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REVIEW ARTICLE

New serum biomarkers for the diagnosis of patients with ulcerative colitis: a review

Novos biomarcadores séricos para o diagnóstico de pacientes com colite ulcerativa: uma revisão

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Abstract

Objective: to conduct a literature review on possible serum markers in patients with UC to identify potential biomarkers. **Methods**: the descriptors "Colitis Ulcerative", "Biomarkers", and "Diagnosis" were used for the search in the PUBMED, LILACS, SciELO, and SCOPUS databases. After applying the inclusion and exclusion criteria in the databases, the 32 articles were classified as samples. **Results**: research indicates that biomarkers can play distinct roles in assessing activity and diagnosing UC. For instance, the peptide nesfatin-1 showed elevated serum levels during active periods of the disease, while the peptide trefoil factor 3 showed promise in predicting UC activity. It is worth highlighting that C-reactive protein (CRP) is a commonly used marker in which high values are observed in patients during the active phase of the disease; however, studies suggest the need to redefine CRP cutoff values to better predict endoscopic remission. Other approaches, such as the analysis of proteins, specific fatty acids, and proteins related to the extracellular matrix, have also been explored, highlighting their potential as biomarkers. **Conclusion**: in summary, there is a diversity of possible clinically important biomarkers that play different roles in the assessment and diagnosis of UC. However, it is essential to conduct further research to validate these biomarkers and achieve greater reliability.

Keywords: ulcerative colitis; biomarkers; diagnosis; trefoil factor 3; C-reactive protein.

Resumo

Objetivo: realizar uma revisão da literatura sobre possíveis marcadores séricos em pacientes com RU com o objetivo de identificar potenciais biomarcadores. **Métodos**: os descritores "Colitis Ulcerative", "Biomarkers" e "Diagnosis" foram utilizados para a busca nas bases de dados PUBMED, LILACS, SciELO e SCOPUS. Após a aplicação dos critérios de inclusão e exclusão nas bases de dados, os 32 artigos foram classificados como amostras. **Resultados**: a pesquisa indica que os biomarcadores podem desempenhar papéis distintos na avaliação da atividade e no diagnóstico da RU. Por exemplo, o peptídeo nesfatin-1 apresentou níveis séricos elevados durante os períodos ativos da doença, enquanto o peptídeo trefoil factor 3 mostrou-se promissor na predição da atividade da RU. Vale destacar que a proteína C-reativa (PCR) é um marcador comumente utilizado, no qual valores elevados são observados em pacientes durante a fase ativa da doença; no entanto, estudos sugerem a necessidade de redefinir os valores de corte da PCR para melhor predizer a remissão endoscópica. Outras abordagens, como a análise de proteínas, ácidos graxos específicos e proteínas relacionadas à matriz extracelular, também têm sido exploradas, destacando seu potencial como biomarcadores. **Conclusão**: em resumo, há uma diversidade de possíveis biomarcadores de importância clínica que desempenham diferentes papéis na avaliação e diagnóstico da CU. No entanto, é essencial conduzir mais pesquisas para validar esses biomarcadores para obter maior confiabilidade.

Palavras-chave: colite ulcerativa; biomarcadores; diagnóstico; fator trefoil 3; proteína C-reativa.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic immune-mediated illness characterized by inflammation of the gastrointestinal tract and alternating periods of remission. IBD is clinically classified as Crohn's disease (CD) or Ulcerative Colitis (UC) based on its symptoms, location, and histopathological characteristics[1,2,3]. Currently, the highest rates of IBD are in industrialized countries

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and newly industrialized areas such as India and South America. However, its incidence varies considerably worldwide, with a rapid increase in the number of cases in recent years[4,5].

Diagnosis generally occurs between 20 and 40 years. However, it can begin at any age[3]. Diagnosis is based on clinical, endoscopic, radiographic, and histological findings of inflammatory and structural changes. It is sometimes difficult to distinguish between CD and UC; therefore, 10–15% of patients are diagnosed with unclassified IBD. Furthermore, approximately 9% of patients initially diagnosed with UC or CD required a change in diagnosis within the first two years after the disease identification[6].

CD usually involves the terminal ileum, cecum, perianal area, and colon but can affect any intestine region in a discontinuous pattern. In contrast, UC involves the rectum and can affect parts of the colon or the entire colon in a continuous pattern. Histologically, CD exhibits thickened submucosa, transmural inflammation, fissured ulceration, and granulomas, whereas inflammation in UC is limited to the mucosa and submucosa with cryptitis and crypt abscesses[1,3,6].

The severity and location of IBD will determine the signs and symptoms; therefore, there is a wide spectrum of clinical presentations. The classic features of CD are abdominal pain, watery diarrhea, and weight loss. In UC, the diarrheal condition can be bloody, with hemorrhages occurring in approximately 1–2% of patients. In these individuals, systemic symptoms, such as fatigue, fever, and weight loss, may also be present, as well as abdominal pain[4,5].

The etiology and pathogenesis of IBD remain unknown; however, it is known that they develop in people with a genetic predisposition who experience certain environmental factors, an altered intestinal microbiome, and an abnormal immune response associated with the dysregulation of innate and adaptive immune responses1,3,4. The pathophysiological process of IBD is characterized by an influx of neutrophils and macrophages, which produce cytokines, proteolytic enzymes, and free radicals, resulting in inflammation and ulceration. Pro-inflammatory cytokines can promote apoptosis, and the high apoptotic rate of epithelial cells also leads to a decrease in epithelial barrier function, which constitutes a key event in the onset of IBD[1,7].

On this basis, studies on possible biomarkers for the diagnosis of UC have been discussed, expanding due to new evidence on antibodies, proteins, proteomic panels, transcriptomic signatures, DNA methylation patterns, and specific glycemic and metabolic disorders associated with UC8. Thus, the development of new biomarkers will favor the care of patients with UC[8,9].

Regardless of the benefits of marker development, their validation, simplification, and direct use in clinical practice can be challenging. Currently, there are few biomarkers already approved for the diagnosis of UC because of several factors, such as the histological activity of the disease, response to medication, and long-term evolution of the disease[8].

Consequently, the need for more research within this segment becomes evident, which could not only help achieve a more effective diagnosis but also contribute to the understanding of the mechanisms of UC pathogenesis and therapeutic tools. Therefore, this study aimed to identify in the specialized literature potential serum biomarkers in adult patients with UC.

METHODS

Research design

This research was a systematic review of the literature based on the following guiding question: "What are potential serum markers for the diagnosis of UC?". To answer this question, the following descriptors were used and applied to the PUBMED, LILACS, SciELO, and SCOPUS databases: "Colitis Ulcerative," "Biomarkers," and "Diagnosis," which combined using the Boolean operator "AND."

Inclusion and exclusion criteria

The following inclusion criteria were used: articles in English published in the last five years (2018-2023); research carried out on adult humans; and articles indexed in scientific journals classified as A1, A2, A3, or A4, according to the WebQualis 2016 evaluation (Qualis 2016). On the other hand, the exclusion criteria were review articles and editorials, research that associated UC with another disease, research focused exclusively on the intestinal microbiota, the immune system, genetic aspects, studies with nonspecific IBD, studies aimed at treating the disease, articles that performed the diagnosis using another technique, and articles that did not fit the objective of the current study.

Research screening

Screening was carried out between May and April 2023, starting with PubMed. After applying the descriptors, 1077 results emerged, but with the last five years filter, 362 remained, followed by the "humans" filter, 358 remained. When sorted by title, it was identified that 13 articles were not available in their digital version, one was of an abstract in the annals, and 180 were excluded because they met the exclusion criteria. Thus, 164 articles remained and were screened using the abstract. At this stage, 43 articles were excluded due to the study category: 37 literature reviews, five editorials, and one guideline. Furthermore, 22 articles were of lower quality than A4, and 64 did not fit the research objective: 1 (animal model), 7 (association with another disease), 3 (children), 4 (CD), 6 (non-specific IBD), 3 (other methods), 7 (fecal marker), 15 (genetic markers), 9 (immune response), 1 (intestinal microbiota), and 8 (treatment). Of the 35 articles that continued to the final stage, five were excluded (two studied fecal markers, one had

an incomplete method, and two did not provide relevant data in relation to UC), thus leaving 30 articles. Screening was then performed using LILACs. When using the descriptors, 13 articles were initially identified, of which only two (2) remained with the selection of the temporal axis. Through title screening, one study was excluded because it addressed fecal markers. Thus, only one article was analyzed in the eligibility stage, which was also excluded as it only addresses therapeutic issues. In SciELO, the descriptors found only two results, and both were published in the last five years. In the titer screening, one duplicate was detected, and the second study analyzed the fecal markers. Therefore, no studies were selected for the next stage. The last database used was SCOPUS, and 355 results were identified using these descriptors. Of these, 215 had been published in the past five (5) years, and 208 articles remained when we applied the "humans" filter. After screening by title, 67 articles were excluded because they addressed topics that did not help resolve the guiding question: 5 (treatment), 9 (CD, celiac and/or colorectal cancer), 10 (fecal or salivary markers), 8 (intestinal microbiota), 11 (genes and microRNA), 7 (association with other diseases), 5 (physiopathogenesis), 3 (animal model), and 9 (study with children and adolescents). The remaining 78 were excluded, such as three (3) book chapters, four summaries in event annals, 16 texts unavailable in full, 20 duplicates, and 35 due to the type of study (review and editorials). In the abstract screening stage, of the remaining 63 articles, 22 were excluded because they had been published in journals classified with qualifications lower than A4. At this stage, an additional 34 were excluded due to the following reasons: 12 (reviews), 1 (editorial), 2 (animal model), 1 (non-specific inflammatory bowel disease), 4 (genes and microRNA), 5 (immune system), 1 (intestinal microbiota), 3 (other methods), 2 (association with other diseases), and 3 (treatment). Therefore, seven studies proceeded to the complete reading stage; five did not help in resolving the guiding research and were excluded at this stage.

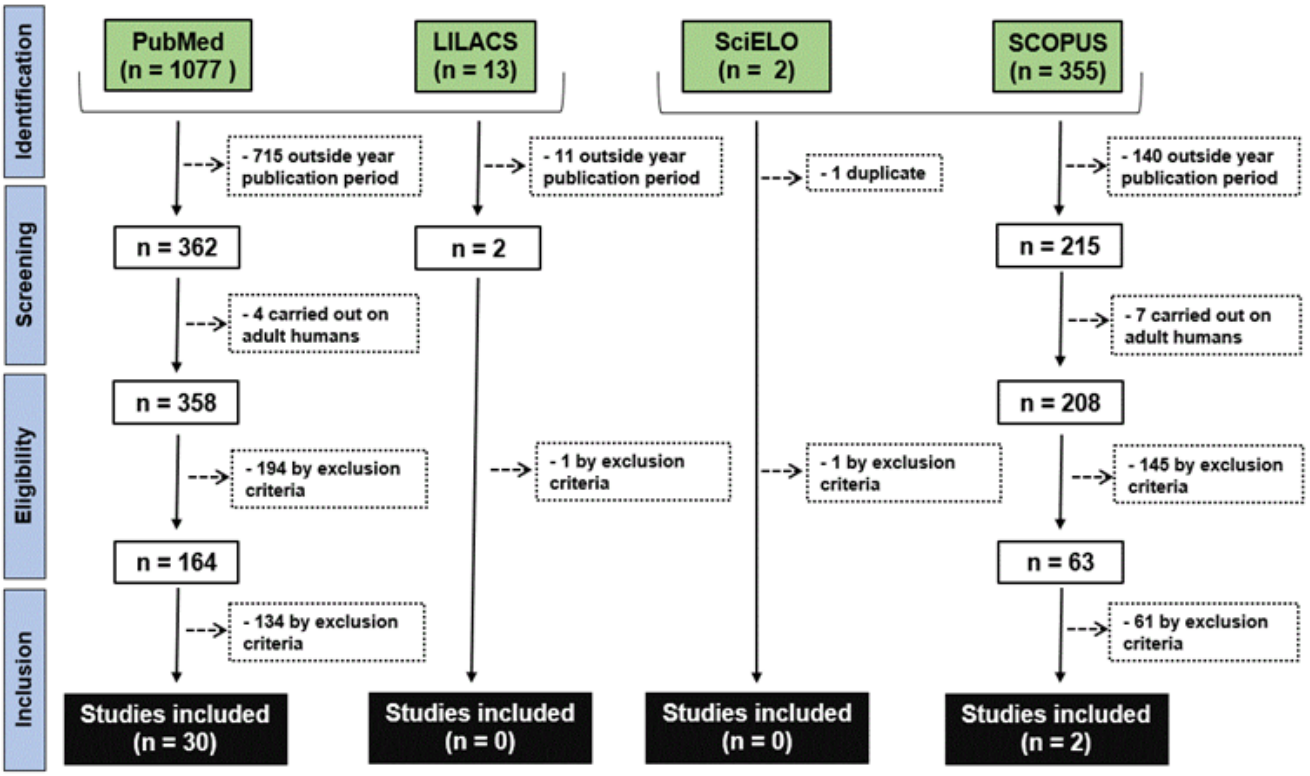
Data extraction and analysis

Data from all studies that comprised the sample were extracted into an Excel spreadsheet, highlighting the following data: author, year of publication, title, journal, location, general objective, sample, method, results, study limitations, and conclusions.

RESULTS

Therefore, through all the steps conducted in the databases, this study included a sample of 32 articles. The publication selection process is illustrated in Figure 1.

Figure 1. Flowchart of the process of selecting publications for the review.



Through the methodological procedure, 32 articles were analyzed, thirteen (13) of which were published in A1 journal, six (06) in A2, six (06) in A3, and seven (07) in A4. The majority of these studies were published in 2021 (nine of the 32 studies), and China and Japan were the ones with the most research within the theme analyzed in this article, each with nine and five studies, respectively. Other information, such as the methods used, diseases, and evaluative biomarkers, is described in Table 1.

Table 1. Methods used, disease and evaluative biomarkers in studies characterized as a research sample.

METHOD	DISEASE	BIOMARKER
Liquid chromatography	Crohn's Disease and Ulcerative Colitis	Amino acids[10]
Nano-liquid chromatography	Ulcerative Colitis	Low molecular weight peptides[11]
Electrochemiluminescence	Ulcerative Colitis	Vitamin D[12]
ELISA	Crohn's Disease and Ulcerative Colitis	IL-7R[13], trefoil factor 3[14], procalcitonin[15], galectins[16], type VI collagen[17], IL-17[18], IL-23[18], fucosylated haptoglobin[19], nesfatin-1[20], laminin[21], fibronectin[21], lipocalin-2[21] e plasma and/or serum calprotectin[22].
Laboratory tests	Crohn's Disease and Ulcerative Colitis	CRP[20,23,24,25,26,27,28], platelets[23], fibrinogen[23], ferritin[23], ESR[23,28], albumin[23,25], plasma and/or serum calprotectin[29], basophils[30], IL-6[31], NeuPla[25], ESR[25], globulin[26], prostaglandin[32], LGR[33] and PCSK9[34]
Electronic medical records	Crohn's Disease and Ulcerative Colitis	Total bilirubin[35], uric acid[35], cholinesterase[36], proteinase-3[37], CRP[38], platelets[39], fibrinogen[39], ferritin[39], ESR39, albumin[39], NAR[40], NPAR[40], AAPR[40], AGR[40] , AFR[40] and FPR[40].
Western Blot	Crohn's Disease and Ulcerative Colitis	Proteomics[41] and lipidomics profile[41].

Caption: Enzyme-linked immunosorbent assay (ELISA), C-Reactive protein (CRP), neutrophil to albumin ratio (NAR), neutrophil to pre-albumin ratio (NPAR), albumin to alkaline phosphatase ratio (AAPR), albumin to globulin ratio (AGR), albumin to fibrinogen ratio (AFR), fibrinogen-pre-albumin ratio (FPR), erythrocyte sedimentation rate (ESR), alpha-2-leucine-rich glycoprotein (LRG), and neutrophil-platelet ratio (NeuPla)

Following this, Italy and Romania had two surveys each, while the other countries had a single study (Germany, Australia, Austria, Bulgaria, Canada, South Korea, Croatia, Denmark, France, Greece, England, Mexico, Poland, and Turkey). It is also worth noting that, despite the focus on ulcerative colitis, some studies have compared patients diagnosed with CD, whose relevant data for the present study are discussed below10,13-15,18,21,26,36.

DISCUSSION

Possible markers of inflammation in the blood applied in the diagnosis of UC

Among the selected studies, C-reactive protein (CRP) values in patients with IBD were the most commonly used markers. In general, studies have identified that patients with IBD have significantly elevated CRP levels in the active phase20,27, just as low CRP values are observed when the injured tissue is in the healing phase[24,26,27]. Despite these findings, a study conducted in Romania did not identify a significant difference in CRP levels in patients with UC[23].

In a survey of 260 patients (122 men, 138 women), CRP values and their relationship with mucosal extension and UC activity in colonoscopic examinations were analyzed using the Mayo scores and Montreal classification. Having identified that the CRP cutoff point ≤ 2.9 mg/l can predict mucosal remission in UC better than the standard CRP cutoff level (≤5 mg/l). Therefore, it is clear that there is a need to redefine a lower CRP cutoff value in UC to predict endoscopic remission[27]. These results were similar to those of another study, in which they also observed that the standard CRP cutoff value is not satisfactory in predicting remission (PR). Therefore, it may be useful to lower the CRP cutoff value to increase its predictive capacity for predicting remission, with the appropriate CRP cutoff value to predict PR in patients with UC being 0.09 mg/dL[24].

Another study hypothesized that the combination of CRP level and peripheral blood monocyte count may be an important prognostic marker for clinical practice in patients with UC. It was found that the peripheral blood monocyte count may be significantly inversely associated with clinical remission and partial mucosal healing in patients with UC. In patients with UC and low CRP levels, peripheral blood monocyte counts can serve as a supplementary blood marker to indicate mucosal healing[38].

Serum globulin, a marker of inflammation, was the focus of a study aimed at evaluating the association between serum globulin and endoscopic activity in patients with UC. In this research, a total of 277 Japanese patients with UC were analyzed (± 51.1 years and ± 8.8 years from UC diagnosis). Serum globulin was divided into three profiles based on the distribution of study participants: low globulin, 2.7 g/dl (reference value); moderate globulin, 2.7–3.1 g/dl; and high globulin, > 3.1 g/dl26. Researchers have identified a positive association between globulin and colon erosion through endoscopic examination. Furthermore, serum globulin levels were found to be independently and inversely associated with mucosal healing. In fact, the inverse association between globulin and mucosal healing was more significant in individuals with low CRP levels. It is pertinent to highlight that this is the first study to demonstrate an association between serum globulin levels and endoscopic activity in patients with UC[26].

Another study demonstrated that there is a good correlation between extraintestinal manifestations and serological inflammatory markers (such as platelets, fibrinogen, and ferritin, not erythrocyte sedimentation rate and albumin) and severity of UC[23].

The same parameters were investigated in the medical records of 187 patients diagnosed with UC, and through the data obtained, it was noticed that serological inflammatory markers were higher in individuals with UC than in healthy individuals39. In a comparison between erythrocyte sedimentation rate (ESR) and CRP, it was noted that more patients diagnosed with UC met the criteria for inflammatory markers for CRP (≥12 mg/L) than for ESR (>30 mm/h). Therefore, CRP is a more sensitive marker for monitoring the disease28. The relationship between CRP levels and peripheral blood reactive basophilia (PBB) in patients with UC was also verified. In this study, analyses were performed on the peripheral blood of 165 patients with UC, and 35 controls were collected for differential leukocyte counts. The results of these analyses suggest that PBB is an uncommon and nonspecific laboratory feature of UC. It is not correlated with CRP and; therefore, cannot represent a useful biomarker for monitoring the disease in UC[30].

Furthermore, serum values of neutrophil-to-albumin ratio (NAR), neutrophil-to-pre-albumin ratio (NPAR), albumin-to-alkaline phosphatase ratio (AAPR), albumin-to-globulin ratio (AGR), albumin-to-fibrinogen ratio (AFR), and fibrinogen pre-albumin ratio (FPR) were investigated in a retrospective study of 362 patients with IBD. NAR, NPAR, and FRP are present at significantly higher levels in patients with UC than in healthy patients, while AAPR and PNI are lower[40].

The neutrophil–platelet ratio (NeuPla) in patients with UC can also be a useful tool for diagnosing and monitoring the progression of the disease, as it has been shown to be suitable for identifying patients with UC in the active phase without the use of invasive techniques such as colonoscopy or expensive fecal biomarkers such as calprotectin. Furthermore, a study carried out with 158 patients obtained a better diagnostic performance compared to other serum biomarkers, such as CRP, erythrocyte sedimentation rate, and albumin[25].

Concerning interleukins (IL), studies analyzed IL-7R13, IL-17, IL-2318, and IL-631. The results regarding the IL-7R pathway indicated that it is locally deregulated in the colon of patients with severe UC and can contribute to the maintenance of chronic inflammation, which is a possible biomarker for monitoring disease progression of the disease[13].

The quantification of serum levels of IL-17 and IL-23 in patients with IBD allowed us to identify that serum levels of IL-23 were higher in patients with UC and were more effective than fecal calprotectin in identifying the group with greater severity of the disease. IL-17, specifically, was higher in UC patients with severe disease than in CD patients but had lower diagnostic accuracy for disease severity when compared to other biomarkers[18].

Serum IL-6 levels were significantly associated with disease activity in patients with CD but not in patients with UC. In patients with UC, serum soluble IL-2 receptor (sIL-2R) levels showed a positive association with clinical and endoscopic remission but not in patients with CD[31].

Investigation of serum molecules as possible markers of UC

Some research had as the main objective to analyze a specific marker, including Nesfatin-120, Trifolio Factor-314, Vitamin D12, total bilirubin35, uric acid35, cholinesterase36, plasma and/or serum calprotectin29,22, prostaglandin32, procalcitonin15, proteinase-337, leucine-rich alpha-2-glycoprotein33 and fucosylated haptoglobin[19].

Nesfatin-1 is a peptide that inhibits antral and duodenal functions, alters gastrointestinal functions, and causes delays in gastric emptying. In addition to its effects on motility, nesfatin-1 also affects secretory functions by decreasing gastric acid secretion. Consequently, a study carried out with 52 adult individuals (17 patients with CD, 18 patients with UC, and 17 healthy volunteers) aimed to investigate the serum levels of nesfatin-1 in patients with IBD20. In this study, serum levels of nesfatin-1 were found to be significantly elevated during the active period of the disease in both UC patients and healthy individuals. Nesfatin-1 serum levels decreased moderately during the remission period; however, they were still significantly higher than those in healthy individuals. The reduction in nesfatin-1 levels between the active and remission periods of UC was not statistically significant[20].

The role of serum trefoil factor 3 (TFF3) was also evaluated as a biomarker in 128 patients. The average TFF3 level in the group of patients with active UC was 10.12 ng/ml, which was higher than the TFF3 levels in the controls. Patients with UC in remission had mean TFF3 values of 6.48 ng/ml, which were lower than those with active UC. Therefore, serum human TFF3 can be used to predict disease activity in patients with UC. Furthermore, this study also found a significant correlation between TFF3 levels and fecal protectin levels, and endoscopic activity; therefore, it can be used as a noninvasive marker to predict disease activity in these patients[14].

Regarding serum levels of vitamin D as a possible marker in patients with UC, researchers have identified that the average vitamin D levels were lower in patients with UC (54.6 nmol/L) than in controls (80.7 nmol/L). Among the UC patients analyzed, a high proportion (80%) had low vitamin D levels, with only 20.3% of UC patients having normal levels, whereas normal levels were present in 49.2% of healthy individuals[12].

Serum total bilirubin (sTB) levels in UC patients were significantly lower than those in the control group, whereas serum uric acid (sUA) levels were significantly higher than those in the control group. Regarding the disease stage, patients in the active phase had lower sTB levels than those in the remission phase, just as patients in the active phase had higher levels of sUA than

patients in the remission stage[35].

Galectins are a family of galactoside-binding proteins commonly altered in the circulation of diseases such as cancer and inflammation, and their serum levels have been investigated as possible biomarkers for determining IBD and disease activity. In this study, 208 serum samples (40 from healthy people, 97 from patients with CD, and 71 from patients with UC) were analyzed, and it was found that serum levels of galectins-1 and -3 were significantly elevated in patients with UC and CD compared to healthy people. Although increased levels of these galectins cannot separate active and inactive UC from CD, they have the potential to be developed as biomarkers for the general determination of IBD[16].

Serum cholinesterase levels can be used as a simple and cost-effective method for diagnosing illnesses. Thus, this study analyzed its effectiveness in the treatment of IBD. In this case, serum cholinesterase levels were significantly lower in UC patients than in healthy individuals (6,376 U/L vs. 8,418 U/L). Compared to patients with CD, cholinesterase values were higher (5,181 U/L versus 6,376 U/L), which could help in the differential diagnosis between these IBDs[36].

Two studies focused on the analysis of plasma and serum calprotectin as markers for UC diagnosis of UC29,[22]. Plasma calprotectin levels were positively correlated with the extent of the disease and could discriminate between patients with UC in remission and those with active disease. In this study, in all analyses, a strong correlation was found between plasma calprotectin and serum calprotectin with UC29. This finding corroborates with other research, in which calprotectin correlated with the endoscopic activity of UC, showing high accuracy in identifying patients with moderate/severe disease activity[22].

Prostaglandin also allowed the identification of changes in the endoscopic score in patients with UC, with the status of the colon mucosa being more accurately reflected by prostaglandin levels than by CRP levels in a longitudinal study. The data obtained in this study showed that prostaglandin values increased significantly with an increase in Mayo Endoscopic Scale scores; therefore, it can be considered a useful biomarker of endoscopic exacerbations during the treatment of UC[32]. Another study analyzed procalcitonin, whose values measured at hospital admission were considered a potential non-invasive predictive biomarker that could predict short-term colectomy failure in patients with severe acute UC[15].

Proteinase-3 is another biomarker studied in patients with UC, which was increased in these patients compared to healthy individuals and those diagnosed with CD; therefore, it may be an important marker to assist in the differential diagnosis of IBD37. Similarly, alpha-2-leucine-rich glycoprotein (LRG) was also correlated with endoscopic results that aided in the diagnosis of UC; however, there was no difference in values between patients with UC and those with CD[33].

Finally, serum fucosylated haptoglobin (Fuc-Hpt) values reflect intestinal inflammation and are a useful biomarker for evaluating endoscopic mucosal healing in UC since Fuc-Hpt detected by ELISA is produced by lymphocytes, which infiltrate sites of inflammation in the intestinal mucosal layer[19].

Analysis of specific proteins and lipids as serum markers for UC
One study analyzed the serum proteins and fatty acids present in the blood of patients with UC using techniques based on mass spectrometry, and the results of this study identified possible biomarkers; however, they must be validated in a larger sample. Specifically, the study identified that tridecanoic acid and octanedioic acid were present in patients with UC, while three fatty acids were downregulated in patients with IBD, namely eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and linoleic acid (LA), which are well-known anti-inflammatory mediators in biological processes[41].

By using ultra-high-pressure liquid chromatography coupled with a mass spectrometer, 37 amino acids were determined in the serum of 158 patients with UC, 130 patients with CD, and 138 healthy controls. Four metabolites (glutamic acid, homocitrulline, homoarginine, and 3-hydroxyproline) and five other metabolites (taurine, ethanolamine, proline, 3-hydroxyproline, and isoleucine) were identified as specific biomarkers for UC and CD, respectively[10].

A study conducted in China used nano-liquid chromatography coupled with mass spectrometry to detect low molecular weight (LMW) peptides in the serum of 60 patients, including 20 patients with active UC, 20 with UC in remission, and 20 healthy controls. It was identified that six peptides can act as biomarkers since patients with active UC were well differentiated from those in remission and healthy people. However, more studies within this segment are necessary, as this only serves as a basis for subsequent large-scale clinical validation[11].

Another study sought to analyze type VI collagen using ELISA and observed that collagen levels increased significantly in patients with UC compared to control individuals. However, these findings should be evaluated in larger studies to elucidate the role of Type VI Collagen. VI as a diagnostic and/or prognostic biomarker for gastrointestinal disorders[17].

One of the potential new biomarkers may be related to the extracellular matrix (ECM), as ECM remodeling plays a crucial role in the pathogenesis of IBD. However, little is known about the diagnostic usefulness of other components of the ECM, including non-collagenous proteins such as laminin, fibronectin, and lipocalin-2, which were investigated in a study using enzyme-linked immunosorbent assay (ELISA). There was a significant difference in the serum concentrations of fibronectin and lipocalin-2 between patients with UC and healthy individuals, indicating that the circulating profile of markers related to the ECM, including the most abundant non-collagenous proteins of the basement membrane, such as laminin and fibronectin, as well as the serum level of lipocalin associated with neutrophil

gelatinase, undergoes significant changes in IBD[21].

Finally, the levels of PCSK9, a protein that promotes the degradation of hepatic LDL receptors, may be an important indicator of UC. They are increased in patients with biochemical and endoscopic evidence of active UC. However, data regarding PCSK9 are still incipient, but studies have been conducted to analyze this protein not only as a biomarker of disease activity but also of cardiovascular risk, along with its application in the therapeutic field[34].

Limitations of biomarker studies

Despite the important results obtained by these studies, researchers have reported some limitations in project execution. Among them, the limited number of patients diagnosed with UC stands out, which may hinder the performance of a more significant evaluation of the investigated biomarker[15, 16, 20, 22, 29, 33, 36, 39-41]. Furthermore, the fact that some studies were conducted in a single medical center was also highlighted; therefore, the studied population became more uniform, favoring a possible bias in the sample selection process[15, 24,33,37,39].

Only one study reported limited clinical information from patients17, while others noted that a limited assessment of the biomarker was carried out; that is, it was analyzed at a single point in the study[17, 36,37,39]. In addition, it is worth noting that they included patients with a long duration of the disease and, therefore, submitted to several previous treatments that may have affected the levels of biomarkers, as well as the endoscopic findings and healing of UC16, 26,38,39. Patients with diseases involving high levels of inflammation, such as collagen diseases, autoimmune liver diseases, and rheumatoid arthritis, which could also influence biomarker levels[26,38].

Finally, in the research carried out with Vitamin D, data were collected over a period of 12 months, but the extent of sun exposure, the amount of daily sunlight during the period in which the blood tests were carried out, and the type of clothing worn by patients participating in the study. Likewise, seasonal variations may have affected serum vitamin D levels, constituting an important limitation of the study[12].

CONCLUSION

Based on the results obtained, an increasing number of studies aimed at developing and identifying potential biomarkers for UC are being conducted. At the outset, it is worth emphasizing that CRP has emerged as a frequently used marker, demonstrating significant variations in UC patients at different stages of the disease and suggesting the need to redefine CRP cutoff values to better predict endoscopic remission. A significant highlight was the first study conducted on serum globulin, which proved to be a promising marker for both the active phase and healing of UC.

These biomarkers can play different roles in the assessment of UC activity and diagnosis, showing a correlation with the endoscopic activity and intestinal inflammation assessment scales. Notably, an ideal biomarker should be specific to the evaluated disease and minimally sensitive to unrelated factors. The diversity of markers found in this study reflects the complexity of UC; however, it can be a positive aspect, as the combination of multiple biomarkers may provide better accuracy.

Investigating many potential biomarkers emphasizes the need for multifaceted approaches to UC diagnosis. However, it is important to emphasize the importance of extensive validation before clinical implementation using larger samples to ensure a higher degree of reliability. Finally, it is reinforced that it is essential to ensure personalized strategies for diagnosis and treatment.

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