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ORIGINAL RESEARCH

The Neutrophil-to-Albumin Ratio (NAR): A Novel Index in Relation to Clinical Symptoms, Quality of Life, and Psychological Status in Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D)

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Introduction: Irritable bowel syndrome (IBS) is a common gastrointestinal disorder characterized by chronic abdominal pain and alterations in bowel habits. Despite the importance of biomarkers in disease management, the quest for precise and non-invasive biomarkers for IBS continues.

Methods: This study focuses on investigating the clinical significance of the neutrophil-to-albumin ratio (NAR) as a potential biomarker in IBS. A cohort of 86 patients diagnosed with diarrhea-predominant IBS (IBS-D) and 106 healthy individuals were assessed for clinical symptoms, quality of life (QOL), psychological status, as well as serum and mucosal cytokine production.

Results: Our findings revealed that NAR levels were notably elevated in patients with IBS-D compared to healthy controls. Positive correlations were observed between NAR levels and IBS clinical symptoms, while negative correlations were noted with QOL. Additionally, NAR showed positive associations with anxiety and depression scores, along with significant relationships with cytokine production (serum IL-6, TNF-α, IL-1β, IL-17A, GM-CSF, IFN-γ, MCP-1; mucosal IL-6, TNF-α, IL-1β, IL-17A) in IBS-D. Interestingly, patients with lower baseline NAR levels demonstrated potentially better clinical outcomes.

Conclusion: The study underscores the potential utility of NAR as a novel biomarker in IBS, emphasizing its role in enhancing disease monitoring, understanding disease pathophysiology, and tailoring treatment strategies for patients with IBS-D.

Keywords: irritable bowel syndrome, the neutrophil-to-albumin ratio, biomarkers, inflammation

Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder characterized by chronic abdominal pain and alterations in bowel habits. It affects a significant portion of the population worldwide, making it a significant health concern.[1] The exact etiology of IBS remains unclear, but it is believed to involve complex interactions between genetic, environmental, and psychosocial factors. Clinically, IBS is diagnosed based on the presence of characteristic symptoms, including abdominal pain or discomfort, bloating, and changes in bowel habits such as diarrhea, constipation, or a combination of both.[2] However, the diagnosis of IBS is challenging due to the absence of specific diagnostic markers or identifiable structural abnormalities in the gastrointestinal tract.[3] This lack of objective diagnostic criteria often leads to delays in diagnosis and misclassification of patients with other gastrointestinal disorders.

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Additionally, monitoring disease activity and treatment response in IBS poses further challenges. Traditionally, clinical symptoms and patient-reported outcomes have been used to assess disease activity and treatment response. However, these subjective measures can be influenced by various factors, leading to difficulties in accurately evaluating disease severity and predicting treatment outcomes.[3–5] As a result, there is a need for objective and reliable biomarkers that can aid in the diagnosis, monitoring, and management of IBS. A biomarker for IBS is crucial as it can offer objective measures to aid in the accurate diagnosis, prognosis, and monitoring of the condition, which is particularly challenging due to its multifactorial nature and subjective symptomatology. Having a reliable biomarker can help improve patient outcomes, guide personalized treatment strategies, and enhance our understanding of the underlying pathophysiology of IBS. Several biomarkers have been investigated in the clinical management of IBS. However, the development of precise, feasible, and non-invasive biomarkers for IBS is still an ongoing research area.[6] Peripheral blood-based biomarker research has made significant progress in various diseases. The neutrophil-to-albumin ratio (NAR) has garnered attention as a valuable marker of systemic inflammation in various medical conditions, including inflammatory diseases, vascular disorders, and cancers.[7–11] Combining blood cell counts and serum biochemical indices, NAR has emerged as an informative parameter in clinical research. Studies have demonstrated the utility of NAR as a diagnostic and prognostic marker in different contexts. For instance, in patients with cardiogenic shock, NAR has shown superior sensitivity as a diagnostic marker compared to blood neutrophil or serum albumin levels alone.[12] This highlights the potential of NAR as a comprehensive marker of inflammation and its relevance in critical conditions. Moreover, investigations in inflammatory bowel disease (IBD) have revealed significant associations between NAR and disease activity and inflammatory burden. NAR has been observed to be significantly increased in patients with IBD, and it has shown positive correlations with both systemic and mucosal inflammation.[9,11]

In this study, we underscored the clinical significance of NAR as a biomarker in IBS. Its associations with symptom severity, quality of life (QOL), and inflammatory mediators highlight its potential in guiding treatment strategies and improving patient outcomes. By exploring the role of this biomarker and its correlation with clinical manifestations, we hope to contribute to the development of non-invasive, rapid, and reliable biomarkers for IBS, which might help to improve disease management strategies and gain better outcomes and improved quality of life for patients with IBS.

Materials and Methods

Participants

The present investigation was granted the approval of the Institutional Review Board of Sichuan Provincial People's Hospital (Approval No. 202198). In accordance with the Declaration of Helsinki, the study was designed to ensure the well-being and rights of the participants. Written informed consent was obtained from each participant, signifying their voluntary agreement to join this study. Patients who met the Rome-IV criteria for diarrhea-predominant IBS (IBS-D) were recruited from Sichuan Provincial People's Hospital. Exclusion criteria: individuals who had abdominal surgery, other GI diseases (such as inflammatory bowel disease, peptic ulcer disease), infections, diabetes mellitus, malignancy, hematopoietic system disease, hepatobiliary disease, kidney diseases, coagulation abnormalities, taking medications that can affect blood cell components or serum biochemistry profiles, hypertension, pregnancy, or lacked informed consent. Ultimately, a carefully selected cohort of 86 patients, consisting of 53 females and 33 males were deemed eligible to participate. The median age of patients was calculated to be 39.9 ± 10.6 years. Patients were taking medication including antispasmodic drugs, anti-diarrheal drugs, and/or neuromodulators (eg, tricyclic antidepressants). Healthy volunteers as controls, comprising 64 females and 42 males, were screened to ensure the absence of IBS or any other functional bowel disorders. This evaluation was conducted through comprehensive medical interviews and the administration of a validated questionnaire based on the Rome IV symptom criteria. The median age of healthy volunteers was 38.5 ± 10.2 years. Both the IBS-D patients and controls were confirmed to be free from any existing infections before serum and blood sampling. Furthermore, neither the patients nor the controls had been subjected to antibiotic treatment in the month prior to blood sampling. Detailed information of participants can be found in Table 1.

Table 1 Demographic Characteristics of the Participating Subjects

	IBS (n = 86)	HC (n = 106)	p value
Age	39.9 ± 10.6	38.5 ± 10.2	0.36 [a]
Sex (female/male)	53/33	64/42	0.86 [a]
BMI (kg/m^2)	24.2 ± 2.7	23.7 ± 2.1	0.73 [a]
Education level			
None/primary	13	21	0.68 [b]
Middle/high school	39	50	
University or higher	34	35	
Work status			
Employees	51	49	0.16 [b]
Unemployed	27	42	
Student	8	15	
Marriage			
Single	21	37	0.03 [b]
Married	46	36	
Other	19	33	
Smoking status			
Smoking/ex-smoker	37	47	0.88 [b]
Never	49	59	
Neutrophil count (*10^9/L)	4.8 ± 0.8	4.6 ± 1.3	0.21 [a]
Neutrophil percentage (%)	59.6 ± 9.6	57.3 ± 10.5	0.77 [a]
Serum albumin levels (g/L)	42.8 ± 2.1	43.3 ± 2.4	0.21 [a]
NAR levels	1.48 ± 0.3	1.32 ± 0.17	< 0.01 [a]

Notes: Data are presented as mean ± SD when applicable. [a]Unpaired *t* test, $p < 0.05$ was considered statistically significant. [b]Chi-square test, $p < 0.05$ was considered statistically significant.

Abbreviations: IBS, irritable bowel syndrome; HC, healthy controls; SD, standard deviation; BMI, body mass index; NAR, the neutrophil-to-albumin ratio.

IBS Severity Scoring Scale (IBS-SSS)

We employed the validated IBS severity scoring system (IBS-SSS) to assess the severity of IBS symptoms.[13] This method used visual analogue scales (VAS), enabling a comprehensive evaluation of IBS symptoms. By combining five items—pain severity, pain frequency, distension, bowel habit dissatisfaction, and life interference—the IBS-SSS yields an overarching score that encapsulates the overall burden experienced by individuals with IBS. Quantifying the range of symptoms, the IBS-SSS scale assigns a maximum score of 500, with higher scores indicating more pronounced symptomatology.

Assessment of Quality of Life (QOL)

To evaluate the QOL of the patients, we employed the IBS-QOL questionnaire, consisting of 34 items.[14] The questionnaire encompasses 8 distinct subscales, including food avoidance, dysphoria, body image, interference with activity, health worry, sexual life, social reaction, and relationships. Responses provided by the participants to all 34 items were aggregated and subsequently transformed into a scale ranging from 0 to 100, facilitating a comprehensive assessment of their QOL.

Evaluation of Psychological Status

To assess the participants' perceived stress levels over the past month, we utilized the 9-item Patient Health Questionnaire (PHQ-9) to gauge symptoms of depression among the subjects.[15] This well-established assessment tool allows for a thorough evaluation of depressive symptoms. The distribution of PHQ-9 scores was categorized into 5 levels: Minimal (0–4), Mild (5–9), Moderate (10–14), Moderately severe (15–19), Severe (20–27). In our follow-up study, a decline in PHQ-9 distribution levels was considered as "improvement in PHQ-9".[15] In addition, we employed the Hospital Anxiety and Depression Scale (HADS) questionnaire as a self-report tool to assess levels of anxiety and depression in individuals.[16] The HADS questionnaire consists of 14 items, with 7 items dedicated to assessing anxiety

symptoms and another 7 items focused on measuring symptoms of depression. Each item is scored on a scale of 0 to 3, with higher scores indicating greater levels of anxiety or depression.

Measurement of Cytokine Production

Serum cytokine production was measured using enzyme-linked immunosorbent assays (ELISAs). Blood samples were collected from patients with IBS-D and allowed to clot for 30 minutes at room temperature. After centrifugation, the serum was carefully separated and stored at −80°C until analysis. For cytokine measurement, commercially available ELISA kits specific for each cytokine of interest were used according to the manufacturer's instructions. The measurement of cytokine production in intestinal mucosal tissues was performed as follow: Tissue samples were obtained from the intestinal mucosa during endoscopic procedures. The collected samples were immediately placed in ice-cold sterile phosphate-buffered saline (PBS) to preserve their integrity. Subsequently, the tissues were homogenized using a tissue homogenizer in the presence of a protease inhibitor cocktail to prevent degradation of cytokines. The homogenates were then centrifuged to obtain the supernatant, which was used for cytokine analysis. As described above, cytokine measurement was performed using commercially available ELISA kits specific for each cytokine of interest according to the manufacturer's instructions.

Statistical Analysis

In the present study, statistical analysis was performed using various methods to analyze the data obtained. We used the unpaired Student's *t*-test, which allowed for the comparison of means between two independent groups. The chi-squared test was employed to analyze categorical variables and assess the association or independence between different groups or variables. Additionally, Pearson's correlation analysis was utilized to determine the strength and direction of the linear relationship between two continuous variables. The significance level was set at $p < 0.05$, indicating statistical significance. All statistical analyses were conducted using GraphPad Prism.

Results

Baseline Characteristics and NAR Levels

As illustrated in Figure 1, among the 95 individuals diagnosed with IBS-D who underwent eligibility assessment, four participants were excluded due to the withdrawal of consent, while five participants did not meet the inclusion criteria. Consequently, a total of 86 patients were included in the study. In the control group, a total of 106 healthy people were

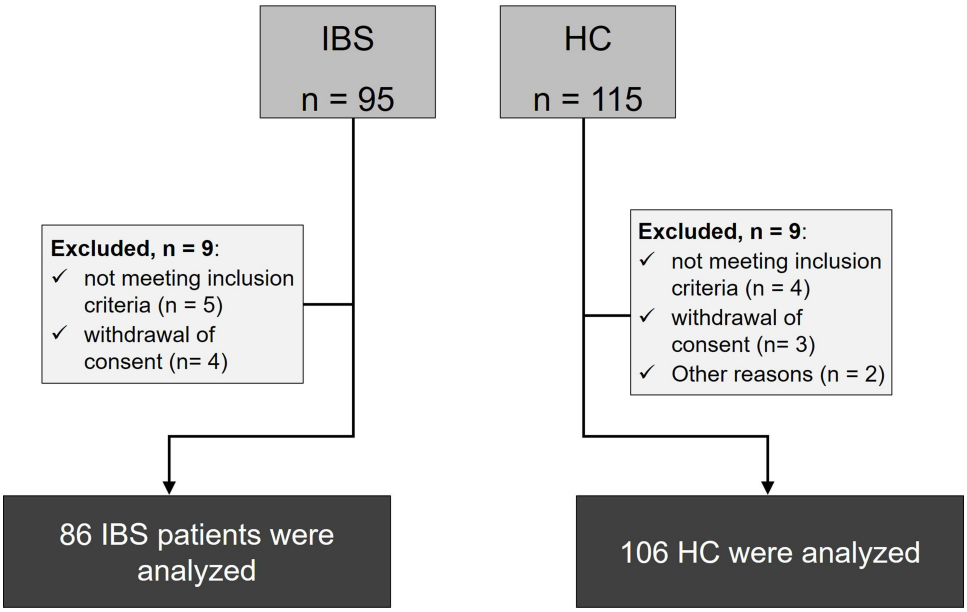


Figure 1 Flowchart of the participants through the study.
Abbreviations: IBS-D, diarrhea-predominant irritable bowel syndrome; HC, healthy controls.

Table 2 Associations of NAR with the Gastrointestinal (GI) Symptoms of IBS

	NAR	
	r	p [a]
Abdominal pain	0.753	< 0.001
Dissatisfaction with bowel habits	0.212	0.058
Abdominal distention	0.737	< 0.001
Flatulence	0.761	< 0.001
Rumbling	0.689	< 0.001
Overall GI symptoms	0.722	< 0.001

Notes: [a] Pearson's correlation analysis, $p < 0.05$ was considered statistically significant.

consequently included in the study. The average age of the participants in the IBS group was 39.9 ± 10.6, whereas in the control group it was 38.5 ± 10.2. Table 1 reveals that there were no statistically significant differences observed in terms of age, sex, and BMI between the IBS patients and the healthy controls. No statistically significant disparities were revealed in regards to the education, employment status, and smoking habits between the IBS-D patients and the healthy controls. Moreover, the groups exhibited no significant disparities in blood neutrophil percentage, absolute number, or serum albumin levels as indicated in Table 1. However, the neutrophil-to-albumin ratio (NAR) was significantly higher in patients with IBS-D compared to healthy controls (1.48 ± 0.3 vs 1.32 ± 0.17; $p < 0.01$; Table 1), and NAR showed significance in discriminating the disease (Supplementary Figure 1).

Correlations Between NAR and IBS Clinical Symptoms

In our quest to explore the clinical significance of NAR in IBS, we analyzed its association with the GI symptoms suffered by patients. Employing the Pearson's correlation analysis, we unearthed a statistically significant positive correlation between NAR levels and the intensity of both abdominal pain ($r = 0.753$, $p < 0.001$) and distention ($r = 0.737$, $p < 0.001$) (Table 2). This suggests that NAR may serve as a potential marker for the severity of these distressing symptoms. Furthermore, our investigation revealed a significant link between NAR and common GI symptoms like flatulence ($r = 0.761$, $p < 0.001$) and rumbling ($r = 0.689$, $p < 0.001$) (Table 2). Lastly, there was a significant positive correlation of NAR with IBS-SSS ($r = 0.718$, $p < 0.001$) (Figure 2).

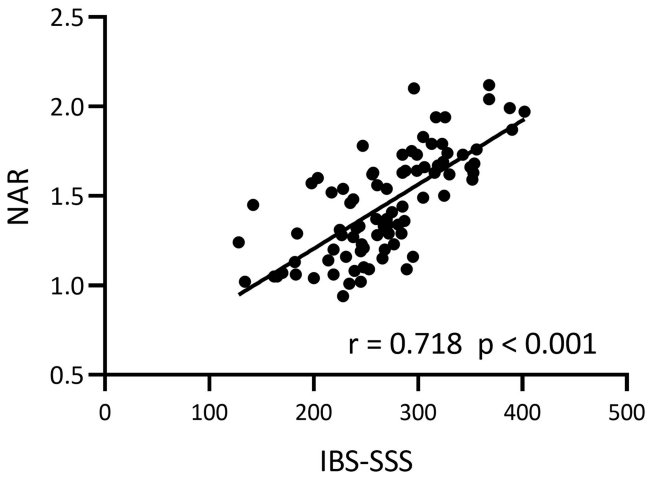


Figure 2 The association of NAR (the neutrophil-to-albumin ratio) levels with the IBS symptom severity score (IBS-SSS) in patients with IBS-D. Pearson's correlation analysis was used for determining the association. The r value represents the strength and direction of the linear relationship between two variables, and the p value < 0.05 was considered statistically significant.

Correlations Between NAR and the Quality of Life in Patients with IBS-D

In addition to the clinical manifestations of GI symptoms, it is imperative to acknowledge the pivotal role played by sociocultural, environmental, and behavioral factors in comprehending the etiology and outcomes of IBS.[17–19] Hence, the assessment of IBS-QOL assumes paramount importance as a comprehensive measure of the impact of IBS. Its inclusion as a fundamental component in clinical studies and treatment trials has been widely recommended.[18] Here, we unveiled a significant inverse correlation between NAR levels and IBS-QOL ($r = -0.772$, $p < 0.001$) (Figure 3A). Moreover, it is worth noting that psychological distress also exerts a substantial impact on IBS-QOL.[20] To delve deeper into the psychological factors affecting IBS patients, we employed the Patient Health Questionnaire-9 (PHQ-9) to assess symptoms of depression. Our results revealed a significant association between higher NAR levels and more severe depression among individuals with IBS ($r = 0.764$, $p < 0.001$) (Figure 3B). Additionally, utilizing the Hospital Anxiety and Depression Scale (HADS) questionnaire, we comprehensively evaluated the mental status of IBS patients, elucidating a positive correlation between NAR and both anxiety ($r = 0.697$, $p < 0.001$) (Figure 3C) and depression ($r = 0.755$, $p < 0.001$) (Figure 3D) scores. These findings indicate that IBS patients with elevated NAR levels may experience heightened psychological distress and diminished QOL.

Associations of NAR with Serum and Mucosal Cytokine Levels in Patients with IBS-D

The role of systemic inflammation in the pathophysiology of visceral hypersensitivity and disruptions in gut motility observed in individuals with IBS is widely acknowledged.[2] Visceral hypersensitivity, a key contributor to the perception of pain and abdominal discomfort, stands as a defining characteristic of IBS.[21] Guided by this understanding, our study aimed to delve into the intricate dynamics of inflammation by examining the levels of serum cytokines, which serve as

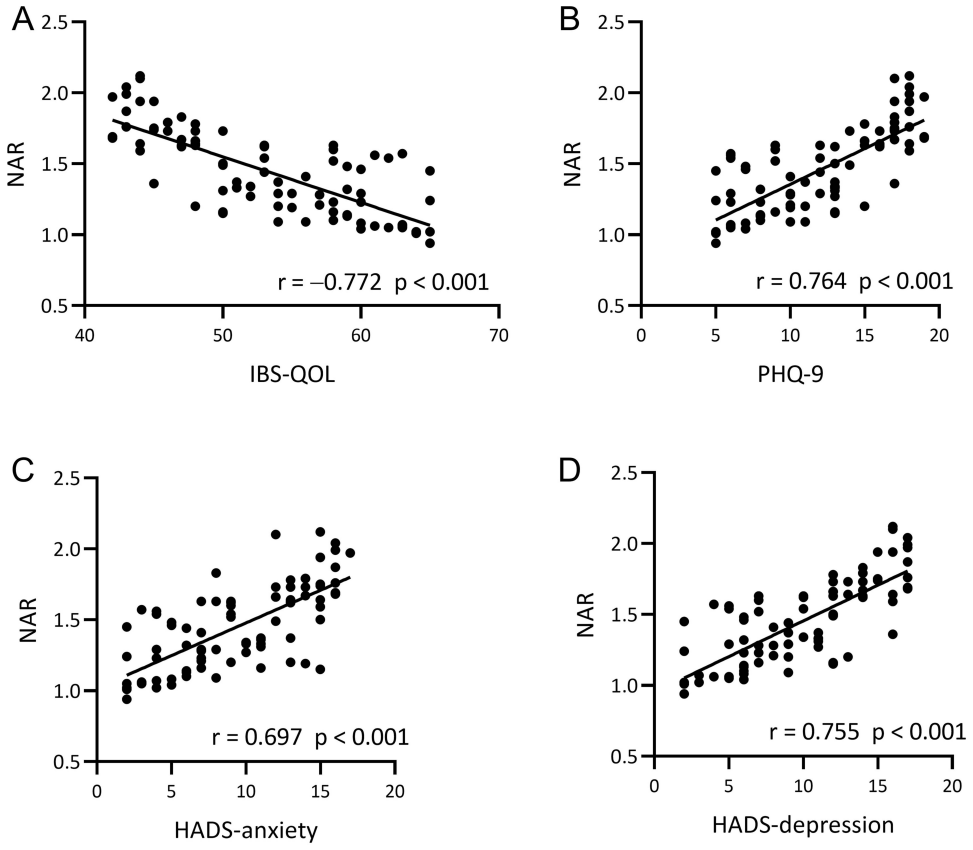


Figure 3 The association of NAR levels with the quality of life (QOL) and psychological status in patients with IBS-D. Pearson's correlation analysis was used for determining the association of NAR with scores obtained from the (**A**) 34-item IBS-QOL questionnaire, (**B**) patient health questionnaire-9 (PHQ-9), and (**C** and **D**) Hospital Anxiety and Depression Scale (Hads) questionnaire. The r value represents the strength and direction of the linear relationship between two variables, and the p value < 0.05 was considered statistically significant.

critical factors of this biological process, within our cohort of patients.[22] The results, as presented in Table 3, uncovered a significant positive correlation between the levels of NAR and several key cytokines, including interleukin (IL)-6 ($r = 0.576$, $p < 0.001$), tumor necrosis factor (TNF)-α ($r = 0.611$, $p < 0.001$), IL-1β ($r = 608$, $p < 0.001$), IL-17A ($r = 593$, $p < 0.001$), and interferon (IFN)-γ ($r = 0.578$, $p < 0.001$). Additionally, we observed a statistically significant albeit somewhat less pronounced positive association between NAR and granulocyte-macrophage colony-stimulating factor (GM-CSF) ($r = 0.214$, $p = 0.048$) and monocyte chemoattractant protein (MCP)-1 ($r = 0.224$, $p = 0.038$). Moreover, we collected endoscopic mucosal tissues from 47 patients out of our cohort, and measured cytokine levels by ELISA, showing that NAR had a significant positive correlation with mucosal IL-6 ($r = 0.426$, $p < 0.001$), TNF-α ($r = 0.611$, $p < 0.001$), IL-1β ($r = 0.284$, $p = 0.022$), and IL-17A ($r = 0.415$, $p = 0.043$) (Table 4).

Table 3 Associations of NAR with Serum Cytokine Levels in Patients with IBS-D

	NAR	
	r	p [a]
IL-8	0.028	0.795
IL-6	0.576	< 0.001
TNF-α	0.611	< 0.001
IL-1β	0.608	< 0.001
IL-17A	0.593	< 0.001
IL-12	0.156	0.143
GM-CSF	0.214	0.048
IFN-γ	0.578	< 0.001
MCP-1	0.224	0.038
MIP-1β	0.174	0.109

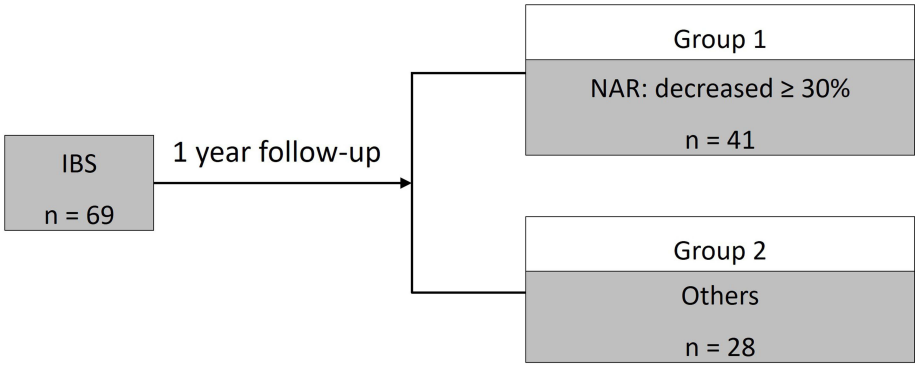
Notes: [a]Pearson's correlation analysis, $p < 0.05$ was considered statistically significant.
Abbreviations: IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; GM-CSF, granulocyte-macrophage colony-stimulating factor; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein.

Table 4 Associations of NAR with Mucosal Expression of Cytokines in IBS-D

	NAR	
	r	p [a]
IL-8	0.126	0.682
IL-6	0.426	< 0.001
TNF-α	0.611	< 0.001
IL-1β	0.284	0.022
IL-17A	0.415	0.043
IFN-γ	0.186	0.098

Notes: [a]Pearson's correlation analysis, $p < 0.05$ was considered statistically significant.
Abbreviations: IL, interleukin; TNF, tumor necrosis factor; IFN, interferon.

A



B

	Improvement in IBS-SSS		Chi-square test
	Yes	No	
Group 1	n = 29	n = 12	p = 0.004
Group 2	n = 10	n = 18	

C

	Improvement in PHQ-9		Chi-square test
	Yes	No	
Group 1	n = 25	n = 16	p = 0.001
Group 2	n = 6	n = 22	

Figure 4 NAR levels indicate the clinical outcome of patients with IBS-D. (**A**) Study design. The number of patients with indicated outcome in (**B**) IBS-SSS and (**C**) PHQ-9. The p value < 0.05 (Chi-square test) was considered statistically significant.

NAR Levels Indicate the Clinical Outcome of IBS Patients

Furthermore, a comprehensive and dynamic tracking study was conducted on a cohort of 69 patients encompassed within the study. The detailed grouping scheme can be discerned in Figure 4A, providing a visual representation of the methodology employed. Those individuals exhibiting a decrease of 30% or more were categorically assigned to Group 1, whereas the remaining constituents were aptly placed in Group 2. To ascertain amelioration in the GI symptoms experienced by IBS-D patients, a decline of no less than 20% in the IBS-SSS was considered as "improvement in IBS-SSS". Subsequent statistical analyses unearthed a remarkable disparity, as the number of patients experiencing substantial improvement in the IBS-SSS (Group 1, 29 out of 41, accounting for 70.7%) vastly exceeded that of their counterparts in Group 2 (10 out of 28, 35.7%) (Figure 4B). Additionally, a decline of PHQ-9 distribution was considered as "improvement in PHQ-9". Group 1 showed a significantly higher ratio of patients (25 out of 41, 61.0%) who ended up with better psychosocial status than Group 2 (6 out of 22, 27.3%) (Figure 4C). This evidence strongly suggests that NAR levels hold tremendous potential for discerning clinical IBS severity and psychosocial status, which could facilitate the evaluation of patient improvement.

Discussion

Our study revealed that NAR was significantly increased in patients with IBS-D compared to healthy controls. These findings suggest that NAR could serve as a novel and convenient biomarker for IBS. The advantage of NAR lies in its

non-invasive nature and ease of measurement, making it a promising tool for monitoring disease progression and treatment response in IBS patients.

Currently, the diagnosis of IBS relies mainly on clinical symptoms and exclusion of other organic diseases. However, these diagnostic criteria lack objectivity and may lead to misdiagnosis or delayed diagnosis.[23,24] Using non-invasive and objective biomarkers for managing IBS patients offers several advantages.[25–28] These biomarkers do not cause additional pain or discomfort, unlike invasive tests such as colonoscopy or biopsies. They can be conveniently performed in a patient's daily life. Additionally, non-invasive biomarkers provide objective measurement results, eliminating the uncertainty of subjective assessments. By measuring biomarkers, it is possible to accurately assess disease status, monitor changes, and evaluate treatment effectiveness in IBS patients. Furthermore, non-invasive biomarkers enable more frequent and continuous monitoring, allowing for timely detection of condition changes. This continuous monitoring guides treatment decisions, facilitating quicker adjustments to meet specific patient needs. NAR, on the other hand, provides an objective and quantifiable measure that can aid in the management of IBS. By assessing the NAR levels in patients, healthcare professionals can have a more accurate and reliable indicator of the clinical condition of IBS. Furthermore, the convenience and simplicity of NAR measurements make it a suitable tool for regular monitoring of IBS patients. The non-invasive nature of NAR measurements eliminates the need for invasive procedures or extensive laboratory tests. Instead, a simple blood sample can be used to determine NAR levels, allowing for easy and frequent monitoring of patients' disease status. This ability to dynamically monitor disease status could facilitate personalized and timely interventions, leading to improved patient outcomes. NAR thus holds significant potential for clinical applications in the management of IBS.

Our study also established a significant positive association between NAR and serum inflammatory cytokine levels in IBS patients. This finding aligns with the current understanding that IBS is related to systemic inflammation.[22,29,30] NAR, as a marker of inflammation, can reflect the inflammatory state of IBS patients. The identification of this correlation between NAR and systemic inflammation suggests that NAR can be utilized as a surrogate marker for assessing the overall inflammatory burden in IBS patients. Chronic low-grade inflammation has been implicated in the pathophysiology of IBS, and elevated levels of inflammatory markers have been observed in IBS patients.[22,31] NAR offers a representation of inflammation by incorporating both neutrophils and albumin levels. Neutrophils are key players in the inflammatory response, while albumin serves as a marker of nutritional status and powerful antioxidants in oxidative stress/inflammation-associated disorders. NAR integrates the effects of two inversely related inflammatory pathways, reflecting the balance between pro-inflammatory neutrophils and anti-inflammatory albumin, providing crucial insights into the inflammatory milieu within the body. Therefore, NAR's uniqueness lies in its dual functionality as a marker of inflammation and nutritional status. While other inflammatory markers may focus solely on immune response elements, NAR encompasses both inflammatory and nutritional components, offering a more comprehensive insight into the inflammatory status of individuals with IBS. This multifaceted approach sets NAR apart and enhances its diagnostic and prognostic value in IBS management. Moreover, understanding the inflammatory processes in IBS is crucial for the development of targeted therapeutic strategies. By utilizing NAR as an indicator of the inflammatory burden, it would be easier to tailor treatment plans to address the underlying inflammation. This personalized approach may lead to more effective and targeted interventions, ultimately improving the management of IBS.

Additionally, our findings indicate that higher NAR levels were accompanied by lower QOL scores and higher IBS-SSS in patients with IBS-D. This observation implies that baseline NAR levels might hold predictive value for monitoring IBS progression. Baseline NAR levels can serve as a valuable reference point for assessing disease progression and treatment response in IBS patients. By establishing a baseline NAR level for each patient, clinicians could potentially predict the trajectory of the disease and anticipate changes in symptom severity and QOL. This predictive capability of NAR could facilitate early intervention and the implementation of tailored treatment plans, ultimately improving patient outcomes in the long term. In addition, the association between NAR and symptom severity suggests that NAR levels could be used as a prognostic indicator for IBS patients. Patients with higher NAR levels at baseline may be at increased risk of experiencing more severe symptoms and decreased QOL over time. Identifying these patients early on allows for targeted interventions and closer monitoring to prevent the exacerbation of symptoms and deterioration of QOL. However, it is important to note that further research is needed to validate the predictive value of

baseline NAR levels in monitoring IBS progression. Prospective studies with larger cohorts and longer follow-up periods are warranted to confirm the relationship between baseline NAR levels and long-term outcomes in IBS patients.

While our study provides valuable insights into the potential clinical applications of NAR in IBS, several limitations should be acknowledged. Firstly, the sample size in our study was relatively small, limiting the generalizability of our findings. Future research with larger cohorts is warranted to validate our results and ensure the robustness of the observed associations. Secondly, this study focused solely on the IBS-D subtype, limiting the generalizability of the findings to all IBS patients. The significance of NAR needs to be further investigated in other subtypes of IBS. Thirdly, since we only tested cytokines in patients with IBS-D, it requires the data from healthy controls and other subtypes of IBS to clarify the uniqueness of the associations observed between cytokines and NAR. Furthermore, our study focused on the association between NAR and clinical outcomes in IBS patients. It would be beneficial for future research to investigate the underlying mechanisms linking NAR, systemic inflammation, and symptom severity in IBS. Understanding these mechanisms would provide a more comprehensive understanding of the role of NAR in IBS pathophysiology.

In conclusion, our findings support the potential of NAR as a novel, non-invasive, and convenient biomarker for monitoring IBS patients. NAR not only reflects the disease severity and systemic inflammation in IBS but also holds predictive value for disease progression. Incorporating NAR into routine clinical practice could provide valuable insights into disease management and facilitate personalized interventions for IBS patients. Further research, including larger prospective studies and investigations into the underlying mechanisms, is necessary to validate our findings and explore the full potential of NAR in the dynamic management of IBS.

Data Sharing Statement

The data underlying the research results are available in the article.

Institutional Review Board Statement

The study protocol was designed in accordance with the Declaration of Helsinki, approved by the Institutional Review Board of Sichuan Provincial People's Hospital (Approval No. 202198).

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Disclosure

The authors declare no conflict of interest.

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