



# A narrative review of prognostic indices in the evaluation of gastrointestinal cancers

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**Background and Objective:** Accurate cancer prognostication allows for conscious decision-making. There is a need for precise indices, along with predictive biomarkers, which aid cancer prognostication. We sought to conduct an overview of the current state of prognostic indices and biomarkers in the evaluation of gastrointestinal (GI) cancers, specifically esophageal, colon and rectal.

**Methods:** We conducted a comprehensive review of articles in the PubMed database between September 2001 and February 2022. Only articles written in English were included. We reviewed retrospective analyses and prospective observational studies.

**Key Content and Findings:** Nomograms are well-described tools that provide estimates of specific cancer-related events, such as overall survival (OS). They are also useful in unroofing specific patient-related variables, which may be associated with cancer survival. Certain prognostic indices have been tested against each other with the goal of discerning superiority. Finally, specific biomarkers have emerged as promising prognostic indicators.

**Conclusions:** Nomograms play a significant role in the prognostication of GI cancer. The identification of specific biomarkers in cancer prognostication is evolving. As we embark on the era of precision medicine, further investigation of reliable prognostic indices and biomarkers is needed.

**Keywords:** Indices; cancer prognostication; gastrointestinal (GI); biomarkers; nomograms

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## Introduction

The value of accurate cancer prognostication cannot be overstated as it allows for conscious decision making for both patients and their families (1). An accurate prognosis may lead to recommendations more fitting for each individual patient, which can have a big impact on treatment plan, such as less aggressive treatment or end-of-life care (2). Despite this, disease prognostication tends to garner less recognition than disease treatment within clinical practice (3). Additionally, providers are often hesitant to provide patients with prognostic estimations (4,5), which is at odds with the findings that many patients prefer to have

these discussions (6,7).

It is reasonable to postulate that this reluctance is, at least in part, due to the lack of a single quintessential calculator for accurately predicting the course of a patient's malignancy. Establishing specific demographic factors, laboratory values and genetic biomarkers as reliable prognostic indicators is a highly investigated topic. We sought to conduct an overview of the current state of prognostic indices in gastrointestinal (GI) cancers. Given the extensive number of studies available for review, we limited our search to esophageal, colon and rectal cancer. Our review highlights studies in which novel calculators have been produced and/or tested against already established calculators. Additionally, we

**Table 1** The search strategy summary

Items	Description
Date of search	Between 22nd August, 2022 and 15th January, 2023
Databases and other sources searched	PubMed
Search terms used	Prognosis, Neoplasms/Mortality, Decision Making, Gastrointestinal, Neoplasms/diagnosis, Nomograms, Esophageal neoplasms, Rectal neoplasms, Colonic Neoplasms, Tumor Biomarkers, Biomarkers
Timeframe	Articles were between 7th September, 2001 and 25th February, 2022
Inclusion, and exclusion criteria	Inclusion criteria: only articles written in English were included. Retrospective analysis and prospective observational studies were included. Exclusion criteria: not applicable
Selection process	Authors DK, TA, and EG conducted the selection of articles. Consensus was reached with discussion among all authors

aim to discuss the prognostic variables utilized within these published indices, specifically the ones found to be associated with survival, including specific biomarkers. We present this article in accordance with the Narrative Review reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-23-159/rc>).

## Methods

To review the current state of indices utilized in the prognostication of esophageal, colon and rectal cancer, a comprehensive electronic search was undertaken of articles in the PubMed database, from 7 September 2001 to 25 February 2022. We reviewed studies that either featured novel nomograms, highlighted specific prognostic variables associated with cancer survival, or sought to compare existing indices. A subset of our search focused on articles reviewing the role of biomarkers in cancer prognostication. Articles were identified using keywords, “prognosis”, “neoplasms/mortality”, “decision making”, “gastrointestinal”, “neoplasms/diagnosis”, “nomograms”, “esophageal neoplasms”, “rectal neoplasms”, “colonic neoplasms”, “tumor biomarkers” and “biomarkers”. We reviewed retrospective analyses and prospective observational studies. We utilized articles written in English only. The texts of the articles were reviewed in entirety. Methods are summarized in *Table 1*.

## Discussion

### *Nomograms: predictive power*

Nomograms are commonly utilized to prognose a patient’s

cancer. Assisted by their user-friendly graphical interfaces, they can provide individual predictive estimates of specific cancer related events (8). Overall survival (OS) is one example and is a common point of emphasis in published nomograms. For example, Deng *et al.* developed a nomogram that was effective in predicting OS in patients with thoracic esophageal squamous cell carcinoma (ESCC) following radical esophagectomy (9). Jin *et al.* established nomograms which predicted 3- and 5-year OS in patients with early onset colorectal cancer (10). Diao *et al.* constructed a nomogram for predicting OS in patients with rectal squamous cell carcinoma (11).

In addition to OS, other cancer related events are predicted using nomograms. Chao *et al.* demonstrated a novel nomogram which showed good performance for predicting pathological complete response after neoadjuvant chemoradiotherapy in patients with ESCC (12). In patients with colorectal carcinoma, a nomogram was developed to estimate recurrence following curative surgery (13). In patients with rectal cancer, Hoshino *et al.* created a nomogram useful in predicting anastomotic leakage following low anterior resection (14). Nomograms play a considerable role in cancer prognostication.

### *Nomograms: prognostic variables*

Nomograms are also utilized to unroof patient-related variables, which may associate with cancer survival. Sex, age, and tumor-node-metastasis (TNM) classification have been described in multiple published nomograms as measures linked to OS amongst patients with esophageal cancer (9,15,16). The number of chemotherapy cycles was

selected in building nomograms aimed to predict survival in patients with ESCC following radical esophagectomy and adjuvant chemotherapy (17). In patients with ESCC treated by surgery alone, body mass index (BMI) was utilized to construct a nomogram predicting long term survival (18). In patients with early onset esophageal cancer, race, and marital status were specific variables found to effect OS (19).

Like esophageal cancer, age was shown to be associated with OS in patients with colon cancer (20). In patients with colon cancer and associated liver metastasis, it was suggested that a nomogram incorporating histological type of both mucinous adenocarcinoma and signet ring cell carcinoma, along with whether the patient had either bone or lung metastasis, could effectively prognose this specific subset of patients (21). Li *et al.* demonstrated that T stage contributed to prognosis, followed by N stage, in patients with early onset locally advanced colon cancer (22). In addition to age, tumor size, and lung metastasis, Jin *et al.* showed that perineural invasion was correlated with OS in patients with early onset colorectal cancer (10).

In patients with locally advanced rectal cancer, Li *et al.* demonstrated how age, marital status, race, tumor size, and carcinoembryonic antigen (CEA) were significantly associated with OS and cancer-specific survival within their created nomograms (23). Wei *et al.* established seven features which were associated with OS, including BMI and nerve aggression, in patients with locally advanced rectal cancer treated with neoadjuvant therapy (24). Whereas Wei *et al.* demonstrated an association between post-operative CEA and OS, Wang *et al.* developed a nomogram identifying pretreatment CEA as independently associated with cancer specific mortality (25). Lastly, tumor deposits as an independent risk factor for OS in patients with stage III–IV rectal cancer were highlighted by Zhong *et al.* (26).

### Evaluation of existing models

Studies aiming to provide external validation of published prognostic indices are present within the literature. Lemini *et al.* compared the performance of the Roswell Park Comprehensive Cancer Center (RPCCC) calculator, Oregon Health & Science University (OHSU) calculator, along with two nomograms published by Shapiro *et al.*, and Sun *et al.* in the prognostication of esophageal cancer (27–29). Although the nomogram published by Shapiro *et al.* attained the greatest performance, no model achieved a high performance.

In patients with stage II–III colon cancer, Lemini *et al.*

estimated patient survival rates using the RPCCC, Memorial Sloan Kettering Cancer Center (MSKCC), and MD Anderson Cancer Center (MDACC) calculators (30). These indices demonstrated similar predictive capability, with the RPCCC calculator displaying the best performance followed by MSKCC and MDACC. In patients with stage II–III colon cancer, who received 5-fluorouracil (5-FU), Gill *et al.* compared Numeracy and Adjuvant, which are two web-based calculators utilized to predict the benefit of adjuvant 5-FU (31). Bardia *et al.* also compared both Numeracy and Adjuvant in their capabilities to estimate benefits in disease free survival (DFS) and OS when comparing three different post-surgical therapy choices, specifically observation, 5-FU and folinic acid/fluorouracil/oxaliplatin (FOLFOX) (32).

The MSKCC and MDACC are two readily available online calculators. To demonstrate the clinical utility of these tools, we compared the predicted 5-year survival rates of both calculators in 8 randomly identified patients with history of colon cancer, the majority of which were stage IIA (n=5), who were treated at Mayo Clinic Florida 5 years ago. All patients with stage IIA disease were alive at 5 years follow up. In each of these patients, the MDACC calculator predicted higher 5-year OS. Interestingly, in patients with stage III disease (n=2), the MSKCC performed better at predicting OS. One patient with stage 4 disease in our cohort had a 14% and 87–90% predicted 5-year OS, when utilizing the MSACC and MSKCC calculators, respectively. This patient was still alive at 5 years. This difference may be explained by the incorporation of lymph node staging in the MSKCC calculator, but it demonstrates that there are also limitations of using these calculators in real world prognostication. Nonetheless, these tools are overall accurate, and can help give patients some reassurance when discussing treatment plans and expected outcomes.

Authors have also attempted to validate their own developed calculators against already established indices. For example, Duan *et al.* reported that their nomogram better predicted OS when compared to the TNM staging system in patients with ESCC following radical esophagectomy and adjuvant chemotherapy (17). The indicators utilized in the construction of this nomogram were gender, tumor length, T stage, N stage, and number of chemotherapy cycles. Three hundred and twenty-eight and 76 patient internal and external validation cohorts were designed, respectively. Similarly, Shao *et al.* showed how their prognostic nomogram displayed superior predictive capability when compared to the 6<sup>th</sup> and 7<sup>th</sup> American Joint

Committee on Cancer (AJCC) TNM classifications when predicting survival in patients with resectable thoracic ESCC (33). Grade, T Stage, Modified N Stage, C-Reactive protein/albumin (CRP/Alb) ratio and neutrophil-lymphocyte ratio (NLR) were variables used in this nomogram. Primary and validation cohorts consisted of 633 and 283 patients, respectively. Weiser *et al.* compared their developed calculator versus both the AJCC or neoadjuvant rectal (NAR) score, reporting more individualized estimates of recurrence free survival (RFS) and OS by the calculator produced by the authors after evaluating 1,400 patients with stage II and III rectal cancer treated with chemoradiation, surgery and adjuvant chemotherapy (34). Specific to RFS, the prognostic variables utilized were AJCC postoperative pathologic tumor (ypT) category, number of positive nodes, distance from the anal verge (or DTAV, in cm), and whether venous invasion or perineural invasion were present. The nomogram created for OS differed only by the addition of age as a variable. Diao *et al.* developed a novel calculator which demonstrated to have better discriminative power over both the Surveillance, Epidemiology, and End Results (SEER) stage and 8<sup>th</sup> AJCC TNM staging classification when predicting OS in patients with rectal squamous cell carcinoma (11). This nomogram utilized age, marital status, T stage, M stage, surgery (local excision/partial proctectomy *vs.* total proctectomy *vs.* no surgery), and both history of concurrent chemotherapy and radiation therapy as variables. Five hundred and thirty-four and 272 patients made up their training and validation set, respectively. It is important to note that due to the retrospective nature of these predictive tools, no specific power calculation was used to identify the number of patients needed to construct these tools. However, this was a common approach among each study and was a generally accepted limitation.

### ***Biomarkers as independent prognostic indicators***

The emphasis on establishing biomarkers in cancer prognostication has grown in recent years. Specific to esophageal cancer, overexpression of microRNA (miRNA) signatures, such as hsa-miR-186-5p and has-let-7d-5p were shown to be independently associated with a poor prognosis in patients with esophageal adenocarcinoma and ESCC, respectively (35). Additionally, it has been demonstrated that specific methylation markers could accurately estimate prognosis in patients with esophageal cancer (36). Yang *et al.* completed a review of the recent advances in prognostic biomarkers, which highlighted both how liquid

biopsies have shown high accuracy and specificity, and the importance of epigenetic markers in the prognostication of esophageal carcinoma (37).

As it pertains to colon cancer, mismatch repair (MMR) status is a well-discussed biomarker for prognostication. Zaanen *et al.* reported that MMR status remains a significant variable for prognosing DFS in patients with stage III colon cancer who are treated with adjuvant FOLFOX chemotherapy (38,39). In contrast, Kim *et al.* demonstrated that MMR status, in addition to p53 positivity were not significantly associated with outcomes in patients with stage II, III and IV colon cancer with R0 resection following adjuvant FOLFOX therapy (40). In addition to MMR status, tumor associated macrophages have been investigated as prognostic biomarkers in colon cancer. Feng *et al.* demonstrated that high cluster of differentiate 206/cluster of differentiate 68 (CD206/CD68) ratio was significantly associated with poor DFS and OS (41).

Regarding rectal cancer, lymphocyte count  $\times$  albumin concentration (LA) was shown to be significantly associated with both OS and RFS in patients with stage II and III disease (42). In patients with mid to lower rectal cancer, mesorectal fat area (MFA) greater than or equal to 10 cm<sup>2</sup> was demonstrated to be an independent biomarker for predicting DFS in patients who underwent curative intent surgery when compared to patients with MFA less than 10 cm<sup>2</sup> (43). Platelet to lymphocyte and lymphocyte to monocyte ratio have also been shown to be independent prognostic factors for OS in patients with locally advanced rectal cancer following neoadjuvant chemoradiation therapy (44).

### **Conclusions**

In conclusion, our review provides a focused overview of indices utilized in the prognostication of patients with GI cancer. Nomograms play a key role in predicting patient outcomes, along with unroofing specific patient-related variables which may be associated with survival. Additionally, our review highlights comparisons made between existing prognostic indices. Lastly, we shed light on recently investigated biomarkers with proven potential as independent prognostic indicators. Despite the tremendous effort in developing predictive indices and establishing biomarkers reliable in evaluating patients with GI cancers highlighted in this report, none were considered faultless, and thus should not be expected to produce perfect and consistent results when applied to all patients presenting

with a specific GI malignancy. As the rate of molecular profiling of patient cancer cells increases, we advocate for the combination of biomarkers with demographic and pathological data into nomograms, with the long-term goal of greater precision and reliability for each individual patient. As we embark on the era of precision medicine, further investigation of reliable prognostic indices and biomarkers is needed.

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## Footnote

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