Impact of cigarette smoking on recurrence of hyperlipidemic acute pancreatitis

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AIM
To investigate the impact of cigarette smoking on the recurrence rate and recurrence-free survival in patients with hyperlipidemic acute pancreatitis (HLAP).

METHODS
A total of 863 patients were admitted to our hospital for acute pancreatitis (AP) from January 2013 to March
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2016, of whom 88 diagnosed with HLP were enrolled in this retrospective study. Demographic data, medical history, previous episodes of pancreatitis, consumption of alcohol and cigarettes, as well as biochemical and hematological data were carefully recorded for univariate and multivariate analyses. During follow-up, the information on current smoking status and recurrent AP was gathered. Recurrence-free survival (RFS) was calculated using the Kaplan-Meier method, and the differences between groups were compared using the log-rank test.

RESULTS
No significant differences were observed between the three groups in age or medical history of hyperlipidemia, fatty liver, diabetes mellitus, hypertension, or AP. The current smokers had a remarkably higher recurrence rate and a greater incidence of repeated episodes of AP (50.0% and 77.8%, respectively) than non-smokers (9.8% and 39.0%), and these two percentages were reduced to 9.1% and 36.4% for patients who gave up smoking. The median follow-up time was 13.5 mo and HLP recurrent after hospital discharge in 23 (26.1%) patients. Multivariate analysis identified current smoking (HR = 6.3, P = 0.020) as an independent risk factor contributing to HLP recurrence. Current smokers had significantly worse RFS than non-smokers (23 mo vs 42 mo), but no significant difference was documented between ex-smokers (34 mo) and non-smokers. The RFS was not significantly different between light and heavy smokers.

CONCLUSION
Smoking is associated with worse RFS and an increased rate of HLP recurrence. Continued smoking correlates with a compromised survival and smoking cessation should be recommended.

Key words: Acute pancreatitis; Hyperlipemia; Smoking; Recurrence; Epidemiology
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Core tip: This present study retrospectively enrolled hyperlipidemic acute pancreatitis (HLP) patients in a large regional central hospital and revealed that cigarette smoking was associated with worse recurrence-free survival and an increased rate of HLP recurrence. For smokers, continued smoking might be strongly correlated with HLP recurrence and compromised survival. Therefore, smoking cessation should be strongly recommended.

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INTRODUCTION
Acute pancreatitis (AP) is a potentially life-threatening acute inflammatory condition of the pancreas with high morbidity and mortality[1,2]. It is widely believed that the most common etiologies of AP are gallstone disease and alcohol abuse. Currently, 12%-20% of patients with AP have previous hypertriglyceridemia, which has become a well-recognized etiology[2-4]. Hyperlipidemic acute pancreatitis (HLP) is a form of AP occurring in the presence of severe hypertriglyceridemia and in the absence of other causes[5]. Some researchers even report hypertriglyceridemia as the underlying cause in more than half of all gestational pancreatitis cases[6]. Numerous studies have suggested that compared with other types of pancreatitis, HLP is associated with more complications, a longer course of disease, and a higher recurrence rate[7].

The exact pathophysiology of HLP is not entirely certain. At present, it is believed that HLP is related to injury in the pancreatic tissue (including acinar cells and pancreatic ducts) and microcirculation disturbance caused by free fatty acids (FFAs) that are produced by the pancreatic lipase, which catalyzes decomposition of triglycerides[5]. The resulting ischemia creates an acidic environment, which further triggers FFAs toxicity. In this way, inflammation can be initiated and amplified within the pancreas. Earlier studies found that cigarette smoking was independently associated with pancreatic cancer and chronic pancreatitis (CP) by leading to pancreatic calcification and abnormal secretion of the pancreatic ducts[8-10]. Notably, some recent studies identified that smoking was significantly associated with non-biliary AP instead of biliary AP[11,12], indicating different pathophysiological mechanisms for these subtypes. However, whether cigarette smoking has any long-term impact on HLP recurrence has not yet been investigated. Because the nicotine in tobacco can cause lipid metabolism disturbance and oxidative stress and further increase blood viscosity and microcirculation dysfunction in the pancreas[13], it is reasonable to hypothesize that smoking may be associated with the high recurrence rate of HLP.

This present study retrospectively enrolled HLP patients treated at a large regional central hospital. The impact of cigarette smoking on recurrence rate and recurrence-free survival (RFS) in HLP patients was investigated.

MATERIALS AND METHODS
Patients and diagnosis
A total of 863 patients were admitted to our hospital...
for AP from January 2013 to March 2016, of whom 90 were hospitalized at least twice. Among these patients, those with biliary pancreatitis, alcoholic pancreatitis, and other causes were excluded from the study. The remaining 88 patients identified with HLAP were enrolled. The diagnosis of HLAP was made if patients had AP in the presence of serum total triglyceride (TG) > 11.3 mmol/L (1000 mg/dL), or had a serum level of 5.65 to 11.3 mmol/L accompanied by chylous serum after excluding other known risk factors for AP. The diagnosis of AP requires at least two of the following three features: acute upper abdominal pain often radiating through to the back, serum amylase and/or lipase levels ≥ three times the upper limit of normal, and evidence of pancreatitis upon abdominal imaging[14]. The work described was carried out in accordance with The Code of Ethics of the World Medical Association. This research was approved by the Ethics Committees of the First Affiliated Hospital of Medical College, Xi'an Jiaotong University.

**Tobacco and alcohol exposure assessment**

Data on tobacco exposure were obtained from the baseline questionnaire and telephone follow-up. All patients were asked if they smoke regularly and, if so, for how many years they had smoked and the average number of cigarettes they smoked per day. Smoking data included smoking pack-years (PY, packages of cigarettes smoked per day multiplied by the number of years for which the individual has smoked). Smoking status was defined as non-smoker (<100 cigarettes during lifetime), ex-smoker, and current smoker. An ex-smoker was defined as one who had quitted smoking for more than 6 mo before the end of follow-up after being discharged from the hospital. A current smoker was defined as one who smoked at least 1 cigarette per day for over 1 year and continued to smoke within 1 year prior to follow-up. Tobacco exposure was characterized as none, light smoker (0 < PY < 10), and heavy smoker (PY ≥ 10)[15,16]. Since alcohol and smoking are often linked behaviors[17], there are questions about the independent influence of smoking. Therefore, exposure of alcohol was also investigated and taken into consideration. In accordance with previous guidelines, a high drinker was defined as one who has drunk at least 40 g/d (20 g/d for female) for over 5 years. Smokers and alcohol abusers were routinely encouraged to give up these bad habits.

**Treatment and follow-up**

All the patients were treated with comprehensive routine therapy, including restriction of oral intake, fluid expansion, parenteral nutrition, analgesia, proton pump inhibitor administration, inhibition of pancreatic enzyme secretion, antibiotics, early enteral nutrition, and plasma exchange, if needed[18].

The information on demographic data, history of hypertriglyceridemia, fatty liver, diabetes, hypertension, previous episodes of pancreatitis, consumption of alcohol and cigarettes, as well as biochemical and hematological data were carefully recorded at admission. During follow-up, we gathered information on current smoking status and recurrent AP. Repeated episodes were defined as patients who were diagnosed with AP more than twice during their lifetime. To avoid recurrence, all patients were counseled to continue dietary fat restriction after treatment. Lipid lowering agents were used for patients when necessary.

### Statistical analysis

Statistical analyses were performed with the SPSS 21.0 software package (SPSS Inc., Chicago, IL, United States). Continuous variables are expressed as the mean ± SE, and comparisons between groups were performed using non-parametric tests, the t-test, or ANOVA, as appropriate. Categorical variables were compared between groups using the χ² test or Fisher’s exact test. RFS was calculated using the Kaplan-Meier method, and the differences between groups were compared using the log-rank test. Risk factors for the recurrence of HLAP were analyzed by univariate analysis first, and those with P < 0.20 and possible clinical effect were included in multivariate analysis using a Cox proportional hazards model. A P value < 0.05 was considered statistically significant. The statistical methods and results of this study were reviewed by a biostatistician (Qian Li, PhD) at Xi’an Jiaotong University.

### Results

Of the 88 patients with HLAP who were enrolled and analyzed (66 men and 22 women with a mean age of 40.9 ± 1.1 year), 36 and 11 patients were documented as current smokers and ex-smokers, respectively, while 41 patients had no cigarette smoking history. The characteristics of the patients in the three groups are shown in Table 1. No significant differences were observed between the three groups in age or medical history of hyperlipemia, fatty liver, diabetes mellitus, hypertension, or AP. Of the current smokers, 55.6% had a history of AP, which was significantly higher than that of non-smokers (31.7%). Cigarette smoking patients were more likely to have concomitant alcohol abuse than non-smokers (P = 0.037), and more male patients than females tended to smoke. Biochemical tests of serum TG, cholesterol (CHOL), amylase, lipase, and calcium levels were not significantly different between these groups, and nor were the leukocyte and platelet counts. Patients who currently or previously smoked had higher systemic inflammatory response syndrome (SIRS) proportions and bedside index for severity in acute pancreatitis (BISAP) scores than non-smokers, but the differences were not significant.
Table 1  Clinical characteristics of the hyperlipidemic acute pancreatitis patients

| Clinical parameter | Non-smokers | Current-smokers | Ex-smokers | P value |
|-------------------|-------------|----------------|------------|---------|
| N                 | 41          | 36             | 11         |         |
| Age (yr)          | 42.7 ± 2.0  | 39.1 ± 1.2     | 40.0 ± 2.2 | 0.446   |
| Gender (M/F)      | 20/21       | 36/0           | 10/1       | <0.001* |
| Heavy alcohol drinking | 4        | 12             | 2          | 0.037*  |
| Smoking pack-years | 0          | 13.5 ± 2.2     | 7.8 ± 2.9  | <0.001* |
| History of hyperlipemia | 39       | 30             | 8          | 0.084   |
| History of fatty liver | 16       | 15             | 4          | 0.943   |
| History of diabetes mellitus | 10      | 14             | 5          | 0.258   |
| History of hypertension | 8       | 3              | 2          | 0.364   |
| History of AP     | 13          | 20             | 5          | 0.065*  |
| Leukocyte (× 10^9/L) | 12.5 ± 0.5 | 13.1 ± 0.7    | 12.3 ± 1.1 | 0.506   |
| Platelet count (× 10^9/L) | 185.2 ± 11.8 | 171.7 ± 8.2 | 175.6 ± 20.1 | 0.680 |
| Serum CHOL (mmol/L) | 18.5 ± 1.7 | 15.1 ± 1.5    | 17.1 ± 2.9 | 0.358   |
| Serum amylase (U/L) | 9.0 ± 0.6 | 8.4 ± 0.6     | 8.0 ± 0.8  | 0.316   |
| Serum lipase (U/L) | 569.3 ± 104.5 | 507.7 ± 111.4 | 629.8 ± 121.9 | 0.270 |
| Serum calcium (mmol/L) | 2.0 ± 0.04 | 2.1 ± 0.04    | 2.0 ± 0.08 | 0.197   |
| SIRS              | 17          | 17             | 8          | 0.182   |
| BISAP score       | 0.8 ± 0.1   | 0.8 ± 0.2      | 1.4 ± 0.3  | 0.224   |
| Hospitalization (d) | 10.9 ± 0.8 | 8.6 ± 0.7     | 11.9 ± 1.6 | 0.015*  |
| Recurrence of AP  | 4           | 18             | 1          | <0.001* |
| Repeated episodes of AP | 16    | 28             | 4          | 0.001*  |

*P < 0.05, current vs non-smokers; *Exclude those discharged without medical advice or transferred to a different hospital. AP: Acute pancreatitis; TG: Total triglyceride; CHOL: Cholesterol; SIRS: Systemic inflammatory response syndrome; BISAP: Bedside index for severity in acute pancreatitis.

In addition, current smokers had a remarkably higher recurrence rate and a greater incidence of repeated episodes of AP (50.0% and 77.8%, respectively) than non-smokers (9.8% and 39.0%, respectively). It is worth noting that these two percentages were reduced to 9.1% and 36.4% for patients who gave up smoking after being discharged from the hospital.

The median follow-up time was 13.5 mo (2-42 mo) by September 2016. HLAP occurred after discharge from the hospital in 23 (26.1%) patients. To investigate the risk factors contributing HLAP recurrence, we examined 19 potential variables and analyzed them by univariate analysis, as shown in Table 2. Univariate analysis identified that smoking history and smoking pack-years were risk factors associated with higher HLAP recurrence. Specifically, current smoking was a risk factor relative to non-smoking (HR = 5.1, 95%CI: 1.7-15.2, P = 0.003). Smoking PY < 10 was a protective factor relative to PY ≥ 10 (HR = 0.4, 95%CI: 0.2-0.9, P = 0.035). Additionally, the following three variables had a P value < 0.20: gender (P = 0.168), history of hyperlipemia (P = 0.141), and history of AP (P = 0.117). When introducing the five variables with P value < 0.20 in univariate analysis into multivariate analysis using a Cox proportional hazards model, we identified current smoking (HR = 6.3, 95%CI: 1.3-29.8, P = 0.020) as an independent risk factor contributing to HLAP recurrence (Table 3).

During follow-up, four non-smoker patients, one ex-smoker patient, and 18 current smoker patients experienced AP recurrence with different RFS time. Figure 1 shows the Kaplan-Meier curves for RFS of non-, ex-, and current smokers. The median RFS time in non-smokers, ex-smokers, and current smokers was 42 mo, 34 mo, and 23 mo, respectively (P = 0.002).

Current smokers had significantly worse RFS than non-smokers (P = 0.001), but no significant difference in RFS was documented between ex-smokers and non-smokers (P = 0.962). Kaplan-Meier curves for RFS in non-smokers (PY = 0), light smokers (0 < PY < 10), and heavy smokers (PY ≥ 10) are shown in Figure 2. The median RFS of non-smokers, light smokers, and heavy smokers was 42 mo, 23 mo, and 30 mo, respectively, indicating that the RFS was significantly worse in smokers than in non-smokers (P = 0.014). However, the RFS was not significantly different between light and heavy smokers (P = 0.749).

**DISCUSSION**

In the present study, univariate and multivariate analyses identified that cigarette smoking status is an independent risk factor contributing to the recurrence of HLAP[19]. To the best of our knowledge, this is the first study evaluating the influence of cigarette smoking on HLAP recurrence. A recent comprehensive study analyzed 2810 patients (1065 with gallstone-related AP, 1222 with non-gallstone related AP, and 523 with recurrent AP/CP) and demonstrated that cigarette smoking was associated with non-gallstone-related AP and recurrent AP/CP[12]. Unfortunately, this study did not evaluate any correlation between cigarette smoking and HLAP recurrence. As non-gallstone-related AP was a broad category including various...
causes and pathogeneses, it was difficult to analyze the pathophysiologic mechanism of cigarette smoking leading to recurrent HLAP. The most significant difference between the study by Setiawan et al[12] and ours is that our study takes HLAP into consideration as a specific disease to evaluate the effects of cigarette smoking on HLAP recurrence.

Notably, current smokers appeared to be associated with a higher recurrence rate and a greater incidence of repeated episodes of AP. In addition, the RFS was significantly worse in smokers than in non-smokers. However, the RFS was not significantly different between light and heavy smokers. This finding implied that cigarette smoking might contribute to HLAP recurrence but not in a dose- or duration-dependent manner; however, this could not be fully demonstrated in the present study due to short follow-up period and the small number of patients enrolled. Rebours et al[9] demonstrated in their study that alcoholic CP occurred earlier at a 20-pack-year threshold, and that patients had more calcifications. Similar results were observed in other research[8,11,20] with regard to CP or AP. Therefore, the importance of smoking in the recurrence of different AP cases might differ. Whether the level of tobacco exposure influences HLAP recurrence and RFS needs to be further evaluated.

Interestingly, ex-smokers who had quit smoking for at least 6 mo after discharge from the hospital had a significant advantage with regard to the recurrence rate and RFS compared to current smokers in the present study. Univariate and multivariate analyses also demonstrated that current smoking was an independent risk factor contributing to HLAP recurrence. Therefore, lifestyle modifications are a key feature in the long-term management of HLAP[21,22]. Due to a possible increase in recurrence rate related to smoking, doctors should always strongly suggest that the patient quit smoking once HLAP has been diagnosed. Moreover, current smokers had a higher

Table 2  Univariate analysis of risk factors for recurrence of hyperlipidemic acute pancreatitis

| Variable                                | n     | Number of recurrence | HR (95%CI) | P value |
|-----------------------------------------|-------|----------------------|------------|---------|
| Age (≤ 40/> 40, yr)                     | 46/42 | 14/9                 | 0.7 (0.3-1.6) | 0.417   |
| Gender (M/F)                            | 66/22 | 20/3                 | 2.4 (0.7-7.9) | 0.168   |
| Heavy alcohol drinking (Y/N)            | 18/70 | 6/17                 | 1.4 (0.5-3.5) | 0.507   |
| Smoking history (Y/N)                   | 47/41 | 19/4                 | 4.3 (1.4-12.5) | 0.009   |
| Non-smokers                             | 41    | 4                    | 1 (ref.)    | 1 (ref.) |
| Current-smokers                         | 36    | 18                   | 5.1 (1.7-15.2) | 0.005   |
| Ex-smokers                              | 11    | 1                    | 1.1 (0.1-9.9) | 0.999   |
| Smoking pack-years (> 0 but < 10/> ≥ 10) | 64/24 | 11/12                | 0.4 (0.2-0.9) | 0.035   |
| 0                                       | 41    | 4                    | 1 (ref.)    | 1 (ref.) |
| 0 < PY < 10                             | 23    | 7                    | 3.8 (1.1-13.1) | 0.032   |
| ≥ 10                                    | 24    | 12                   | 4.6 (1.5-14.2) | 0.009   |
| History of hyperlipemia (Y/N)           | 77/11 | 18/5                 | 0.5 (0.2-1.3) | 0.141   |
| History of fatty liver (Y/N)            | 35/53 | 9/14                 | 1.0 (0.4-2.2) | 0.917   |
| History of diabetes mellitus (Y/N)      | 29/59 | 10/13                | 1.7 (0.7-3.9) | 0.208   |
| History of hypertension (Y/N)           | 13/75 | 2/21                 | 0.7 (0.2-2.9) | 0.585   |
| History of AP (Y/N)                     | 36/52 | 13/10                | 1.9 (0.8-4.4) | 0.117   |
| Leukocyte (< 10/> ≥ 10, × 10³/L)        | 23/65 | 5/18                 | 0.6 (0.2-1.7) | 0.379   |
| Platelet count (< 100/> ≥ 100, × 10³/L) | 4/84  | 1/22                 | 0.8 (0.1-5.7) | 0.790   |
| Serum TG (< 11.3/> ≥ 11.3, mmol/L)      | 32/56 | 7/16                 | 0.9 (0.4-2.2) | 0.813   |
| Serum CHOL (< 5.5/> ≥ 5.5, mmol/L)      | 16/72 | 4/19                 | 1.0 (0.3-2.8) | 0.934   |
| Serum amylase (< 540/> ≥ 540, U/L)      | 62/26 | 18/5                 | 1.6 (0.6-4.4) | 0.335   |
| Serum lipase (< 600/> ≥ 600, U/L)       | 31/34 | 8/9                  | 0.6 (0.2-1.5) | 0.275   |
| Serum calcium (< 2.0/> ≥ 2.0, mmol/L)   | 28/60 | 8/15                 | 1.0 (0.4-2.3) | 0.918   |
| SIRS (Y/N)                              | 42/46 | 11/12                | 1.1 (0.5-2.4) | 0.858   |
| BISAP score (< 2/> ≥ 2)                 | 69/19 | 19/4                 | 1.3 (0.5-3.9) | 0.610   |

1Data of the parameter in 65 of patients were available. AP: Acute pancreatitis; TG: Total triglyceride; CHOL: Cholesterol; SIRS: Systemic inflammatory response syndrome; BISAP: Bedside index for severity in acute pancreatitis; HR: Hazard ratio; CI: Confidence interval.

Figure 1 Kaplan-Meier curves for the recurrence-free survival of non-, ex-, and current smokers.
Hyperlipidemic acute pancreatitis (HLAP) is a form of AP occurring in the presence of severe hypertriglyceridemia and in the absence of other causes. The exact pathophysiology of HLAP is not entirely certain. It is believed that HLAP is related to pancreatic tissue injury and microcirculation disturbance caused by free fatty acids. Some recent studies identified that smoking was significantly associated with non-biliary AP instead of biliary AP, but whether cigarette smoking has any long-term impact on HLAP recurrence has not yet been investigated. This is the first study evaluating the influence of cigarette smoking on HLAP recurrence.

**Research background**

Hyperlipidemic acute pancreatitis (HLAP) is a form of AP occurring in the presence of severe hypertriglyceridemia and in the absence of other causes. The exact pathophysiology of HLAP is not entirely certain. It is believed that HLAP is related to pancreatic tissue injury and microcirculation disturbance caused by free fatty acids. Some recent studies identified that smoking was significantly associated with non-biliary AP instead of biliary AP, but whether cigarette smoking has any long-term impact on HLAP recurrence has not yet been investigated. This is the first study evaluating the influence of cigarette smoking on HLAP recurrence.

**Research motivation**

Authors performed this study to better understand the relationship between cigarette smoking and pain, as well as the pathophysiologic mechanism of recurrent pain.

**Research objectives**

The main objective of this study was to investigate the impact of cigarette smoking on the recurrence rate and recurrence-free survival in HLAP. The authors found that cigarette smoking was associated with worse RFS and an increased recurrence rate of HLAP. These findings provide references for further clarifying the mechanism of HLAP.

**Research methods**

A total of 88 patients diagnosed with HLAP were enrolled in this retrospective study. Demographic data, medical history, previous episodes of pancreatitis, consumption of alcohol and cigarettes, as well as biochemical and hematological data were carefully recorded for univariate and multivariate analyses. During follow-up, the information on current smoking status and smoking cessation was recorded.

**Research results**

Current smokers had a remarkably higher recurrence rate and a greater percentage of cases with pancreatic tissue injury and microcirculation disturbance compared to non-smokers. The main cause of HLAP is the high concentration of free fatty acids caused by smoking. These findings provide references for further clarifying the mechanism of HLAP.

**ARTICLE HIGHLIGHTS**

- **Research background**
  - Hyperlipidemic acute pancreatitis (HLAP) is a form of AP occurring in the presence of severe hypertriglyceridemia and in the absence of other causes.
  - The exact pathophysiology of HLAP is not entirely certain. It is believed that HLAP is related to pancreatic tissue injury and microcirculation disturbance caused by free fatty acids.
  - Some recent studies identified that smoking was significantly associated with non-biliary AP instead of biliary AP.
  - Whether cigarette smoking has any long-term impact on HLAP recurrence has not yet been investigated.

- **Research motivation**
  - Authors performed this study to better understand the relationship between cigarette smoking and pain, as well as the pathophysiologic mechanism of recurrent pain.

- **Research objectives**
  - The main objective of this study was to investigate the impact of cigarette smoking on the recurrence rate and recurrence-free survival in HLAP.
  - The authors found that cigarette smoking was associated with worse RFS and an increased recurrence rate of HLAP.

- **Research methods**
  - A total of 88 patients diagnosed with HLAP were enrolled in this retrospective study. Demographic data, medical history, previous episodes of pancreatitis, consumption of alcohol and cigarettes, as well as biochemical and hematological data were carefully recorded for univariate and multivariate analyses.

- **Research results**
  - Current smokers had a remarkably higher recurrence rate and a greater incidence of repeated episodes of AP than non-smokers, and these two percentages were reduced to 9.1% and 36.4% for patients who gave up smoking.
  - The median follow-up time was 13.5 mo. Multivariate analysis identified current smoking as an independent risk factor contributing to HLAP recurrence.
recurrence. Current smokers had significantly worse RFS than non-smokers, but no significant difference was documented between ex-smokers and non-smokers.

Research conclusions
In the present study, the authors found that cigarette smoking was associated with worse RFS and an increased recurrence rate of HLAP. For smokers, continued smoking might be strongly correlated with HLAP recurrence and compromised survival. Smoking cessation for at least 6 mo would lead to a significant advantage in recurrence rate and RFS compared to current smokers.

Research perspectives
The study revealed that smoking is associated with worse RFS and higher recurrence rate of HLAP. Besides, smoking cessation for at least 6 mo would lead to a significant advantage in recurrence rate and RFS compared to current smokers. For the future research, more detailed classification is needed to clarify the potential dose- and duration-dependent correlation between cigarette smoking and HLAP. Besides, expanding the number of cases and long-term follow-up are needed.

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