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# A novel inflammatory biomarker in assessing disease activity in ulcerative colitis: gasdermin D

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## Abstract

**Background** Ulcerative colitis (UC) is a chronic inflammatory disease with a worldwide prevalence of around 5 million patients. Assessment of disease activity is crucial in management of UC patients. Gasdermin D (GSDMD) is a protein which belongs to the gasdermin protein family and plays a role in inflammatory cell death, pyroptosis. GSDMD activation has been shown to be related to inflammatory states in a variety of disorders, including inflammatory bowel diseases. With this study, we aimed to reveal a potential new inflammatory serum marker for assessing disease activity and severity in UC patients in a non-invasive manner.

**Materials and Methods** This prospective study was carried out at Antalya Training and Research Hospital, Turkey, between September 2022 and March 2024. 93 UC patients were enrolled in the study. Patient and disease characteristics, laboratory workout data, and severity indexes comprising Truelove and Witts' severity index (TWSI) and Mayo endoscopic subscore (MES) were analyzed with serum GSDMD levels.

**Results** GSDMD, CRP (C-reactive protein), and body-mass index were statistically significant independent predictors of increasing disease severity according to TWSI. GSDMD and CRP were statistically significant independent predictors of higher MES scores. GSDMD demonstrated excellent discriminative performance in distinguishing patients with moderate-to-severe MES from those with normal or mild MES, with an area under the curve value of 0.976. A cut-off value of 6.0 ng/mL for GSDMD was identified as optimal, yielding a sensitivity of 95.0%, a specificity of 86.3%, and a Youden Index of 0.813.

**Conclusion** The results of the study revealed that GSDMD is a robust biomarker in predicting a more severe disease state for UC in terms of TWSI and MES, putting this novel protein into highlight as a potential new biomarker in patients with UC.

**Keywords** Gasdermin d, Ulcerative colitis, Disease activity, Severity

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## Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the rectum and varying segments of colon. The worldwide prevalence is estimated to be around 5 million patients as of 2023, with increasing incidence [1]. Assessment of disease activity is crucial in management of UC patients. While colonoscopy is the mainstay modality for both diagnosis and follow-up of the disease, several biomarkers are used in daily practice to determine disease activity non-invasively such as erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), and white blood cell (WBC) count [2].

Gasdermin D (GSDMD) is a protein which belongs to the gasdermin protein family and plays a role in inflammatory cell death, pyroptosis. GSDMD activation has been shown to be related to inflammatory states in a variety of disorders, including inflammatory bowel diseases [3].

Given the role of GSDMD in inflammation, we hypothesized that serum GSDMD levels of UC patients may be linked to disease activity; thereby revealing a potential new inflammatory serum marker for assessing disease activity and severity in UC patients in a non-invasive manner.

## Materials and methods

### Study design and patient selection

This prospective study was carried out at Antalya Training and Research Hospital, Turkey, between September 2022 and March 2024. UC patients who were diagnosed at Antalya Training and Research Hospital and were on follow-up at the inflammatory bowel diseases (IBD) outpatient clinic of Antalya Training and Research Hospital were enrolled in the study. Patients with a concurrent infection of any kind, malignancy, and co-morbid inflammatory-driven disorders like active rheumatologic conditions were not enrolled in the study, as these diseases would alter the inflammatory status of the patient thus serum GSDMD levels.

Age, sex, body mass index (BMI), smoking status, time since UC diagnosis, treatment modality used at the time of enrollment, concurrent use of steroids, involvement site of UC (proctitis, left-sided colitis, extensive colitis, pancolitis), and Truelove and Witts' severity index (TWSI) results were recorded at the day of blood sampling. Laboratory workout utilized in the study comprised WBC, ESR, CRP, and GSDMD. Blood samples for GSDMD were obtained from participants at the same blood sampling session for serum parameters utilized in the study. Mayo endoscopic subscores (MES) of the patients were recorded.

Patients were divided into four groups according to the extent of disease involvement: proctitis (involvement of rectum only), left-sided colitis (involvement extending

to descending colon), extensive colitis (involvement extending proximal to descending colon), and pancolitis. Patients were also split into two groups in terms of the treatment they were on at the time of enrollment in the study. First group comprised of patients on conventional therapy, which included 5-aminosalicylic acid and/or azathioprine treatments. Second group comprised of patients on biologic therapy, which included biological agents and small-molecule therapies. Concurrent corticosteroid usage was also recorded and analyzed, regardless of the dosage and type of corticosteroids.

This research was approved by University of Health Sciences, Antalya Training and Research Hospital Ethics Committee (Date: 11/08/2022, No: 2022-244). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was acquired from each participant in the study.

### Severity indexes for UC

TWSI for UC is an easy to use tool to stratify UC patients in terms of disease severity. This classification system is composed of six components which are obtained through patient history, physical examination, and laboratory workout. Bowel movements per day, blood in stool, pyrexia (defined as temperature equal to or above 37.8°C (100.04°F)), pulse, anemia, and ESR are the six parameters included in TWSI for UC. According to the status of these parameters, the patients fall into one of three categories for disease severity: mild, moderate, and severe [4].

MES classifies UC patients into four subgroups, from 0 to 3. MES 0 corresponds to inactive disease. MES 1 (mild disease) is characterized by erythema, decreased vascular pattern, and mild friability. MES 2 (moderate disease) is characterized by marked erythema, absent vascular pattern, friability, and erosions. MES 3 (severe disease) is characterized by spontaneous bleeding and ulcerations [5].

### Analysis of serum GSDMD levels

Serum GSDMD levels of patients were studied with Human Gasdermin ELISA kits (SunRed Biotechnology, China). 4 to 5 milliliters of blood samples were obtained from each participant. The samples were centrifuged at 4000 revolutions per minute for 10 min and stored at -80 °C until the laboratory workout. The results were given as ng/ml.

### Statistical analysis

Data were collected in Excel format. Statistical analyses were conducted using SPSS version 27 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables were presented as frequencies and percentages, while continuous variables were reported as medians with ranges.

Kolmogorov-Smirnov and Shapiro-Wilk tests were employed to assess the normality of data distributions. Since most variables did not follow a normal distribution, non-parametric tests were applied. To compare clinical and laboratory parameters across TWSI groups (mild, moderate, severe), and MES groups (0, 1, 2, 3) the Kruskal-Wallis test was employed for continuous and ordinal variables. For categorical variables such as smoking status and treatment type, Chi-square tests were used. In cases where more than 20% of cells had expected frequencies below five, the Fisher-Freeman-Halton exact test was utilized. For binary group comparisons (e.g., mild vs. moderate/severe), the Mann-Whitney U test was applied to continuous variables.

To identify independent predictors of disease severity, ordinal logistic regression was conducted using either the TWSI or MES as the ordinal outcome variable. Variables showing a significant or borderline association ( $p < 0.10$ ) in univariate analysis were included in the multivariate model. The test of parallel lines was used to verify the proportional odds assumption.

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the discriminative ability of biomarkers such as GSDMD and CRP in differentiating between normal/mild versus moderate/severe MES groups. The Area Under the Curve (AUC) was calculated to quantify diagnostic performance, and the optimal cut-off value for GSDMD was determined using the Youden Index ( $sensitivity + specificity - 1$ ). Sensitivity, specificity, and AUC values were reported with 95% confidence intervals where applicable.

All statistical tests were two-tailed, and a  $p$ -value less than 0.05 was considered statistically significant.

Results

Demographics and study parameters of patient population

93 patients were enrolled in the study. 50 patients (53.8%) were female. Median age of the study population was 45 years (18–72). Median BMI of the study population was 24.1 kg/m<sup>2</sup> (18.1–28.9). 17 patients (18.3%) were active smokers. Majority of the patients were on conventional therapy ( $n = 85$ , 91.4%). 6 patients (6.5%) were using concurrent corticosteroids adjunct to their therapy. Median time since UC diagnosis was 57 months (2–348).

20 patients (21.5%) had proctitis, 41 patients (44.1%) had left-sided colitis, 12 patients (12.9%) had extensive colitis, and 20 patients (21.5%) had pancolitis. According to TWSI, 58 patients (62.4%) had mild disease, 23 patients (24.7%) had moderate disease, and 12 patients (12.9%) had severe disease. In terms of MES, 34 patients (36.6%) had a score of 0. 39 patients (41.9%) had a MES of 1, 12 patients (12.9%) had a MES of 2, and 8 patients (8.6%) had a MES of 3.

Table 1 Patient characteristics of the study population

|                                    | Number of patients<br>(n = 93) | Per-<br>cent-<br>age<br>(%) |
|------------------------------------|--------------------------------|-----------------------------|
| Sex                                |                                |                             |
| Female                             | 50                             | 53.8                        |
| Male                               | 43                             | 46.2                        |
| Active Smoker                      |                                |                             |
| No                                 | 76                             | 81.7                        |
| Yes                                | 17                             | 18.3                        |
| Treatment Modality                 |                                |                             |
| Conventional                       | 85                             | 91.4                        |
| Biologic                           | 8                              | 8.6                         |
| Concurrent Corticosteroids         |                                |                             |
| No                                 | 87                             | 93.5                        |
| Yes                                | 6                              | 6.5                         |
| Truelove and Witts' Severity Index |                                |                             |
| Mild                               | 58                             | 62.4                        |
| Moderate                           | 23                             | 24.7                        |
| Severe                             | 12                             | 12.9                        |
| UC Involvement Site                |                                |                             |
| Proctitis                          | 20                             | 21.5                        |
| Left-sided colitis                 | 41                             | 44.1                        |
| Extensive colitis                  | 12                             | 12.9                        |
| Pancolitis                         | 20                             | 21.5                        |
| Mayo Endoscopic Subscore           |                                |                             |
| 0                                  | 34                             | 36.6                        |
| 1                                  | 39                             | 41.9                        |
| 2                                  | 12                             | 12.9                        |
| 3                                  | 8                              | 8.6                         |

UC: Ulcerative colitis

Table 2 Demographic and laboratory data of the study population

|                                  | Median (minimum-maximum) |
|----------------------------------|--------------------------|
| Age (years)                      | 45 (18–72)               |
| BMI (kg/m <sup>2</sup> )         | 24.1 (18.1–28.9)         |
| Time since UC diagnosis (months) | 57 (2–348)               |
| GSDMD (ng/ml)                    | 3.47 (0.29–12)           |
| WBC (/mm <sup>3</sup> )          | 7600 (4600–17000)        |
| ESR (mm/h)                       | 11 (2–54)                |
| CRP (mg/l)                       | 4.5 (0.2–48.3)           |

BMI: Body mass index, UC: Ulcerative colitis, GSDMD: Gasdermin D, WBC: White blood cells, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein. Descriptive statistics

Median WBC count of the study population was 7600/mm<sup>3</sup> (4600–17000). Median ESR and CRP levels of the study population were 11 mm/h (2–54) and 4.5 mg/l (0.2–48.3) respectively. Median GSDMD level of the patients was 3.47 ng/ml (0.29–12).

Characteristics and laboratory data of the study population are given in Tables 1 and 2.

### Relationship of GSDMD and other study parameters with TWSI and MES

Two main indicators of disease activity for UC utilized in our study were TWSI and MES. Relationship of study parameters with these two indexes were investigated.

Demographic characteristics, disease characteristics and treatment modalities of the patients were compared with severity indexes utilized in the study. Kruskal-Wallis test was performed to compare multiple clinical and laboratory variables across three TWSI categories (mild, moderate, severe), as well as across four MES categories (0, 1, 2, 3). The results revealed statistically significant differences in several variables. Age, BMI, CRP, smoking status and GSDMD were found to be statistically significantly different across TWSI and MES categories. Univariate analysis results are given in Table 3.

To identify independent predictors of disease severity, an ordinal logistic regression analysis was conducted using the TWSI (mild, moderate, severe) as the dependent variable. The model included age, BMI, CRP, smoking status and GSDMD as predictors.

The overall model demonstrated that GSDMD, CRP, and BMI were statistically significant independent predictors of increasing disease severity according to TWSI. Higher levels of GSDMD were strongly associated with increased odds of being classified into a more severe category (estimate = 0.789,  $p < 0.001$ , 95% CI: 0.469–1.109). Similarly, higher CRP values were significantly associated with greater disease severity (estimate = 0.082,  $p = 0.020$ , 95% CI: 0.013–0.151). In contrast, higher BMI was associated with a lower likelihood of being in a more severe category (estimate = -0.353,  $p = 0.022$ , 95% CI: -0.655 to -0.051). Age ( $p = 0.822$ ) and smoking status ( $p = 0.683$ ) were not statistically significant predictors in the multivariate model.

To evaluate independent predictors of endoscopic disease severity, an ordinal logistic regression analysis was performed using the MES as the dependent variable (ordinal levels: 0, 1, 2, and 3). The model included age, BMI, CRP, smoking status and GSDMD as covariates.

The model identified GSDMD and CRP as statistically significant independent predictors of higher MES scores. GSDMD demonstrated a strong positive association

**Table 3** Univariate analysis across TWSI and MES subgroups

|         | TWSI             |         | MES              |         |
|---------|------------------|---------|------------------|---------|
|         | Kruskal-Wallis H | p value | Kruskal-Wallis H | p value |
| Age     | 5.096            | 0.078   | 11.933           | 0.008   |
| BMI     | 25.772           | < 0.001 | 18.953           | < 0.001 |
| CRP     | 17.819           | < 0.001 | 29.048           | < 0.001 |
| Smoking | 16.515           | < 0.001 | 23.203           | < 0.001 |
| GSDMD   | 50.928           | < 0.001 | 50.953           | < 0.001 |

TWSI: Truelove and Witts' severity index, MES: Mayo Endoscopic Subscore, GSDMD: Gasdermin D, BMI: Body mass index, CRP: C-reactive protein. Kruskal-Wallis test

with increased MES severity (estimate = 0.951,  $p < 0.001$ , 95% CI: 0.579–1.322). CRP levels were also positively associated with higher MES scores (estimate = 0.199,  $p < 0.001$ , 95% CI: 0.104–0.294). Other variables, including age ( $p = 0.602$ ), BMI ( $p = 0.294$ ), and smoking status ( $p = 0.656$ ), did not reach statistical significance in this model.

These findings indicate that inflammatory activity, as reflected by GSDMD and CRP levels, significantly contributes to mucosal severity. Ordinal logistic regression estimates for TWSI and MES are given in Table 4.

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the ability of GSDMD and CRP to distinguish patients with moderate-to-severe MES from those with normal or mild MES.

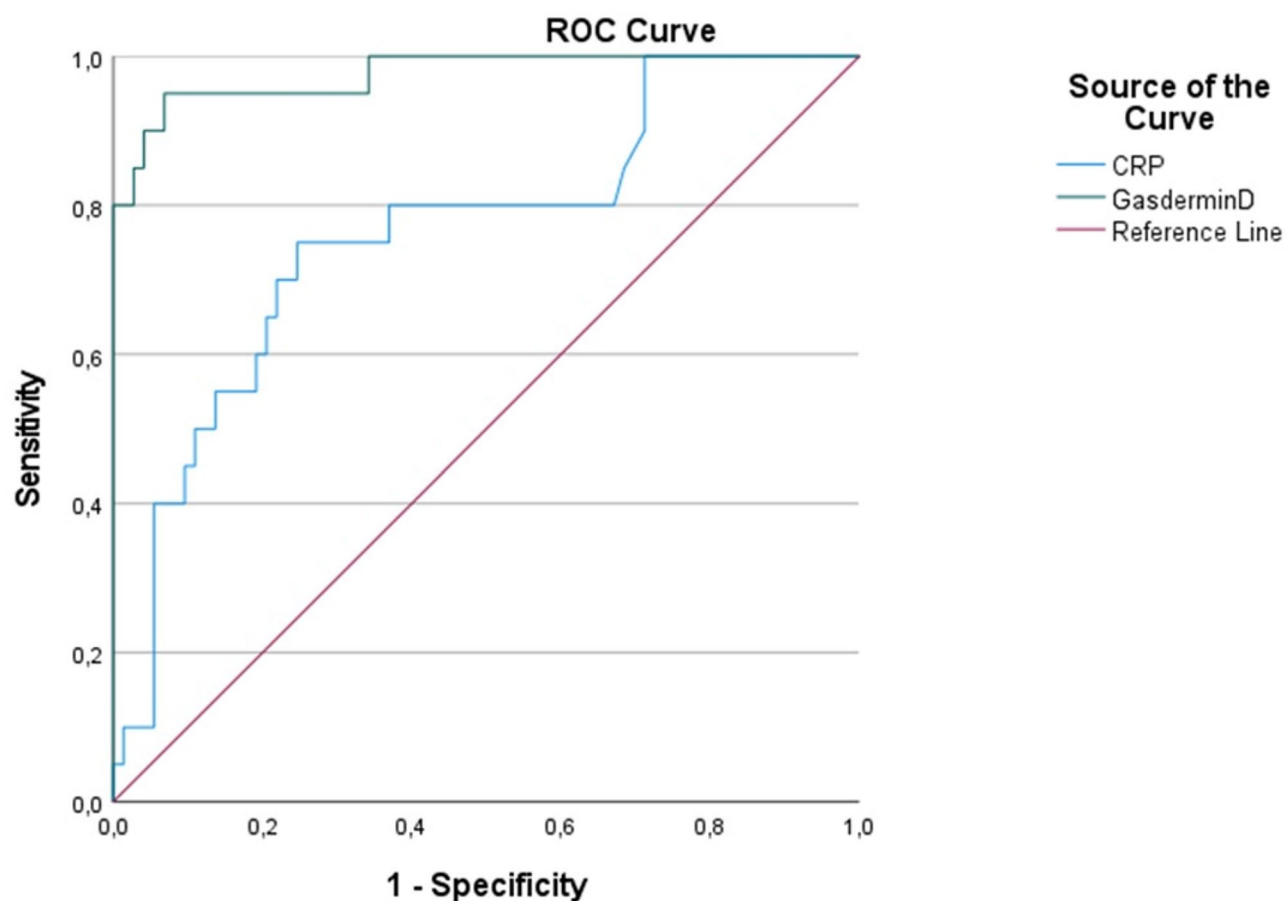
GSDMD demonstrated excellent discriminative performance, with an area under the curve (AUC) of 0.976, while CRP showed moderate accuracy with an AUC of 0.764. It is important to note that the CRP analysis included ties between positive and negative actual state groups, which may introduce a bias in the AUC estimation. ROC analysis between GSDMD and CRP levels and MES is shown in Fig. 1.

To determine the optimal threshold for GSDMD, the Youden Index was calculated for various cut-off values. A cut-off value of 6.0 ng/mL was identified as optimal, yielding a sensitivity of 95.0%, a specificity of 86.3%, and a Youden Index of 0.813. This threshold provided the best overall diagnostic accuracy based on the maximum value of (sensitivity + specificity). These findings support the utility of Gasdermin D as a robust biomarker for predicting endoscopic disease severity in ulcerative colitis.

**Table 4** Ordinal logistic regression estimates for TWSI and MES

|         | TWSI     |         |                 | MES      |         |              |
|---------|----------|---------|-----------------|----------|---------|--------------|
|         | Estimate | p value | 95% CI          | Estimate | p value | 95% CI       |
| Age     | 0.005    | 0.822   | -0.04–0.05      | -0.011   | 0.602   | -0.05–0.029  |
| BMI     | -0.353   | 0.022   | -0.655 – -0.051 | -0.142   | 0.294   | -0.406–0.123 |
| CRP     | 0.082    | 0.020   | 0.013–0.151     | 0.199    | < 0.001 | 0.104–0.294  |
| Smoking | 0.362    | 0.683   | -1.376–2.101    | -0.337   | 0.656   | -1.822–1.147 |
| GSDMD   | 0.789    | < 0.001 | 0.469–1.109     | 0.951    | < 0.001 | 0.579–1.322  |

TWSI: Truelove and Witts' severity index, MES: Mayo Endoscopic Subscore, CI: Confidence interval, GSDMD: Gasdermin D, BMI: Body mass index, CRP: C-reactive protein. Ordinal logistic regression estimates



**Fig. 1** ROC analysis between GSDMD and CRP levels and MES

**Table 5** Relationship of study parameters with GSDMD levels

|         | Unstandardized Coefficients |            | Standardized Coefficients | t     | p value | 95% Confidence Interval for $\beta$ |             |
|---------|-----------------------------|------------|---------------------------|-------|---------|-------------------------------------|-------------|
|         | $\beta$                     | Std. Error | $\beta$                   |       |         | Lower Bound                         | Upper Bound |
| Age     | -0.01                       | 0.01       | -0.05                     | -0.83 | 0.406   | -0.04                               | 0.02        |
| BMI     | -0.03                       | 0.10       | -0.02                     | -0.32 | 0.751   | -0.23                               | 0.17        |
| CRP     | -0.03                       | 0.02       | -0.01                     | -0.16 | 0.871   | -0.04                               | 0.03        |
| Smoking | 1.93                        | 0.570      | 0.21                      | 3.39  | 0.001   | 0.80                                | 3.07        |

GSDMD: Gasdermin D, BMI: Body-mass index, CRP: C-reactive protein. Multivariate logistic regression analysis (F = 48.76,  $p = 0.0001$ , D-W: 1.966,  $R^2 = 0.734$ )

Correlations between study parameters and GSDMD levels were investigated. GSDMD was found to be statistically significantly negatively correlated with age ( $r = -0.27$ ,  $p = 0.01$ ), BMI ( $r = -0.38$ ,  $p = 0.0001$ ), and disease duration ( $r = -0.23$ ,  $p = 0.027$ ). GSDMD was found to be statistically significantly positively correlated with CRP ( $r = 0.32$ ,  $p = 0.002$ ). There was no correlation between GSDMD and ESR or CRP levels. UC involvement site did not have a relationship with serum GSDMD levels. Smoking was strongly correlated with increased GSDMD levels. Non-smokers ( $n = 76$ ) had a median serum GSDMD level of 3.14 ng/ml, compared to 12.0 in smokers ( $n = 17$ ) and this difference was statistically significant ( $p = 0.0001$ ). Independent variables affecting serum GSDMD levels

were investigated with multivariate logistic regression analysis. GSDMD levels were independently correlated with smoking status ( $\beta$ : 1.93,  $p = 0.001$ ) of the patients. Other parameters were found not to be correlated with GSDMD levels in multivariate logistic regression analysis. Relationship of study parameters with GSDMD levels are given in Table 5.

**Discussion**

This prospective study was planned to investigate the role of GSDMD in predicting the severity of UC and its relationship with disease characteristics of UC. The results of the study revealed that GSDMD is a robust biomarker in predicting a more severe disease state for UC in terms of



TWSI and MES, putting this novel protein into highlight as a potential new biomarker in patients with UC.

The multifaceted and unpredictable nature of disease course in UC made it imperative for healthcare professionals to monitor disease activity and predict disease flares to accommodate treatment options accordingly. Severity indexes, serum and fecal biomarkers, and recently deep learning models are being used and developed constantly to assess UC disease course [6, 7, 8, 9, 10, 11, 12]. This study can be considered one of numerous ongoing studies in the search for a biomarker of disease activity in UC, and the results led us to a potential new protein reflecting disease course for UC: GSDMD.

Pyroptosis is the inflammatory death of cells and the mechanism is triggered by infections and signals secondary to dangers to cellular structure and integrity. Following these signals, caspase system is activated and GSDMD protein is cleaved. GSDMD-N is the active form of GSDMD and triggers pore formation in cell membrane, which then leads to membrane disruption and cell death, as well as release of intracellular components including interleukins to extracellular space, resulting in inflammation [13, 14]. Primarily a host defence mechanism, pyroptosis can also lead to an uncontrolled state of inflammation, forming the basis and playing role in various inflammatory-driven disorders [3].

Role of pyroptosis, and GSDMD, in pathogenesis of IBD has been investigated in a number of studies. Pyroptosis has been shown to play a pivotal role in IBD in a review by Zhang et al. [15]. Parallel to this finding, pyroptosis burden in terms of inflammasome-associated gene expressions were linked to both disease course and treatment response to anti-tumor necrosis factor (TNF) therapy [16]. In an experimental colitis model in mice, disruption of GSDMD function was found to be related with increased therapeutic effects [17]. A study by Bulek et al. revealed that GSDMD mediated release of interleukin-1 $\beta$  (IL-1 $\beta$ ) is present in mice with colitis, which was found to be correlated with increased disease severity [18]. GSDMD was found to partake in two more aspects of disease pathogenesis in mouse colitis model, reported in a paper by Gao and colleagues. GSDMD deficient mice were found to have less severe disease course, and the underlying mechanisms were found to comprise both GSDMD induced release of IL-18 and dysregulation of gut microbiota [19]. An interesting study by Wang et al. [20] investigated the mechanism of action of Honokiol, which is the active component of a traditional Chinese herb used in treatment of UC, *Magnolia officinalis*. Honokiol was shown to exert its function on alleviation of UC through suppression of GSDMD mediated pyroptosis, which confirms the role of GSDMD in UC from a different point of view. The culmination of all these aforementioned studies emphasizes the role of GSDMD in

disease pathogenesis, course, and prognosis in patients with UC, which forms the basis of our research in investigating GSDMD as a potential biomarker in UC.

GSDMD was also found to be related with other gastrointestinal disorders than IBD. Being a prominent actor in inflammation, GSDMD was shown to play roles in esophageal, gastric and colorectal cancers [21, 22, 23, 24]. Gasdermin protein family also partake in disease pathogenesis of gastrointestinal disorders other than cancer such as infections and immune-mediated disorders, although further studies are needed to establish their role in these disease states [25]. As an important actor in inflammation, GSDMD has been investigated in inflammatory-driven disorders of various organ systems. A study by Han and colleagues revealed that inhibition of GSDMD led to a reduction in pancreas injury, systemic inflammation response and failure of organ function in mice [26]. Silva and colleagues have shown that disease severity in COVID-19 patients is correlated to both serum and tissue levels of GSDMD [27]. Several studies have also investigated and revealed the role of GSDMD both in pathogenesis of and as a potential therapeutic target in neurological disorders including migraine and acute ischemic stroke [28, 29, 30].

Our study data revealed that GSDMD is linked to disease severity in UC and can be utilized as a biomarker to track disease activity and severity in a non-invasive and easy manner. We utilized TWSI, which is an easy-to-use severity index, and MES to assess the state of UC in the study population. GSDMD level was found to be a predictor of a more severe disease state in terms of both of these severity indexes. Furthermore, a GSDMD cut-off level of 6.0 ng/ml was found to be highly sensitive and specific in differentiating patients with more severe disease from milder ones. These findings are promising, since a serum biomarker that can predict both clinical and colonoscopic state of UC patients will surely widen the armamentarium of the healthcare team in disease management.

CRP level of patients were also found to be statistically significantly related with disease activity in terms of both TWSI and MES. This statistically significant relationship of CRP was still less strong than the relationship between GSDMD and disease activity indexes. ROC analysis revealed the strength of GSDMD over CRP in predicting disease severity for UC, with AUC values of 0.976 and 0.764 respectively. Costs of CRP and GSDMD tests are comparable, with prices of each test around 5 United States dollars per patient for readily available tests in the market, although the prices may vary according to national regulations. CRP and GSDMD were also found to be positively correlated, an expected result considering CRP is an established inflammatory marker in UC [31].

There are two additional finding of our study regarding BMI and smoking. Higher BMI was found to be linked with a less active disease state according to TWSI, which is an interesting finding given the link between obesity and inflammation [32, 33]. UC patients tend to have less food intake to prevent symptoms and are in a catabolic state; which can explain our study finding. Serum GSDMD levels were statistically significantly higher in active smokers. Smoking is shown to have immunomodulatory effects through toxins, and to induce chronic inflammation [34, 35]. Given the role of GSDMD in inflammation, the correlation between smoking and elevated levels of GSDMD is not surprising but an important coexistence nonetheless. Contrary to this finding, smoking was not found to have a statistically significant relationship with TWSI or MES. From our study findings, we can propose that smoking causes an elevation in serum GSDMD levels and this mechanism might be taking part in proinflammatory effect of smoking. However, this increase in GSDMD levels secondary to smoking did not translate into increased disease activity in our study.

The main strength of our study is being the first study in the literature investigating the role of GSDMD as a biomarker in UC. The link between disease activity and serum GSDMD levels, whilst incorporating both clinical and endoscopic severity indexes in the analysis, opens the possibility of utilizing this new biomarker in daily practice. A limitation of the study was not including fecal calprotectin levels of the patients into the analysis. Unfortunately, fecal calprotectin test is not available in our institution, hence we could not add this biomarker into our study parameters. Future studies on the utility of GSDMD in UC including fecal calprotectin levels of the patients into the analysis with a bigger study population will surely give valuable data on this topic. The relatively small size of study population, and lack of widespread use of GSDMD in current clinical practice can also be considered as limitations of the study. We believe research on inflammatory disorders across multiple disciplines will better reflect the role of GSDMD and its applicability to disease management algorithms.

## Conclusion

In conclusion, this is a pioneer study in revealing the utility of GSDMD as a potential biomarker of disease activity and severity in UC. Future studies will not only shed more light on the value of this marker as a tracker of disease course, but hopefully also pave the path for a potential therapeutic target in this burdensome disorder for both the patient and the healthcare team.

## Abbreviations

|     |                          |
|-----|--------------------------|
| AUC | Area under the ROC curve |
| BMI | Body-mass index          |
| CRP | C-reactive protein       |

|       |                                    |
|-------|------------------------------------|
| ELISA | Enzyme-linked immunosorbent assay  |
| ESR   | Erythrocyte sedimentation rate     |
| GSDMD | Gasdermin D                        |
| IBD   | Inflammatory bowel diseases        |
| IL    | Interleukin                        |
| MES   | Mayo endoscopic subscore           |
| ROC   | Receiver operating characteristic  |
| SD    | Standard deviation                 |
| TWSI  | Truelove and Witts' severity index |
| UC    | Ulcerative colitis                 |
| WBC   | White blood cells                  |

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None.

## Author contributions

OCB, SO, SA, YC, AHC: Study conceptualization and design. OCB, SO, SA, GEA, BK, MDI, OK, FAH, YC, AHC: Patient enrollment and data acquisition. OCB, SO, SA, OK, FAH, YC, AHC: Analysis and interpretation of data. OCB, SO, SA, GEA, BK, MDI, OK, FAH, YC, AHC: Drafting the article. OCB, SO, SA, AHC: Critically revising the article. All authors agree to the final version of the manuscript to be published.

## Funding

None.

## Data availability

We can provide our Excel and SPSS data files upon request.

## Declarations

### Ethics approval and consent to participate

This research was approved by University of Health Sciences, Antalya Training and Research Hospital Ethics Committee (Date: 11/08/2022, No: 2022–244). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was acquired from each participant in the study.

### Consent for publication

The manuscript does not contain any individual person's data as in details, images or videos.

### Competing interests

The authors declare no competing interests.

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