Colorectal carcinoma – epidemiology, risk factors, prognostic biomarkers

Kolorektálny karcinóm – epidemiológia, rizikové faktory, prognostické biomarkery

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Summary

Background: In terms of epidemiology, colorectal carcinoma (CRC) represents one of the most prevalent tumors worldwide. Progress in research has translated into reduced mortality of the disease, but the trend of early onset CRC troubles most of the developed countries. Identification and validation of effective prognostic biomarkers are crucial for improving diagnostic accuracy and treatment outcomes. ***Purpose:*** The objective of the work is to analyze the latest data on the epidemiology and risk factors of CRC. A narrative review also aims to summarize current knowledge about various prognostic biomarkers in the treatment of CRC, including indicators of performance status, nutritional, and inflammatory markers. ***Conclusion:*** CRC pose major health problem in most of the countries and the tumor biomarkers as well as patients pre-treatment condition are crucial to establish prognosis of the disease. Nutritional and performance status indicators play an essential role in assessing the patient's condition and influence treatment decisions, with a potential impact on treatment outcomes. Inflammatory markers have demonstrated significant prognostic value, correlating with the patient's immune response to the tumor and inflammatory processes that may promote disease progression. Despite promising predictive capabilities, these biomarkers are not yet routinely used in clinical practice due to the need for further research validation. The integration of new biomarkers into clinical practice could lead to more personalized treatment decisions and improved treatment outcomes. For a more comprehensive assessment of the validity of these biomarkers and their application in regular clinical practice, further research is necessary.

Key words

colorectal carcinoma – epidemiology – risk factors – TNM classification – protooncogenes –inflammation – nutrition

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Súhrn

Východiská: Z hľadiska epidemiológie predstavuje kolorektálny karcinóm (KRK) celosvetovo jeden z najčastejšie sa vyskytujúcich nádorov. Pokrok vo výskume sa premietol do zníženia úmrtnosti na toto ochorenie, avšak zníženie veku vzniku KRK vytvára obavy vo väčšine rozvinutých krajín. Identifikácia a validácia účinných prognostických biomarkerov sú kľúčové pre zvýšenie presnosti diagnostiky a individualizáciu liečby. ***Cieľ:*** Cieľom práce je analyzovať najnovšie údaje o epidemiológii a rizikových faktoroch KRK. Naratívny prehľad sa zameriava aj na zhrnutie súčasných poznatkov o rôznych prognostických biomarkeroch pri liečbe KRK, vrátane ukazovateľov výkonnostného stavu, nutričných a zápalových markerov. ***Záver:*** KRK predstavuje závažný zdravotný problém vo väčšine krajín a nádorové biomarkery, ako aj stav pacienta pred liečbou, sú rozhodujúce pre určenie prognózy ochorenia. Ukazovatele nutričného a výkonnostného stavu zohrávajú zásadnú úlohu pri hodnotení stavu pacienta a ovplyvňujú rozhodnutia o liečbe, s potenciálnym dopadom na jej výsledky. Zápalové markery sa javia ako významný prognostický faktor, korelujúc s imunitnou odpoveďou pacienta na nádor a zápalovými procesmi, ktoré môžu viesť k progresii ochorenia. Napriek ich sľubnej prediktívnej sile sa tieto biomarkery zatiaľ bežne nepoužívajú v klinickej praxi z dôvodu potreby ďalšej vedeckej validácie. Integrácia nových biomarkerov do klinickej praxe by však mohla viesť k personalizovanejším liečebným stratégiám a tým k zlepšeniu prežívania pacientov. Pre komplexnejšie posúdenie validity týchto biomarkerov a ich aplikácie v bežnej klinickej praxi je potrebný ďalší výskum.

Kľúčové slová

kolorektálny karcinóm – incidencia – mortalita – rizikové faktory – TNM klasifikácia – protoonkogény – zápal – výživa

Introduction

This narrative review aims to provide a comprehensive overview of colorectal carcinoma (CRC) by analyzing the epidemiological data and risk factors associated with CRC, summarizing current knowledge of prognostic biomarkers, and exploring their implications for personalized treatment strategies. These objectives are particularly relevant given CRC's substantial global burden, ranking as one of the most prevalent and lethal malignancies worldwide. The review also highlights the increasing incidence of early-onset CRC and its significant regional variations, underscoring the need for improved understanding and management strategies.

The scope of this review includes a detailed analysis of epidemiological trends and risk factors, categorized into modifiable (e.g., lifestyle-related factors) and non-modifiable (e.g., genetic predispositions) categories. Additionally, it examines prognostic biomarkers with a focus on indicators of tumor biology, such as proto-oncogenes, tumor-infiltrating lymphocytes, and tumor budding, alongside patient-specific factors like nutritional status and inflammatory markers. The prognostic utility of these biomarkers is critically evaluated in terms of their ability to predict treatment outcomes and guide clinical decision-making.

The review methodology involves a structured search of relevant scientific databases, including PubMed, Scopus, and Web of Science, to identify high-quality epidemiological datasets, peer-reviewed journal articles, and current clinical guidelines. Sources were selected based on their relevance and rigor to provide a synthesized understanding of the topic. By integrating existing knowledge, this article emphasizes the potential of validated biomarkers to enhance diagnostic precision, stratify patients more effectively, and improve prognostic assessments. Ultimately, this review seeks to contribute to the advancement of personalized treatment strategies for CRC by advocating for the integration of comprehensive biomarker evaluation into clinical practice.

Epidemiology

CRC poses a global public health challenge since it is the third most common and the second most deadly malignancy worldwide. Data show there are 1.9 million new cases and 0.9 million deaths to CRC every year. Statistics predict incidence rising to 3.2 million new cases in 2040 [1].

In Slovakia, the most recent statistically processed and nationally published hard data on CRC incidence (ICD-10 diagnoses C18 – colon, C19 – colorectal junction, C20 – rectum, and C21 – anus and anal canal) are from 2014 [2]. At that time, there were a total of 3,915 newly diagnosed cases (2,268 C18 cases; 431 C19 cases; 1,169 C20 cases; and 58 C21 cases): 2,256 cases in males (1,226 C18; 239 C19; 769 C20; and 22 C21) and 1,659 in females (1,042 C18; 181 C19; 400 C20; and 36 C21). This corresponds to a standardized incidence rate (ASR-W) of 40.2 per 100,000 in both females and males; 55.2 per 100,000 in males (30.0 per 100,000 for C18; 5.8 per 100,000 for C19; 18.9 per 100,000 for C20; and 0.5 per 100,000 for C21) and 29.1 per 100,000 in females (18.0 per 100,000 for C18; 3.2 per 100,000 for C19; 7.3 per 100,000 for C20; and 0.6 per 100,000 for C21) [2]. The CRC incidence prediction for 2024 published by the National Cancer Registry of the Slovak Republic (NCR SR) is 5,126 cases for both females and males combined (N = 3,043 in males, ASR-W 56.1 per 100,000, and N = 2,083 in females, ASR-W 29.5 per 100,000) [3]. In males, 24.9% of patients were diagnosed at clinical stage I in the year 2014, 23.3% at stage II, 29.9% at stage III, 21.3% at stage IV, and the clinical stage was unknown in 0.6% of cases. In females, 21.0% of patients were diagnosed at stage I, 22.9% at stage II, 31.9% at stage III, 22.8% at stage IV, and the clinical stage was unknown in 1.4% of cases [2].

Data on CRC mortality are published annually by the Statistical Office of the Slovak Republic [4]. In 2023, CRC caused a total of 1,724 deaths (1,021 in males and 703 in females), corresponding to an ASR-W mortality rate of 13.8 per 100,000 (19.8 per 100,000 in males and 9.3 per 100,000 in females) [4].

The prevalence of the disease was latest published for the year 2012, in males it was higher than in females, ac-

counting for 12,308 cases in males and 10,288 cases in females [5].

The incidence of CRC varies between countries and regions, across age groups [6]. According to the International Agency for Research on Cancer of the World Health Organization (IARC WHO) estimates, the global ASR-W incidence in 2022 was 18.4 per 100,000 (15.2 per 100,000 in females and 21.9 per 100,000 in males), making CRC the fourth most common newly diagnosed malignancy in females and males combined. In Europe, the number of newly diagnosed CRC cases in 2022 was estimated to be 538,532, corresponding to an ASR-W incidence of 30.5 per 100,000 (24.8 per 100,000 in females and 37.7 per 100,000 in males). The highest incidence worldwide was estimated in Denmark (48.1 per 100,000), Norway (45.3 per 100,000), and Hungary (44.2 per 100,000). Due to the unavailability of local hard data, IARC WHO estimated the CRC incidence in Slovakia to be 35.7 per 100,000 (4,219 cases), ranking it on the 9th place globally [6]. The number of incident cases estimated by IARC WHO is significantly lower than the NCR SR prediction (4,945) [6]. The incidence of CRC in the Czech Republic was estimated to be 30.5 per 100,000, in Poland 30.9 per 100,000, in Austria 21.8 per 100,000, and in Ukraine 24.2 per 100,000. According to IARC WHO estimates, CRC caused 247,784 deaths worldwide in 2022, with an ASR-W of 12.1 per 100,000 (9.4 per 100,000 in females and 15.7 per 100,000 in males), making it the third most common cause of death from malignancy [6]. Worldwide, the highest mortality rates were estimated in Hungary (20.2 per 100,000), Croatia (18.5 per 100,000), Brunei (17.4 per 100,000), and Slovakia (17.2 per 100,000) [6]. Compared with the IARC WHO estimate, the actual ASR-W mortality in Slovakia in 2022 was lower, at 14.27 per 100,000 [4]. In neighboring countries, the IARC WHO estimated CRC mortality rates varied: Poland 15.6 per 100,000, Ukraine 12.3 per 100,000, Czech Republic 12.1 per 100,000, and Austria 8.4 per 100,000 [6].

CRC presents a significant global public health challenge. Each year, there are 1.9 million of new cases and 900,000 deaths attributed to CRC. In less developed countries, CRC incidence is increasing due to westernization, which leads to greater exposure to risk factors and increased life expectancy. Projections estimate that the number of new cases will rise to 3.2 million by 2040 [1].

Risk factors

The risk factors for CRC can be categorized into modifiable and non-modifiable types. Modifiable risk factors primarily involve lifestyle choices, such as diet, physical activity, and substance use (smoking, alcohol, drugs). Non-modifiable risk factors include factors such as age, sex, race, and genetic predisposition.

Non-modifiable risk factors

Sex

Cancer statistics in the United States show interesting sex disparities in CRC incidence. Although lifetime risk is similar for both men and women (4.4% in men, 4.1% in women), the age-standardized incidence of CRC is 31% higher in men due to their shorter life expectancy [1]. This trend is even more distinctive in rectal cancer with a 75% higher incidence in men than in women. However, there has been a multinational cohort study preformed in multiple European countries which demonstrated a higher prevalence of proximal colon cancer in women [7]. One of the potential explanations is the shift to more proximal CRC location with age subsequently leading to a higher incidence in women due to their longevity [8,9].

Age

CRC is considered a disease of the elderly with a significant increase in incidence after the age of 50 years. This is due to the accumulation of DNA mutations and prolonged exposure to carcinogenic risk factors. However, one of the most challenging topics is the current rise in incidence of early-onset CRC. Screening programs in most developed countries target subjects aged 50 years old and above, making the detection of an early onset CRC difficult. Data from a multinational European study analyzing incidence of subjects younger than 50 years showed an increase in incidence, specifically 7.9% per year among people aged 20–29, 4.9% per year in the 30–39 age group and 1.6% per year in the 40–49% age group [8]. The cause of this trend remains unknown. This increase in incidence in the younger population has led to the American Cancer Society recommendation to start screening at age 45 years instead of 50 years [10]. Current European guidelines remain unchanged (recommendation for screening starts at 50 years of age).

Genetic risk factors

Most cases of CRC (60–65%) are considered sporadic without known family history and without discovered genetic alterations [11]. The remaining 35–40% of cases may be driven by hereditary components (family history, IBD, hereditary cancer syndromes (such as familial adenomatous polyposis or Lynch syndrome)) [12]. Patients with hereditary CRC tend to be younger at the age of the diagnosis (40 years old compared to 68 in cases of sporadic CRC). It is important to note that even in patients with a family history of genetic burden, environmental factors and lifestyle choices may still have a major influence on CRC development.

Modifiable risk factors

The incidence and mortality of CRC greatly depend on modifiable risk factors, such as low physical activity, obesity, poor diet, drug intake and alcohol consumption. A sedentary lifestyle increases CRC incidence by 25–50% when the risk for inactive people was compared to those physically active [13]. Obesity increases the incidence by 50% in men and 10% in women [14]. High consumption of processed food, red meat and a low calcium diet increase the risk of CRC [15]. Alcohol is a well-known carcinogen causing damage to colorectal mucosa and leading to epigenetic alterations which increase CRC incidence [16]. Other potential risk factors not yet deeply examined but suspected in the potentially increased risk of developing CRC are arterial hypertension, chronic kidney disease, hypovitaminosis (especially in vitamin D) and occupational exposure to organic dusts [17].

Prognostic factors

The prognosis and survival of CRC patients vary dramatically, ranging from 90% to 10% related to a five-year survival rate, depending on stage and other factors [18]. This leads to an urgent need of further prognostic and predictive markers in order to implement the character and biology of each tumor, which would help guide the clinician in an increasingly personalized decision-making process. Prognostic factors are clinical, pathological, or molecular characteristics that provide information about the likely course and outcome of CRC independent of treatment. These factors are crucial in guiding medical decisions, as they help stratify patients based on their risk profiles, predict disease progression, and inform the choice of therapeutic strategies. Patients with favorable prognostic indicators may be candidates for less aggressive treatment or even surveillance. Patients with poor prognostic factors may require more intensive treatment to improve outcomes. The use of prognostic factors is crucial for predicting recurrence, guiding treatment decisions, enabling personalized treatment, considering patient-specific factors, and enhancing shared decision-making to optimize outcomes.

Predictive markers, on the other hand, indicate the likely benefit from a specific therapy, such as the *RAS* mutation predicting resistance to anti-EGFR therapy, guiding clinicians to use the most accurate treatment for each patient.

The TNM classification is currently the most widely used staging tool and a potent prognostic factor in CRC [19]. However, it does not account for the molecular subtypes of tumors, which can result in significant discrepancies in clinical outcomes among patients with the same clinical-pathological TNM stage. This limitation highlights the need for further risk and prognostic stratification to identify high-risk patients more accurately. Such stratification is crucial for guiding clinical management and predicting survival outcomes effectively.

In addition to TNM staging, patient comorbidities represent another important prognostic factor. Additional diseases or conditions coexisting with CRC, such as cardiovascular disease, diabetes, chronic kidney disease, and obesity can have major influence on disease outcome. Comorbidities can significantly affect a patient's ability to tolerate treatment, influencing both surgical and systemic therapy approaches. For instance, patients with multiple comorbidities may face increased risks of morbidity during or after surgery. Similarly, aggressive chemotherapy regimens may be unsuitable for such patients due to the heightened risk of adverse effects, further complicating treatment planning.

This underscores an unmet need in clinical practice for more comprehensive and multifactorial evaluation systems that can enable better stratification of patients and more tailored treatment approaches, combining established fundamental factors with emerging molecular and genetic advancements.

TNM classification

This staging classification was introduced to define the local and distant extent of malignancy and from its introduction in 1968 by the American Joint Committee on Cancer (AJCC). This classification remains the gold standard for assessing the stage of most of the solid tumors. It helps to determine prognosis and tailor further treatment. The TNM classification has the strongest prognostication in stage I and IV; in stage II and III the heterogeneity of the disease requires further stratification to assess prognosis and the best therapeutic approach. TNM staging is highly associated with a five-year overall survival in CRC, ranging from 92% in stage I to 11% in stage IV [20].

Tumor staging

Tumor staging ("T" in the TNM classification) explains the extent of invasion of the intestinal wall by the tumor. Higher T stage is associated with worse overall survival as well as disease-free survival and relapse [21]. Tsikitis et al. [22] found a three-fold increased risk of recurrence in T4 tumors compared to T3 tumors. The T-stage is causally linked to nodal involvement and distant metastases – higher T is directly proportional to higher nodal and distant metastases.

Nodal staging

Nodal staging ("N" in the TNM classification) describes the number of regional lymph nodes affected by malignancy. The current consensus states that in colon cancer it is necessary to collect and examine at least 12 lymph nodes for the staging to be reliable [23]. Regional lymph node involvement is a negative prognostic factor, with five-year overall survival in the range of 30–60% in patients with positive regional lymph nodes involved, compared to 70–90% in patients with negative lymph node findings [24]. The recurrence rate is also higher in cases with nodal positivity, approximately 35%, with most recurrences happening within the first three years after surgery [25]. Nodal staging plays a crucial role in determining the need for adjuvant treatment, with nodal involvement being one of the key indicators for such therapy. Adjuvant treatment in lymph-node positive disease reduces the risk of distant metastases, decreases the risk of death by 10–20% and the risk of recurrence by 40% [23,25].

Metastasis staging

The occurrence of distant metastasis ("M" in the TNM classification) is a key prognostic factor in CRC, significantly contributing to poor outcomes. Approximately 35–50% of patients present with distant metastases at the time of diagnosis, which is a major driver of the high mortality rate in CRC [26]. In such cases, systemic therapy with palliative intent is typically administered, extending the median survival from 5 to 18 months [27]. The liver is the most common site of metastasis in CRC due to the lymphatic and portal drainage from the colon through the portal vein. However, because of the anatomical differences in the venous system of the rectum, metastases from rectal cancer may initially appear in the lungs, as the inferior rectal veins drain into the inferior vena cava rather than the portal system [28,29].

Tumor grade

Tumor/histological grade is defined as the degree of cancer differentiation. A higher grade has been proven to be

a poor prognostic factor in CRC in all stages of the disease, independent of T and N stages [30]. This worsening is seen in overall survival, disease-free survival as well as recurrence rate. Ueno et al. calculated the five-year disease-free survival rates to be 96%, 85%, and 59% for G1, G2, and G3, respectively [31]. A higher histological grade is associated with deeper tumor invasion, positive lymph nodes, and lymphovascular and perineural invasion. A limitation of tumor grading is the subjectivity of its assessment. Pathologists do not have unanimous agreement on whether the histological grade should be based on the predominant pattern of differentiation or on the cells with the least differentiation, even if the latter are present in only a small amount [30]. Similar to some other poor prognostic factors, patients with high-grade tumors are more likely to be eligible for adjuvant systemic treatment.

Tumor budding

Tumor budding was first described in 1954 as "sprouting" of the invasive carcinoma leading to more rapid tumor growth [32]. Nowadays it is believed to represent an example of epithelial-mesenchymal transition characterized by the loss of cell adhesion molecules and the ability to degrade basement membrane resulting in a process of tumor cell migration – metastasis [33]. These tumor "buds" are clusters of one to four dissociated malignant cells most commonly seen at the invasive front of the tumor. The link between tumor budding and a higher presence of lymphovascular invasion and lymph node involvement has been repeatedly established [34]. Currently it is believed that tumor budding is the sign of acquired tumor capacity to invade lymphatic structures. This has been documented by "budding nests" most commonly found close to lymphatics and some studies even proved that the buds are located in fact in small lymphatic spaces [35]. The relationship between tumor budding and the vascular system has not been documented; it is currently believed to be linked uniquely to the lymphovasculature. In multiple analyses, tumor budding has been linked with an increased malignant potential of a tumor and understood to be a poor prognostic factor worsening overall survival, disease free survival and recurrence rate [36]. It is often linked with poor tumor differentiation and other aggressive pathological features. Tumor budding therefore has the potential to distinguish high-risk patients who would benefit from adjuvant systemic treatment. The prognostic value of tumor budding is the most significant in the early stages because after the spread of a tumor to the lymph nodes, the presence of tumor budding near the primary tumor becomes less relevant. Lugli et al. [37] have shown that immune lymphocytic reaction to tumor budding is linked to better prognosis. This reaction may be a sign of patient's immunocompetence to target the tumor buds, leading to a reduction in the metastatic potential of a tumor.

Like other histological features, the assessment of tumor budding shows considerable inter-observer variability. This variability has been noted in both hematoxylin and eosin staining as well as in immunohistochemistry. The inconsistency in evaluation is one reason it has not been widely adopted in routine pathological reporting. Another challenge is the lack of well-defined evaluation criteria. However, further research in the coming years may help establish a standardized cutoff definition.

Inflammation

Cancer-related inflammation is considered one of the hallmarks of cancer [38]. Cancer associated fibroblasts, endothelial cells, tumor-associated macrophages and other pro-inflammatory variables form a pro-cancerous microenvironment leading to tumor growth and aggressiveness. It is the reason why multiple inflammatory markers are studied as potential prognostic markers.

High serum C-reactive protein (CRP) levels correlated with worse survival in patients after primary tumor surgery [39]. Another serum inflammatory marker is the pre-treatment neutrophil to lymphocytes ratio (NLR). The inflammatory state of the patients is believed to determine disease progression [40].

The platelet-to-lymphocytes ratio compares the number of platelets to lymphocytes and a higher value suggests a hypercoagulable state with a lower immune response to the tumor. It seems to be a poor prognostic factor [41].

The lymphocyte to monocytes ratio (LMR) was evaluated in multiple settings. Higher LMR (above 3.11) in chemotherapy-naïve patients with metastatic CRC lead to better prognostic outcomes – better disease-free survival (9.2 vs. 7.6 months) as well as overall survival (19.4 vs. 16.6 months) compared to patients with a lower LMR [42]. The Glasgow prognostic score (GPS) is defined by the presence of elevated CRP level (above 1.0 mg/dL) and hypoalbuminemia (below 3.5 g/dL). With both parameters present, the patient's score is 2, and with one of them, the score is 1. Patients with a score of 2 have been found to have reduced cancer-specific survival and also lower chemotherapy tolerance [43,44]. The diagnostic value of other serum compounds has been studied. Some of them are the fractional albumin rate (FAR = 100 × fibrinogen/albumin) and the fibrinogen to prealbumin ratio (FPR). Their role in CRC is not yet clear. Some studies have shown that NLR, FPR and FAR are increased in the early stage of CRC compared to the healthy population, which may lead to implementing these markers in screening in the future [45].

Tumor-infiltrating lymphocytes

Tumor-infiltrating lymphocytes (TILs) are a histopathological feature representing patient's immunogenicity, which is believed to be the protective factor against tumor progression. Lymphocytes in the tumor activates other immune cells suppressing tumor growth and dissemination, leading to slower tumor progression [46]. A deeper dive into the topic goes beyond the extent of this article, however, we may notice that the tumor-infiltrating leukocytes are a very large cohort of a heterogenous population divided into numerous subsets of immune cells. Results of mouse tumor models revealed that the contribution of individual leukocyte subsets has a different impact on tumor progression (either by

directly affecting tumor cells/immune cells or by influencing tumor microenvironment). It has been documented that different leukocyte populations may correlate with either better or with worse prognoses. For example, the infiltration of the tumor by myeloid cells and some specific regulatory T-lymphocytes seems to correlate with accelerated tumor progression [46,47]. However, the presence of a high density of TILs is an overall positive prognostic factor in CRC, associated with prolonged overall survival and even more favorable histopathological characteristics, such as a lower rate of lymphovascular, vascular and perineural invasion, a lower number of affected lymph nodes and a lower distant metastatic count [48,49]. As we have stated before, tumor-infiltrating lymphocytes are often associated with microsatellite instable (MSI) tumors. Of all lymphocyte subtypes, $CD3^+$ (and $CD8^+$ to a lesser extent) seems to possess the strongest association with survival benefit [50,51]. Consistent with some other histopathologic measures, there is currently no standardized method of TILs evaluation, leading to a lack of reproducibility and high interindividual subjectivity [48,50]. The modification in TILs evaluation could lead to the development of new immunological scoring systems like Immunoscore. This approach combines immunohistochemical analysis of two distinct tumor regions – the core and the invasive margin – resulting in more accurate assessments and, consequently, more precise prognostic predictions [52].

Molecular biomarkers

BRAF

The *BRAF* (v-raf murine sarcoma viral oncogene homolog B1) is a protooncogene that encodes the B-RAF protein kinase, which is a part of the so-called mitogen-activated protein kinase/extracellular signal-regulated (MAPK/ERK) pathway [53]. This pathway is a crucial part of physiologic cellular processes and is important for human cancer cell survival, dissemination and resistance to certain anti-cancer drugs. Mutation in this pathway can lead to an alteration of signaling from external growth factors, stimulations of other cells and an impact on tumor microenvironment. Mutations can occur upstream in membrane receptor genes (e. g. *EGFR*), in signal transducers (RAS) or downstream kinases belonging to the MAPK/ERK pathway (BRAF) [53]. *BRAF* mutation occurs in approximately 11% of all CRC. There are around 30 types of *BRAF* mutations, the most common one is *T1799A* transversion in exon 15, which results in a valine amino acid substitution – V600E (around 90% of BRAF-mutated tumors). This results in auto-regulatory phosphorylation leading to a 10-fold increase in *BRAF* activity compared to non-mutated tumors. Interestingly, BRAF-mutated tumors seem to arise more often from serrated polyps compared to classic adenomatous polyps. Serrated polyps are considered its precursor lesions [54]. The prognostication of patients carrying a *BRAF* mutation is not yet totally clear, most studies lean to classification of this trait as a poor prognostic factor [54]. Patients with BRAF-mutated tumors are more frequently older at diagnosis and more often females. There seems to be an association between BRAF-mutated CRC and mucinous pathohistology, higher grade and proximal location (which are – as we have seen before – independent poor prognostic factors) [55]. The prognostic value of *BRAF* mutation varies across different stages of the disease and may be influenced by MSI status. However, there is currently no evidence to suggest that *BRAF* mutation impacts the survival of patients in stage I [56]. Most studies on the prognostic value of *BRAF* mutations have been conducted in the metastatic setting of the disease. Patients with *BRAF* mutations generally exhibit worse overall survival and progression-free survival. However, some studies suggest varying outcomes based on the tumor's microsatellite stable (MSS) or MSI status. No significant difference in survival has been observed in BRAF-mutated MSI tumors, while worse survival has been noted in BRAF-mutated MSS tumors [57,58]. This may be influenced by relatively low frequency of MSI-H BRAF-mutated metastatic CRC. The poorer outcomes in patients with BRAF-mutated tumors are partly due to the reduced benefit these tumors derive from treatment with anti-epidermal growth factor receptor antibodies, making it also a predictive biomarker as well as a prognostic one. Unlike certain other malignancies, such as BRAF-mutated melanoma, monotherapy with *BRAF* inhibitors in metastatic CRC has shown limited efficacy. Additionally, the pattern of metastasis differs compared to BRAF-wild type tumors; BRAF-mutated tumors are less likely to affect the liver and lungs and tend to infiltrate the peritoneum more frequently [59]. The accuracy of prognostication should be increased by combining with other biomarkers such as RAS, PIK3CA, MSI and also with overall pathologic staging.

RAS

The *RAS* gene family encodes four cytoplasmic proteins with GTPase activity: *H-RAS, K-RAS4a, K-RAS4b* and *N-RAS*. Their function is to transduce extracellular signals into transcription factors and cell cycle proteins in the nucleus for cell growth, differentiation and proliferation. Once activated, *RAS* receives stimuli and subsequently signals from a number of pathways, including MAPK/ERK [60]. It is an upstream gene of the *BRAF* gene in the MAPK/ERK pathway, resulting in certain overlapping characteristics with BRAF-mutated tumors, being therefore also a potent predictive biomarker in terms of efficacy of treatment with anti-EFGR therapy. Activating *RAS* mutations have been found in approximately 20–25% of human cancers. These mutations lead to permanently activating state increasing proliferation, angiogenesis, decreased apoptosis and altered cellular metabolism. The most commonly mutated are *K-RAS* (22% of human cancers), *N-RAS* (8%) and *H-RAS* (3%). *K-RAS* mutations are commonly found in gastrointestinal cancers, lung cancer, and biliary tract cancer; *N-RAS* mutations are found in melanoma and hematologic malignancies. *H-RAS* may be present in head and neck cancers and malignancies of the urinary tract [58,60]. *K-RAS* and *N-RAS* are typically mutually exclusive. *RAS* mutations usually precede the development of malignancy [61].

Microsatellite instability

Microsatellites are short tandem repeats of DNA sequences located throughout the genome. MSI is the term for a deficient DNA mismatch repair (MMR) system leading to a failure in the correction of these repeating units during replication of the DNA. Mutation in MMR is commonly caused by inactivation of four MMR genes (*MLH1* (around 95% of MSI tumors are due to inactivation of the *MLH1* gene), *MSH2, MSH6* and *PMS2*). Reduced expression of these genes classifies the tumor as MSI (or MMR deficient – dMMR). The stable system is classified as MSS or proficient MMR (pMMR). Microsatellite instability is found in approximately 15% of CRC. Out of them, 3% are associated with Lynch syndrome (hereditary non-polyposis CRC) [62]. There has been evidence that the prevalence of MSI tumors is different in different stages of the disease. In stages II and III around 15% are MSI and in stage IV it drops to 4–5% [63]. MSI tumors have some distinctive features – they are more commonly located on the right side of colon, they are more often present with mucin or signers ring cell histology, with higher TILs and less differentiation [64]. Despite these histopathological characteristics (of which some are linked with poor prognosis), MSI-high patients show better prognosis compared to MSS patients [62,65]. They are more often younger, female and diagnosed at an early stage [57]. Similar to BRAF-mutated tumors, MSI tumors commonly develop from sessile polyps. In sporadic MSI tumors, the *BRAF* gene is also often mutated (*BRAF* mutation essentially excludes a diagnosis of Lynch syndrome). The exact correlation is unclear since the *BRAF* gene does not contain a coding microsatellite sequence. Some studies propose that the improved prognosis is attributed to the protective role of MSI and the resulting immunogenicity of TILs, which act against tumor dissemination [66]. This would explain the lower prevalence of MSI in a metastatic setting. In metastatic CRC, the data on the prognostic influence of MSI status are not well understood yet. Certain studies demonstrate a worse prognosis in MSI-H metastatic tumors compared to MSS ones [59,67]. In terms of its predictive value, it is believed that the resistance to 5-fluorouracil (5-FU) therapy observed in MSI-high metastatic CRC may be one of the factors contributing to a worse prognosis [68]. In addition, the stage III CRC patients with Lynch syndrome treated with 5-FU do not demonstrate a five-year survival benefit compared to untreated patients [12]. The better outcome of patients is certainly sustained by the introduction of immunotherapy, which has a substantial effect on patient's prognosis.

Nutritional prognostic index

It has been documented that an inflammatory response after tumorigenesis leads to cancer-associated malnutrition [69]. The inflammatory cytokine interleukin 6 plays a key role in regulating albumin production by hepatocytes, which partly explains why chronic inflammation contributes to hypoproteinemia in CRC patients [70]. Patients with gastrointestinal cancers are particularly susceptible to poor nutritional status, and their preoperative nutritional condition is closely linked to their clinical outcomes [69,71]. Several nutritional assessment tools have been developed, including the Onodera's Prognostic Nutritional Index (OPNI). This index uses two serum parameters – albumin and total lymphocyte count – to evaluate both the nutritional and inflammatory status of a patient through a mathematical formula. Research has demonstrated that OPNI is linked to patient prognosis, with those having a higher pretreatment OPNI showing significantly improved overall survival [72].

Conclusion

Our investigation into epidemiology, risk factors and prognostic biomarkers provides substantial evidence that a patient's preexisting conditions, along with the immunohistopathological features of their tumor, play a critical role in determining both survival outcomes and treatment efficacy across all stages of CRC. Nutritional status, inflammation, immune response, and the presence of comorbidities are intricately connected to the progression and prognosis of the disease. These findings reinforce the importance of considering a broad range of biological factors when evaluating patients, as they contribute to variations in clinical outcomes.

As we move further into the era of personalized medicine, where treatment strategies are increasingly tailored to individual patients, the demand for reliable, accessible biomarkers becomes even more pressing. The growing complexity and cost of novel therapeutic options make it crucial to identify biomarkers that can not only guide treatment decisions, but also do so in a way that is both efficient and affordable. In this context, the development of accurate, cost-effective biomarkers has the potential to optimize treatment strategies, improve patient outcomes, and address the financial burden associated with advanced cancer therapies. This underscores the urgent need for ongoing research to establish biomarkers that meet these evolving clinical needs.

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