	Peritoneal carcinomatosis	8044	0.78-0.80	Absent	Present	Age, cancer location, pT, pN, radicality, type of surgery, preoperative radiotherapy, nodes examined, adjuvant chemotherapy	Only web-calculator was available
Ying *et al*[10]	2014	Colorectal	Stage Ⅰ-Ⅲ	RFS, OS, CSS	205	0.80-0.81	Absent	Absent	Chemotherapy, tumor size, cell differentiation, TNM stage, neutrophil-to-lymphocyte ratio	
Zhang *et al*[11]	2013	Colon	Stage Ⅱ	RFS	735	0.65-0.82	Present	Present	Expression of microRNA, pT, internal obstruction or perforation, nodes examined, tumor grade	
Goossens-Beumer *et al*[12]	2015	Colorectal	Stage Ⅱ/Ⅲ	RFS	93	0.80	Present	Present	Expression of microRNA, TNM stage, age, gender	
Peng *et al*[13]	2014	Rectal	Stage Ⅱ/Ⅲ	OS, distant metastasis	883	0.68-0.76	Present	Absent	Gender, age, CEA, cancer location, pT, pN, ratio of metastatic lymph nodes, adjuvant chemotherapy, adjuvant chemoradiotherapy	
Valentini *et al*[14]	2011	Rectal	Clinical stage Ⅱ/Ⅲ patients undergoing adjuvant radiotherapy or chemora-diotherapy	OS, local recurrence, distant metastasis	2795	0.68-0.73	Present	Present	pT, cT, pN, age, concomitant and adjuvant chemotherapy, surgical procedure, gender, dose of radiotherapy	
van Gijn *et al*[15]	2015	Rectal	Stage Ⅰ-Ⅲ	OS, local recurrence, distant metastasis	2881	0.75-0.79	Absent	Absent	Age, pT, pN, PA-stage, distance, residual cancer, surgical type, gender, radiotherapy, complications	

RFS: Recurrence-free survival; OS: Overall survival; CSS: Cancer-specific survival; C-index: Concordance index; CEA: Carcinoembryonic antigen.

biased. If a reported C-index that used patient data from an external institution was comparable to the C-index of the derivation data set, the nomogram was regarded as generally applicable across institutions. Finally, a calibration plot should be provided. The C-index only provides the overall stratifying ability of a nomogram, whereas a calibration plot represents the actual correlation between the nomogram-predicted probability and the observed incidence.

Nomograms predicting stage Ⅰ-Ⅲ CRC oncological prognosis

In terms of nomograms that predict long-term prognosis after CRC surgery, no nomogram that predicts prognosis for all stages has been developed because the prognosis for stages Ⅰ-Ⅲ differs substantially from that of stage Ⅳ and variables associated with prognosis also differ markedly. As shown in Table 1, our search retrieved 8 nomograms predicting the prognosis of

Table 2 Nomograms predicting stage Ⅳ colorectal cancer oncological prognosis

Ref.	Year	Targeted cancer	Treatment	Predicted outcome	Number of patients	C-index	Validation	Calibration	Variables
Beppu *et al*[18]	2012	Liver metastasis	Hepatic resection	DFS	727	Not assessed	Validated by Okuno *et al*[26]	Absent	Metachronous or synchronous, pN, No. of tumors, largest tumor diameter, extrahepatic metastasis, CA19-9
Kanemitsu *et al*[19]	2008	Liver metastasis	Hepatic resection	OS, CSS	578	0.66-0.68	Validated by Takakura *et al*[27]	Present	Histology, No. of lymph node metastases, No. of tumors, extrahepatic metastasis, metastasis of hilar lymph nodes, surgical margin, CEA
Kattan *et al*[20]	2008	Liver metastasis	Hepatic resection	CSS	1477	0.61	Validated by Takakura *et al*[27], Reddy *et al*[28], and Nathan *et al*[29]	Present	Gender, age, primary site, disease-free interval, CEA, No. of tumors, largest tumor diameter, bilateral resection, > 1 lobe, pN
Kanemitsu *et al*[21]	2004	Lung metastasis	Thoracotomy	OS	313	0.66-0.72	Validated by Kanemitsu *et al*[30]	Present	Histology, No. of tumors, hilar/mediastinal lymph nodes, extrathoracic metastasis, CEA
Elias *et al*[22]	2014	Liver and/or Peritoneal metastasis	Optimal surgery plus chemotherapy	OS	287	0.61	Absent	Present	No. of lymph node metastases, peritoneal carcinomatosis index, planified procedure
Kawai *et al*[23]	2015	Metastatic CRC	Curative resection	DFS, OS	1133	0.60-0.64	Present	Present	Postoperative CEA, pT, pN, No. of metastatic organs, peritoneal dissemination
Manceau *et al*[24]	2014	Metastatic CRC, KRAS-wild-type, refractory to chemotherapy	Anti-EGFR antibodies	Risk of progression	132	> 0.7	Present	Absent	MicroRNA expression and BRAF mutations
Massacesi *et al*[25]	2000	Locally advanced or metastatic CRC	Chemotherapy	OS	1057	Not assessed	Absent	Absent	Response to chemotherapy, No. of metastatic sites, CEA, performance status

DFS: Disease-free survival; OS: Overall survival; CSS: Cancer-specific survival; CRC: Colorectal cancer; C-index: Concordance index; CEA: Carcinoembryonic antigen; KRAS: Kirsten rat sarcoma viral oncogene homolog; EGFR: Epidermal growth factor receptor; BRAF: B-Raf proto-oncogene, serine/threonine kinase.

stage Ⅰ-Ⅲ CRC patients[8-15]. Two nomograms were for colon cancer, three were for colorectal cancer, and the remaining three were for rectal cancer. Most of these nomograms were published within the past few years.

In 2008, Weiser *et al*[8] developed a nomogram predicting recurrence after surgery using general clinicopathological variables. Although the C-index of this nomogram was sufficiently high, the overall survival (OS) was not included in the outcome, and external validation was not performed. Recently, two nomograms for CRC, which were available in municipal hospitals, were published. One nomogram, developed by Segelman *et al*[9] was unique because it specialized in predicting peritoneal carcinomatosis recurrence. The other nomogram, developed by Ying *et al*[10], succeeded in achieving a high (greater than 0.8) C-index by adding preoperative neutrophil-to-lymphocyte ratio (NLR) to the conventional clinicopathological variables as an additional predictor. In several precedent studies, high NLR has been reported to correlate with a poorer prognosis in CRC[16,17], and this group established the clinical applicability of NLR by incorporating it into nomograms that calculated the probabilities of recurrence free survival (RFS), OS, and cancer-specific survival (CSS). Because the number of patients included was relatively small and no validation was performed, future studies validating the nomograms developed by Ying *et al*[10] with larger amounts of external patient data would reinforce their results. MicroRNA classifiers were incorporated in the remaining two nomograms. One such nomogram developed by Zhang *et al*[11] demonstrated that six microRNAs (miR-21-5p, miR-20a-5p, miR-103a-3p, miR-106b-5p, miR-143-5p, and miR215) independently predict prognosis, and one nomogram developed by Goossens-Beumer *et*

Table 3 Nomograms predicting short-term outcomes of surgery for colorectal cancer

Ref.	Year	Cancer location	Targeted patients	Predicted outcome	Number of patients	C-index	Validation	Calibration	Variables	Comments
Kiran *et al*[31]	2013	Colorectal	All colorectal surgeries	30-d mortality	30900	0.89	Present	Present	Age, ASA, albumin, functional dependency, renal failure, emergency surgery, disseminated cancer	
Hedrick *et al*[32]	2013	Colorectal	All colorectal surgeries	Superficial SSI, deep incisional SSI, and combination thereof	18403	0.64-0.65	Absent	Present	Diabetes, smoking, disseminated cancer, BMI, open or laparoscopic surgery	
de Campos-Lobato *et al*[33]	2009	Small bowel/ colorectal	All colorectal surgeries	Organ space SSI	12373	0.65	Present	Present	Surgical site, smoking, ASA, wound class, diabetes, steroid use, prior surgery, radiotherapy, open or laparoscopic surgery, age, BMI, creatinine, albumin, gender, transfusion, operative time	
Frasson *et al*[34]	2014	Colon	All colorectal surgeries	Anastomotic leakage	3193	0.62-0.63	Absent	Absent	Oral anticoagulants, intraoperative complications, BMI, total protein, gender, No. of beds	Decision-tree diagram was also presented
Yao *et al*[35]	2014	Rectal	Laparoscopic anterior resection with intracorporeal rectal transection and double-stapling technique anastomosis	Anastomotic leakage	476	0.84	Internal validation	Absent	Cancer location, operative time, preservation of the left colic artery	
Russell *et al*[36]	2013	Rectal/ rectosigmoid	Stage Ⅰ-Ⅲ	Rate of margin positivity	85190	0.75	Absent	Present	Age, gender, ethnicity, cancer location, TNM stage, tumor size, tumor grade, insurance status, histology	

SSI: Surgical site infection; ASA: American Society of Anesthesiologists; BMI: Body mass index; C-index: Concordance index.

al[12] focused on two microRNAs (miR-25-3p and miR-339-5p). Although these studies demonstrated the importance of microRNAs in CRC prognosis, currently, it may be difficult to apply these nomograms at municipal hospitals.

Three nomograms for rectal cancer prognosis have been reported to date. Most notably, the nomograms by Valentini *et al*[14] were developed using data from five major European clinical trials. Because OS, local recurrence, and distant metastasis were all included in the predicted outcome and because both validation and calibration were presented, these nomograms should have high clinical applicability. However, their usage is limited to patients who underwent radiotherapy or chemoradiotherapy (CRT).

Therefore, of the nomograms predicting stage Ⅰ-Ⅲ CRC prognosis, the nomograms developed by Weiser and Valentini for colon and rectal cancer, respectively, appear to be the most promising for clinical practice because, in these nomograms, the number of patients enrolled was large, no variables that are unavailable in municipal hospitals were incorporated, and the developed nomograms were well calibrated.

Nomograms predicting Stage Ⅳ colorectal cancer oncological prognosis

Nomograms predicting the prognosis of metastatic CRC are presented in Table 2[18-25]. Because stage

Table 4 Other nomograms relevant to colorectal cancer

Ref.	Year	Targeted patients	Treatment	Predicted outcome	Number of patients	C-index	Validation	Calibration	Variables	Comments
Jwa *et al*[37]	2014	Non-metastatic rectal cancer	CRT + surgery	ypN status	891	0.77-0.81	Present	Present	ypT, cN, histology, lymphovascular invasion, perineural invasion, age	
van Stiphout *et al*[38]	2011	Rectal cancer	CRT + surgery	Pathologic complete response	953	Not assessed	Present	Present	tumor length, RI, SUV	Pre- and post-CRT PET-CTs were used to predict response
van Stiphout *et al*[39]	2014	Rectal cancer	CRT + surgery	Pathologic complete response	190	0.70-0.78	Present	Absent	Maximal diameter at day 15, RI, cN	Pre- and intra-CRT PET-CTs were used to predict response
Omata *et al*[40]	2011	Asymptomatic individuals		Colorectal neoplasms	1085	Not assessed	Absent	Absent	Quantitative fecal immunochemical test, gender, age, BMI	
Kawai *et al*[41]	2014	Colorectal cancer	Surgery	Postoperative development of metachronous colorectal neoplasms	309	0.71	Present	Present	Gender, age, No. of synchronous adenomas and colorectal cancers	
Wells *et al*[42]	2014	Age > 45		Colorectal cancer development	180630	0.68	Absent	Present	Age, ethnicity, smoking, alcoholic drinks, BMI, education, aspirin, estrogen, family history of CRC, NSAIDs, multivitamins, red meat intake, diabetes, physical activity	

CRT: Chemoradiotherapy; PET-CT: Positron emission tomography-computed tomography; RI: Response index; SUV: Standardized uptake value; CRC: Colorectal cancer; BMI: Body mass index; C-index: Concordance index; NSAID: Non-steroidal anti-inflammatory drug.

Ⅳ CRC includes a wide variety of clinical settings, the C-indexes were relatively low with most being below 0.70. In contrast, most C-indexes of the nomograms for stage Ⅰ-Ⅲ CRC were above 0.75, as shown in Table 1. In terms of patients who underwent complete resection of metastases, three nomograms predicting the prognosis after resection of liver metastasis with curative intent have been established[18-20]; the widespread applicability of these nomograms was demonstrated by external validation studies[26-29]. These nomograms include both synchronous and metachronous liver metastasis, and two of these nomograms incorporated the interval between primary CRC surgery and hepatic resection as a variable because the prognosis of metachronous liver metastasis was better than that of synchronous lesions. Kanemitsu *et al*[21] and Kattan *et al*[20] demonstrated carcinoembryonic antigen (CEA) to be a strong prognosis-predictive marker, whereas Beppu focused on CA19-9. Kanemitsu *et al*[21] also constructed a nomogram predicting OS after thoracotomy for lung metastasis from CRC[21], which they subsequently validated in a separate study[30]. Elias *et al*[22] reported a nomogram specifically for those with liver and/or peritoneal metastasis and for those that underwent surgery including hyperthermic intraperitoneal chemotherapy (HIPEC) with no macroscopically residual cancer[22]. The nomogram was unique in that it was based on the outcome of 156 HIPEC patients. Recently, we built nomograms predicting DFS and OS after curative resection of stage Ⅳ CRC, namely, the complete resection of both primary CRC and synchronous distant metastasis[23]. We focused on the CEA concentration shortly after surgery because high postoperative CEA may be indicative of residual cancer cells and, consequently, of recurrence. The nomograms should have an advantage over previous nomograms because they may apply to all stage Ⅳ cases regardless of the metastatic organ, although their C-indexes were no

greater than 0.7, which is similar to other stage Ⅳ nomograms.

The remaining two nomograms predicted the outcome of chemotherapy for those who were unable to undergo complete surgical resection. One nomogram demonstrated the significance of hsa-miR-31-3p expression as a risk factor for cancer progression in patients who were refractory to chemotherapy and were treated with anti-EGFR therapy[24], and the other nomogram demonstrated the 2-year survival of locally advanced or metastatic CRC patients[25]. Because the latter was developed using patient data gathered between 1990 and 1998, the predicted survival may currently be improved due to the subsequent development of diverse chemotherapeutic agents.

Nomograms predicting short-term outcomes of surgery for colorectal cancer

There have been six published nomograms predicting short-term operative outcomes, namely, mortality[31], surgical site infection (SSI)[32,33], anastomotic leakage[34,35], and the rate of margin positivity[36] (Table 3). Because of the low incidences of these outcomes, most of the nomograms were constructed using large national databases such as the American College of Surgeons' National Surgical Quality Improvement Program; consequently, the numbers of enrolled patients were greater than 10000 in five of these nomograms, which was an order of magnitude greater than the number of patients in the majority of the studies predicting long-term oncological prognosis.

The 30-d mortality risk, which was the most serious postoperative complication, was predicted by Kiran *et al*[31]'s nomogram. This nomogram achieved a C-index of 0.89 by focusing particularly on age. There have also been three nomograms for calculating the incidence of SSI or anastomotic leakage in general colorectal surgery[32-34]. Because the occurrence of these complications was largely affected by the surgical procedures, it may be difficult to accurately anticipate the complications in advance using statistical models. Therefore, the C-indexes of these nomograms were only 0.65 at most. Recently, Yao *et al*[35] reported another nomogram predicting anastomotic leakage. Although its C-index was high (0.84), this exclusive nomogram only covered patients who underwent laparoscopic anterior resection with intracorporeal rectal transection and anastomosis using the double-stapling technique. In addition to postoperative complications, the rate of margin positivity in rectal cancer surgery was also predicted. Because the circumferential resection margin is a major determinant of local recurrence, predicting the rate preoperatively should be of considerable clinical benefit. However, a nomogram developed by Russell *et al*[36] incorporated factors that could not be confirmed preoperatively, such as tumor stage and size, and its actual clinical applicability was therefore limited.

Other nomograms relevant to CRC

Among the remaining six nomograms related to CRC, three concerned the prediction of the response to preoperative CRT in rectal cancer[37-39]. This was quite important in deciding the post-CRT treatment because accurate prediction of lymph node metastasis after CRT might enable the reduction of the surgical resection to local excision of the tumor instead of performing total mesorectal excision. Similarly, perfect prediction of the pathological complete response (pCR) might make it possible to omit even the surgery itself. One nomogram reported by Jwa *et al*[37] predicted the lymph node metastasis status of rectal cancer after CRT. Because this nomogram used the ypT stage, lymphovascular invasion, and perineural invasion as variables, it could not determine a suitable surgical procedure in advance. Alternatively, to clinically utilize the nomogram, local excision and pathological examination must first be performed, and if the risk of nodal metastasis calculated by the final pathological findings is acceptably low, omission of further surgical treatment accompanied by lymph node dissection could be one of the therapeutic options. van Stiphout *et al*[38] reported two nomograms predicting pCR by using positron emission tomography (PET)-computer tomography (CT) as the predictor[38,39]. In their first study, PET-CT was performed before and after CRT, and they incorporated the response ratio calculated by the standardized uptake values of these two PET-CTs into their nomogram[38]. Alternatively, they performed PET-CT before and two weeks after the start of CRT in their latter nomogram and demonstrated that the response ratio between the two PET-CT scans (*i.e.*, early response to CRT) is also a promising predictive factor available in the nomogram[39]. In the future, the accumulation of these data may enable the identification of patients who can either avoid unnecessary overtreatment or who should receive additional chemotherapy or radiotherapy.

Finally, we describe three nomograms that attempt to detect or predict newly developed CRCs[40-42]. Omata *et al*[40] demonstrated the diagnostic performance of the quantitative fecal immunochemical test (QTFIT) for colorectal neoplasms in asymptomatic individuals, and the addition of sex, age, and body mass index to the nomograms could amplify the accuracy of QTFIT as a screening test. Recently, we developed a nomogram that could predict the development of metachronous colorectal neoplasms after surgical resection of primary CRC[41] because patients who previously had CRC are at a high risk for developing second primary adenoma or CRC. Wells *et al*[42] also provided a nomogram calculating the 10-year risk of CRC development. The latter two nomograms were of clinical utility in identifying those patients who should receive intensive colonoscopy screening.

DISCUSSION

In the field of prostate cancer, a number of nomograms predicting a wide variety of outcomes, such as cancer prognosis[43], diagnosis[44], and screening[45], have been developed and well validated. In contrast, nomograms for CRC fall behind nomograms for prostate cancer, with the targeted patients and performed validation studies being limited. Therefore, further developments and validations of novel nomograms for CRC are needed. Developing nomograms always presents a dilemma. On the one hand, the desire to cover as wide a patient range as possible tends to produce nomograms that are too complex and yet have C-indexes that are not sufficiently high. Conversely, confining the target patients might impair the clinical applicability of constructed nomograms. The information provided in this review should be of use in selecting a nomogram suitable for obtaining desired predictions in daily clinical practice.

COMMENTS

Background

A nomogram is a graphic calculating scale designed to provide the likelihood of the occurrence of a specific event. In clinical practice, a nomogram is typically used to predict the probability of a particular outcome as related to a disease.

Research frontiers

In recent years, a number of nomograms concerning the treatment of cancers, including prostate cancers, gastric cancers, and colorectal cancers (CRCs), have been reported because of their user friendly interface and strong statistical ability to predict individualized outcome.

Applications

In this systematic review, the authors discuss the currently available CRC-related nomograms, including those that predict the prognosis, the short-term outcome of treatments, such as surgery or neoadjuvant chemoradiotherapy, and CRC prevalence. The information provided in this review should be of use in selecting a nomogram suitable for obtaining desired predictions in daily clinical practice.

Peer-review

It is an interesting paper with a good review of a frequently disperse information, well-written review and may have a potential significance for clinical practice of CRC.

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