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*Original Article*

# Different lipid metabolic profiles and their associated genes in sessile serrated adenoma or polyps compared to hyperplastic polyps

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**Abstract:** The serrated pathway is important in the development of colorectal cancer; currently, knowledge about the lipid metabolism profiles of serrated lesions is limited. Clinical characteristics were compared via Pearson's chi-squared test, nonparametric Kruskal-Wallis test and ANOVA. For some missing values, the MCAR test and multiple imputations were performed. Compared to patients with HP, the rates of younger patients (<50) and male patients with SSA or SSP were increased (P<0.05). Additionally, the BMI index and triglyceride levels were increased in patients with SSA or SSP. Inversely, patients with SSA/P had lower levels of HDL (P<0.05). Interestingly, the value of uric acid and tumor size in SSA/P patients tended to be greater than those in HP patients, and the ratio of patients who smoked was also increased. Other characteristics, such as LDL, ALB, γ-GT, and the N/L ratio, were similar among the subtypes of serrated lesions. Analysis of GEO data (GSE43841) showed that 9 genes were associated with lipid metabolism, including ADRB3, DEGS2, PRKACB, SLC44A1, and CA4. PRKACB was downregulated in SSA/P tissue compared to HP tissue samples from the GSE76987 dataset and our hospital. In conclusion, compared to benign HP, lower HDL levels and higher triglyceride levels tended to occur in CRC precursor SSA/P lesions, and these factors may be associated with metabolic genomic markers, such as PRKACB.

**Keywords:** Serrated lesion, high-density lipoprotein, triglyceride, SSA/P, HP

## Introduction

Colorectal cancer (CRC), as the most common cause of cancer death, is derived from comprehensive causes [1]. At present, CRC arises from adenomatous, serrated pathways and colitis-associated-cancer pathways, of which the serrated pathway represent a distinct pathway [2]. According to the WHO classification, serrated lesions are a set of early precursor lesions comprising hyperplastic polyps (HPs); sessile serrated lesions (SSLs), including sessile serrated adenomas (SSAs), sessile serrated polyps (SSPs), sessile serrated adenomas/polyps without or with dysplasia, and traditional serrated adenomas (TSAs); and other unclassified serrated lesions [2, 3]. Among those classifications, HP accounts for the majority of serrated lesions, followed by SSA and SSP, whereas TSA is the least common [3]. Previously, serrated lesions were mainly considered to be HPs and were not considered malignant; however, in recent years, serrated lesions characterized by a saw-toothed appearance were found to have malignant potential and heterogeneity compared to other polyps [4, 5].

Currently, our understanding of serrated lesions has increased with increasing research. The majority of HPs are located in the distal colon, and only less than 30% occur in the proximal colon. Compared to HPs, SSA/Ps are mainly located in the proximal colon [6]. Moreover, HPs are often small, and some are very small (<0.5 cm). In contrast, SSA/Ps are often larger, and some are up to 2 cm [6]. Some differences in genomic expression are noted between HPs and SSA/Ps. For instance, HPs less commonly harbor BRAF mutations, whereas SSA/Ps are frequently positive for BRAF mutations [7, 8]. In addition to mucin expression, SSA/Ps often produce excessive mucin proteins, such as

MUC5AC and MUC2 [9]. Regarding lifestyle risk factors for colorectal cancer precursors, some studies reported that smoking, obesity, high intake of simple sugars and high alcohol intake are highly correlated with precursor lesions [10, 11]. Furthermore, obesity is also an important risk factor for early-onset colorectal cancer [12, 13]. Knowledge about the profile of lipid metabolism in serrated lesions is limited. A study reported that a high triglyceride to high-density lipoprotein ratio is associated with serrated polyps, providing limited knowledge of the lipid metabolism profile of serrated lesions [14]. Clinically, the levels of triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) in serum could function as indicators of lipid metabolism [14, 15].

Regarding insufficient evidence to report differences among the different types of serrated lesions, we performed a retrospective study to examine the difference in lipid metabolism between HP and SSA/P by collecting associated data from patients from our hospital.

## Methods

### *Patient extraction*

All patients were selected from the First Affiliated Hospital of Nanchang University (FAHNU). The detailed process was performed according to the following inclusion criteria: (1) patients who were diagnosed with serrated lesions (SSA and SSP) by histological examination from January 2015 through October 2021 and patients diagnosed with HP from January 2018 through October 2021; (2) patients with detailed data on triglycerides, HDL and LDL; and (3) all patients who underwent endoscopic surgery. The exclusion criteria were as follows: (1) patients with a concomitant diagnosis of adenocarcinoma or adenoma; (2) patients with severe diseases, such as cirrhosis, renal failure, and cardiac failure; and (3) patients who were treated with cholesterol-lowering or triglyceride-lowering medication before polyp resection. All patients were followed up by telephone to obtain information on certain characteristics, such as BMI and tumor size, when differences were analyzed. Patient information 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 patients provided informed consent.

### *Definitions of variables*

In this study, the clinical features extracted from our hospital included age, sex, body mass index (BMI), albumin (ALB), total bilirubin (TB), direct bilirubin (DB), high-density lipoprotein (HDL), low-density lipoprotein (LDL), uric acid, γ-GT, hemoglobin (Hb), triglycerides, tumor size, tumor site, neutrophil/lymphocyte ratio (N/L ratio) and drinking. Age was divided into two groups according to the definition of early-onset colorectal cancer [16]: age <50 years and age ≥50 years. Sex was recorded as male or female. The site of the lesion was classified as the colon and rectum. In addition to drinking, smoking habits were classified as yes or no. Other characteristics, such as ALB, HDL and uric acid, were recorded as actual values and presented as median values.

### *GEO data and GO analysis*

The bioinformatics analysis was performed in accordance with a previous study [17]. The terms “serrated lesion”, “hyperplastic polyp” and “sessile serrated adenoma and polyp” were searched in the Gene Expression Omnibus database (GEO). In addition, other database criteria proved to be helpful with additional analysis: I) clinical study must have patients with serrated lesion, and II) mRNA data from tumor tissue were retrieved. Data from GSE43841 and GSE76987 were used to analyze the differentially expressed mRNAs of genes associated with lipid metabolism according to previous methods [18]. GO analysis was completed using the DAVID website (https://david.ncifcrf.gov/).

### *Gene set enrichment analysis (GSEA)*

To determine the PRKACB expression pattern in SSA/P and HP, the GSE76987 dataset used in this study was downloaded from the Gene Expression Omnibus (GEO). To gain further insight into the biological pathways involved in SSA/P pathogenesis through the PRKACB pathway, gene set enrichment analysis (GSEA) was performed. The canonical pathway gene sets (c2.cp.v4.0.symbols.gmt) from the Molecular Signatures Database-MsigDB (http://

**Table 1.** The basic information of enrolled patients

| | Total | HP | SSA | SSP | *P* value |
|---|---|---|---|---|---|
| Total | 767 | 455 | 98 | 214 | |
| Age | | | | | *0.003* |
| <50 | 203 (26.47%) | 104 (22.86%) | 24 (24.49%) | 75 (35.04%) | |
| ≥50 | 564 (73.53%) | 351 (77.14%) | 74 (75.51%) | 139 (64.96%) | |
| Gender | | | | | *0.021* |
| Male | 450 (58.67%) | 249 (54.73%) | 66 (67.35%) | 135 (63.08%) | |
| Female | 317 (41.33%) | 206 (45.27%) | 32 (32.65%) | 79 (36.92%) | |
| BMI (kg/m^2) | 23.29 (21.2-25.15) | 22.88 (21.42-24.75) | 24.09 (22.15-26.2) | 23.80 (21.62-26.07) | *<0.001* |
| ALB (g/L) | 42.83 (40.55-45.65) | 42.86 (41.15-45.8) | 43.09 (41.42-45.3) | 42.64 (40.45-45.40) | 0.865 |
| TB (umol/L) | 11.97 (7.2-13.5) | 11.36 (7-13.2) | 11.65 (6.92-14.6) | 13.39 (7.50-14.05) | 0.37 |
| DB (umol/L) | 3.01 (1.6-3.2) | 3.01 (1.62-3.5) | 2.35 (1.45-2.8) | 3.32 (1.5-3.0) | *<0.001* |
| HDL (mmol/dl) | 1.45 (1.00-1.52) | 1.62 (1.09-1.59) | 1.21 (1-1.44) | 1.21 (0.98-1.42) | *<0.001* |
| Triglycerides (mmol/dl) | 1.81 (0.95-2.11) | 1.62 (0.89-1.98) | 2.04 (1.14-2.65) | 2.08 (0.99-2.28) | *0.002* |
| LDL (mmol/dl) | 2.85 (2.23-3.43) | 2.82 (2.13-3.4) | 2.92 (2.36-3.41) | 2.88 (2.19-3.52) | 0.549 |
| Uric acid (umol/L) | 338.58 (271.5-391) | 325.85 (252-375.5) | 349.21 (302.25-394.97) | 360.80 (298.12-406.5) | *<0.001* |
| γ-GT (U/L) | 38.96 (15-38) | 38.33 (15-34) | 38.63 (16-38) | 40.44 (17-42.07) | 0.957 |
| Hb (g/L) | 133.35 (124-148) | 131.74 (119.5-146) | 137.63 (127.25-151) | 134.81 (125-150.75) | *0.024* |
| N/L ratios | 2.91 (1.57-3.09) | 2.91 (1.47-3.11) | 2.73 (1.6-2.99) | 3.00 (1.62-3.08) | 0.824 |
| Tumor size (cm) | | 0.4 (0.1-1.0) | 1.2 (0.5-1.7) | 0.6 (0.3-0.9) | *<0.001* |
| Smoking | | | | | <0.001 |
| No | 492 (64.15%) | 323 (70.99%) | 54 (55.10%) | 115 (53.74%) | |
| Yes | 275 (35.85%) | 132 (29.01%) | 44 (44.90) | 99 (46.26%) | |
| Drinking | | | | | 0.743 |
| No | 572 (74.58%) | 341 (74.95%) | 70 (71.43%) | 161 (75.23%) | |
| Yes | 195 (25.42%) | 114 (25.05%) | 28 (28.57%) | 53 (24.77%) | |
| Site | | | | | 0.316 |
| Colon | 513 (66.88%) | 297 (65.27%) | 64 (65.31%) | 152 (71.03%) | |
| Rectum | 254 (33.12%) | 158 (34.73%) | 34 (34.69) | 62 (28.97%) | |

Italic values indicate statistical significance when P<0.05.

www.broad.mit.edu/gsea/msigdb/index.jsp) were used for enrichment analysis. Only gene sets represented by at least 15 genes were retained [19].

*Immunohistochemistry (IHC)*

Endoscopic HP and SSA/P tissues were warmed at 70°C for 2 h, dewaxed with xylene and anhydrous ethanol for 40 min, and incubated in citrate to complete antigen retrieval. Finally, tissue microarrays were covered with primary antibody (PRKACB, Proteintech, 55382-1-AP, 1:200) overnight at 4°C. On the second day, microarrays were incubated with the corresponding secondary antibody for 30 min at room temperature. After the samples were washed with PBS, the tissue was stained with DAB reagent (TransGen Biotech, Beijing), and the nuclei were stained with hematoxylin. IHC results were assessed using a previously described method [20]. Briefly, protein expression was assessed according to the intensity of staining and the percentage of positively stained cells. Two independent pathologists analyzed the results and recorded scores of 0-9.

*Statistical analysis*

For basic statistical analysis, all extracted patients were divided into HP, SSA and SSP groups according to diagnosis. Clinical characteristics were compared via Pearson's chi-squared test, nonparametric Kruskal-Wallis test and ANOVA. If the data were categorical variables, we applied 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 have homogeneity of variance; otherwise, we applied ANOVA (≥3 groups) and an unpaired t test (2 groups). For the partially missing values, we first per-

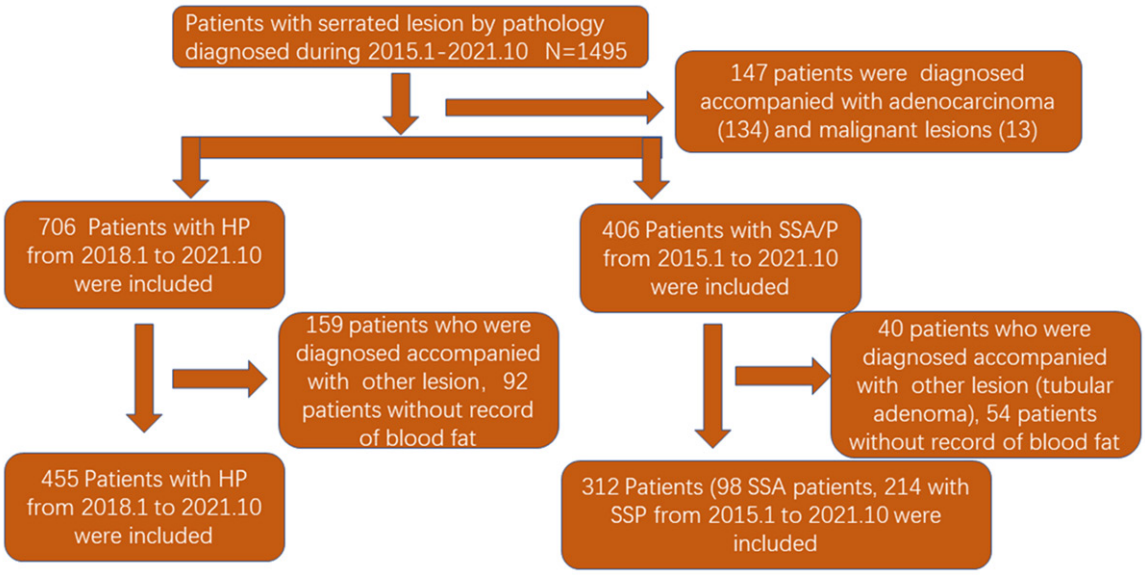


**Figure 1.** The flow chart of extracting patients' information in our study.

formed the MCAR test to demonstrate that the data were missing at random. Then, we performed multiple imputation via R software. Finally, we obtained the pooled results [21, 22] (**Table 1**). Part of the statistical analysis was performed in R software, and all associated packages were obtained from the R software program website (https://cran.r-project.org/web/packages/). The chi-squared test was performed using SPSS (version 24.0), and other tests were performed using GraphPad Prism 8 software. The results were considered statistically significant when the *P* value was less than 0.05.

## Results

### *Basic information of patients with serrated lesions*

In our study, we included 767 patients with a diagnosis of serrated lesions according to the flow chart (**Figure 1**). Of the 767 enrolled patients, 455 patients fulfilled the inclusion criteria for HP, whereas 98 patients with SSA and 214 with SSP met the inclusion criteria for SSA/P. As shown in **Table 1**, patients with HP were prominently diagnosed at an age of greater than 50 years old, whereas the rate of diagnosis of younger patients (<50) with SSA or SSP was increased (P=0.003). Regarding the distribution of sex, a similar number of male patients with HP were noted compared to female patients (54.73% vs. 45.27%), whereas male patients with SSA or SSP were more frequently observed than female patients (P= 0.021). Compared to HP, the BMI index was larger in patients with SSA or SSP, suggesting that patients with SSA or SSP were inclined to be fatter. Patients with SSP had the largest DB value followed by patients with HP and patients with SSA. SSA/P patients had a smaller value of HDL compared with patients with HP (P<0.001); conversely, patients with SSA/P had a higher level of triglycerides (P=0.002). Interestingly, uric acid levels and tumor sizes in SSA/P patients tended to be greater than that in HP patients. The ratio of patients who smoked was greater in SSA/P patients compared with HP patients. Other characteristics, such as LDL, ALB, γ-GT and the N/L ratio, were similar among the subtypes of serrated lesions.

### *More seriously disordered lipid metabolic profiles are observed in SSA/Ps compared to HP*

To further explore the difference in lipid metabolic profiles and other biochemical indices, we generated a scatter diagram to present detailed information on each biochemical index (**Figures 2** and **3**). As shown in **Figures 2** and **3**, most results were consistent with the results mentioned above. Interestingly, we found that compared to patients with HP, Hb levels were

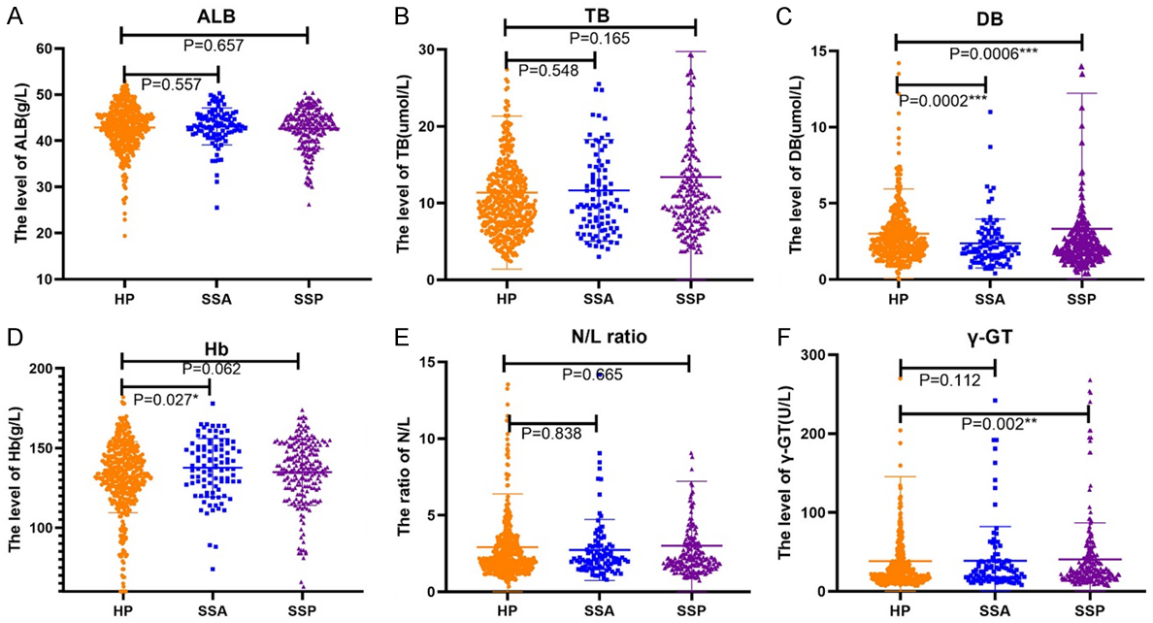


**Figure 2.** Scatter plot showed the level of ALB (A), TB (B), DB (C), Hb (D), N/L ratio (E), γ-GT (F).

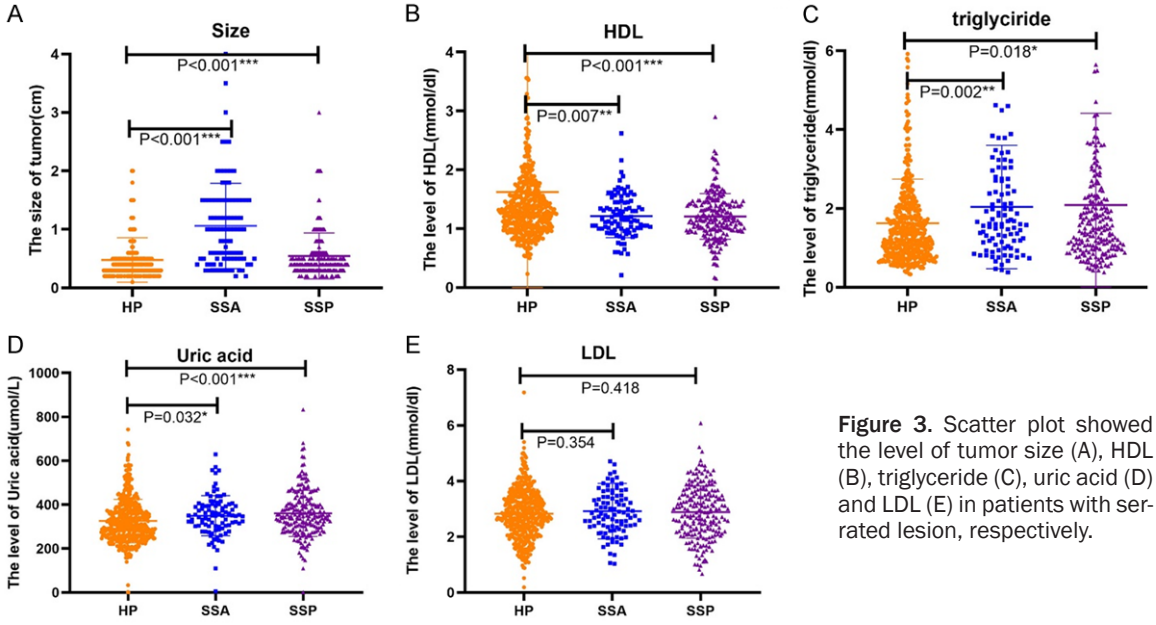


**Figure 3.** Scatter plot showed the level of tumor size (A), HDL (B), triglyceride (C), uric acid (D) and LDL (E) in patients with serrated lesion, respectively.

increased in patients with SSA (P=0.027), whereas the difference between HP and SSP was not significant (P=0.062). Similarly, patients with SSP had increased γ-GT levels compared with patients with HP, and the difference was significant (P=0.002). Both **Table 1** and **Figure 2** show that patients with SSA and patients with SSP had higher levels of triglycerides and lower levels of HDL than patients with HP.

*Subgroup analysis of lipid metabolic profiles in SSA/Ps compared to HP*

Considering the uneven distribution of age, tumor size and smoking patients, we performed subgroup analysis to compare the differences. As shown in **Figure 4**, we divided tumor size into two groups, namely, <1 cm and ≥1 cm. Regarding the comparison of triglycerides, we found that patients with SSA had higher levels

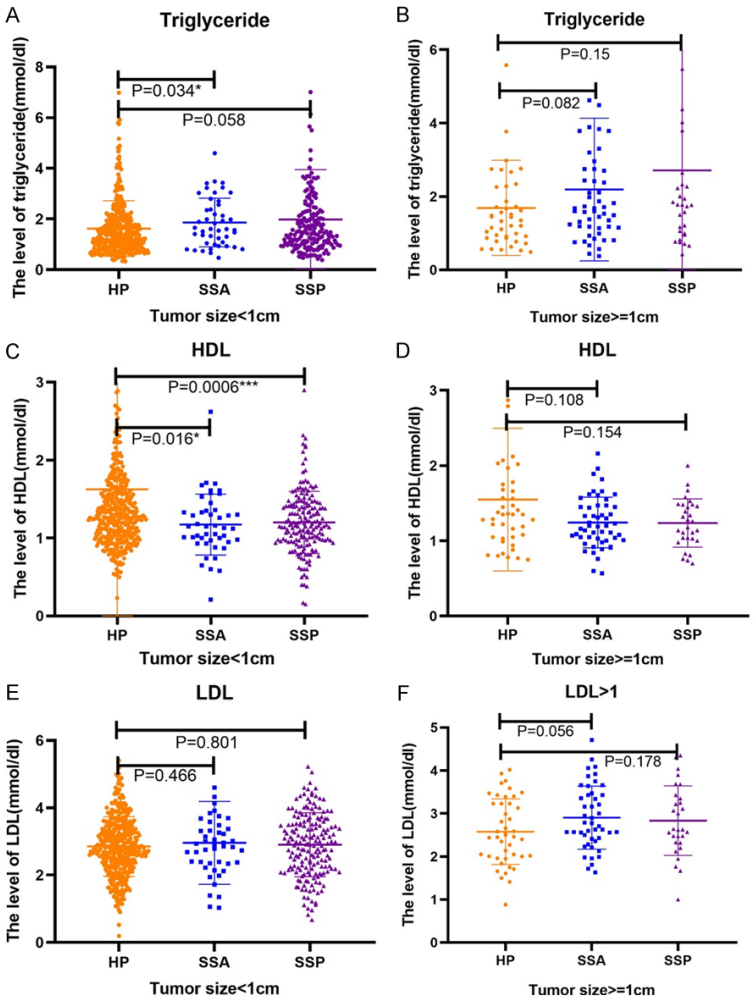


**Figure 4.** Scatter plot showed the level of triglyceride (A, B), HDL (C, D), and LDL (E, F) in patients with serrated lesion stratified by tumor size, respectively.

of triglycerides than patients with HP (P=0.034); however, the difference between SSP and HP was not significant (P=0.058) (**Figure 4A**). To our surprise, no significant differences between SSA with HP and SSP were noted in patients with larger tumors (>1 cm) (P>0.05) (**Figure 4B**). For patients with tumors <1 cm, patients with SSA or SSP had lower HDL levels than patients with HP (P<0.05); however, the difference was not significant for patients with tumors ≥1 cm (**Figure 4C** and **4D**). However, both in the group with <1 cm tumors and in the group with >1 cm tumors, the difference in the level of LDL was not significant; however, mean value was different (**Figure 4E** and **4F**). In the group of patients <50 years of age, the difference in triglycerides among the three subtypes of serrated lesions was not significant (P>0.05). However, in the group of patients ≥50 years of age, patients with SSA had a significantly higher level of triglycerides than HP patients (P=0.002) (**Figure 5A** and **5B**). Both in the groups of patients <50 years of age and ≥50 years of age, the HDL levels in SSA patients and SSP patients were obviously lower than those in HP patients (P<0.05) (**Figure 5C** and **5D**). The difference in LDL levels was not statistically significant (P>0.05) (**Figure 5E** and **5F**). Furthermore, considering that tobacco smoking influences alterations in lipid metabolism, we also divided all patients into two groups: no smoking and smoking [23]. Among patients who do not smoke, patients with SSA or SSP had higher levels of triglycerides and lower HDL levels than HP patients (**Figure 6A** and **6C**), whereas LDL levels were similar among the three subtypes of serrated lesions (P>0.05) (**Figure 6E**). Among patients who smoke, patients with SSP had higher levels of triglycerides and LDL and lower levels of HDL than HP patients (P<0.05), whereas the difference in HDL in SSA patients was not significant (**Figure 6B**, **6D** and **6F**). Hence, the results mentioned above suggested that patients with SSA/P had lower levels of HDL and higher levels of LDL than HP patients; however, LDL levels did not significantly differ.

*DEGs associated with lipid metabolism in SSA/Ps compared to HPs*

To investigate the genomic mechanisms involved in lipid metabolism differences, we downloaded the sequence data of GSE43841, which contained gene expression data from SSA/Ps and HP patients, to differentiate genes associated with lipid metabolism. First, we performed gene expression profiling and

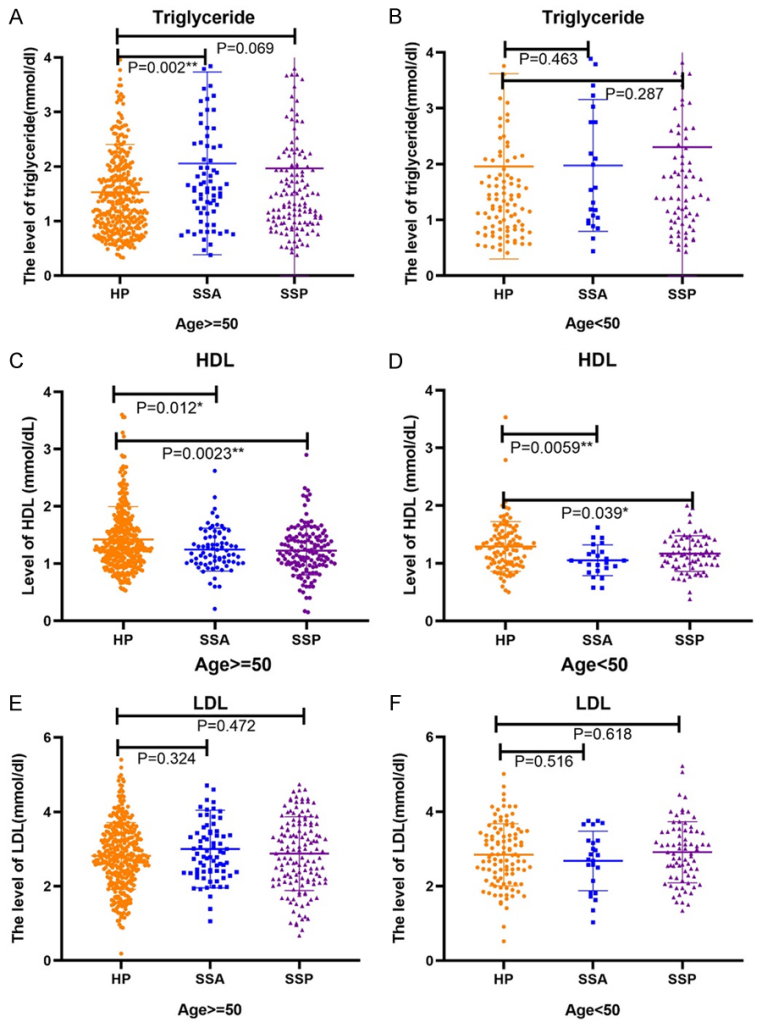


**Figure 5.** Scatter plot showed the level of triglyceride (A, B), HDL (C, D), and LDL (E, F) in patients with serrated lesion stratified by age, respectively.

identified the differentially expressed genes (DEGs) (**Figure 7A**). Second, we performed GO analysis using the DAVID tool and presented the results as a bubble diagram (**Figure 7B**). We found that DEGs were enriched in the following processes: fatty-acyl-CoA biosynthesis, positive regulation of gene expression and response to oxidative stress. Of the genes associated with fatty-acyl-CoA biosynthesis, we found that 9 genes were highly correlated with lipid metabolism: ADRB3, DEGS2, PRKACB, SLC44A1, CA4, LDLRAD3, DUSP15, GRK1 and AVPR2 (**Figure 7C**). To further validate our results, we analyzed another database to measure the expression of the genes listed above. As shown by the heat plot in **Figure 8A**, we found that the differences in CA4, SLC44A1, GRK1 and PRKACB expression were consistent with previous results. Moreover, we performed GSEA to gain further insight into the biological pathways involved in SSA/P progression through the PRKACB pathway and found that genes associated with cholesterol metabolism, glycan biosynthesis and fructose metabolism were enriched and correlated with PRKACB expression (**Figure 8B-D**). Therefore, the results indicated that PRKACB expression was associated with lipid metabolism. Additionally, we collected HP and SSA/P tissues to investigate PRKACB levels. As shown in **Figure 9A** and **9B**, we found that PRKACB protein was overexpressed in HP tissue compared to SSA/P tissue, which was consistent with the in silico analysis results. Based on IHC results, we analyzed the relationship among the levels of HDL, triglycerides, and LDL and found that PRKACB was positively associated with HDL but negatively associated with triglyceride levels (**Figure 9C-E**). Therefore, some differentially expressed mRNAs disturb lipid metabolism in the development of SSA/P.

## Discussion

To our knowledge, the serrated pathway accounts for 30%-35% of CRC. As principal precursors of CRC, the detection, classification and removal of serrated lesions represents a significant challenge for clinicians [24]. Regarding these challenges, it is important to understand serrated lesions from different aspects. Our study is the first to explore the profiles of lipid metabolism. Our study revealed that SSA/P patients had a lower level of HDL and a higher level of triglycerides than HP patients, whereas LDL levels did not significantly differ between these patients. When stratified by age, tumor size and smoking status, the results also implied that lower levels of HDL and higher levels of triglycerides occurred in SSA/P patients than in HP patients. These results suggested that disordered lipid metabolism promotes the development of SSA/P. Further-

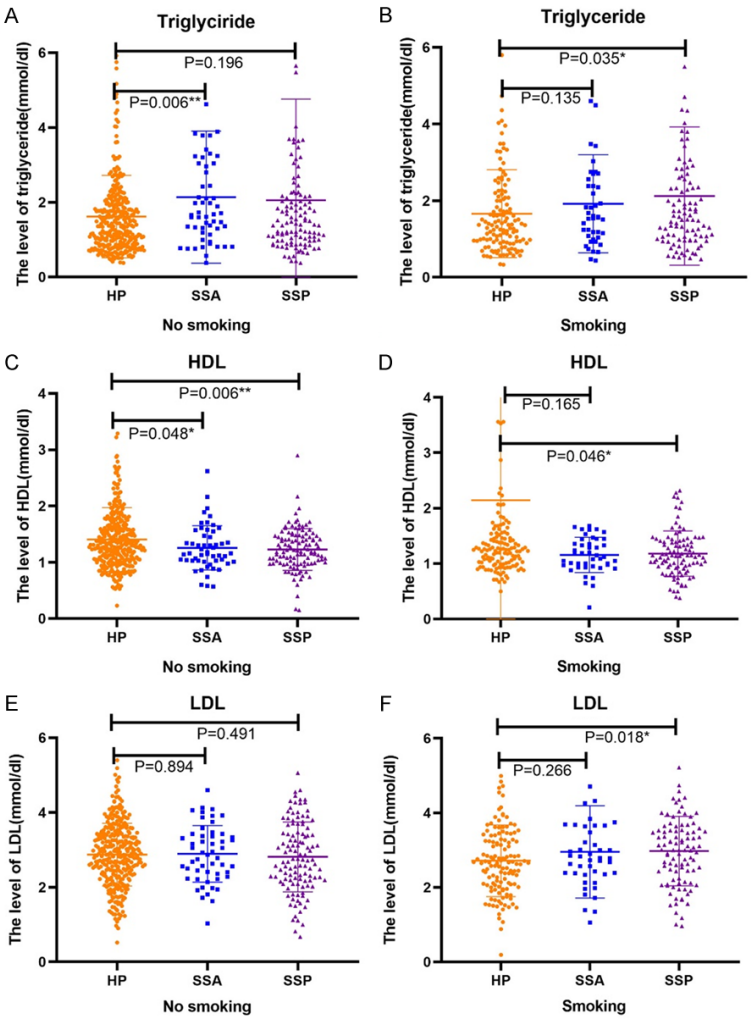


**Figure 6.** Scatter plot showed the level of triglyceride (A, B), HDL (C, D), and LDL (E, F) in patients with serrated lesion stratified by smoking, respectively.

more, genetic analysis also found some associated genes, such as PRKACB and CA4. In other words, genetic alterations disrupt the homeostasis of lipid metabolism and promote the progression of precursor lesions.

A large amount of evidence has demonstrated that increased BMI is strongly associated with CRC and CRC precursor lesions, such as adenomas and serrated polyps [25, 26]. Consistent with these findings, we also found that patients with SSA/P had a higher BMI than HP patients, suggesting a predisposition to obesity. This finding suggests that a higher BMI is strongly correlated with SSA/P [27]. Currently, early-onset precursor lesions are defined as cases that are diagnosed before 50 years of age [11, 28]. Compared to HP, SSA/P was more frequently noted in early-onset patients. Consistent with our results, a previous study also found that the ratio of early onset in SSA/P was markedly increased compared with other normal polyps [29]. Few studies have assessed the difference in bilirubin among the three subtypes of serrated lesions. Some studies have suggested that serum bilirubin could function as an antioxidant substance and that its level is associated with the redox status [30, 31]. Thus, these results suggest that the redox status differed between SSA/P and HP. Regarding the difference in tumor size, HP is generally smaller than 0.5 cm, whereas SSA or SSP is less than 1 cm [32, 33]. Consistent with previous studies, our findings also showed that HP was often less than 0.5 cm in size, whereas SSA could be up to 1 cm in size. Undoubtedly, the rate of smoking in SSA or SSP patients was greater than that in HP patients because some studies also demonstrated that smoking was an important lifestyle factor for SSA or SSP [34, 35].

Regarding lipid metabolism in serrated lesions, several studies have reported alterations in metabolic factors, such as obesity, hypertension and hyperuricemia, in patients with sessile serrated lesions (SSLs) or adenomas [14, 35]. At present, limited evidence has shown that patients with SSLs have hypertriglyceridemia; however, other indices have not been reported. In our study, we found that increased triglyceride levels and decreased HDL levels were more strongly associated with SSA or SSP, whereas the difference in LDL levels was not statistically significant. Similarly, a study reported that a high triglyceride to HDL ratio was associated with serrated polyps [14]. Genomic alterations associated with lipid metabolism have not been reported to date. Our study was the first to illustrate the genomic

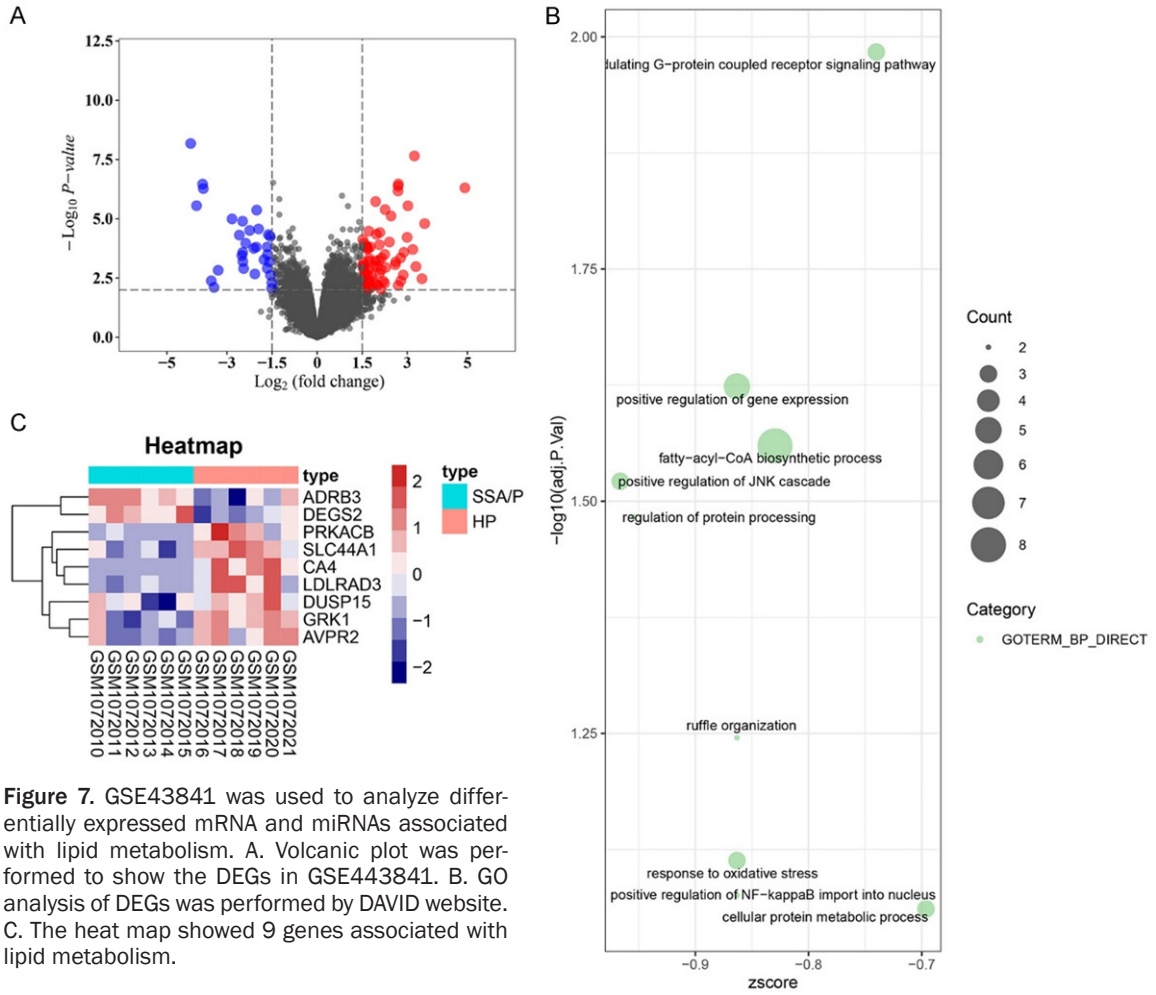


**Figure 7.** GSE43841 was used to analyze differentially expressed mRNA and miRNAs associated with lipid metabolism. A. Volcanic plot was performed to show the DEGs in GSE443841. B. GO analysis of DEGs was performed by DAVID website. C. The heat map showed 9 genes associated with lipid metabolism.

mechanism leading to a distinct profile of lipid metabolism in SSA or SSP compared to HP. Among those 9 genes, ADRB3, PRKACB, SLC44A1 and CA4 were reported to be associated with obesity and lipoprotein metabolism [36-39]. The association of ADRB3 with obesity and lipids has been extensively studied, and a mutation in ADRB3 could result in high LDL levels, high triglycerides, and lower HDL levels compared to normal controls [36, 40]. Some previous studies strongly supported reduced PRKACB expression in SSA/P. PRKACB is a catalytic subunit of protein kinase A (PKA), which regulates the ability of cyclic adenosine monophosphate (cAMP) molecules to bind to targets and the activity of PKA, subsequently mediating the activity of numerous enzymes, including lipase E and pancreatic enzymes [41, 42]. Howe et al. found that in the brains of PRKACB knockout mice, PKA activity was reduced by 26%, resulting in the accumulation of triglycerides and decreased lipid degradation [43]. Furthermore, in peripheral blood mononuclear cells (PBMCs), a study found that PRKACB was positively correlated with APOA1, which is a component of HDL [44]. In fact, oncological research has demonstrated that downregulation of PRKACB is involved in cell proliferation, apoptosis and cellular metabolism [42, 45]. However, further study is needed to demonstrate the association between lipid metabolism and PRKACB.

Finally, our study has some limitations. First, some data, such as BMI and ALB, were missing, causing some difficulties. However, multiple imputations were performed to complete the analysis. Second, because most serrated lesions were HP, we only included patients with HP from January 2018 to October 2021. In contrast, patients with SSA or SSP were diagnosed from January 2015 to October 2021.

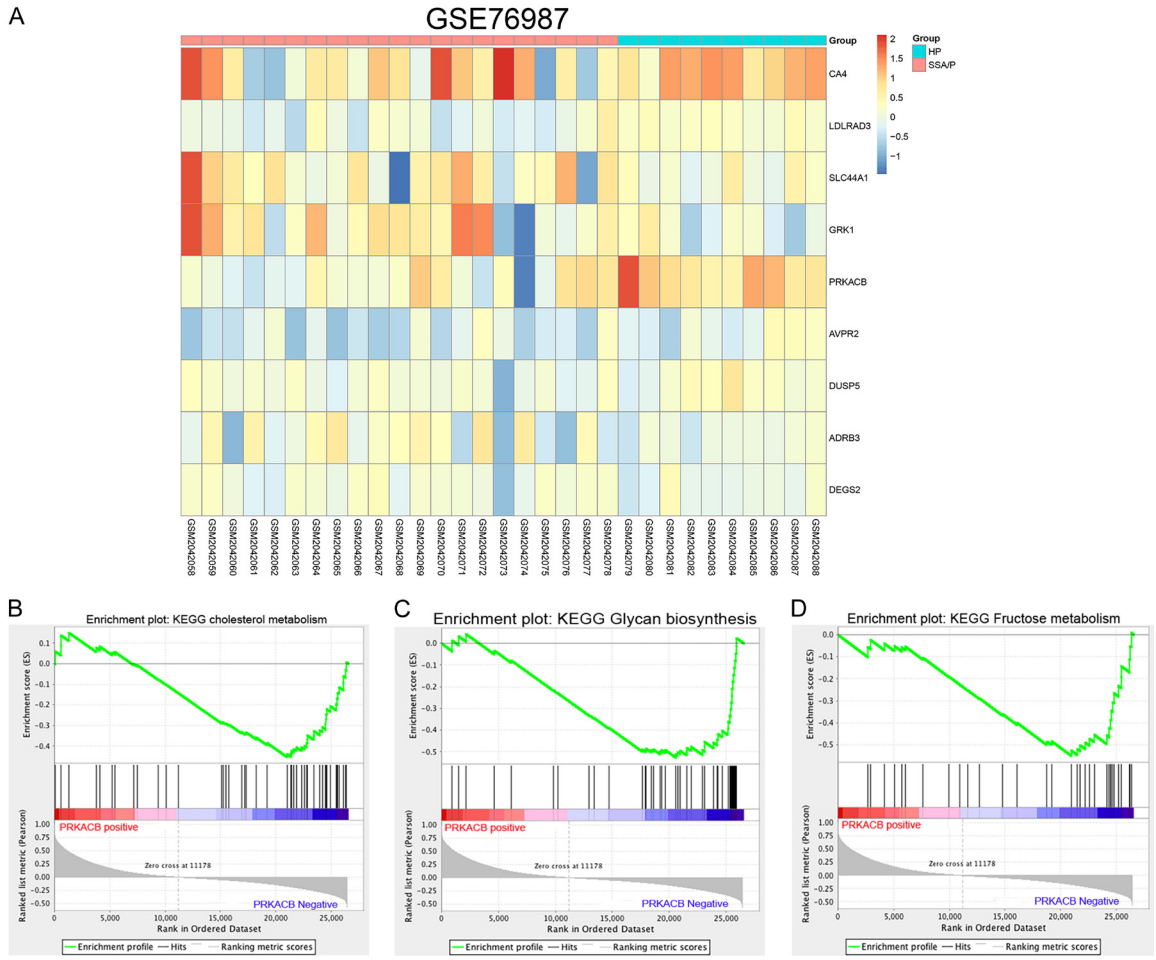


**Figure 8.** GSE76987 was used to demonstrated the results of GSE43841. A. The heat map showed 9 genes in GSE443841 associated with lipid metabolism. B-D. GSEA was performed by R software.

Thus, some HP patients were lost. Next, for the subgroup analysis, the difference in triglycerides and HDL in some subgroups was not significantly different potentially due to the limited sample size. Finally, some variables were not included in the analysis, such as cholesterol and blood pressure.

In conclusion, in a single-center retrospective study, we found that compared to benign HP, lower levels of HDL and higher levels of triglycerides tended to occur in CRC precursor SSA/P lesions. Consistent with previous studies, our results indicated that disordered lipid metabolism could be a risk factor for precursor lesions, which are associated with some metabolic genomic markers and miRNAs.

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## Disclosure of conflict of interest

None.

## Abbreviations

CRC, Colorectal cancer; SSA/P, Sessile serrated adenoma/polyp; HP, Hyperplastic polyp; HDL, High density lipoprotein; LDL, Low density lipoprotein; ALB, Albumin; Hb, Hemoglobin; DEGs, Differentially expressed genes; TB, Total bilirubin; DB, Direct bilirubin; SSLs, Sessile serrated lesions.

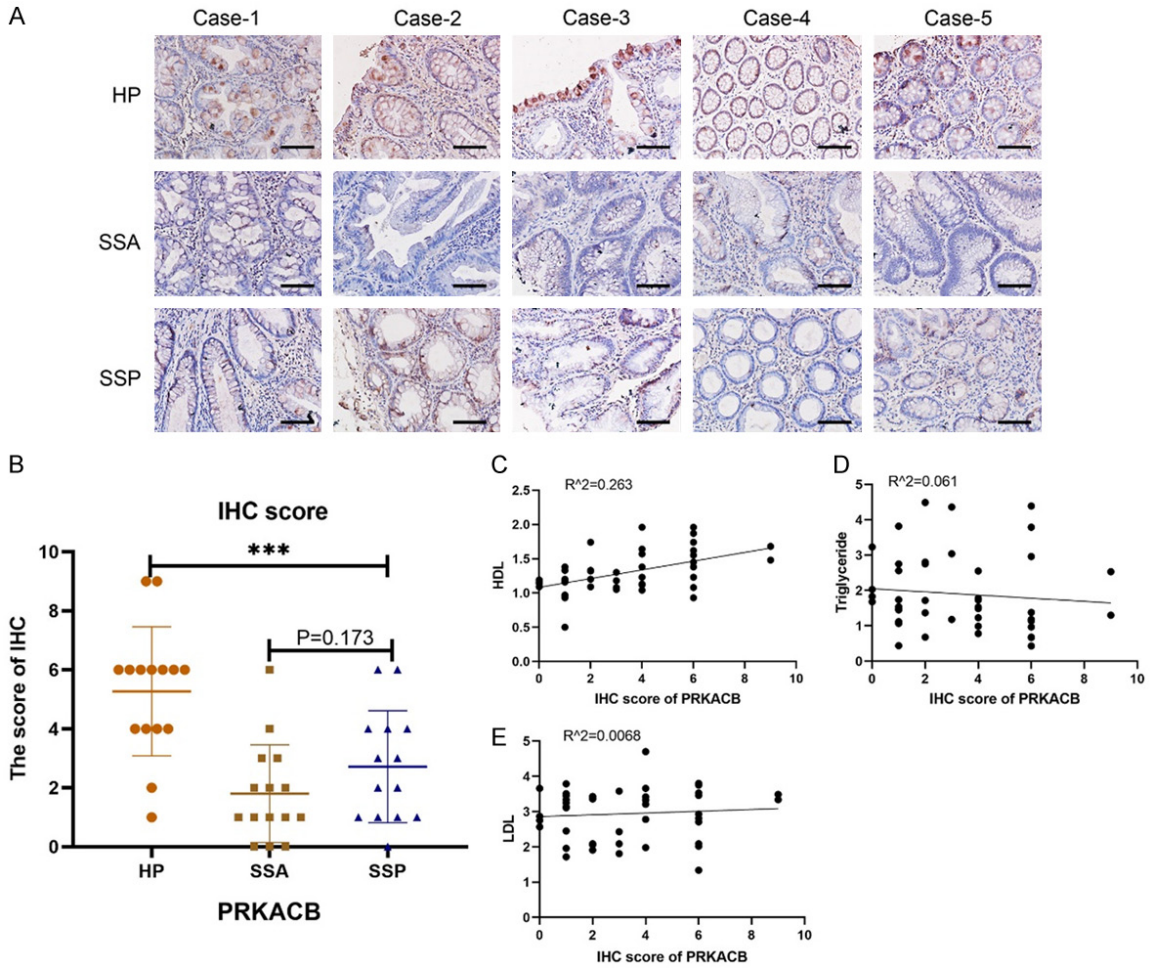


**Figure 9.** PRKACB was overexpressed in HP tissue compared to SSA/P. (A) The represented pictures of IHC (scale bar, 200×). (B) The statistical analysis of IHC results. The association of PRKACB expression with HDL (C), Triglyceride (D), LDL (E).

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