ANUL 2025

UNIVERSITATEA DE MEDICINĂ ŞI FARMACIE
„CAROL DAVILA", BUCUREŞTI
ŞCOALA DOCTORALĂ
DOMENIUL MEDICINĂ/MEDICINĂ DENTARĂ/FARMACIE

EVALUATION OF PROGNOSTIC FACTORS FOR THE PREVENTION OF POSTOPERATIVE COMPLICATIONS IN RECTAL CANCER SURGERY

Conducător de doctorat:
PROF. UNIV. DR. VALENTIN TITUS GRIGOREAN

Student-doctorand:
PÎRÎIANU DUMITRU-CĂTĂLIN

ANUL 2025

According to Global Cancer Data 2020, colorectal cancer (CRC) has become the third most commonly diagnosed malignancy and the second leading cause of cancer-related deaths worldwide [1–4].

In 2020, approximately 1,931,590 individuals were diagnosed with colorectal cancer (CRC), and 935,173 deaths were attributed to the disease [5, 6]. According to the World Health Organization (WHO), by 2030, the number of new CRC cases is expected to increase by 77%, while CRC-related deaths are projected to rise by 80% [7, 8]. The primary treatment modalities for CRC include surgical intervention, localized radiotherapy, and systemic therapies such as chemotherapy and targeted therapy [9, 10].

At present, radical surgery remains the cornerstone of colorectal cancer (CRC) treatment [11–13]. Several previous studies have shown that postoperative complications frequently impact the prognosis of patients with CRC [10, 14, 15]. Since CRC affects both the intake and absorption of food and nutrients, it often leads to malnutrition in affected patients [16, 17].

Malnutrition can lead to alterations in immune, respiratory, and renal function, and may impair wound healing [18, 19]. Therefore, comprehensive preoperative assessment and timely intervention should be a primary focus for clinicians.

The main aim of this study was to identify predictive factors for surgical site infections (SSI) in colorectal cancer surgery. Additionally, the study sought to explore whether C-reactive protein (CRP) levels and CRP ratios, tumor distance from the anal verge, the number of preoperative comorbidities, Charlson Comorbidity Index (CCI) scores, and operative time could serve as potential predictors of postoperative complications following rectal cancer surgery. This latter component was defined as Specific Objective O1.

In addition, differences were observed based on the demographic and clinical characteristics of patients diagnosed with rectal cancer, in relation to their predisposition to postoperative complications. This represented Specific Objective O2.

This thesis is structured into a general section and a special section. The general section includes a brief historical overview of rectal cancer surgery, a review of the clinical characteristics of patients with rectal cancer, and an analysis of predictive factors for postoperative complications in patients undergoing rectal cancer surgery. The special section consists of three studies: a systematic review with meta-analysis and two empirical studies.

Within the systematic review and meta-analysis, we identified the main predictive factors for postoperative complications in patients with rectal cancer. The analysis included patient-related factors (such as gender, age, preoperative comorbidities, and ASA score) as well as

treatment-related factors (such as laparoscopic surgery, stoma creation, and the use of wound retractors).

The systematic search was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [20], using the Medline-PubMed, Cochrane Library, and EMBASE databases, starting in March 2023 (cut-off date: March 28, 2023).

The following Medical Subject Headings (MeSH) terms were used in the PubMed database: '(colorectal neoplasms) AND ([surgical wound infection OR surgical site infection] OR [infectious OR wound OR skin complications]) AND (risk factors OR diabetes mellitus OR obesity OR body mass index OR aging OR hypertension OR neoplasm staging OR operative time OR hypothermia OR anti-infective agents OR hypoproteinemia OR hand hygiene OR laparotomy OR laparoscopy).

The PICOS framework (i.e., Population, Intervention, Comparator, Outcomes, and Study design) was used to define the inclusion criteria for the study.

The following inclusion criteria were applied for the meta-analysis:

1. Patients who underwent surgical intervention for colorectal cancer;
2. Assessment of the relationship between risk factors and surgical site infections (SSI);
3. A standardized definition of the outcome measure for SSI, reported by dedicated clinical personnel;
4. Reported odds ratios (OR) or relative risks (RR) for SSI, along with 95% confidence intervals (CI);
5. Patients aged over 18 years;
6. Case-control or cohort studies.

The exclusion criteria were as follows:

1. Animal or in vitro studies;
2. Review articles, case reports, letters, or conference abstracts;
3. Duplicate publications;
4. Studies with incomplete data;
5. Studies conducted on benign lesions that did not include cancer patients;
6. Studies published in languages other than English.

The empirical research included patients who underwent surgical intervention for rectal cancer (Tables 7.1 and 7.2). The study period overlapped with the COVID-19 pandemic, during which the selection of surgical approaches—particularly laparoscopic surgery—was influenced by the limitations and challenges imposed by the pandemic context.

The inclusion criteria were patients aged 18 years or older, with a histologically confirmed diagnosis of rectal adenocarcinoma, and tumors located between 0 and 15 cm from the anal verge.

The exclusion criteria included colon cancer with tumors located more than 15 cm from the anal verge, incomplete medical records, and non-cancerous rectal pathologies.

Patients were included in the data collection process after meeting the inclusion criteria and providing informed consent, in accordance with the provisions of Law no. 95/2006, Law no. 46/2003 on patients' rights, Order of the Ministry of Health no. 1410/2016, and Ministerial Order no. 482/2007. The signed consent forms were included in the admission files.

Patients underwent one of three surgical procedures: anterior resection (AR), abdominoperineal excision of the rectum (APER), or the Hartmann procedure. All surgeries were performed with curative intent and in accordance with established oncological guidelines, including the use of total mesorectal excision (TME) when indicated.

Preoperative and postoperative CRP levels were assessed on specific days: day 1, day 3, and day 5. For patients with extended hospital stays, additional measurements were taken on day 7. CRP levels were determined using a high-sensitivity immunoassay. The CRP-to-platelet ratio (CPR) was calculated for each postoperative day to serve as an indicator of inflammation. In addition, the CRP-to-lymphocyte ratio (CLR) and the CRP-to-neutrophil ratio (CNR) were computed to investigate their correlation with surgical complications.

CRP levels were assessed using the CRP Vario assay, a latex-enhanced immunoturbidimetric test performed on ARCHITECT C systems (Abbott Laboratories). This assay utilizes two reagents: a glycine buffer (pH 7.0) and latex particles coated with anti-CRP polyclonal antibodies, enabling precise quantification of CRP in serum or plasma. Blood samples were collected using standard venipuncture techniques, allowed to clot, and subsequently processed by centrifugation.

The high-sensitivity mode was employed, allowing for accurate detection across a wide range of CRP concentrations. Samples were stored at 2–8 °C for up to 15 days, or at −20 °C for long-term storage of up to one year. The reagents remained stable on board the analyzer for up to 60 days, with recalibration performed when there were indications of reagent integrity

compromise. This methodology enabled reliable monitoring of CRP dynamics in relation to postoperative complications.

Patient demographic data, including age, sex, body mass index (BMI), and comorbidities, were retrieved from electronic medical records. Tumor characteristics were also documented, such as size, degree of differentiation, and distance from the anal verge. Surgical details—including estimated blood loss, operative time, and whether intraoperative blood transfusion was required—were recorded. Postoperative complications were classified using the Clavien-Dindo grading system.

Statistical analyses were performed using SPSS version 28.0 (IBM, Armonk, NY, USA) and Origin Pro 2018 software. Logistic regression models were used to predict postoperative complications based on CRP levels and CRP ratios. Chi-square tests, t-tests, Mann-Whitney U tests, and ANOVA were applied as appropriate to assess group differences. A p-value of less than 0.05 was considered statistically significant.

The primary focus was placed on the incidence of postoperative complications, such as surgical site infections, anastomotic leaks, and other significant adverse outcomes. Additional outcomes examined included the length of hospital stay and the financial burden associated with postoperative complications. Costs were estimated by multiplying the number of hospitalization days by an average daily cost of €75.

Descriptive statistics were used to concisely summarize patient characteristics, procedural details, and postoperative outcomes. Continuous data were presented using measures of central tendency, such as means with standard deviations or medians with interquartile ranges, depending on data distribution. Categorical variables were summarized using frequency distributions and percentages. Comparative analyses involved t-tests or Mann-Whitney U tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables. Analysis of variance (ANOVA) was employed to examine CRP levels across different surgical procedures. Logistic regression analysis was conducted to identify independent variables predictive of postoperative complications.

The study incorporated the following covariates: CRP levels, CRP ratios, surgical approach, and patient demographic data. The strength of associations was assessed by calculating odds ratios (OR) along with 95% confidence intervals (CI). A p-value below 0.05 was considered statistically significant.

Postoperative complications were classified according to the Clavien-Dindo system, a standardized and validated approach commonly used in surgical research to assess the severity of complications [21].

Additionally, four scoring systems were used to assess patient risk and predict postoperative outcomes. The E-PASS system evaluates physiological and surgical factors by calculating the Preoperative Risk Score, Surgical Stress Score, and Comprehensive Risk Score. POSSUM (Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity) is used to predict morbidity and mortality based on standardized criteria. The ACPGBI scoring system incorporates patient demographics and tumor-specific characteristics to estimate risk and outcomes. Finally, CR-POSSUM (Colorectal POSSUM) provides mortality risk predictions specific to colorectal surgery, enabling a more accurate assessment for this surgical population.

In the second, empirical study, we tested the following research hypotheses:

- I1. It is assumed that statistically significant differences exist based on the personal characteristics of patients diagnosed with colorectal cancer (including age, sex, BMI, tumor location, preoperative comorbidities, CCI scores, smoking status, tumor marker levels, ASA score, preoperative and postoperative CRP levels and ratios, and estimated blood loss), as well as environmental factors such as type of surgical procedure, operative time, surgical approach, length of hospital stay, and financial costs, in relation to the occurrence of postoperative complications.
- I2. It is assumed that C-reactive protein (CRP) levels and CRP ratios, tumor distance from the anal verge, the number of preoperative comorbidities, CCI scores, and operative time influence the occurrence of postoperative complications in patients undergoing surgery for rectal cancer.

With regard to the results, it can be stated that the first hypothesis was partially supported by the collected data, while the second hypothesis was confirmed by the analyzed data.

This study introduces the CRP-to-platelet ratio (CPR) as a statistically significant predictor of complications during the first three postoperative days ($p = 0.0466$). The CRP ratio appears to be a more effective predictor, offering improved diagnostic accuracy compared to CRP levels alone. The Charlson Comorbidity Index (CCI) serves as a valid measure of healthcare costs, length of hospital stay, and mortality risk in colorectal cancer patients undergoing surgery. Patients with a CCI score of 3 or higher incur higher costs and experience longer hospitalizations.

While CRP and CCI are valuable tools for predicting postoperative complications and managing healthcare costs, it is essential to consider additional factors, including patient demographics, surgical procedures, and institutional protocols, all of which may also influence outcomes. The prognostic significance of CRP varies depending on the specific surgical

procedure and patient characteristics, highlighting the need for tailored strategies in different clinical settings.

Lastly, the third study highlighted the robust predictive role of cumulative risk scores from prognostic systems such as E-PASS, CR-POSSUM, POSSUM, and ACPGBI in forecasting and managing postoperative complications in rectal cancer surgery.

The elements of originality stem both from the theoretical aspects discussed in this research project and from the findings obtained through the empirical study.

Firstly, a key element of originality lies in the development of a meta-analysis based on a comprehensive, up-to-date, and field-relevant body of literature. This synthesis enables surgeons, through the preoperative interview process, to better anticipate and prevent postoperative complications in patients with rectal cancer. Both patient-related and treatment-related factors are considered in the prevention and prediction of potential postoperative complications in rectal cancer surgery.

Secondly, Study 2 introduces the CRP-to-platelet ratio (CPR) as a statistically significant predictor of complications during the first three postoperative days—an aspect that has been scarcely explored in existing literature. The CPR ratio proves to be a more effective predictor, providing greater diagnostic accuracy compared to CRP levels alone.

Lastly, another element of originality lies in the use of CCI scores as predictors of postoperative complications in patients undergoing rectal cancer surgery. The Charlson Comorbidity Index (CCI) serves as a valid measure of healthcare costs, length of hospital stay, and mortality risk in colorectal cancer patients undergoing surgical procedures. Patients with a CCI score of 3 or higher tend to incur greater costs and experience longer hospitalizations.

While CRP and CCI are valuable tools for predicting postoperative complications and managing healthcare costs, it is essential to also consider other factors, including patient demographics, surgical procedures, and institutional protocols, all of which may influence outcomes. The prognostic significance of CRP varies depending on the specific surgical procedure and individual patient characteristics, highlighting the need for tailored strategies across different clinical contexts.

Another element of originality lies in highlighting the predictive role of cumulative risk scores from prognostic systems such as E-PASS, CR-POSSUM, POSSUM, and ACPGBI in relation to postoperative complications in rectal cancer surgery.

In conclusion, a holistic approach to the rectal cancer patient can benefit both the physician through improved case management and the patient, by enhancing overall quality of life.

In conclusion, our research project can be considered a starting point for surgical practice in both the prediction and prevention of postoperative complications in rectal cancer, through the use of structured interviews and well-informed preoperative consent. Moreover, the application of specific surgical methods and techniques tailored to patients' demographic and clinical characteristics contributes to favorable long-term outcomes and improved quality of life.

REFERENCES

[1] Liu X-Y, Kang B, Lv Q, et al. Phase angle is a predictor for postoperative complications in colorectal cancer. *Front Nutr*; 11. Epub ahead of print 16 August 2024. DOI: 10.3389/fnut.2024.1446660.

[2] Xia C, Dong X, Li H, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chin Med J (Engl)* 2022; 135: 584–590.

[3] Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. *CA: A Cancer Journal for Clinicians* 2019; 69: 363–385.

[4] Liu X-Y, Zhang B, Cheng Y-X, et al. Does chronic kidney disease affect the complications and prognosis of patients after primary colorectal cancer surgery? *World J Gastrointest Oncol* 2022; 14: 1199–1209.

[5] Siegel RL, Wagle NS, Cercek A, et al. Colorectal cancer statistics, 2023. *CA: A Cancer Journal for Clinicians* 2023; 73: 233–254.

[6] Bislenghi G, Vanhaverbeke A, Fieuws S, et al. Risk factors for surgical site infection after colorectal resection: a prospective single centre study. An analysis on 287 consecutive elective and urgent procedures within an institutional quality improvement project. *Acta Chir Belg* 2021; 121: 86–93.

[7] Binefa G, Rodríguez-Moranta F, Teule A, et al. Colorectal cancer: from prevention to personalized medicine. *World J Gastroenterol* 2014; 20: 6786–6808.

[8] Sung H-C, Chang S-M, Lee W-L, et al. The effects of group music with movement intervention on agitated behaviours of institutionalized elders with dementia in Taiwan. *Complement Ther Med* 2006; 14: 113–119.

[9] Kuipers EJ, Grady WM, Lieberman D, et al. Colorectal cancer. *Nat Rev Dis Primers* 2015; 1: 15065.

[10] Liu X-Y, Li Z-W, Zhang B, et al. Effects of preoperative bicarbonate and lactate levels on short-term outcomes and prognosis in elderly patients with colorectal cancer. *BMC Surgery* 2023; 23: 127.

[11] Cheng H, Clymer JW, Po-Han Chen B, et al. Prolonged operative duration is associated with complications: a systematic review and meta-analysis. *J Surg Res* 2018; 229: 134–144.

[12] Chern Y-J, You J-F, Cheng C-C, et al. Decreasing Postoperative Pulmonary Complication Following Laparoscopic Surgery in Elderly Individuals with Colorectal Cancer: A Competing Risk Analysis in a Propensity Score–Weighted Cohort Study. *Cancers* 2022; 14: 131.

[13] Dekker E, Tanis PJ, Vleugels JLA, et al. Colorectal cancer. *The Lancet* 2019; 394: 1467–1480.

[14] Newton DA, Dell AG. Assistive Technology. *J Spec Educ Technol* 2011; 26: 47–49.

[15] Liu X-Y, Li Z-W, Kang B, et al. Does Preoperative Waiting Time Affect the Short-Term Outcomes and Prognosis of Colorectal Cancer Patients? A Retrospective Study from the West of China. *Canadian Journal of Gastroenterology and Hepatology* 2022; 2022: 8235736.

[16] Vandewoude M. Nutritional assessment in geriatric cancer patients. *Support Care Cancer* 2010; 18: 51–56.

[17] Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior tochemotherapy in cancer patients. *The American Journal of Medicine* 1980; 69: 491–497.

[18] Cavagnari MAV, Silva TD, Pereira MAH, et al. Impact of genetic mutations and nutritional status on the survival of patients with colorectal cancer. *BMC Cancer* 2019; 19: 644.

[19] Barbosa-Silva MCG, Barros AJD. Bioelectric impedance and individual characteristics as prognostic factors for post-operative complications. *Clinical Nutrition* 2005; 24: 830–838.

[20] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.

[21] Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240: 205–213.