Survival prediction tools for esophageal and gastroesophageal junction cancer: A systematic review

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ABSTRACT

Background: Clinical, pathological, and molecular information combined with cancer stage in prognostication algorithms can offer more personalized estimates of survival, which might guide treatment choices. Our aim was to evaluate the quality of prognostication tools in esophageal cancer.

Methods: We systematically searched MedLine and Embase from 2005 to 2017 for studies reporting development or validation of models predicting long-term survival in esophageal cancer. We evaluated tools using the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies guidelines and the American Joint Committee on Cancer acceptance criteria for risk models.

Results: We identified 16 prognostication tools for patients treated with curative intent and 1 for patients with metastatic disease. These tools frequently excluded adenocarcinoma, contained outdated data, and were developed with a limited sample size. Nine tools were developed in China for squamous cell cancer, and 11 used data on patients diagnosed before 2010. Most tools excluded key prognostic factors such as age and sex. Tumor stage and grade were the most commonly, but not universally, included factors. Twelve tools were designed to predict overall survival; 5 predicted cancer-specific survival. Bootstrap internal validation was performed for most tools; c-statistics ranged from 0.63 to 0.77 and graphically evaluated calibration was “good.” Five tools were externally validated; c-statistics ranged from 0.70 to 0.77.

Conclusions: Existing tools cannot be confidently used for esophageal cancer prognostication in current clinical practice. Better-quality tools might help to more individually and accurately estimate disease course, select further treatments, and risk-stratify for future clinical trials. (*J Thorac Cardiovasc Surg* 2018;156:847-56)

Well recognized prognostic factors are not universally included in prediction tools.

Central Message

Existing survival prediction tools for esophageal and gastroesophageal junction cancer cannot be confidently used for individualized prognostication in current clinical practice.

Perspective

Clinical, pathological, and molecular information combined in prognostication algorithms can offer more personalized estimates of survival. Existing tools cannot be confidently used for esophageal cancer prognostication in current clinical practice. Better-quality tools might help to more individually and accurately estimate disease course, select further treatments, and risk-stratify for clinical trials.

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Accurate estimates of survival help patients and oncologists improve their ability to make better treatment decisions. This is particularly important in high-fatality cancers such as esophageal cancer (EC), for which the fatality rate approaches 90%.¹⁻³ Incidence of this disease is rapidly increasing in Western countries,³ enhancing the relevance of such predictions. Currently, survival in EC is predicted

Scanning this QR code will take you to a supplemental video for the article.

Abbreviations and Acronyms

AJCC	= American Joint Committee on Cancer
EC	= esophageal cancer
GEJ	= gastroesophageal junction
TNM	= Tumor, Node, Metastases
TRIPOD	= Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis

solely on the basis of anatomic stage using the American Joint Committee on Cancer (AJCC) Tumor, Node, Metastases (TNM) staging criteria. However, stage is limited to information about the extent of disease available postoperatively for patients who underwent resection and does not include additional factors that affect survival. Furthermore, heterogeneity in survival is observed even within similarly-staged patients.⁴

Clinical prediction tools combine key prognostic factors to provide more accurate and precise estimates of survival; this can improve outcomes as well as reduce costs by better selecting patients for appropriate treatment.⁵ Patient factors such as age, sex, and comorbidity are associated with survival in many diseases and are increasingly being incorporated into cancer prognostication models to improve accuracy.⁶⁻⁸ In esophageal cancer, tumor factors such as histology and treatment response also influence survival.⁹⁻¹¹ In addition, for patients who undergo surgical resection, pathologic factors associated with survival in the postoperative setting include tumor grade, response to preoperative therapy, number of lymph nodes resected/positive, resection margins, and the presence of lymphovascular or perineural invasion.¹²⁻¹⁵

In the eighth edition of the TNM staging manual released in 2017, the AJCC formally recognized the importance of using patient and pathological data along with cancer stage to improve prognostication and advocated strongly to improve risk prediction in cancer.¹⁶ The AJCC has published guidelines for the appraisal of cancer prediction tools.⁶ These guidelines are available in the form of a checklist with 13 inclusion and 3 exclusion criteria that readers can apply in evaluating a prediction tool to ensure its quality and applicability to practice. To summarize, they ensure that tools: predict survival outcomes, have clinical relevance, include important predictors, specify the target population, test validation to ensure generalizability, clearly define when the prediction is calculated, assess and meet certain statistical standards, and report appropriate details such that the model can be implemented by the user.

Using these guidelines, the AJCC has reviewed the quality of tools across a number of cancer sites,^{7,8,17,18} and endorsed tools that have met this standard for

colorectal, lung, melanoma, breast, and prostate cancer.¹⁹

It is unclear whether or not gaps exist in the EC prognostic tool literature or any recommendations for which tools should be used in practice. Therefore, the objective of this study was to systematically review the literature for studies reporting development or validation of models predicting survival in EC.

METHODS**Search Strategy and Selection Criteria**

Our review was inclusive of tools predicting long-term (not perioperative) survival for esophageal and gastroesophageal junction (GEJ) cancer, adenocarcinoma, or squamous cell carcinoma, curative-intent or metastatic patients, and designed for use either pre- or postoperatively. Prognostication tools were identified using 2 strategies: (1) a search of the peer-reviewed published literature (a systematic literature review and cited reference search); and (2) a Google Web-based search.

The search strategy was executed in OVID MedLine and OVID Embase from Jan 1, 2005 to April 19, 2017. Medical subject headings did not exist for prognostication tools and so a combination of alternate headings and key words identified in consultation with a scientific librarian for a previous review were used.⁷ Each set of search terms was modified for the specific search engine. The following search terms were used in MedLine: “models, statistical/,” “prognosis,” “predict* model*,” “nomogram/,” “prognos* model*,” “esophageal neoplasms/,” “esophageal squamous cell carcinoma/,” “adenocarcinoma of the esophagus/,” and “esophagogastric junction.” The searches were limited to English language. Seemingly eligible studies were excluded if they met any of the following a priori exclusion criteria: (1) assessment of the prognostic effect of a single factor (unless it was updating the accuracy of an existing prognostic tool), (2) inappropriate analytic purpose (eg, multivariate modeling not aimed at prognostication, development of novel statistical methods), (3) not limited only to EC patients, (4) not original data/research (eg, editorial, review), or (5) the outcome was not long-term survival. Studies reporting on perioperative mortality (eg, predicting 30-day mortality after esophagectomy) were not the focus of this review and were excluded.

Prognostication tools in this report include those developed to estimate the probability of survival at a particular point along the disease trajectory (eg, at diagnosis, after treatment) or for the purpose of using a survival probability to inform treatment decision-making. Eligible survival end points included any time-to-death analyses (eg, overall survival, cause-specific survival, relative survival), as well as vital status analyses (eg, probability of death at 5 years after diagnosis). Generally speaking, some form of statistical model underlies most prognostication tools, and we use the terms prognostication tool and prognostication model interchangeably. Two reviewers (V.G., A.L.M.) assessed the titles and abstracts of citations for inclusion. Percent agreement was 95%. Differences were resolved through a discussion of discordant decisions. A cited reference search using Web of Science was performed to decrease the probability of missing a relevant article. These peer-reviewed literature search strategies to identify prognostic tools in EC were supplemented by a Google Web-based search. Search terms included: “clinical prediction tool,” “online calculator,” or “nomogram,” combined with “esophageal cancer,” “esophagogastric cancer,” or “gastroesophageal cancer.”

Data Abstraction

A detailed report on data abstraction form development and key definitions was published previously.^{7,20} The data abstracted allowed an evaluation of tool development and validation methodology and clinical

relevance. The final criteria include all key elements described by the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines and the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies checklist.²⁰ General descriptive information such as study design,

study population characteristics, prognostic factors considered, and outcome measurement were abstracted, as were specific details on tool development (statistical modeling decisions, candidate variable selection), and validation (internal and external validation methods, measures of model predictive accuracy).

FIGURE 1. Results of the search for clinical prognostic tools and their validation articles on esophageal cancer. CR, Cited reference.

TABLE 1. Details on included prognostic tools for esophageal cancer

Tool/ reference	Data source	Population	Data collection	Exclude nCRT?	Study design	Sample size	Follow-up time	Outcome	Outcome anchor (time zero)	Number of events*	Variables	Internal validation C-statistic†	External validation C-statistic†
Resected AC and SCC Cao et al ²³	USA	Esophagus	1988 to 2007	NR	R	4109	Med. 28 mo	CSS	Dx date	NR	Age, race, histology, tumor site, tumor size, grade, T stage, N stage, number of LNs harvested	0.72 (0.71- 0.73)	0.70 (0.64- 0.76)
Eil et al ²⁹	USA	Esophagus, >65 y	1997 to 2005	No	R	824	NR	OS	NR	NR	Age, sex, histology, T stage, N stage, number of LNs harvested, CRT	0.72	None
Shapiro et al ³⁵	The Netherlands	Esophagus	2001 to 2013	No	P	626	NR	OS	OR date	NR	Clinical N stage, pathological T and N stage	0.63	None
Resected AC Gabriel et al ³⁰	USA	Esophagus	2006 to 2012	No	R	6129	Med. 48.8 mo	OS	NR	3491	Age, T stage, N stage, grade, comorbidity, nCRT	0.68	None
Zhou et al ⁴³	USA	GEJ	2004 to 2011	NR	R	953	Avg. 25.5 mo	OS	NR	NR	Age, sex, depth of invasion, number of LNs positive, number of LNs harvested, grade	0.69 (0.66- 0.72)	0.75 (0.71- 0.79)
Lagarde et al ^{32,44}	The Netherlands	Esophagus	1993 to 2003	Yes	P	364	Min. 20 mo	CSS	CSS	228	T stage, LN ratio, extracapsular LNI	0.77 (0.74- 0.80)	0.76
Resected SCC Su et al ³⁷	China	Esophagus	2000 to 2009	Yes	R	797	Min. 18 mo	OS	OR date	NR	Tumor size, surgical approach, number of LNs harvested/ positive, grade, depth of invasion	0.73 (0.69- 0.76)	0.72 (0.67- 0.76)
Shao et al ³⁴	China	Esophagus	2002 to 2012	Yes	R	916	Med. 39 mo	OS	OR date	NR	Grade, T stage, N stage, CRP/Alb ratio, NLR	0.77 (0.74- 0.81)	0.76 (0.71- 0.82)
Wang et al ⁴⁰	China	Esophagus	2006 to 2008	NR	R	205	Med. 48 mo	OS	OR date	153	T stage, LN status, TNM stage, grade, vascular invasion, UBEC2C expression, MGP expression	NR	None
Chen et al ²⁵	China	Esophagus	2005 to 2008	Yes	R	308	NR	CSS	Dx date	NR	Age, sex, T stage, N stage, M stage, PLR, CRP/PNI ratio	0.69	None
Yu et al ⁴²	China	Esophagus	2004 to 2011	Yes	R	1004	Med. 67.5 mo	OS	OR date	NR	Adjuvant treatment, grade, tumor embolus, LN ratio, T stage, tumor site	0.70 (0.67- 0.73)	None
Chen et al ²⁴	China	Esophagus	2006 to 2008	Yes	R	277	Med. 42.6 mo	CSS	OR date	NR	Age, sex, T stage, N stage, RDW	0.68	None
Liu et al ³³	China	Esophagus	2006 to 2008	Yes	R	326	Med. 45 mo	CSS	OR date	NR	T stage, N stage, PLR, LMR, GPS	0.72	None
Duan et al ²⁸	China	Esophagus	2006 to 2010	Yes	R	328	Med. 44.9 mo	OS	OR date	NR	Sex, tumor size, T stage, N stage, CT	0.71 (0.63- 0.79)	0.77 (0.60- 0.93)

(Continued)

TABLE 1. Continued

Tool/ reference	Data source	Population	Data collection	Exclude nCRT?	Study design	Sample size	Follow-up time	Outcome anchor			Variables	Internal validation C-statistic†	External validation C-statistic†
								Outcome	time	zero			
Deng et al ²⁷	China	Esophagus	1980 to 2014	No	R	407	Med. 26.0 mo	OS	CRT start	NR	Age, sex, tumor length, treatment response, resection margin, proximal margin length, LN status, anastomotic leak	0.71 (0.65-0.76)	None
Definitive CRT (Unresected) AC and SCC Suzuki et al ³⁹	USA	Esophagus and GEJ	2002 to 2010	N/A	P	196	Med. 39.2 mo	OS	NR	NR	Stage, grade, histology, cCR, iSU	0.7	None
Metastatic SCC Jung et al ³¹	Korea	Esophagus	2000 to 2010	N/A	R	239	NR	OS	CT start	NR	ECOG, weight loss, low albumin, esophagectomy	0.61	None

nCRT, Neoadjuvant chemoradiotherapy; AC, adenocarcinoma; SCC, squamous cell carcinoma; USA, United States; NR, not reported; R, retrospective; Med, median; CS, cancer-specific survival; Dx, diagnosis; LN, lymph node; OS, overall survival; CRT, chemoradiotherapy; P, prospective; GEJ, gastroesophageal junction; Min, minimum; LNI, lymph node invasion; CRP, C-reactive protein; Alb, albumin; NLR, neutrophil to lymphocyte ratio; TNM, Tumor, Node, Metastases; UBE2C, ubiquitin-conjugating enzyme 2C; MGP, matrix gla protein; PLR, platelet lymphocyte ratio; PNI, prognostic nutritional index; RDW, red cell distribution width; LMR, lymphocyte to monocyte ratio; GPS, Glasgow prognostic score; CT, chemotherapy; N/A, not applicable; cCR, clinical complete response; iSU, initial standard uptake values; ECOG, Eastern Cooperative Oncology Group performance status. *Number of events refers to those in the development set. †Internal and external validation C-statistic and 95% confidence intervals are presented.

Summary

Descriptive statistics related to tool development and validations are reported in summary tables. The assessment of a tool’s discrimination and/or calibration was defined as a formal statistical evaluation of the internal or external validity. Model discrimination assesses the ability of the model to distinguish between high- and low-risk patients. Model calibration assesses how closely the predicted values of the outcome match the observed outcomes in the study sample. These established methods are considered the best means of evaluating a clinical prediction model.^{5,21,22} We did not describe when tools were assessed informally through a comparison of survival time distributions across prognostic groups (Kaplan–Meier survival curves). Although these are the same statistical methods that are often used to evaluate the prognostic ability of TNM stage, they are not considered statistically robust, nor best practice for assessment of clinical prediction tool predictive performance.^{5,22}

Evaluation of Tool Quality

The Precision Medicine Core of the AJCC has developed and published criteria to evaluate the quality of prognostication tool development and whether they can be recommended for use in clinical practice.⁶ We evaluated all tools against these criteria.

RESULTS

Literature Search Results

Figure 1 shows the search results. The scientific literature review, cited reference, and Web-based search identified 19 prognostication tools^{23–43} and 1 article that contained an external validation only.⁴⁴ No articles were published to update previously developed tools with additional prognostic information. We did not identify any articles that evaluated the effectiveness or implementation of tools in clinical practice. One article evaluated the net benefit of using the tool in clinical practice using decision curve analyses.³⁴

Overall, 15 tools were developed for EC, 1 for GEJ cancers, 1 for esophageal as well as GEJ cancers, and 2 for gastroesophageal cancers. The 2 gastroesophageal cancer tools included stomach cancer patients, and were excluded.^{26,36} In the remainder of this article we discusses the 17 esophagus and GEJ cancer tools.

Thirteen tools (76%) provided a visual nomogram, 1 tool was available as a Web-based calculator, 2 tools were presented as risk scores or risk groupings, and 1 tool was provided as an equation only. Four tools provided the statistical equation, including coefficients and the intercept for a particular time point of prediction (when appropriate). The TRIPOD guidelines recommend this information is published along with the clinical operationalization of the prediction tool to allow adequate external validation with appropriate statistical methods.⁵

Tool Development Methods

Table 1 describes key information abstracted from each study. Further supporting aggregate information is reported.

None of the included studies were prospectively designed to collect data with the purpose of creating a clinical prediction tool. Three studies used data that were

prospectively collected in a clinical database to understand prognosis and disease recurrence, but not with the goal of creating a prediction tool. Most tools (56%) used data from patients diagnosed and treated in China or the United States (29%). Most tools (65%) were developed using data collected from patients diagnosed or treated in 2010 or earlier. The median prediction tool development cohort sample size was 407, ranging from 196 to 6129 patients. Twelve tools (71%) were designed to predict overall survival; 5 predicted cancer-specific survival. Four articles (24%) did not report the amount of follow-up and 14 (82%) did not report the number of deaths occurring during the study period. The median amount of follow-up ranged from 26 to 67.5 months and the number of reported deaths ranged from 153 to 3491.

Table 2 summarizes tool development methodology information. Almost all tools (14 of 17) identified prognostic factors for inclusion through some *P* value-based variable selection method. In addition, 3 tools selected prognostic variables opportunistically according to the availability of data in existing databases. Most tools did not report how missing data on variables were handled, whereas 2 indicated using an imputation-based approach, as recommended in TRIPOD.⁵ Most tools (76%) dichotomized or categorized continuous prognostic factors (eg, age). Categorization of continuous data is not recommended by the TRIPOD guidelines, but is often cited as necessary to ease practical application of a clinical prediction tool.⁵ All but 3 studies used Cox proportional hazards regression models to develop their prognostication tool. Four tools did not provide an anchor point (the event that marks time 0) to measure survival; of those that did, most (9 of 13) were designed to predict survival from the date of surgery, 1 from the start of chemoradiotherapy, 1 from the start of chemotherapy, and 2 from the date of diagnosis. Very few (2 of 17) studies reported verifying the statistical assumptions of the underlying mathematical models.

Populations and Prognostic Factors

Table 1 shows the populations addressed by each prognostication tool. Most tools (10 of 17) were developed to address prognostication in patients with squamous cell carcinoma. Most prognostication tools targeted patients with EC undergoing surgical resection (15 of 17); of those, only 4 tools included patients also receiving neoadjuvant chemoradiotherapy (trimodality therapy), which is the current standard of care as curative-intent treatment.¹⁰

There was significant heterogeneity in the prognostic factors included in tools. For example, in the 9 tools designed to prognosticate for patients with squamous-cell esophageal tumors undergoing surgical resection, the median number of prognostic factors included in each tool was 6 (range, 5-8), and 31 factors were included in total. None of the prognostic factors were common to all 9 tools. Most of

the factors (22 of 31) were included exclusively in a single tool (Table 3). T and N stage were the most commonly included, present in 7 and 5 tools each (Figure 2).

Internal Validity

Table 4 shows a summary of assessment of each tool's predictive performance. All but 1 of the studies assessed the internal validity.⁴⁰ More than half of the studies (11 of 16) assessed model performance using bootstrapping, which decreases the likelihood of overestimating model performance, and is an approach recommended by TRIPOD.⁵ Model calibration was assessed graphically for 9 tools, and typically "good" calibration was interpreted by the authors without a corresponding evaluation of model fit statistics, subgroup comparisons, the line of identity, or calibration slopes. All studies that assessed internal validity reported a concordance index, which might vary from 0.5 (model predictions are similar to chance) to 1.0 (model predictions are perfect). Model discrimination ranged from 0.63 to 0.77. When studies using bootstrapping techniques only were evaluated, the concordance index range did not change.

External Validity

More than half of the tools (11 of 17) did not have an evaluation of model performance in a group of similar patients seen at a different institution or during a different time period (external validation). Five prognostication tools each had a single evaluation; none of the external validations were performed by researchers independent of those involved in tool development. The external validation cohort sample size ranged from 76 to 382 patients (median, 181). Only 1 study reported the number of events in the validation cohort.³² Concordance indices reported across external validations ranged from 0.70 to 0.77. Most studies reported wide 95% confidence limits, as the result of their small sample sizes.

TOOL QUALITY

Of the 17 tools identified, only 2 did not trigger either of the 2 exclusion criteria set by the AJCC. Most were excluded because of the lack of reporting on the extent and effect of missing data. Table 5 shows the assessment of the remaining 2 tools against the AJCC criteria.^{6,30,32} The tool developed by Gabriel et al to assess the benefit of neoadjuvant chemoradiotherapy could meet all criteria for use, if the authors provided the point of time that prognostication for their patient population began (eg, survival from the time of surgery, diagnosis) and the number of deaths in the development cohort.³⁰

DISCUSSION

We systematically reviewed the literature on clinical prediction tools for long-term survival in EC (Video 1). We found 16 tools for patients treated with curative intent and 1 tool for patients with metastatic disease. Discrimination

TABLE 2. Methodological criteria evaluated for clinical prognostication tools for patients with esophageal cancer (n = 17)

Methodological criterion	n (%)
Prognostic factor selection method	
Literature-based/clinical reasoning	2 (12)
Screened using univariable/multivariable selection methods	14 (82)
Method not specified	1 (6)
Methods for handling missing data	
Complete case analysis	2 (12)
Imputation	2 (12)
Method not specified	13 (76)
Description of handling continuous predictors*	
Linear	2 (12)
Cubic spline	3 (18)
Transformed	1 (6)
Dichotomized/categorized	13 (76)
Method not specified	2 (12)
Analytic model used	
Cox proportional hazards regression	14 (82)
Log-Logistic regression	1 (6)
Cluster analysis	1 (6)
Method not specified	1 (6)
Statistical model assumptions checked	2 (12)

*Studies may have used multiple methods if they had multiple continuous variables, so that percentages do not add up to 100. Dichotomization/categorization is not the recommended method of handling continuous predictors.

was weak or moderate and calibration was good (observed survival frequently approximated predicted survival) for all models. Most of the tools did not meet the minimum set of criteria developed by the AJCC to identify high-quality, clinically useful prognostication tools. The tool developed by Gabriel and colleagues met almost all of the published AJCC criteria for a well developed and clinically relevant tool.^{6,30} It is built from a cohort of 6129 patients identified in the National Cancer Database who underwent neoadjuvant chemoradiotherapy and surgery for esophageal adenocarcinoma between 2006 and 2012. They included important prognostic variables, applied appropriate statistical methods, and showed good predictive performance. The Gabriel tool is an ideal candidate for external validation provided the outcome anchor and number of deaths in the cohort are clarified. The extent of available, well developed tools relative to the number of novel tools published in the past 5 years represents an important gap in current care, and the development and validation of robust tools in clinically important scenarios would be an important step toward realizing personalized care in EC.

In many regards, the quality of prognostication tool reporting for EC is superior to other reviewed cancer sites.^{7,8,17,18} All tools identified had a corresponding, peer-reviewed publication describing the development and technical details. Most studies reported an appropriate

TABLE 3. List of prognostic factors common to only 1 of the 9 tools predicting survival for patients with resected squamous cell esophageal cancer

Number of adjuvant chemotherapy cycles
Number of LNs positive
Number of LNs examined
Adjuvant treatment
Anastomotic leak
CRP/Alb ratio
CRP/PNI ratio
Depth of invasion
Tumor embolus
Extent of positive LNs
Glasgow prognostic score
MGP expression
Neutrophil/lymphocyte ratio
Proximal margin length
Red cell distribution width
Resection margin
Surgical approach
TNM stage
Treatment response
Tumor site
UBEC2C expression
Vascular invasion

LN, Lymph node; CRP, C-reactive protein; Alb, albumin; PNI, prognostic nutritional index; MGP, matrix gla protein; TNM, Tumor, Node, Metastases; UBEC2C, ubiquitin-conjugating enzyme 2C.

outcome anchor, described their variable selection strategy and handling of continuous variables, and internally validated the model with bootstrapping. In addition, these studies appropriately used standard discrimination and calibration statistics to assess model performance, whereas in other cancer sites, tool performance is often only evaluated by comparing survival curves between different prognostic groups.

Despite these strengths, however, shortcomings were documented with regard to development, reporting, and current clinical relevance of prognostic tools in EC. Most tools used data from the 1980s to the early 2000s, with few cohorts including patients treated in the current decade. This is important because the landmark studies that guide treatment today were published between 2005 and 2015,¹⁰ and thus tools on the basis of earlier data reflect treatment with outdated protocols. Neoadjuvant (preoperative) chemoradiation is the current standard of care for locally advanced EC, however, only 4 studies specifically included patients who underwent this treatment protocol.^{27,30,35,45} Furthermore, data from the 1990s and early 2000s do not reflect the results of modern chemotherapy, radiotherapy, and surgical care. External

FIGURE 2. The number of prognostic factors common to more than 1 tool predicting survival for patients with resected squamous cell esophageal cancer (n = 9).

validation and recalibration of these tools in modern cohorts could help address these issues, but has not been completed for most tools, thus significantly limiting their applicability to practice today.

Similar to other reviews of oncology prognostication tools, significant variation was documented in the number and types of prognostic factors included in the identified tools. Variation in variable inclusion might be driven by the use of statistical rules, rather than clinical knowledge, to select predictors in the model, the secondary use of data from sources or studies not designed to develop a

prognostication tool at the time point of interest, or because the study was designed to evaluate the prognostic ability of biomarkers not routinely used in practice. Well established prognostic factors such as cancer stage, age, and sex were missing from many tools, limiting their utility in the real world. Data-driven selection strategies are likely to overestimate predictive ability because they optimize case mix and statistical relationships specific to the development data set (overfitting); models developed in this way are less likely to perform well in other populations. The ideal tool would incorporate clinically relevant factors *a priori* in the model to improve face validity and facilitate tool adoption in the community.

The lack of information on missing data on prognostic variables, number of deaths, and follow-up time were significant issues in prognostic tool development reporting and create barriers to clinical use. Because many tools were developed and published before the circulation and widespread dissemination of the TRIPOD guidelines across the medical community, these limitations might be easily addressed in future research at the time of study design. Better reporting and understanding of the effect of missing data could mean more reliable and accurate predictions. Authors of existing tools might benefit from reaching out to organizations such as the AJCC to bridge the current gap between model development and implementation, thereby facilitating effective knowledge translation.

During this review we identified 3 articles that evaluated gene signatures to study their relationship to survival; these tools did not consider any existing, known predictors but rather explored the significance of new genes in

TABLE 4. Details of evaluations of tool internal and external validity (n = 17 tools)

Performance measure	Internal validation (n = 16 tools)	External validation (n = 6 validations)
Internal validation method		
Apparent	5 (31)	–
Bootstrapping	11 (69)	–
External validation method		
Independent	–	0 (0)
Geographic	–	4 (67)
Temporal	–	2 (33)
Calibration		
Graph (plot/intercept/slope)	9 (56)	4 (67)
Other*	1 (6)	1 (17)
Discrimination		
C-statistic†	16 (100)	5 (83)

*Plotted observed and expected survival in a Kaplan–Meier curve. †Concordance index on the basis of the receiver operating characteristic area under the curve for binary data, Harrell C statistic for models using time to event data.

TABLE 5. Quality assessment of tools that did not trigger the AJCC exclusion criteria

Citation	Population	Inclusion criteria met, n	AJCC recommended
Gabriel et al ³⁰	Esophageal adenocarcinoma patients undergoing resection and nCRT	13 of 14	Tentative yes
Lagarde et al ^{32,44}	Esophageal adenocarcinoma patients undergoing resection	10 of 14	No

AJCC, American Joint Commission on Cancer; nCRT, neoadjuvant chemoradiotherapy.

isolation.^{38,46,47} Genomic analysis might be important in the future as DNA/RNA sequencing becomes widely available for clinical application, but genomic data alone do not currently constitute a useful basis for prognostication in individual patients.⁴⁸

There are some limitations to note in this systematic review, specifically our definition of prognosis and literature search parameters. We focused on the prognostication of long-term survival and did not include studies predicting perioperative mortality. Warnell and colleagues specifically reviewed this literature in 2015 and concluded these studies suffered some of the same limitations we described, including poor discrimination, unreliable performance, and poorly-managed biases.⁴⁹ We also limited our search to English-language studies and might not have captured tools developed or implemented in some parts of the world. This might especially be true because of the large proportion of tools published outside of North America and Europe. We mitigated this by performing a Web-based search for all tools regardless of a corresponding publication. This review also followed TRIPOD, Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies Checklist, and AJCC guidelines to

identify and critically appraise studies, which limits the potential for bias in our conclusions.

Prediction tools in cancer care can help achieve more personalized, patient-centered care. In addition to cancer stage, considering an individual’s age, sex, comorbidities, treatment received, response to therapy, and specific surgical pathology (where available) can make survival predictions more accurate and patient-centered. With the exception of the tool developed by Gabriel et al, none of the tools identified in our review are ideal for use in current clinical practice.³⁰ This tool might be suitable for clinical application when the outcome anchor for prognostication and number of deaths is described, it is externally validated, and potentially recalibrated in a population-based data set. The availability and acceptability of a well developed and validated tool might help to more individually and accurately estimate disease course, select further treatments, and risk-stratify for future clinical trials.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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VIDEO 1. Dr Vaibhav Gupta explains the importance and relevance of the study. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)30937-1/fulltext](https://www.jtcvs.org/article/S0022-5223(18)30937-1/fulltext).

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Key Words: prediction model, nomogram, survival, esophageal cancer, personalized medicine