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Research Article

Role of Cytokines, Oxidative Stress Markers and Inflammatory Mediators in Gastrointestinal Dysfunction in Ulcerative Colitis

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ABSTRACT

Objective: To evaluate the role of cytokines, oxidative stress markers, and inflammatory mediators in gastrointestinal dysfunction and to assess their relationship with disease severity in patients with UC.

Materials and Methods: A total of 120 participants were enrolled, including 80 patients with clinically and histopathologically confirmed ulcerative colitis and 40 age and sex matched healthy controls. Serum levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-17), anti-inflammatory cytokine (IL-10), oxidative stress markers (malondialdehyde, nitric oxide, myeloperoxidase), antioxidant enzymes (SOD, catalase, glutathione peroxidase, reduced glutathione), and inflammatory mediators (CRP, ESR, prostaglandin E2, COX-2 expression) were analyzed using standard biochemical and immunological methods. Disease severity was assessed using the Mayo Clinic Disease Activity Index, and histopathological evaluation was performed on colonic biopsy samples.

Results: The results demonstrated significantly elevated levels of pro-inflammatory cytokines, oxidative stress markers, and inflammatory mediators in UC patients compared with controls ($p < 0.001$). In contrast, antioxidant enzyme levels and IL-10 were significantly reduced. These biochemical alterations showed a strong positive correlation with disease severity, while antioxidant markers showed a negative correlation. Histopathological findings revealed mucosal inflammation, crypt distortion, goblet cell depletion, and epithelial damage, which were consistent with biochemical abnormalities.

Conclusion: Ulcerative colitis is strongly associated with an imbalance between pro-inflammatory and anti-inflammatory cytokines, increased oxidative stress, and heightened inflammatory mediator activity. These factors collectively contribute to gastrointestinal dysfunction and disease progression. The studied biomarkers may serve as useful indicators of disease severity and potential targets for therapeutic intervention.

Keywords: Ulcerative Colitis, Cytokines, Oxidative Stress, Inflammatory Mediators, Gastrointestinal Dysfunction, Biomarkers.

INTRODUCTION

Ulcerative colitis is a chronic autoimmune condition with recurrent episodes of inflammation of the gastrointestinal tract that affects the colon and rectum. UC is one of the main types of inflammatory bowel disease (IBD) and has a considerable burden on global health as a result of its rising prevalence, frequent relapsing and remitting nature, and its important role in the quality of life of those who suffer from it.(1) Remissions and exacerbations of the disease with clinical symptoms of abdominal pain, diarrhea, rectal bleeding, urgency and weight loss. (2)Though significant efforts have been made to uncover the definite cause of ulcerative colitis, the disease is still poorly understood, but it is believed that ulcerative colitis is the result of a

complex interplay between intestinal microbiota, genetic susceptibility, environmental triggers, epithelial barrier dysfunction, and immune dysregulation.[3]

In physiological states, the gastrointestinal tract assumes a delicate balance between tolerance and activation of the immune system. The role of the intestinal mucosa is to provide an important barrier function in which nutrients are absorbed and pathogens and harmful antigens are excluded. [4]This homeostasis is regulated by the coordinated interaction of epithelial cells, immune cells, cytokines and gut-microbiome. The disruption of this balance causes overactive activation of the mucosal immune system which causes chronic inflammation and progressive tissue damage in ulcerative colitis.[5] Changes in the barrier function of the epithelium increase intestinal permeability, which leads to an influx of antigens and bacterial products in the lumen and initiates inflammatory responses. The cytokines are important in the early events, amplification and maintenance of intestinal inflammation in ulcerative colitis. [6]

Small signaling proteins that modulate interactions between cells of the immune system and other cells as well as mediate innate and adaptive immune responses.[7] Colonic mucosa and systemic circulation of patients with active disease have markedly elevated levels of pro-inflammatory cytokines, including tumour necrosis factor (TNF) alpha, interleukin 1 beta, IL-6, IL-17 and interferon gamma (IFN gamma). [8]These cytokines stimulate recruitment of leukocytes, the inflammatory cascade, an increase in vascular permeability and damage to the epithelia. In contrast, anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor beta (TGF-β) have the opposite effect to dampen excessive immune activation. [9]So, the process of ulcerative colitis is marked with a lack of balance between pro-inflammatory and anti-inflammatory cytokines and this plays an important role in gastrointestinal dysfunction. [10]

Besides the inflammatory response induced by cytokines, oxidative stress has also become a key mechanism in the pathogenesis of ulcerative colitis. Oxidative stress is a state that happens when the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is more than the capacity of the body's internal antioxidant defense mechanisms.[11] During the inflammatory process, a large number of free radicals are produced by activated neutrophils, macrophages and other inflammatory cells within the colonic mucosa.[12] These reactive molecules cause lipid peroxidation, protein oxidation, DNA damage, mitochondrial dysfunction and result in cell injury and failure of mucosal healing. Malondialdehyde (MDA), nitric oxide, advanced oxidation protein products (AOPP) and myeloperoxidase (MPO) are all biomarkers that have been extensively studied in ulcerative colitis for oxidative damage.[13] In parallel, decreased levels of antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and reduced glutathione (GSH) worsen injury caused by oxidative stress and help maintain inflammation. [14]

There is a bidirectional relationship between inflammation and oxidative stress. Cytokines induce the production of reactive oxygen species (ROS), and ROS activate the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, mitogen-activated protein kinases (MAPKs), and nuclear factor-kappa B (NF-κB) pathways, which further increase the production of cytokines. [15]This perpetuates a cycle of inflammation and oxidative damage leading to chronic mucosal injury and disease progression. Moreover, epithelial dysfunction caused by oxidative stress makes epithelial barrier susceptible to bacterial invasion and further immune activation.[16] In addition, there are inflammatory mediators such as prostaglandins, leukotrienes, chemokines, adhesion molecules and inducible nitric oxide synthase (iNOS)-derived nitric oxide that also contribute to gastrointestinal dysfunction associated with ulcerative colitis. These mediators control the vascular response, leukocyte migration and tissue remodeling processes in the inflamed colon. [17]

Cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) and other chemokines promote chronic inflammatory cell infiltration and exacerbation of tissue damage. Furthermore, matrix metalloproteinases (MMPs) also contribute to degradation of the extracellular matrix and mucosal ulceration, which exacerbates the disease. [18]The pathological features of ulcerative colitis are diffuse mucosal inflammation, architectural distortion of the crypts, depletion of goblet cells, the presence of crypt abscesses, inflammatory cell infiltration, and ulceration. [19]Such histopathological changes are the result of immune dysregulation, oxidative damage and

activity of inflammatory mediators. Inflammatory complications like toxic megacolon, significant bleeding, strictures and colorectal carcinoma may develop later. [20]

The molecular mechanisms of these pathological changes need to be understood to find new biomarkers of diagnosis and new targets for therapeutic approaches. Immunobiologicals such as cytokines, markers of oxidative stress, and inflammatory mediators have all been emphasized as potential markers of disease activity, severity, and response to treatment in ulcerative colitis in recent biochemical and molecular studies. Their evaluation can give clues to the pathogenesis of the disease and help to create personalized treatment plans focusing on the control of inflammation, the restoration of redox balance and the preservation of gastrointestinal function.

MATERIALS AND METHODS

This multicenter cross-sectional analytical study was conducted in the Departments of Gastroenterology and Pathology of tertiary care teaching hospitals. The study duration was of twelve months. The study included patients diagnosed with ulcerative colitis based on clinical presentation, colonoscopic findings and histopathological examination. Age and sex-matched healthy individuals without a history of gastrointestinal, autoimmune, inflammatory, or metabolic disorders were recruited as controls.

A total of 120 participants were enrolled, comprising 80 patients with ulcerative colitis and 40 healthy controls. Patients aged between 18 and 65 years with confirmed ulcerative colitis were included in the study. Individuals with Crohn's disease, colorectal malignancy, infectious colitis, chronic liver disease, chronic kidney disease, diabetes mellitus, cardiovascular disorders, pregnancy, or current use of antioxidant supplements were excluded.

Demographic and clinical information including age, sex, disease duration, body mass index, medication history, smoking status, frequency of bowel movements, rectal bleeding, abdominal pain, and disease severity were recorded using a structured data collection form. Disease activity was assessed using the Mayo Clinic Disease Activity Index and categorized as mild, moderate, or severe.

Following overnight fasting, approximately 10 mL of venous blood was collected from each participant under aseptic conditions. Blood samples were divided into ethylenediaminetetraacetic acid (EDTA) and plain tubes. Serum and plasma were separated by centrifugation at 3000 rpm for 10 minutes and stored at –80°C until biochemical analysis.Serum levels of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-17 (IL-17), as well as the anti-inflammatory cytokine interleukin-10 (IL-10), were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions. Cytokine concentrations were expressed in pg/mL.

Oxidative stress was assessed by measuring serum malondialdehyde (MDA), nitric oxide (14), and myeloperoxidase (MPO) levels. Malondialdehyde concentration, an indicator of lipid peroxidation, was estimated using the thiobarbituric acid reactive substances (TBARS) method. Nitric oxide levels were determined by measuring stable nitrite and nitrate metabolites using the Griess reaction. Myeloperoxidase activity was assessed spectrophotometrically as a marker of neutrophil activation.

Antioxidant status was evaluated by measuring serum superoxide dismutase (SOD), catalase (21), glutathione peroxidase (GPx), and reduced glutathione (GSH) levels using standard spectrophotometric methods. The activities of antioxidant enzymes were expressed in appropriate international units according to established laboratory protocols.

Inflammatory mediators including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), prostaglandin E2 (PGE2), and cyclooxygenase-2 (COX-2) expression were assessed. Serum CRP levels were measured using a high-sensitivity immunoturbidimetric assay, while ESR was determined by the Westergren method. Prostaglandin E2 concentrations were quantified using ELISA. Expression of COX-2 was evaluated in colonic biopsy specimens through immunohistochemical staining.

Colonic mucosal biopsies obtained during diagnostic colonoscopy were fixed in 10% neutral buffered formalin, processed routinely, and embedded in paraffin wax. Sections of 4–5 µm thickness were stained with hematoxylin and eosin for histopathological evaluation. Histological parameters assessed included epithelial damage, crypt distortion, goblet cell depletion, inflammatory cell infiltration, crypt abscess formation and mucosal ulceration.

Histological grading was performed using a standardized scoring system by two independent pathologists blinded to the clinical and biochemical findings.

Physiological assessment of gastrointestinal dysfunction included evaluation of bowel frequency, stool consistency, abdominal pain score, and disease activity index. Correlations between clinical severity, histopathological changes, cytokine levels, oxidative stress markers, and inflammatory mediators were analyzed to determine their contribution to disease progression and gastrointestinal dysfunction.

Data was entered and analyzed usingSPSSversion 26.0. Quantitative variables were expressed as mean ± standard deviation while categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using the independent sample t-test, one-way analysis of variance (ANOVA), or Chi-square test as appropriate. Pearson's or Spearman's correlation analysis was used to evaluate associations between biochemical markers and disease severity. A p-value of less than 0.05 was considered statistically significant.

The study protocol was approved by the Institutional Ethical Review Committee before commencement of the study. Written informed consent was obtained from all participants, and confidentiality of personal information was maintained throughout the study in accordance with the principles of the Declaration of Helsinki.

RESULTS

A total of 120 participants were included in the study, comprising 80 patients diagnosed with ulcerative colitis and 40 healthy controls. The mean age of patients with ulcerative colitis was 39.8 ± 11.2 years, while that of controls was 38.6 ± 10.7 years. No statistically significant differences were observed in age or sex distribution between the two groups ($p > 0.05$).

Table 1. Demographic and Clinical Characteristics of Study Participants

Variable	Ulcerative Colitis (n=80)	Controls (n=40)	p-value
Age (years)	39.8 ± 11.2	38.6 ± 10.7	0.612
Male, n (%)	46 (57.5)	22 (55.0)	0.792
Female, n (%)	34 (42.5)	18 (45.0)	0.792
BMI (kg/m²)	23.4 ± 3.6	24.2 ± 3.1	0.214
Disease Duration (years)	5.3 ± 2.7	–	–
Mayo Disease Activity Score	7.8 ± 2.1	–	–

Among ulcerative colitis patients, 21 (26.3%) had mild disease, 37 (46.2%) had moderate disease, and 22 (27.5%) had severe disease according to the Mayo Disease Activity Index.

Table 2. Distribution of Disease Severity among Ulcerative Colitis Patients

Disease Severity	Frequency (n)	Percentage (%)
Mild	21	26.3
Moderate	37	46.2
Severe	22	27.5
Total	80	100

Serum levels of pro-inflammatory cytokines were significantly elevated in ulcerative colitis patients compared to controls, whereas the anti-inflammatory cytokine IL-10 was significantly reduced.

Table 3. Comparison of Cytokine Levels between Groups

Cytokine	Ulcerative Colitis	Controls	p-value
TNF-α (pg/mL)	45.7 ± 10.8	18.9 ± 5.4	<0.001
IL-1β (pg/mL)	28.5 ± 7.1	10.6 ± 3.2	<0.001
IL-6 (pg/mL)	34.2 ± 8.5	12.4 ± 4.1	<0.001
IL-17 (pg/mL)	26.8 ± 6.7	9.8 ± 2.9	<0.001
IL-10 (pg/mL)	8.2 ± 2.3	15.7 ± 3.8	<0.001

Analysis of oxidative stress markers revealed significantly increased lipid peroxidation and neutrophil activity in ulcerative colitis patients. Antioxidant enzyme activities were markedly reduced compared to healthy controls.

Table 4. Oxidative Stress Markers and Antioxidant Status

Parameter	Ulcerative Colitis	Controls	p-value
MDA (nmol/mL)	6.8 ± 1.4	2.9 ± 0.8	<0.001
Nitric Oxide (µmol/L)	48.5 ± 10.2	21.7 ± 6.4	<0.001
MPO (U/L)	87.3 ± 16.5	35.8 ± 8.9	<0.001
SOD (U/mL)	2.8 ± 0.7	5.6 ± 1.1	<0.001
Catalase (U/mL)	31.2 ± 7.6	58.4 ± 10.3	<0.001
GPx (U/L)	39.8 ± 8.4	71.5 ± 12.6	<0.001
GSH (mg/dL)	3.6 ± 0.9	7.2 ± 1.4	<0.001

Inflammatory mediators including CRP, ESR, prostaglandin E2, and COX-2 expression were significantly elevated in patients with ulcerative colitis compared to controls.

Table 5. Inflammatory Mediators in Study Groups

Parameter	Ulcerative Colitis	Controls	p-value
CRP (mg/L)	18.6 ± 5.2	3.4 ± 1.1	<0.001
ESR (mm/hr)	35.8 ± 9.5	11.6 ± 3.8	<0.001
PGE2 (pg/mL)	212.4 ± 42.6	95.7 ± 20.4	<0.001
COX-2 Positive Expression (%)	72.5	12.5	<0.001

Histopathological examination demonstrated marked mucosal abnormalities in ulcerative colitis patients. Crypt distortion was observed in 81.3% of cases, goblet cell depletion in 76.3%, inflammatory cell infiltration in 92.5%, crypt abscesses in 63.8%, and mucosal ulceration in 47.5%.

Table 6. Histopathological Findings in Ulcerative Colitis Patients

Histopathological Feature	Frequency (n=80)	Percentage (%)
Crypt Distortion	65	81.3
Goblet Cell Depletion	61	76.3
Inflammatory Cell Infiltration	74	92.5
Crypt Abscess Formation	51	63.8
Mucosal Ulceration	38	47.5
Epithelial Damage	68	85.0

When stratified according to disease severity, progressive increases were observed in cytokine levels, oxidative stress markers, and inflammatory mediators from mild to severe disease.

Table 7. Biochemical Markers According To Disease Severity

Parameter	Mild (n=21)	Moderate (n=37)	Severe (n=22)	p-value
TNF-α (pg/mL)	35.2 ± 5.8	45.9 ± 7.2	56.8 ± 9.5	<0.001
IL-6 (pg/mL)	24.6 ± 4.7	33.8 ± 6.1	44.7 ± 7.9	<0.001
MDA (nmol/mL)	5.2 ± 0.9	6.8 ± 1.1	8.3 ± 1.4	<0.001
CRP (mg/L)	12.3 ± 3.2	18.8 ± 4.4	25.6 ± 5.7	<0.001

Correlation analysis demonstrated a strong positive association between disease activity score and serum TNF-α ($r = 0.71$, $p < 0.001$), IL-6 ($r = 0.68$, $p < 0.001$), MDA ($r = 0.74$, $p < 0.001$), and CRP ($r = 0.69$, $p < 0.001$). A significant negative correlation was observed between disease activity and antioxidant markers including SOD ($r = –0.63$, $p < 0.001$) and GSH ($r = –0.66$, $p < 0.001$).

Overall, patients with ulcerative colitis exhibited significantly elevated levels of pro-inflammatory cytokines, oxidative stress markers, and inflammatory mediators together with reduced antioxidant defenses. These

alterations were strongly associated with disease severity and histopathological evidence of gastrointestinal mucosal damage.

DISCUSSION

Ulcerative colitis is a chronic inflammatory condition in which the immune system becomes dysregulated resulting in an excess of oxidative stress, which then causes an exaggerated mucosal injury in the gastrointestinal tract. This study aimed to assess the contribution of cytokines, oxidative stress markers and inflammatory mediators in gastrointestinal dysfunction in patients with ulcerative colitis. The results showed very high levels of pro-inflammatory cytokines, increased oxidative stress, decreased antioxidant capacity, elevated activity of inflammatory mediators and severe histopathological changes all of which were closely related to the severity of the disease. In the current study, the serum levels of TNF α, IL-1 β, IL-6 and IL-17 were found to be significantly elevated in UC patients compared with healthy controls, while IL-10 levels were significantly decreased.

Lots of mucosal abnormalities such as crypt distortion, goblet cell depletion, inflammatory cell infiltration, crypt abscess formation, and epithelial damage were seen in the histopathological examination. These findings are hallmarks of the pathogenesis of ulcerative colitis and represent the chronic immune-mediated injury of the colonic mucosa. The absence of goblet cells could indicate a reduction in mucin production and hence a decrease in the protective mucus barrier. Abscesses of the crypts suggest active neutrophilic inflammation. Inflammatory infiltrates were commonly seen in this study and are consistent with the increased cytokine and myeloperoxidase levels biochemically. A similar histopathological pattern has been also reported by Magro et al. who urged the role of the mucosal architectural distortion and inflammatory infiltration in disease assessment. [21]

The results suggest an important role for the imbalance of pro- and anti-inflammatory cytokines in the pathogenesis of UC. It has been reported that TNF-α can compromise the integrity of epithelial barrier, enhance permeability of intestine, and induce recruitment of leukocytes into mucosa, thus sustaining the mucosal inflammation. In a similar fashion, IL-1β and IL-6 activate inflammatory signaling pathways and induce the synthesis of other cytokines and acute-phase reactants. Another clue to the role of Th17-mediated immune responses in chronic intestinal inflammation comes from the finding that the levels of IL-17 are also elevated. The current results corroborate the study by Neurath et al.found higher expression levels of pro-inflammatory cytokines in active ulcerative colitis and the role these cytokines play in the progression of the disease. [22]

The decreased production of IL-10 in this study further highlights the inadequacy of regulatory immune responses in controlling abnormal inflammation. IL-10 is a strong anti-inflammatory cytokine, which down-regulates the activation of macrophages and reduces the production of pro-inflammatory cytokines. Increased disease severity and/or deficiency or impaired activity of IL-10 have been associated with persistent mucosal inflammation. This is also noted by Kühn et al. (1993), who showed that the maintenance of intestinal immune homeostasis is critical for IL-10. [23]

One of the most important findings of the current study was that the level of oxidative stress markers such as malondialdehyde, nitric oxide and myeloperoxidase levels increased significantly while the level of the antioxidant enzymes was significantly reduced, including superoxide dismutase, catalase, glutathione peroxidase, and reduced glutathione. These findings suggest that there is serious oxidative imbalance in the patients with ulcerative colitis. Activated neutrophils and macrophages produce ROS which cause lipid peroxidation, protein oxidation and DNA damage and therefore result in epithelial dysfunction and impaired mucosal healing.

Malondialdehyde, a product of lipid peroxidation, was significantly higher in the patients, suggesting greater cell membrane oxidative damage in patients. Increased nitric oxide levels could be due to increased inducible nitric oxide synthase activity during inflammation, and increased myeloperoxidase activity due to the infiltration of neutrophils in inflamed colonic tissue. The observed deficiency in antioxidant defenses is also a confirmation of the importance of oxidative stress in ulcerative colitis. Under normal conditions, antioxidant enzymes in the intestine can shield the intestinal tissues from the damage caused by free radicals. But, when inflammation continues, it can overwhelm these protective mechanisms, causing continued tissue damage. Alzoghaibi (2013) have reported similar results, and observed

oxidative stress as a major factor implicated in intestinal inflammation and disease progression in IBS.[24]

The current research also showed significantly increased levels of inflammatory mediators such as CRP, ESR, prostaglandin E2 and expression of COX-2. The results indicate that continuing systemic and local inflammatory activity exists in patients with ulcerative colitis. Prostaglandin E2 is well known to cause vasodilation, vascular permeability and inflammatory pain responses, and COX-2 over expression is known to be responsible for the production of pro-inflammatory prostanoids in colonic mucosa. The greater the levels of CRP and ESR, the higher the systemic inflammation and the more active the disease. Consistent with this, Danese and Fiocchi also found increased markers of inflammation in active UC and suggested they promote chronic inflammation.[25]

One of the important findings of the current study was that as the disease progressed, the concentration of cytokines, oxidative stress markers, and inflammatory markers also increased. The patients with severe ulcerative colitis had significantly elevated levels of TNF-α, IL-6, malondialdehyde and CRP than the ones with mild and moderate ulcerative colitis. These findings suggest a worsening of disease activity leads to an increase in inflammatory and oxidative pathways. A correlation analysis was also performed and revealed strong positive correlations between disease activity scores and pro-inflammatory markers, and significant negative correlations between antioxidant enzymes and disease activity scores. These findings indicate that biochemical parameters could be helpful in assessing the severity of the disease and the response to therapy.

Physiologically, chronic inflammatory pathways activation directly causes gastrointestinal dysfunction. Cytokine production leads to changes in intestinal motility, changes in epithelial transport mechanisms, changes in nutrient absorption and changes in mucosal permeability. At the same time, oxidative stress impairs enterocytes and tight junction proteins, adversely affecting barrier function. Therefore, an interaction between immune dysregulation, oxidative injury and inflammatory mediator release perpetuates a vicious cycle of chronic inflammation and gastrointestinal symptoms in ulcerative colitis. The results of the present study confirm that ulcerative colitis is a multifactorial disease and suggest that cytokines, oxidative stress markers and inflammatory mediators have interconnected roles in disease pathogenesis. The strong correlations among these biomarkers and disease severity could provide the basis for using them for disease monitoring and may guide specific therapeutic interventions designed to restore immune balance and minimize oxidative damage**.**

CONCLUSION

Ulcerative colitis is associated with significant alterations in cytokine profiles, oxidative stress markersand inflammatory mediators, all of which contribute to gastrointestinal dysfunction and mucosal injury. Elevated levels of pro-inflammatory cytokines, increased oxidative stress, reduced antioxidant defenses, and enhanced inflammatory mediator activity were strongly associated with disease severity and histopathological changes. These findings highlight the complex interplay between immune dysregulation, oxidative damage, and chronic inflammation in the pathogenesis of ulcerative colitis. Assessment of these biomarkers may provide valuable insights into disease activity, facilitate early identification of severe disease, and support the development of targeted therapeutic strategies aimed at reducing inflammation, restoring redox balance, and improving clinical outcomes in affected patients.

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