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Markers of gastrointestinal diseases

Ostanko V.L.[1], Kalacheva T.P.[1], Kulumaeva K.A.[1], Li N.A.[2], Beloborodova E.V.[1], Purlik I.L.[1], Kalyuzhina E.V.[1], Brazovskaya N.G.[1], Kalyuzhin V.V.[1]

[1] Siberian State Medical University
2, Moscow Trakt, Tomsk, 634050, Russian Federation

[2] Regional Oncology Center
115, Lenina Av., Tomsk, 634050, Russian Federation

ABSTRACT

The lifestyle of people nowadays and poor diet are factors affecting the increasing incidence of digestive diseases in people all over the world. The search for new methods of early diagnosis of the disease is an urgent issue of modern medicine. In the last decade, much attention has been paid to various biological markers that can be used to assess the risk of disease development, the response to therapy, and the possible development of complications. Biomarkers in clinical medicine can be used as additional tools not only to improve early diagnosis of gastrointestinal diseases but also to assess the effectiveness of therapy.

The aim of this lecture was to analyze and systematize biomarkers in various gastrointestinal diseases.

Keywords: biomarker, atrophic gastritis, inflammatory bowel disease, pancreatic cancer, fecal calprotectin, fatty acid-binding protein, microRNA

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Маркеры заболеваний желудочно-кишечного тракта

Останко В.Л.[1], Калачева Т.П.[1], Кулумаева К.А.[1], Ли Н.А.[2], Белобородова Е.В.[1], Пурлик И.Л.[1], Калюжина Е.В.[1], Бразовская Н.Г.[1], Калюжин В.В.[1]

[1] Сибирский государственный медицинский университет (СибГМУ)
Россия, 634050, г. Томск, Московский тракт, 2

[2] Томский областной онкологический диспансер
Россия, 634050, г. Томск, пр. Ленина, 115

РЕЗЮМЕ

Образ жизни современного человека, неправильное питание – факторы, влияющие на рост заболеваний органов пищеварения у людей во всем мире. Поиск новых методов ранней диагностики болезни – актуальный вопрос современной медицины. В последнее десятилетие большое внимание уделяется различным биологическим маркерам, позволяющим оценивать риск развития заболевания, ответ на терапию и возможное развитие осложнений. Биомаркеры в клинической медицине могут использоваться в качестве

✉ *Kalacheva Tatyana P.,* tatyana-kalachyova@yandex.ru

дополнительных инструментов, способных не только улучшить своевременную диагностику заболеваний желудочно-кишечного тракта, но и оценить эффективность проводимой терапии.

Цель настоящей лекции заключается в анализе и систематизации биомаркеров при различных заболеваниях желудочно-кишечного тракта.

Ключевые слова: биомаркер, атрофия желудка, воспалительные заболевания кишечника, рак поджелудочной железы, фекальный кальпротектин, белок, связывающий жирные кислоты, микроРНК

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Digestive diseases are a socially significant problem as the morbidity and mortality rates are increasing every year. Rosstat data for 2022 reported that the mortality rate from digestive diseases in the Russian Federation is 70.4 per 100,000 population. According to the World Health Organization (WHO), by the mid-21st century, diseases of the digestive system will occupy the leading place in the general morbidity and mortality (https://www.who.int/docs/default-source/gho-documents/world-health-statistic-reports/world-health-statistics-2014.pdf). One of the reasons for this growth lies in the lifestyle of modern man: reduced physical activity, unbalanced diet, bad habits, and stress [1].

The increase in the incidence of digestive diseases among the population has resulted in the situation when doctors have recently been focusing their efforts on identifying the specific features of the disease and using tools to develop a personalized approach, ensuring the choice of the most effective and safest treatment for each patient. The need to improve the approach to an individual patient, taking into account the exact characteristics of their pathological condition or their response to a specific treatment, is a priority goal of personalized medicine [2].

Biomarkers are a key part of the concept of personalized medicine. They are crucial in improving early identification of patients at risk, increasing the accuracy of diagnosis, and facilitating the selection of the best treatment. In addition, biomarkers are essential for understanding the molecular mechanisms underlying diseases and facilitating the identification of potential new therapeutic targets. A biomarker is mainly a serum protein that is found in a particular concentration in various disorders and is also used as an indicator of the response to therapy [3].

Biomarkers have been used in clinical medicine for decades. Back in 2001, the Biomarker Working Group, assembled by the National Institutes of Health (NIH, USA), established the following definition: “A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention” [4].

According to the Biomarker Working Group (2001) nomenclature, biomarkers are classified into three types:

– type 0 reflects the natural history of the disease and correlates over time with known clinical indicators;

– type I reflects the effect of therapy, taking into account the mechanism of action of the drug;

– type II includes surrogate endpoints that predict clinical efficacy or harm when using a drug.

The biomarker must meet the criteria of the SMART concept, which means it has to be [5]:

S – specific and sensitive;

M – measurable;

A – available and affordable;

R – responsive and reproducible;

T – timely.

The FDA (Food and Drug Administration) and NIH Biomarker Working Group classifies biomarkers into different types based on their primary clinical application. These types include susceptibility / risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamic/response, and safety (Table 1) [6, 7].

Table

Types of biomarkers based on their primary clinical application [6, 7]

Types of biomarkers	Main features
Diagnostic biomarkers	They play an important role in establishing an accurate diagnosis.
Monitoring biomarkers	This category includes biomarkers measured at different time points to assess the presence and status of disease. Fluctuations in these biomarkers can be used as a tool to assess disease progression or the effectiveness of a therapeutic intervention.
Pharmacodynamic biomarkers	They are used to prove that the effect of the drug on its primary target modifies the progression of the disease.
Predictive biomarkers	They determine the response to therapy and/or drug toxicity.
Prognostic biomarkers	They determine the likelihood of a clinical event, relapse, or disease progression.
Susceptibility/risk	They indicate the potential for disease development in an individual who does not currently have clinically apparent disease. The main difference between this category and prognostic biomarkers is the fact that susceptibility/risk biomarkers are measured in individuals who do not currently have the disease.
Safety	The relevance of these biomarkers consists in predicting toxic side effects caused by drugs, medical interventions, or exposure to environmental agents. Biomarker detection or changes in biomarker levels can reflect toxicity, enabling necessary actions to prevent irreversible damage. These actions may include dose adjustments, treatment interruption, or initiation of specific therapy.

Biomarkers are typically measured in blood, urine, and other tissues [3, 11]. To date, many serum proteins have been evaluated as potential markers for disease diagnosis, but only a few are currently used in clinical practice. When evaluating a biomarker, it is important to compare its level with the clinical pattern and other features [8, 12].

In recent years, an increasing number of studies have aimed at identifying biomarkers that are highly sensitive, highly specific, and minimally invasive. It is important to note that high sensitivity is desirable for biomarkers used in screening, while high specificity is necessary for disease diagnosis [9–11].

BIOMARKERS OF GASTRIC MUCOSAL ATROPHY

Chronic atrophic gastritis and intestinal metaplasia may contribute to the development of dysplasia and adenocarcinoma. Chronic atrophic gastritis is usually asymptomatic for a long time, which makes it difficult to diagnose it early. Studies have demonstrated that the severity of inflammatory and dystrophic mucosal changes does not correlate with the presence and severity of clinical symptoms [13]. Early diagnosis of chronic atrophic gastritis is recommended as a preventive measure, regardless of the presence or absence of dyspepsia symptoms. Researchers are actively seeking screening methods for atrophic gastritis. Determination of pepsinogens and *Helicobacter pylori* (*H. pylori*) infection in serum is considered the optimal method [14].

Pepsinogen I (PG-I) is synthesized by the main gland cells of the gastric mucosa, and its decrease is the first marker of gastric mucosal atrophy. In severe atrophic gastritis, the major cells are lost, leading to a decrease in PG-I, while the level of pepsinogen II (PG-II) remains relatively constant [15]. PG-II is secreted not only by the glands of the fundus but also by the pyloric glands of the antral stomach and Brunner's glands of the proximal duodenum. Therefore, a low serum PG-I level (≤70 ng / ml) and / or a low PG-I / PG-II ratio (≤3.0) indicate the presence of chronic atrophic gastritis and a high risk of gastric cancer [16]. The study by C.B. Conti et al. demonstrated that a reduction in serum pepsinogen levels and a decrease in the PG-I / PG-II ratio are indicative of atrophic changes in the gastric mucosa [17]. The laboratory method has specificity and sensitivity in diagnosing chronic atrophic gastritis of 92.2–97.8% and 15–75%, respectively [18].

Gastrin-17 (G-17) is another biomarker of gastric mucosal atrophy. It is synthesized and released by G cells of the mucous membrane in response to food intake. G-17 stimulates enterochromaffin-like cells (ECL) to secrete histamine, which in turn induces acid release from parietal cells [19]. Disruption of acid-mediated inhibition of gastrin leads to atrophic gastritis, an increased population of ECL, and parietal cells. G-17 is also a proliferative and anti-apoptotic hormone that is thought to play an important role in gastric carcinogenesis. It has been reported that patients with gastric cancer have higher serum G-17 levels than patients without it [20]. Therefore, serum G-17 levels can be used to identify individuals at high risk of gastric cancer.

Another important indicator to consider is *H. pylori*, which is a gram-negative bacterium with 4–8 polar flagella. Although *H. pylori* is not a biomarker as such, the so-called helicobacteriosis has a high prognostic value. In 1994, the International Agency

for Research on Cancer (IARC) expert group classified *H. pylori* as a type 1 carcinogen [21]. The process of gastric carcinogenesis, also known as the Correa's cascade, is a stepwise progression from normal gastric epithelium to chronic non-atrophic gastritis, chronic atrophic gastritis, intestinal metaplasia, dysplasia, and cancer [15]. Many clinical trials in recent years have shown that *H. pylori* infection is associated with a high risk of gastric cancer in patients with atrophic gastritis and intestinal metaplasia [17]. Furthermore, a correlation has been found between a decrease in the prevalence of *H. pylori* in Western Europe, the USA, and Japan and a decrease in the incidence of peptic ulcer disease and gastric cancer [21].

The cag pathogenicity island (cagPAI) and its effector protein, cytotoxin-associated gene A (cagA), are considered virulence factors of *H. pylori*. *H. pylori* strains can be classified as *cag*A-positive or *cag*A-negative based on the presence or absence of the *cagA* gene in their bacterial genome. Literature reports that individuals infected with *cag*A-positive strains are at a greater risk of developing gastric ulcers and cancer than those infected with *cag*A-negative strains of *H. pylori* [22]. In a recent study by K.M. Miernyk et al. involving 263 patients in Alaska, intact cagPAI was detected in 150 (57%) strains of *H. pylori*, which appeared to be associated with the development of more severe gastric pathology. Of the 12 *H. pylori* strains isolated from patients with gastric cancer, 10 (83%) had intact cagPAI [23].

In addition, *H. pylori* secrete vacuolating cytotoxin A (vacA). VacA can alter the permeability of the plasma membrane, destroy mitochondria and endosomes, and affect mitochondrial activity, contributing to apoptosis. It is worth noting that although all *H. pylori* strains possess the *vacA* gene, some bacterial species have mutations in their vacA sequences. Patients infected with strains containing *vacA s1, i1*, or *m1* variants are at an increased risk of developing gastric cancer [24].

BIOMARKERS OF INTESTINAL MUCOSAL DAMAGE

Abnormal gut barrier function plays a central role in the pathogenesis of chronic intestinal inflammation. Tight junctions change, and the frequency of apoptosis events increases. These barrier defects are attributed to the increased activity of proinflammatory cytokines that are highly expressed in the chronically inflamed gut [25]. It is still discussed whether changes in epithelial permeability in patients with inflammatory bowel disease (IBD) play a primary role in the pathogenesis of the disease or whether there is a secondary effect in response to inflammation. IBDs have demonstrated a growing incidence and prevalence since their discovery. Therefore, the search for non-invasive, high-quality, and inexpensive biomarkers of intestinal inflammation activity is becoming increasingly important. Fecal biomarkers are widely recognized as biomarkers of IBD. Fecal markers are a group of substances that are produced in inflammation of the intestinal mucosa. Fecal calprotectin, fatty acid-binding protein (FABP), zonulin, and eosinophil-derived neurotoxin are the most promising markers [26].

Fatty acid-binding proteins (FABP) are a family of transport proteins for fatty acids and other lipophilic substances. These proteins facilitate the transport of fatty acids between extracellular and intracellular membranes. FABPs are classified according to their tissue tropism: adipocyte (A), epidermal (E), cardiac and muscular (H), small intestine (I), liver (L), large intestine (Il), brain (B), and testicular (T) [27].

Intestinal fatty acid-binding protein (I-FABP) is present exclusively in enterocytes throughout the small intestine. This small 15 kDa cytosolic protein rapidly appears in the bloodstream after intestinal epithelial cell damage. I-FABP is expressed in mature enterocytes but not in crypts. The level of I-FABP is quite low under physiological conditions. H. Funaoka et al. determined that the serum concentration of I-FABP in healthy people is 2.0 ng / ml or less [28]. Its amount increases in response to damage to the cell membrane of the small intestinal epithelium [29]. I-FABP circulates in the blood for several hours after tissue damage and is then excreted from the body. I-FABP is measured in serum (or plasma), urine, and coprofiltrate [26]. Several studies have shown that elevated serum or urine I-FABP concentrations are associated with impaired intestinal permeability and may be a marker of early diagnosis of IBD, celiac disease, and ischemic colitis.

The study by M.P. Adriaanse et al. suggests that serum I-FABP is an early marker of gluten-induced enteropathy in patients with celiac disease [30]. Furthermore, it has been studied as a marker of mechanical (strangulation) intestinal obstruction of the small bowel and necrotizing enterocolitis. Thus, the study by M. Schurink et al. demonstrated that I-FABP measured in plasma helps identify patients with necrotizing enterocolitis among preterm infants with non-specific symptoms. Moreover, in patients diagnosed with necrotizing enterocolitis, I-FABP

levels can predict disease complications at early stages. Its highest levels are typically observed within the first 24 hours after the onset of symptoms, and then they gradually decrease [31].

Zonulin, an analogue of cholera toxin, is another biomarker of intestinal mucosal damage. It is synthesized in the liver and intestinal epithelial cells [32]. In 2000, the research group under the supervision of A. Fasano reported the discovery of zonulin, a human protein analogue of Zonula occludens toxin derived from cholera vibrio that regulates paracellular permeability [33]. The chemokine receptor type 3 (CXCR3) is the main regulator of zonulin release in the gut. It is an inflammatory chemokine receptor. The primary function of CXCR3 is to stimulate chemotaxis, cell migration, and adhesion of immune cells. CXCR3 is present in the intestinal lamina and epithelial cells, and its expression is elevated in patients with celiac disease or IBD [34]. Zonulin levels have been found to be elevated in individuals with irritable bowel syndrome, IBD, and necrotizing enterocolitis, which is associated with impaired mucosal barrier function [35]. The degree of change in zonulin concentrations in various biological media (blood, feces) does not always coincide and depends on the form of pathology. For example, in patients with ulcerative colitis, serum zonulin is preferred as a marker of increased intestinal permeability over fecal zonulin. In contrast, fecal zonulin levels are significantly higher than plasma levels in HIV-seropositive patients with gastrointestinal symptoms [36].

Calprotectin is an antimicrobial, immunomodulatory, and antiproliferative protein with a mass of 36 kDa, a member of the S100 protein family. It is found in the membranes of macrophages, in the cytoplasm of neutrophils, in monocytes, and in mucosal epithelial cells. Calprotectin was first described in 1980. It is a heterodimer consisting of S100A8 and S100A9 proteins. Antimicrobial effects of calprotectin are related to its ability to chelate metal ions. Its concentration in feces is approximately six times higher than in plasma [37]. This protein is stable in the external environment and remains the same in feces for up to 7 days. Calprotectin is present in small amounts in the feces of healthy individuals [6].

The level of calprotectin in different tissues of the body is directly proportional to the degree of inflammation. Fecal calprotectin levels are used as one of the diagnostic criteria for IBD. Failure to control inflammatory activity in IBD is associated with both poorer quality of life in patients and worse long-term outcomes (increased risk of colorectal carcinogenesis). Therefore, it is crucial to prevent clinical relapse and maintain remission in the long term [37]. According to the latter concept, clinical remission in patients with IBD should be supported by both biological and endoscopic evidence of the absence of mucosal inflammatory activity. Biological inactivity may be indicated by the absence of inflammatory markers in peripheral blood or feces (calprotectin), whereas mucosal healing is the most appropriate endoscopic goal. Commonly used biomarkers, such as C-reactive protein and erythrocyte sedimentation rate, lack sensitivity and specificity. Fecal calprotectin has a high negative predictive value in ruling out IBD in undiagnosed patients with symptoms and high sensitivity to the diagnosis of the disease [38]. The meta-analysis by T. Rokkas et al. demonstrated that the best sensitivity (90.6%) was achieved for fecal calprotectin levels of 50 μg / g in IBD, whereas the best specificity (78.2%) was found at levels >100 μg / g [39]. Therefore, there is increasing evidence that fecal calprotectin estimation may be useful for monitoring disease activity and response to therapy, as well as for predicting relapse.

Many research groups have focused on microRNAs (miRNAs) over the past 10 years. A significant level of scientific evidence emphasizes the functional role and potential value of small RNA molecules. MicroRNAs are small non-coding RNAs consisting of 18–25 nucleotides. Currently, miRNAs are being investigated as biomarkers for IBD [40]. Firstly, microRNAs are known to be functional molecules that can be dysregulated at early stages of the disease. Secondly, deregulation of microRNAs can cause significant changes in gene expression and contribute to inflammatory and neoplastic diseases. Thirdly, microRNAs are unique molecules with incredible resistance to degradation [41]. Various studies have repeatedly shown that IBD is associated with changes in microRNA expression in the colonic mucosa. In addition to their potential role in monitoring disease activity, whether it is clinical, biochemical, or endoscopic activity [40], microRNAs can also be used as predictors of response to therapy. For example, in an evaluation of patients with severe ulcerative colitis who did not respond to initial corticosteroid therapy, I. Morilla et al. identified 15 microRNAs associated with response to corticosteroids, 6 microRNAs associated with response to infliximab, and 4 microRNAs associated with response to cyclosporine, thus emphasizing the role of microRNA as a predictor of response to therapy in IBD [41].

MARKERS OF LIVER DAMAGE

Among all digestive diseases, liver diseases have been the main cause of death in Russia for many years. About 2 million people die annually of cirrhosis and hepatocellular carcinoma (HCC) worldwide (Global Cancer Statistics 2022).

The main factors in liver damage are alcohol and drugs, infection with hepatitis A, B, C, D, and E, and metabolic disorders. According to the literature reviewed, more than half of patients who abuse alcohol suffer from toxic liver damage and then develop cirrhosis, and 10 years after the beginning of alcohol abuse, they develop HCC [42]. According to WHO, the prevalence of obesity has increased from 4.6% in 1980 to 14.0% in 2020. As a result, the incidence of non-alcoholic fatty liver disease (NAFLD) has also increased. In 2020, the new term metabolic-associated fatty liver disease was introduced [43]. The growth of liver diseases leads to the need to search for new methods of early diagnosis. A number of serum biomarkers can be used to assess the pathological state and disease progression.

The FDA has supported total cytokeratin 18 (K18), glutamate dehydrogenase (GLDH), and microRNA-122 (miR-122) as promising biomarkers for diagnosing liver damage [44]. The study by R.J. Church et al. found a positive correlation between GLDH activity and alanine aminotransferase (ALT) activity. Additionally, K18 and miR-122 levels were positively correlated with ALT activity, indicating a positive association of these biomarkers with cytolytic syndrome [45].

The clinical standard for assessing liver damage is the measurement of serum ALT and aspartate aminotransferase levels. These enzymes are released into the bloodstream due to hepatocyte damage. However, it is important to note that these tests have limitations despite their widespread clinical use. Firstly, the enzymes are not absolutely specific to hepatocytes. Aspartate aminotransferase is expressed in the liver, heart, skeletal muscles, kidneys, brain, pancreas, and lungs. ALT is an intracellular enzyme that is predominantly found in liver and kidney cells and in small amounts in heart and skeletal muscles. Secondly, liver enzymes do not always reflect the severity of the disease [46]. According to the study by H.P. Llewellyn et al., a panel consisting of several biomarkers, including GLDH, K18, and microRNA-122, can differentiate between patients with muscular dystrophies and those with liver pathology. This model has significant advantages over ALT measurement [44].

MiR-122 is the most abundant liver-specific microRNA (accounting for 70% of the total liver microRNA pool) and exists in two mature isoforms: miR-122-3p and miR-122-5p. The deficiency of miR-122 results in inflammation, cholestasis, and, ultimately, liver fibrosis. MiR-122 regulates the synthesis and oxidation pathway of cholesterol and fatty acids and is involved in hepatocyte proliferation and differentiation. In their study, M.I. Kan Changez et al. demonstrated that patients with NAFLD who were obese had higher expression of miR-122-5p in the liver. It should be noted that miR-122 levels in the liver increase during the early stages of NAFLD but gradually decrease as non-alcoholic steatohepatitis (NASH) and fibrosis progress [47].

MARKERS OF PANCREATIC DAMAGE

Pancreatic disease is a serious problem for the healthcare system in the 21st century. Risk factors for pancreatic disease include a high-fat diet, overweight and obesity, as well as alcohol abuse and smoking. Globally, over the past few decades, obesity has been an urgent medical and social problem that has become a non-communicable pandemic [48]. Obesity is a statistically significant risk factor for pancreatic cancer (PCa).

Thus, a 2021 meta-analysis by D. Aune et al. included 10 prospective studies with 1,693,657 participants and showed that a 5 kg / m^2 increase in body mass index was associated with an 18% (95% CI 1.03–1.35) increase in the relative risk of acute pancreatitis, and a 10-cm increase in waist circumference increased the risk by 36% (95% CI 1.29–1.43) [49].

It is important to understand the mechanisms by which obesity affects the onset and progression of pancreatic disease. The main mechanisms are increased inflammation and necrosis due to increased intra- and peripancreatic fat. It has been suggested that, as in pancreatitis, the creation of an inflammatory microenvironment leads to the growth of oncogenically transformed cells, promoting the attraction of immune cells that cause tumor development [48]. Early diagnosis of PCa is difficult because the disease is usually asymptomatic for a long time. This means that it is often detected late, when treatment is already ineffective, leading to poor survival outcomes. Studies are increasingly focusing on the need to find potential

serum biomarkers as additional tests for screening and diagnosis of PCa.

Carbohydrate antigen 19-9 (CA19-9) is a tetrasaccharide expressed on the surface of cancer cells. It is the best known serological biomarker used in the diagnosis of PCa. In 1979, it was first described as a tumor antigen that was recognized by the monoclonal antibody NS19-9 in a colorectal cancer cell line [50]. CA19-9 is the Lewis antigen system expressed exclusively in patients who belong to the Lewis blood group (α-β+) or (α+β-). About 5–10% of the population has a Le (α-β-) phenotype, which lacks the enzyme 1,4-fucosyltransferase required for CA19-9 production. CA19-9 levels are known to be elevated in only 70–80% of patients with PCa. However, a normal CA19-9 level does not exclude PCa [51]. The CA19-9 tumor marker has low specificity for PCa as it is also elevated in other types of cancer, including colorectal, gastric, liver, lung, and ovarian cancers. Various studies have demonstrated that CA19-9 levels can be elevated in benign conditions, such as chronic pancreatitis, pancreatic cysts, biliary obstruction, and cholangitis [52]. The upper range of CA19-9 is more than 37–40 U / ml. It was found that 80–90% of patients with stage III–IV PCa had CA19-9 levels >100 U / ml, while patients with stage I–II tumors had lower CA19-9 values [53].

According to the literature, CA19-9 levels are significantly higher in PCa than in chronic pancreatitis. Therefore, higher threshold values (>100 U / ml) should be used for differential diagnosis of cancer and chronic pancreatitis [54]. In their work, Y. Liang et al. found that patients with PCa have metastasis to lymph nodes when serum CA19-9 levels are ≥ 1,000 U / ml [55].

Finally, let us consider the serum tumor marker CA242, which is a carbohydrate antigen containing sialic acid [56]. Elevated CA242 concentration in blood serum >20 U / ml is found in PCa (sensitivity varies from 41 to 75% and the specificity is 85–95%), whereas in benign diseases the levels of the tumor marker slightly increase [11]. CA242 has advantages over CA19-9, including higher specificity in diagnosing PCa and independence of its level of Lewis antigen expression [57].

CONCLUSION

The biomarkers discussed can be used as additional tools that can not only provide timely recognition of gastrointestinal diseases but also increase the accuracy of assessing the effectiveness of therapy. At the same time, it should be taken into account that the clinical relevance of various studies is generally limited because they focus on individual biomarkers that represent only one of several features within a specific pathological condition. Therefore, one promising approach would be to combine several markers into a multimarker panel to increase their diagnostic and prognostic value, thus improving case management.

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Authors' information

Ostanko Valentina L. – Cand. Sci. (Med.), Associate Professor of the Advanced Therapy Division with Rehabilitation, Physiotherapy and Sports Medicine Course, Siberian State Medical University, Tomsk, valentina209@yandex.ru, http://orcid.org/0000-0002-9950-721X

Kalacheva Tatyana P. – Cand. Sci. (Med.), Associate Professor of the General Medical Practice and Outpatient Therapy Division, Siberian State Medical University, Tomsk, tatyana-kalachyova@yandex.ru, http://orcid.org/0000-0002-4292-7723

Kulumaeva Karina A. – Resident, Advanced Therapy Division with Rehabilitation, Physiotherapy and Sports Medicine Course, Siberian State Medical University, Tomsk, karina.kulumaeva12@mail.ru, http://orcid.org/0009-0002-5933-3873

Li Natalia A. – Head of the Endoscopy Unit, Tomsk Regional Oncology Center, Tomsk, nat.an.li@mail.ru, http://orcid.org/0000-0001-5733-8561

Beloborodova Ekaterina V. – Dr. Sci. (Med.), Professor of the Advanced Therapy Division with Rehabilitation, Physiotherapy and Sports Medicine Course, Siberian State Medical University, Tomsk, belobekaterina@yandex.ru, http://orcid.org/0000-0002-8776-5924

Purlik Igor L. – Dr. Sci. (Med.), Professor of the Pathological Anatomy Division, Siberian State Medical University, Tomsk, igor0812@rambler.ru, http://orcid.org/0000-0003-3757-0173

Kalyuzhina Elena V. – Dr. Sci. (Med.), Professor of the Advanced Therapy Division with Rehabilitation, Physiotherapy and Sports Medicine Course, Siberian State Medical University, Tomsk, kalyuzhina.e@mail.ru, http://orcid.org/0000-0002-7978-5327

Brazovskaya Natalia G. – Cand. Sci. (Med.), Associate Professor of the Medical and Biological Cybernetics Division, Siberian State Medical University, Tomsk, brang@mail.ru, http://orcid.org/0000-0002-0706-9735

Kalyuzhin Vadim V. – Dr. Sci. (Med.), Professor, Head of the Advanced Therapy Division with Rehabilitation, Physiotherapy and Sports Medicine Course, Siberian State Medical University, Tomsk, kalyuzhinvv@mail.ru, http://orcid.org/0000-0001-9640-2028

(✉) **Kalacheva Tatyana P.,** tatyana-kalachyova@yandex.ru

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