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RESEARCH ARTICLE

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Comparison of some biochemical markers between early-onset and late-onset colorectal precancerous lesions: A single-center retrospective study

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Abstract

Objective: Given that the onset of diseases including colorectal cancer precursors is affecting younger individuals and that obesity is an important risk factor for early-onset, we conducted a study to explore the biochemical profile of differences in serum between early-onset patients and late-onset colorectal precancerous lesions.

Methods: A total of 1447 patients, including 469 early-onset patients and 978 late-onset patients, were enrolled from the First Affiliated Hospital of Nanchang University (FAHNU), of which there were 311 sessile serrated adenoma/polyps (SSA/P) and 1136 normal adenomas. The distribution of the included categorical variables was compared via Pearson's chi-squared test, whereas continuous variables were compared by using the nonparametric Kruskal–Wallis test and ANOVA.

Results: Compared with late-onset patients, the levels of total bilirubin and HDL-C were lower ($p < 0.05$), whereas triglyceride and uric acid levels were higher, in early-onset patients. Interestingly, in the subgroup analysis, triglyceride and uric acid levels remained at higher levels, whereas HDL-C remained at lower levels, in early-onset patients than in late-onset patients. Other characteristics, such as LDL-C, drinking, γ-GT, and the N/L ratio, were similar between the two groups. An additional analysis of the association of tumor size with markers showed that lower levels of HDL-C and higher levels of uric acid were associated with increased tumor size ($p < 0.05$).

Conclusions: Early-onset CRC precursor cases exhibit higher levels of triglycerides and lower levels of HDL-C than late-onset cases. Additionally, levels of HDL-C are negatively associated with tumor size, whereas uric acid was positively correlated with tumor size.

KEYWORDS
colorectal cancer precursor, early-onset, HDL-C, lipid metabolism

Chao-Tao Tang, Jun Li and Zhenzhen Yang have contributed equally to this work.

1 | INTRODUCTION

Based on the latest 2020 statistics, colorectal cancer (CRC) is the third most common cancer, and its cancer mortality was ranked second compared with other cancer mortalities.[1] The causes leading to a high incidence rate include genetic factors and environmental function, as well as lifestyle developmental factors.[2] To date, it is well known that adenomatous and serrated pathways are critical precursors of CRC and belong to the adenoma–carcinoma sequence.[1] Conventional adenomas include tubular adenomas, tubule-villous adenomas, villous adenomas, and other rare subtypes.[3] Serrated lesions can be separated into hyperplastic polyps (HPs), sessile serrated lesions (SSLs, including sessile serrated polyps [SSPs] and sessile serrated adenomas [SSAs]), and traditional serrated adenomas (TSAs).[4] Adenomas and serrated lesions are defined as the most common precancerous lesions of CRC.[5,6] Screening tests, such as fecal DNA tests and serology markers, are favorable for clinicians because of their ability to detect early precancerous lesions.[7] For instance, serum gamma-glutamyl-transferase (GGT) was found to be positively associated with colorectal adenoma and has been useful for predicting adenoma without steatohepatitis.[8] Similarly, serum bile acid and serum insulin have a diagnostic ability for colorectal neoplasia.[9,10] Additionally, high levels of total cholesterol and low-density lipoprotein were significantly correlated with the prevalence of colorectal adenomas.[11,12] When considering that many clinicodemographic factors are associated with age, the question of whether biochemical characteristics with age of onset are different in colorectal cancer precursors is currently unknown.[13,14]

The incidence of CRC has increased among patients aged <50 years.[1,15] Currently, those patients who are diagnosed at 20–49 years with CRC are defined as having early-onset CRC; therefore, in our study, patients with adenoma and SSA/SSP who were diagnosed at <50 years were considered to have early-onset precancerous lesions.[15–17] Accumulating evidence suggests that distinct biological characteristics and mechanisms underlie the development of early-onset precancerous lesions or CRC, compared with late-onset lesions.[18] For example, previous studies have suggested that diet-related alterations significantly contribute to early-onset CRC precursors, and such a high intake of fattening food or glucose may induce overweight conditions or obesity, thus promoting the development of early-onset lesions.[5,19–21] Obviously, a sedentary lifestyle also accounts for the increased incidence of early-onset CRC precursors.[19–21] Patterns of diet and lifestyle are closely linked with metabolic alterations, which can be demonstrated by biochemical characteristics and BMI.[5] Biochemical markers, such as uric acid and triglycerides, represent the status of metabolism, which triggers carcinogenic mechanisms.[22] Regular CRC screenings are recommended for vulnerable patients over the age of 50 years because early detection can identify early-stage lesions or precancerous lesions.[23] To put these factors into perspective, as a screening method, there is a question as to whether serology markers are distinct between early-onset and late-onset patients. Additionally, given the scant evidence as to which obesity and sedentary behaviors are risk factors for early-onset CRC, the comparison of some biochemical characteristics between the two groups in CRC precursors can serve as a bridge that links obesity with pathogenic mechanisms.

Thus, to investigate whether the serologic markers in early-onset precursors are different compared with late-onset precursors, we performed a retrospective investigation in a well-established cohort of patients with detailed information on the laboratory tests.

2 | METHODS

2.1 | Patient extraction

All of the patients were selected from the First Hospital of Nanchang University. The detailed selection process was performed according to the following inclusion criteria: (1) patients who were diagnosed with serrated lesions (SSA and SSP) via histological examination from January 2015 to October 2021 and patients aged <50 years with adenoma from January 2015 to October 2021 (however, patients aged over 50 years with adenoma from January 2018 to October 2021 were included because the number of late-onset patients was larger); (2) patients with detailed records of triglyceride, HDL-C, and LDL-C levels; and (3) all patients who underwent endoscopic surgery or normal surgery. The exclusion criteria included (1) patients who had a concomitant diagnosis of adenocarcinoma or other malignant tumors; (2) patients with severe diseases such as cirrhosis, renal failure, and cardiac failure; and (3) patients without records of tumor size, γ-GT, uric acid, and TB. The characteristic information of the patients from our hospital is provided in Table 1. All included cases were recorded in the Human Genetic Resources Center of the First Affiliated Hospital of Nanchang University. The research protocol of the Chinese cohort was approved by the Ethics Committee of FAHNU. All the patients provided informed consent.

2.2 | Definitions of variables

In this study, the clinical features that were extracted from our hospital included age, sex, albumin (ALB), total bilirubin (TB), direct bilirubin (DB), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol, uric acid, γ-GT, hemoglobin, triglyceride, ApoA1, ApoB, tumor size, tumor site, neutrophil/lymphocyte ratio (N/L ratio), and drinking status. Age was divided into two groups according to the definition of early-onset colorectal cancer precursor lesions,[24] including age <50 years and age ≥50 years. Sex was recorded as either male or female. Moreover, the site of the lesion was separated into the colon and rectum. In addition to drinking, smoking status was recorded as either "No" and "Yes." Other characteristics, such as ALB, HDL-C, and uric acid, were recorded according to actual values, whereas they were presented as the mean values. All of the laboratory data were obtained from the initial examinations of patients who were tested within 24 h of admission without surgery. Serum characteristics were measured by

TABLE 1 Basic information of enrolled patients

	Total	Early-onset	Late-onset	*p* Value
Total	1447	469 (32.41%)	978 (67.59%)	
Lesion type				
SSA/SSP	311 (21.49%)	98 (20.90%)	213 (21.78%)	0.702
Adenoma	1136 (78.51%)	371 (79.10%)	765 (78.22%)	
Gender				
Male	870 (60.12%)	284 (60.55%)	586 (59.92%)	0.817
Female	577 (39.88%)	185 (39.45%)	392 (40.08%)	
ALB (g/L)	43.29 (41.20–45.60)	44.20 (42.40–46.90)	42.85 (40.60–45.00)	*0.038*
Cholesterol (μmol/L)	4.77 (4.06–5.42)	4.77 (4.08–5.40)	4.76 (4.05–5.42)	0.302
TB (μmol/L)	12.22 (7.90–14.30)	11.57 (7.4–13.9)	12.53 (8.1–14.4)	*0.045*
DB (μmol/L)	2.69 (1.5–2.8)	2.50 (1.5–2.8))	2.69 (1.5–2.8)	0.345
HDL-C (mmol/dl)	1.22 (1.01–1.41)	1.18 (0.98–1.35)	1.24 (1.01–1.44)	*0.002*
Triglycerides (mmol/dl)	1.99 (1.01–2.23)	2.30 (1.07–2.29)	1.83 (1.00–2.19)	*0.029*
LDL-C (mmol/dl)	2.93 (2.36–3.43)	2.87 (2.37–3.36)	2.95 (2.35–3.45)	0.166
Uric acid (μmol/L)	340.94 (275–395)	351.63 (278–413)	335.81 (274.2–388)	*0.013*
γ.gt (U/L)	36.08 (15–35)	37.85 (14–38)	35.22 (15–33.95)	0.452
N/L ratios	2.92 (1.66–3.08)	2.99 (1.66–3.11)	2.87 (1.66–3.05)	0.562
Tumor size (cm)	1.36 (0.50–2.00)	1.37 (0.6–2.2)	1.35 (0.5–2.0)	0.782
Smoking				
No	1055 (72.91%)	367 (78.25%)	688 (70.35%)	*0.002*
Yes	392 (27.09%)	102 (21.75%)	290 (29.65%)	
Drinking				
No	1142 (78.92%)	382 (81.45%)	760 (77.71%)	0.117
Yes	305 (21.08%)	87 (18.55%)	218 (22.29%)	
Site				0.982
Colon	925 (63.93%)	300 (63.97%)	625 (63.91%)	
Rectum	522 (36.07%)	169 (36.03%)	353 (36.09%)	

Note: Italic values indicate statistical significance when $p < 0.05$.

using a biochemical analyzer (AU5800, Beckman Coulter, Inc.) with responding test reagent (Chongqing Zhongyuan Biological Co., Ltd); the reference interval was made according to the recommended value, in accordance with the national standard.

2.3 | Statistical analysis

For basic statistical analyses, all of the extracted patients were divided into early-onset and late-onset groups according to the age at diagnosis, after which the included clinical characteristics were compared via a Pearson's chi-squared test, nonparametric Kruskal–Wallis test, and ANOVA. If the data were categorical variables, we applied a Pearson's chi-squared test. For multiple groups of continuous variables, we applied the Kruskal–Wallis test (≥3 groups) and Mann–Whitney test (2 groups) when experimental data did not exhibit homogeneity of variance; otherwise, we applied ANOVA (≥3 groups) and an unpaired *t* test (2 groups). The chi-squared test was performed with SPSS (version 24.0), and other tests were performed by using GraphPad Prism 8 software. The results were statistically significant when the $p < 0.05$.

3 | RESULTS

3.1 | Basic information of included patients

As shown by the flowchart (Figure 1), we finally included 98 sessile serrated adenomas and 214 sessile serrated polyps from January 2015 to October 2021 in our hospital, according to the inclusion criteria and exclusion criteria. Similarly, we enrolled 371 patients who were diagnosed at an age of less than 50 years from January 2015 to October 2021, as well as 765 patients who were aged over 50 years from January 2018 to October 2021. For the basic information of all the patients, we listed all the patients in Table 1 by dividing them into two groups (the early-onset group and the late-onset group), according to the definition of early-onset precursors of CRC. As shown in Table 1, compared with the late-onset group, the ratio of

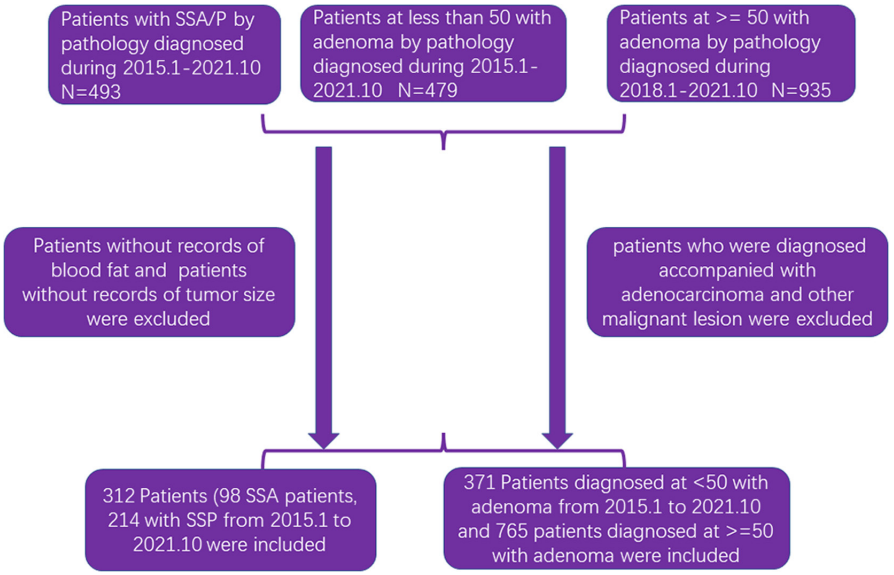

FIGURE 1 Flowchart of extracting SSA/P and colorectal adenoma patients' information in our study

the distribution of lesion type and sex was similar in the early-onset group ($p > 0.05$). Additionally, the mean value of ALB was higher in the early-onset group than in the late-onset group ($p = 0.038$), whereas the mean value of cholesterol was not significantly different ($p = 0.302$). When regarding the level of bilirubin, early-onset patients had a lower level of TB than late-onset patients ($p = 0.045$), whereas the level of DB was similar ($p = 0.345$). Interestingly, the level of HDL-C in early-onset precursors was obviously lower than that in late-onset precursors ($p = 0.002$), and the level of uric acid in early-onset patients was also higher than that in late-onset patients ($p = 0.013$). Similarly, the level of triglycerides in the early-onset group was higher than that in the late-onset group ($p = 0.029$), whereas the difference in LDL-C levels between the two groups was not significant ($p = 0.166$). However, we did not observe a significant difference in the level of γ-GT, the N/L ratio, or tumor size. The distribution of tumor site and ratio for drinking status had similar frequencies between the early-onset group and the late-onset group ($p > 0.05$); however, late-onset patients were more frequent than early-onset patients ($p = 0.02$).

3.2 | Poorer metabolic profile of early-onset patients compared to late-onset patients

In addition, among our data, we included ApoA1 and ApoB variables to further analyze lipoprotein metabssolism. Moreover, 301 patients had records of ApoB and ApoA1, which are also shown in Figure 2A,B, respectively. Similar to the HDL-C and LDL-C results, early-onset patients had lower levels of ApoA1 ($p = 0.0005$) and similar levels of ApoB ($p = 0.685$) than late-onset patients. To further demonstrate our findings, we performed a subgroup analysis. As shown in Figure 3, we divided patients into nonsmoking and smoking groups to analyze the metabolic profiles. For nonsmoking patients, early-onset patients had higher levels of uric acid and lower levels of HDL-C than late-onset patients (Figure 3B,C); nevertheless, the levels of triglycerides were not different (Figure 3A). Surprisingly, the level of LDL-C in early-onset patients was lower than that in late-onset patients ($p < 0.004$) (Figure 3D). For patients who had smoked, we found that the triglyceride and uric acid levels of early-onset patients were higher than those of late-onset patients ($p < 0.05$) (Figure 3E,F). Similar to the results of nonsmoking patients, early-onset patients had lower levels of HDL-C ($p = 0.026$) (Figure 3G); however, the levels of LDL-C between the early-onset group and the late-onset group for smoking status were contradictory to the abovementioned results ($p = 0.013$) (Figure 3H). Furthermore, in the subgroup analysis of tumor type, we found that early-onset SSA/SSP patients had higher levels of triglycerides and uric acid than late-onset SSA/SSP patients, whereas early-onset SSA/SSP patients had higher levels of HDL-C ($p < 0.05$) (Figure 4A,B,D). For patients with adenoma, early-onset patients had higher levels of uric acid and lower levels of HDL-C ($p < 0.05$), whereas the level of triglycerides in the early-onset group was higher; however, the difference was not significant ($p = 0.083$) (Figure 4E–G). Both subgroups showed that the difference in LDL-C levels was not statistically significant (Figure 4C,G).

3.3 | The association of metabolic profile with tumor size

Previously, we demonstrated that early-onset patients had poorer metabolic profiles, including higher levels of uric acid and triglycerides. The size of CRC precursors is usually associated with the selection of the treatment methods.[25] Therefore, we investigated whether there was a relationship between tumor size and metabolic characteristics. As shown in Figure 5, we divided patients into a normal-level group and a high-level group, according to the levels of uric acid, LDL-C, cholesterol, and triglycerides (Figure 5A,B,D,E), and we found that only the level of uric acid was associated with tumor size ($p = 0.038$), as well as the fact that patients with a higher

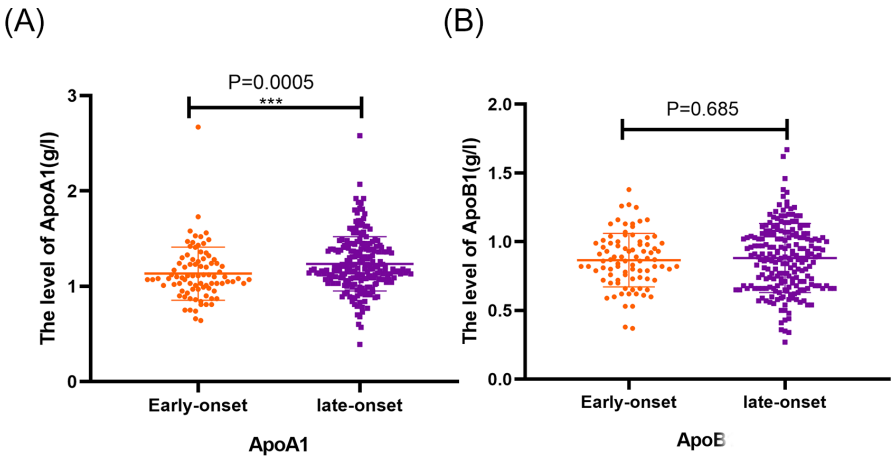

FIGURE 2 Scatter plot showed the level of ApoA1 (A), uric acid (B) in patients with CRC precursors, respectively.

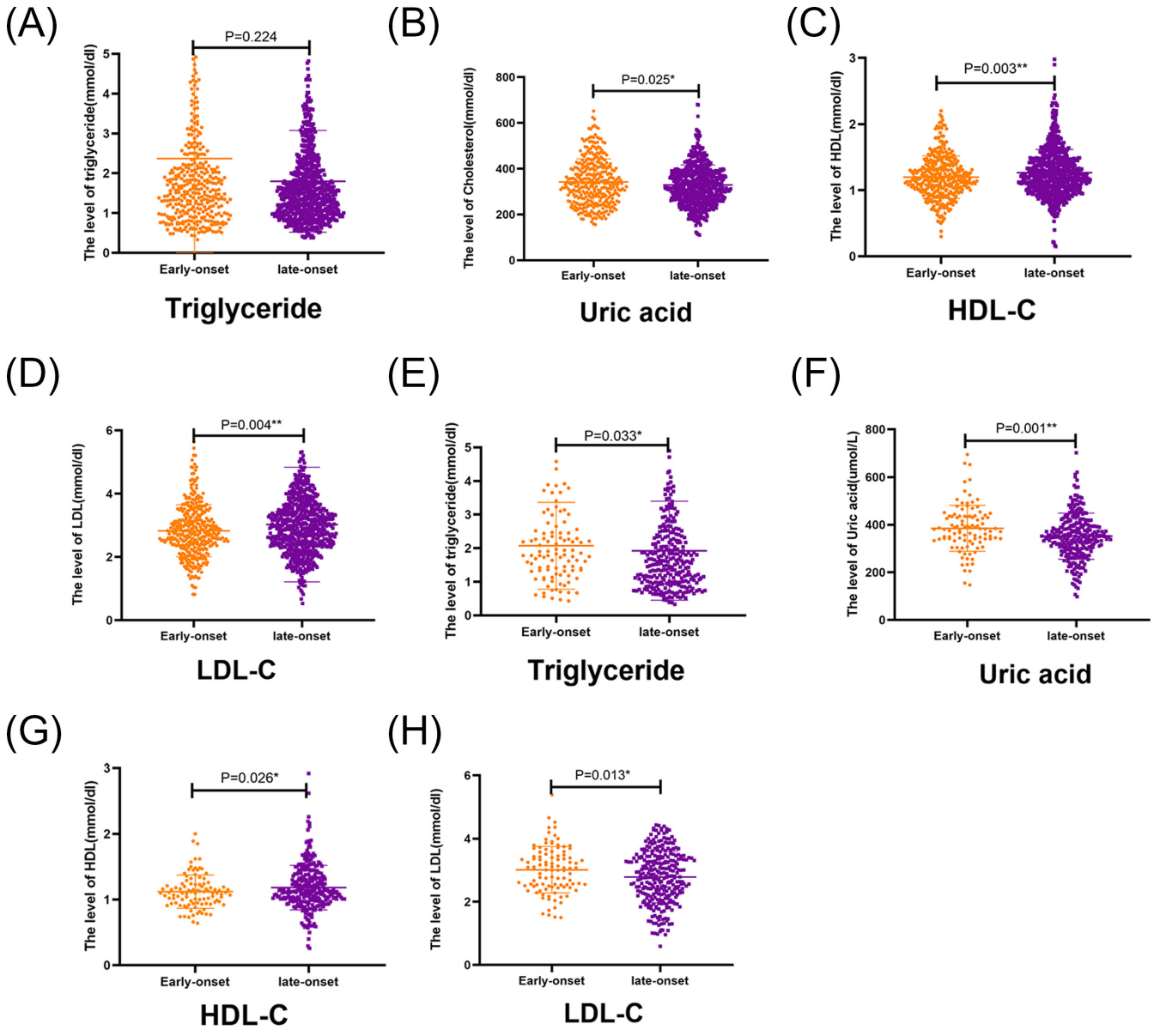

FIGURE 3 Scatter plot showed the level of triglyceride (A,E), uric acid (B,F), HDL-C (C,G), and LDL-C (D,H) in patients with CRC precursors stratified by smoking. A–D pictures were non-smoking patients while E–H pictures were patients with smoking.

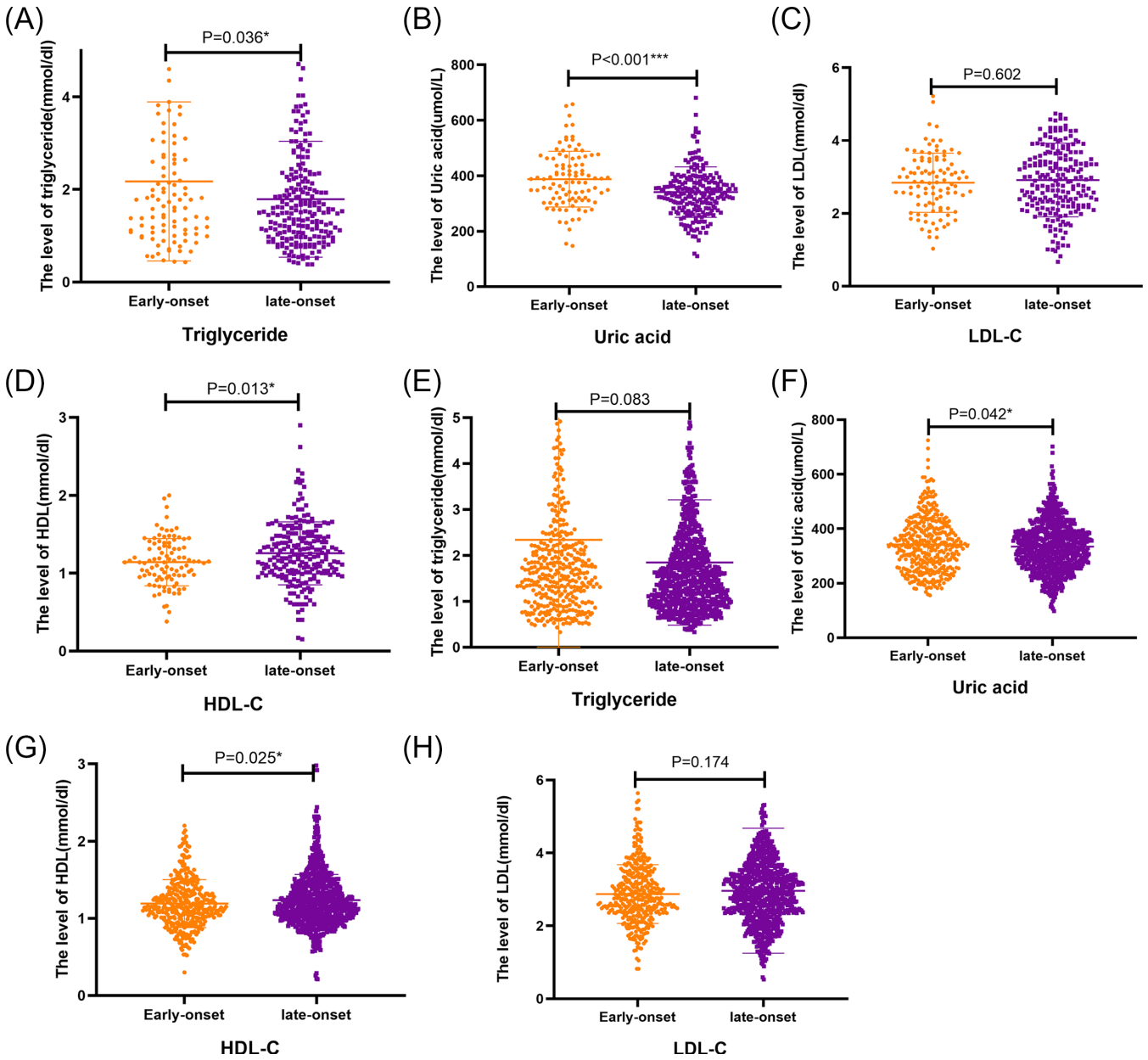

FIGURE 4 Scatter plot showed the level of triglyceride (A,E), uric acid (B,F), LDL-C (C,G), and HDL-C (D,H) in patients with CRC precursors stratified by tumor type. A–D pictures were SSA/P patients while E–H pictures were patients with adenoma.

level of uric acid had a larger tumor size. Furthermore, we included patients with low levels of HDL-C (<1.29 mmol/dl) and patients with high levels of HDL-C (>1.55 mmol/dl) to compare the difference in tumor size, which suggested that the tumor size of patients with high levels of HDL-C was larger than that of patients with low levels of HDL-C ($p < 0.001$) (Figure 5C).

4 | DISCUSSION

Adenomas that are known as precursors of colorectal cancer are suggested to be removed when they are found, especially regarding villous adenoma and serrated polyps.[4] When considering the risk factors for adenomas, it has been reported that smoking, low physical activity, and increased alcohol intake were highly associated with colorectal adenoma.[26] Currently, obesity and reduced physical activities are common to observe in adolescents, which increases the prevalence of adenoma. According to previous studies, those individuals with body mass index (BMI) >25 exhibit a 1.412-fold increased prevalence, compared to those with BMI < 23.[14,27] When regarding the increased prevalence of obesity in adolescent and early-onset CRC, no study has analyzed the level of lipid metabolism in younger patients (<50 years) compared with older patients. The present study demonstrated lower levels of HDL-C in early-onset patients with CRC precursors than in late-onset patients, and higher levels of uric acid and triglycerides were found in the serum of early-onset patients. Additionally, strong associations were observed between the level of HDL-C and tumor size.

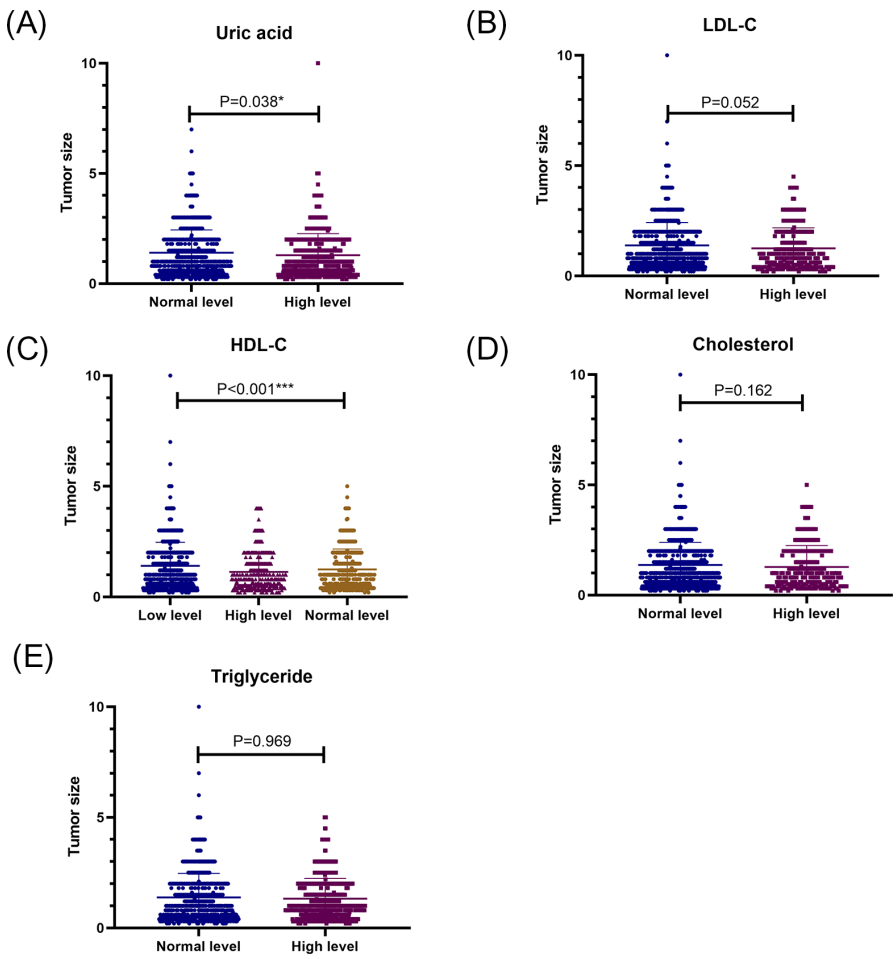

FIGURE 5 Scatter plot showed the association of tumor size with uric acid (A), LDL-C (B), HDL-C (C), cholesterol (D), and triglyceride (E) in patients with CRC precursors.

Previous studies have extensively confirmed that the lipid profile is related to colorectal adenoma. Many studies have shown that higher levels of triglycerides and cholesterol were associated with an increased risk of adenoma; however, other studies have failed to demonstrate a link between these factors, or some studies have even suggested an inverse association between them.[11,12,28,29] Although our study did not compare the difference in lipid metabolism levels between patients with adenoma and normal controls, we indeed found that the majority of patients with adenoma had elevated levels of triglycerides and decreased levels of HDL-C. Some studies have observed that metabolic syndrome was not associated with the size of the adenoma[30]; however, our study found that only the level of HDL-C (other than triglycerides and cholesterol) was inversely correlated with tumor size. Moreover, we found that patients with lower HDL-C levels had larger tumor sizes. In our study, strongly inverse associations of age with the levels of HDL-C and triglycerides were observed in patients with adenoma or SSA/P, which was contradictory to our notion. Nevertheless, some studies have found that obese patients with adenoma tended to be younger than normal patients with adenoma.[31,32] Moreover, early-life disorders of lipid metabolism are the first step in the process of inducing early-onset CRC by obesity.[19,33] In fact, alterations in lipid metabolism or other metabolic characteristics occur in CRC precursors, including adenoma and serrated polyps.[17,34] Our findings suggest that poorer disorders of lipid metabolism may play a critical role in the occurrence and development of early-onset precursors. Interestingly, a retrospective study reported that individuals with one, two, or at least three metabolic disorders were observed to have a 9%, 12%, and 31% higher risk for early-onset CRC, respectively, whereas individuals aged 50–64 years did not exhibit this phenomenon.[35] When regarding this difference, the genomic alterations in early-onset lesions could provide some explanations. For instance, orphan nuclear receptor NR0B2 was found to be a novel susceptibility gene for the metabolic manifestation of early-onset CRC.[36] Moreover, a multiomics analysis revealed that the metabolites yielded significant interaction effects between early-onset and late-onset CRC patients.[37]

Elevated uric acid is common in patients with obesity, diabetes, and hyperlipidemia or other metabolic syndromes. Several studies have shown that hyperuricemia is an independent risk factor for colorectal adenoma or cancer.[38,39] Similar to the lipid metabolism results, the uric acid level in the early-onset group was higher than that in the late-onset patients, thus suggesting that early-onset patients with poorer lipid profiles have higher uric acid levels. The level of uric acid is associated with the redox state balance idea that elevated oxidative stress induces increased excretion of uric acid.[40] Compared with late-onset CRC, the multiomics analysis showed that genes associated with the NRF2-mediated oxidative stress response were abnormally enriched in early-onset disease, thus suggesting this as

a reason for higher uric acid levels in early-onset CRC precursors.[37] In addition, previous studies have also shown that a high level of uric acid promoted the development of CRC, including carcinogenesis, invasion, and metastasis.[40]

Several limitations of our study should be mentioned. First, the lack of evidence supporting a poorer metabolic profile as a risk factor for early-onset CRC precursors was a shortcoming of our study; therefore, the clinical significance of our study was impaired. Additionally, we included late-onset patients who were diagnosed with adenoma from 2018 to 2021, which was distinct from the selection of early-onset cases, resulting in little selection bias. However, the time variable is a random variable that decreases selective bias. Finally, our study did not give the detailed reasons for this interesting phenomenon. Hence, in the future, we will conduct further studies to investigate the mechanism leading to the poorer metabolic profile of early-onset precursors.

5 | CONCLUSIONS

In conclusion, compared with late-onset colorectal precancerous lesions, early-onset patients have higher levels of triglycerides and lower levels of HDL-C. Higher levels of HDL-C and lower levels of uric acid are associated with smaller tumors.

AUTHOR CONTRIBUTIONS

CTT contributed to experiment performing, data analysis, and manuscript writing. JL contributed to sample collecting and data analysis. CYZ and YXC contributed to project development.

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CONFLICT OF INTEREST

The authors disclose no conflicts.

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