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Retrospective Study

Elderly patients over 80 years undergoing colorectal cancer resection: Development and validation of a predictive nomogram for survival

Elderly CRC Resection Survival Nomogram

Abstract

BACKGROUND

Surgery remains the primary treatment for localized colorectal cancer (CRC). Improving surgical decision-making for elderly CRC patients necessitates an accurate predictive tool.

AIM

To build a nomogram to predict the overall survival of elderly patients over 80 years undergoing CRC resection.

METHODS

295 elderly CRC patients over 80 years undergoing surgery at Singapore General Hospital between 2018 and 2021 were identified from the American College of Surgeons – National Surgical Quality Improvement Program (ACS-NSQIP) database. Prognostic variables were selected using univariate Cox regression, and clinical feature selection was performed by the least absolute shrinkage and selection operator (LASSO) regression. A nomogram for 1- and 3-year overall survival was constructed based on 60% of the study cohort and tested on the remaining 40%. The performance of the nomogram was evaluated using the concordance index (C-index), area under the

receiver operating characteristic curve (AUC), and calibration plots. Risk groups were stratified using the total risk points derived from the nomogram and the optimal cut-off point. Survival curves were compared between the high- and low-risk groups.

RESULTS

Eight predictors: age, Charlson Comorbidity Index, body mass index, serum albumin level, distant metastasis, emergency surgery, postoperative pneumonia, and postoperative myocardial infarction, were included in the nomogram. The AUC values for the 1-year survival were 0.843 and 0.826 for the training and validation cohorts, respectively. The AUC values for the 3-year survival were 0.788 and 0.750 for the training and validation cohorts, respectively. C-index values of the training cohort (0.845) and validation cohort (0.793) suggested the excellent discriminative ability of the nomogram. Calibration curves demonstrated a good consistency between the predictions and actual observations of overall survival in both training and validation cohorts. A significant difference in overall survival was seen between elderly patients stratified into low- and high-risk groups ($P < 0.001$).

CONCLUSION

We constructed and validated a nomogram predicting 1- and 3-year survival probability in elderly patients over 80 years undergoing CRC resection, thereby facilitating holistic and informed decision-making among these patients.

Key Words: Colorectal cancer; Elderly; Nomogram; Overall survival; Prognostic; Risk stratification

Core Tip: This is the first predictive nomogram evaluating the survival outcomes among elderly colorectal cancer patients over 80 years. This nomogram has incorporated age, Charlson Comorbidity Index, body mass index, serum albumin level, the presence of metastatic disease, emergency surgery, as well as postoperative pneumonia and myocardial infarction. Our study is the first to link these variables together in predicting overall survival in elderly colorectal cancer patients over 80 years. This novel nomogram that accurately predicts survival probabilities may facilitate preoperative treatment decisions in the advancing age group.

INTRODUCTION

The world's population is rapidly aging, with currently over 84 million people aged 75 and above[1]. Population aging will impact cancer control, as around 50% of all cancers affect the older population[2]. Colorectal cancer (CRC) is the second most prevalent malignancy, with an incidence of 1.36 million cases yearly[3]. CRC is the third leading cause of cancer-related mortality, with 50% of new CRC diagnoses being made in patients aged over 70, and 20% in those over 80 years[4]. In Singapore, the incidence of CRC has risen over the last four decades and is now the most common malignancy in the country[5].

Surgery remains the primary treatment for localized CRC. With increasing life expectancy and advances in surgical techniques, there is a growing number of elderly patients over 80 years undergoing CRC resection nowadays[6]. Besides the technical considerations of surgical resectability of the primary CRC, elderly patients continue to pose challenges for the surgeon, as they often have significant comorbidities, such as cardiovascular or pulmonary diseases, which would increase operative risks and potentially lead to postoperative morbidity and mortality[6-8]. Other factors, such as emergency presentation[9] and poor nutritional status, may also result in adverse perioperative outcomes and overall survival (OS).

Therefore, for elderly CRC patients over 80 years, a more individualized approach is essential in the decision-making process, weighing the risks and benefits of surgery on a case-by-case basis[10, 11]. Although some studies have suggested that advanced age is a risk factor following specific surgical procedures[12-14], certain results are procedure-specific and limited to the experiences of single centers. Moreover, no study has fully established the impact of advanced age and clinical risk factors on the probability of survival at one year or longer among elderly patients undergoing CRC resection[15-17].

In this study, we developed and validated a predictive nomogram to quantify the probability of overall survival at one and three years among elderly CRC patients over 80 years, to enable patients, caregivers, and surgeons to make better-informed decisions.

MATERIALS AND METHODS

Patient selection

This study was approved by our institutional review board (IRB No. 2022/2438). Data from the American College of Surgeons – National Surgical Quality Improvement Program (ACS-NSQIP) Participant User File between 2018 and 2021 were analyzed. Colectomy and proctectomy procedures were identified by the current procedural terminology (CPT) codes. A total of 295 elderly patients aged over 80 years with stage I-IV CRC who underwent surgery at Singapore General Hospital during the study period were included. Of these, 60% of cases were randomly selected into the training cohort to construct the nomogram. The remaining 40% of cases were used to validate the nomogram.

Clinical feature selection

Clinical variables from NSQIP database were: age, American Society of Anesthesiologists (ASA) classification, body mass index (BMI), chronic disease history, preoperative medical conditions, serum albumin level, surgical information, tumor-

node-metastasis (TNM) staging, postoperative complications, and 30-day mortality. Diagnosis information was collected from our electronic health record system (Sunrise Clinical Manager version 5.8, Eclipsys Corp., Atlanta, GA, USA). Charlson comorbidity index (CCI) was calculated based on a patient's diagnosis using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes. The primary endpoint was overall survival (OS), which was defined as the time from surgery completion to death of all causes or to the date of the last outpatient clinic follow-up in 2022. Patients who were alive at the time of the last follow-up were censored. Clinical features for constructing a nomogram were screened in three steps. Clinical perspective was the most critical consideration for variable screening. Based on our clinical experiences, we first selected those confirmed factors with a strong association with OS. Secondly, univariate Cox regression was used to identify variables statistically associated with OS. The list of candidate clinical features is presented in **Supplement Table 1**. Variables with a *P* value < 0.20 of univariate analysis were selected. Lastly, the least absolute shrinkage and selection operator (LASSO) regression algorithm was employed to screen all selected features. The 10-fold cross-validation was used to confirm the significant clinical variables and optimal tuning parameter (λ) of LASSO Cox regression.

Nomogram construction and evaluation

The nomogram was constructed using clinically significant risk factors identified in the univariate and multivariate Cox proportional hazards analyses and important features recommended by LASSO. The 1- and 3-year OS probabilities were predicted by the nomogram. The performance of the nomogram was evaluated using the concordance index (C-index) and area under the receiver operating characteristic (ROC) curve (AUC)[18]. Similar to AUC, the C-index quantified the discrimination performance of the nomogram. C-index and AUC values ranged from 0 to 1, with 0.5 representing random chance and 1.0 indicating a perfect fit. Values greater than 0.7 suggested a reasonable and accurate model prediction. Calibration curves based on the bootstrap re-sampling

method were used to assess the goodness-of-fit of the nomogram[19]. Calibration was determined by comparing the 1- and 3-year OS probabilities predicted by the nomogram to the observed OS probabilities.

Nomogram to predict overall survival and stratify risk groups

The total risk points for each elderly CRC patient were computed using the nomogram. The optimal cut-off risk point was determined by the "*survivalROC*" model using the Kaplan-Meier estimator[20]. A time-dependent survival ROC curve was plotted to evaluate the prediction of OS based on the total risk points. All elderly patients were stratified into low- and high-risk groups according to the optimal risk threshold. Survival curves of low- and high-risk groups were generated with a hazard ratio (HR) and the *P* value of the log-rank test.

Statistical analysis

All statistical calculations were performed using R programming language (version 4.2.1). Continuous variables were shown as median (interquartile range [IQR]). Categorical variables were presented as frequency distributions (percentage). The Wilcoxon-Mann-Whitney and χ^2 or Fisher's exact tests were used to analyze continuous and categorical variables, respectively. *P* values of < 0.05 indicated statistical significance.

RESULTS

Clinical and surgical characteristics

The baseline demographic, clinicopathologic, and surgical characteristics of 295 elderly CRC patients are shown in **Table 1**. All patients were randomly divided into a training cohort (n = 177) and a validation cohort (n = 118) in a ratio of 6:4. The median duration of follow-up was 22.68 (IQR: 13.54–37.00) months for the entire cohort. In total, there were 135 male patients (45.8%) and 160 female patients (54.2%) with a median age of 83 (IQR: 81–86) years. 269 patients (91.2%) were between 80 and 89 years old, whereas 26

(8.8%) were nonagenarians. The training and validation cohorts possessed nearly identical characteristics ($P > 0.05$), with the proportion of patients with significant comorbidities, including congestive heart failure and diabetes mellitus, similar between both groups. Within the entire study cohort, 206 patients (69.8%) underwent surgery on an elective basis. Minimally invasive approach (MIS) was used for 160 patients (54.2%), while the remaining 135 patients (45.8%) underwent open surgery. Right hemicolectomy was performed in 110 patients (37.3%), and anterior resection was performed in 138 patients (46.8%). No stoma formation was required in 205 patients (69.5%). The majority of patients in the study cohort had non-metastatic disease (94.2%, $n = 278$), with the largest proportion having stage III disease (43.7%, $n = 129$). None of the patients received adjuvant chemotherapy. In terms of perioperative outcome, 19 patients (6.4%) developed postoperative pneumonia, and 6 patients (2.0%) had an anastomotic leak. The perioperative 30-day mortality was 2.0%.

Nomogram feature selection
All candidate clinical features with their univariate Cox regression P values are listed in **Supplement Table 1.** According to univariate analyses, 19 variables with P values < 0.20 were statistically associated with OS. CCI, serum albumin, TNM staging, postoperative pneumonia, and postoperative myocardial infarction were most significantly associated with OS ($P < 0.001$). All these 19 characteristics were then evaluated as potential predictors. A LASSO regression was employed to assess prognostic factors, and eight variables (age, CCI, BMI, priority of operation, serum albumin, TNM staging, postoperative pneumonia, and postoperative myocardial infarction) with nonzero coefficients were retained in the LASSO regression (**Figure 1**). The optimal tuning parameter log (λ) was 0.056 when the mean square error (MSE) reached its smallest value. **Table 2** shows the eight variables ultimately selected for the multivariate Cox model. Age ($P = 0.002$), BMI (< 18.5 kg/m², $P = 0.038$), serum albumin (< 2.5 g/dL, $P = 0.002$), CCI ($P < 0.001$), postoperative pneumonia ($P = 0.004$), and postoperative myocardial infarction ($P = 0.012$) were determined to be independent

predictors of OS. Although every increase of one year in age was associated with a 10% increase in the risk of mortality (HR = 1.10, 95%CI: 1.04–1.17), there was no significant difference in OS between nonagenarians (90–99y) and those aged 80–89y (*P* = 0.470). Two additional variables, TNM staging (stage IV, *P* = 0.068) and priority of operation (emergency surgery, *P* = 0.278), were relevant clinical factors significantly associated with OS on univariate analyses and hence included in the nomogram construction.

Nomogram construction and validation

A nomogram applicable to all elderly CRC patients was created using eight selected predictors' point scales, with the sum of the eight variables' points defining the total number of points. Estimated 1- and 3-year OS probabilities could be obtained by drawing a vertical line from the "Total Points" axis down to the two-outcome probability axis (**Figure 2**). The AUC of the nomogram for predicting 1-year OS was 0.843 (95%CI: 0.827–0.935) in the training cohort and 0.826 (95%CI: 0.816–0.912) in the validation cohort, while AUC for predicting 3-year OS was 0.788 (95%CI: 0.762–0.889) in the training cohort and 0.750 (95%CI: 0.734–0.883) in the validation cohort (**Figure 3**). The C-index value was 0.845 (95%CI: 0.789–0.889) in the training cohort and 0.793 (95%CI: 0.754–0.887) in the validation cohort. Both AUC and C-index values indicated the constructed nomogram provided favorable discrimination. The calibration curves of the nomogram were evaluated by plotting the predicted 1- and 3-year OS against the observed 1- and 3-year OS. A 45-degree line would be obtained if the predictions were accurately calibrated. The 1- and 3-year calibration curves in both training and validation cohorts showed a good concordance between the predicted and observed OS probabilities (**Figure 4**).

Nomogram prediction of overall survival in risk-stratified elderly CRC patients

The total risk points of each elderly CRC patient were calculated based on the nomogram. The optimal risk cut-off point of 81 was determined using the Kaplan-Meier estimation[20]. On the nomogram, the risk threshold of 81 points approximately

corresponded to the 1-year OS probability of 87% and the 3-year OS probability of 56%. A time-dependent 3-year survival ROC curve was generated for all patients using the total risk points computed by the nomogram (**Figure 5A**). The AUC of the total risk points (0.769, 95%CI: 0.724–0.883) indicated that the optimal risk threshold was adequate for risk stratification in elderly CRC patients. All patients were categorized into low-risk (total risk points < 81) or high-risk (total risk points ≥ 81) groups. The Kaplan-Meier curves accurately distinguished the low- and high-risk groups (**Figure 5B**). The 3-year OS probabilities of elderly CRC patients in the high-risk groups were significantly lower (HR = 6.58, 95%CI: 4.06–10.7, $P < 0.001$).

DISCUSSION

Increasing age is a well-known risk factor for the development of CRC, with a majority of patients diagnosed after 70 years old[21]. Moreover, elderly patients tend to have a higher prevalence of frailty, comorbidities, and mortality risk from other causes[22]. Nevertheless, there is still significant heterogeneity in terms of physiological capacity and performance status among the elderly population. Considering the increased life expectancy of an aging population as well as new advances in surgical technology and perioperative care, it is, therefore, necessary to stratify the risk associated with elderly patients undergoing surgery. As the proportion of elderly CRC patients continues to rise, there is a greater need to comprehend the risks associated with surgical resection.

In the present study, we developed and validated a nomogram based on clinical risk factors predicting the probabilities of 1- and 3-year OS in elderly CRC patients over 80 years undergoing surgical resection using the ACS-NSQIP data. Although there are existing nomograms[23, 24] predicting cancer-specific and OS among CRC patients, this is the first predictive nomogram evaluating the survival outcomes among elderly CRC patients over the age of 80. Our ACS-NSQIP dataset was comprehensive and well-organized, allowing us to obtain critical clinical data regarding the association between risk factors and OS after colorectal resection. We identified eight variables as independent prognostic factors based on clinical observations and LASSO regression,

which efficiently processed demographic and clinical feature selection as a statistical strategy for high-dimensional data.

This nomogram incorporated age, CCI, BMI, serum albumin level, TNM staging, priority of surgery, postoperative pneumonia, and postoperative myocardial infarction. Some characteristics included in the nomogram construction have previously been reported to have a significant correlation with mortality and OS, but our study is the first to link them together in predicting OS in elderly CRC patients over 80 years. We found that every additional year of age beyond 80 was associated with a 10% increase in mortality risk. In terms of the comorbidity profile, an increase of one point in the CCI score was associated with a 41% increase in mortality risk. Of note, CCI has been reported as an independent prognostic factor in older CRC patients[25]. Elderly CRC patients with high CCI scores tended to have a lower OS[25]. In addition, surgical outcomes of the geriatric population have been stratified using frailty assessments involving age and CCI[26, 27]. A systematic review revealed that frailty was associated with an increased incidence of postoperative complications, mortality, readmissions, reoperations, and prolonged hospital length of stay, but age by itself was not associated with any adverse outcomes[28]. Suboptimal nutritional status reflected by BMI < 18.5 kg/m^2 and serum albumin level < 2.5 g/dL were also independent risk factors for poorer OS. It has been reported that lower BMI and serum albumin levels were nutritional risk factors associated with shorter survival in cancer patients[29, 30]. Lymph node metastasis is another risk factor for OS. It is well-known that lymph node metastasis is associated with worse outcomes in CRC patients with poor prognoses[31]. Emergency surgery was identified to be significantly associated with poorer OS in our elderly CRC cohort. Among the 17 elderly patients with stage IV disease who underwent colorectal cancer resection, 12 had surgery performed in an emergency setting. Some studies have highlighted the need for improved risk stratification based on emergency because surgeries performed urgently are more likely to have distinct morbidity and mortality rates than surgeries performed electively[32, 33].

In this study, MIS was found to have a positive impact on OS in elderly CRC patients in the univariate Cox regression (P = 0.01). The LASSO regression, however, eliminated the method of operation, indicating that it was not a predictor of OS in CRC patients over 80 years undergoing surgery. The majority (90.6%) of the 160 elderly patients in the MIS group underwent laparoscopic surgery, whereas 15 patients (9.4%) underwent robotic surgery. Laparoscopic surgery for colon cancer has been shown to be associated with improved postoperative outcomes with similar long-term oncological outcomes in recent years[34, 35]. It has been recommended as the preferred approach for elective surgery[36]. While the long-term oncological outcomes of laparoscopic rectal cancer surgery have yet to be conclusive, it does confer improved postoperative outcomes and has been included in society guidelines to be considered in centers with technical expertise and experience. Although laparoscopic surgery is associated with superior postoperative outcomes such as reduced wound pain and ileus, without compromising long-term oncological outcomes[37-39], its role among elderly patients remains unclear given the longer operating time and the effect of pneumoperitoneum on the cardiorespiratory system.

Elderly patients, after surgery, are at increased risk of postoperative complications such as surgical site infections, pneumonia, cardiac complications, and anastomotic leak. In our study cohort, primary anastomosis was performed in 69.5% of the patients. There were 6 cases (2.03%) had the postoperative anastomotic leak. These findings are consistent with other recent studies. Hashimoto *et al.*[40] reported an anastomosis rate of 86.0% with a leak rate of 2.3%, while Zeng *et al.*[41] reported an anastomosis rate of 62.9% with a leak rate of 2.1%. Furthermore, it has been estimated that a patient older than 80 years is more than five times as likely to suffer from postoperative pulmonary complications compared to a patient younger than 50 years[42]. Unsurprisingly, postoperative pneumonia and myocardial infarction were identified as prognostic factors of OS in elderly CRC patients. Therefore, the identification of elderly patients at risk of postoperative cardiopulmonary complications can facilitate the early involvement of the multidisciplinary team in pre-

habilitation and postoperative care, including adequate pain control, chest physiotherapy, and early mobilization. In line with our predictive nomogram, the successful mitigation of postoperative pneumonia and myocardial infarction risks can result in higher probabilities of improved OS at one and three years among elderly patients undergoing CRC resection.

We consolidated the eight selected predictors into the nomogram and evaluated the performance using bootstrapping and cross-validation methods in calculating AUC, C-index, and calibration curves. Both AUC and C-index values were replicated well in the training and validation sets. The calibration curves of 1- and 3-year OS in both sets displayed favorable agreement between the predicted and observed survival probabilities. We further stratified elderly CRC patients into low- and high-risk groups according to their total risk points and optimal threshold values. The Kaplan-Meier method and Cox proportional hazards model revealed statistically significant differences between the two risk groups in terms of OS. Our results demonstrate that the nomogram accurately identifies the high-risk population and predicts OS, thereby facilitating appropriate clinical decision-making. It provides a distinct visual representation that enables information sharing between clinicians and patients. For example, it is clear that advanced age is not the only predictive factor influencing OS. In addition, an elderly patient in the high-risk group with multiple comorbidities and poor nutrition, may benefit from a period of pre-habilitation and optimization prior to CRC resection.

Our study has some limitations, including its retrospective nature and selection bias. First, elderly CRC patients who are physically fit are more likely to undergo surgery. In our study cohort, octogenarians comprised a more significant percentage (91.2%) than nonagenarians. Nevertheless, the primary data was complete with a median follow-up duration of 22.68 mo. Secondly, our data were limited in size and derived from a single institution, which may limit the generalizability of the nomogram. Despite these limitations, the ability of our constructed nomogram to accurately predict survival probability in elderly CRC patients over 80 years undergoing colorectal

resection has substantial clinical implications. In this advancing age group, it is challenging to make management decisions in light of the risks associated with surgery. Therefore, the application of the nomogram lies in its capacity to guide the individualization of clinical decisions in complex scenarios.

CONCLUSION

In summary, colorectal surgery in elderly CRC patients is associated with a lower likelihood of survival. We used data from ACS-NSQIP to construct and validate an original nomogram for the postoperative survival of elderly CRC patients over 80 years. By accurately predicting 1- and 3-year survival probabilities, our novel nomogram, which incorporated age, CCI, BMI, serum albumin level, distant metastasis, emergency surgery, postoperative pneumonia, and postoperative myocardial infarction, may facilitate preoperative clinical decisions for patients, caregivers, and clinicians.

ARTICLE HIGHLIGHTS

Research background

Colorectal surgery is associated with a decreased probability of survival in elderly cancer patients. Several factors can affect the postoperative survival of elderly colorectal cancer (CRC) patients.

Research motivation

A precise predictive tool is required to enhance the decision-making process for elderly CRC patients undergoing colorectal resection.

Research objectives

To construct and validate a nomogram to predict the overall survival of elderly CRC patients over 80 years undergoing colorectal surgery.

Research methods

This retrospective study included 295 elderly CRC patients over 80 years undergoing colorectal resection. Variables were selected using regression methods, and a nomogram for 1- and 3-year overall survival was constructed from 60% of the cohort and validated on the remaining 40%. The performance of the nomogram was evaluated using various metrics, and the risk group was stratified based on the risk points of the nomogram.

Research results

The nomogram, which comprised age, comorbidities, body mass index, serum albumin level, distant metastasis, emergency surgery, postoperative pneumonia, and postoperative myocardial infarction, demonstrated excellent discriminative ability and consistency between predictions and actual observations. The risk group was stratified based on the nomogram's risk points, and a significant difference in overall survival was observed between low- and high-risk groups.

Research conclusions

This novel nomogram provides a valuable tool for informed decision-making in elderly CRC patients undergoing colorectal resection.

Research perspectives

We developed a nomogram using demographic and clinical variables to estimate the survival of elderly CRC patients undergoing colorectal surgery. This nomogram may guide treatment decisions, facilitate patient counseling, and enhance surgical outcomes.

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