Novel Prognostic Role of Serum CA19-9 Identified in Colorectal Terminal Tumor Site and Tubular Adenocarcinoma

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Abstract

Background: It is still illusive that the origination and contribution of different primary tumor sites in Colorectal Cancer (CRC).

Methods: A total 1039 consecutive CRC patient's profiles were collected to discover the prediction role of multiple biomarkers in this cohort study. Multiple serum biomarkers were tested and tracked during survival period. The correlation and survival analysis were applied to explore the prognostic value of clinical traits (primary tumor sites, and tumor subtypes, the incidence rate) and multiple biomarkers for forecasting patient's overall clinical.

Results: The sigmoid and rectum (73%) demonstrated the highest incidence rate among primary tumor sites (27%). Tubular adenocarcinoma, mainly rise from the terminal bowel tumor sites, has significantly worse clinical outcome, lower 5-year survival rate and shorter overall survival time. Serum level of CA19-9 was significantly positive correlated with sigmoid and rectum originated-CRC (Cor =0.88, p=2.2e-16). Higher serum level of CA19-9 (>37 U/mL) was significantly associated with terminal tumor sites, tubular adenocarcinoma and tumor with non-infiltrating. It could be applied for the precise diagnosis of CRC and terminal bowel cancer, especially in the tubular adenocarcinoma.

Results: The sigmoid and rectum (73%) demonstrated the highest incidence rate among primary tumor sites (27%). Tubular adenocarcinoma, mainly rise from the terminal bowel tumor sites, has significantly worse clinical outcome, lower 5-year survival rate and shorter overall survival time. Serum level of CA19-9 was significantly positive correlated with sigmoid and rectum originated-CRC (Cor =0.88, p=2.2e-16). Higher serum level of CA19-9 (>37 U/mL) was significantly associated with terminal tumor sites, tubular adenocarcinoma and tumor with non-infiltrating. It could be applied for the precise diagnosis of CRC and terminal bowel cancer, especially in the tubular adenocarcinoma.

Conclusions: Therefore, terminal tumor sites (sigmoid and rectum) demonstrated potential prognostic value in early screening for CRC patients. CA19-9 could be a promising biomarker for the diagnosis of terminal colorectal cancer, especially for the Tubular adenocarcinomas originated from sigmoid and rectum, and improve the clinical outcome.

Background

Colorectal cancer (CRC) is a global health threaten for all populations in the world. The incidence rate of CRC has been fast growing, leading it to be commonly death-caused cancer in the world (1, 2). Especially in the past ten years, the morbidity and mortality of CRC increased to the top ten among many types of cancers in China (3). CRC is treated as complex diseases: over 90% of colorectal carcinomas are identified as adenocarcinomas that originate from epithelial cells of the colorectal mucosa. The typically intestinal subtypes of adenocarcinoma contain tubular adenocarcinoma, mucinous adenocarcinoma, adenocarcinoma with necrosis, and mixed adenocarcinoma (4). Tubular adenocarcinoma, with high cellular density and quick cell proliferation, was the dominant pathologic type of CRC (5).

Beyond the cellular characterizations, these clinical traits were established as potential indicators to predict the clinical outcome, including age, gender and tumor stage, etc. The incidence rate and gender preference were varied with huge difference among the colorectal carcinomas, demonstrated by investigations in Western and Eastern populations (3, 6, 7). The majority (80%) of patients with colon cancer was diagnosed over 60-years-age old and the incidence rate of male's patients was higher in than the female's (6). In addition, the primary tumor sites of CRC indicated the different contribution in overall survival of patients. CRC patients who are with tumor metastasized in left-side (distal, splenic flexure to rectosigmoid) have better survival rate than those whose tumor metastasized in right-side (proximal, cecum to transverse). Similarly, patients with metastasized rectal cancer showed better clinical outcome than those with metastasized colon cancer (8). However, the exactly prognostic value of primary tumor sites has not been well established to predict the clinical outcome of CRC in previously studies.

Except clinical traits, serum biomarkers have been broadly used in prediction of clinical outcomes. Multiple biomarkers, including carcinoembryonic antigen (CEA), C-reactive protein (CRP) and carbohydrate antigen 19 – 9 (CA19-9), have been successfully translated into evaluation and management of the patients with CRC in clinical practice (9). Among them, CEA has been regarded as a promising prognostic biomarker for tumor progress and metastasis in CRC, and integrated into patients monitoring in clinical application (10). Serum level of CRP was adopted as potential biomarker to evaluate the potential risk of colorectal cancer. However, it is still not clear that the positive correlation between elevated serum CRP level and CRC (11). Serum concentration of CA19-9 is a well-known tumor biomarker to screen and detect the carcinomas in the digestive tract, and about 18% of CRC cases were associated with higher serum CA19-9 levels. Although CA19-9 has been applied as a tumor biomarker in colon carcinoma over 40 years (12), especially worked as prognostic indicator of advance stage (13) and metastatic colorectal cancer (14), it was still controversial that the specificity and sensitivity of CA19-9 applied in the CRC clinical screening (15, 16).

In this study, we retrieved to investigate over 1000 clinical profiles of the hospitalized CRC patients in Zhenjiang, a local area in Jiangsu province of China. Multiple clinical traits and biomarkers levels were associated with these CRC patient's profiles. The serum level of CA19-9 was significantly positive associated with a poor prognosis and high recurrence rate, especially the CRC patients that primary tumor located at terminal sites (Rectum and sigmoid). These results suggest that CA19-9 work as potential precise prognostic indicator for tubular adenocarcinoma and tumor non-infiltration in terminal colorectal cancer.

Materials & Methods

Clinical Information Collection

This retrospective study was approved by the local ethics committee of the hospital affiliated university and waved for requirement of informed consent. The primary cohort study comprised an evaluation of the patient's medical records from hospital database. It contained 1039 consecutive cases with surgical

and pathological identification, which was representative CRC patients between November 2006 and February 2014 through surgical resection with curative intent for the evaluation at the hospital. Totally, this cohort contained 1006 cases with clear primary tumor site information and distributed as 566 males and 440 females. The serum level of CA19-9, CRP, ALB (albumin) and CEA were identified in varied cases of 334, 602, 602 and 602, respectively.

Histopathological Grade Evaluation

Original histopathological slides were evaluated by the gastrointestinal pathologists of pathology department. The pathologist reviewed the hematoxylin and eosin section of each colorectal tumor and used well-established criteria to evaluate tumor pathological staging of malignant. Tumor stage, tumor grade and tumor-infiltrating of cases were determined according to the 7th edition of TNM (Classification of Malignant Tumors) classification for differentiated colorectal carcinomas of the American Joint Committee on Cancer (17).

Detection of Serum Biomarkers

The serum biomarkers detection (CA19-9, CEA, ALB, and CRP) were performed by standard preoperative protocol (within 2 weeks) before surgery. These biomarkers were determined by the local pathological unit for all patients. The serum CA19-9 levels were measured with electrochemiluminescence immunoassay using the Roche Cobas E601 (Roche, Switzerland) immunoassay system. The serum level of CA19-9 below or equal to 37 U/mL was identified as normal reference value (defined as level 1), and greater than 37 U/mL was setup as abnormal value (defined as level 2). According to the hospital defined normal range, the threshold values for CEA was 0 ~ 5 μg/mL, CRP was 0 ~ 8 mg/L and ALB was 40 ~ 55 g/L (all patients were associated with abnormal level with < 40 g/L).

Lymph Node Metastases Detection

Lymph node metastases involvement was diagnosed by PET-CT in all patients. The regional number of lymph node were identified and calculated based on PET-CT images.

Statistical Analysis

Statistical analysis was conducted with R software (version 3.6.1; http://www.Rproject.org) and GraphPad Prism 6 (GraphPad Software, Inc.). The Pearson correlation (r) was employed to measure a linear dependence correlation analysis between two variables of patient's physiological indicators, and demonstrated as correlation Matrix. In the analysis, CA19-9 level below 37 U/mL, other primary tumor sites, early stage, infiltration tumor and normal indicators were defined as "1"; CA19-9 level over 37 U/mL, terminal tumor sites, advanced stage, non-infiltration tumor and abnormal were defined as "2". The category study variable was used independent t test or one-way analysis of variance test. The overall survival probabilities were estimated by Kaplan-Meier method and compared using log-rank test. The statistical significance level was set as p value < 0.05.

Results

Clinical characterization of cases

These original cases were selected from diagnosed CRC patients, and these cases with missing the key parameters or clinical markers were excluded for next step general and specific level analysis. The process and characteristic analyses were demonstrated by flow chart (Figure.1). Characterization of these cases was summarized, including corresponding clinical features, 5-year survival rate and tumor distribution of primary site (Table.1). First of all, the qualified the patients were divided into four age-groups (Table.1), including below 50-years-old group (124 cases, 12.3%), 50-60-years-old group (273 cases, 27.1%), 61 ~ 70-years-old group (326 cases, 32.4%) and over 70-years-old group (282 cases, 28.0%). The majority of cases (882 cases, 87.7%, $p < 0.001$) were significantly distributed in the range of over 50 -years-old (Figure.S1A). The 5-year survival rate of over 60-year-old patients (median 55.5 months, 44%) was significantly lower than below 60-year-old patients [median 62 months, 52%, log rank $p = 0.0004$] (Figure.S1B). It suggests that population of over 60-year older patients have higher risk to develop into CRC and lower survival rate. There is not significantly differences in the five-year survival rates between gender groups.

Characterization of tumor primary sites

Totally, 737 cases (73.3% incident rate) were distributed in the terminal tumor site (median survival period = 57 months, 5-year survival rate = 48.4%), while the other cases (n = 269, 26.7%) were allocated in others tumor sites (median survival period = 59 months, and 5-year survival rate = 48.3%) (**Table.1**). Altogether, 11 primary tumor sites were identified as rectum (59.3%), sigmoid (13.9%), right hemicolon (7.6%), colon (6.3%), ileocecal (4.5%), descending colon (1.1%), hepatic flexure colon (0.8%), ascending colon (2.4%), transverse colon (1.7%), junction of the rectum and sigmoid (0.6%), and left hemicolon (1.9%). Rectum and sigmoid were classified as the terminal tumor sites (18), and determined with higher incidence rate compared to other tumor sites (Fig. 3A&B).

Combined gender bias with primary tumor sites analysis, male patients (58%) had significantly higher incident rate than female patients (42%), especially in the terminal tumor sites. The distribution ratio of male patients (61%, 86 cases; 57%, 341 cases) is higher than female patients (39%, 54 cases; 43%, 256 cases) in sigmoid cancer and rectal cancer, respectively (Fig. 3C&D). Combined age with primary tumor sites analysis, 74.8% of 50-70-years-old cases were distributed in terminal tumor sites, 25.2% of patients allocated in others tumor sites. The diagnosis rate of early stage terminal colorectal cancer (41.1%) was significantly higher than that of other primary tumor sites (31.2%) (Table 2), while the advance stage of terminal colorectal cancer (58.9%) was significantly lower than that other primary tumor sites (68.8%). The OS and five-year survival rates of terminal tumor sites (sigmoid and rectum, 48.4%) were similar with other primary tumor sites (48.3%).

In this study, the percentage of tumor non-infiltrated cases was significantly higher than tumor infiltrated cases. The OS of tumor non-infiltrated cases (median 54 months, 40%, log rank $p = 2e\text{-}15$, Figure.S4A) was significantly lower than tumor-infiltrated cases (median 67 months, 57%, $p < 0.01$). The majority of tumor non-infiltrated cases were similarly distributed in the terminal tumor sites (441/656, 67%) and other

tumor sites (163/229, 71%), but 98% of tubular adenocarcinoma cases were identified as non-infiltrated tumor (Figure.S4B).

Tumor stage, lymph node metastasis, adenocarcinoma subtypes and survival outcomes

Patients with advanced stage (median 55 months, 43%), high degree of differentiation (median 55 months, 43%), lymph node metastasis (median 54 months, 42%) and severe lymph node metastasis (over number 5, median 44 months, 27%) have significantly shorter OS and lower 5-years survival rate than those with early stage (median 64 months, 55%, log rank p = 7e-10, Fig. 2A), lower degree of differentiation grade (median 67 months, 56%, log rank p = 0.024, Fig. 2B), without lymph node metastasis (median 61 months, 51%, Fig. 2C, log rank p = 0.007) and mild lymph node metastasis (below number 5, median 60 months, 49%, log rank p = 1e-05, Fig. 2D). More interesting, the tumor stage (r= -0.18, p = 5.77e-09), lymph node metastasis (r= -0.14, p = 1.47e-05) and the number of lymph node metastasis (r= -0.17, p = 3.79e-08) were significantly negative correlated with patient's OS (Figure S2A). The lymph node metastasis (r = 0.67, p < 2.2e-16) and the number of lymph node metastasis (r = 0.55, p < 2.2e-16) showed significantly positive correlation with tumor stage. The lymph node metastasis (r = 0.82, p < 2.2e-16) was significantly positive correlated with the number of lymph node metastasis (Figure S2A). The patient's 5-year survival rate of different lymph node metastasis number dropped from 52–26% (Figure S2B), and the patients with lymph node metastasis number over number 5 have significantly worse survival outcome than those below 5 (Figure S2C, p = 0.016).

Through tumor subtype analysis, 988 patients were identified with pathohistological feature and classified as subtype of tubular adenocarcinoma, mucinous adenocarcinoma, adenocarcinoma, adenocarcinoma with necrosis and mixed type (without tubular adenocarcinoma, contained more than two other subtypes), respectively (Figure.S1C). Among four subtypes of adenocarcinoma, the survival rate of tubular adenocarcinoma patients (median 38 months, 5%) was significantly lower than others histological tumors (median 60.5 months, 50%, log rank p = 2e-15, Figure.4A). Furthermore, the majority of tubular adenocarcinoma cases were mainly distributed in the terminal tumor site (78%), and especially occurred in the sites of sigmoid (14/58, 24%) and rectum (31/58, 53%) (Figure.4B, p = 2e-15).

Correlation of serum markers with the CRC primary tumor

Multiple serum indicators of CRC patients were tested and summarized (Table. S2). The correlation analysis revealed that different patterns of these physiological indicators were correlated with primary tumor sites (Fig. 3C, Figure.S3A), tumor stage (Figure.S3B) and overall survival time. First of all, the serum level of CA19-9 was positive correlated with CRC tumor sites (r = 0.88, p = 2.2e-16), Overall Survival time (r = 0.11, p value = 0.05454) and negative correlated with tumor stage (r=-0.13, p = 0.0214) (Fig. 3C). The serum level of CEA was significantly positive correlated with CRC tumor stage (r = 0.19, p = 3.53-e06) and very weak negative correlated with CRC tumor site (r=-0.06, p = 0.16) and overall survival time (r=-0.06, p value = 0.1546) (Fig. 3C). In the meanwhile, the other two markers CRP (r= -0.21, p = 2.65e-7) and ALB (r= -0.19, p = 3.54e-6) were significantly negative correlated with CRC tumor sites (Figure S3C),

and showed weak correlation with CRC tumor stage (CRP, r = 0.06, p = 0.1544; ALB, r= -0.05, p = 0.23) and Overall survival time (CRP, r=-0.08, p value = 0.03882; ALB, r = 0.00159, p value = 0.969) (Figure. S3C). The others physiological indicators show little correlation with CRC stage and tumor sites. The advanced stage tumor patients, with higher abnormal level of CEA (> 5 μg/L, 41%), CRP (> 8 mg/L, 33%) and ALB (< 40 g/L, 57%), were mainly distributed in terminal tumor sites (Figure.4D). The others seven physiological indicators (Table.S1), including leukocyte, blood platelet, neutrophil, lymphocyte, monocyte, did not show significantly difference between normal and tumor patients. In addition, the patients (99%) with higher level of CA19-9 (CA19-9-2) were mainly distributed in the terminal tumor sites of colorectal cancer, and only small portion allocated in other primary tumor sites (Table.1, Figure.4E). However, there was no significant difference in overall survival time of the two different CA19-9 levels patient groups. Combined with the tumor stage analysis, lower CA19-9 level patients (73%) were more likely to be associated with advanced stage than higher CA19-9 level patients (58%). The serum level of CA19-9 was weak positive correlated with tumor non-infiltrating state (Figure.S4C, r = 0.07, p = 1.2e-6). Furthermore, the majority of patients diagnosed as tubular adenocarcinoma (81%) were associated with the higher level of CA19-9 (Figure.4F). Combined several markers' analysis with primary tumor sites (Figure.4D), CA19-9 may work as a promising biomarker for terminal bowel cancer and tubular adenocarcinoma of CRC.

Discussion

In this study, we have collected the first hands clinical data of 1006 patients from local hospital to discover these risk factors that exactly contributed to the colorectal carcinogenic, pathologic process and explore potential novel treatment strategy. The contribution of patient's age and gender, tumor stage and differentiated grade, lymph node metastasis was evaluated and deeply analyzed. The majority (88%) of colorectal cancer patients were mainly distributed in the over 50-years-old group, which is with twice higher incidence rates than the below 50-years-old patients group. In addition, the 5-year survival rate of patients was significant decreased in the group over 60-years-old. Previously cohort studies indicated that millions of patients were diagnosed as colorectal cancer and median age dropped from 70 years to 50 years (3, 19). It suggests that over 50-year-old patient's population have higher risk to develop as CRC and would be listed as screening target during annually physical examination. Through survival analysis, the patients diagnosed with advance stage tumor, higher differentiated grade, accompanied with lymph node metastasis and higher number of lymph node metastasis were significantly decreased the overall survival time and 5-year survival rate (Fig. 2A-C). It was identified that the correlation between overall survival time and tumor stage, lymph node metastasis and the number (> 5) of lymph node metastasis, respectively. Furthermore, the number of lymph node metastasis was negative correlated with the patients 5-year survival rate. Compared with the standard of 8th edition AJCC staging system, these results match the previously reported trend, which identified the prognostic value of lymph node metastasis and tumor stage in colorectal cancer (20). In addition, the number of metastasis lymph node could be translated as a clinical measurable predictor for tumor progress and patients' 5-years survival outcome. In the same time, the prognostic value of tumor-infiltration was also evaluated for these cases. The non-tumor-infiltration cases showed significantly lower survival rate and shorter overall survival time

than tumor-infiltration cases. Furthermore, the majority cases of tubular adenocarcinoma (53/54) were identified as non-tumor infiltration. It hints that tumor-infiltration lymphocytes could be as overall survival prognostic biomarker for CRC. It matches the results of previously large-scale population meta-analysis study, which identified the high level of tumor-infiltrating lymphocytes linked with better patient's survival rate and worked as prognosis indicator for colorectal cancer (21, 22).

The colon adenocarcinoma mainly rose from adenomatous polyps, including three histologic types of tubular, tubulovillous and villous adenomas. Tubular adenomas contribute about 85% adenomatous polyps and only 5% portion will transform as malignancy (23). CRC was originated from different anatomic position with varied molecular genetic alternation and different pathogenic mechanism (1, 24, 25). The traditional dichotomy of colon and colorectum were facing challenge and potential delayed in early diagnosis and impacted on patient's survival (26). In this study, 90% of patient's cases were identified as adenocarcinoma or mixed subtype, and only small portion cases (6%) were determined as tubular adenocarcinoma with significantly lower 5-years survival rate and shorter overall survival time (Figure.4A). To further explore the heterogeneity of colorectal cancer, this study investigated the distribution of multiple primary tumor sites in CRC cases population. The 73% cases were concentrated on the terminal tumor sites. The rectum and sigmoid (terminal tumor sites) were listed as the top two tumor sites with the highest incidence rate. In addition, the incidence rate of male's patients was significantly higher than female's patients (Figure.S2C&D). Although the early diagnosis rate of terminal colorectal cancer (41%) was significantly higher than other primary sites (31%), the overall survival time was no significant difference among primary tumor sites. Furthermore, the tubular adenocarcinoma cases were mainly distributed in terminal tumor sites (Figure.4B). It strongly suggests that rectum and sigmoid would be listed as the first priority screening target for colorectal health during annually physical examination and benefit for early diagnose tubular adenocarcinoma.

Multiple serum biomarkers, like CEA, CA19-9 and CRP, were identified as the standard for screening CRC patient in clinical practice (9, 10, 13, 27). The serum levels of CA19-9 and CEA played differentiated prognostic value in the CRC. The higher serum level of CA19-9 (> 200 U/ml) was reported as significant predictor for poor survival of colorectal cancer patients with liver metastasis (28). The serum level of CEA worked as the best tumor biomarker for chemotherapy drug response prediction, while CA19-9 worked as one of the best prognostic indicators for advanced colorectal carcinoma (13, 29). In this study, we investigated the internal connection and potential prediction of these biomarkers for patient's clinical outcome. Through the correlation analysis, we discovered the significantly correlation between serum level of CA19-9 with patient's CRC tumor sites and stage, respectively, while the serum level of CEA was significantly positive correlated with CRC tumor stage (Figure.4C). Furthermore, terminal tumor cases (99%) were mainly associated with abnormal higher level of these markers (CA19-9, CEA, CRP and CEA) (Figure.4E). More interesting, abnormal higher serum level of CA19-9 was significantly positive correlated with terminal tumors, especially associated with tubular adenocarcinoma cases (81%, Figure.4F), and non-lymphocytes-infiltrating tumors (90%, Figure.S4C). It suggests that the serum level of CA19-9 work as more precise prognostic predictor for terminal colorectal cancer.

Carbohydrate antigen 19 – 9 (CA19-9), a modified Lewis blood group antigen associated with specific malignancies, increases in patients with gastrointestinal cancers (30). CA19-9 was utilized as sensitive biomarker to evaluate the adenocarcinomas of the colon and rectum, and advance stage colorectal cancer with metastasis (25, 31–33). However, the correlation between the local expression level of CA19-9 and colorectal terminal tumor sites (sigmoid and rectum) is still unclear. Limitations for evaluation effective of CA19-9 in clinical tumor assessment include several factors. First of all, about 5 ~ 7% individuals in population are Lewis negative, who are with fucosyltransferase defection and do not produce CA19-9 into blood (34). Thus, their serum levels of CA19-9 keep pretty lower or undetectable even cancer recurrence (16, 35). Secondary, concentration of serum CA19-9 is affected by liver metabolism, or disturbed by environment epidemiology (25). Thirdly, serum level of CA19-9 also frequently increased in the patients with other cancers such aspancreatic adenocarcinomas (36), which interferes the clinical diagnostics accuracy for colorectal cancer. In this study, the original patient's data missing the information about the Lewis blood identification or more detail of clinical chemotherapy drug treatment. It may cause less patients samples with higher serum level of CA19-9 correlated with terminal tumor sites even associated with advance CRC. Taken these factors into future study, it will be helpful to illuminate the precise application of CA19-9 in clinical assessment for colorectal cancer.

Some limitations were existing in this study. First of all, although it is many years retrieved study, the absence of patient's pathologic characteristic data caused the exclusion of some cases and destroyed the statistics power of large samples. Secondly, lacked the somatic mutations and microsatellite instability status of primary tumor, which indicated the patterns of CRC metastasis, it blocked the deeper exploration of internal connection of CRC. Thirdly, without the clinical chemotherapy detail and multiple prognostic scores, and the serum level CA19-9 of patients before and after chemotherapy, it deterred the precise application as clinical prognostic biomarker. Lastly, missing the genetic mutation status of key oncogenes in patients, such as mutations in KRAS (exons 2–4) and BRAF (V600E), which are mainly associated with metastasis CRC and broadly used in the metastasis CRC patient's management (37–40), will impair the prognostic effect of CA19-9. Despite these limitations, our results demonstrated novel sight of CA19-9 as precise biomarker for terminal colorectal cancer, especially for tubular adenocarcinoma. In the future studies, larger patient's size and multiple centers independently studies will conduct to verify the prognostic value of CA19-9 in colorectal tubular adenocarcinoma.

Conclusions

In summary, our results provided the clinical evidences that the incidence rate and overall survival outcomes were significantly difference in the terminal tumor sites and other tumor sites of colorectal cancer. Colorectal tubular adenocarcinoma demonstrates the significantly lower survival rate in terminal tumor sites (sigmoid and rectum). The serum level of CA19-9 is a promising precise diagnostic biomarker for the terminal colorectal cancer, especially in the tubular adenocarcinoma. Integrated CA19-9 level detection with precise terminal tumor sites surgery in clinical application, it may significantly change the clinical outcome and extend survival time for CRC patients.

Abbreviations

CA19-9
Carbohydrate antigen 19 – 9
CRC
Colorectal Cancer
CEA
Carcinoembryonic antigen
CRP
C-reactive protein
ALB
Albumin
TNM
Classification of Malignant Tumors
OS
Overall Survival

Declarations

Acknowledgements

Not applicable.

Authors Contributions

Conception and design the overall project study: S.L., and YY. H. Collection and assembly of data: S. H., Z.H. Data analysis and interpretation: Z.H., S.L. Data interpreted and summarized the results: Z.H., X. C., J.C, S.L., and YY. H. Manuscript writing: Z.H., S.L., and YY. H. wrote and revised the manuscript. Final approval of manuscript: all authors have read and approved the final version of manuscript.

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Ethics approval and consent to participate

This retrospective study was approved by the local ethics committee of the hospital affiliated university and waved for requirement of informed consent.

Data availability

The datasets used and/or analyzed during the current study are available online in supplementary materials.

Consent for publication

Not applicable.

Competing Interests

All author(s) announced no potential conflicts of interest.

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Tables

Due to technical limitations, table 1-2 is only available as a download in the Supplemental Files section.

Figures

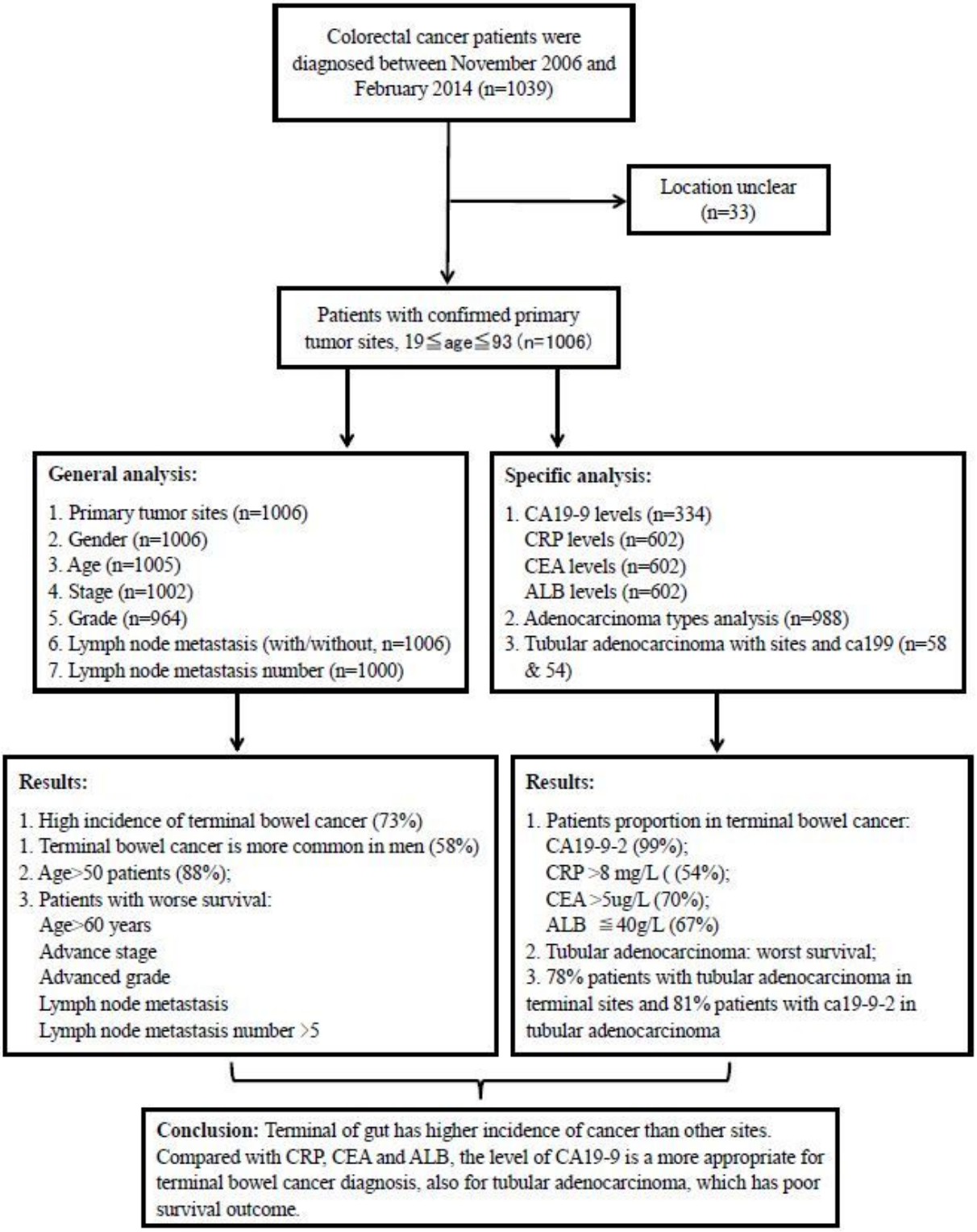
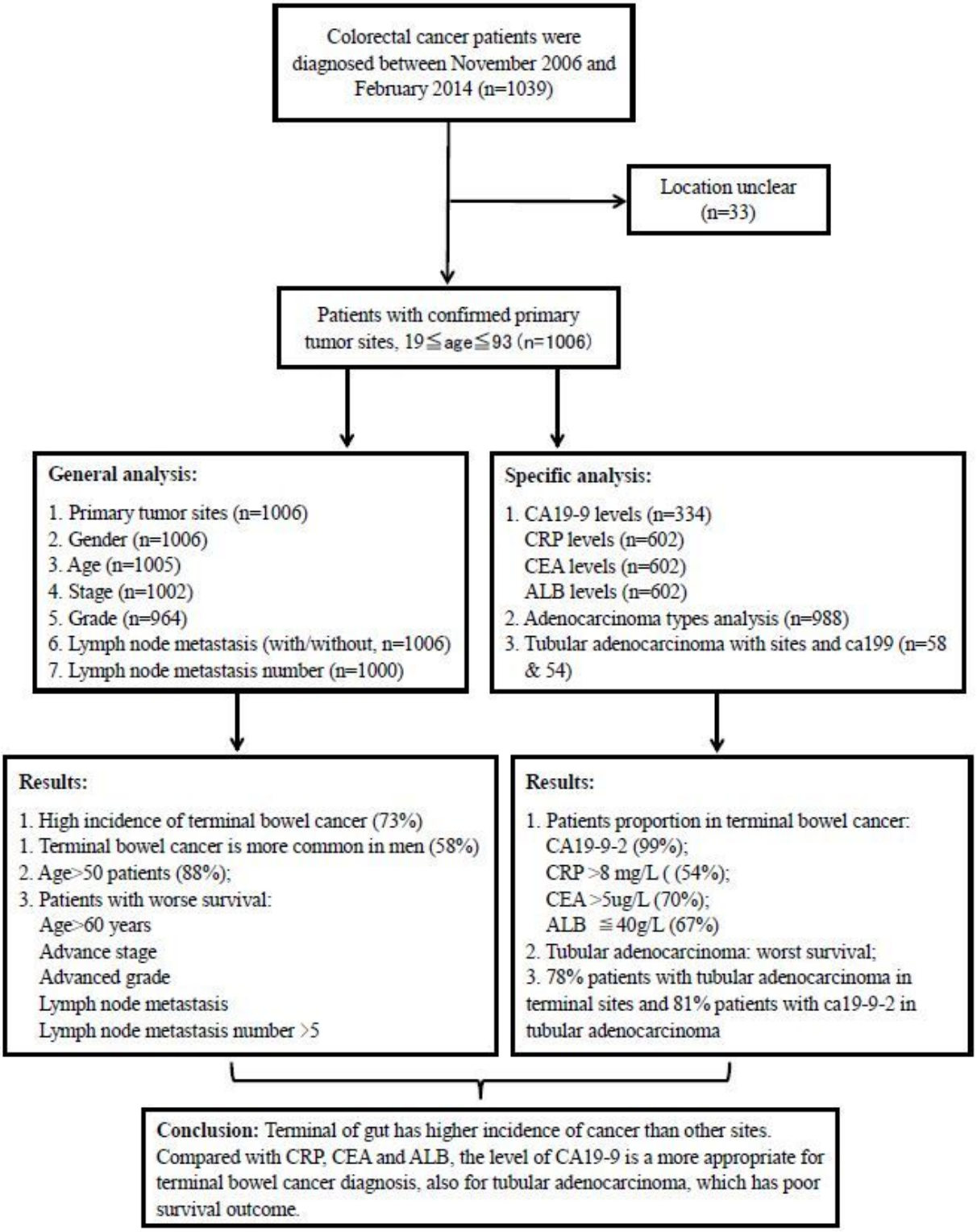


Figure 1

Workflow chart of selecting colorectal cancer patients with the primary tumor sites for category analysis and summary.



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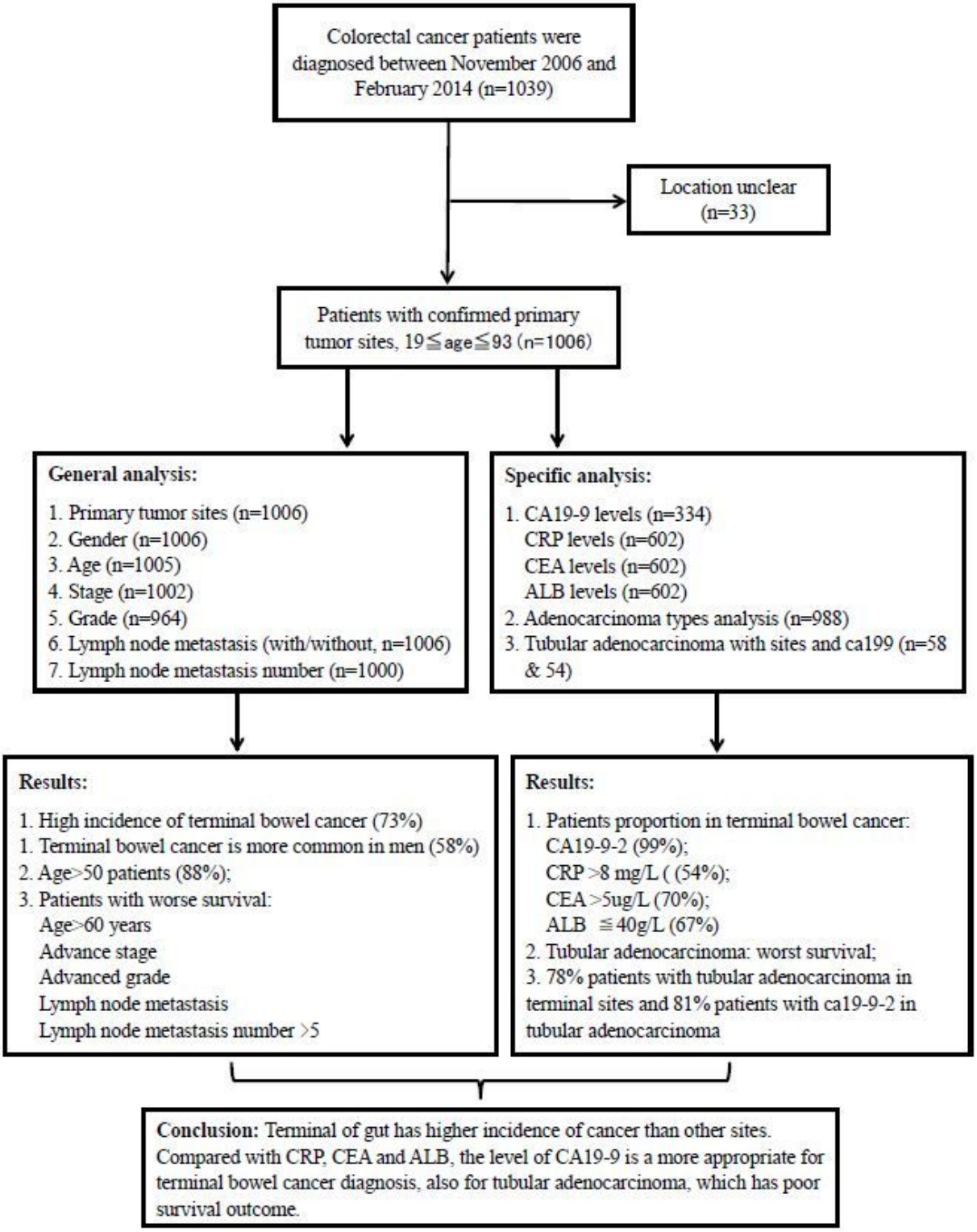

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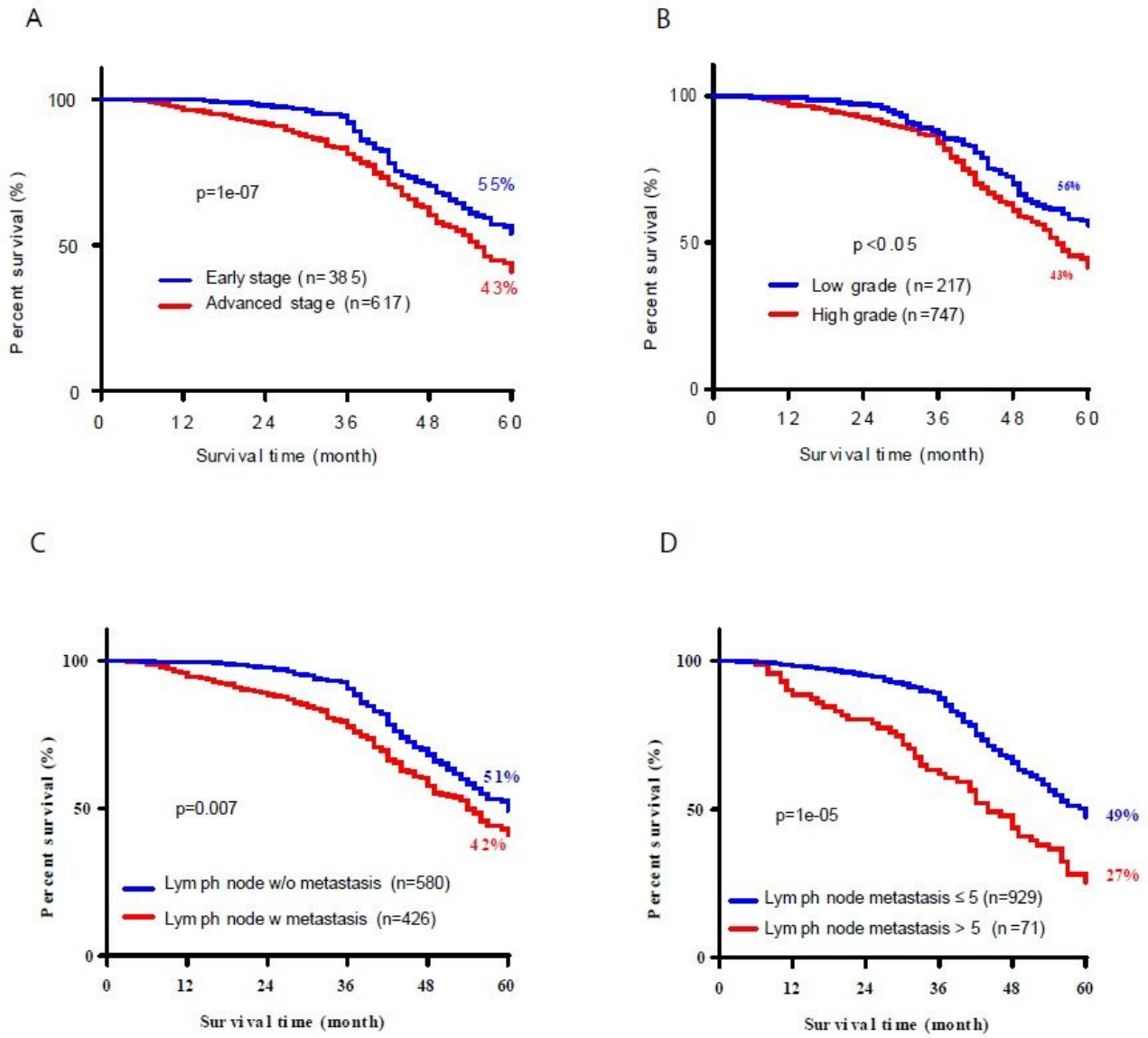
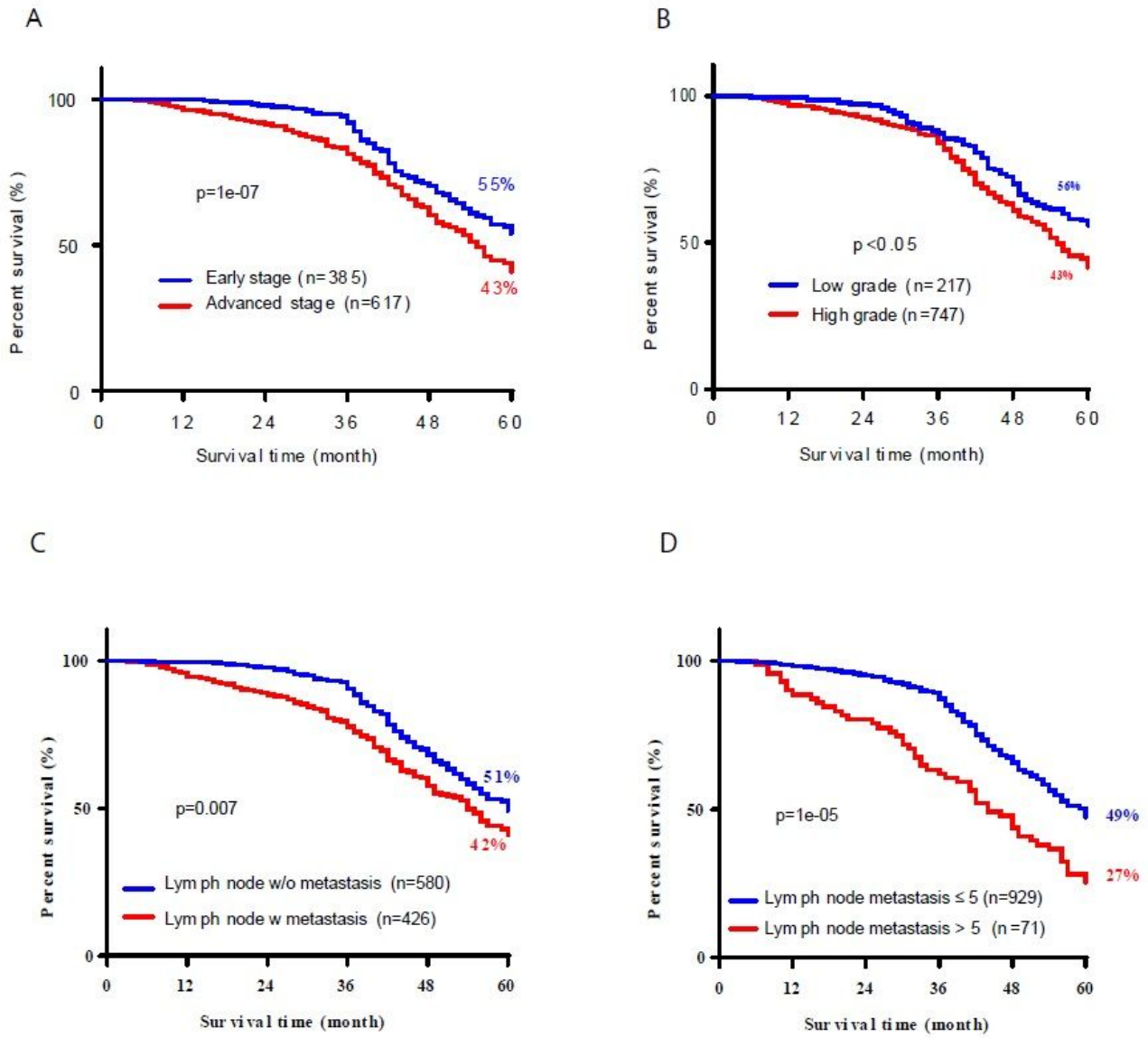


Figure 2

Overall survival analysis the contribution of stage, grade, lymph node metastasis in CRC cases. (A) Overall survival time of all colorectal cancer cases with different stages, (B) different histological grading, (C) lymph node metastasis and (D) lymph node metastasis with different number.



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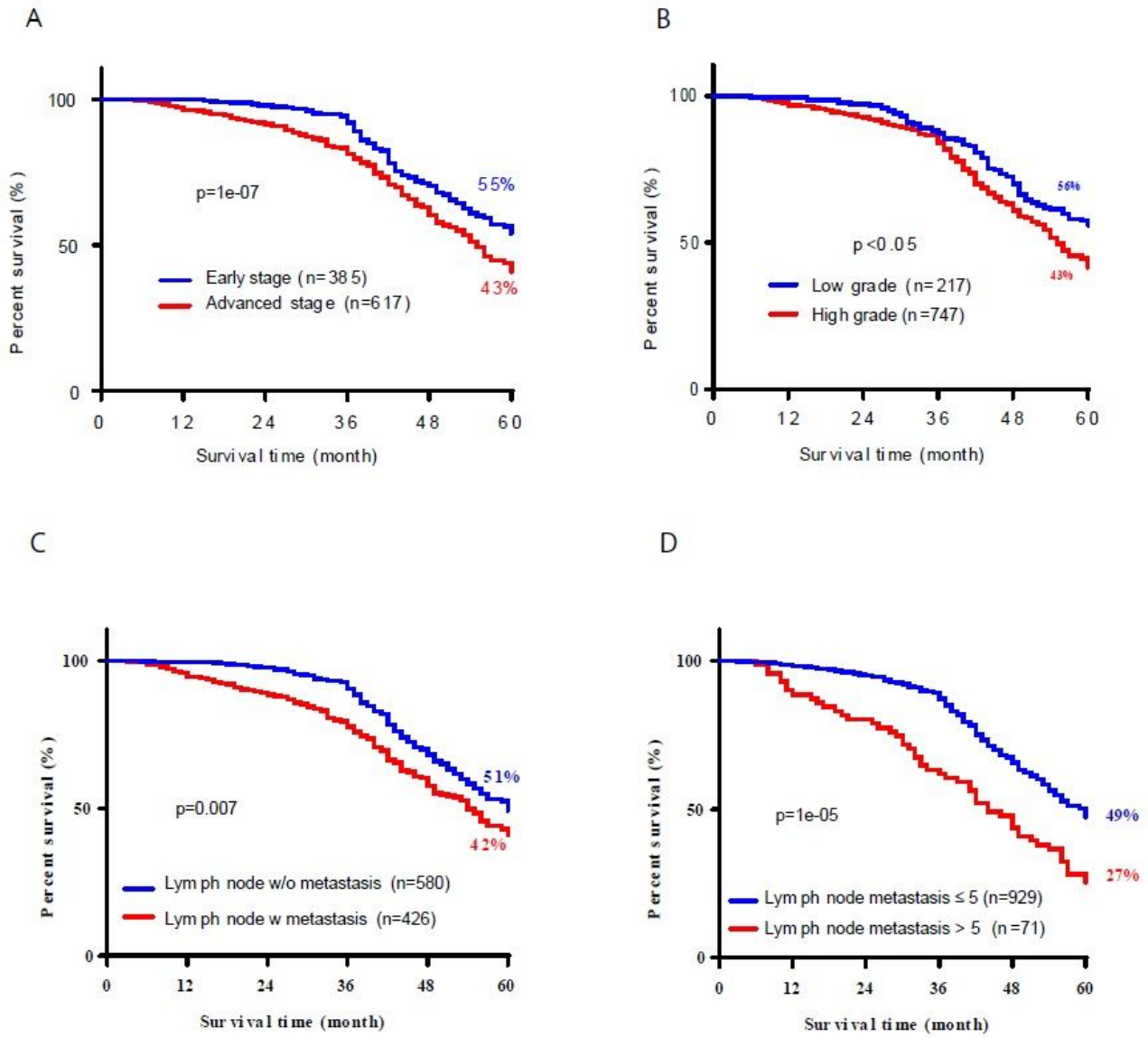

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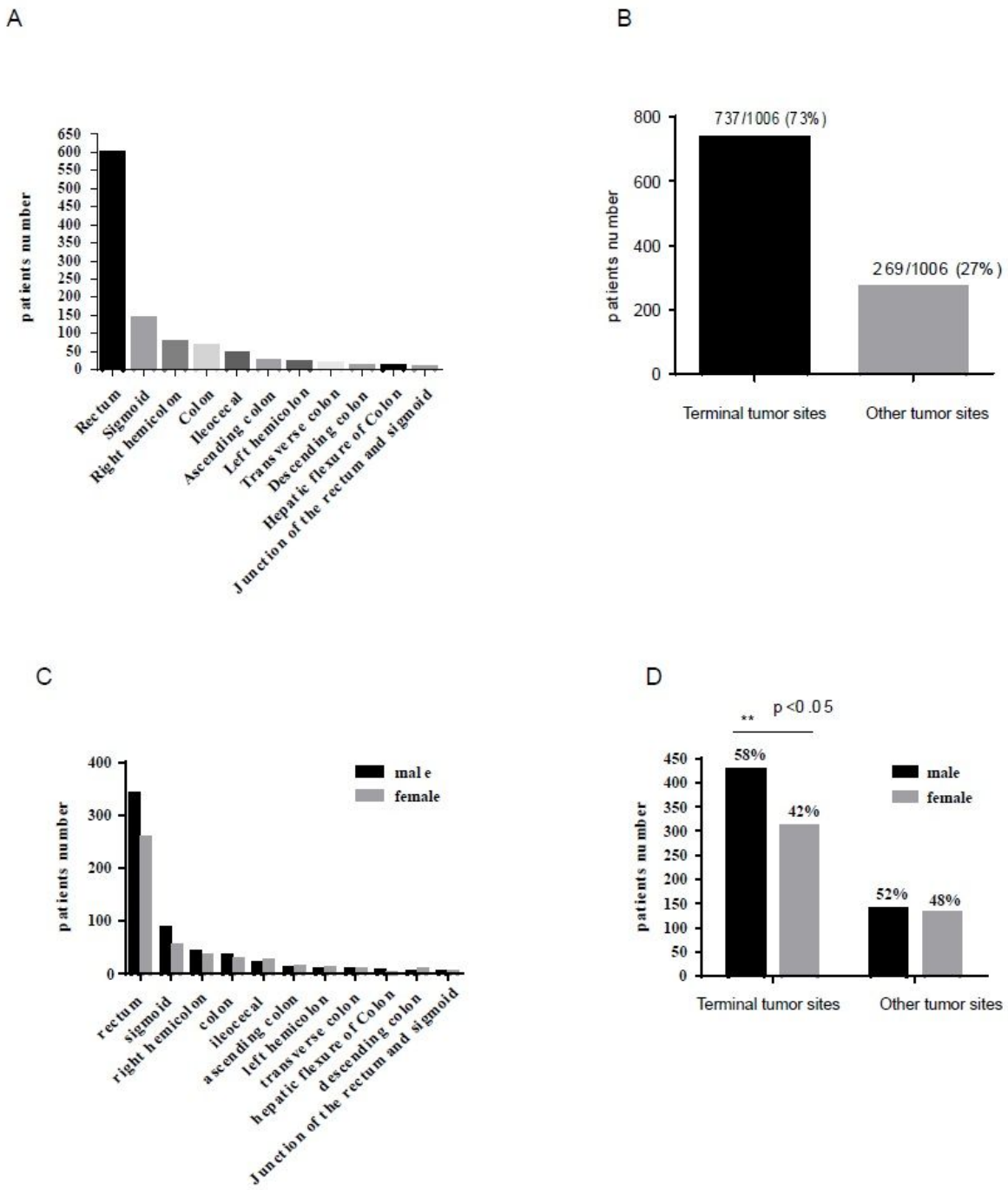
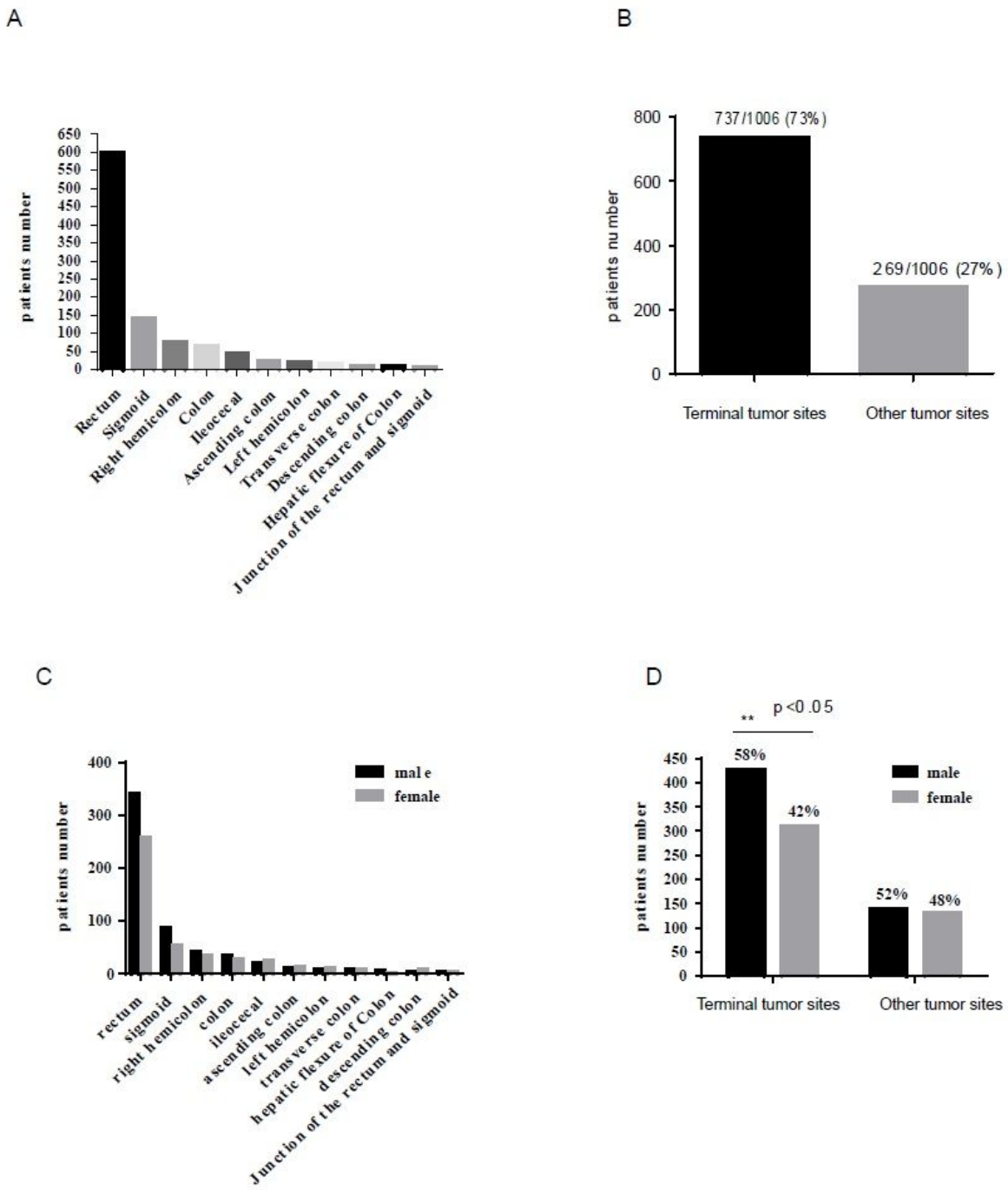


Figure 3

Patients distribution in each primary tumor sites (A). Patients distribution in terminal and other tumor sites (B). The distribution of patients with each primary tumor sites in male and female(C). The distribution of patients with terminal and other tumor sites in male and female (D).



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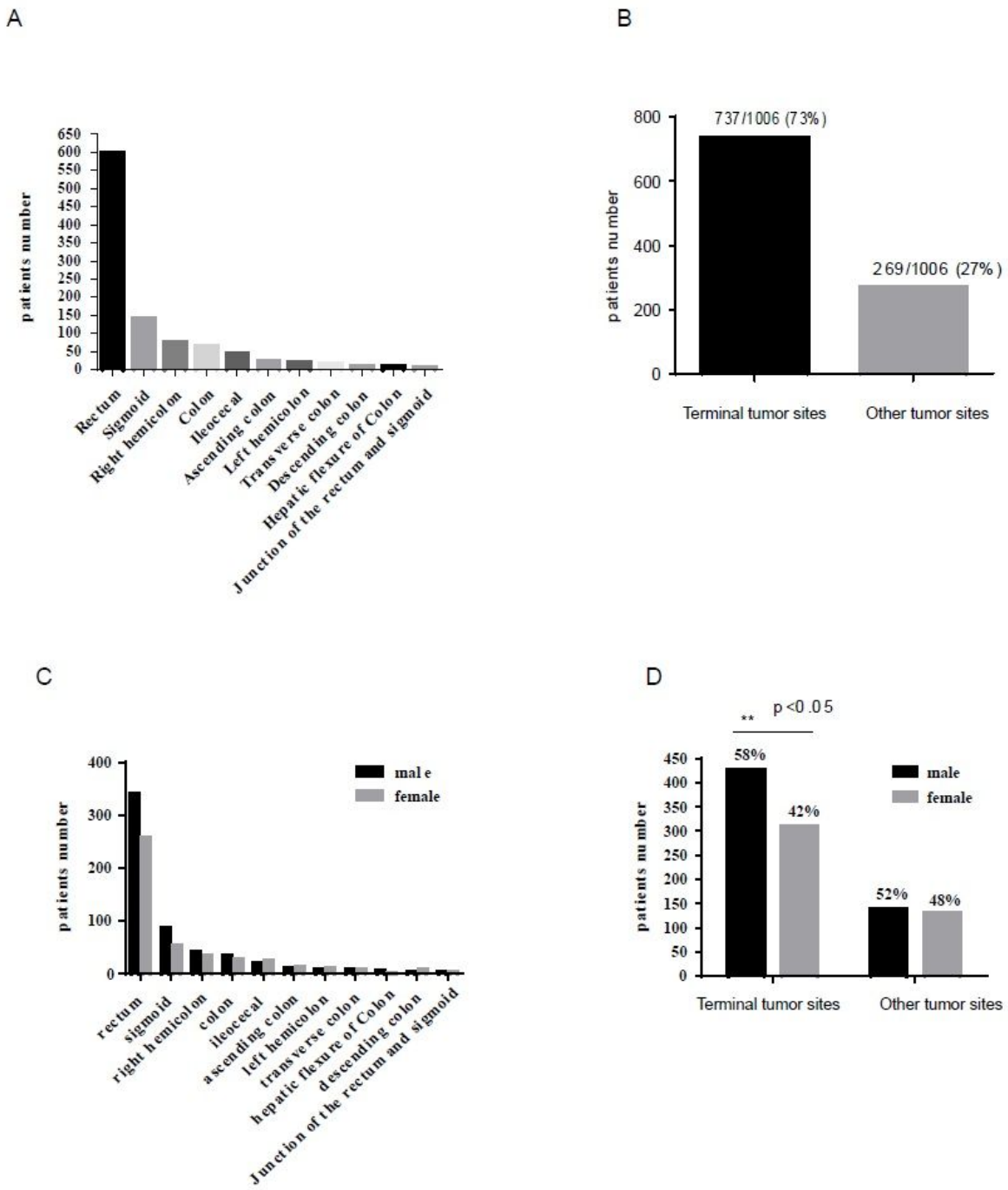

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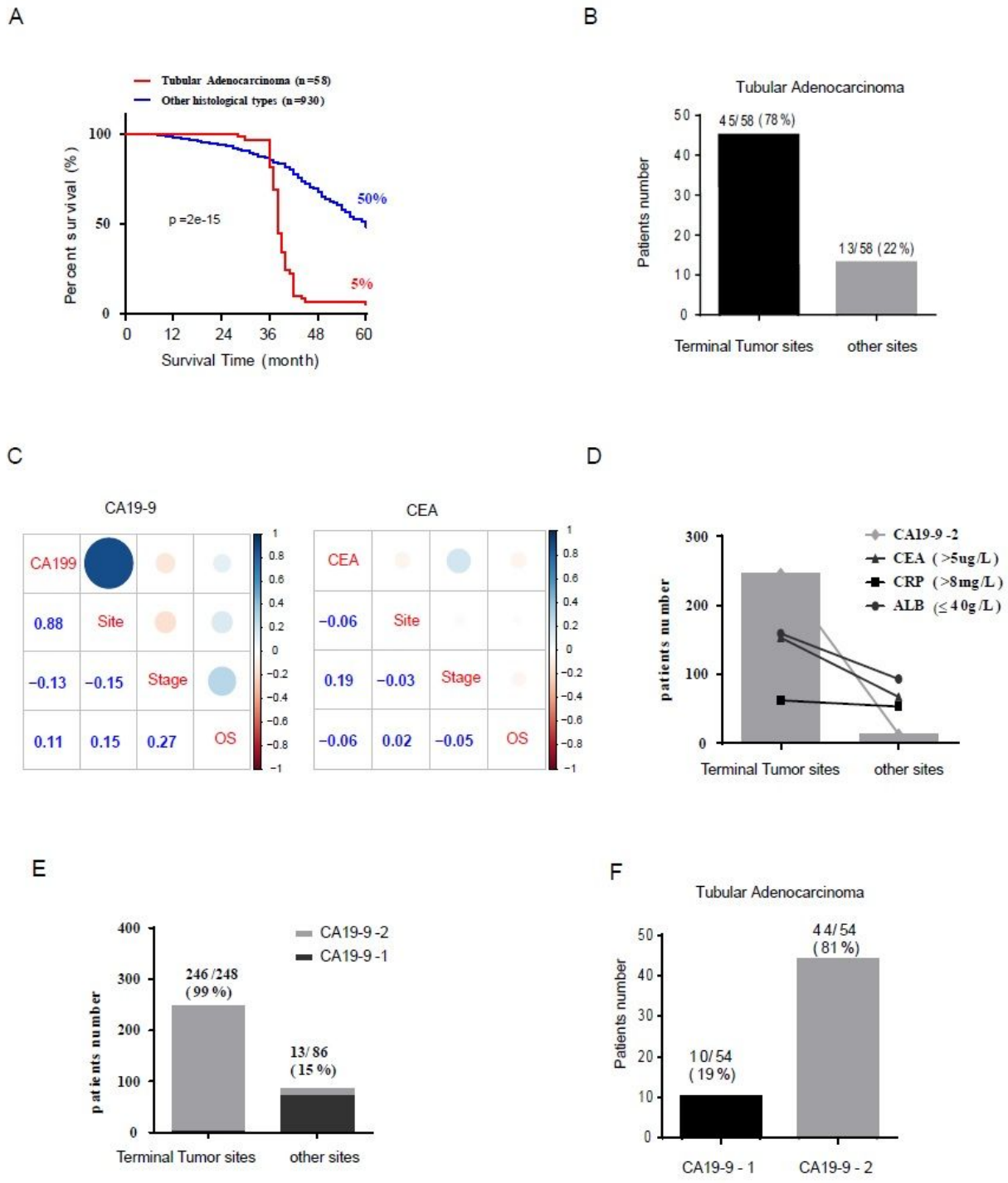

Figure 4

Correlation analysis of CA199 and CEA with primary tumor sites, Stage and survival time in CRC. (A) Survival analysis for different histological types of colorectal adenocarcinoma. (B) Cases distribution of tubular adenocarcinoma in terminal and other primary tumor sites (n=58). (C) Correlation analysis of CA199 and CEA with tumor site, stage and overall survival time of CRC. (D) The distribution of patients with CA19-9-2 (n=248), abnormal CEA (n=220), CRP (n=115) and Alb (n=252) in terminal and other

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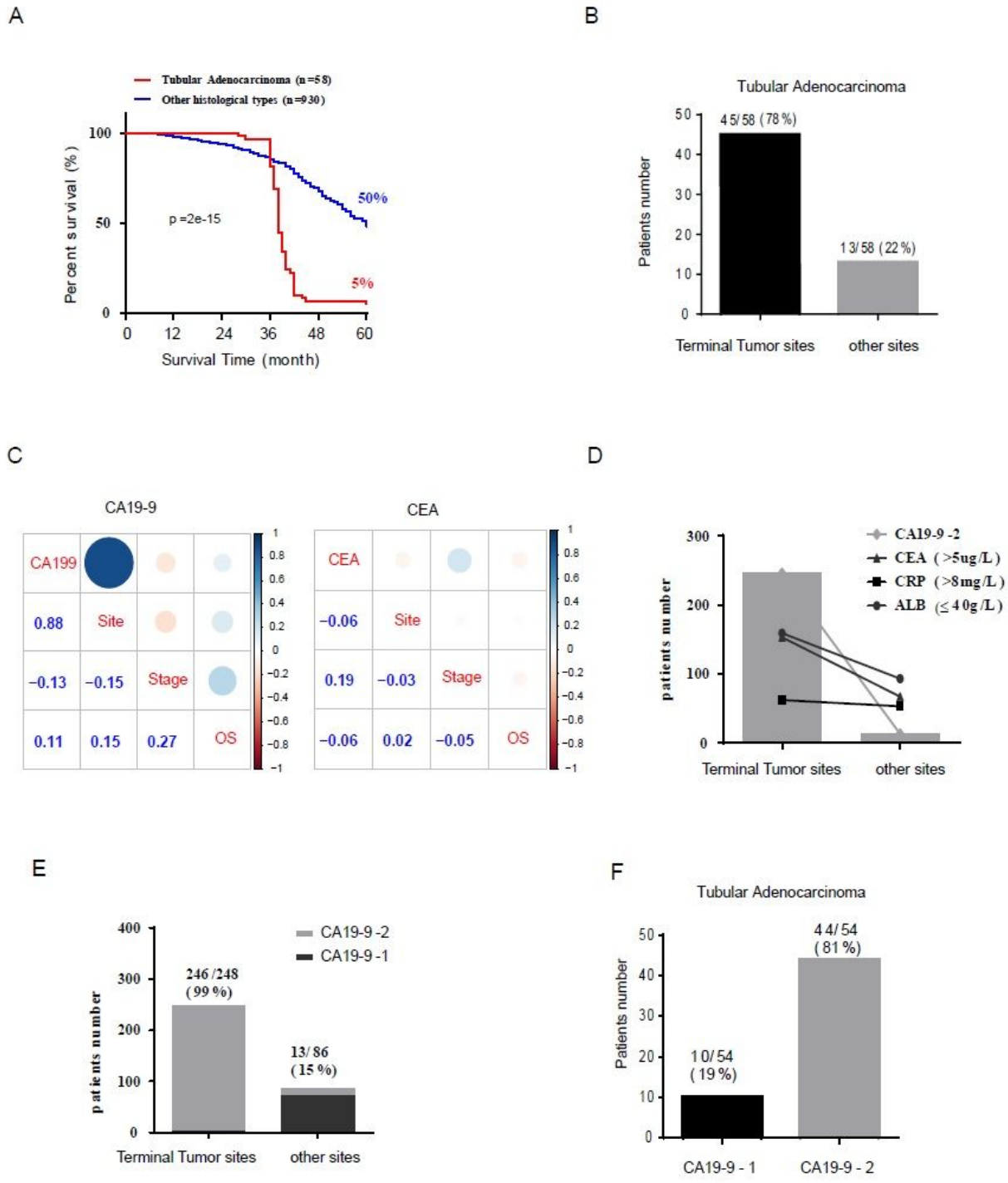

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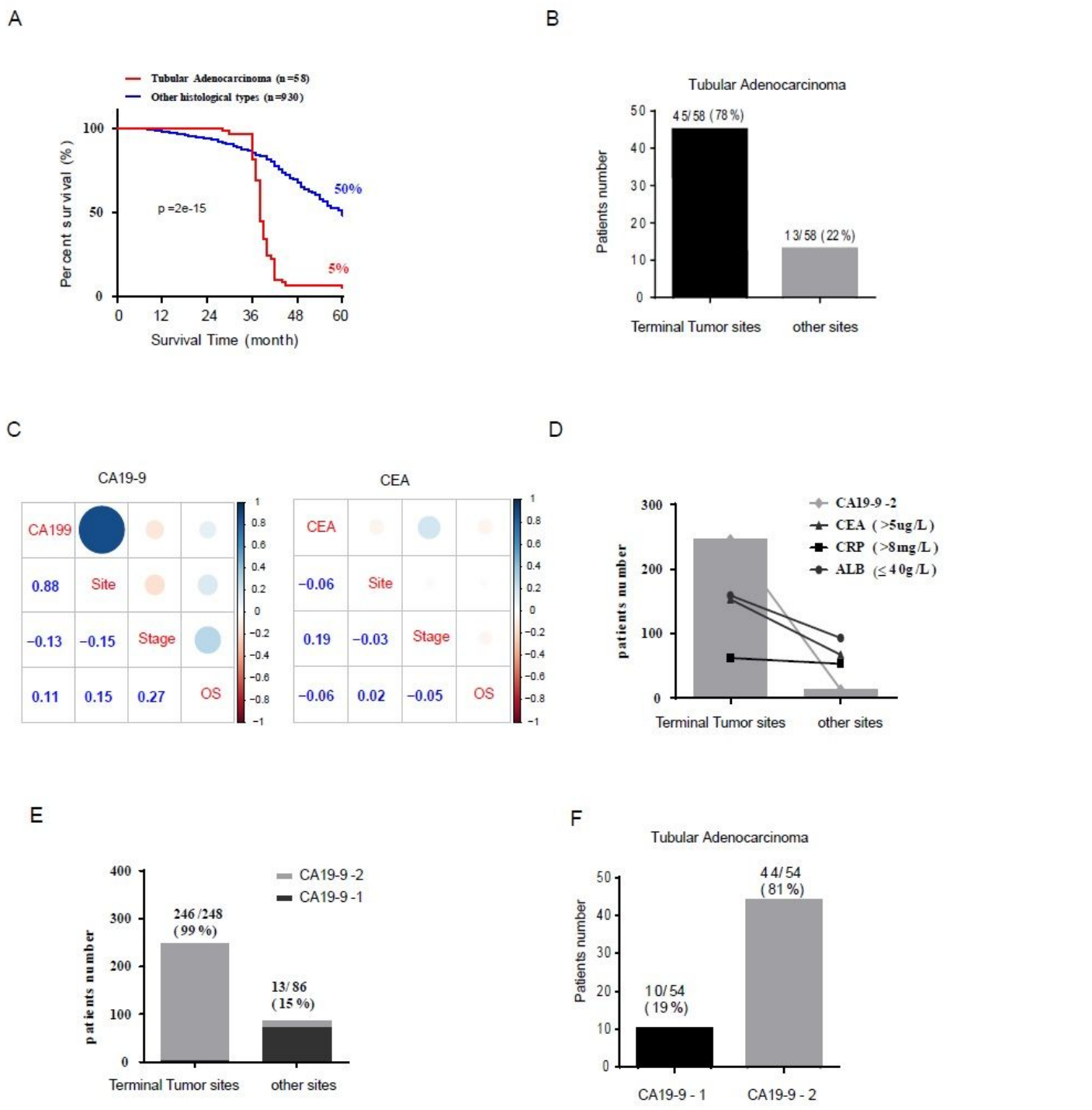

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