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**MINIREVIEWS**

- 6373** Current status of associating liver partition with portal vein ligation for staged hepatectomy: Comparison with two-stage hepatectomy and strategies for better outcomes
Au KP, Chan ACY

ORIGINAL ARTICLE**Basic Study**

- 6386** Ubiquitin-conjugating enzyme E2T knockdown suppresses hepatocellular tumorigenesis *via* inducing cell cycle arrest and apoptosis
Guo J, Wang M, Wang JP, Wu CX
- 6404** Mitochondrial metabolomic profiling for elucidating the alleviating potential of *Polygonatum kingianum* against high-fat diet-induced nonalcoholic fatty liver disease
Yang XX, Wei JD, Mu JK, Liu X, Li FJ, Li YQ, Gu W, Li JP, Yu J

Case Control Study

- 6416** Altered profiles of fecal metabolites correlate with visceral hypersensitivity and may contribute to symptom severity of diarrhea-predominant irritable bowel syndrome
Zhang WX, Zhang Y, Qin G, Li KM, Wei W, Li SY, Yao SK

Retrospective Cohort Study

- 6430** Segmental intrahepatic cholestasis as a technical complication of the transjugular intrahepatic porto-systemic shunt
Bucher JN, Hollenbach M, Strocka S, Gaebelein G, Moche M, Kaiser T, Bartels M, Hoffmeister A

Retrospective Study

- 6440** Serum amyloid A levels in patients with liver diseases
Yuan ZY, Zhang XX, Wu YJ, Zeng ZP, She WM, Chen SY, Zhang YQ, Guo JS
- 6451** Application of preoperative artificial neural network based on blood biomarkers and clinicopathological parameters for predicting long-term survival of patients with gastric cancer
Que SJ, Chen QY, Qing-Zhong, Liu ZY, Wang JB, Lin JX, Lu J, Cao LL, Lin M, Tu RH, Huang ZN, Lin JL, Zheng HL, Li P, Zheng CH, Huang CM, Xie JW

Observational Study

- 6465** Metabolic syndrome attenuates ulcerative colitis: Correlation with interleukin-10 and galectin-3 expression
Jovanovic M, Simovic Markovic B, Gajovic N, Jurisevic M, Djukic A, Jovanovic I, Arsenijevic N, Lukic A, Zdravkovic N

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Observational Study

Metabolic syndrome attenuates ulcerative colitis: Correlation with interleukin-10 and galectin-3 expression

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Abstract

BACKGROUND

Ulcerative colitis (UC) is a chronic disease characterized by inflammation of intestinal epithelium, primarily of the colon. An increasing prevalence of metabolic syndrome (MetS) in patients with UC has been documented recently. Still, there is no evidence that MetS alters the course of the UC.

AIM

To test the influence of the MetS on the severity of UC and the local and systemic immune status.

METHODS

Eighty nine patients with *de novo* histologically confirmed UC were divided in two groups, according to ATP III criteria: Group without MetS (no MetS) and group with MetS.

RESULTS

reported.

Data sharing statement: All data used to support the findings of this study are included within the article. Technical appendix, statistical code, and dataset available from the corresponding author at bojana.simovicmarkovic@medf.kg.ac.rs.

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Clinically and histologically milder disease with higher serum level of immunosuppressive cytokine interleukin-10 (IL-10) and fecal content of Galectin-3 (Gal-3) was observed in subjects with UC and MetS, compared to subjects suffering from UC only. This was accompanied with predominance of IL-10 over pro-inflammatory cytokines tumor necrosis factor α (TNF- α), interleukin-6 (IL-6), and interleukin-17 (IL-17) in the sera as well as Gal-3 over TNF- α and IL-17 in feces of UC patients with MetS. Further, the patients with both conditions (UC and MetS) had higher percentage of IL-10 producing and Gal-3 expressing innate and acquired immune cells in lamina propria.

CONCLUSION

Local dominance of Gal-3 and IL-10 over pro-inflammatory mediators in patients with MetS may present a mechanism for limiting the inflammatory process and subsequent tissue damage in UC.

Key words: Ulcerative colitis; Metabolic syndrome; Galectin-3; Inflammation; Interleukin-10; Systemic immune response

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Core tip: Metabolic syndrome (MetS) is among most common ulcerative colitis (UC) comorbidity. Still, there is no data considering whether the comorbidity of UC and MetS affects the pathology of UC. The aim of this study was to investigate the effects of MetS on severity and immunopathology of UC. Our results revealed that patients with MetS have milder form of UC accompanied with higher level of Galectin-3 and interleukin-10 and altered functional phenotype and intracellular content of lymphocytes infiltrating affected tissue.

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INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD), characterized by inflammation of the intestinal lamina propria, starting from the rectum and potentially involving the whole colonic mucosa. The course of UC is unpredictable, characterized by spontaneous remission and relapses^[1,2]. There is evidence suggesting that the disease occurs in genetically susceptible subjects, triggered by environmental factors, which lead to an exaggerated and uncontrolled immune response to the intestinal flora^[1].

It is established that many other diseases are associated with UC such as rheumatoid arthritis, multiple sclerosis, lupus, psoriasis, hypothyroidism, and metabolic syndrome (MetS)^[3-6]. Among these diseases, the MetS is the most common comorbidity with pathogenic, clinical and therapeutic implications^[3]. MetS represents significant public health concern for its high global prevalence and association with an increased risk for developing chronic diseases^[7]. In addition, MetS has been found to have suppressive effect on the immune response, which is confirmed by the higher incidence of unsuccessful vaccinations and complications in infections registered in patients with MetS^[8,9].

There is no data considering whether the comorbidity of UC and MetS affects the pathology of UC^[3]. Although specific studies dealing with the very mechanism of this aspect have not yet been implemented, this phenomenon deserves attention.

Despite the sustained interest of the researchers in Galectin-3 (Gal-3) and the pronounced and constitutive expression of this molecule in the epithelium of the digestive tract of mice and humans, only a few studies have addressed the possible role of this member of β -galactoside binding proteins in IBDs^[10,11]. Gal-3 is produced mainly by monocytes/macrophages and in UC is expressed on CD68⁺ colon-

infiltrating macrophages^[12,13].

The aim of our study was to investigate the effects of MetS on severity and immunopathology of UC.

Herewith, we provide the evidence that patients with MetS have milder form of UC accompanied with higher fecal and serum level of Gal-3 and altered functional phenotype and intracellular content of lymphocytes infiltrating affected tissue.

MATERIALS AND METHODS

Study population

Eighty nine patients (52 male and 37 female), between 21 and 80 years of age, with *de novo* histologically confirmed UC, were included in observational cross-sectional study. Recruited UC patients were divided in two groups, using ATP III criteria for the diagnosis of MetS: Group without MetS (no MetS) and group with MetS^[25]. According to these criteria, for the diagnosis of the MetS, it is necessary that patients have at least 3 of 5 disorders: Disglycemia (fasting plasma glucose higher than 5.5 mmol/L and/or 2 h-post load plasma glucose higher than 7.8 mmol/L or active treatment of disglycemia), arterial hypertension (arterial tension higher than 130/85 mmHg or active treatment), central type of obesity, and high-density lipoprotein cholesterol below and triglycerides higher than reference values. All patients within UC + MetS group fulfill all of these criteria.

In each individual case, the diagnosis and assessment of the severity of UC was determined by histological and clinical scores^[14-18]. All endoscopies were performed by the same experienced endoscopist (NZ) thus ensuring uniformity in mucosal assessment. The severity of endoscopic lesions was defined using the Mayo endoscopic sub-score that includes erosions/ulcerations, mucosal erythema, visibility of vascular pattern and bleeding provoked/spontaneous, with scores ranging from 0 to 3^[17,18]. The clinical score was determined using the *Truelove* and *Witts* clinical activity index and the Mayo clinical index^[15,19,20]. Histological score was determined based on Geboes grading^[16] and histological sections were examined in a blinded manner by two pathologists, independently. Sections were analyzed for architectural changes, crypt destruction, erosion of the mucous membranes, eosinophilic infiltration, neutrophilic infiltration and chronic inflammatory infiltration. Patients with UC were classified according to Montreal classification of the localization of the UC lesions, as E1 (proctitis), E2 (left-sided colitis), or E3 (pancolitis)^[21]. Thirty-four patients had detectable extraintestinal manifestations (fatty liver metamorphosis, primary sclerosing cholangitis, cholelithiasis, bone-joint changes, hematopoietic changes, changes in the reproductive system, eye changes, and dermatologic manifestations- pyoderma gangrenosum or erythema nodosum).

For all study participants, demographic and clinical data were entered in SPSS database. Patients with previously diagnosed colorectal cancer, as well as patients with Crohn's disease or UC who were previously treated with antibiotics, aminosalicylates, corticosteroids, immunosuppressive agents, statins, and biological therapy were not included in the study. All patients had complete medical history, including physical examination, routine laboratory tests and diagnostic imaging (chest X-ray, abdominal ultrasound, abdominal computed tomography scan, and endoscopy). The study was conducted at Center for Gastroenterology, Clinical Center of Kragujevac and Center for Molecular Medicine and Stem Cell Research, Faculty of Medical Sciences, University of Kragujevac, Serbia and was approved by Ethics Committees of these institutions. Additionally, adherence was made to the Principle of Good Clinical Practice and the Declaration of Helsinki at all times. All patients gave their informed consent for blood and tissue analysis. Patients were under continuous medical supervision at the Clinical Center Kragujevac.

Measurements of fecal and serum cytokines levels

Fecal samples were prepared as previously described^[22]. Briefly, 1g of fecal samples was diluted, mixed, and homogenized in 5mL of protease inhibitor cocktail (Sigma Aldrich, St. Louis, MO, United States; P83401)^[22]. Blood was obtained from patients and healthy control subjects at 8 am and serums were separated, collected and stored at 80 °C before use. Concentrations of tumor necrosis factor α (TNF- α), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-17 (IL-17), and Gal-3 were measured in serum and fecal supernatants of UC patients by using commercially available ELISA tests, according to the manufacturer's instructions.

Flow cytometry analysis of colon infiltrating cells in patients with UC

Immune cells were isolated from colons of patients with UC, as previously

described^[23,24]. Briefly, after biopsy, tissue samples were washed and incubated in medium with 1 mmol/L EDTA for 10 min at 37 °C with gentle shaking to remove intestinal epithelial cells. Further, specimens were incubated for 20-30 min in 2 mL Dulbecco's Modified Eagle Medium (Lonza, Basel, Swiss) with 1 mg/mL collagenase type I, 0.1 mg/mL DNase and 1 mg/mL hyaluronidase (Sigma-Aldrich, St-Louis, MO, United States, respectively) without fetal bovine serum at 37 °C. Cells were washed and finally submitted to Ficoll density gradient centrifugation for 20 min at 690 g. The interphase was carefully removed. Single-cell suspensions were obtained and the cells were washed twice with FACS medium.

For flow cytometry, 1×10^6 cells per sample were incubated with anti-human CD4, CD8, CD56, and Gal-3 antibodies conjugated with fluorescein isothiocyanate (FITC; BD Biosciences, Franklin Lakes, NJ, United States), phycoerythrin (PE; BD Biosciences), Peridinin Chlorophyll A Protein (PerCP; BD Biosciences), or allophycocyanin (APC; BD Biosciences). For the intracellular staining, cells were stimulated with phorbol myristate acetate and ionomycin for 4 h at 37 °C with the addition of 1 µg/mL Golgi plug. Intracellular staining for IL-10 and Foxp3 was performed using the BD Bioscience fixation/ permeabilization buffer kit. Flow cytometry was conducted on a BD Biosciences FACSCalibur and the data were analyzed using FlowJo (Tree Star).

Statistical analysis

Data were analyzed using commercially available software (SPSS version 22). Results were analyzed using Student's *t* test, Mann-Whitney *U* test, Chi-squared test or Kruskal-Wallis test where appropriate. Data are presented as mean \pm standard error of the mean and the difference was considered significant when $P < 0.05$.

RESULTS

Clinical feature and MetS in patients with UC

Laboratory findings and clinical features of all patients are presented in Table 1. We have compared laboratory findings. Significantly lower white blood cells count (WBC) and increased blood cholesterol, triglycerides, low-density lipoprotein, aspartateaminotransferase, alanine aminotransferase, as well as urea and creatinine were detected in UC patients with MetS, compared to UC patients without MetS (Table 1). There was no significant difference in platelet count and in the concentration of hemoglobin, albumin and globulin between patients with MetS and without MetS (Table 1).

Patients with MetS have milder form of UC

Despite the fact that cholesterol, triglycerides and liver enzymes were higher in MetS, the local findings of UC were milder in MetS + UC patients. Patients with UC and MetS had significantly lower Mayo endoscopic subscore ($P = 0.038$; Figure 1A) and Mayo clinical score ($P = 0.005$; Figure 1B). Within these group of patients (UC + MetS), Mayo ES 1 was recorded in 56.95% patients, while Mayo CS 1 was recorded in 59.72% patients. Therefore, the Mayo ESs and CSs classified the majority of the patients with MetS as having mild UC. We have also registered lower Truelove and Witts clinical score of disease in patients with MetS, but the difference did not reach statistical significance (Figure 1C). Endoscopic data are illustrated in Figure 1D. Endoscopic findings in patients with UC + MetS revealed normal mucosa or slight mucosal erythema, decreased vascular pattern, mild friability, comparing to frank friability, marked erythema, absent vascular pattern and erosions that are characteristic for UC patients without MetS (Figure 1D). Clinical and endoscopic data are supported by pathohistological findings (Figure 2): Chronic inflammatory infiltration ($P = 0.044$; Figure 2A) and eosinophilic infiltration ($P = 0.031$; Figure 2B) in affected tissue of UC patients with MetS were milder than in UC patients without MetS. Neutrophil infiltration, crypt destruction, erosion of the mucous membranes, architectural changes were also milder in UC patients with MetS, but these differences did not reach statistical significance (Figure 2C-F). Representative pathohistological characteristics are shown in Figure 2G.

MetS affects inflammatory and regulatory cytokines in sera and feces of patients with UC

We have assessed concentration of pro and anti-inflammatory cytokines in sera and fecal liquid fraction of all UC patients (Figure 3). Patients with MetS had significantly lower serum level of pro-inflammatory cytokine IL-17 ($P = 0.045$; Figure 3A), while immunosuppressive IL-10 was significantly higher ($P = 0.045$; Figure 3B). There was

Table 1 Clinical and laboratory findings in ulcerative colitis patients

Characteristics	All (n = 89)	Without MetS (n = 17)	With MetS (n = 72)	P value
Age (yr)				
Median (range)	50 (21-80)	34 (23-54)	53 (21-80)	0.001
Gender, n (%)				
Male	52 (58.43)	11 (64.71)	41 (56.95)	> 0.05
Female	37 (41.57)	6 (35.29)	31 (43.05)	
Smoking status, n (%)				
Yes	42 (47.19)	7 (41.18)	35 (48.61)	> 0.05
No	47 (52.81)	10 (58.82)	37 (51.39)	
Localization (PT/LC/PC)	13/51/25	3/7/7	10/44/18	> 0.05
Extraintestinal manifestations (+/-)	34/55	7/10	27/45	> 0.05
WBC (10 ⁹ /L)	8.18 ± 0.48	10.27 ± 1.04	7.69 ± 0.49	0.025
Platelet (10 ⁹ /L)	377.2 ± 11.4	400.80 ± 28.10	371.60 ± 11.60	> 0.05
Hb (g/L)	125.7 ± 1.97	120.90 ± 4.10	126.80 ± 2.10	> 0.05
Cholesterol (mmol/L)	4.91 ± 0.18	3.71 ± 0.21	5.19 ± 0.19	0.001
Triglycerides (mmol/L)	1.63 ± 0.11	0.89 ± 0.07	1.81 ± 0.11	0.001
HDL (mmol/L)	1.54 ± 0.07	1.73 ± 0.14	1.50 ± 0.07	> 0.05
LDL (mmol/L)	2.62 ± 0.18	1.49 ± 0.28	2.89 ± 0.19	0.001
AST (U/L)	30.08 ± 1.87	20.65 ± 2.27	32.31 ± 2.07	0.002
ALT (U/L)	33.19 ± 4.50	23.29 ± 2.24	35.53 ± 5.28	0.039
GGT (U/L)	36.00 ± 6.70	20.94 ± 2.51	39.56 ± 7.88	> 0.05
Urea (mmol/L)	5.13 ± 0.30	3.69 ± 0.43	5.47 ± 0.33	0.014
Creatinine (μmol/L)	81.89 ± 2.79	68.71 ± 3.31	85.00 ± 3.09	0.014
Albumin (g/L)	41.33 ± 0.88	41.88 ± 0.88	41.19 ± 0.40	> 0.05
Globulin (g/L)	27.44 ± 0.37	27.82 ± 0.59	27.35 ± 0.42	> 0.05

Values are expressed as mean ± standard error of the mean. PT: Proctitis; LC: Left-sided colitis; PC: Pancolitis; MetS: Metabolic syndrome; WBC: White blood cells count; Hb: Hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; AST: Aspartateaminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transpeptidase.

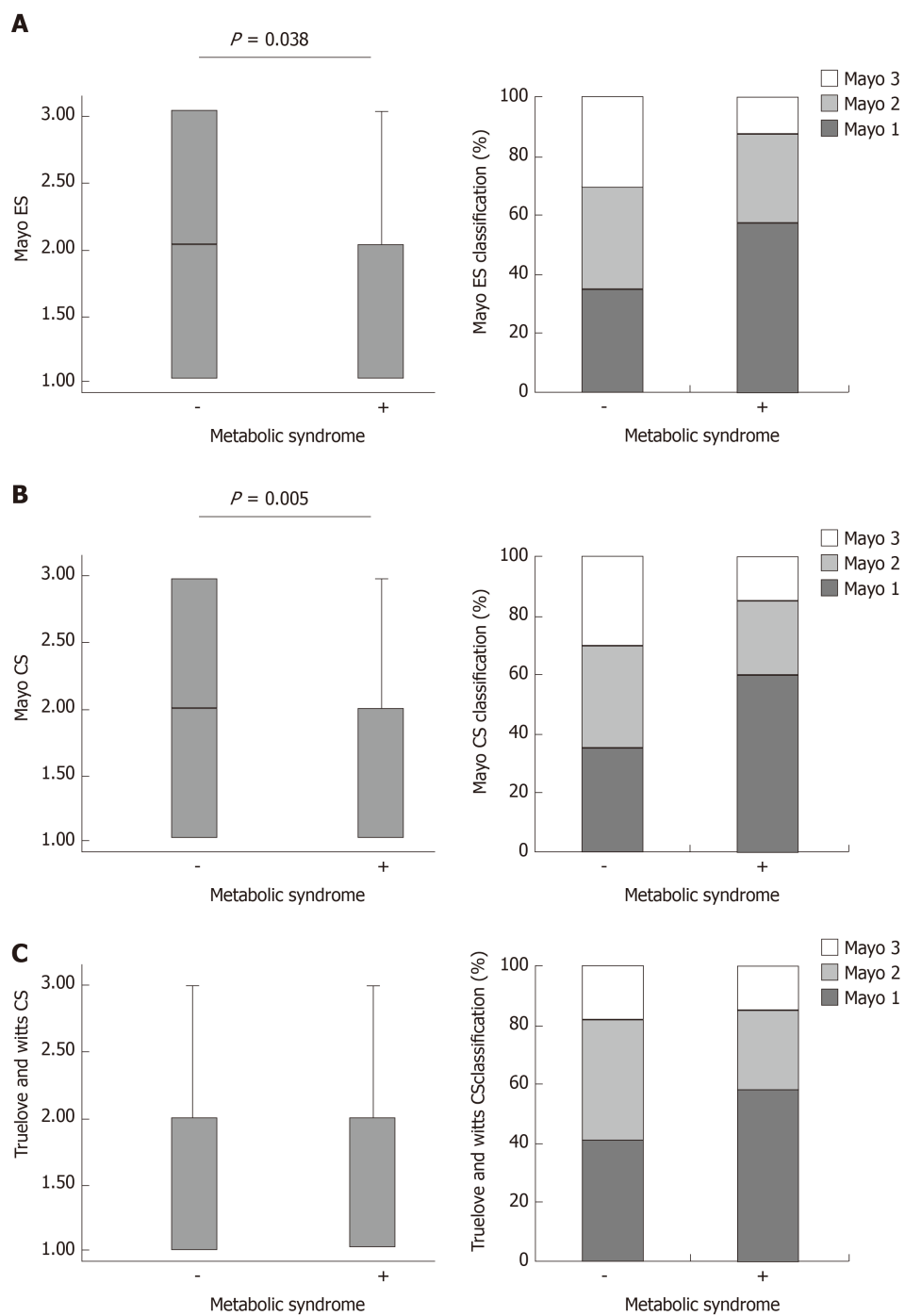
no significant difference in systemic concentration of proinflammatory TNF-α between patients with and without MetS ($P = 0.542$; **Figure 3C**).

It is considered that the ratio of counter-regulatory cytokines can be relevant indicator of disease activity^[22]. Ratios of TNF-α/IL-10, IL-6/IL-10, and IL-17/IL-10 were significantly lower in the group of patients with MetS ($P = 0.014$; $P = 0.018$; $P = 0.017$; respectively; **Figure 3D**).

In feces samples, there was no significant difference in the concentration of any tested cytokine. However, there was strikingly higher level of Gal-3 in UC + MetS patients, compared to UC patients (**Figure 3E**). Accordingly, ratios of Gal-3 and the two inflammatory cytokines (TNF-α and IL-17, were significantly higher in UC + MetS patients in comparison to UC patients ($P = 0.039$; $P = 0.029$; respectively; **Figure 3F**).

MetS alters inflammatory and regulatory cytokines in sera and feces in all endoscopic, clinical and histopathological stages of UC

We further analyzed serum level of cytokines of interest and fecal level of Gal-3 in groups with and without MetS in especially same clinical, endoscopic and histopathological stage of UC, respectively. We detected significantly lower serum level of IL-17 in MetS patients with Mayo endoscopic subscore 1 ($P = 0.049$) and 3 ($P = 0.017$), Mayo clinical score 2 ($P = 0.031$) and 3 ($P = 0.032$), Truelove and Witts clinical score 2 ($P = 0.027$) and 3 ($P = 0.024$) as well as chronic inflammatory infiltration score 3 ($P = 0.030$), in comparison to UC patients without MetS but in exactly the same scores (**Figure 4A**). There was no significant difference in systemic concentration of TNF-α between patients with and without MetS in same endoscopic, clinical and histopathological scores (data not shown). Higher serum level of IL-10 was detected in MetS patients with Mayo endoscopic subscore 2 ($P = 0.028$) and 3 ($P = 0.029$), Mayo clinical score 1 ($P = 0.031$), all 3 Truelove and Witts clinical scores ($P = 0.035$; $P = 0.048$; $P = 0.031$, respectively) and chronic inflammatory infiltration score 1 ($P = 0.042$) (**Figure 4B**). Higher level of Gal-3 in feces was observed in MetS patients with all



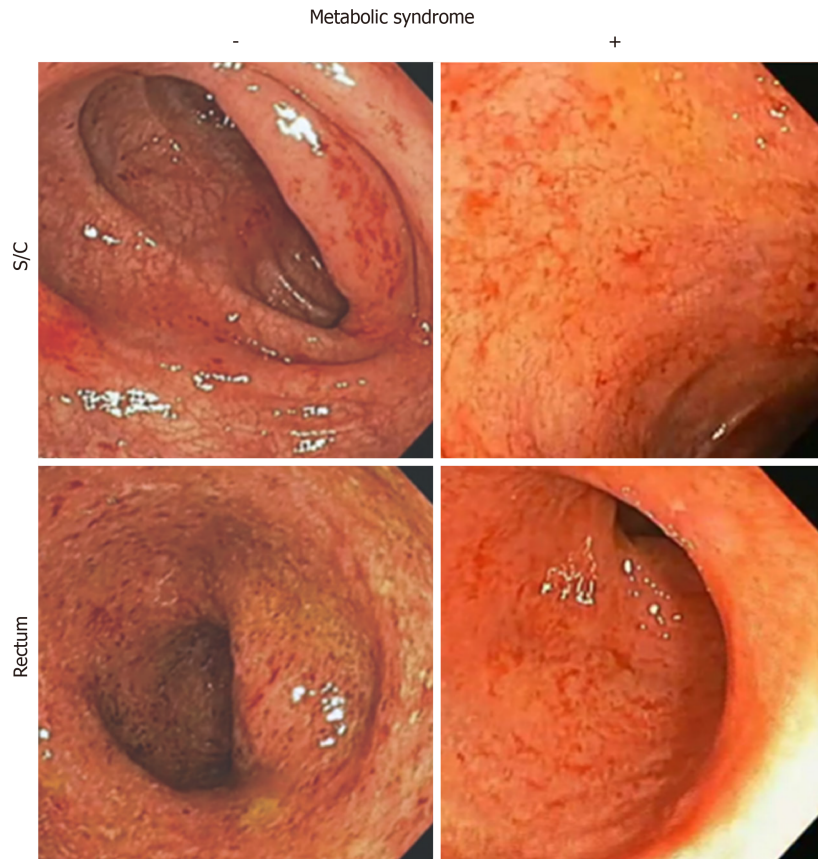
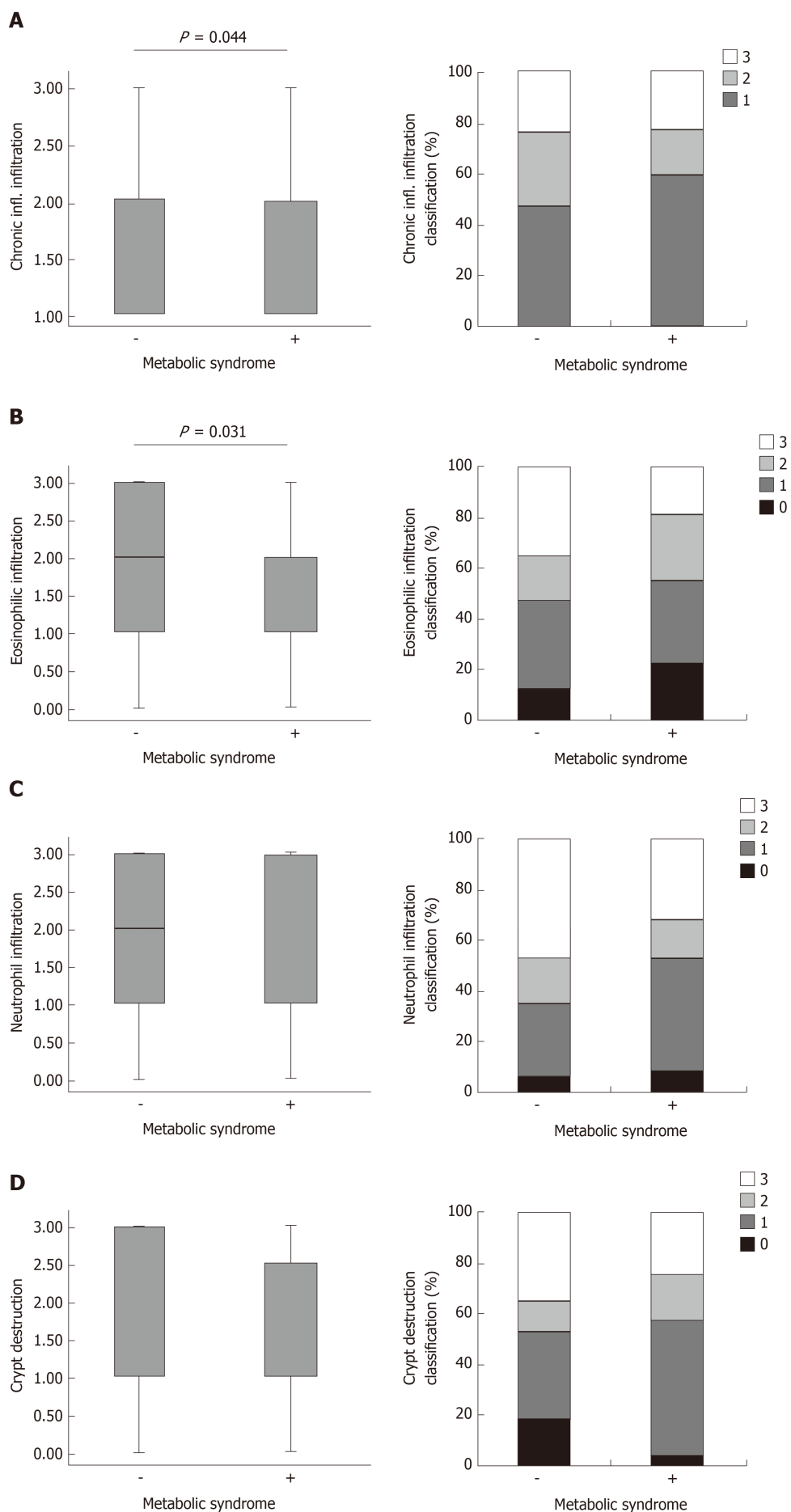
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Figure 1 Clinical feature of ulcerative colitis in patients with metabolic syndrome. A: Comparison of Mayo endoscopic subscore between ulcerative colitis (UC) patients without and with metabolic syndrome (MetS) was performed by the Chi-squared test or Kruskal-Wallis test and *P* values are presented above the box plots. B: Mayo clinical scores (CS) between UC patients without and with MetS was performed by the Chi-squared test or Kruskal-Wallis test and *P* values are presented above the box plots. C: Truelove and Witts CS between UC patients without and with MetS was performed by the Chi-squared test or Kruskal-Wallis test and *P* values are presented above the box plots. D: Representative images was presented. ES: Endoscopic subscore; CS: Clinical scores.

Mayo endoscopic subscores ($P = 0.038$; $P = 0.028$; $P = 0.038$, respectively), Mayo clinical scores ($P = 0.017$; $P = 0.035$; $P = 0.019$, respectively) Truelove and Witts clinical scores ($P = 0.038$; $P = 0.008$; $P = 0.017$, respectively) and chronic inflammatory infiltration scores ($P = 0.013$; $P = 0.048$; $P = 0.020$, respectively) (Figure 4C). The same trend was observed for cytokines of interest in all other histopathological scores (eosinophilic infiltration, neutrophil infiltration, crypt destruction, erosion of the mucous membranes, architectural changes), but the difference did not reached statistical significance (data not shown).

Predominance of regulatory cells in colon of patients with UC and MetS

Flow cytometric analysis of colon infiltrating lymphocytes showed no significant differences in the percentage of CD56⁺ NK cells, CD3⁺CD56⁺ NKT cells, CD4⁺Th cells and CD19⁺ B cells (data not shown). Significantly lower percentage of CD8⁺ T cells ($P = 0.035$) and higher percentage of CD4⁺Foxp3⁺ regulatory T cells ($P = 0.025$) were detected in UC patients with MetS (Figure 5A and B). Interestingly, percentage of both, CD3⁺CD56⁺ NKT cells and CD8⁺Foxp3⁺ regulatory T cells expressing Gal-3 was significantly higher in UC + MetS patients ($P = 0.029$; $P = 0.034$; respectively; Figure 5C and D). Finally, we analyzed cytokine content in infiltrating immune cells. We have not found the difference in the percentage of infiltrating Th cells, CD8⁺ T cells and NK cells producing pro-inflammatory cytokines IFN- γ and IL-17 (data not shown). There was higher percentage of regulatory innate CD56⁺ NK cells and CD4⁺Th cells producing IL-10 in lamina propria of patients with UC + MetS *vs* UC only ($P = 0.034$; $P = 0.012$; respectively; Figure 5E and F).



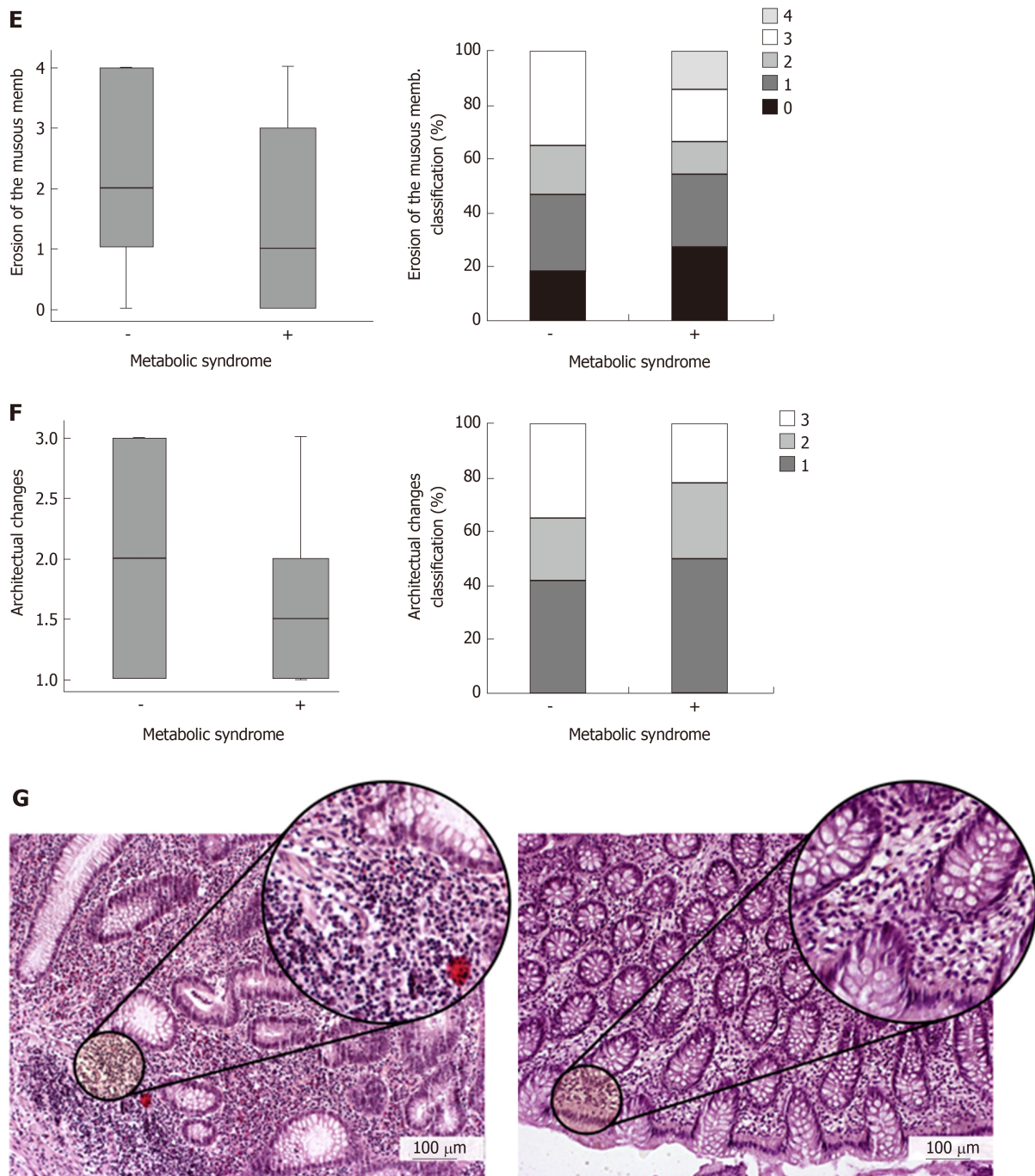


Figure 2 Pathohistological parameters of ulcerative colitis in patients with metabolic syndrome. A-G: Histological score was analyzed for chronic inflammatory infiltration, eosinophilic infiltration, neutrophilic infiltration, crypt destruction, erosion of the mucous membranes and architectural changes. Ulcerative colitis patients without metabolic syndrome (MetS) confirmed the presence of chronic inflammatory infiltration and eosinophilic infiltration in the injured colons (down left panel, 200 x). On the contrary, damage of colon tissue in patients with MetS was manifested by resolution of inflammation, less chronic inflammatory infiltration and eosinophilic infiltration in the colon (down right panel, 200 x).

DISCUSSION

We analyzed the effect of MetS as comorbidity in patients with UC. In this study we included *de novo* histologically confirmed UC patients without previous treatment with antibiotics, aminosalicylates for at least two mo, without corticosteroids, statins, immunosuppressive agents as well as any kind of biological therapy previously. The limitation of our work is that this was cross-sectional study with only one time point evaluation. Patients with MetS are significantly older than patients without MetS (Table 1). As all patients were *de novo* diagnosed with UC and MetS, we could not elucidate the influence of MetS durability on UC severity. Our findings suggest that in general MetS attenuates inflammatory and immunopathogenic correlates of UC. Protective effect of MetS is reflected by clinical and endoscopic score (Figure 1) as well

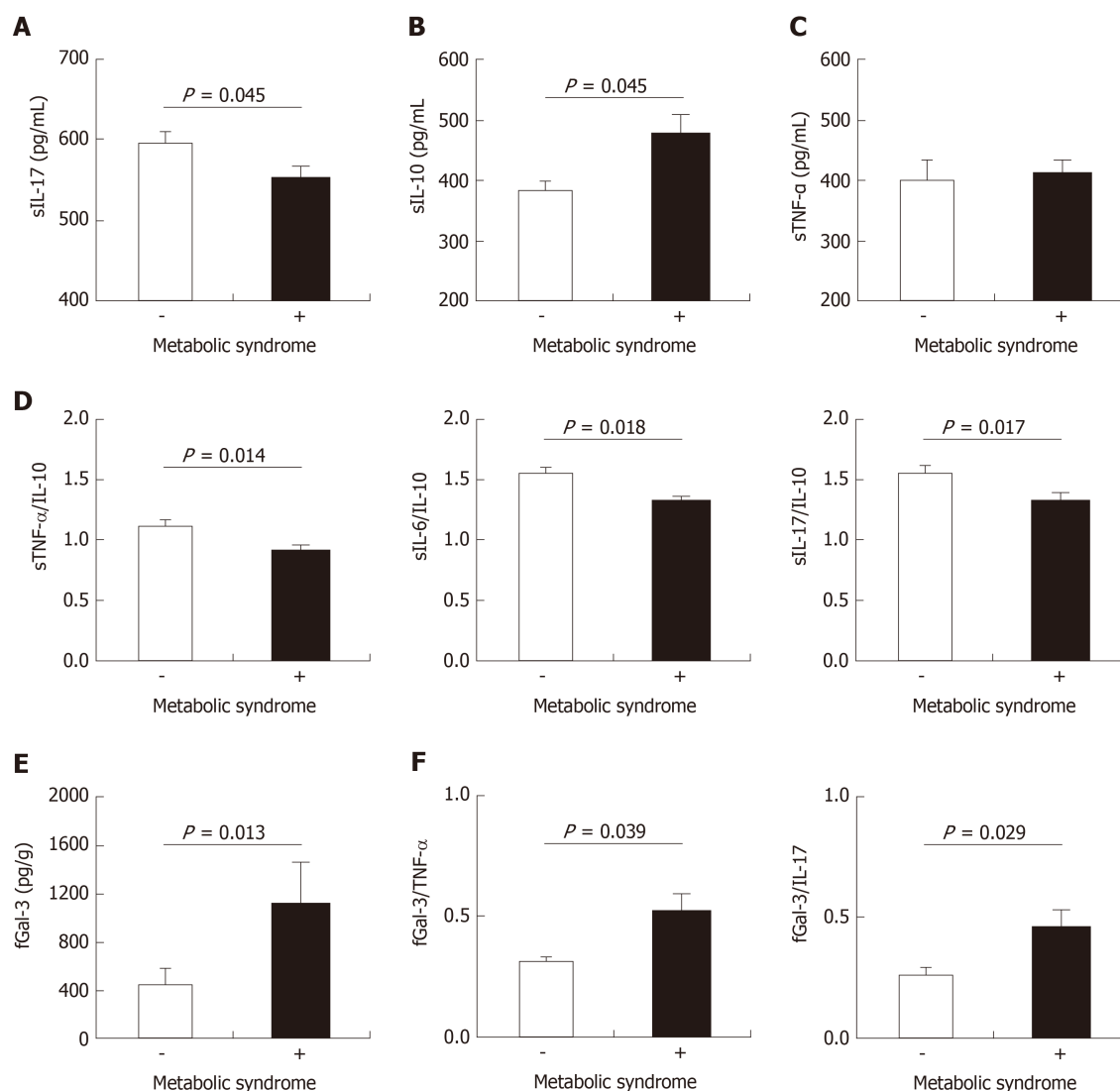
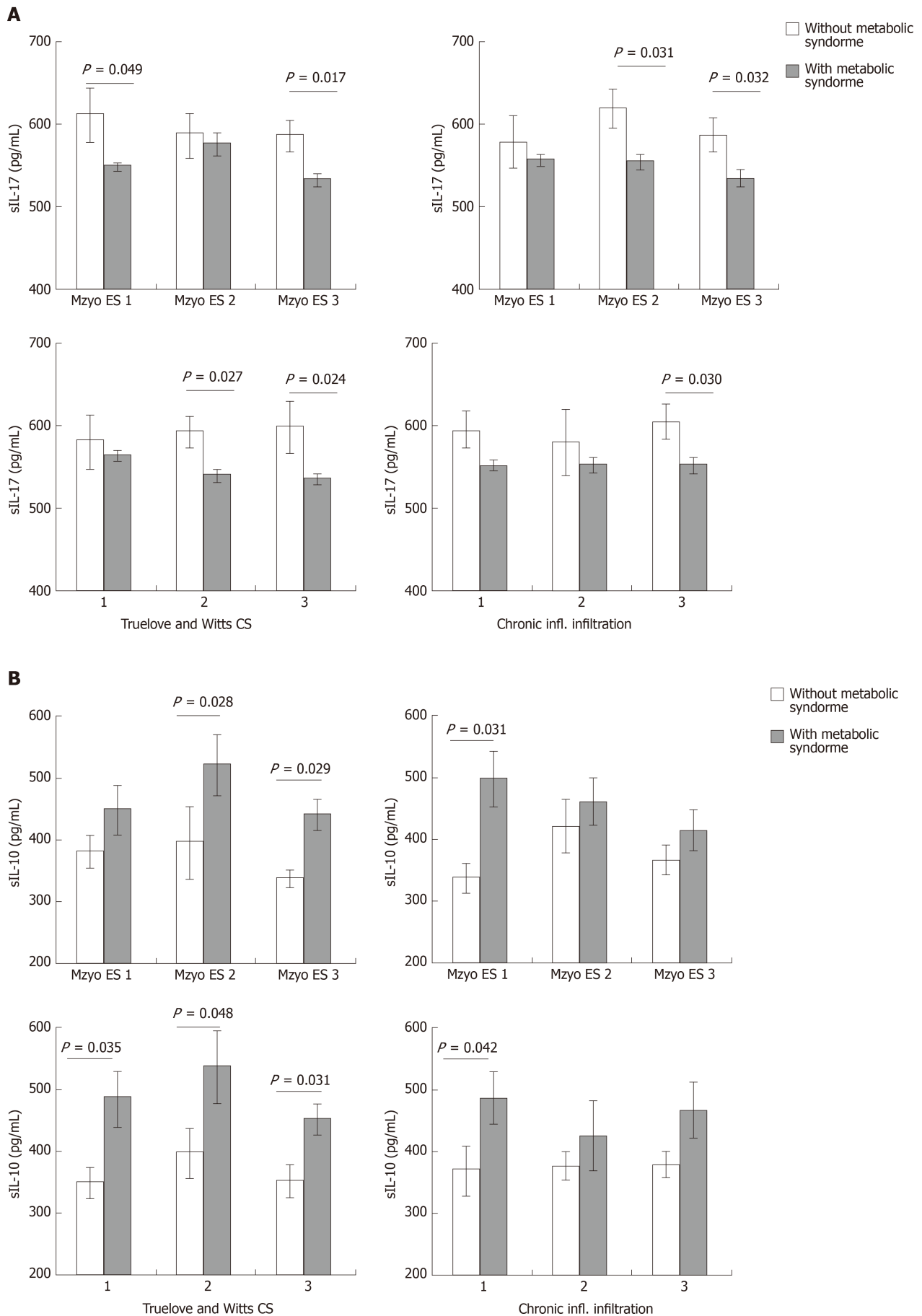


Figure 3 Systemic and local cytokine profile of ulcerative colitis patients according to metabolic syndrome. A: Interleukin-17 (IL-17) were measured by ELISA in the sera of ulcerative colitis (UC) patients without and with metabolic syndrome (MetS). B: Interleukin-10 (IL-10) were measured by ELISA in the sera of UC patients without and with MetS. C: Tumor necrosis factor α (TNF- α) were measured by ELISA in the sera of UC patients without and with MetS. D: sTNF- α /IL-10, sIL-6/IL-10 and sIL-17/IL-10 ratios were evaluated for each patient, separately. E: Concentration of fecal Galectin-3 (Gal-3) was determined in UC patients without and with MetS. F: Ratio of fGal-3/TNF- α and fGal-3/IL-17 in UC patients according to MetS was evaluated for each patient, separately. Patients with UC were divided into two groups: without and with metabolic syndrome (negative "-" or positive "+"). The Student's *t* or Mann-Whitney *U* test was applied as appropriate to evaluate statistical significant differences. TNF- α : Tumor necrosis factor α ; IL-17: Interleukin-17; IL-10: Interleukin-10; Gal-3: Galectin-3.

as on histopathology (Figure 2), phenotype of inflammatory cells (Figure 4) and cytokine levels in liquid fraction of feces (Figure 3).

It is believed that immunopathology is the main mechanism in the genesis and progression of UC^[1]. The destruction of the intestinal epithelium, which is directly related to the severity of the disease, is due to an intense immune response^[26]. There are ample evidences that both, cells of innate and acquired immunity participate in immunopathogenesis of UC^[1,2]. This is clearly showed in human^[11-13] and experimental studies in animal models by us^[10] and others^[27-29]. It appears that MetS favors immunosuppressive environment in diseased colon, as evidenced by increased percentage of Foxp3⁺ regulatory T cells (Figure 5) and IL-10 production (Figures 3 and 5). The lower systemic values of pro-inflammatory IL-17, with higher IL-10 values, and lower ratios of TNF- α /IL-10, IL-6/IL-10, and IL-17/IL-10 (Figure 3A-C) support the prevalence of immunosuppressive over pro-inflammatory mediators in the serum of subjects with MetS. In order to clarify the correlation between UC and cytokine levels in patients with or without MetS, we analyzed serum cytokines and fecal Gal-3 in the same endoscopic, clinical or histopathological score. Significantly lower serum level of IL-17 with higher IL-10 values in sera and Gal-3 values in feces in MetS patients with almost all Mayo endoscopic subscores, Mayo clinical scores, Truelove and Witts clinical scores and chronic inflammatory infiltration scores (Figure 4)



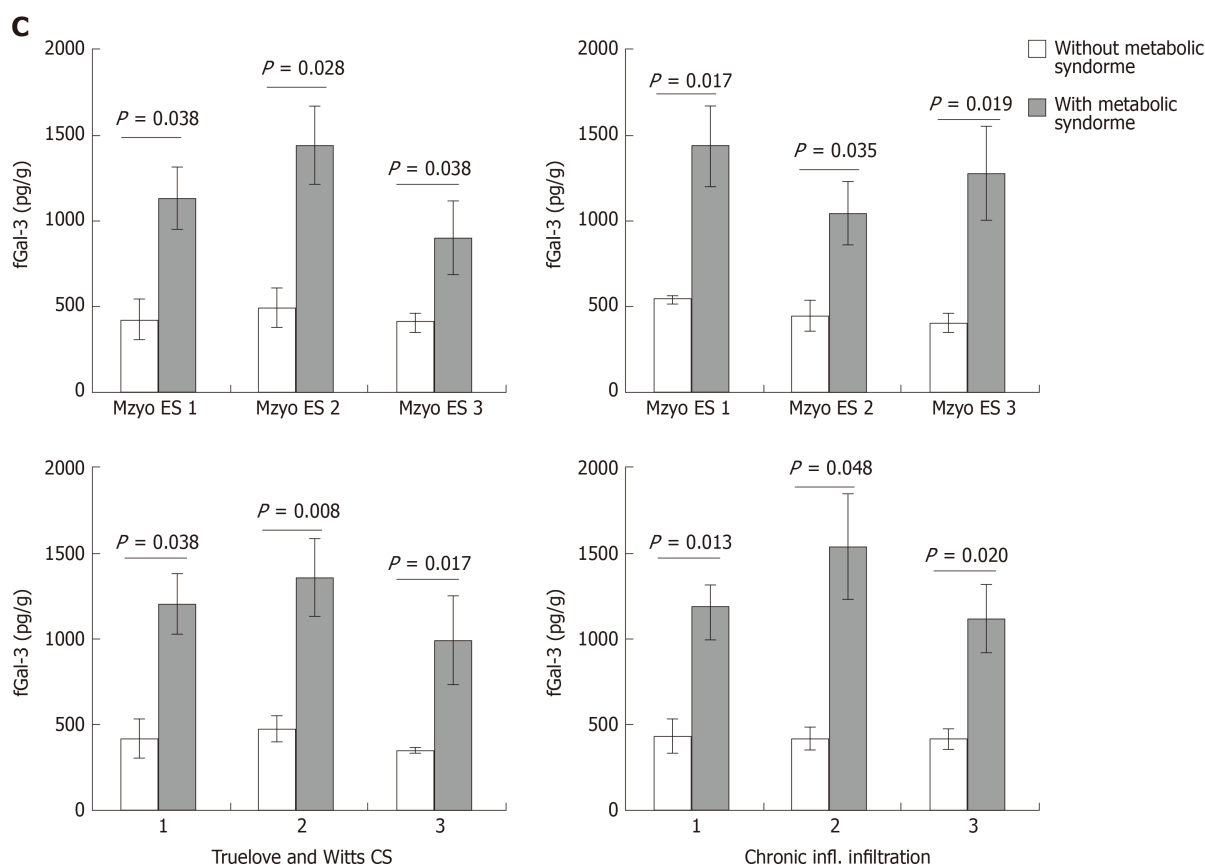


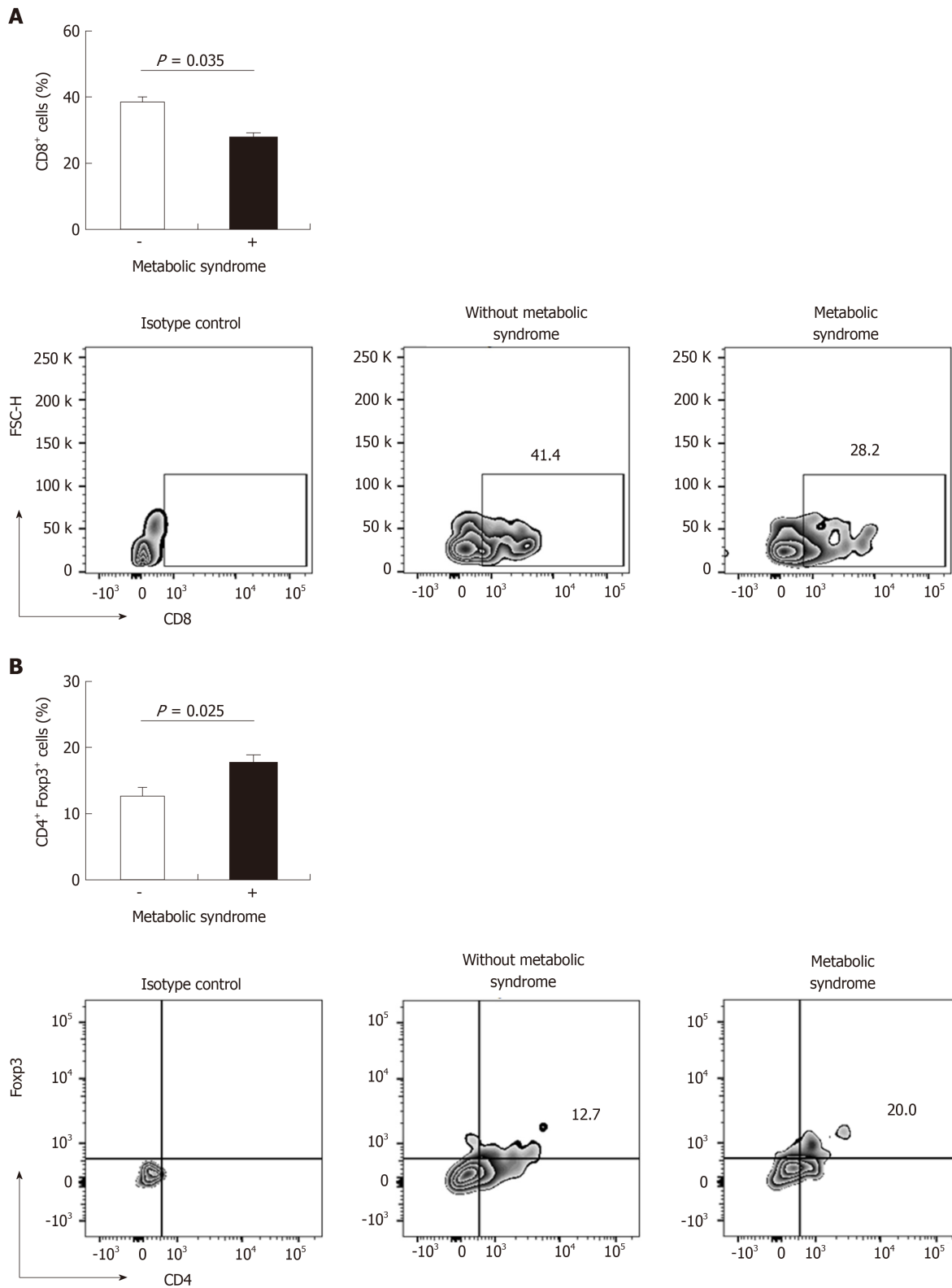
Figure 4 Systemic and local cytokine profile of patients with especially same clinical, endoscopic and histopathological stage of ulcerative colitis, according to metabolic syndrome. Patients with ulcerative colitis (UC) were divided into groups according to clinical, endoscopic and histopathological stage of UC, respectively. A: Interleukin-17 were measured by ELISA in the sera of UC patients without and with metabolic syndrome (MetS). B: Interleukin-10 were measured by ELISA in the sera of UC patients without and with MetS. C: Galectin-3 were measured by ELISA in the sera of UC patients without and with MetS. The Student's *t* or Mann-Whitney U test was applied as appropriate to evaluate statistical significant differences. IL-17: Interleukin-17; IL-10: Interleukin-10; Gal-3: Galectin-3.

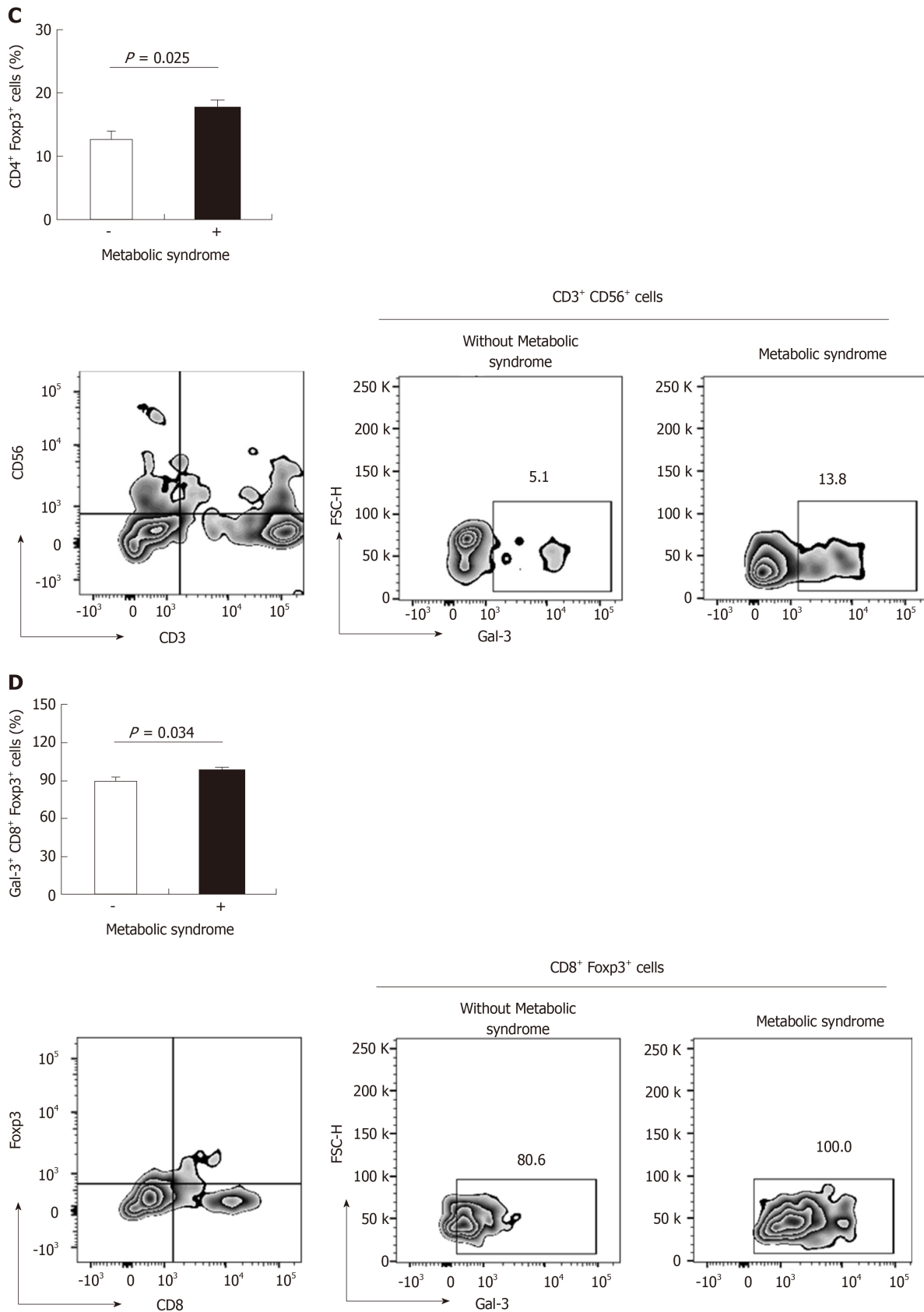
implicate that disease severity does not affect difference in the concentration of systemic and fecal proinflammatory and immunosuppressive cytokines between UC patients with and without MetS.

Analysis of functional phenotype of lymphoid cells revealed increased accumulation of IL-10 producing NK cells and Th lymphocytes (Figures 3B, 5E and F), in agreement with higher IL-10 level in the serum of the patients with MetS. In line with our finding, study on UC patients, by Acovic *et al*^[24], revealed that mucosal healing was accompanied by decreased serum and fecal levels of pro-inflammatory cytokines and elevation of anti-inflammatory IL-10 as well as significantly higher percentage of immunosuppressive regulatory T cells- Tregs, IL-10- producing Th lymphocytes and NK cells, indicating that the milder form of UC in subjects with MetS is most likely due to altered local immune response. Other study^[30] showed two fold increase of the number of peripheral Th lymphocytes in patients with MetS, compared to healthy controls, with the prevalence of Th2 cells. Increased percentage of Th lymphocytes and reduced percentage of CD8⁺ T lymphocytes in peripheral blood of patients with MetS which is in line with our results was also recorded^[31].

Recent studies have suggested the association of MetSs with immune system dysfunction^[32,33]. MetS induces the activation of the immune system in some tissues, which is often manifested by slightly elevated markers of chronic inflammation^[32,33], but also negatively affects the immune response, which is confirmed by the higher incidence of unsuccessful vaccinations and complications in infections^[8,9].

Gal-3 concentration is significantly increased in feces of UC + MetS patients, as well as Gal-3/TNF- α and Gal-3/IL-17 ratios (Figure 3E and F). Recently, Li *et al*^[34] have shown that Gal-3 causes cellular and systemic insulin resistance. It is also interesting that Gal-3 appears to be involved in protective role of MetS in UC (Figures 3-5). Despite that Gal-3 has been found to promote inflammation in some experimental models^[11,35], there is also evidence that it may attenuate pathologic condition in the others^[36,37]. Our recent research has shown higher systemic concentration of Gal-3 in end stage renal disease patients infected with hepatitis C virus, suggesting on hepatoprotective role of Gal-3 from virus destruction^[38]. Our other study revealed





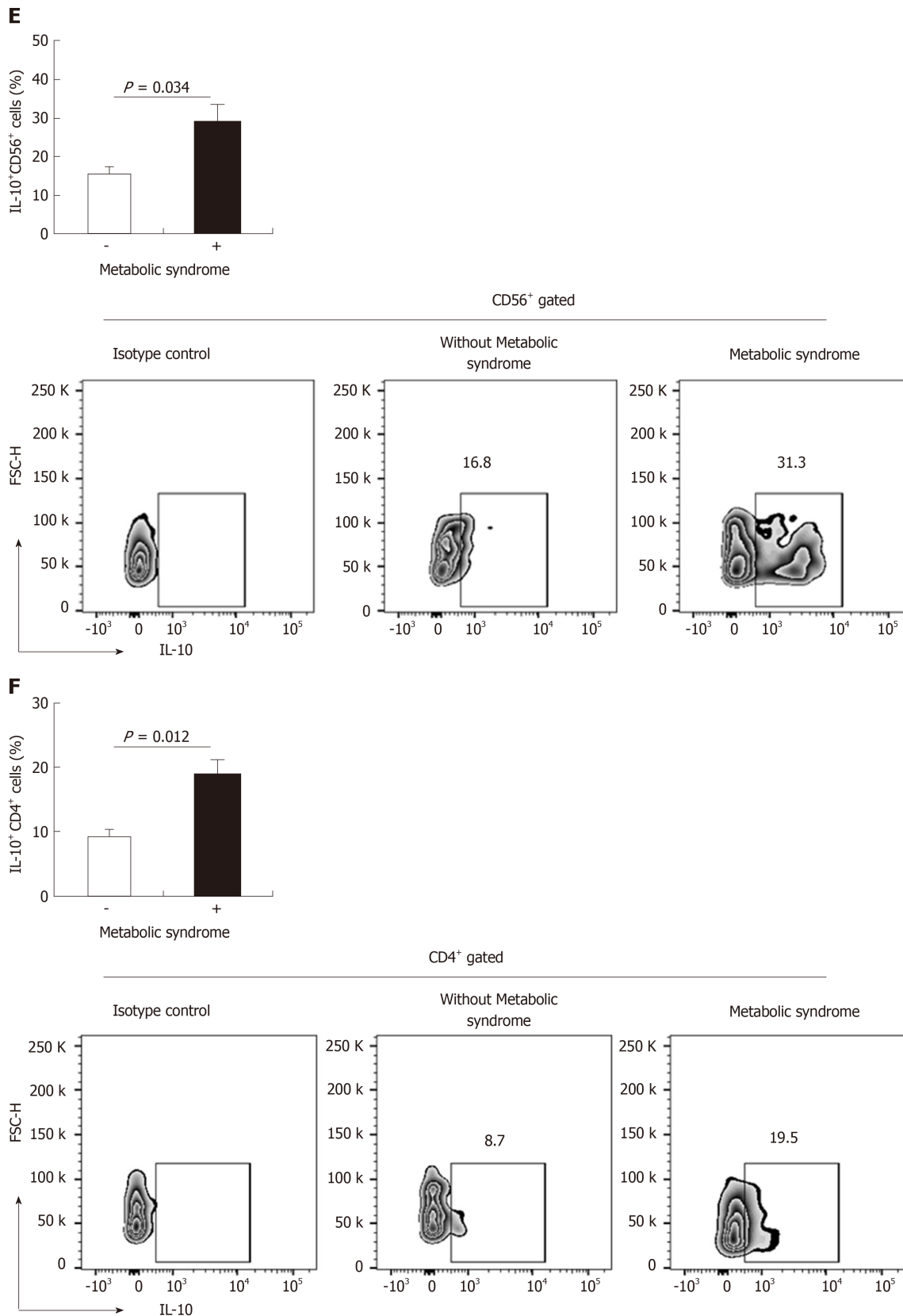


Figure 5 Functional phenotype of immune cells in colonic mucosa. A: The graph and representative FACS plots displaying the percentage of CD8⁺ T cells derived from colonic mucosa of ulcerative colitis (UC) patients without and with metabolic syndrome (MetS). B: The graph and representative FACS plots displaying the percentage of T regulatory cells (CD4⁺Foxp3⁺) derived from colonic mucosa of UC patients without and with MetS. C: The graph and representative FACS plots displaying the percentage of Galectin-3⁺ (Gal-3⁺) NKT (CD3⁺CD56⁺) cells derived from colonic mucosa of UC patients without and with MetS. D: The graph and representative FACS plots displaying the percentage of CD8⁺Foxp3⁺ cells derived from colonic mucosa of UC patients without and with MetS. E and F: The graph and representative FACS plots displaying the percentage of Interleukin-10 producing CD56⁺ and CD4⁺ cells derived from colonic mucosa of UC patients without and with MetS. Cellular make up of colon-infiltrating immune cells were examined by flow cytometry. The Student's *t* or Mann-Whitney U test was applied to evaluate statistical significant differences among the two groups. IL-10: Interleukin-10; Gal-3: Galectin-3.

higher fecal concentration of Gal-3 and higher Gal-3/TNF- α ratio in patients with more severe form of colorectal cancer, thus suggesting immunosuppressive effect of Gal-3 on antitumor immune response^[39]. Moreover, Tsai *et al.*^[40] showed that Gal-3 favors accumulation of regulatory T cells in the colon mucosa which suppresses inflammation and decreases the severity of dextran sulfate sodium-induced colitis. In line with these studies are our results showing significantly higher number of NKT cells and CD8⁺ regulatory T cells expressing Gal-3 in affected lamina propria derived from UC + MetS patients (Figure 5). Moreover, significantly higher fecal values of Gal-3 and Gal-3/TNF- α and Gal-3/IL-17 ratios (Figure 3D) indicate pronounced local Gal-3 predominance over pro-inflammatory mediators in patients with MetS.

In summary, our data shows for the first time clinically and endoscopically milder disease in UC patients with MetS. The presence of MetS may attenuate colon inflammation, possibly by deviating local inflammatory response toward enhanced participation of immunosuppressive cells and molecules. The increase in systemic IL-10 and local Gal-3 production as well as expression on Tregs and immunocompetent cells accumulating in affected colon tissue implicate on IL-10 and Gal-3 dependent immunomodulation. The precise mechanism of Gal-3 effect in MetS and UC comorbidity is still to be clarified.

ARTICLE HIGHLIGHTS

Research background

Ulcerative colitis (UC) is a chronic disease associated with many other diseases such as rheumatoid arthritis, multiple sclerosis, lupus, psoriasis, hypothyroidism, and metabolic syndrome (MetS). Among these diseases, the MetS is the most common comorbidity. There is no evidence considering whether the comorbidity with MetS alters the course of the UC.

Research motivation

We hope to offer reliable evidence that MetS affects the outcome of the UC, given the increasingly common comorbidity.

Research objectives

Test the impact of the MetS on the severity of UC and the local and systemic immune response.

Research methods

A total of 89 patients with *de novo* confirmed UC were enrolled in this cross-sectional study, and they were further divided in two groups, according to ATP III criteria: group without MetS (no MetS) and group with MetS. Severity of UC was determined by histological and clinical scores, fecal and serum cytokines levels were determined using an enzyme-linked immunosorbent assay, while cellular makeup of colon infiltrations was determined by flow cytometry.

Research results When compared to UC patients without MetS, clinically and histologically milder disease with higher serum level of immunosuppressive cytokine interleukin-10 (IL-10) and fecal content of Galectin-3 (Gal-3) was observed in subjects with UC and MetS. This was accompanied with predominance of IL-10 over pro-inflammatory cytokines tumor necrosis factor α (TNF- α), interleukin-6, and interleukin-17 (IL-17) in the sera as well as Gal-3 over TNF- α and IL-17 in feces of UC patients with MetS. Significantly lower systemic values of IL-17, higher values of IL-10 and Gal-3 values in feces were determined in MetS patients in especially same clinical, endoscopic and histopathological stage of UC as patients without MetS. In addition, UC + MetS patients had higher percentage of IL-10 producing and Gal-3 expressing innate and acquired immune cells in lamina propria of affected colon tissue.

Research conclusions

UC patients with MetS have clinically and histologically milder disease. Predominance of Gal-3 and IL-10 over pro-inflammatory mediators in patients with MetS may present a mechanism for limiting the inflammatory process and subsequent tissue damage in UC.

Research perspectives

Future studies are needed to investigate the exact mechanism underlying the protective effect of MetS in biology of UC. And it is necessary to determinate the influence of developmental stages of MetS on the severity of UC. Large sample size studies are also required to confirm the current findings.

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