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Retrospective Study

Epidemiologic characteristics and risk factors associated with overall survival for patients with mucinous colorectal cancer: a population-based study

Epidemiology and survival of mucinous CRC

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Abstract

BACKGROUND

Mucinous adenocarcinoma (MC) has attracted much attention as a distinct histologic subtype of colorectal cancer in recent years. However, data about its epidemiologic and prognostic characteristics are limited. Therefore, patient data extracted from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program were collected to analyze the epidemiologic and clinicopathological characteristics of MC.

AIM

We conducted a population-based analysis of the epidemiologic and clinicopathological characteristics of MC.

METHODS

The incidence trend of MC was calculated through the Joinpoint Regression Program. Cox regression analyses were performed to identify prognostic factors associated with

overall survival (OS). A nomogram was established to predict the survival probability of individual patients with MC.

RESULTS
We found that rates of MC decreased from 4.50/100,000 in 2000 to 1.54/100,000 in 2018. Rates of MCs in patients aged ≤50 years decreased 2.27%/year during 2000–2018. The incidence of appendiceal MCs increased from 0.14/100,000 in 2000 to 0.24/100,000 in 2018, while the incidence in other anatomic subsites continued to decrease. On multivariable Cox analyses, age, race, tumor site, T stage, N stage, M stage, surgery, and chemotherapy were associated with OS. A nomogram was developed based on these factors, and the area under the curve for 1-, 3-, and 5-year OS in the training cohort was 0.778, 0.778, and 0.768, respectively.

CONCLUSION
Our results demonstrated that MC incidence decreased in almost all anatomic subgroups except for the appendix. A nomogram predicting the survival probability of patients with MCs showed good performance.

Key Words: Mucinous adenocarcinoma; Colorectal cancer; Epidemiology; Prognostic factor; Nomogram; SEER database

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Core Tip: The incidence of mucinous colorectal cancer (CRC) decreased in both young and older patients, which may play a role in the formation of guidelines on screening for CRC. When stratified by anatomic location, incidence rates declined in almost all

anatomic subgroups except for mucinous adenocarcinoma (MC) in the appendix. Hence, clinicians should also pay attention to the increasing incidence of appendiceal MC. During the survival analysis, we found that age, race, tumor site, surgery, and chemotherapy were significantly associated with survival. A nomogram based on those factors as well as the tumor, node, and metastasis (TNM) tumor stages showed good predictive performance, which indicated that in addition to the TNM stages, characteristics such as tumor site, age, and race were also important in developing individualized treatment plans for patients with mucinous CRC.

INTRODUCTION

Colorectal cancer (CRC) is the third most frequent cancer and ranks second with respect to cancer-related mortality worldwide[1]. Mucinous adenocarcinoma (MC), defined as having more than 50% tumor component of extracellular mucin, is a distinct histologic subtype of CRC and accounts for 5%–15% of CRC cases[2,3]. Mucinous adenocarcinoma differs from nonmucinous colorectal cancer in terms of clinicopathological characteristics and genetic features. Compared with nonmucinous colorectal cancer, mucinous CRC is more often diagnosed at advanced stages and more commonly found in younger and female patients[3,4]. In view of the increasing incidence of young-onset CRC[5], there is an interest in determining whether the incidence of MC continues to increase because MC is more commonly diagnosed in younger patients. However, there are limited and antiquated epidemiologic data for mucinous colorectal cancer.

To date, the prognostic significance of MC remains controversial. Few studies have determined the prognostic risk factors that are associated with the overall survival (OS) of mucinous CRC. Currently, the tumor, node, metastasis (TNM) staging system created and updated by the American Joint Committee on Cancer and the International Union Against Cancer serves as the standard to evaluate cancer status and is the main method to assess the prognosis of cancer patients. However, other elements, such as age, sex, race and ethnicity, and primary tumor site, probably play a role in predicting the prognosis of cancer patients[6,7]. Considering the limitations of the TNM staging system,

nomograms have emerged and have been widely used as a simpler but more sophisticated method, given that nomograms could integrate diverse prognostic variables into the model from biological to clinicopathological characteristics[8].

Therefore, in the present study, we conducted a population-based analysis of the epidemiologic and clinicopathological characteristics of mucinous CRC on the basis of data extracted from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program and developed a nomogram to predict the 1-, 3-, and 5-year OS of patients with mucinous CRC.

MATERIALS AND METHODS

Study design and population

This is a retrospective cohort study based on data collected from 18 cancer registries in the SEER Program, which covers approximately 27.8% of the U.S. population. This study is reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology statement. Two researchers conducted the data collection process independently to avoid potential selection bias. The review and informed consent were exempted by the institutional review board for the use of a freely available database.

Patients were enrolled with the following criteria: diagnosed with mucinous CRC according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) and receiving a diagnosis between 2000 and 2018. Patients with preexisting malignant tumors were excluded. To ensure a follow-up time of at least 3 years, only those patients diagnosed between 2010 and 2015 with complete medical records and sufficient survival data (of complete follow-up and a survival >1 mo) documented were included in the construction of the nomogram model to predict OS. The study design is presented in Figure 1.

Variable evaluation and definition

Because of their potential association with OS, the following clinicopathological characteristics were converted into categorical variables and analyzed: age, sex, race

(White, Black, Asian and Pacific Islander, and American Indian and Alaska Native), tumor site, primary tumor size, grade (well differentiated, moderately differentiated, poorly differentiated, and undifferentiated), disease stage (localized, regional, and distant according to SEER staging system), TNM stage derived from AJCC staging system 7th edition, surgery, radiation, and chemotherapy. Notably, tumors fell into 4 anatomic categories: proximal colon (cecum, ascending colon, and hepatic flexure), transverse colon, distal colon (splenic flexure, descending colon, sigmoid colon, and rectosigmoid junction), and rectum.

Statistical analysis

Incidence rates were age-adjusted to the 2000 U.S. population and acquired by using SEER*Stat software (version 8.4.0.1). Joinpoint Regression Program (version 4.9.1.0) was used to identify yearly trends in annual percent change (APC) in rates. The tool calculated the APC with data fitted to the simplest joinpoint regression model and tested the significance using a Monte Carlo permutation method.

The outcome of interest was OS, defined as the time period that elapsed from diagnosis to death of any cause or the last follow-up. Patients were randomly divided into 7:3 training (n = 4379) and validation (n = 1877) groups using the R program (version 4.2.1, www.r-project.org). Univariate and multivariate Cox proportional hazards regression analyses were performed to identify prognostic factors associated with OS, with hazard ratios (HRs) and 95%CIs being calculated. The analyses were conducted with SPSS, version 27 (IBM Corp). A nomogram was constructed to predict 1-, 3-, and 5-year OS probability based on those factors identified by multivariable Cox regression analysis.

The concordance index (c-index) and area under the receiver operating characteristic curve (AUC) were calculated to evaluate the predictive accuracy of the nomogram. The calibration curve was plotted to determine how far the predicted survival was from the actual survival. Kaplan–Meier survival curves were used to present overall survival, and differences were compared using the log-rank test. The "rms", "Survival",

"survivalROC", and "foreign" packages of R were used in the construction and verification of the nomogram. Statistical significance was defined as a 2-tailed *P* value less than 0.05.

RESULTS

Patient characteristics

From 2000 to 2018, a total of 45481 patients with mucinous colorectal cancer were identified, with a median age of 68 years at diagnosis (interquartile range, 57-78). Among them, 81.6% were White patients, 11.2% were Black patients, 6.3% were Asian or Pacific Islander patients, and 0.5% were American Indian and Alaska Native patients (Table 1). Women made up a slightly greater proportion of those cancer cases (51.7% compared to 48.3% for men). For primary tumor sites of these mucinous CRC cases, the proximal colon was most commonly involved (45.5%), followed by the distal colon (24.3%), rectum (11.3%), appendix (7.9%), and transverse colon (7.7%). Of 38970 mucinous CRCs with a known grade, 5051 were well differentiated (11.1%), 25253 were moderately differentiated (55.5%), 7703 were poorly differentiated (16.9%), and 963 were undifferentiated (2.1%). Among 44818 mucinous CRCs with a known stage, 11973 were localized (26.3%), 21436 were regional (47.1%), and 11407 were distant (25.1%).

The age-adjusted incidence of colorectal mucinous adenocarcinoma

The overall age-adjusted incidence of CRC decreased from 44.56/100,000 in 2000 to 29.65/100,000 in 2018, with the steepest decline observed between 2016 and 2018 (APC = -3.1, *P* = 0.06). The rates of mucinous CRC also showed a downward trend over the entire period, decreasing from 4.50/100,000 in 2000 to 1.54/100,000 in 2018. For CRC patients aged younger than 50 years, i.e., early-onset CRCs, the incidence rate increased 1.49% per year during 2000–2013 and 5.57% per year during 2013–2016 before declining insignificantly during 2016–2018. In contrast to that upward trend, rates of mucinous CRCs in patients younger than 50 years decreased 2.27% per year during 2000–2018

(Figure 2). Of all CRC cases, the proportion of mucinous adenocarcinoma decreased similarly during the same period, from 10.1% in 2000 to 5.1% in 2018 (Figure 3).

With regard to the sex of patients with mucinous CRC, the incidence rates of male and female patients both decreased significantly over time, with rates decreasing from 4.80/100,000 in 2000 to 1.64/100,000 in 2018 for men and from 4.22/100,000 to 1.43/100,000 for women. With respect to the race and ethnicity of patients, the age-adjusted incidence rates of mucinous CRC decreased from 4.60/100,000 in 2000 to 1.56/100,000 in 2018 among the white population and from 4.88/100,000 to 1.68/100,000 during the same period among the black population. The rates for the American Indian and Alaska Native population and the Asian or Pacific Islander population also decreased, with APCs of 6.70 and 5.51, respectively (Supplementary Figure 1).

When stratified by age, declining incidence rates of mucinous CRC were observed among all age groups. The highest mucinous CRC rate was observed in patients aged ≥70 years, which fell from 26.96/100,000 in 2000 to 7.36/100,000 in 2018, with the steepest drop occurring during 2004–2007. In the 55–69-year-olds, mucinous CRC rates decreased from 10.66/100,000 to 3.27/100,000 during the entire period, with the steepest drop occurring during 2005–2009. Rates decreased 2.72%/year from 2.73/100,000 in 2000 to 1.72/100,000 in 2018 in the 40–54-year-olds and decreased 1.83%/year from 0.36/100,000 to 0.25/100,000 in the 15–39-year-olds. With regard to rates of mucinous CRCs in different anatomic subsites, mucinous adenocarcinoma was most commonly observed in the proximal colon, followed by the distal colon and rectum. The rates of mucinous CRCs in the proximal colon decreased 6.5%/year from 2.14/100,000 in 2000 to 0.66/100,000 in 2018. The rates of mucinous CRCs in the distal colon decreased from 1.20/100,000 in 2000 to 0.34/100,000 in 2018, with the steepest drop occurring during 2005–2008. The incidence of mucinous CRCs located in the transverse colon and rectum also showed a downward trend, presenting a sharp contrast to the increasing incidence of appendiceal mucinous adenocarcinoma, which increased from 0.14/100,000 in 2000 to 0.24/100,000 in 2018 (Figure 4).

Univariate and multivariate Cox analyses of the risk factors for OS

A total of 6775 patients were included in this process. Among them, 4742 were randomly allocated to the training cohort, and 2033 were randomly allocated to the validation cohort (Supplementary Table 1). We performed our analysis based on the training cohort. Univariate and multivariate Cox regression models were chosen to explore the independent prognostic risk factors for 1-, 3-, and 5-year OS for patients with mucinous CRC during the follow-up. Variables found to be significantly associated with OS were further applied in the multivariate Cox regression analysis. By univariate Cox regression analysis, age, race, tumor site, tumor size, grade, disease stage, T stage, N stage, M stage, surgery, and chemotherapy were identified to be significantly associated with OS. Statistical significance of age, race, tumor site, T stage, N stage, M stage, surgery, and chemotherapy persisted during the multivariate Cox regression analysis. In particular, elderly patients (≥40 age ≤69 years: HR, 1.28; 95%CI, 1.00-1.64; ≥70 years: HR, 2.41; 95%CI, 1.88-3.08), Black patients (HR, 1.26; 95%CI, 1.11-1.43), patients with T3 stage (HR, 1.37; 95%CI, 1.03-1.83) or T4 stage (HR, 2.28; 95%CI, 1.68-3.08), patients with lymph node metastasis (N1 stage: HR, 1.72; 95%CI, 1.51-1.97; N2 stage: HR, 2.58; 95%CI 2.25-2.96), patients with distant metastasis (HR, 2.67; 95%CI, 2.01-3.55), patients without surgery (HR, 4.82; 95%CI, 3.57-6.51), and patients without chemotherapy (HR, 1.58; 95%CI, 1.42-1.76) had poorer overall survival. Compared with tumors primarily located in the proximal colon, tumors located in the distal colon were associated with poorer overall survival (HR, 1.15; 95%CI, 1.04-1.28), whereas tumors located in the appendix suggested better survival (HR, 0.58; 95%CI, 0.47-0.72). Details are presented in Table 2.

Nomogram construction and validation

A nomogram model was constructed to predict the 1-, 3-, and 5-year overall survival of patients with mucinous CRC according to multivariate Cox regression analysis (Figure 5). Each vector of these variables was assigned a point value, and the cumulative point

score of all variables for a particular individual was matched to the probability of survival. Supplementary Table 2 shows the specific value of each variable. The nomogram had a C-index of 0.730, which was internally validated with a C-index of 0.728 using the validation cohort. The AUCs of the nomogram predicting 1-, 3-, and 5-year OS were 0.778, 0.778, and 0.768, respectively. The discrimination performance was validated in the validation cohort with an AUC of 0.805 in predicting the 1-year OS, an AUC of 0.779 in predicting the 3-year OS, and an AUC of 0.760 in predicting the 5-year survival (Figure 6). Additionally, calibration curves were plotted to assess the accuracy of the nomogram model, which presented a good alignment between the nomogram prediction and the actual risk (Supplementary Figure 2).

To estimate the survival probability of patients with different levels of those factors, Kaplan–Meier survival curves were plotted. Significant decreases were observed in patients aged ≥70 years (1-, 3-, and 5-year OS rates: 84.4%, 63.7%, and 50.5%, respectively, Figure 7A), with tumors located in the distal colon (1-, 3-, and 5-year OS rates: 89.3%, 65.4%, and 50.8%, respectively, Figure 7B), Black race (1-, 3-, and 5-year OS rates: 87.5%, 66.4%, and 54.8%, respectively, Supplementary Figure 3A), and T4 stage (1-, 3-, and 5-year OS rates: 81.8%, 51.7%, and 39.8%, respectively, Supplementary Figure 3B). Patients diagnosed with N2 and M1 stage also had a lower survival probability (Supplementary Figure 3C and 3D).

DISCUSSION

In this study, by using a national and population-based dataset, we evaluated the incidence trend of mucinous CRC and then constructed a nomogram to predict its overall survival. We found that the age-adjusted incidence rate of mucinous colorectal adenocarcinoma decreased yearly from 2000 to 2018, both in male and female patients and among all age groups. However, a previous study reported that the incidence of mucinous CRC remained stable in earlier time periods, and others reported almost unchanged mucinous CRC rates in males but a slight increase in female incidence[3,9]. The incidence of overall CRC has declined in recent years, mainly because of the

enhanced practices of CRC screening and colonoscopic polypectomy[10], which could probably explain the recent decrease in mucinous CRC rates. In addition, the proportion of MCs among all CRC cases also decreased over time from approximately 10% in 2000 to 5% in 2018.

While previous studies reported that mucinous adenocarcinoma was more commonly found in younger patients than nonmucinous CRC[9,11], our results indicated that in contrast to the upward trend in the incidence of overall early-onset CRC, the incidence of early-onset CRC with a mucinous histology decreased over the study period. However, a previous study stratifying early-onset CRC incidence by histologic subtype reported that the incidence of adenocarcinoma increased in most age subgroups, with the steepest subsite increase observed in rectal adenocarcinoma, and carcinoid rate increases outpaced adenocarcinoma rates in all age groups. Hence, early-onset CRC rate increases seemed to be driven by other adenocarcinoma subtypes and rectal carcinoid tumors in place of mucinous adenocarcinoma[12].

Mucinous CRC rates stratified by anatomic subsites showed a decreasing trend among all subgroups apart from the appendix. In agreement with previous studies, our results demonstrated that the incidence of appendiceal mucinous adenocarcinoma in the U.S. has been increasing over time, partly due to the improved detection and appreciation of the disease entity[13,14].

In the present study, the results demonstrated that MCs were more commonly found in the proximal colon (45.5%). It was reported that MCs were associated with higher mucin-2 (MUC2) expression and high-frequency microsatellite instability (MSI-H), which was partly due to mutations of genes in the RAS/MAPK pathway. Furthermore, MUC2 and MSI were associated with proximal location[15,16]. In terms of tumor differentiation and the extent of disease, the largest proportion of MCs were moderately differentiated (55.5%) and were diagnosed at a regional stage (47.1%), similar to previous findings of MCs in the colon and rectum. Nevertheless, MCs in the appendix were more commonly well differentiated but most often diagnosed at a distant stage[17,18].

To date, the prognostic significance of MC remains elusive. Studies comparing the survival and prognosis of mucinous CRC and nonmucinous CRC have shown conflicting results. A few studies found that patients with mucinous CRC had a poorer prognosis than their nonmucinous counterparts[19,20], while others indicated that MC was not an independent prognostic factor[21]. Moreover, some research reported that the survival disadvantage of MC was observed only in specific anatomic subsites[22-24]. Accordingly, it seemed to portend that the prognosis of MC was associated with anatomic location. During the multivariate Cox regression analysis, we found that the primary tumor site was associated with the overall survival of patients with mucinous CRC. Compared with MCs in the proximal colon, MCs in the appendix indicated improved survival (HR, 0.58). As a previous study reported, the survival rates of gastrointestinal MC varied by anatomic location, and the best OS was observed in the appendix. When stratified by stage and grade, MCs in the appendix had better OS than those in the colon and rectum, except for grade III/IV appendiceal MC[17]. Appendiceal mucinous adenocarcinoma is currently recognized as part of appendiceal mucinous neoplasms (AMNs), which are now divided into low-grade appendiceal mucinous neoplasms (LAMNs) and high-grade appendiceal mucinous neoplasms (HAMNs). Appendiceal mucinous neoplasms arise most often from LAMNs and are relatively indolent in terms of biological behavior compared with CRC[25,26]. Given that tumor grade is an independent prognostic factor[25], the superior survival of AMNs compared with MCs in the colon and rectum was partly attributed to a greater proportion of well or moderately differentiated tumors. In addition, our findings demonstrated that compared with MCs in the proximal colon, MCs in the distal colon had poorer prognosis (HR, 1.15), discordant with previous findings that tumor location was not associated with survival differences[20,27], whereas a recent study also found that a tumor site in the left-sided colon was associated with poorer prognosis (HR, 1.16)[28]. CRC is a molecularly and clinically heterogeneous disease, and a large part of its heterogeneity is driven by anatomic location. In particular, molecular and clinical disparities were observed between CRCs in the proximal colon and in the distal

colon[29]. Further evaluation of the prognostic significance of tumor location entails studies that focus on the underlying mechanisms.

Other demographic characteristics like age and race, were also associated with patient survival. Older age at diagnosis portended poor prognosis. During the univariate Cox analysis, advanced tumor grade and disease stage indicated inferior survival but were not significantly associated with OS in multivariate Cox analysis. Surgery as a protective factor for MC patients was the most valuable factor in the nomogram, underscoring the importance of surgical treatment for patients with mucinous CRC.

There were still some limitations in our study. First, this is a retrospective study having inherent selection bias. Second, although the SEER program covers a large population, some potential prognostic factors, such as Ki-67, are not included in the database. Another limitation pertains to the accuracy of data related to appendiceal mucinous adenocarcinoma because pathologic classification and grading systems for AMNs have undergone significant changes over time. Finally, the lack of an external validation cohort limits the generalizability and application of this nomogram. Future research studying the underlying mechanisms of those prognostic risk factors is warranted.

CONCLUSION

In this population-based study, we explored the epidemiologic characteristics of mucinous CRC and found that the incidence of mucinous CRC decreased in both young and older patients. When stratified by anatomic location, incidence rates declined in almost all anatomic subgroups except for MCs in the appendix. In addition, we predicted the 1-, 3-, and 5-year OS of patients with MCs by developing a nomogram that could integrate T, N, and M stage with other fundamental characteristics, such as age, race, and primary tumor site. The nomogram model was internally validated and showed good performance.

ARTICLE HIGHLIGHTS

Research background

Mucinous adenocarcinoma (MC) is a distinct histologic subtype of colorectal cancer (CRC), which differs from nonmucinous CRC in terms of clinicopathological characteristics and genetic features.

Research motivation

There are limited data about epidemiologic characteristics of MC, and little is known about the risk factors associated with the survival rates.

Research objectives

In this study, we aimed to determine the epidemiologic and clinicopathological characteristics of mucinous CRC.

Research methods

We conducted a population-based analysis of the epidemiologic and clinicopathological characteristics of mucinous CRC on the basis of data extracted from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program.

Research results

Rates of mucinous CRC decreased from 4.50/100,000 in 2000 to 1.54/100,000 in 2018. Rates of mucinous CRCs in patients aged ≤50 years decreased 2.27%/year during 2000–2018, in sharp contrast to the upward trend in early-onset CRC. Incidence of appendiceal MCs increased from 0.14/100,000 in 2000 to 0.24/100,000 in 2018. On multivariable Cox analyses, age, race, tumor site, T stage, N stage, M stage, surgery, and chemotherapy were associated with OS. A nomogram was developed based on these factors, and the area under the curve for 1-, 3-, and 5- year OS in the training cohort was 0.778, 0.778 and 0.768, and was 0.805, 0.779 and 0.760 in the validation cohort, respectively.

Research conclusions

We found that incidence of mucinous CRC decreased both in young and older patients. However, the incidence of appendiceal MCs continued to increase. During the survival analysis, in addition to the tumor, node, and metastasis (TNM) tumor stages, we found that age, race, tumor site, surgery, and chemotherapy were also significantly associated with survival. And a nomogram based on these factors as well as the T, N, and M stages showed a good predictive performance.

Research perspectives

We lay a foundation for future research exploring the prognostic implications of mucinous colorectal adenocarcinoma.