Real-World Practice of Gastric Cancer Prevention and Screening Calls for Practical Prediction Models

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INTRODUCTION: **Some gastric cancer prediction models have been published. Still, the value of these models for application in real-world practice remains unclear. We aim to summarize and appraise modeling studies for gastric cancer risk prediction and identify potential barriers to real-world use.**

METHODS: **This systematic review included studies that developed or validated gastric cancer prediction models in the general population.**

RESULTS: **A total of 4,223 studies were screened. We included 18 development studies for diagnostic models, 10 for prognostic models, and 1 external validation study. Diagnostic models commonly included biomarkers, such as *Helicobacter pylori* infection indicator, pepsinogen, hormone, and microRNA. Age, sex, smoking, body mass index, and family history of gastric cancer were frequently used in prognostic models. Most of the models were not validated. Only 25% of models evaluated the calibration. All studies had a high risk of bias, but over half had acceptable applicability. Besides, most studies failed to clearly report the application scenarios of prediction models.**

DISCUSSION: **Most gastric cancer prediction models showed common shortcomings in methods, validation, and reports. Model developers should further minimize the risk of bias, improve models' applicability, and report targeting application scenarios to promote real-world use.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A891

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INTRODUCTION

Gastric cancer ranks fifth in the global cancer spectrum with an incidence rate of 14.0 per 100,000 and fourth in mortality with a rate of 9.9 per 100,000 (1). The prognosis of gastric cancer was poor, but it might be improved significantly when detected early (2,3). Although mass screening for gastric cancer has been conducted in countries with a high incidence, such as Japan and South Korea (4–8), in the circumstance that more health resources have been input to control coronavirus disease 2019, limited gastroscopies can be allocated more efficiently by exact risk prediction. Risk prediction models may also inform individual risks and finally contribute to the improvements in the attendance and compliance of cancer screening for high-risk groups (9). Meanwhile, the population assessed with nonhigh risk can avoid nosocomial infection, mental burden, and other physical injuries. Besides, risk stratification could facilitate primary prevention of gastric cancer, including *Helicobacter pylori* eradication and adoption of early interventions, which was also a valid way to reduce gastric cancer burden (10,11).

Till now, some risk prediction models for gastric cancer have been developed to support the risk-stratified strategy, differing in study design, statistical methods, and performance (12–15). It is unclear which of these models is high-quality, well-performed, and easy to use. Systematic reviews of prediction models for colorectal cancer (16,17), breast cancer (18), and lung cancer were available (19). Still, there were no corresponding reviews for gastric cancer, as far as we know. In this study, we aimed to systematically summarize the published risk prediction models for gastric cancer for the general population, map their characteristics, and assess the risk of bias (ROB) and applicability of the included models, so as to provide information for candidate selection of further practice of gastric cancer prevention and screening.

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MATERIAL AND METHODS

This systematic review was prospectively registered at the International Prospective Register of Systematic Reviews (registration number: CRD42021203804) and was conducted following the Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (20). Supplementary Table S1 presents the key items to guide the framing of this review (see Supplementary Table S1, Supplementary Digital Content 1, http://links.lww.com/CTG/A891).

Search strategy

A systematic search for relevant publications was conducted in 2 electronic bibliographic databases (PubMed and EMBASE) from inception to August 1, 2021, without language restriction. Search strategies consisted of both free text words and MeSH/Emtree, and the details are provided in the Supplementary Material (see Supplementary Digital Content 1, http://links.lww.com/CTG/A891). Besides, the references and citing articles of all the articles eligible for inclusion were screened to ensure the comprehensiveness of the search.

Eligibility criteria

We included studies that met the following criteria: (i) published as an original article in a peer-reviewed journal; (ii) developing or validating a tool, score, or algorithm that could calculate individual relative or absolute risk, so as to perform risk stratification; (iii) including only incident gastric cancer as the outcome; (iv) presenting the area under the receiver-operating characteristic (AUC) curves; (v) applicable to asymptomatic individuals or population at average risk of gastric cancer; and (vi) published in English. For articles that reported more than 1 prediction model for gastric cancer, we selected only the model regarded as the primary outcome of the study (e.g., the enhanced model, but not the conventional model) or the one with best performance (e.g., the highest *c*-statistic).

Studies were excluded if they were (i) not population-based, such as those developed based on natural history, meta-analysis, or literature review; (ii) collecting data from patients with a definite diagnosis of gastric diseases; and (iii) models with less than 2 indicators. Because we intended to review models to be used to select high-risk individuals for endoscopy, we removed diagnosis models that included predictors derived from endoscopy, fluoroscopy, or gastric tissues. Still, prognostic models with endoscopy-derived variables were included.

Data extraction and quality assessments

According to the Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies, 2 reviewers independently finished the article screening and conducted data extraction. Any disagreement was resolved by consensus discussion. For each eligible article, we collected information on study design; participants; and the development, validation, and evaluation of prediction models. To assess the quality of the included studies, we used the Prediction model Risk of Bias Assessment Tool (PROBAST) to evaluate the ROB and applicability of each prediction model through signaling questions in 4 domains of participants, predictors, outcome, and statistical analysis (applicability assessment focuses on the former 3 domains) (21).

RESULTS

In this review, 4,223 articles were identified and full texts of 127 articles were screened. Of these, 104 articles were removed because of irrelevant topic, lack of required data, unmatched participants, and language. A total of 28 articles met all the inclusion criteria, reporting 18 diagnostic models (12,13,22–37) and 10 prognostic models for risk prediction of gastric cancer (14,15,38–45). Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection.

Basic characteristics

In general, the prognostic models were basically developed from prospective researches while the diagnostic models were based on case-control studies or medical records. Of all the 18 diagnostic models, 13 models (72.2%) were developed on the Asian population (Table 1). Half were developed only, and 1 model conducted both internal and external validation. There was diversity in the sample size, ranging from 58 to 9,838. Five models (27.8%) focused on gastric adenocarcinomas, with 1 on noncardia adenocarcinoma. Besides, the difference of gender distribution was not negligible in several studies, especially between the case and control groups, while sex was not considered in the development of prediction models (13,15,22).

Regarding the prognostic models, a great majority (60.0%) was developed in Japan. There were 5 studies only reporting the model development, 1 study conducting external validation of an existing model, and 4 studies reporting both processes. Over half (60.0%) contained missing values, possibly because of the need for long-term follow-up, and 1 study adopted the imputation method. The prognostic models did not limit the subtype of gastric cancer. Although the uneven ratio of men to women also occurred in prognostic models, half studies included sex as a predictor, and Eom et al. developed prediction models of gastric cancer for each sex (41).

From the perspective of real-world practice, the diagnostic models selected in this review were mainly aimed to provide a reliable tool for the pre-examination of large-scale endoscopic screening (12,22,23), surveillance after intervention (27,36), early diagnosis of gastric cancer, or preliminary diagnosis of symptomatic patients based on nongastroscopic predictors (35,37). The prognostic models were applied to screen the appropriate high-risk targets for further endoscopic examination (14,38,40) or to promote cancer prevention (including health education, behavior change, encouraging screening) as a risk reminder (15,41). However, most studies just stated a general purpose, failing to clearly describe models' targeting application scenarios.

Development and performance

Traditional methods, including logistic and Cox proportional hazards regression models, were commonly used to develop prediction models for gastric cancer (Table 2). Machine learning was also adopted in the included studies for modeling. The discrimination of diagnostic models was acceptable, with a range of 0.73–0.99. Different methods were applied to conduct internal validation, such as Bootstrap, random splitting, and leave-one-out cross-validation. Except for 1 study (37), the differences in AUCs between the development and validation processes were not significant, which suggests that the selected diagnostic models might not overfit the training data set (Figure 2). In addition, the performance in external validation did not decrease significantly,

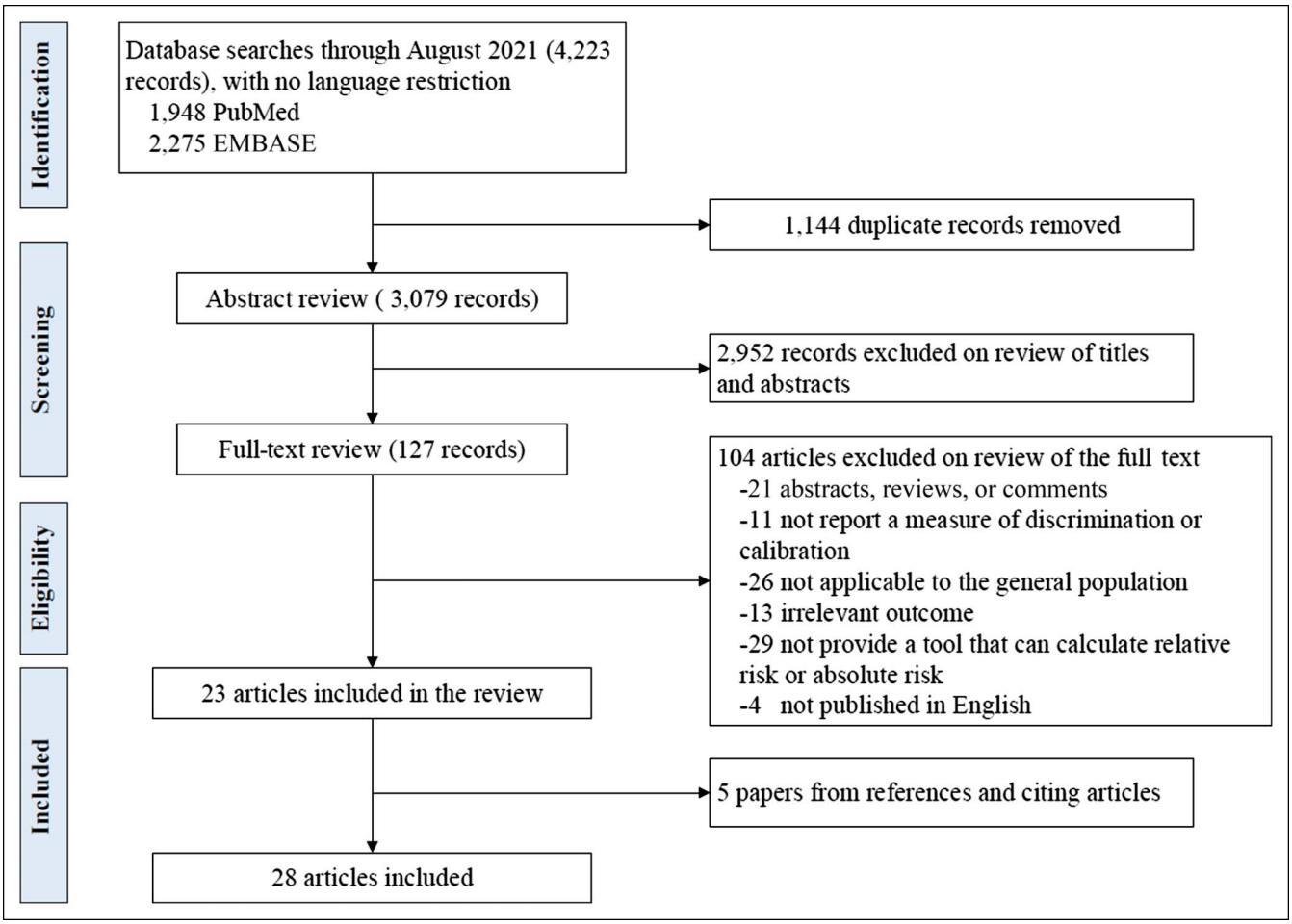

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection.

so models in this review might not face the modeling error of underfitting. However, only 3 in 18 models reported the performance of calibration. The events per variable (EPVs) values of 10 diagnostic models were over 20, but 4 were with a value less than 10, whose reliability should be taken cautiously.

In general, the performance of prognostic models was inferior to that of diagnostic models, with the AUCs ranging from 0.66 to 0.86. The model based on machine learning showed better discrimination. The results of external validation for the model were close to the AUCs of the original models, and the EPVs were high, suggesting that the model was more reliable. However, for half of the prognostic models, the EPVs did not reach 20 and were not internally or externally validated, which needed to be further verified and optimized. In addition, there was a diversity of the follow-up time among the included models, with a range of 3–20 years.

Considered variables of the prediction models

Laboratory indicators were most commonly considered in diagnostic models, mainly routine examinations on *H. pylori* infection and pepsinogen as well as molecular-level detection on protein, gene, microRNA, and hormone (Table 3). Specifically, a variety of proteins were applied to predict the risk of gastric cancer, including typical carcinoembryonic antigens (CEA, CA125 and CA19-9), antibodies, and proteins involved in life activities (responsible for metabolism, blood coagulation, chemotaxis, and other cytokines). Personal characteristics were also adopted frequently in diagnosing suspected individuals, mainly sociodemographic variables (age and sex), lifestyle-related factors (dietary habits, alcohol intake and smoking), and health conditions.

By contrast, each prognostic model tended to be developed based on multiple predictors. The most frequent variable considered was age, followed by smoking, age, BMI, and family history of gastric cancer. Salt intake was included in 3 models, and alcohol assumption and physical activity were also adopted because of the possible associations with gastric cancer. Moreover, the laboratory indicators were more convenient to test, such as the levels of glycosylated hemoglobin and total cholesterol. In 2 models, the results of *H. pylori* infection and pepsinogen were integrated into 1 predictor.

ROB and applicability

According to the evaluation by PROBAST, all the included models were assessed to have high ROB and were attributed to the statistical method (Figure 3). Specifically, most diagnostic models did not enroll sufficient samples, selected candidate variables by univariate analysis, or lacked reports of calibration. For example, age and sex were predictors of gastric cancer that could achieve nontrivial risk discrimination when applied alone, whereas some studies (12,28,31–34,43), which took a data-driven method for candidate variable selection, is likely to drop such essential

Table 1. General characteristics of included studies

Study	Type of study[a]	Country/region	Study period of baseline[b]	Data source	Sample size (events)	Missing values (method)	Sex (male, %)	Age (mean ± SD), years	Primary outcome
Diagnostic models									
Lee et al. (23)	2a	South Korea	2005	Questionnaire	382 (183)	None	P: 65.0; C: 47.7	NI	Gastric cancer
Kaise et al. (29)	1a	Japan	P: 2007–2009 C: 2008–2009	Laboratory test	748 (187)	None	NI	P: 64.3 ± 9.7 C: 52.3 ± 12.4	Gastric cancer
Ahn et al. (13)	2a	South Korea	P: 2002–2003/ 2006–2007 C: 2004	Laboratory test	D: 240 (120) IV: 146 (95)	None	P: 59; C: 28	P: 59.4 ± 11.1 C: 52.1 ± 6.6	Gastric adenocarcinomas
Cho et al. (27)	1a	South Korea	P: 2006–2008 C: 2007–2010	Medical record	948 (474)	None	P: 65.0; C: 65.0	P: 52.6 ± 9.1 C: 52.9 ± 9.6	Gastric adenocarcinomas
Yang et al. (36)	1a	China	2011–2013	Laboratory test	426 (106)	None	P: 72.64; C: 62.5	P: 59.7 ± 13.4	Gastric cancer
Zhu et al. (37)	2a	China	2007–2011	Laboratory test	D: 80 (40) IV: 150 (48)	None	D: P: 72.5; C: 72.5 IV: P: 72.9; C: 70.6	D: P: 53.83 ± 10.34; C: 53.55 ± 10.11 IV: P: 56.63 ± 10.37; C: 54.03 ± 10.45	Gastric noncardia adenocarcinoma
Kucera et al. (24)	1a	Czech	2013–2015	Laboratory test	105 (36)	None	NI	P: 65.2; C: 63.6	Gastric cancer
Tong et al. (35)	2a	China	2008–2010	Laboratory test	D: 418 (228) IV: 95 (48)	None	P: 71.93; C: 63.16	P: 59.82 ± 11.32 C: 59.15 ± 9.27	Primary gastric adenocarcinoma
In et al. (22)	1a	United States	NI	Questionnaire	140 (90)	NI	P: 50.0; C: 24.0	NI	Gastric cancer
Wang et al. (25)	3a	China	2013–2015	Laboratory test	D: 558 (279) EV: 327 (186)	None	D: 74.9; EV: 73.7	D: 58.7 ± 12.0 EV: 58.8 ± 11.6	Gastric cancer
Cai et al. (12)	3a	China	2015–2017	Questionnaire + laboratory test	D: 9,838 (267) EV: 5,091 (138)	Yes (delete)	D: 49.63; EV: 49.77	D: 56.2 ± 9.6 EV: 56.3 ± 9.7	Gastric cancer
Dong et al. (28)	1a	China	2016–2017	Laboratory test	150 (119)	None	P: 74.79	P: range (23–82)	Gastric cancer
In et al. (26)	1a	United States	NI	Questionnaire	14 0 (40)	Yes (subgroup)	P: 50.0; C: 24.0	NI	Gastric cancer
Kong et al. (31)	1a	China	2016–2017	Questionnaire + laboratory test	1,017 (474)	None	P: 43.88; C: 47.88	P: 58.00 ± 6.98 C: 57.41 ± 5.50	Gastric cancer
Liu et al. (33)	1a	United States	2017	Public domain	407 (375)	None	P: 37.33	P: 64.92 ± 10.65	Stomach adenocarcinoma
Kim et al. (30)	2a	South Korea	NI	Laboratory test	D: 484 (69) IV: 207 (30)	None	NI	P: 61 ± 11.0 (27–88) C: 57 ± 8.8 (38–79)	Stomach cancer
Lee et al. (32)	4a	South Korea	2012–2015	Laboratory test	D: 85 (54) EV: 58 (35)	None	D: 61.18; EV: 81.03	D: P: 55; C: 48 EV: P: 59; C: 54	Gastric cancer

Table 1. (*continued*)

Study	Type of study[a]	Country/region	Study period of baseline[b]	Data source	Sample size (events)	Missing values (method)	Sex (male, %)	Age (mean ± SD), years	Primary outcome
Song et al. (34)	2a	Poland	1994–1996	Laboratory test	200 (100)	None	61	65	Stomach cancer (ICD-O 151 or ICD-O-2 C16)
Prognostic models									
Shikata et al. (40)	1a	Japan	1988	Questionnaire + medical record	2,446 (69)	Yes (delete)	41.5	57.3 ± 11.4	Gastric cancer
Eom et al. (41)	3a	South Korea	1996–1997	Questionnaire + medical record		Yes (imputation)	Model for males and females, respectively	D: P: 45.08 ± 10.47; C: 48.7 ± 11.0 EV: P: 46.83 ± 12.80; C: 51.08 ± 12.05	Gastric cancer (C16)
Charvat et al. (15)	2a	Japan	1993–1994	Questionnaire + laboratory test	19,028 (412)	Yes (delete)	P: 61.9; C: 35.7	P: 63.3 C: 59.3	Gastric cancer (C160-C169)
Ikeda et al. (38)	1a	Japan	1988	Questionnaire + medical record + laboratory test	2,446 (123)	Yes (delete)	41.5	58.3 ± 11.4	Gastric cancer
Iida et al. (14)	3a	Japan	1988–2002	Questionnaire + laboratory test	D: 2,444 (90) EV: 3,204 (35)	Yes (delete)	D: 41.6; EV: 42.1	D: 58 ± 11 EV: 62 ± 13	Gastric cancer
Taninaga et al. (44)	2a	Japan	2006–2017	Medical record	D: 1,144 (74) IV: 287 (15)	None	P: 84.2; C: 77.6	P: 56.7 ± 8.8 C: 46.2 ± 1.0	Gastric cancer
Charvat et al. (42)	5a	Japan	1990–1993	Questionnaire + laboratory test	1,292 (27)	None	34.1	56.52 ± 5.78	Gastric cancer (C160-C169)
Jang et al. (39)	1a	South Korea	1993–2004	Questionnaire + laboratory test	476 (238)	Yes (delete)	41.01	53.50 ± 10.23	Gastric cancer
Sarkar et al. (43)	1a	United States	2015–2016	Questionnaire	140 (40)	None	31.4	NI	Gastric cancer
Trivanovic et al. (45)	1a	Croatia	NI	Laboratory test	116 (25)	None	60.3	68.34 ± 13.93	Gastric cancer

C, control group; D, deviation; EV, external validation; IV, interval validation; NI, no information; P, patient group; V, validation.
[a]Type of study: 1a, development only; 2a, development + internal validation; 3a, development + external validation; 4a, development + internal validation + external validation; 5a, external validation only.

Table 2. Key information on the development and validation of included models

Study	Model development			Model evaluation		Model validation	
	EPV	Type of predictor	Modeling method	Discrimination	Calibration	Internal validation	External validation
Diagnostic models							
Lee et al. (23)	16.64	Demographic characteristics + medical history + lifestyle-related factors	Logistic regression	0.888	H-L test: $P = 0.1747$	Bootstrap resampling technique: 0.904 (0.876–0.932)	None
Kaise et al. (29)	93.5	Blood measurements	Logistic regression	0.883 (0.856–0.909)	NR	None	None
Ahn et al. (13)	10.91	Blood measurements	Support vector machine	0.955	NR	None	None
Cho et al. (27)	79	Demographic characteristics + disease stages	Logistic regression	0.783	NR	None	None
Yang et al. (36)	26.5	Blood measurements	Logistic regression	0.959 (0–1)	NR	None	None
Zhu et al. (37)	8	Blood measurements	Logistic regression	0.989	NR	Random split sampling: 0.812	None
Kucera et al. (24)	7.2	Blood measurements	Logistic regression	0.9553	NR	None	None
Tong et al. (35)	45.6	Blood measurements	Random forest	0.8788 (0.8127–0.9449)	NR	Random split sampling (NR)	None
In et al. (22)	11.25	Demographic characteristics + lifestyle-related factors + family history + immigration/ acculturation	Logistic regression	0.941 (0.901–0.982)	H-L test: $P = 0.8562$	None	None
Wang et al. (25)	46.5	Blood measurements	Logistic regression	0.841 (0.808–0.871)	NR	None	Wang et al.: 0.856 (0.812–0.893)
Cai et al. (12)	38.14	Demographic characteristics + lifestyle-related factors + blood measurements	Logistic regression	0.76 (0.73–0.79)	H-L test: $P = 0.605$; calibration in the large: $P < 0.001$	Bootstrap resampling technique: 0.76 (0.71–0.80)	Cai et al.: 0.73 (0.68–0.77)
Dong et al. (28)	59.5	Blood measurements	Logistic regression	0.821 (0.750–0.878)	NR	None	None
In et al. (26)	5	Demographic characteristics + lifestyle-related factors + family history + immigration/ acculturation	Logistic regression	0.95 (0.92–0.98)	NR	None	None
Kong et al. (31)	118.5	Lifestyle-related factors + results from genomics	Logistic regression	0.745	NR	None	None
Liu et al. (33)	37.5	Results from genomics	Lasso logistic regression	0.986	NR	None	None
Kim et al. (30)	5.75	Results from proteomics	Generalized linear models + random forest	0.9098	NR	Random split sampling: 0.9706	None
Lee et al. (32)	10.8	Results from transcriptomics	Logistic regression	0.924 (0.845–0.970)	NR	Bootstrap resampling technique: 0.896 (0.894–0.898)	Lee et al.: 0.988 (0.916–1.000) Bootstrap: 0.947 (0.946–0.949)

Table 2. (*continued*)

Study	Model development			Model evaluation		Model validation	
	EPV	Type of predictor	Modeling method	Discrimination	Calibration	Internal validation	External validation
Song et al. (34)	25	Results from immunoproteomics	Lasso logistic regression	0.73	NR	Leave-one-out cross validation (NR)	None
Prognostic models							
Shikata et al. (40)	5.75	Demographic characteristics + medical history + lifestyle-related factors + health examination results	Cox proportional hazards model	0.809 (0.761–0.856)	NR	None	None
Eom et al. (41)	Men: 2433.13 Women: 929.83	Demographic characteristics + family history + lifestyle-related factors	Cox proportional hazards model	Men: 0.764 (0.760–0.768); women: 0.706 (0.698–0.715)	Calibration plot and slope: men: 1.000 (0.983–1.017); women 1.000 (0.962–1.038)	None	Eom et al.: men: 0.782 (0.777–0.787); women: 0.705 (0.696–0.714)
Charvat et al. (15)	68.67	Demographic characteristics + family history + lifestyle-related factors + blood measurements	Cox proportional hazards model	0.777	H-L test: $P = 0.06$; and calibration plot	Bootstrap resampling technique: 0.768	Charvat et al.: 0.798 (0.725–0.861)
Ikeda et al. (38)	12.3	Demographic characteristics + lifestyle-related factors + health examination results + blood measurements	Cox proportional hazards model	0.773	NR	None	None
Iida et al. (14)	18	Demographic characteristics + lifestyle-related factors + blood measurements	Cox proportional hazards model	0.79 (0.74–0.83)	H-L test: $P = 0.31$	None	Iida et al.: 0.76 (0.69–0.83)
Taninaga et al. (44)	9.25	Health examination results	XGBoost	0.899	NR	Cross validation: 0.874	None
Charvat et al. (42)	4.6	Demographic characteristics + family history + lifestyle-related factors + blood measurements	Parametric survival regression model	0.798 (0.725–0.861)	The Nam-d' Agostino χ^2 test: $\chi^2 = 5.57$, $P = 0.23$	/	/
Jang et al. (39)	47.6	Demographic characteristics + lifestyle-related factors + blood measurements	Logistic regression	0.71 (0.64–0.78)	NR	None	None
Sarkar et al. (43)	10	Demographic characteristics	Logistic regression	0.859 (0.796–0.922)	NR	None	None
Trivanovic et al. (45)	12.5	Blood measurements	Logistic regression	0.700 (0.57–0.83)	NR	None	None

EPV, events per variable; H-L test, Hosmer-Lemeshow test; NR, not reported.

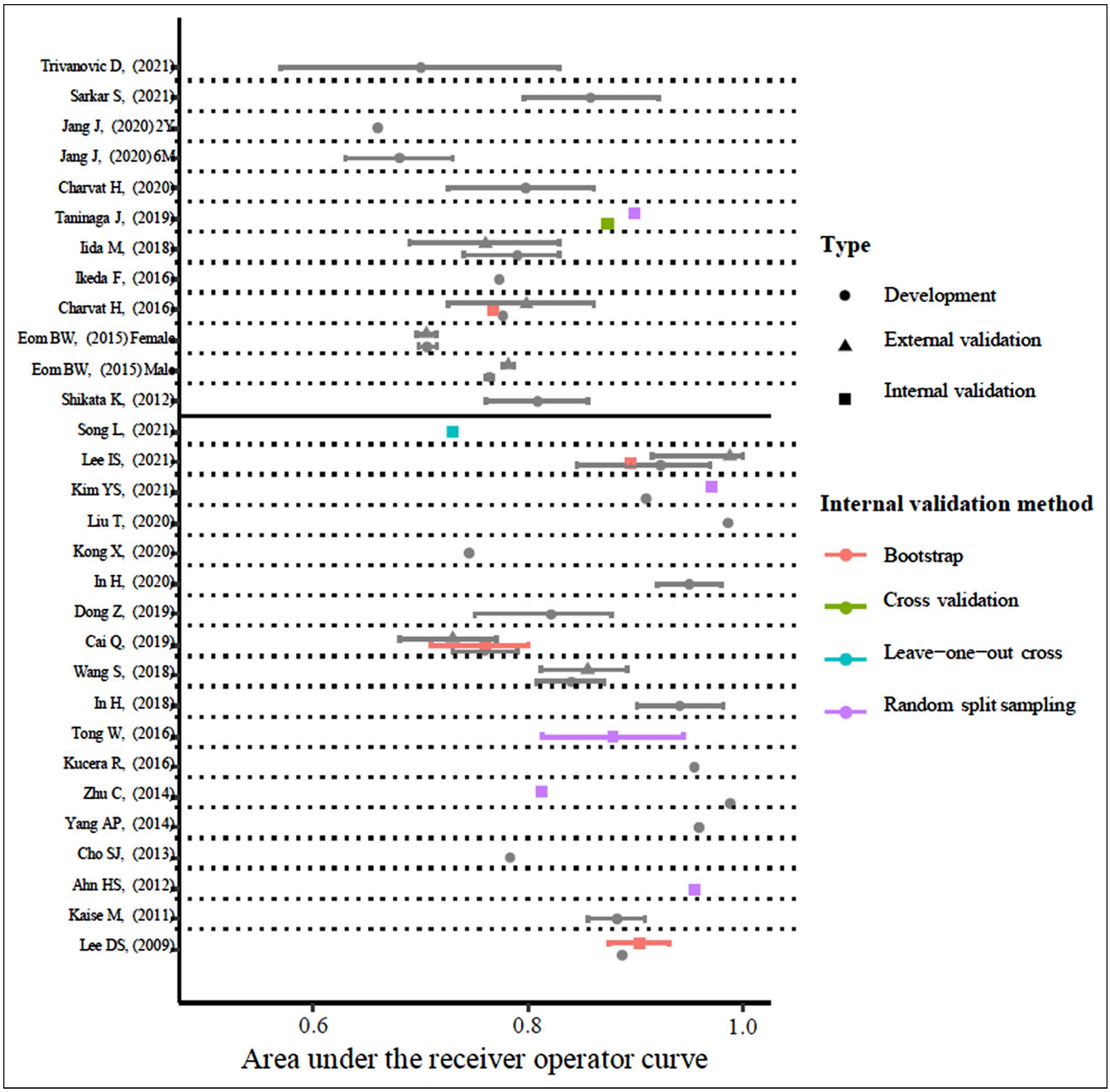

Figure 2. The c-statistics reported by the included models. The models are grouped into prognostic and diagnostic models; the uppers were values reported in prognostic models, and the lowers were values from diagnostic models. The type of model (development, external validation, and internal validation) and internal validation method are indicated in the figure.

predictors. Instead, the limited sample sizes, failure to analyze all recruited participants, and incomplete model evaluation contributed to the bias of prognostic models.

Among all the included models, 75% of the models did not assess calibration, so the reliability remained unclear. Over 70% models assessed calibration through the Hosmer-Lemeshow test, failing to indicate the existence and magnitude of miscalibration. Although the sample sizes of 3-quarter models met the traditional EPV rules of thumb by the EPVs ≥10 rule, less than half reached 20 EPVs. Limitations in study design was another main source of bias for included prediction models. Several in this review were developed from case-control studies (43–45), where the weight of the sampling population was not readjusted to the source population, involving concerns of bias in the baseline risk estimation, or from routine care registries with variable data quality. In addition, both types of models lacked the explicability of data complexity, for instance, the competitive risk and treatment of the censored data.

Regarding the model's applicability, 11 in 18 of the diagnostic models were evaluated to be applicable. The models with low applicability may be explained as follows: (i) selection bias introduced by poor matching between the concerned and actual

Table 3. Predictors included in the risk prediction models for gastric cancer

		Demographic characteristics			Health situation				Lifestyle-related factors				Laboratory measurement		
Study	No.	Age	Sex	Others	Family history	Disease history	BMI	Others	Smoking	Alcohol drinking	Eating habit	Others	*H. pylori* infection	PG testing	Others
Diagnostic models															
Lee et al. (23)	11	•		Financial status		•		History of gastroscopy or UGI series; health status				Occupational hazards			
Kaise et al. (29)	2													•	Gene: TFF3
Ahn et al. (13)	11														Protein: EGFR, proApoA1, ApoA1, TTR, DD, A2M, CRP, RANTES, IL-6, VN, and PAI-1
Cho et al. (27)	6	•	•		•			OLGIM stage	•				•		
Yang et al. (36)	4														Oncofetal protein: CA72-4, CA125, CA19-9, and CEA
Zhu et al. (37)	5														miRNA: miR-16, miR-25, miR-92a, miR-451, miR-486-5p
Kucera et al. (24)	5												•	•	Oncofetal protein: CA72-4 and CEA; enzyme: MMP7
Tong et al. (35)	5												•	•	Protein: ADAM8 (CD156); VEGF
In et al. (22)	8	•	•	Race, education, US generation, acculturation	•						Cultural food consumption frequency				
Wang et al. (25)	6														Autoantibody against TAAs: p62, c-Myc, NPM1, 14-3-3ξ, MDM2, and p16
Cai et al. (12)	7	•	•								Pickled food and fried food		•	•	Hormone: G-17
Dong et al. (28)	2														Oncofetal protein: CEA mRNA: MT1-MMP mRNA
In et al. (26)	8	•		Race, education, and US generation	•					•	Cultural food consumption frequency and salt intakes				
Kong et al. (31)	4									•	Pickled food, tea drinking				SNP: MEG3 gene polymorphism (rs7158663)
Liu et al. (33)	10														m6A gene: METTL14, METTL16, WTAP, KIAA1429, ZC3H13, RBM15, ALKBH5, YTHDF1, YTHDF2, and YTHDC1

Table 3. (*continued*)

		Demographic characteristics			Health situation				Lifestyle-related factors				Laboratory measurement		
Study	No.	Age	Sex	Others	Family history	Disease history	BMI	Others	Smoking	Alcohol drinking	Eating habit	Others	*H. pylori* infection	PG testing	Others
Kim et al. (30)	12														Oncofetal protein: CA125, CA19-9, AFP, and tPSA; CEA Other protein: ApoA1, ApoA2, β2M, CRP, TTR, CYFRA21-1, and HE4
Lee et al. (32)	5														Gene: HBB, KRT7, UBD, PLA2G2A, and ISG15
Song et al. (34)	4														Autoantibody: anti-Ggt, anti-HslU, anti-NapA, and anti-CagA
Prognostic models															
Shikata et al. (40)	12	•	•		•	•	•	Diabetes	•	•		Physical activity	•	•	Total cholesterol
Eom et al. (41) Men	8	•			•		•		•	•	Regularity of eating and salt intakes	Physical activity			
Eom et al. (41) Women	6	•			•		•		•	•	Salt intakes				
Charvat et al. (15)	6	•	•		•				•		Salt intakes		•△	•△	
Ikeda et al. (38)	10	•	•				•		•		Salt intakes, total energy		•	•	HbA1C and total cholesterol
Iida et al. (14)	5	•	•						•				•△	•△	HbA1C
Taninaga et al. (44)	8	•				•	•	Postgastrectomy					•		HbA1c, MCV, and lymphocyte ratio
Jang et al. (39)	5	•							•						Gene: CagA; CagA-relating GRS Factor: HGF
Sarkar et al. (43)	4	•	•	Race and education											
Trivanovic et al. (45)	2													•	

A2M, α-2 macroglobulin; ADAM8, A disintegrin and metalloproteinase domain-containing protein 8; Apo, apolipoprotein; CA, cancer antigen; CEA, carcinoembryonic antigen; CRP, C-reactive protein; DD, D-dimer; EGFR, epidermal growth factor receptor; HbA1c, hemoglobin (Hb)A1c; HGF, hepatocyte growth factor; IL, interleukin; MCV, mean corpuscular volume; MDM2, mouse double minute 2; NPM1, nucleophosmin 1; PAI-1, plasminogen activator inhibitor-1; PG, pepsinogen; ProApo, pro-apolipoprotein; RANTES, regulated upon activation, normally T-expressed and presumably secreted; TAA, tumor-associated antigen; TFF3, trefoil factor 3; TTR, transthyretin; VEGF, vascular endothelial growth factor; VN, vitronectin.
• Presents for one single variable; •△ presents for a combined predictor.

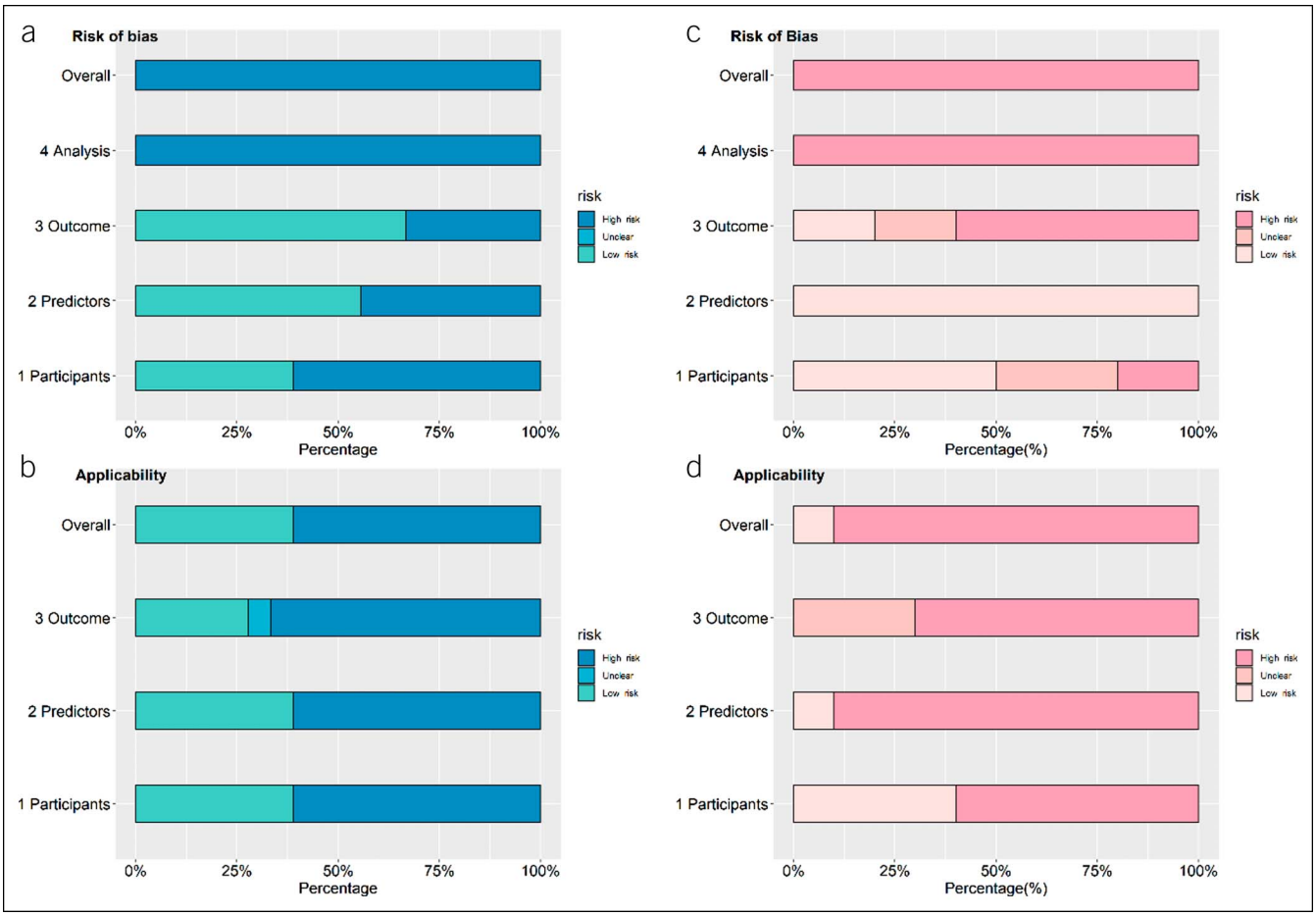

Figure 3. Assessments on risk of bias and applicability for 28 prediction models of gastric cancer based on the Prediction model Risk of Bias Assessment Tool. (**a**) Proportion of diagnostic models evaluated as high risk/low risk/unclear in the aspect of risk of bias. (**b**) Proportion of diagnostic models evaluated as high risk/low risk/unclear in the aspect of applicability. (**c**) Proportion of prognostic models evaluated as high risk/low risk/unclear in the aspect of risk of bias. (**d**) Proportion of prognostic models evaluated as high risk/low risk/unclear in the aspect of applicability.

participants (such as college students, exclusion of individuals with inflammation); (ii) poor accessibility in the measurement of predictors; and (iii) limited primary outcome (e.g., only focusing on the stage I gastric cancer). Only 1 prognostic model was assessed as having low applicability because of the convenient predictor measurement, fewer sample requirements, and better representativeness of data. In addition, nearly one-third of the models did not clearly state the inclusion criteria, which would limit the evaluation on applicability and further verification of the models.

DISCUSSION

To the best of our knowledge, this is the first review to systematically summarize and evaluate prediction models of gastric cancer, aiming to assist the selection for model users and call for improvements for future model development. The background, design, structure, and performance of 18 diagnostic and 10 prognostic models were mapped in detail. We also summarized current situations of gastric cancer prediction tools and common problems. Furthermore, we underlined the significance of reporting potential application scenarios specifically, which was frequently ignored, and classified models by application scenario.

Common pitfalls and perspectives

Although there were 28 prediction models for gastric cancer, few could be expected to be translated into real-world practice because of the high ROB, difficult balancing of accuracy and applicability, and unclear report of application scenario (Figure 4). More attention is warranted to consider the above 3 aspects for future studies.

ROB of all included gastric cancer prediction models were identified as facing high ROB. Actually, similar findings were often observed in the fields of other diseases' prediction models (46,47). The low quality of risk prediction models is associated with the nature of post hoc analysis for most studies. We have to acknowledge that frequently a model was simply created with available data and statistical tools to satisfy researchers' aim of publishing articles instead of affecting practice (48). Researchers should be educated to be responsible for the quality and clinical implications of the model. In our study, the leading bias of the included models was derived from data analysis, including limited sample size, inappropriate predictor selection, and lack of validation or calibration assessment. Therefore, we recommend researchers to use relevant standard tools during model development, such as PROBAST. Moreover, there was a large cross in the selected predictors but a lack of external validation. Instead

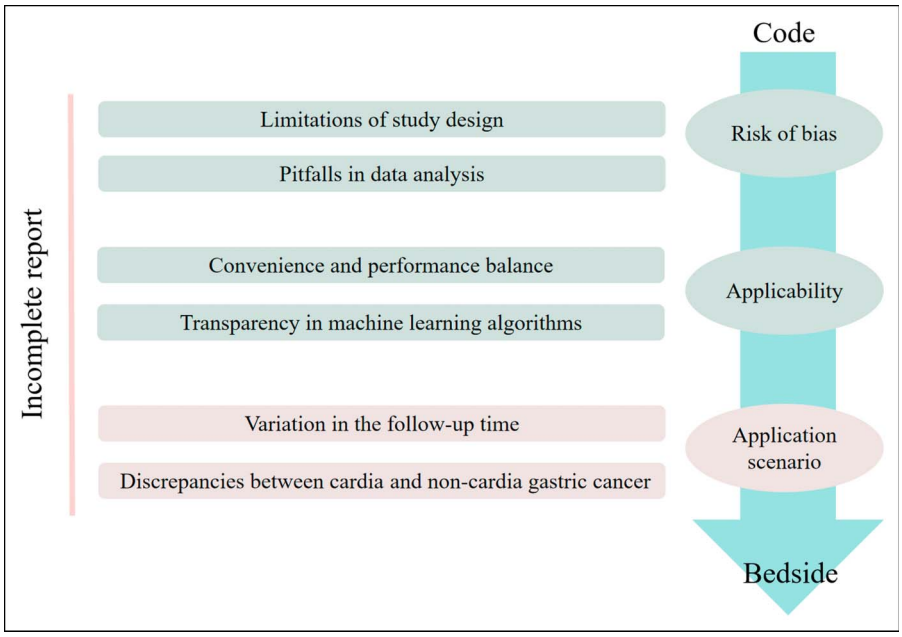

Figure 4. Common limitations of the included models and suggestions for application from code to bedside.

of mass production of prediction models, verifying or optimizing previous models is supposed to better accelerate the transformation from code to public health practice (49,50). Transregional cooperation would contribute to controlling ROB, through enlarging sample size and validating the model among extensive independent population. However, the data homogeneity and comparability between groups also require full guarantee.

Applicability

The prediction models were supposed to achieve better performance using laboratory-related and questionnaire-based variables, given that cancer is caused by both intrinsic characteristics and external environment (51). Researchers tended to explore predictors for gastric cancer from a micro perspective at this stage, which might raise burdens of economic expenditure and inevitably affect the data accessibility in the clinical practice of model application. In such circumstances, reasonable useful questionnaires were expected to accurately describe individuals' behavioral patterns, rather than simply classifying them into 2 categories (yes or no). In addition, given that immunological predictors have been widely adopted because of their good acceptability and convenient measurement, joint indicators are expected to have better application value for massive screening or regions with limited health resources. For example, the combination of *H. pylori* and PG was recommended as the ABC method in Japan (52) and included in subsequent models (14,15). Instead, other indicators with high prediction efficiency but lower accessibility, such as carcinoembryonic antigens, genetic predictors, and multiomics data, should be considered for early diagnosis or individualized screening for gastric cancer.

Machine learning brings new ideas and challenges to prediction models. Compared with the traditional modeling methods, machine learning has been proven to better match the complex and unpredictable nature of human physiology, thus has been gradually applied in medicine (53–55). However, the transparency issue of the models also concerns (56). When adopted for clinical screening, it must be fully considered for the model developers how to present the risk calculation process to ensure the individual's right to know and correct possible errors in time.

Application scenario

The application-oriented nature of prediction models should be further underscored with the explosion of gastric cancer prediction models. Cardia and noncardia cancer were subtypes of gastric cancers, different in the epidemic trends, risk factors, and prognosis (57,58). Almost all prediction models in this review define both types of gastric cancers as the target outcome. Nevertheless, some studies suggest that developing models separately for the 2 types of gastric cancers may be more effective. For example, one study on noncardia cancer showed superior diagnostic efficiency, with an AUC of 0.989 (37). Considering its worse prognosis and the increasing incidence trends (59–61), the development of risk prediction models focusing on cardia cancer is a practical way to explore in the future. At the same time, the corresponding workload, necessity of screening, and practical applicability also matter in real-world, large-scale screening practice.

The models in this review showed discrepant follow-up periods, which targeted various application scenarios and should also be considered before translation to clinical practice. For example, In et al. developed a questionnaire-based diagnostic model for both the community and healthcare settings to identify high-risk individuals instantly before screening endoscopy (22) while Charvat et al. provided an algorithm for predicting the 10-year probability of gastric cancer occurrence (15), aiming to assist clinicians in health education on cancer prevention. However, most studies just stated a general purpose (29,36,42), failing to clearly describe models' targeting application scenarios, bringing barriers to real-world practice. Unfortunately, academia shows irrational tolerance with the unclear report of prediction models' real-world application scenarios. The transparent reporting of a multivariable prediction model for individual prognosis or diagnosis statement and PROBAST did not include the application

scenario as a requirement (21,62). Moreover, only a few studies in this review have entirely presented key information (including parameter calculation and stratification criteria) for risk prediction (31–33,37,43–45). A complete report of predictive algorithms is fundamental to promoting prediction models' translation from code to public health practice and requires more attached importance (63).

Strengths and limitations

This review systematically searched and summarized the risk prediction models for gastric cancer, and the supplementary search of references and citations also ensured the comprehensiveness of retrieval. Researchers seeking for a suitable model could balance model performance, data accessibility, and their own purpose to make a final decision. Although the best model for gastric cancer cannot be obtained, researchers could also verify an existing model in population with temporal or regional differences or optimize it with new predictors, which set lower requirements for data and achieved more robust predictions in comparison with developing new models. In addition, we listed the considered predictors for each prediction model and summarized the commonly used predictors, which could provide references for identifying high-risk individuals. We also concluded the most common methodological pitfalls during the whole process of model development, aiming to remind readers of potential bias and provide suggestions for future steps.

There are also some limitations in this work. This study did not include relating models on predicting precancerous lesions of gastric cancer, which also contributed to the cancer control. However, the number of studies was still relatively limited. Besides, studies using other classification measures (e.g., sensitivity, predictive values) were excluded, given that the preset probability thresholds might not be clinically relevant. The entire range of the model-predicted probabilities was not fully used.

CONCLUSION

All gastric cancer prediction models included in this review were assessed to have high ROB, mainly caused by inappropriate statistical analysis and incomplete model evaluation. Most models had acceptable applicability, and the leading limitations were the inconvenient measurement, high sample requirements, and limited data representativeness. Besides, application scenario was urgently needed to be stated specifically in future prediction models on gastric cancer to provide references for interest groups.

CONFLICTS OF INTEREST

Guarantor of the article: Wanqing Chen, PhD.

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