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RESEARCH ARTICLE

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MALT1 reflects inflammatory cytokines, disease activity, and its chronological change could estimate treatment response to infliximab in Crohn's disease patients

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Abstract

Background: Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) mediates the immunity and inflammatory response in multiple ways to be intimately involved in the progression of autoimmune diseases. This study intended to explore the linkage of MALT1 with inflammation, disease activity, and its change with infliximab treatment response in Crohn's disease (CD) patients.

Methods: MALT1 in peripheral blood mononuclear cell samples from 72 active CD patients (at baseline, 2 weeks [W2], W6, and W12 after infliximab treatment), 20 remissive CD patients (after enrollment), and 20 healthy controls (after enrollment) were detected by RT-qPCR.

Results: MALT1 was highest in active CD patients, followed by remissive CD patients, and lowest in healthy controls ($p < 0.001$). MALT1 was positively linked with C-reactive protein ($p = 0.001$), erythrocyte sedimentation rate ($p = 0.014$), clinical disease activity index ($p = 0.003$), tumor necrosis factor (TNF)-α ($p = 0.006$), interleukin (IL)-1β ($p = 0.049$), and IL-17A ($p = 0.004$), but not other clinical characteristics (all $p > 0.05$) in active CD patients. After infliximab treatment, MALT1 was decreased from baseline to W12 in active CD patients ($p < 0.001$), especially in responders ($p < 0.001$), but not in nonresponders ($p = 0.053$). The reduction of MALT1 at W6 ($p = 0.049$) and W12 ($p = 0.004$) was associated with a good treatment response to infliximab in active CD patients. Moreover, the response rate or MALT1 at any time point was not different between active CD patients with and without TNFi history (all $p > 0.05$).

Conclusion: MALT1 reflects aggravated inflammation and disease activity. Meanwhile, the decrement of MALT1 from baseline to W12 could reflect infliximab treatment response in CD patients.

KEYWORDS
crohn's disease, inflammation, infliximab, mucosa-associated lymphoid tissue lymphoma translocator protein 1, treatment response

1 | INTRODUCTION

Crohn's disease (CD) is a chronic autoimmune disease that occurs in the gastrointestinal region and often causes complications such as intestinal fistulas, fibrotic strictures, bowel cancer, etc.[1,2]. Although the incidence and prevalence of CD exhibit a declining trend in Western countries, they are still gradually elevated in Asia[3]. Currently, aminosalicylic acid is initially given to mild CD patients; while for moderate or severe patients, they are generally treated with corticosteroids combined with immunosuppressants[4,5]. However, the disease activity may be uncontrolled even under the administration of these above-mentioned treatments, which require monoclonal antibodies to further control the symptoms[2,6]. Infliximab is the first biologic approved for CD treatment in China, which has comparable therapeutic efficacy to other TNF inhibitors, higher practical value, and lower costs for CD patients[7–9]. However, since only 40%–50% of CD patients would respond to infliximab treatment, their clinical outcomes remain miserable[8,10,11]. As a result, it is crucial to find biomarkers that forecast the treatment response in CD patients receiving infliximab, thus enabling stratified management of these patients.

Mucosa-associated lymphoid tissue lymphoma translocator protein 1 (MALT1), whose coding RNA is located on chromosome 18q21, has been reported to modulate inflammation and thus involves in the pathogenesis of inflammatory bowel diseases (IBD)[12–15]. For instance, MALT1 inhibitor suppresses the release of proinflammatory cytokines by inactivating nuclear factor (NF)-κB and NLRP3 inflammasome in dextran sulfate sodium (DSS)-induced experimental colitis[12]. Additionally, a study reveals that inactivated MALT1 hinders the activation of T-helper (Th)1/Th17 cells, thereby attenuating colitis[14]. Apart from these, MALT1 acts as a biomarker for IBD and reflects the TNF inhibitor (TNFi) response in rheumatoid arthritis (RA) patients[13,15]. Based on the above considerations, it could be speculated that MALT1 might serve as a candidate biomarker for CD patients receiving infliximab treatment. Nevertheless, no relevant study has been conducted.

Accordingly, this study intended to explore the dysregulation of MALT1, and its linkage with inflammation, disease activity, along with infliximab treatment response in CD patients.

2 | METHODS

2.1 | Subjects

Seventy-two active CD patients treated with infliximab between March 2018 and April 2021 were recruited in this study. The enrollment criteria were: (1) diagnosis of CD per radiological evidence, endoscopic examination, and biopsy results; (2) aged over 18 years; (3) clinical disease activity index (CDAI) score ≥ 150 points; (4) scheduled to receive infliximab treatment; (5) volunteered to comply with the study protocol. The exclusion criteria were: (1) had severe comorbidities based on symptoms, or laboratory examinations; (2) presented as infection; (3) had a prior history or complicated with a solid tumor or hematologic malignant disease; (4) during pregnancy or breastfeeding. In addition, 20 remissive CD patients were also recruited during the same period. The recruitment criteria were: (1) confirmed as CD; (2) more than 18 years old; (3) CDAI score < 150 points; (4) with matched age and sex to active CD patients; (5) without severe comorbidity, infection, cancer, and hematologic malignancy; (6) nonpregnant and nonbreastfeeding. Besides, 20 healthy subjects were included in the study as healthy controls. The inclusion criteria were: (1) without any abnormalities in physical examinations; (2) over 18 years old; (3) matched age and sex to active CD patients. The study was permitted by Ethics Committee of Handan Central Hospital. Each subject signed the informed consent.

2.2 | Collection of clinical data and samples

Demographic data of subjects were obtained, and disease characteristics were collected from CD patients. Peripheral blood (PB) samples were collected from active CD patients after enrollment (at baseline) to isolate peripheral blood mononuclear cell (PBMC) samples and serum samples, and from remissive CD patients and healthy controls to separate PBMC samples. Besides, PBMC samples of active CD patients were obtained at 2 weeks (W2, $n = 72$), 6 weeks (W6, $n = 71$), and 12 weeks (W12, $n = 67$) after treatment.

2.3 | Examination

PBMC MALT1 expression was quantified by reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Concisely, total RNA was extracted by RNeasy Protect Mini Kit (Qiagen), which was submitted to reverse transcription via PrimeScript™ RT reagent Kit (Takara). After that, qPCR was completed by KOD SYBR® qPCR Mix (Toyobo). Subsequently, MALT1 expression was calculated by the $2^{-\Delta\Delta Ct}$ method, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was treated as an internal reference. The primers were in accordance with a former study[16]. Serum samples were used to examine the levels of inflammatory cytokines, including TNF-α, interleukin (IL)- 1β, IL-6, and IL-17A, by enzyme-linked immunosorbent assay (ELISA) using commercial ELISA kits (Bio-Techne China Co., Ltd.,) per instructions.

2.4 | Treatment and assessment

The active CD patients were given infliximab 5 mg/kg intravenously at 0 weeks, 2nd week, and 6th week. Besides, other treatments such as nutritional support were combined with infliximab treatment for appropriate patients according to the disease status. At W12 after treatment, the clinical response was assessed according to CDAI score, which involved 8 dimensions and ranged from 0 to 600[17]. Patients who had a decline in the CDAI score

of ≥70 points were considered as responders; patients who had a decline in the CDAI score of <70 points were considered as nonresponders[18].

2.5 | Statistics

Data analyses were completed using SPSS V.24.0 (IBM Corp.,), and graphs were made using GraphPad Prism V.6.01 (GraphPad Software Inc.,). The differences among three groups were determined using Kruskal-Wallis H rank-sum test, X^2 test, or one-way analysis of variance (ANOVA) test, and comparisons between two groups were analyzed using Student's *t*-test, Wilcoxon rank-sum test, or X^2 test. Post hoc comparison was carried out using Bonferroni test. The ability of MALT1 expression in differentiating subjects was illustrated using receiver operating characteristic (ROC) curves. Association analysis was made using Spearman's rank correlation test. The change of MALT1 expression over time was assessed using Friedman's test. $p < 0.05$ was considered significant.

3 | RESULTS

3.1 | Study flow

Totally, 72 active CD patients, 20 disease controls (remissive CD patients), and 20 healthy controls (healthy subjects) were recruited for this study. In respect of active CD patients, demographic data and disease characteristics were collected. Meanwhile, the PBMC samples were acquired at baseline, W2, W6, and W12 for detecting MALT1. The serum samples were acquired at baseline only for detecting inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-17A). During follow-up, 5 active CD patients dropped out, including 3 patients who had poor efficacy and 2 patients who lost to follow-up. Finally, the clinical response of active CD patients was assessed based on the CDAI score at W12 after infliximab treatment.

Regarding remissive CD patients, demographic data and disease characteristics were also assembled; while PBMC samples were collected after enrollment only for detecting MALT1 expression. Concerning healthy subjects, demographic data were obtained and PBMC samples were collected after enrollment for detecting MALT1 expression as well (Figure 1).

3.2 | Clinical characteristics

The mean age of active CD patients, remissive CD patients, and healthy controls was 35.3 ± 10.1, 36.7 ± 8.8, and 37.6 ± 11.0 years, respectively ($p = 0.623$). Regarding the gender, there were 33 (45.8%) males and 39 (54.2%) females in active CD patients, 10 (50.0%) males and 10 (50.0%) females in remissive CD patients, 8 (40.0%) males and 12 (60.0%) females in healthy controls ($p = 0.814$). The median of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were highest in active CD patients, followed by remissive CD patients, and lowest in healthy controls (both $p < 0.001$). Meanwhile, disease duration ($p = 0.160$) and history of TNFi ($p = 0.845$) were similar in active and remissive CD

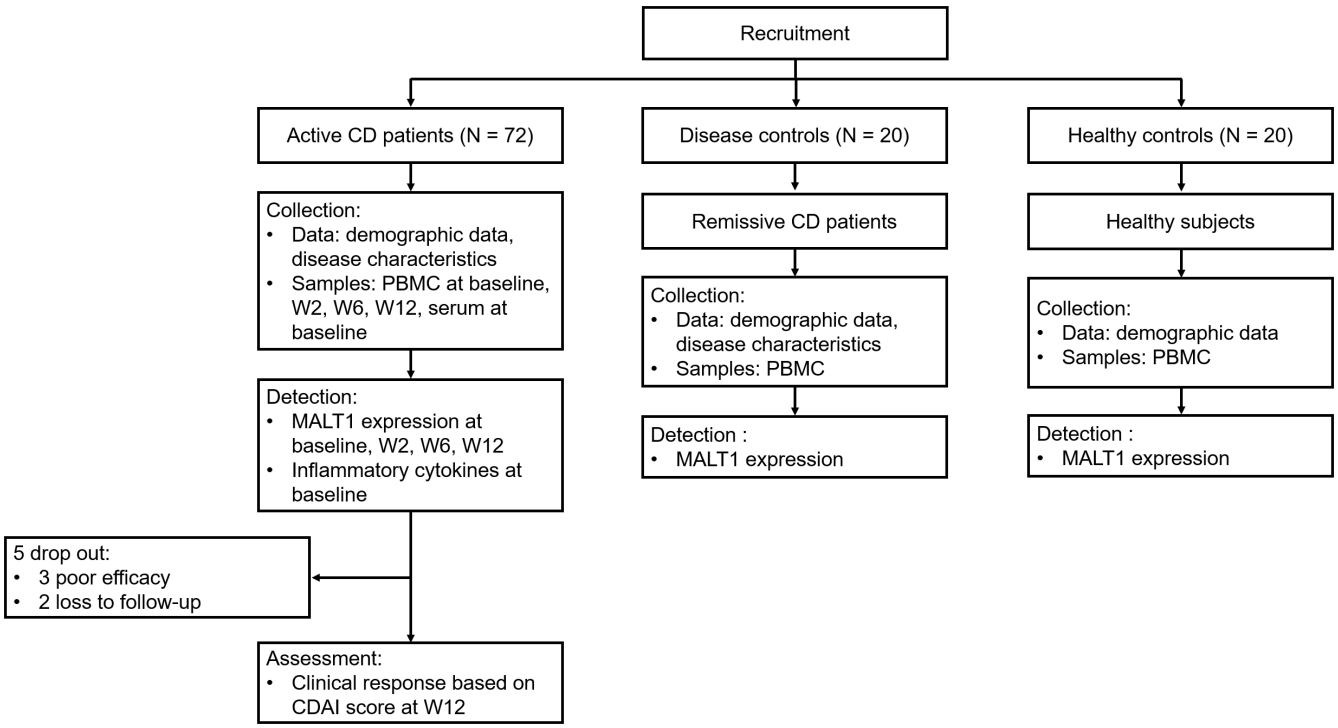


FIGURE 1 Flow chart

patients; however, CDAI score was increased in active CD patients (270.2 ± 77.9) compared to remissive CD patients (108.3 ± 26.8) ($p < 0.001$). Finally, the median (IQR) value of TNF-α, IL-1β, IL-6, and IL-17A was 103.7 (57.6–147.0), 6.9 (3.9–9.8), 54.9 (42.8–77.7), and 91.6 (74.9–141.1) pg/mL, respectively, in active CD patients. Furthermore, in active CD patients, 24 (33.3%) patients had erythema nodosum, 15 (20.8%) patients had peripheral arthritis, 10 (13.9%) patients had sacroiliitis, and 12 (16.7%) patients had uveitis. Regarding remissive CD patients, 3 (15.0%) patients had erythema nodosum, 2 (10.0%) patients had peripheral arthritis, 2 (10.0%) patients had sacroiliitis, and no remissive CD patients had uveitis (Table 1).

3.3 | MALT1 expressions

MALT1 was the highest in active CD patients, followed by remissive CD patients, and the lowest in healthy controls ($p < 0.001$); further post hoc comparison analysis revealed that MALT1 was increased in active CD patients compared to remissive CD patients ($p = 0.018$) and healthy controls ($p < 0.001$), but no difference was observed in MALT1 between remissive CD patients and healthy controls ($p = 0.097$) (Figure 2A). Further ROC curve analysis disclosed that MALT1 had an acceptable ability for distinguishing active CD patients from remissive CD patients (area under the curve (AUC): 0.713, 95% confidence interval (CI): 0.589–0.838) (Figure 2B); while it had a decent capacity for differentiating active CD patients from healthy controls (AUC: 0.885, 95% CI: 0.809–0.962) (Figure 2C), and showed an acceptable ability for identifying remissive CD patients from healthy controls (AUC: 0.740, 95% CI: 0.586–0.894) (Figure 2D).

3.4 | Correlation between MALT1 and clinical characteristics

No linkage was perceived in MALT1 with age ($p = 0.457$) (Figure 3A), gender ($p = 0.323$) (Figure 3B), and disease duration ($p = 0.106$) (Figure 3C). However, MALT1 was positively related to CRP ($p = 0.001$) (Figure 3D), ESR ($p = 0.014$) (Figure 3E), and CDAI score ($p = 0.003$) (Figure 3F), respectively. However, no association was discovered between MALT1 and the history of TNFi ($p = 0.763$) (Figure 3G) in active CD patients.

3.5 | Association between MALT1 and inflammatory cytokines

MALT1 was positively linked with TNF-α ($p = 0.006$) (Figure 4A) and IL-1β ($p = 0.049$) (Figure 4B). No association was found between MALT1 and IL-6 ($p = 0.142$) (Figure 4C). Nevertheless, a positive correlation was found between MALT1 and IL-17A ($p = 0.004$) (Figure 4D) in active CD patients.

3.6 | Correlation between MALT1 and infliximab treatment response

After infliximab treatment, MALT1 was reduced in both active CD patients ($p < 0.001$) (Figure 5A) and responders in active CD patients ($p < 0.001$) (Figure 5B) from baseline to W12; while no variation of MALT1 was observed from nonresponders in active CD patients ($p = 0.053$) (Figure 5C).

MALT1 at baseline ($p = 0.788$) and W2 ($p = 0.256$) were not correlated with infliximab treatment response; however, decreased MALT1 at W6 ($p = 0.049$) and W12 ($p = 0.004$) was linked with infliximab treatment response in active CD patients (Figure 6).

3.7 | The linkage between MALT1 and the history of TNFi

The history of TNFi was not related to the infliximab treatment response ($p = 0.099$) (Figure 7A). Besides, after infliximab treatment, MALT1 at any time point was not associated with a history of TNFi in active CD patients (all $p > 0.05$) (Figure 7B).

4 | DISCUSSION

The primary findings of this study were as follows: (1) MALT1 was highly expressed in active CD patients by comparison to remissive CD patients and healthy controls; (2) positive linkage was discovered in MALT1 with inflammatory markers (reflected by CRP, ESR, TNF-α, IL-1β, and IL-17A) and disease activity (reflected by CDAI) in active CD patients; (3) after infliximab treatment, MALT1 showed a declining trend from baseline to W12; meanwhile, reduced MALT1 at W6 and W12 was related to infliximab treatment response; furthermore, no association was discovered between infliximab treatment response and history of TNFi; while MALT1 at any time point was not linked with the history of TNFi in active CD patients.

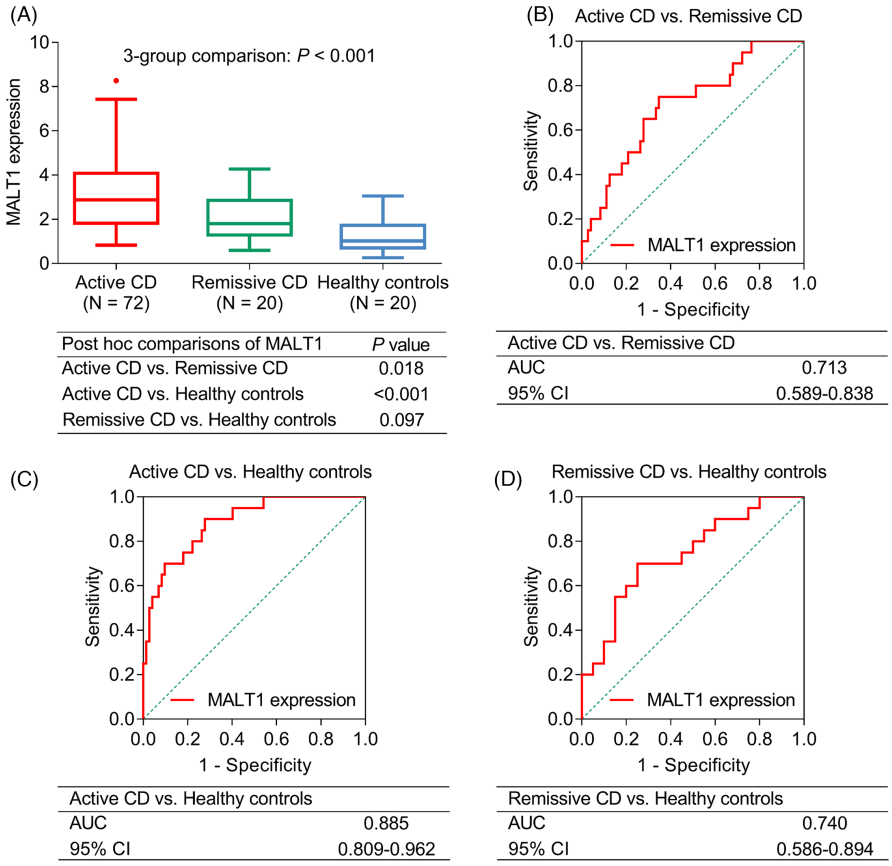
MALT1 is highly expressed in autoimmune diseases, such as RA and IBD patients[13,19]. For instance, MALT1 is increased in RA patients compared to healthy controls[19]. In addition, a higher expression has been found in IBD patients compared with healthy individuals[13]. The current study discovered the high expression of MALT1 in active CD patients compared to remissive CD patients and healthy individuals. The possible explanations would be that: MALT1 could reflect the inflammation status[12,20]; while inflammation status had been reported to be anabatic in CD patients[13]. Therefore, high expression of MALT1 was found in active CD patients in comparison to remissive CD patients and healthy subjects.

MALT1 is positively related to the inflammation status in autoimmune diseases[13,15]. According to a previous study, a positive linkage is discovered between MALT1 and inflammation in RA patients[15]. Moreover, MALT1 is positively associated with the release of inflammatory cytokines in IBD patients[13]. However, no relevant

TABLE 1 Clinical characteristics

Items	Active CD (*N* = 72)	Remissive CD (*N* = 20)	Healthy controls (*N* = 20)	*p* value
Age (years), mean ± SD	35.3 ± 10.1	36.7 ± 8.8	37.6 ± 11.0	0.623
Gender, No. (%)				0.814
Male	33 (45.8)	10 (50.0)	8 (40.0)	
Female	39 (54.2)	10 (50.0)	12 (60.0)	
Disease duration (years), mean ± SD	6.1 ± 4.4	7.6 ± 3.3	–	0.160
CRP (mg/L), median (IQR)	51.5 (33.4–76.4)	23.6 (15.9–33.8)	2.3 (1.9–4.1)	<0.001
ESR (mm/h), median (IQR)	45.2 (34.6–59.4)	20.5 (10.9–34.5)	10.1 (6.9–13.2)	<0.001
TNF-α (pg/mL), median (IQR)	103.7 (57.6–147.0)	–	–	–
IL-1β (pg/mL), median (IQR)	6.9 (3.9–9.8)	–	–	–
IL-6 (pg/mL), median (IQR)	54.9 (42.8–77.7)	–	–	–
IL-17A (pg/mL), median (IQR)	91.6 (74.9–141.1)	–	–	–
CDAI score, mean ± SD	270.2 ± 77.9	108.3 ± 26.8	–	<0.001
History of TNFi, No. (%)	20 (27.8)	6 (30.0)	–	0.845
Complications, No. (%)				
Erythema nodosum	24 (33.3)	3 (15.0)	–	0.111
Peripheral arthritis	15 (20.8)	2 (10.0)	–	0.346
Sacroiliitis	10 (13.9)	2 (10.0)	–	1.000
Uveitis	12 (16.7)	0 (0.0)	–	0.062

Abbreviations: CD, Crohn's disease; CDAI, clinical disease activity index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-17A, interleukin-17A; IL-1β, interleukin-1beta; IL-6, interleukin-6; IQR, interquartile range; SD, standard deviation; TNFi, tumor necrosis factor inhibitor; TNF-α, tumor necrosis factor-alpha.



Post hoc comparisons of MALT1	*P* value
Active CD vs. Remissive CD	0.018
Active CD vs. Healthy controls	<0.001
Remissive CD vs. Healthy controls	0.097

Active CD vs. Remissive CD	
AUC	0.713
95% CI	0.589-0.838

Active CD vs. Healthy controls	
AUC	0.885
95% CI	0.809-0.962

Remissive CD vs. Healthy controls	
AUC	0.740
95% CI	0.586-0.894

FIGURE 2 MALT1 was increased in active CD patients compared to remissive CD patients and healthy controls. Comparison of MALT1 in active CD patients, remissive CD patients, and healthy controls (A); ROC curve of MALT1 in distinguishing active CD from remissive CD patients (B); active CD from healthy controls (C); remissive CD patients from healthy controls (D)

study reports the relation between MALT1 and inflammation status in CD patients. The present study identified that MALT1 was positively linked to inflammation (reflected by CRP, ESR, TNF-α, IL-1β, and IL-17A) and disease activity (reflected by CDAI) in CD patients. Probable arguments would be that: (1) in terms of inflammation, MALT1 might stimulate the release of proinflammatory cytokines

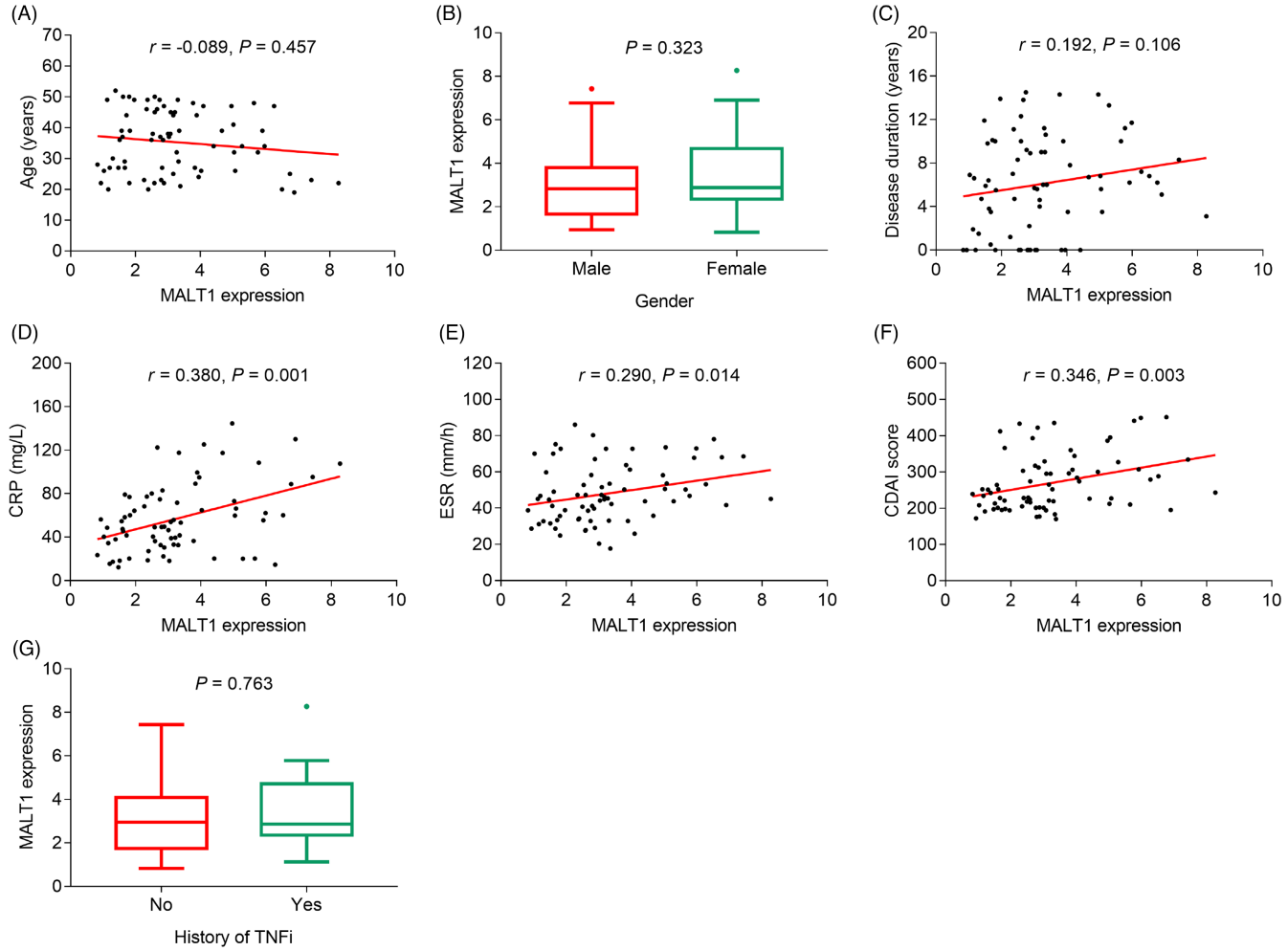


FIGURE 3 MALT1 was positively related to CRP, ESR, and CDAI score in active CD patients. Association of MALT1 with age (A), gender (B), disease duration (C), CRP (D), ESR (E), CDAI score (F), and history of TNFi (G)

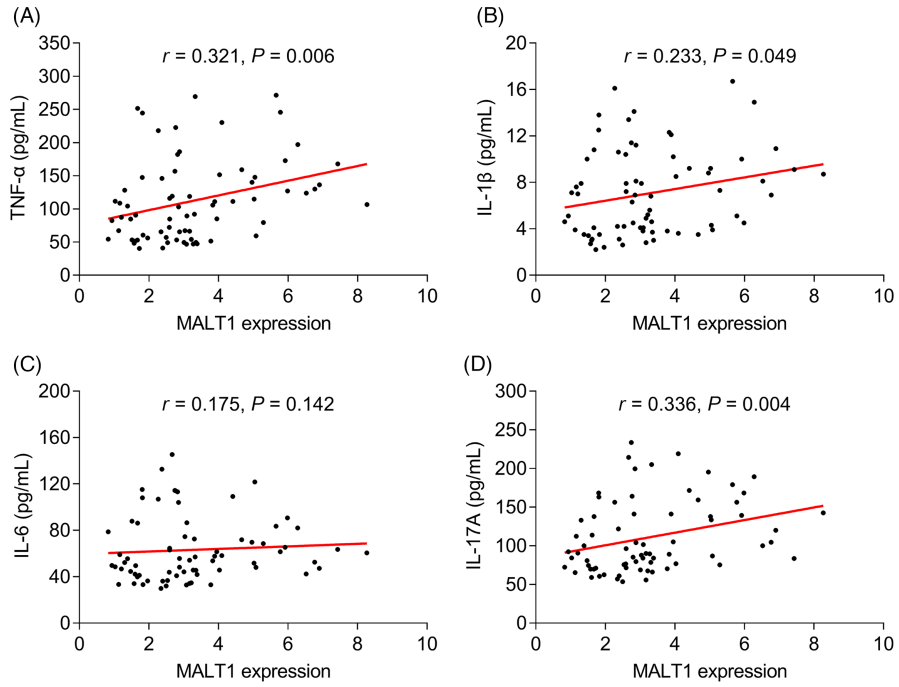


FIGURE 4 MALT1 was positively linked with TNF-α, IL-1β, and IL-17A in active CD patients. Linkage of MALT1 with TNF-α (A), IL-1β (B), IL-6 (C), and IL-17A (D)

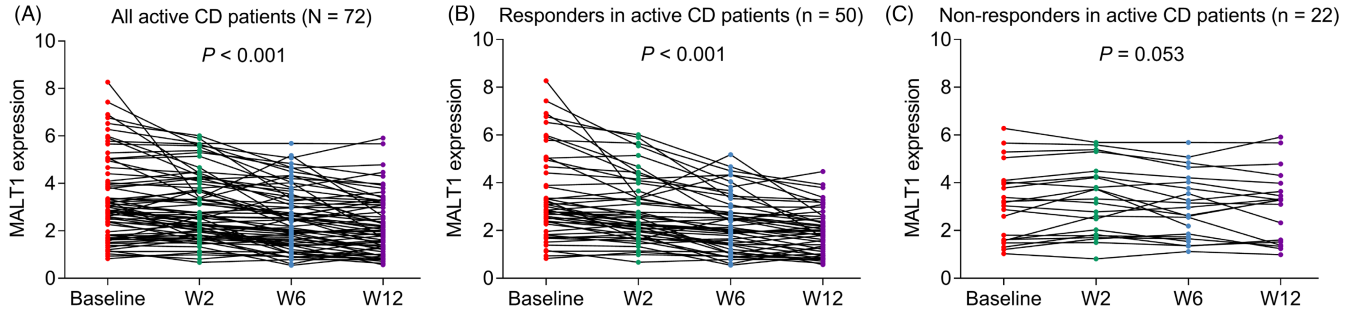
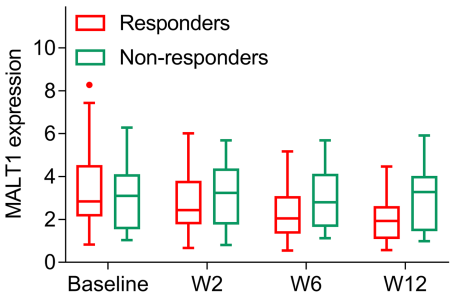


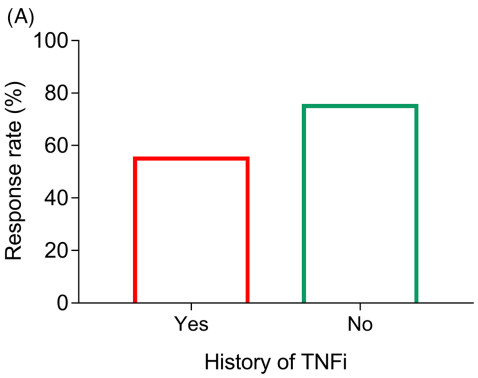
FIGURE 5 MALT1 was decreased from baseline to W12 in active CD patients and responders after infliximab treatment. Variation of MALT1 from baseline to W12 in all active CD patients (A), responders in active CD patients (B), and nonresponders in active CD patients (C)

FIGURE 6 MALT1 at W6 and W12 was reduced in responders compared to nonresponders in active CD patients

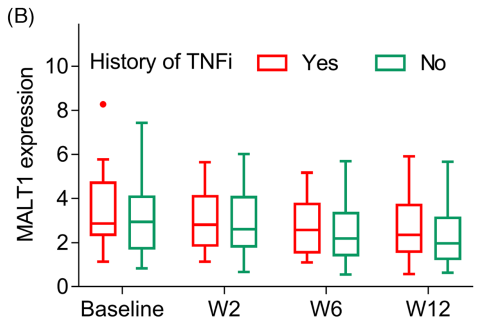


Comparison of MALT1	
Responders vs. Non-responders	*P* value
Baseline	0.788
W2	0.256
W6	0.049
W12	0.004

FIGURE 7 No difference was observed in MALT1 at any time point between active CD patients with and without a history of TNFi. The response rate in patients with and without a history of TNFi (A); no correlation was found between MALT1 at any time point and the history of TNFi (B)



Response patients (rate, %)		*P* value
History of TNFi		
Yes	11 (55.0)	0.099
No	39 (75.0)	



Comparison of MALT1	
History of TNFi: yes vs. no	*P* value
Baseline	0.890
W2	0.860
W6	0.277
W12	0.235

via activating B cell lymphoma/leukemia (BCL) 10, IL-23/T17 axis, as well as NF-κB and NLRP3 inflammasome[12,21,22]; meanwhile, the formation of CARD11-BCL10-MALT1 complex played a key role in inflammation and immunity; thus, the dysregulated MALT1 might be linked with immunodeficiency or inflammation flare[23]; therefore, a positive association was found between MALT1 and inflammation in CD patients. However, the linkage between MALT1 and IL-6 was weakened. Potential reason might be that IL-6 secretion was mainly stimulated by TNF-α and IL-1; while MALT1 is reported to affect the TNF-α secretion by regulating T-cell receptor (TCR) signaling[24]; therefore, MALT1 might be closely linked with TNF-α; while the linkage between MALT1 and IL-6 was indirectly mediated by TNF-α, thus, the linkage between MALT1 and IL-6 was weakened. As a result, MALT1 showed a trend to relate to IL-6 but the correlation was not obvious; (2) regarding disease activity, as mentioned above, MALT1 was positively correlated with inflammation, while inflammation was positively linked with disease activity[25,26]; therefore, MALT1 was positively related to disease activity in CD patients.

Finally, another finding in this study was that MALT1 was decreased from baseline to W12, and its reduction was associated with treatment response; meanwhile, the infliximab treatment response was not affected by the history of TNFi in CD patients. The specific findings and corresponding discussions were as follows. First of all, the findings exhibited that MALT1 was reduced after infliximab treatment. The probable reasons would be that MALT1 inhibitors suppressed inflammation via various signaling pathways (mentioned above), therefore, it reflected inflammation to some extent[12,14,22]; concurrently, after infliximab treatment, the inflammation was reduced, so MALT1 was decreased in CD patients[27,28]. Secondly, decreased MALT1 was associated with infliximab treatment response. It could be explained that: (1) as stated before, MALT1 was positively linked to CDAI score, while CD patients with declined MALT1 indicated a reduced CDAI score, which also represented a greater possibility of achieving a treatment response in CD patients after infliximab; (2) infliximab might reshape host immune regulation by reducing inflammatory factors (such as TNF-α, IL-1β, and IL-17A) and would be associated with restoration of immune microenvironment; thus, after infliximab treatment, inflammation and microbial environment would be improved, which might cause the downregulation of MALT1 expression[29]. Therefore, declined MALT1 was linked with infliximab treatment response. Thirdly, the response rate was similar between CD patients with and without a history of TNFi, which indicated that the history of TNFi did not affect the efficacy of infliximab treatment response in CD patients.

Several limitations existed in this study: (1) the scale of this study was relatively inadequate, which resulted in insufficient statistical power; (2) since infliximab was more commonly used in China, the current study mainly investigated the linkage between MALT1 and infliximab treatment response; however, the association of MALT with other TNFi or other kinds of biologics (such as adalimumab, etanercept, certolizumab pegol, golimumab, etc.) in CD patients remained unknown; (3) the follow-up period in this study was relatively short, and the long-term variations of MALT1 in these patients should be further explored in subsequent studies; (4) multivariate regression analysis could be conducted by further studies to determine whether MALT1 independently linked to infliximab treatment response; (5) subsequent studies could consider detecting MALT1 expression in the feces of CD patients if they developed fistula.

It could be concluded that high expression of MALT1 may have the potency to indicate aggravated inflammatory status and disease activity. Meanwhile, the decrement of MALT1 from baseline to W12 could reflect infliximab treatment response in CD patients. As a result, MALT1 may act as a potential biomarker for monitoring the disease activity and predicting the infliximab treatment outcome in CD patients.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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