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Inferencing Medical Knowledge from an Artificial Neural Network in Inflammatory Bowel Disease

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Abstract
Introduction: Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), pose significant challenges to both clinicians and researchers. The complex interaction of genetic predisposition, environmental influences, and dysregulated immune responses underpins the heterogeneous nature of these diseases. This complexity often leads to diagnostic uncertainties and therapeutic dilemmas. Artificial intelligence (AI), particularly neural networks, offers promising solutions for these challenges. Our study aimed to develop a neural network that integrates multiple non-invasive parameters for monitoring inflammatory status in patients with IBD, assess the network's diagnostic accuracy, and use the training data to classify the clinical relevance of biomarkers. *Materials and Methods:* The study included patients diagnosed with CD or UC based on endoscopic and histopathological criteria following their consent for colonoscopy. Participants were recruited from the Regional Institute of Gastroenterology and Hepatology Cluj-Napoca, Romania. A subset was enrolled prospectively from 2020 to 2022, and the remainder was identified retrospectively from hospital records spanning 2017 to 2020. Data from 70% of the patients were utilized to train the neural networks, and 30% to validate it. The data used as inputs were clinical scores, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fecal calprotectin (FC). *Results:* The neural networks showed significant diagnostic capabilities, particularly for endoscopic activity in UC (AUC of 0.955) and CD (AUC of 0.813), though histologic activity prediction was less accurate. Regarding the importance of the markers used for the decision, we found that the Crohn's Disease Activity Index (CDAI) was the most significant predictor for CD endoscopic activity and FC for UC. The study highlights the potential of AI in supporting less experienced endoscopists, reducing observer variability, and minimizing the need for repeated colonoscopies. However, further refinement is needed to improve histologic assessment accuracy.

Keywords: Inflammatory bowel diseases (IBD); Crohn's disease (CD); Ulcerative colitis (UC); Neural networks (NN)

Introduction

Inflammatory bowel diseases (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are chronic diseases that present complex challenges for clinicians and researchers. In the last decades, there has been an increase in cases of IBD globally, a fact correlated with industrialization and the adoption of Western lifestyles in the eastern regions. In Romania, the prevalence was estimated at 1.5 per 100,000 for CD and 2.4 per 100,000 for UC, while the incidence was 1.7 per 100,000 persons/year for CD and 2.5 per 100,000 persons/year for UC and this continues to increase, imposing a significant burden on healthcare systems [1]. Although the etiology and pathogenesis of IBD are not fully understood, research suggests that these diseases result from an imbalance

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between pro-inflammatory and anti-inflammatory forces. This involves genetic susceptibility, environmental factors, and diet impacting the gut microbiome, leading to intestinal barrier alterations and inadequate immune responses. The interplay of these factors contributes to the heterogeneous nature of IBD, resulting in diagnostic uncertainties and therapeutic dilemmas [2].

Despite significant advancements in conventional diagnostic modalities and treatment strategies, the pursuit of personalized and precision medicine in IBD remains a challenge. Early diagnosis of IBD is essential, as in severe cases, disease progression may lead to surgical interventions and serious complications. Colonoscopic evaluation is the gold standard and, therefore, crucial for selecting appropriate treatment. However, there is variability among observers [3] and endoscopists require a period of training of at least 500 colonoscopies to archive the technical skill necessary for independent gastrointestinal practice and to accurately assess inflammatory activity [4]. Experts acknowledge the current limitations of various endoscopic scoring tools for disease activity in IBD and seek potential solutions with new advanced techniques [5].

Various biomarkers have been studied individually or in combination to assess and monitor patients with IBD and reduce the number of required colonoscopies; however, non-invasive tools cannot completely replace endoscopic examinations [6].

Recently, the field of artificial intelligence (AI) has proven to be a promising tool in medicine [7]. Virtual machine learning systems are AI systems that enable a model to learn and improve iteratively when exposed to data. Such systems can process various types of data, including clinical outcomes, biological values, or even physiological processes quantifying relationships between them. The model's accuracy and reproducibility are tested with a new set of similar information. Ultimately, the algorithm provides a final result. [8]. Several machine learning algorithms can be used in medical practice. The most popular ones are linear regression, logistic regression, decision trees, and last but not least, neural networks [7, 9].

Neural networks are, therefore, a field of machine learning that enables the development of artificial neural networks. In other words, neural networks are a set of machine learning models built using complex algorithms inspired by the organization of the human brain [9]. The operation of a neural network is complex. If we take the example of a neural network developed to analyze radiological images, the input layer of imaging neural networks contains image features such as brightness, homogeneity, and saturation, in addition to other descriptors used for image quantification. Each input node value (equivalent to a neuron) is then multiplied by a node weight. Downstream nodes are activated when the weighted input value exceeds a threshold, similar to how a synapse activates connected neurons. The interconnected hidden layers ultimately end in an output node that classifies the image. When dealing with imaging data, a neural network learns the features associated with image annotations by adjusting the weights between nodes iteratively. This process utilizes a training set consisting of thousands of pre-existing images [8].

Experience significantly influences the accurate assessment of disease activity in IBD based on endoscopic findings. Expert endoscopists (who performed more than 2000 colonoscopies) demonstrate better concordance in inter- and intraobserver agreements than less experienced endoscopists (who performed less than 200 colonoscopies [4, 10]. In this case, using neural networks is promising, supporting less experienced endoscopists and reducing variability among observers when evaluating the severity of endoscopic inflammation in patients with IBD. [11]. Thus, new machine learning and deep learning technologies promise to significantly improve the understanding of IBD as well as the more objective assessment of disease activity, ultimately leading to better outcomes for patients. Their utility in facilitating radiological, histological, and endoscopic assessment of IBD has been extensively demonstrated [9]. Furthermore, advances in neural network development have led to impressive results ranging from replicating medical thinking to predicting clinical outcomes, especially in medical imaging [8].

Our study aimed to develop a neural network that integrates multiple non-invasive parameters used in monitoring patients with inflammatory bowel diseases to evaluate intestinal inflammatory activity and test the diagnostic accuracy of this neural network. Additionally, the data provided from training the neural networks are used to classify the clinical importance of biomarkers. Essentially, our study assumed two main objectives: building an artificial intelligence system based on neural networks that automatically reproduces accumulated clinical thinking from evaluated cases and presenting to physicians a classified set of factors that influenced their decision-making.

Materials and Methods

Selection and Description of Participants

Our study comprised patients recruited from the Regional Institute of Gastroenterology and Hepatology Cluj-Napoca, all of whom resided in Romania. A portion of the participants were prospectively enrolled between 2020 and 2022, while the remainder were retrospectively identified from hospital records spanning the period between 2017 and 2020. Each patient underwent a single evaluation at the time of presentation.

Ethical approval for the study was obtained from the Ethics Committee of the University of Medicine and Pharmacy Cluj-Napoca (approval no 93/09.03.2020).

Inclusion criteria encompassed patients diagnosed with CD or UC based on endoscopic and histopathological findings following their consent to undergo colonoscopy. Exclusion criteria encompassed individuals under 18 and those with other pathologies featuring an inflammatory component (e.g., neoplasia, acute or chronic infections, other autoimmune diseases).

Methods

Disease activity assessment relied on clinical, endoscopic, and histopathological criteria utilizing commonly employed scores in clinical practice, previously validated and endorsed [12]. Clinical activity was evaluated using the Crohn's Disease Activity Index (CDAI) for CD and the Mayo partial score for UC. Endoscopic activity was assessed using the Simplified Endoscopic Score for Crohn's disease (SES-CD) and the Mayo Endoscopic Score for UC. An SES-CD score of < 2 points and a Mayo score of 0 points were considered indicative of endoscopic remission. Histopathological activity was evaluated using the Naini and Cortina score for CD and the Nacy score for UC. Due to the challenges associated with applying these scores and the lack of precise delineation intervals between different degrees of histological activity, statistical analysis was conducted based on the pathologist's assessment of activity or remission.

To evaluate systemic inflammation, parameters monitored included C-reactive protein (CRP) levels (mg/dl) and erythrocyte sedimentation rate at one hour (ESR) (mm). Fecal calprotectin (FC) levels (µg/g) were monitored to assess intestinal inflammation.

Statistics

The collected data were utilized to train neural network systems in two distinct programs to validate the results: IBM SPSS version 27 and Neural Designer 6.0.8 (Artificial Intelligence Techniques, Ltd, 2023). The classification capability was compared using receiver operating characteristic curves (ROC). The relative importance of biomarkers was compared using both absolute and normalized values.

The neural networks were designed so that the structure corresponded to the input and output data, identically for all analysis variants used: the two conditions studied (CD and UC), with differences arising only from the use of two different scoring systems for the input layer, CDAI for CD and Mayo for UC.

Figure 1 illustrates the network architecture, comprising an input layer with 4 scaling neurons, a hidden layer with 3 neurons, and an output layer with 1 neuron for prediction. The inputs encompassed clinical scores (CDAI for CD and Mayo for UC), CRP levels, ESR and FC levels.

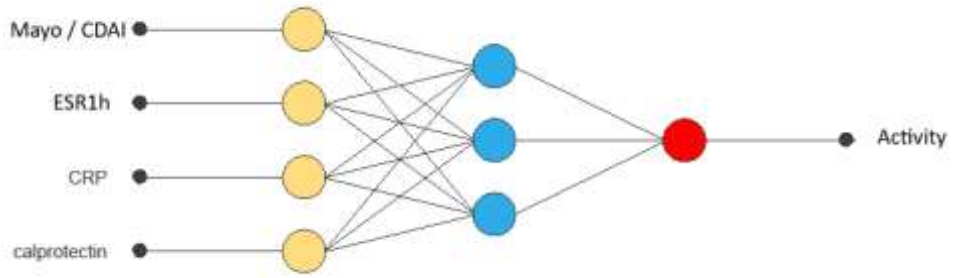

Figure 1. Multilayer perceptron architecture was used: a scaling layer with 4 neurons (yellow), a perceptron layer with 3 neurons (blue), and a probabilistic layer with 1 neuron (red).

To optimize prediction accuracy, the dataset was divided into two using a random algorithm with a partitioning variable: 70% for training and 30% for model validation. Across all neural networks in both applications, the hidden layer employed a hyperbolic tangent activation function, while the output neuron utilized a softmax function for both training and activation.

The training strategy adjusts the parameters of the neural network to minimize the loss function. The loss function defines the objective of the neural network and serves as a metric for the quality of the representation required for learning. To achieve this, we have considered two aspects: error and regularization.

The error term quantitatively evaluates how well the neural network fits the dataset. In this context, we have chosen the Weighted Squared Error (WSE).

The regularization term assesses the magnitude of the parameters in the neural network. Integrating it with the error term encourages the neural network to have smaller weights and biases, resulting in smoother responses and preventing overfitting. In this instance, we employed a regularization method based on the squared sum of all parameters in the neural network.

Results

Four distinct trained neural networks were obtained, corresponding to the two diseases and two different activities: endoscopic and histopathological. The SPSS neural network training was validated using Neural Designer, employing the same architecture and training partitions. A representative trained network for Cs is depicted in Figure 2.

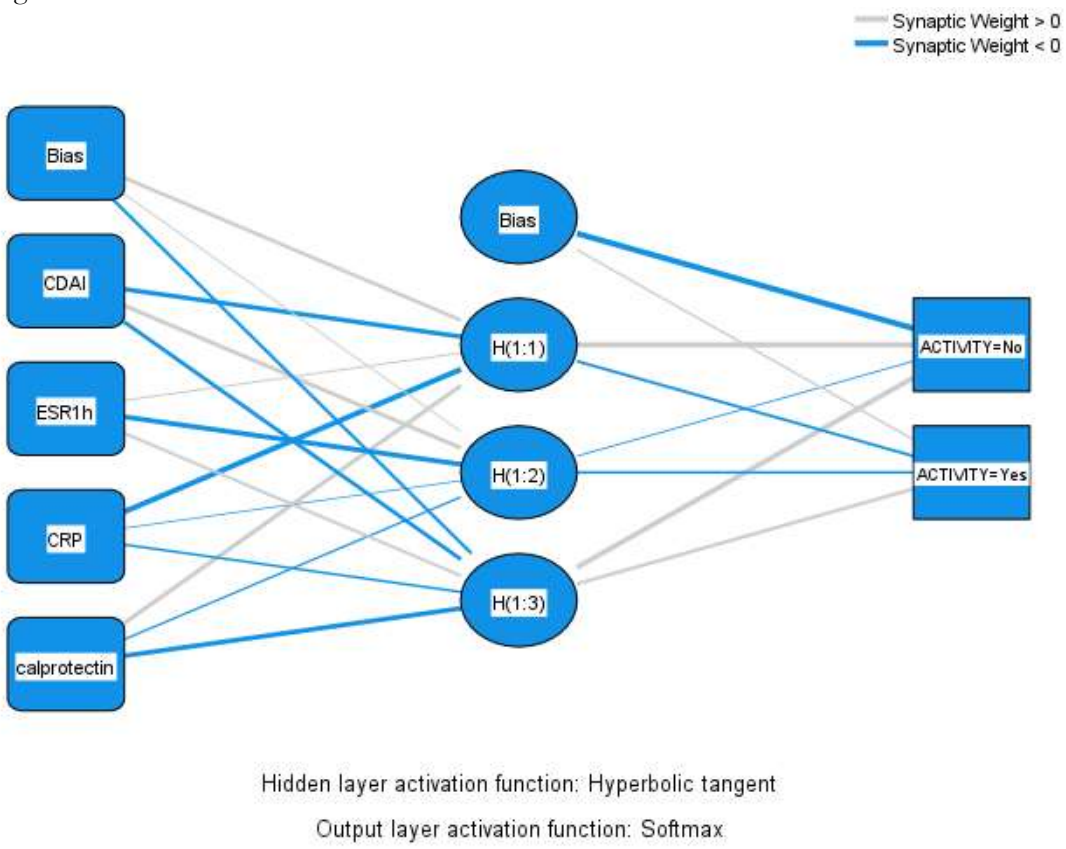

Figure 2. Neural network architecture after training (for example, Crohn's disease) with synaptic weights was added during training biases.

The diagnostic capability of this network is highlighted by the ROC curve from the testing phase, for which we obtained an area under the curve (AUC) of 0.813 (0.722 to 0.912) for diagnosing endoscopic activity and only 0.649 (0.579 to 0.698) for diagnosing histologic activity (Figure 3).

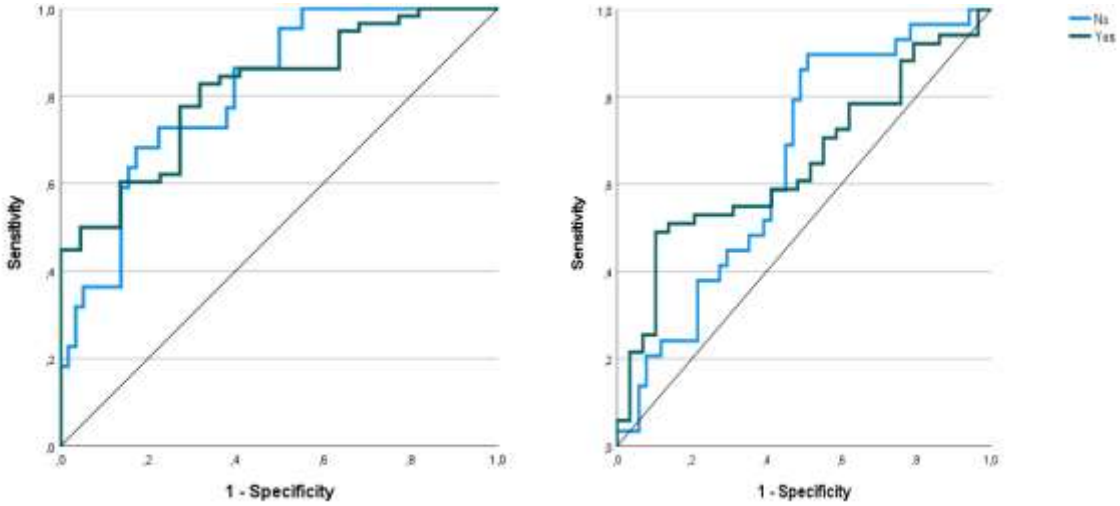

Figure 3. The ROC curves for the validation of endoscopic (left) and histological (right) activity in Crohn's disease.

Table 1 presents the normalized importance of the factors used for diagnosing endoscopic and histopathologic activity, as determined by training the neural network.

Table 1. The importance of the markers used for the decision by the neural network for endoscopic and histological activity in Crohn's disease.

		Importance	Normalized Importance (5)
Endoscopic activity	CDAI	0.594	100.0
	ESR1h	0.097	16.3
	CRP	0.259	43.5
	Calprotectin	0.051	8.5
Histologic activity	CRP	0.474	100.0
	ESR1h	0.397	83.9
	CDAI	0.067	14.2
	Calprotectin	0.062	13.0

CDAI: Crohn's disease activity index, ESR1h: erythrocyte sedimentation rate at one hour, CRP: C-reactive protein levels (mg/dl)

The diagnostic capability of this network is highlighted by the ROC curve from the testing phase, for which we obtained an area under the curve (AUC) of 0.955 (0.899 to 0.987) for diagnosing endoscopic activity and only 0.826 (0,756 to 0,897) for diagnosing histologic activity (Figure 3).

Table 2 presents the normalized importance of the factors used for diagnosing endoscopic and histopathologic activity, as determined by training the neural network for ulcerative colitis patients.

Table 2. The importance of the markers used for the decision by the neural network for endoscopic and histological activity in ulcerative colitis.

		Importance	Normalized Importance (%)
Endoscopic activity	Calprotectin	0.348	100.0
	ESR1h	0.317	91.0
	Mayo Score	0.251	72.1
	CRP	0.084	24.0
Histologic activity	Mayo Score	0.360	100.0
	Calprotectin	0.298	82.7
	CRP	0.172	47.8
	ESR1h	0.298	82.7

CDAI: Crohn's disease activity index, ESR1h: erythrocyte sedimentation rate at one hour, CRP: C-reactive protein levels (mg/dl)

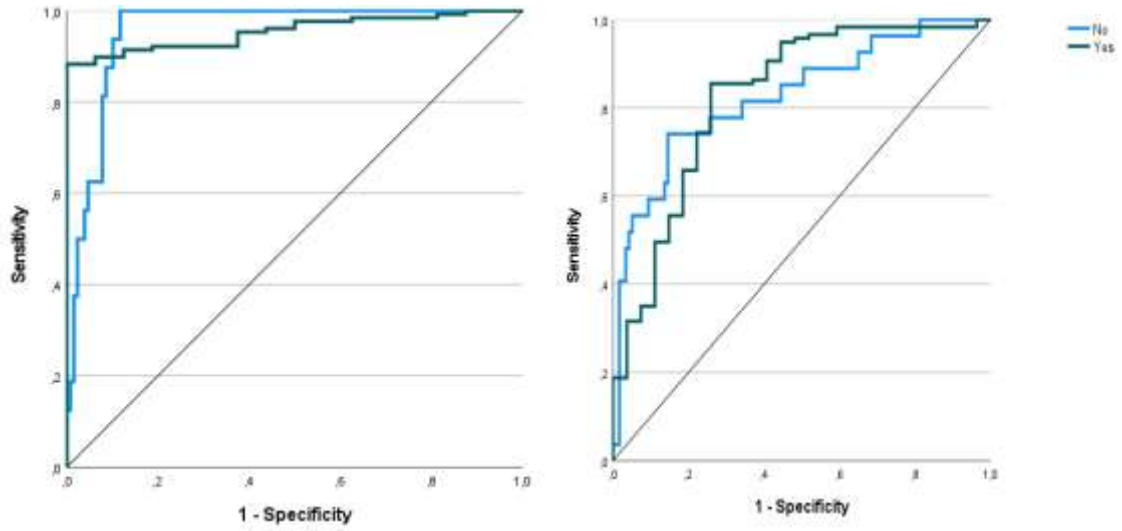

Figure 3. The ROC curves for the validation of endoscopic (left) and histological (right) activity in ulcerative colitis.

Discussions

This study aimed to develop and validate a neural network-based system capable of integrating multiple non-invasive parameters for evaluating intestinal inflammatory activity in patients with IBD. Our neural network models showed varying degrees of success in predicting endoscopic and histologic activity for both CD and UC, highlighting both the promise and the limitations of AI in this context.

The integration of AI and machine learning technologies in medical research and practice represents a significant stride toward precision medicine [13]. Our study demonstrated that neural networks exhibit robust diagnostic capabilities, particularly in assessing endoscopic activity for both Crohn's disease (CD) and ulcerative colitis (UC). While the area under the curve (AUC) indicated strong differentiation between active disease and remission in endoscopic evaluations, the accuracy was notably higher for UC compared to CD. However, the AUC for histologic activity was lower, suggesting room for improvement in predicting histological outcomes. This discrepancy may stem from the inherent complexity of histological assessment, which biomarkers and clinical scores used in our model may not fully capture. Another study investigating neural networks' diagnostic abilities in evaluating intestinal mucosa and predicting histologic inflammation in UC found high accuracy in predicting histological remission using endoscopic images [14]. The findings underscore the potential of neural networks in enhancing diagnostic precision in IBD, while also highlighting the need for further refinement to optimize their application in histological assessment, particularly for CD.

The study also evaluated the relative importance of various biomarkers in the neural network's decision-making process. For CD, the CDAI was the most significant predictor for endoscopic activity, followed by CRP levels, ESR, and FC. Interestingly, for histological activity, CRP emerged as the most important marker. In contrast, for UC, FC was the most crucial marker for endoscopic activity, and the Mayo score was predominant for histologic activity. The observed differences highlight the distinct pathophysiological mechanisms underlying CD and UC. CD typically involves transmural inflammation and can affect any part of the gastrointestinal tract, leading to a wider systemic inflammatory response. In contrast, UC primarily affects the mucosal layer of the colon and rectum, resulting in a more localized inflammation. This fundamental difference may influence how biomarkers correlate with disease activity in each condition and suggest that personalized biomarker profiles are essential for accurate disease monitoring. The varying clinical presentations of CD and UC may also influence biomarker associations with disease activity. The dominance of CRP as a predictor for histological activity in CD reflects its correlation with systemic inflammation and tissue pathology, whereas FC's role in UC highlights its sensitivity to mucosal inflammation in the colon and rectum. The Mayo score, which includes assessments of stool frequency, rectal bleeding, and endoscopic findings, was predominant for histological activity in UC, underscoring the close relationship between clinical symptoms and mucosal inflammation. The observed differences underscore the

importance of personalized biomarker profiles in accurately monitoring disease activity and tailoring treatment strategies for patients with CD and UC. Tailoring treatment based on individual biomarker responses could potentially optimize therapeutic outcomes and minimize disease progression in these chronic inflammatory conditions.

The variability in neural network performance between endoscopic and histologic activity assessment underscores the complexity of IBD and the challenges in developing reliable AI-based diagnostic tools. The application of neural networks in clinical practice offers several advantages. Firstly, it can support less experienced endoscopists [15] by reducing observer variability and improving the consistency of disease activity assessments [5]. This is particularly beneficial in settings where access to highly experienced endoscopists is limited. Secondly, by integrating non-invasive biomarkers, neural networks can minimize the need for repeated colonoscopies, thereby reducing patient burden and healthcare costs [16]. Thirdly, AI models can facilitate early diagnosis and timely intervention [13], which are crucial in preventing disease progression and complications in IBD. By providing a more objective assessment of disease activity [14], these models can aid in monitoring response to therapy and adjusting treatment plans accordingly [17, 18]. Moreover, neural networks' ability to classify the clinical importance of different biomarkers provides valuable insights for personalized medicine. Physicians can tailor treatment strategies based on their patients' specific biomarker profiles, potentially leading to more effective and targeted therapies. This approach aligns with the current trend towards precision medicine, which aims to customize healthcare based on individual patient characteristics.

The results of this study align with previous research demonstrating the utility of AI in medical imaging and disease diagnosis. The use of neural networks and other AI techniques in IBD has been explored in recent years, with studies showing the potential of these technologies in improving diagnostic accuracy and predicting clinical outcomes [19]. However, our study uniquely focuses on integrating multiple non-invasive biomarkers and clinical scores into a neural network model, providing a comprehensive approach to disease assessment.

Despite the promising results, this study has several limitations. The sample size, particularly for the testing phase, was relatively small, which may affect the generalizability of the findings. However, the dual validation approach using SPSS and Neural Designer software ensures the robustness of our results. Additionally, the study was conducted at a single center, and external validation in diverse populations is necessary to confirm the robustness of the neural network models.

Future research should focus on expanding the dataset and incorporating additional biomarkers to enhance the predictive accuracy of the neural networks. Integrating other advanced machine learning techniques, such as ensemble methods, could further improve diagnostic performance. Also, longitudinal studies are needed to evaluate the ability of neural networks to predict long-term clinical outcomes and guide treatment adjustments over time. Moreover, collaborative efforts between clinicians, researchers, and AI specialists are crucial to refine these models further, ensuring they can be seamlessly integrated into routine clinical workflows. Training programs to familiarize healthcare professionals with AI tools and continuous updates based on real-world performance data will also be essential for the successful implementation of AI in IBD management.

Conclusion

In conclusion, our study demonstrates the potential of neural network-based AI systems in assessing disease activity in IBD, particularly in reducing the reliance on invasive procedures and supporting clinical decision-making. The integration of non-invasive biomarkers and clinical scores into a neural network model offers a comprehensive approach to disease assessment, with promising diagnostic performance, especially for endoscopic activity in UC. Future research should focus on expanding the dataset, incorporating additional biomarkers, and exploring advanced AI techniques to enhance model performance. The ultimate goal is to develop reliable, non-invasive diagnostic tools that can be seamlessly integrated into clinical practice, improving outcomes for patients with IBD. The application of AI in IBD represents a significant step towards personalized and precision medicine, with the potential to transform disease management and improve patient care.

List of Abbreviations: AI-artificial intelligence; AUC- area under the curve; CD-Crohn diseases; CDAI-Crohn's disease activity index; CRP-C reactive protein; ESR1h-erythrocyte sedimentation rate at one hour, FC-fecal calprotectin, IBD-

inflammatory bowel diseases; ROC-receiver operating characteristic curves; SES-CD- Simplified Endoscopic Score for Crohn's disease; UC-ulcerative colitis.

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Conflict of Interest: The authors declare no conflict of interest.

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