Received: 16 July 2022 | Revised: 19 October 2022 | Accepted: 13 November 2022

DOI: 10.1002/jcla.24790

RESEARCH ARTICLE

WILEY

Differential expression of Chitinase 3-Like 1 protein in appendicitis and appendix carcinomas

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Funding information
Nursery Project of the Affiliated Taian City Central Hospital of Qingdao University, Grant/Award Number: 2022MPM11; Technology Research and Development Program of Taian, Grant/Award Number: 2018NS0140

Abstract

Background: Chitinase 3-Like 1 (CHI3L1) has been used as an inflammatory biomarker for a variety of diseases, but its expression in acute appendicitis and appendix carcinomas remains unclear.

Methods: Sixty cases of patients were studied, including 46 acute appendicitis and 14 appendix carcinomas. We divided the acute appendicitis group into acute uncomplicated appendicitis (AUA), suppurative appendicitis (SA), and gangrenous appendicitis (GA). The appendix carcinoma group was divided into appendiceal neuroendocrine neoplasms (ANENs) and appendiceal mucinous neoplasms (AMN). Controls were 32 healthy donors. Blood neutrophil to lymphocyte ratio (NLR), CHI3L1, C-reactive protein (CRP), interleukin-6 (IL-6), and serum amyloid A (SAA) were measured in the patients. Meanwhile, immunohistochemistry and immunofluorescence were used to identify the expression level and location of CHI3L1 in different cell types in appendix tissues.

Results: Compared with the controls, CHI3L1 serum levels were up-regulated in SA, GA, and AMN groups, while no significant difference was observed in the AUA and ANEN groups. Immunofluorescence revealed that CHI3L1 expression was high in macrophages and adenocarcinoma cells of appendix tissues but not in the neuroendocrine carcinoma tissues. Moreover, levels of NLR and CRP in the SA and GA groups were considerably higher than in the control group. IL-6 and SAA in SA, GA, ANENs,

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and AMN groups were also increased compared with the control group. In addition, CHI3L1 displayed good performance in predicting appendicitis, with an AUC of 0.862. **Conclusion:** CHI3L1 was highly expressed in acute appendicitis and appendiceal mucinous neoplasms, which can be used as a novel biomarker predicting appendicitis.

KEYWORDS
appendicitis, appendix carcinomas, biomarker, CHI3L1

1 | BACKGROUND

Appendicitis is among the most prevalent abdominal emergencies.[1] It is usually diagnosed based on a consistent set of signs and symptoms, and it can be efficiently treated with surgery, with moderate morbidity and mortality. Although direct luminal blockage caused by lymphoid hyperplasia, fecolith, or the bent section of the appendix is regarded as the most common mechanical cause of inflammation, neoplasms can also cause appendicitis. However, the incidence rate of primary appendiceal neoplasms following appendicitis is less than 2%.[2,3] The patient's history and clinical examinations are complemented by biomarkers, notably in children and older patients, as well as in women of reproductive age.[4] A range of novel biomarkers, including C-reactive protein, white blood cell count, and procalcitonin, can accurately diagnose appendicitis.[5,6]

Chitinase-3-like protein 1 (CHI3L1) is a 40-kDa heparin-and-chitin binding glycoprotein, mainly produced by some cell types, including colonic epithelial cells (CECs) chondrocytes, osteosarcoma cells, macrophages, smooth muscle cells, and neutrophils.[7–9] Its precise pathophysiological role and manner of action are yet unclear, but it is believed to contribute to inflammation, tissue remodeling, and angiogenesis.[10] CHI3L1 has been significantly linked to diseases such as asthma, sepsis, arthritis, liver fibrosis, diabetes, and coronary artery disease.[11] High levels of CHI3L1 are associated with poor prognosis and accelerate the proliferation of colon cancer cells.[12,13] However, only a few studies have explored CHI3L1 levels in patients with appendicitis. This study measured serum CHI3L1 in patients with different types of appendicitis and appendix carcinomas, combined with NLR, CRP, and IL-6. We found that CHI3L1 was significantly elevated in patients with appendicitis and AMN but not in those with ANENs. This provides a new basis for a better diagnosis of appendicitis and appendiceal tumor.

2 | MATERIAL AND METHODS

2.1 | Clinical specimens and ethical approval

Human blood and appendix samples were collected from 60 patients who had surgery at Taian Central Hospital between May 2019 and November 2021. Patient demographics, histopathological data, and appendectomy surgery details were retrospectively examined in this study. Prior to the appendectomy, whole blood and serum were collected. All clinicopathological diagnoses were confirmed by at least two pathologists.

The patients were classified into five groups, according to the appendectomy specimen findings under microscopy, in the pathology report; (1) AUA: acute uncomplicated appendicitis, (2) SA: suppurative appendicitis, (3) GA: gangrenous appendicitis, (4) ANENs: appendiceal neuroendocrine neoplasms, and (5) AMN: appendiceal mucinous neoplasms. The control group (32 cases) was comprised of healthy donors. The Taian Central Hospital Ethics Committee (ID: 2022-05-04) approved this research. All patients provided written consent to participate.

2.2 | SAA, CRP, IL-6, and NLR detection

The patients' venous blood samples were taken before the appendicectomy. The Upper Bio-TECH Pharma Co. Ltd. provided the SAA kits (Cat. No.20211104) and CRP kits (Cat. No. 20210801). The Shenzhen Lifotronic Biotech Co. Ltd. provided the IL-6 kits. NLR was analyzed from a blood routine test. The control group samples followed the same procedure.

2.3 | Section staining

For hematoxylin and eosin (H&E) staining of paraffin tissue sections, we used the standard H&E process. Briefly, we stained the tissue with Mayer's hematoxylin (C0105S, Beyotime), rinsed them in distilled water for 5 min, and counterstained them with eosin (C0105S, Beyotime) for 7 min. Finally, dehydration, clearing, and sealing of the sections were conducted as standard.

For immunohistochemical staining, sections were rinsed in distilled water three times, and the Quick Antigen Retrieval Solution (P0090, Beyotime) was used for antigen retrieval. Next, 3% bovine serum albumin was used for nonspecific binding blockage, and the sections were incubated with an anti-CHI3L1 antibody (1:200, proteintech) at 4°C overnight. After three washes in phosphate-buffered saline, the slides were incubated with secondary antibodies (ImmPRESS®-HRP Horse Anti-Rabbit IgG MP-7401-NB, Vector) at room temperature for 1 h and washed thrice with phosphate-buffered saline. Horseradish peroxidase was used as the chromogen for 1 h. Next, the sections were counterstained with hematoxylin. Finally, dehydration and sealing of slides were performed as standard. Non-immune IgG was used as a negative control.

TABLE 1 Patient characteristics.

Variable	Control group	Acute uncomplicated appendicitis (AUA)	Suppurative appendicitis(SA)	Gangrenous appendicitis(GA)	Appendiceal neuroendocrine neoplasms(ANENs)	Appendiceal mucinous neoplasms(AMN)
n	32	12	20	14	2	12
Sex						
Female	16	7	12	5	2	9
Male	16	5	8	9	0	3
Age(y)						
Median, range	42.5 ± 19.9 (18–84)	37.5 ± 15.34 (16–59)	37.5 ± 16.95 (15–72)	46.28 ± 19.33 (16–85)	27 ± 2 (25–29)	61.5 ± 13.2 (45–85)
<60	24	12	17	10	2	6
≥60	8	0	3	4	0	6
Operated	No	Yes	Yes	Yes	Yes	Yes

2.4 | Immunofluorescence staining

For immunofluorescence detection of CHI3L1, the paraffin tissue sections were permeabilized with 0.1% Triton X-100/PBS for 30 min. Then, rabbit polyclonal anti-CHI3L1 antibody (1:200; proteintech) and mouse monoclonal anti-CD68 antibody (1:1000; Abcam) were applied in a humidified chamber overnight, after 3% bovine serum albumin blocking. Following three PBS washes, mouse anti-rabbit Alexa 488 secondary antibody (1:1000; Waltham, USA) and goat anti-mouse 594 (1:1000; Waltham, USA) were applied for 1 h. After three more washes in PBS, DAPI (1:10000; C1002, Beyotime Biotechnology) was used to counterstain nuclei. Finally, the sections were mounted with an antifade mounting medium (Beyotime Biotechnology) on glass microscope slides. Fluorescence images were obtained using an Olympus FV3000 microscope.

2.5 | Statistical analysis

The data were shown as the mean ± standard error of the mean, with n indicating replicates from individual experiments. Unless specified otherwise, a one-way analysis of variance (ANOVA) with post hoc Tukey's test was utilized for all analyses. ImageJ software was used for localization quantitation.

3 | RESULTS

3.1 | Clinical parameters

Characteristics and major parameters of patients with appendicitis and appendix carcinomas are presented in Table 1. In the discovery set, the clinical parameters of patients with appendicitis versus the healthy controls were generally similar.

3.2 | CHI3L1 increased in appendicitis but not in appendiceal neuroendocrine neoplasms

We selected typical pathological H&E staining to distinguish the clinicopathological features of appendicitis and appendiceal cancer. As illustrated in Figure 1A, AUA appendectomy specimens presented mild alterations confined to the mucosa and submucosa, with an intact mucosal layer and a small amount of neutrophil infiltration. SA appendectomy specimens were hyperemic, edematous, and necrotic, with numerous neutrophils. Moreover, GA appendices showed infiltration of inflammatory cells in the submucosa, accompanied by much tissue congestion and necrosis. Morover, we collected two kinds of appendix tumors in our clinical work: appendiceal neuroendocrine neoplasms and appendiceal mucinous neoplasms. Appendiceal neuroendocrine neoplasms are rare, with an estimated incidence of 0.15–0.6/100000/year.[14,15] Typically, the characteristics of these irregular-shaped tumors include appendiceal wall submucosal

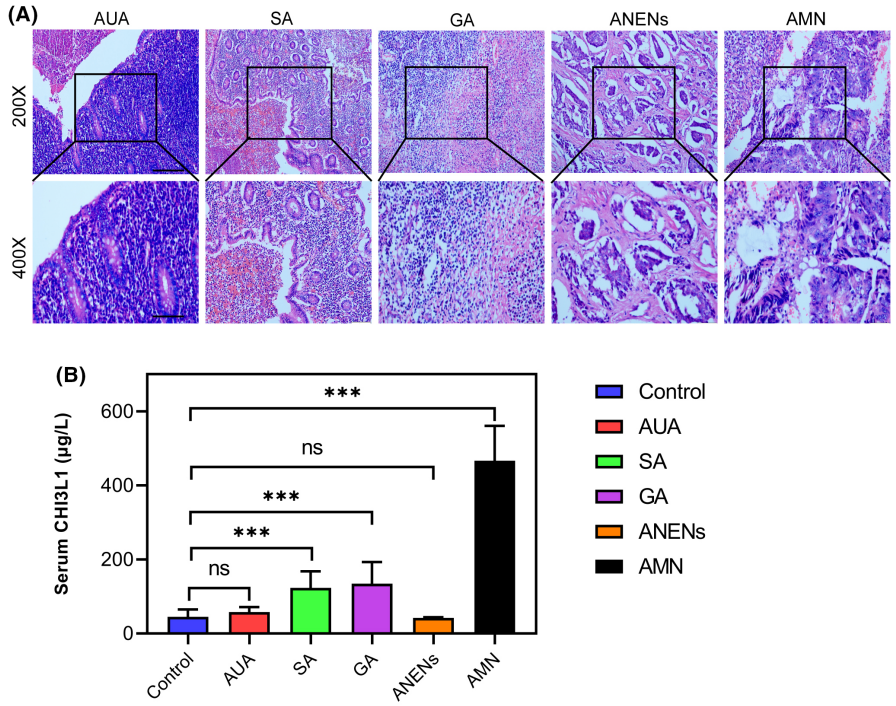

FIGURE 1 H&E staining and serum CHI3L1 levels in different types of appendicitis and appendix carcinoma. (A) Representative H&E staining in different types of appendicitis and carcinoma of the appendix. (200× magnification, scale bar = 200 μm, 400× magnification, scale bar = 50 μm). (AMN, Appendiceal mucinous neoplasms; ANENs, Appendiceal neuroendocrine neoplasms; AUA, Acute uncomplicated appendicitis; GA, Gangrenous appendicitis; SA, Suppurative appendicitis). (B) Serum CHI3L1 levels in different types of appendicitis and appendix carcinoma of the appendix. One-way ANOVA with post hoc Tukey's test. Values expressed as mean ± SEM, ***$p < 0.001$, ns = no significance.

development and concentric infiltration; the mucosa was disease-free, except for the tumor cell nests and the crypt bases interactions.[16] The cells were generally mildly to intermediately atypical, showed slight mitotic activity (Ki-67 index <20%), and were focally positive for synaptophysin, CgA, and CD56, while they are diffusely positive for cytokeratin 20 and MUC2.[17] Appendiceal mucinous neoplasm has high-grade dysplasia, characterized by changes including cribriform growth, polarity loss with full-thickness nuclear stratification, enlarged nuclei, markedly hyperchromatic or vesicular, prominent nucleoli, and numerous or atypical mitotic figures.[18,19]

Moreover, we detected CHI3L1 serum levels in these groups. Appendicitis patients showed higher CHI3L1 levels. Patients in AUA group had low CHI3L1 levels, while CHI3L1 in the GA group was higher than in patients with other appendicitis types. The AMN group showed the highest CHI3L1 levels. Interestingly, the ANENs groups showed no significant increment of CHI3L1 compared with the control group (Figure 1B).

3.3 | CHI3L1 is expressed in the appendix specimens from patients with appendicitis but not in appendiceal neuroendocrine neoplasms

To further confirm the source of CHI3L1 in serum, we performed CHI3L1 immunohistochemistry analyses using the samples obtained from patients with appendicitis and appendix tumors. As depicted in Figure 2A, CHI3L1 is strongly expressed in macrophages and many scattered cells in the lamina propria. Moreover, the AMN carcinomas were more positively stained with an anti-CHI3L1 polyclonal antibody. In contrast, ANENs carcinomas appeared to have low expression of CHI3L1. We used Image J software to evaluate CHI3L1 expression in the appendix. As revealed in Figure 2B, ANENs showed the same low CHI3L1 expression as AUA, while SA, GA, and AMN had high expression of CHI3L1 in appendectomy specimens.

3.4 | Levels of NLR, CRP, IL-6, and SAA in samples from appendicitis patients and appendix carcinomas

To evaluate the levels of inflammation in appendicitis and appendix carcinomas patients at first admission, we evaluated the NLR, CRP, IL-6, and SAA in patients before surgery. NLR and CRP are considered disease activity and severity biomarkers in many disorders.[20] In AUA group, CRP, NLR, IL-6, and SAA showed no significant difference compared with the control group ($p < 0.001$), while NLR, CRP, IL-6, and SAA were significantly higher in SA and GA groups in comparison with the control group ($p < 0.001$). As shown in Figure 3, we found that blood NLR and CRP were not elevated in patients with appendix carcinomas in ANENs and AMN groups, while IL-6 and SAA were elevated. Additionally, levels of SAA in ANENs group were highest than in other groups (Figure 3).

3.5 | Receiver operating characteristic (ROC) curve of NLR, SAA, IL-6, CRP, CHI3L1 in patients with appendicitis

Because of the insufficient appendiceal carcinoma patients in the current research, we did not evaluate the role of blood inflammatory indicators in diagnosing appendiceal carcinoma, but only appendicitis. Thus, we researched the serum CHI3L1 effectiveness in diagnosing appendicitis patients. The CHI3L1 specificity and sensitivity

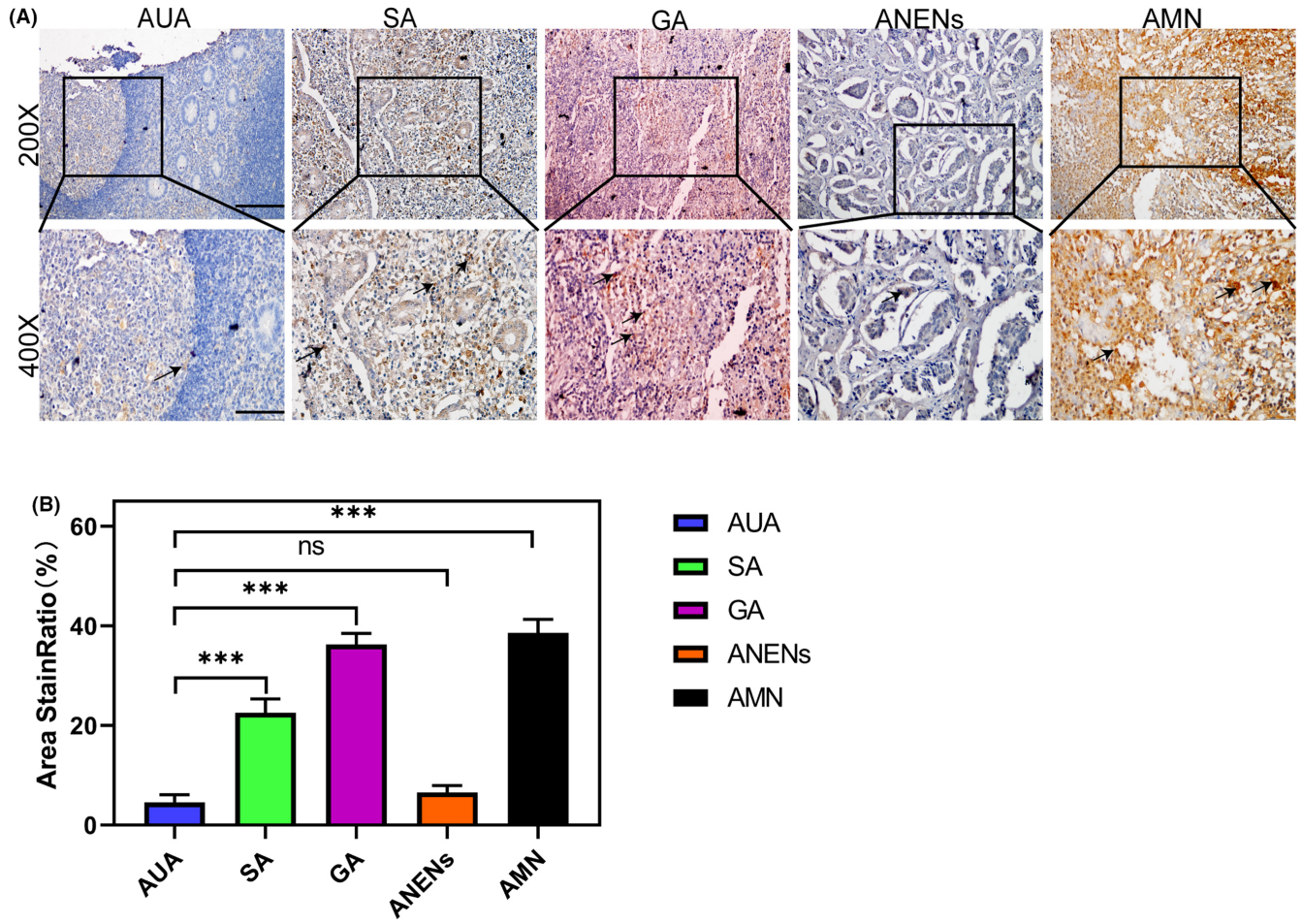

FIGURE 2 Immunohistochemical staining and analysis of CHI3L1 in the appendix of appendicitis and appendix carcinoma. (A) Representative images are shown. IgG was used as a control. Arrows point out positive cells of lung tissue. Magnification ×200. Scale bar indicates 100 μm (400× magnification, scale bar = 50 μm). (B) Quantitative results of CHI3L1 in different groups. One-way ANOVA with post hoc Tukey's test. Values expressed as mean ± SEM, ***$p < 0.001$, ns = no significance.

to predict appendicitis were 87.1% and 83.3%, respectively, as ROC curve analysis revealed. The cut-off value was 53.6 μg/L, and AUC was 0.862 (95% CI: 0.766–0.929; Figure S1). However, SAA revealed that CHI3L1 specificity and sensitivity to predict appendicitis were 100% and 89.36%, respectively, and the cut-off value was 17.5 mg/L with 0.945 (95% CI: 0.869–0.984) AUC area.

According to our findings, the CHI3L1 levels might be utilized to diagnose appendicitis. Furthermore, the performance of NLR, CRP, IL-6, and SAA was compared using ROC analysis. We found that SAA displayed a better performance than NLR and CRP (SAA vs. NLR: AUC = 0.168, 95% CI: 0.047–0.287, $p = 0.0061$; SAA vs. CRP: AUC = 0.145, 95% CI: 0.0285–0.261, $p = 0.0147$) in predicting significant appendicitis (Figure 4), but its performance did not significantly differ from that of the CHI3L1 (SAA vs. CHI3L1: AUC = 0.0798; 95% CI: −0.0102–0.170; $p = 0.0823$). Thus, serum SAA serves as a noninvasive marker for identifying appendicitis patients.

3.6 | Heterogeneity of macrophage and CHI3L1 protein distribution in appendicitis and appendicitis carcinoma

We sought to determine which cells secreted CHI3L1 in the appendectomy specimens, so we used immunofluorescence to label macrophages and CHI3L1 expression. CD68 was used to identify macrophages in tissue sections.[21] As revealed in Figure 4, in comparison with AUA group, CD68-positive macrophages were increased in SA group with CHI3L1 expression, while CD68 staining showed modest amounts of macrophages in GA group due to tissue necrosis. Interestingly, we found that in appendiceal neuroendocrine neoplasms, tumor cells did not secrete CHI3L1, which was limited to merely macrophages around the carcinomas; in contrast, we observed high expression of CHI3L1 secreted by carcinomas and macrophages in the AMN group (Figure 5).

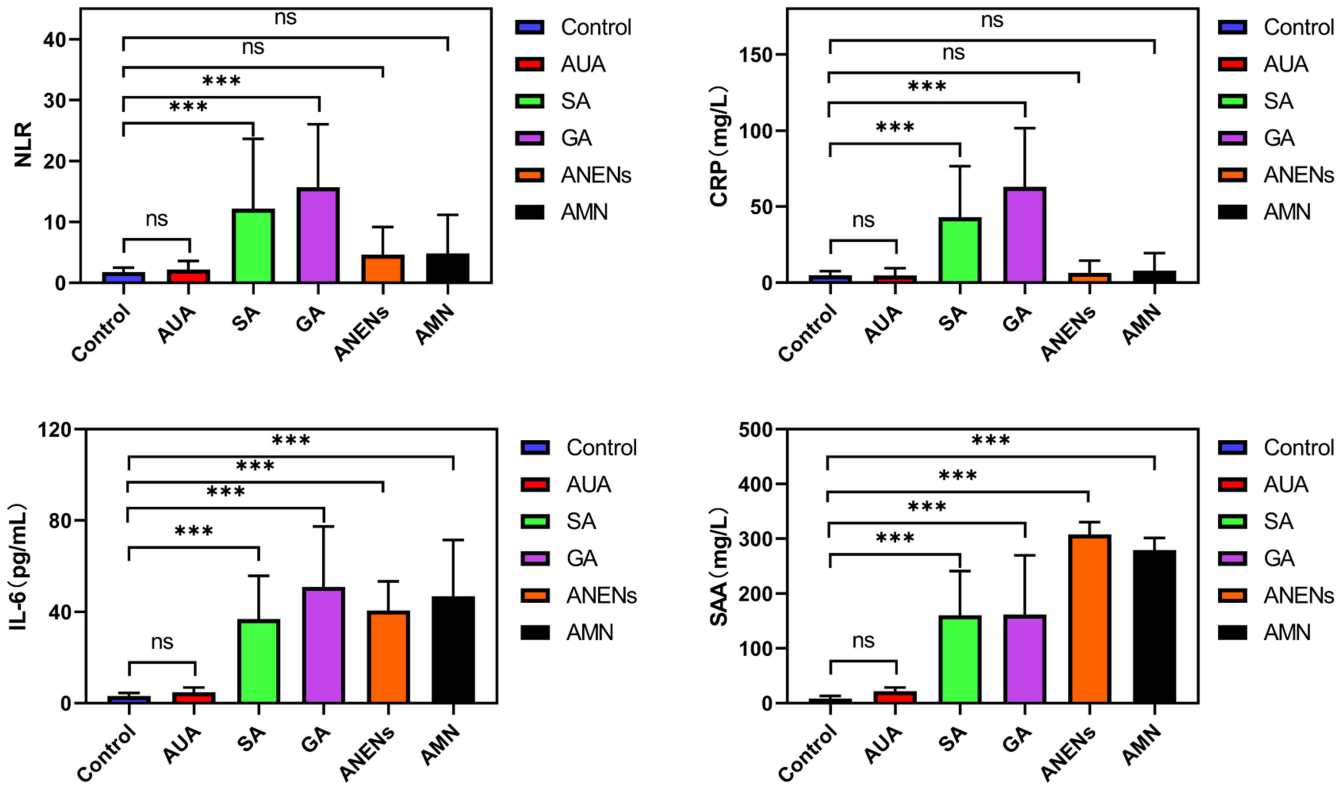

FIGURE 3 Levels of NLR, CRP, IL-6 and SAA in different types of appendicitis and carcinoma of the appendix. One-way ANOVA with post hoc Tukey's test. Values expressed as mean ± SEM, ***$p < 0.001$, ns = no significance. (CRP, C-reaction protein; IL-6, Interleukin- 6; NLR, Neutrophil to Lymphocyte ratio; SAA, Serum amyloid A)

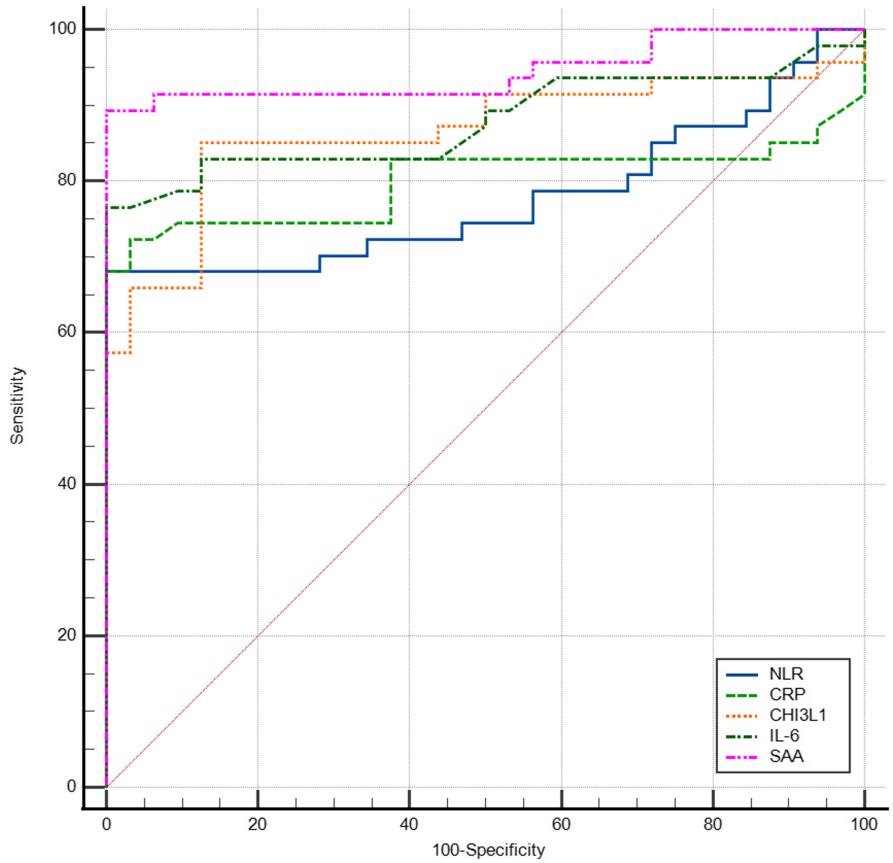

FIGURE 4 Comparison of ROC curves for prediction of appendicitis with the use of different blood inflammatory factors. ROC curve of NLR, CRP, CHI3L1, IL-6 and SAA for diagnosis of patients with the appendix, with the AUC of 0.777, 0.800, 0.862, 0.878 and 0.945, respectively. (CRP, C-reaction protein; IL-6, Interleukin-6; NLR, Neutrophil to Lymphocyte ratio; SAA, Serum amyloid A)

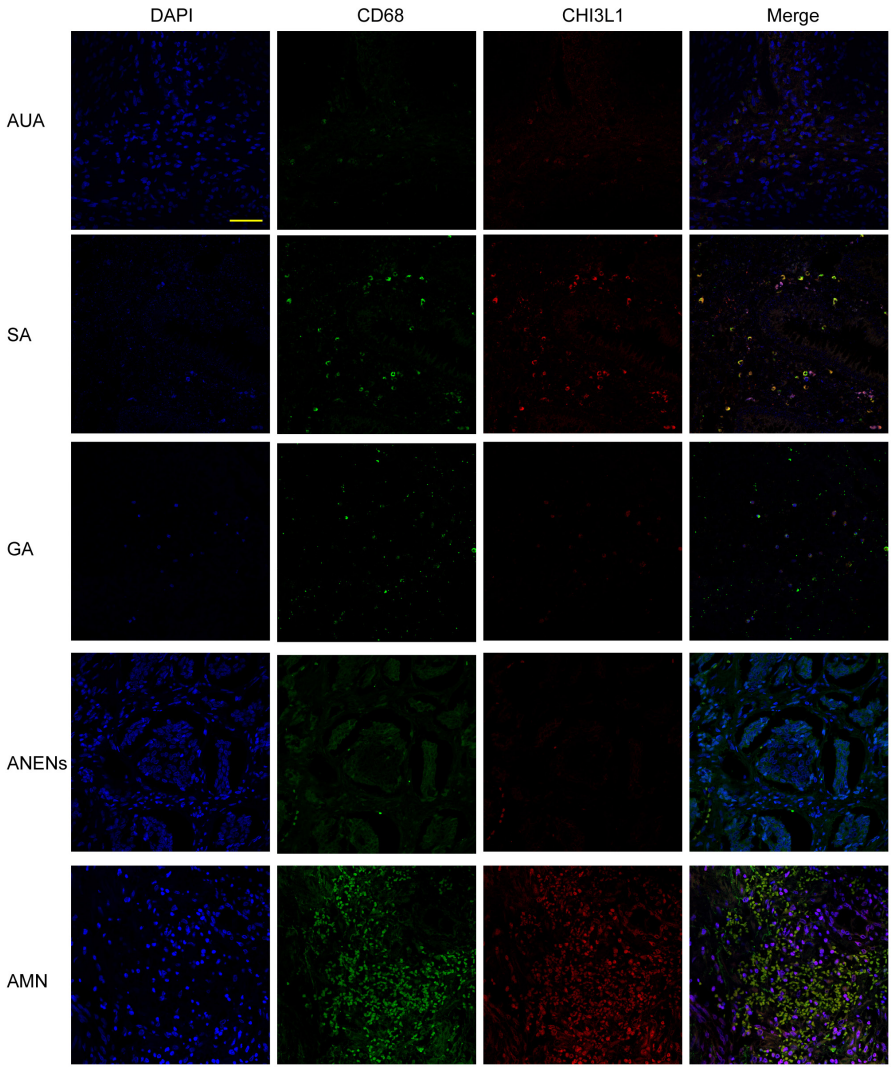

FIGURE 5 Double immunofluorescence staining of CD68 and CHI3L1 verified macrophages that secreted CHI3L1 proteins in the appendix of appendicitis and appendix carcinoma. Scale bar = 50 μm.

4 | DISCUSSION

In this study, serum levels of CHI3L1 were significantly increased in patients with appendicitis and appendiceal mucinous neoplasms. This suggests that CHI3L1 can reflect the inflammatory response of patients with appendicitis, which was consistent with the research of Koc.[22] Moreover, we also determined the serum levels of CHI3L1 in patients with appendiceal neuroendocrine neoplasms and appendiceal mucinous neoplasm. The research work has brought about a discovery that CHI3L1 was highly expressed in appendiceal mucinous neoplasm and lowly expressed in appendiceal neuroendocrine neoplasms.

The increased level of CHI3L1 in serum enhanced bacterial adhesion and invasion into intestinal epithelial cells (IECs), and activation of activated protein kinase B (AKT) in IECs, specifically.[23,24] CHI3L1 overexpression, on the other hand, may have extremely damaging consequences in mucosal tissues, immediately beginning and maintaining chronic inflammation, as well as colitis-associated carcinogenic change of IECs.[25] As determined by immunochemistry, we evaluated the high CHI3L1 levels in patients with AMN, further supported by Chen,[26] who reported the same findings in colonic mucinous adenocarcinoma. However, Chen showed the opposite result for ANENs, with higher expression of CHI3L1. The opposite result might be attributed to the degree of tumor differentiation.

Inflammatory markers in blood tests revealed the levels of inflammation in patients with appendicitis. CRP, NLR, IL-6, and SAA were considerably higher in SA and GA groups. These data supported the notion of an inflammatory environment in patients with appendicitis in SA and GA groups. Unexpectedly, the IL-6 levels were higher in AMN and ANENs patients. Previous research indicated significant levels of IL-6 in the serum of ovarian cancer patients[27] and colon cancer patients.[28] A high serum IL-6 level is linked to a poor prognosis in individuals with ovarian cancer.[27] This suggests that high levels of IL-6 in appendix carcinoma have an impact on tumor progression and prognosis. Consistent with IL-6, SAA was also elevated in appendiceal carcinoma, consistent with reports of Edgell in ovarian cancer.[29] These findings highlight an attractive biomarker for appendix carcinoma. ROC curve analysis revealed that CHI3L1 had good specificity and sensitivity in the appendicitis diagnosis, consistent with the results reported in Koc.[22]

Through immunofluorescence staining, we concluded that the expression of CHI3L1 in appendicitis tissues was mainly found in macrophages, while the expression of AMN was mainly in cancer cells, with a small number of macrophages. Tissue from ANENs did not express CHI3L1, with a few surrounding macrophages. This was the first preliminary study to suggest that scattered macrophages around the appendiceal mucinous neoplasm also secreted CHI3L1. Mucinous tumors at other tissue sites also support our conclusions.[30] Furthermore, we did not find any reports related to the secretion of CHI3L1 by appendiceal neuroendocrine neoplasms. We will pay attention to the collection of such cases and tissues in future work.

5 | CONCLUSION

We demonstrate that the patients with appendicitis had an enhanced CHI3L1 expression, associated with increased NLR, CRP, IL-6, and SAA. Moreover, CHI3L1 was crucial in patients with appendiceal neuroendocrine neoplasms. Additionally, we should pour attention into the low expression of CHI3L1 in patients with appendiceal neuroendocrine neoplasms. The data we present here may serve as the springboard for further investigation of appendicitis and appendix carcinoma. In the meantime, these findings may provide further insight into the biology of tumors and could lead to improvements in appendix carcinoma treatment.

AUTHOR CONTRIBUTIONS

Study concept and design: Wenyang Wang and Yi Zhang. Acquisition of data: Yong Zhang and Han Wang, Analysis and interpretation of data: Yanping Li and Chunling Zhang. Drafting of the manuscript: Wenyang Wang and Yun Chen. Critical revision of manuscript: Fei Li and Lingxing Li. All authors read and approved the final manuscript.

FUNDING INFORMATION

This study was supported by the Nursery Project of the Affiliated Taian City Central Hospital of Qingdao University (2022MPM11), Technology Research and Development Program of Taian (2018NS0140).

CONFLICT OF INTEREST

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zhang Y, Li Y, Li F, et al. Differential expression of Chitinase 3-Like 1 protein in appendicitis and appendix carcinomas. *J Clin Lab Anal*. 2022;36:e24790. doi:10.1002/jcla.24790