CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST

DOCTORAL SCHOOL

MEDICINE FIELD

Statistical Predictive Methods for Survival in Colonic Neoplasms

PhD Thesis Summary

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2024

SUMMARY OF THE DOCTORAL THESIS

The doctoral thesis is structured into two parts. The general part consists of four chapters that present the known risk and protective factors for colorectal cancer. It also includes a series of relevant prognostic scores pertinent to this work. The personal contributions section includes the results of the three studies conducted during the doctoral research.

GENERAL PART

Chapter 1: Epidemiology

Colonic cancer is a frequently encountered pathology with high mortality influenced by genetic and environmental factors. Its incidence varies based on gender, geography, and lifestyle, being more common in men and black patients. In recent decades, colonic cancer locations have predominantly shifted to the proximal colon, possibly due to current screening methods that better detect adenomatous polyps in the distal colon. Advanced age is a major risk factor for colonic cancer, with incidence significantly increasing after the age of 40 and peaking between ages 40 and 50. There has been an annual increase in incidence among people under 50 in the United States, suggesting a combination of genetic, environmental, and lifestyle factors, with hereditary genetic syndromes contributing to about 35% of cases. Although screening methods have improved early diagnosis and reduced colonic cancer mortality in many countries, five-year survival varies significantly depending on the disease stage, being much lower in cases with metastasis.

Chapter 2: Risk Factors

Genetic and environmental factors can increase the risk of developing colonic cancers, but most of these cancers are sporadic, not familial. Risk factors for colonic cancer can be classified into high-risk factors that significantly influence screening recommendations, intermediate-risk factors that may influence screening recommendations, and low-risk factors that do not change screening recommendations. High-risk factors include hereditary genetic syndromes, personal or family history of colonic cancers or adenomatous polyps, inflammatory bowel diseases, and abdominal-pelvic radiotherapy. Syndromes such as familial adenomatous polyposis and Lynch syndrome, though responsible for a small percentage of total colonic cancers, require genetic counseling and intensive screening. Factors like age, race, sex, acromegaly, renal transplantation, and others such as obesity, diabetes, consumption of red meat, alcohol, and tobacco are risk factors that can variably influence the risk of colonic cancer but do not directly alter screening recommendations. Obesity and diabetes, for instance, are associated with an increased risk of colonic neoplasm, and the consumption of red meat and processed meats is considered potentially carcinogenic. Furthermore, androgen deprivation therapy and cholecystectomy are associated with an increased risk of colonic cancer. It is essential to identify and adequately monitor patients with known risk factors to enable early detection and effective treatment of colonic cancer.

Chapter 3: Protective Factors

Reducing the risk of colonic cancer is associated with various factors, including regular physical

activity, diet, the use of non-steroidal anti-inflammatory drugs (NSAIDs), and hormonal therapy in women. Physical activity can reduce the risk of proximal and distal cancer by approximately 27% and 26%, respectively. A diet rich in fruits, vegetables, and fiber, as well as the consumption of calcium, vitamin D, and omega-3 fatty acids, may have protective effects, although studies are sometimes contradictory. Additionally, regular intake of aspirin or other NSAIDs can reduce the risk of adenomas and colorectal cancer by 20-40%, and post-menopausal hormone therapy provides additional protection for women. Other dietary factors and supplements such as vitamin B6, magnesium, garlic, and coffee have been associated with a reduced risk of colonic cancer, though the evidence is not always consistent. The use of drugs like erlotinib and statins has shown variable results in colorectal cancer prevention, while the protective role of bisphosphonates and angiotensin II inhibitors is still under study. Although antioxidants and folic acid have been suggested to have protective effects, they have not yet demonstrated a clear and consistent link in the prevention of colorectal adenomas. These findings underscore the importance of a balanced and integrated approach to colonic cancer prevention.

Chapter 4: The Role of Systemic Inflammation Markers in the Prognosis of Colorectal Cancer

The host immune response plays a crucial role in the prognosis of various types of cancer, including colorectal cancer. Tumor-infiltrating lymphocytes (TILs), especially CD8+ and CD45RO+ T cells, have been associated with a favorable prognosis, reflecting earlier disease stages and improved patient survival. In colorectal cancer, increased density of regulatory T cells (CD4+CD25+) has shown robust prognostic significance, superior to CD8+ and CD45RO+ cell infiltration. These lymphoid infiltrates correlate with microsatellite instability (MSI), an indicator of mutations in mismatch repair (MMR) genes, and have been identified as independent prognostic factors. In medullary carcinoma, a subtype of CRC associated with Lynch syndrome, both MSI-H status and intratumoral lymphocytic infiltration are positive prognostic factors.

The Immunoscore is a tool for quantifying the in situ immune infiltrate in colorectal cancer, evaluating CD3+ lymphocytes and CD8+ cytotoxic T cells in the tumor center and invasive margin. It provides independent prognostic value, validated for stage II and III colon cancer, and is useful in identifying patients at risk of recurrence, influencing clinical decisions regarding surveillance and adjuvant treatment. The Immunoscore joins other inflammatory biomarkers like the Glasgow Prognostic Score (GPS) and modified Glasgow Prognostic Score (mGPS), which integrate the systemic inflammatory response to predict survival in CRC patients. The GPS/mGPS is based on serum levels of CRP and albumin, serving as a significant prognostic factor for survival, correlated with malnutrition and sarcopenia in CRC.

The neutrophil-to-lymphocyte ratio (NLR) is another important prognostic marker, reflecting the balance between the pro-tumoral inflammatory state and the anti-tumoral immune response. NLR is calculated by dividing the absolute neutrophil count by the lymphocyte count and has been associated with CRC patient survival. Although preoperative NLR is a simple and popular predictor of survival and disease recurrence, combining it with GPS/mGPS in a new prognostic model has proven superior. Elevated preoperative and postoperative NLR have been correlated with poor prognosis and rapid tumor recurrence after metastasectomy. In unresectable metastatic CRC, high NLR has been associated with poor response to palliative chemotherapy and reduced overall survival. Thus, monitoring NLR along with other inflammatory markers can provide a comprehensive picture of the inflammatory response and prognosis in colorectal cancer.

PERSONAL CONTRIBUTIONS

Chapter 5: Hypothesis and General Objectives

Study Motivation and Working Hypothesis:

The main goal of the thesis was to develop and validate a prognostic and predictive score for colon cancer patients undergoing oncologic treatment.

Secondary Goals:

- Confirmation of the role of existing inflammatory scores.
- Analysis of clinical and paraclinical characteristics of patients with colonic cancer.
- Selection of relevant variables for progression-free survival (PFS) and overall survival (OS).
- Evaluation of clinico-biological parameters and their correlations with PFS/OS.

Key Questions Addressed in the Study:

- Are there significant clinico-biological parameters for PFS/OS in colon cancer?
- What are the threshold ranges of these parameters?
- Can a prognostic score be developed using these parameters?
- Is the prognostic score valid on a separate patient cohort?
- Is the score relevant for both PFS and OS?
- Can previously developed prognostic markers be validated on the study's patient population?

Research Directions:

- **Study 1:** Immune dynamics in the progression and response to chemotherapy in colon cancer.
- **Study 2:** Inflammatory markers, nutritional status, and tumor burden as prognostic factors in colorectal cancer.
  Gustave Roussy Immune Score (GRIm-Score) as a prognostic and predictive score in metastatic colorectal cancer.
- **Study 3:** Development and validation of the SPCC prognostic score based on analyzed clinicopathological characteristics.

Chapter 6: General Research Methodology - Database Composition and Statistical Analysis

This chapter presents the fulfillment of objectives through the three doctoral studies:

- The first study, presented in Chapter 6, addresses key questions 1, 2, and 5.
- The second study, presented in Chapter 7, answers key question 6.
- The third study, presented in Chapter 8, responds to key questions 3 and 4.
  The inclusion and exclusion criteria applied to the patients included in the studies are presented. The variables of interest and the statistical tests applied are also outlined.

Chapter 7: The Role of Immune Cell Dynamics as a Prognostic Factor in Colorectal Cancer

Introduction:

The role of the immune system in the pathogenesis and antitumoral response of cancer has been intensively studied. Research has shown a link between inflammatory factors in the tumor microenvironment and the size, growth rate, and metastasis of the tumor. Chronic inflammation is associated with an increased risk of colorectal cancer (CRC), especially in patients with inflammatory bowel disease. Inflammatory response markers such as cytokines, C-reactive protein (CRP), Glasgow Prognostic Score, and neutrophil/lymphocyte (NLR) and platelet/lymphocyte (PLR) ratios have revealed prognostic value in various solid tumors. NLR, in particular, has been identified as an independent prognostic factor for overall survival and progression-free survival. However, it has not yet been integrated into accepted predictive models.

Objectives:

The aim of this study was to investigate the relationship between NLR and other inflammatory markers and the prognosis and progression-free survival of patients with metastatic colorectal cancer (mCRC). The study also assessed the dynamics of the immune response during chemotherapy and its correlation with prognosis.

Materials and Methods:

The study included a cohort of patients with histologically confirmed mCRC who underwent chemotherapy treatment. Patients' clinical and laboratory data were collected, and the NLR, PLR, and other inflammatory markers were calculated pre- and post-treatment.

Results:

The analysis revealed that elevated pre-treatment NLR and PLR were associated with poor prognosis and reduced overall survival. Additionally, a decrease in NLR during treatment was correlated with improved patient outcomes. The study concluded that NLR and PLR are significant prognostic factors in mCRC and can be useful in predicting response to chemotherapy.

Conclusions:

This study demonstrated the importance of monitoring immune cell dynamics and inflammatory markers in predicting the prognosis of patients with mCRC. NLR and PLR can serve as useful tools in the clinical management of these patients, providing additional information for personalized treatment approaches.

Chapter 8: Nutritional Status, Tumor Burden, and Inflammatory Markers in Colorectal Cancer

Introduction:

Nutritional status and inflammatory markers play a crucial role in the prognosis of colorectal cancer. Malnutrition and cachexia are common in patients with advanced CRC and are associated with poor prognosis. The Gustave Roussy Immune Score (GRIm-Score) is a prognostic score that integrates immune and nutritional parameters and has been shown to be useful in predicting survival in various cancers.

Objectives:

The aim of this study was to evaluate the prognostic significance of the GRIm-Score in patients with mCRC and to validate its use as a predictive tool for chemotherapy response.

Materials and Methods:

The study included a cohort of patients with mCRC who received chemotherapy treatment. The GRIm-Score was calculated based on albumin levels, neutrophil-to-lymphocyte ratio (NLR), and lactate dehydrogenase (LDH) levels.

Results:

The analysis revealed that a high GRIm-Score was associated with poor prognosis and reduced overall survival. Patients with a low GRIm-Score had a better response to chemotherapy and longer progression-free survival.

Conclusions:

The GRIm-Score is a valuable prognostic tool in mCRC, providing additional information on the immune and nutritional status of patients. It can be used to stratify patients and tailor treatment approaches based on individual risk profiles.

Chapter 9: Development and Validation of the SPCC Prognostic Score

Introduction:

Prognostic scores are essential tools in oncology, providing valuable information for treatment decisions and patient management. The SPCC prognostic score was developed based on clinical and pathological characteristics of patients with mCRC and validated in a separate cohort.

Objectives:

The aim of this study was to develop and validate the SPCC prognostic score and assess its utility in predicting overall survival and progression-free survival in patients with mCRC.

Materials and Methods:

The study included a cohort of patients with mCRC who received chemotherapy treatment. Clinical and pathological data were collected, and the SPCC score was calculated based on relevant prognostic factors.

Results:

The analysis revealed that the SPCC score was a significant predictor of overall survival and progression-free survival in patients with mCRC. The score was validated in a separate cohort, demonstrating its robustness and applicability in clinical practice.

Conclusions:

The SPCC prognostic score is a valuable tool for predicting outcomes in patients with mCRC. It provides additional information for treatment decisions and can help identify patients at higher risk of poor prognosis.

Chapter 10: Final Conclusions

The doctoral research conducted in this thesis has provided valuable insights into the role of immune cell dynamics, nutritional status, and inflammatory markers in the prognosis of colorectal cancer. The development and validation of the SPCC prognostic score offer a new tool for predicting outcomes in patients with mCRC, contributing to personalized treatment approaches and improved patient management.

Chapter 11: Originality and Innovative Contributions

The thesis has made several original and innovative contributions to the field of oncology. These include the development of the SPCC prognostic score, the validation of the GRIm-Score in mCRC patients, and the demonstration of the importance of immune cell dynamics and inflammatory markers in predicting patient outcomes. The research has provided new insights

into the complex interplay between the immune system, nutrition, and cancer progression, paving the way for future studies and potential clinical applications.

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