Full Title

Effects of laparoscopic sleeve gastrectomy on non-alcoholic steatohepatitis and liver fibrosis in Japanese patients with severe obesity

Short Title Effects of LSG on NASH and liver fibrosis

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Title: Effects of laparoscopic sleeve gastrectomy on non-alcoholic steatohepatitis and liver fibrosis in Japanese patients with severe obesity

Abstract

Background The prevalence of nonalcoholic steatohepatitis (NASH) in Japanese patients with severe obesity is extremely high. The aim of the present study was to evaluate the metabolic and histological effects of laparoscopic sleeve gastrectomy (LSG) on NASH and liver fibrosis in Japanese patients with severe obesity.

Methods Between June 2008 and March 2019, all 79 patients with severe obesity who underwent LSG were included in the study. Sixty-eight patients had an intraoperative liver biopsy performed at the time of LSG. Ultrasound-guided liver biopsies were performed in patients with fibrosis at 12 months after LSG.

Results NASH was present in 43 patients (63.2%) and 10 patients had a unique feature in which their fibrosis were observed without steatosis at the time of LSG. Of the 28 patients with NASH, 25 showed improvement and no longer met the diagnostic criteria of NASH at 12 months after LSG. Mean pericellular fibrosis scores showed significant improvement from 1.62 at baseline, to 1.50, 1.00, and 0.78, respectively ($p < 0.001$). Univariate analysis of the preoperative predictors in the improvement of fibrosis showed significant effects in preoperative weight ($p = 0.037$), HbA1c ($p = 0.037$), and serum insulin ($p = 0.037$). Multivariate analysis revealed HbA1c to be the only preoperative

predictor of improvement in fibrosis (p = 0.004; odds ratio 0.440, 95% CI: 0.229–0.842).

Conclusion LSG has great potential as an effective treatment for patients with NASH.

Keywords

Non-alcoholic steatohepatitis, Morbid obesity, Bariatric surgery, Laparoscopic sleeve gastrectomy

Introduction

The increasing global prevalence of obesity (BMI > 30 kg/m^2) presents major social and public-health burdens [1]. Although in Japan the prevalence of morbid obesity remains lower than in the United States, it is bound to increase owing to several lifestyle changes

[2,3]. Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases worldwide, and obesity represents a well-documented risk factor for NAFLD [4,5]. The prevalence of NAFLD is the highest in patients with metabolic diseases such as type 2 diabetes mellitus (T2DM) and dyslipidemia. The spectrum of NAFLD encompasses simple nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). Patients with NASH are at increased risk for cirrhosis and liver disease-related death, due to advanced fibrosis.

In obese patients, NAFLD favorably responds to weight loss and treatment of insulin resistance [4]. However, maintaining long-term weight loss by pharmaceutical treatment or lifestyle modification has proven difficult. In contrast, several types of metabolic surgery (MS) produce enduring weight loss and improvements in obesity-related diseases [6,7]. Although some studies suggest that MS also improves NAFLD [4,5,8], few available reports document long-term postoperative improvements of liver histopathology. The aim of the present study was to evaluate the metabolic and histological effects of laparoscopic sleeve gastrectomy (LSG) on NASH and liver fibrosis in Japanese patients with severe obesity.

Methods

Patients

Severely obese patients who underwent LSG at the Iwate Medical University Hospital between June 2008 and March 2019 were considered for inclusion. All patients met the following inclusion criteria for LSG treatment established by Japanese insurance practice: between 18 and 65 years of age, severe obesity (BMI > 35 kg/m^2), and the presence of at least one comorbidity with resistance to medical treatment (hypertension, T2DM, dyslipidemia, and obstructive sleep apnea). Exclusion criteria were history of alcohol abuse, secondary obesity (drug-induced or due to endocrine diseases), and the presence of major psychiatric disorders. With a target of preoperative weight loss of 5% or more, we use a total of 1,200 to 1,400 kcal daily meals including a formula diet once a day.

A prospective database of patients treated within a single institution was studied retrospectively. The following data were collected at baseline and at 6, 12, and 24 months: BMI, hemoglobin A1c (HbA1c), glucose, insulin, C peptide, HOMA-IR, ferritin, type IV collagen 7S, hyaluronic acid, AST, ALT, NAFLD activity score (NAS) [9], and fibrosis score. In addition, the liver volume, quantity of visceral fat at the level of the navel, and the liver-to-spleen (L/S) ratio were measured by CT using SYNAPSE VINCENT imaging

software (FUJIFILM, Tokyo, Japan).

Based on clinical data obtained at baseline, we established the NAFIC score [10], the FIB-4 index [11], and the NAFLD fibrosis score (NFS) [12]. This study was approved by the institutional ethics committee of Iwate Medical University (approval number: H27-47). We obtained informed consent from all participants before their LSGs were performed, and patient anonymity was strictly preserved.

Liver histology

All 79 patients with severe obesity underwent LSG. Eleven patients were excluded due to the following: no liver biopsies (9 patients) or insufficient specimens (2 patients). Consequently, a total of 68 patients were enrolled in this study (Fig.2).

Postoperative ultrasound-guided liver biopsies were obtained at 6, 12, and 24 months after LSG in patients diagnosed with NASH or those whose intraoperative biopsy showed fibrosis. A specialized pathologist evaluated the diagnosis of NAFLD, NAS scores, and staging of the Brunt classification [13] according to the evaluation methods proposed by the Japanese Society of Pathology [14]. A specially developed “pericellular fibrosis score,” was also assessed. This score reflected the extent of pericellular fibrosis around the central

veins as follows: no fibrosis (Score 0), pericellular fibrosis confined to the proximity of central veins and present in <50% of central veins (Score 1), pericellular fibrosis confined to the proximity of central veins and present in 50% or more of central veins (Score 2), pericellular fibrosis around the central veins with periportal fibrosis or bridging fibrosis (Score3) (Fig.1).

Potential predictors for postoperative improvement of pericellular fibrosis were also explored. We compared the pericellular fibrosis scores of intraoperative and postoperative liver biopsies, and performed logistic regression analysis of the improved versus the unchanged group of patients at 12 months after LSG. However, we accepted liver biopsies performed 6 months before and after the standard time point because the timing of liver biopsy differed due to the patient's social factors.

Statistical analysis

Data are presented as numbers and percentages for categorical variables, and as means ± standard deviations for continuous variables. Statistical analysis was performed using chi-square tests for categorical variables; Student's *t*-tests or Mann–Whitney U tests for

continuous variables. We used paired *t*-tests or Wilcoxon tests for continuous variables to enable comparison of all parameters between pre- and postoperative measures. Potential factors predicting improvement of fibrosis were then analyzed by univariate and multivariate analyses, and by using a logistic regression model. First, we performed a univariate logistic regression analysis with several independent factors affecting improvement of pericellular fibrosis scores. Then, we added significant ($p < 0.05$) variables to the logistic regression model. P-values < 0.05 were considered statistically significant. All statistical analyses were performed using JMP pro, version 14 (SAS Institute Inc., Cary, NC, USA).

Results

Liver histology of intraoperative biopsies

NASH was present in 43 patients (63.2%), 14 patients showed NAFL, and one patient had a healthy liver at the time of the intraoperative liver biopsies. In addition, 10 patients had a unique feature in which their fibrosis were observed without steatosis. The clinical characteristics of all patients are summarized in Table 1. The mean preoperative weight

loss period was 61.5 days. The mean preoperative decrease of BMI was significantly lower in NASH than in non-NASH patients (3.4 vs. 5.9 kg/m^2, $p < 0.001$). Furthermore, the prevalence of T2DM was significantly higher in NASH than in non-NASH patients (78.5 vs. 48.0%, $p = 0.01$).

Clinical and metabolic changes after surgery

Patients' clinical and metabolic parameters improved after LSG (Table 2). At 12 months after LSG, the mean percent total body weight loss (% TWL) was 26.4% in NASH and 31.4% in non-NASH patients. Visceral adipose tissue content, liver volume, platelets, insulin, HbA1c, HOMA-IR, AST, ALT, and TG were significantly improved at 12 months after LSG in both groups. In NASH patients, AST and ALT significantly improved ($p < 0.001$). Conversely, the two measured markers of liver fibrosis, hyaluronic acid and type IV collagen 7S had not improved in either group.

Predictive validity of the preoperative scoring system for NASH diagnosis

When using the NAFIC score, FIB-4 index, and NFS, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy are shown in Table 3. When applying these cutoff scores of NFS, 62% patients were classified as having

intermediate values of NFS.

Changes in liver histology

Postoperative liver biopsies were performed in 34 patients after LSG. Twenty-eight of 34 patients were diagnosed NASH at baseline. Twenty-five of 28 patients (89.2%) with NASH showed improvement of NASH and no longer met the diagnostic criteria of NASH. In NASH patients, mean NAS scores showed significant decreases at 6 months after LSG (Fig. 3A, 3B). Mean pericellular fibrosis scores showed significant improvement at 12 months after LSG (Fig. 3C). Compared with steatosis and inflammation, fibrosis required a longer period before improvement.

On the other hand, in the patients with fibrosis but without steatosis, NAS scores was very low at the time of LSG; however, liver fibrosis remains from intraoperative to two years after LSG (Fig. 4).

Analysis of predictors for postoperative improvement of pericellular fibrosis

Univariate analysis identified significant group differences in weight ($p = 0.037$), HbA1c ($p = 0.037$), and serum insulin ($p = 0.037$) at baseline. Multivariate analysis revealed HbA1c to be the only preoperative predictor of improvement in pericellular fibrosis

scores (p = 0.004, odds ratio 0.440; 95% CI: 0.229–0.842) (Table 4).

Discussion

In Japan, according to the National Health and Nutrition Examination Survey of 2017, 25.2% (male 29.7%, female 21.2%) of the population had a BMI of ≥25 kg/m² [15]. Eguchi et al. reported that the overall prevalence of NAFLD in adults is 29.7%. The prevalence of NAFLD was 89.1% in obese patients (BMI > 30 kg/m²). The authors reported that the estimated prevalence of NASH based on the BAAT score [16] was 2.7%, whereas based on the FIB-4 index, it was 1.9% in the general population [17]. Seki et al. reported that the prevalence of NASH in Japanese morbidly obese patients who underwent bariatric surgery was 77.5% (79 of 102 patients) based on intraoperative liver biopsies [3]. In our study, 43 of 68 patients were diagnosed with NASH. Moreover, 10 patients showed unique histological features; their liver fibrosis were observed without steatosis.

We have not performed preoperative ultrasound guided liver biopsies because it is difficult to perform safely due to thick subcutaneous fat. Most of the patients were

suspected to have fatty liver from CT, so we assumed that most patients were NASH or NAFL at the first visit, and that there was almost no normal liver. Therefore, we performed intraoperative liver biopsies in all patients and diagnose liver histological findings. Intraoperative liver biopsy revealed 10 cases in which only liver fibrosis was observed without steatosis. These patients showed larger preoperative weight loss than the NASH patients. In addition, in the postoperative liver biopsies, the similar histopathological findings were observed in some patients diagnosed as NASH at intraoperative liver biopsy. Therefore, we speculated that these were the histopathological features in the healing process of NASH. These findings were regarded to be resulting from improvement that occurred in a time lag; the steatosis may have immediately improved, but fibrosis required more time for improvement. Hence, it was inferred that NASH had been present prior to their preoperative weight loss. The prevalence of NASH in this cohort was 77.9% (53 of 68 patients) at first visit. The overall prevalence of NASH in Japanese patients with severe obesity is high [3,17]. Therefore, for patients with severe obesity, the likelihood of emerging medical complications of NASH must always be considered, and diagnosis and treatment adjusted accordingly.

Currently, the usefulness of scoring systems for Japanese populations has not been

validated. The gold-standard diagnostic technique for NASH relies on liver biopsy. In our study, the NPV of NAFIC scores for excluding advanced fibrosis was low (40.4%) in severely obese patients. Our results do not infer that liver biopsies can be avoided by using NAFIC scores. The FIB-4 index is useful in predicting advanced fibrosis [11]. Sumida et al. reported that the high cutoff point (>3.25) yielded a low PPV (53%) in Japanese patients. They concluded that the small population of advanced fibrosis in the general Japanese patient population was inadequate to validate the high cutoff point [18]. The NFS is useful for predicting advanced fibrosis and has the advantage of not comprising a special examination item [12]. Sumida et al. in Japan and Wong et al. in China reported that the low cutoff point for NFS (<−1.455) yielded high NPV (98% and 91%, respectively), but the high cutoff point (>0.676) produced a low PPV (43% and 0%, respectively) [10, 19]. Similarly, our study showed a low prevalence of advanced fibrosis (8.8%); the low cutoff point (NFS < −1.455) yielded a high NPV (93.7%), whereas the high cutoff point (NFS > 0.676) yielded a low PPV (8.3%). The low PPV may be owing to the lower prevalence of advanced fibrosis in Japanese NAFLD patients with severe obesity. Therefore, intraoperative liver biopsy remains necessary for diagnosing NASH.

The histopathological features of NASH include steatosis, lobular inflammation,

hepatocyte ballooning, Mallory-Denk bodies, and fibrosis. NAS was defined as the sum of scores for steatosis, lobular inflammation, and ballooning [9]. Other methods include the Matteoni [20] and the Brunt classification, which are indicators with an emphasis on prognosis [13]. Brunt classification is commonly used for assessing fibrosis; however, it applies only to NASH. In some patients, fibrosis remained but they no longer met the diagnostic criteria for NASH. The prognosis of NASH is probably related to the resolution of fibrosis, but further long-term observations of fibrosis will be necessary to confirm this. Therefore, we evaluated using the "pericellular fibrosis score" focusing on fibrosis around the central veins.

Treatment of obese patients with NAFLD has been based on weight loss and medical interventions to improve insulin resistance. In Europe and the United States, bariatric surgery has been performed since the 1950s, and has been shown to be effective in maintaining enduring weight loss and improving obesity-related morbidity. Consequently, it has more recently been renamed "metabolic surgery (MS)" [21,22]. Considerable evidence supports the superior efficacy of MS treatment for T2DM compared to medical treatments [23,24]. Although the application of bariatric surgery in NASH patients has been described as premature [25], several studies have reported the efficacy of MS for

NAFLD [4,5,8,26]. The mechanisms by which MS exerts its beneficial effects in NAFLD are complex and incompletely understood. MS has potential benefits owing to ameliorating factors such as insulin resistance, lipid profile, inflammation, weight loss, and adipokine signaling that contribute markedly to the pathogenesis of NAFLD [8].

In Japan, the increased application of MS has been relatively slow because of the lower prevalence of obesity than that in Europe and the United States, and the effects of MS were not widely known among physicians. LSG is the only procedure approved and covered by the National Health Insurance system, and no bypass surgeries are covered by insurance. From this background, all patients undergo LSG for MS, and no other procedures are performed in our hospital. Meanwhile, MS has demonstrated good results in Japanese patients with obesity-related comorbidities such as T2DM, dyslipidemia, and hypertension [6,27]. In NAFLD-patient studies at a single center, Uehara et al. and Endo et al. reported significant beneficial effects of MS on weight loss, clinical and metabolic changes, and L/S ratio, as established by CT [28,29]. In this study, significant improvements were observed, not only regarding weight loss but also in liver function, lipid metabolism, sugar metabolism, and L/S ratio, which further confirms the effectiveness of LSG in NAFLD patients.

Regarding histopathological findings in biopsies from NAFLD patients following MS, Witigo et al. reported improvements in NAS [30]. Bower et al. conducted a systematic review of 29 articles reporting effects on postoperative liver enzymes and histopathology in liver biopsies [4]. In this study, fibrosis improved even more than in previous studies, but this may be related to the fact that the proportion of Japanese patients with severe fibrosis was smaller than that reported in other studies. Long-term results of histopathological changes in NAFLD after MS in the Japanese population have not yet been reported. From the results of this study, it may be concluded that LSG may exhibit beneficial effects and prognostic improvement for Japanese obese patients with NAFLD and NASH. The severity of liver fibrosis is an important prognostic factor for NASH [31,32], and risk factors for progression of fibrosis include weight gain, T2DM, and/or increased insulin resistance [33,34]. In this study, HbA1c at first visit was the most important predictor of fibrosis improvement. Thus, LSG, which has been shown to induce significant weight loss and improvement of T2DM, may also be expected to improve liver fibrosis, which might improve the prognosis of NASH to a greater extent than with existing medical treatments.

Baldwin et al. have performed a systematic review of Roux-en-Y gastric bypass

(RYGB) and LSG and concluded that both procedures were equivalent. The mean reductions in NAS were −2.8 and −2.3 for RYGB and LSG, respectively. In this study, it was −2.4 at 12 months, which is a result comparable to the findings of the review. Caiazzo et al. compared the effects of RYGB and Adjustable gastric banding [36]. The %TWL was 15.1% for AGB and 29.5% for RYGB; in this study, LSG was 28.2%, which was similar to RYGB. For NAS, it was 3.4±1.9 at baseline in this study compared to 1.8±1.4 in the study by Caiazzo et al., which was difficult to compare. These results suggest that LSG and RYGB could be equivalent.

In conclusion, while observations in larger patient groups and longer-term monitoring of outcomes are needed, our data suggest that LSG has a great potential as a treatment alternative for patients with NAFLD and NASH.

Compliance with ethical standards

Conflicts of Interest The authors declare no conflict of interest.

Ethical Approval All procedures performed in our study involving human participants were in accordance with the ethical standards of the institutional and/or Japanese national

research committees and with the 1964 Helsinki Declaration and later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in this study.

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Figure legends

Fig. 1 Pericellular fibrosis scores

Score 0, No fibrosis; Score 1, Pericellular fibrosis confined to the proximity of central veins, and present near less than 50% of those veins; Score 2, Pericellular fibrosis confined to the proximity of central veins and present near 50 or more percent of the central veins; Score 3, Pericellular fibrosis around the central veins with periportal fibrosis or bridging fibrosis.

Fig. 2 Flowchart of eligible patients included in the study

Fig. 3 Changes in histologic features at 6, 12, and 24 months after LSG in NASH patients

(A) Changes in mean score of steatosis, lobular inflammation, and hepatocellular ballooning

(B) Changes in mean NAS

(C) Changes in mean pericellular fibrosis scores

*$p < 0.05$

Fig. 4 Changes in histologic features at 6, 12, and 24 months after LSG in the patients with liver fibrosis but without steatosis

(A) Changes in mean score of steatosis, lobular inflammation, and hepatocellular ballooning

(B) Changes in mean NAS

(C) Changes in mean pericellular fibrosis scores

Table 1 Baseline characteristics of NAFLD patients

	Total (n=68)	**NASH (n=43)**	**Non-NASH (n=25)**
Age (years)	44.7±12.4	44.2±13.5	45.5±10.5
Sex (n)			
Male	37	20	17
Female	31	23	8
Body weight (kg)	118.7±22.1	114.2±22.2	126.3±20.1
BMI (kg/m^2)	43.0±6.2	41.8±5.2	44.9±7.3
Preoperative weight loss (kg)	11.9±8.2	9.2±5.5	16.5±10.0
Preoperative reduction in BMI (kg/m^2)	4.3±3.0	3.4±2.0	5.9±3.8
Comorbidities, n (%)			
T2DM	46 (67.6%)	34 (79.0%)	12 (48.0%)
Dyslipidemia	49 (72.0%)	30 (69.7%)	19 (76.0%)
Hypertension	59 (86.7%)	34 (79.0%)	25 (100%)
OSA	67 (98.5%)	42 (97.6%)	25 (100%)

Values are mean ± standard deviation. *BMI* body mass index, *T2DM* type 2 diabetes mellitus, *OSA* obstructive sleep apnea

Table 2 Clinical parameters at baseline and 6, 12 and 24 months after LSG

	NASH				Non-NASH			
	Baseline (n=43)	6 months (n=37)	12 months (n=32)	24 months (n=23)	Baseline (n=25)	6 months (n=25)	12 months (n=22)	24 months (n=18)
Body weight (kg)	114.7±22.2	85.6±15.8*	84.7±19.6*	84.8±16.3*	126.3±20.1	90.6±13.7*	87.2±15.1*	86.3±14.9*
% Total weight loss (%)	-	24.0±5.9	26.4±7.1	30.8±20.1	-	27.9±7.3	31.4±8.5	32.1±7.1
BMI (kg/m^2)	41.9±5.2	31.7±3.7*	31.1±4.6*	31.4±4.2*	45.0±7.3	34.3±5.4*	31.1±5.6*	30.9±5.6*
Visceral adipose tissue (cm^2)	265.1±87.2	156.4±68.8*	144.5±64.6*	153.8±65.6*	283.7±90.6	161.3±76.8*	134.0±64.7*	135.3±45.1*
Liver volume (mL)	2243.9±593.9	1581.5±319.1*	1517.5±277.7*	1493.3±269.7*	2281.7±533.6	1767.6±357.6*	1750.8±294.2*	1610.2±275.8*
Platelets ($10^4/\mu L$)	25.3±7.14	23.4±7.8*	21.9±5.8*	21.4±6.6*	26.3±5.2	23.2±4.6*	22.1±5.8*	21.9±5.7*
Insulin (μU/mL)	22.1±18.0	8.7±5.0*	8.2±4.3*	6.7±4.8*	14.2±7.8	4.9±2.4*	5.1±3.1*	5.8±2.6*
HbA1c (%)	7.4±1.6	5.7±0.7*	5.7±0.7*	5.8±0.6*	6.7±1.8	5.6±0.7*	5.5±1.7*	5.5±0.6*
HOMA-IR	7.1±7.2	2.0±1.2*	2.0±1.2*	1.7±1.3*	3.8±2.0	1.1±0.5*	1.1±0.7*	1.3±0.5*
AST (IU/L)	50.7±34.3	19.5±15.1*	20.4±13.9*	20.4±9.4*	26.6±15.9	15.6±4.3*	17.0±5.8*	18.6±6.8
ALT (IU/L)	73.3±52.6	24.0±37.8*	18.3±12.0*	19.5±10.6*	37.0±34.4	15.0±4.8*	17.5±7.6*	15.1±3.8*
TG (mg/dL)	162.6±115.9	98.3±40.5*	88.6±53.8*	86.3±46.7*	138.3±60.1	78.3±31.1*	77.9±34.8*	78.6±23.3*
LDL-cholesterol (ml/dL)	116.3±31.9	109.9±24.8	105.0±26.6	109.9±24.6	127.0±29.0	115.5±28.3	114.3±30.2	112.6±34.5
Hyaluronic acid (ng/mL)	35.3±27.4	32.3±22.0	32.1±21.7	34.5±15.8	26.9±15.3	42.6±29.0*	44.1±38.1	55.1±33.6*
Type 4 collagen‧7S (ng/mL)	4.8±1.2	4.5±0.8	4.5±1.2	4.5±1.1	4.3±0.9	4.7±0.7	4.8±0.7	4.9±0.9
L/S ratio	0.7±0.27	1.3±0.2*	1.3±0.2*	1.3±0.2*	0.9±0.2	1.2±0.1*	1.3±0.1*	1.2±0.1*

Values are mean ± standard deviation. *BMI* body mass index, *HbA1c* hemoglobin A1c, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *TG* triglyceride

*$p < 0.05$

Table 3 Preoperative scoring system for NASH diagnosis and advanced fibrosis

Score	Cutoff value	Identification	Sensitivity	Specificity	PPV	NPV	Accuracy
NAFIC score [10]	> 2	diagnosis of NASH	33.3%	76.0%	70.0%	40.4%	48.5%
FIB-4 index [11]	>2.67	advanced fibrosis (Stage >3 of Brunt classification)	16.6%	94.8%	25.0%	91.6%	87.5%
NAFLD fibrosis score [12]	< −1.455	advanced fibrosis (Stage >3 of Brunt classification)	83.3%	24.1%	9.6%	93.7%	29.4%
	> 0.676		16.6%	81.0%	8.3%	90.3%	75.0%

NAFIC score ferritin ≥ 300 ng/ml (males) or ≥ 200 ng/mL (females) and two points for IRI levels ≥ 10μU/mL and type IV collagen 7S levels ≥ 5 ng/mL, *FIB-4 index*; Age [years] × AST [U/L] / platelets [10^9/L] × (ALT [U/L]$^{1/2}$), *NAFLD fibrosis score* (−1.675+0.037 × Age [years] + 0.094 × BMI [kg/m²] + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio–0.013 × platelet [×10^9/L]–0.66 × albumin [g/dL]), *PPV* positive predictive value, *NPV* negative predictive value.

Table 4 Univariate and multivariable analysis of predictors of fibrosis score improvement

Univariate analysis		
	Odds ratio (95%CI)	*P* value
Age (years)	1.026 (0.972-1.083)	0.336
Body weight (kg)	0.963 (0.930-0.997)	0.037
BMI (kg/m²)	0.894 (0.794-1.006)	0.063
Preoperative weight loss(kg)	0.925 (0.846-1.012)	0.092
AST (IU/L)	0.989 (0.970-1.009)	0.308
ALT (IU/L)	0.994 (0.982-1.007)	0.411
Albumin (g/dL)	0.888 (0.159-4.945)	0.893
T-Bil (mg/dL)	8.628（0.470-158.2)	0.146
Hyaluronic acid (ng/mL)	0.993 (0.970-1.018)	0.617
Type 4 collagen‧7S (ng/mL)	0.682 (0.377-1.234)	0.206
C peptide (ng/mL)	0.714 (0.422-1.207)	0.208
Insulin (μU/mL)	0.915 (0.842-0.994)	0.037
HOMA-IR	0.788 (0.618-1.004)	0.055
HbA1c (%)	0.587 (0.355-0.968)	0.037
Multivariable analysis		
	Odds ratio (95%CI)	*P* value
Body weight (kg)	0.953 (0.904-1.004)	0.075
Insulin (μU/mL)	0.897 (0.803-1.002)	0.054
HbA1c (%)	0.440 (0.229-0.842)	0.004

CI confidential interval, *BMI* body mass index, *AST* aspartate aminotransferase, *ALT*

alanine aminotransferase, *T-Bil* total bilirubin, *HbA1c* hemoglobin A1c

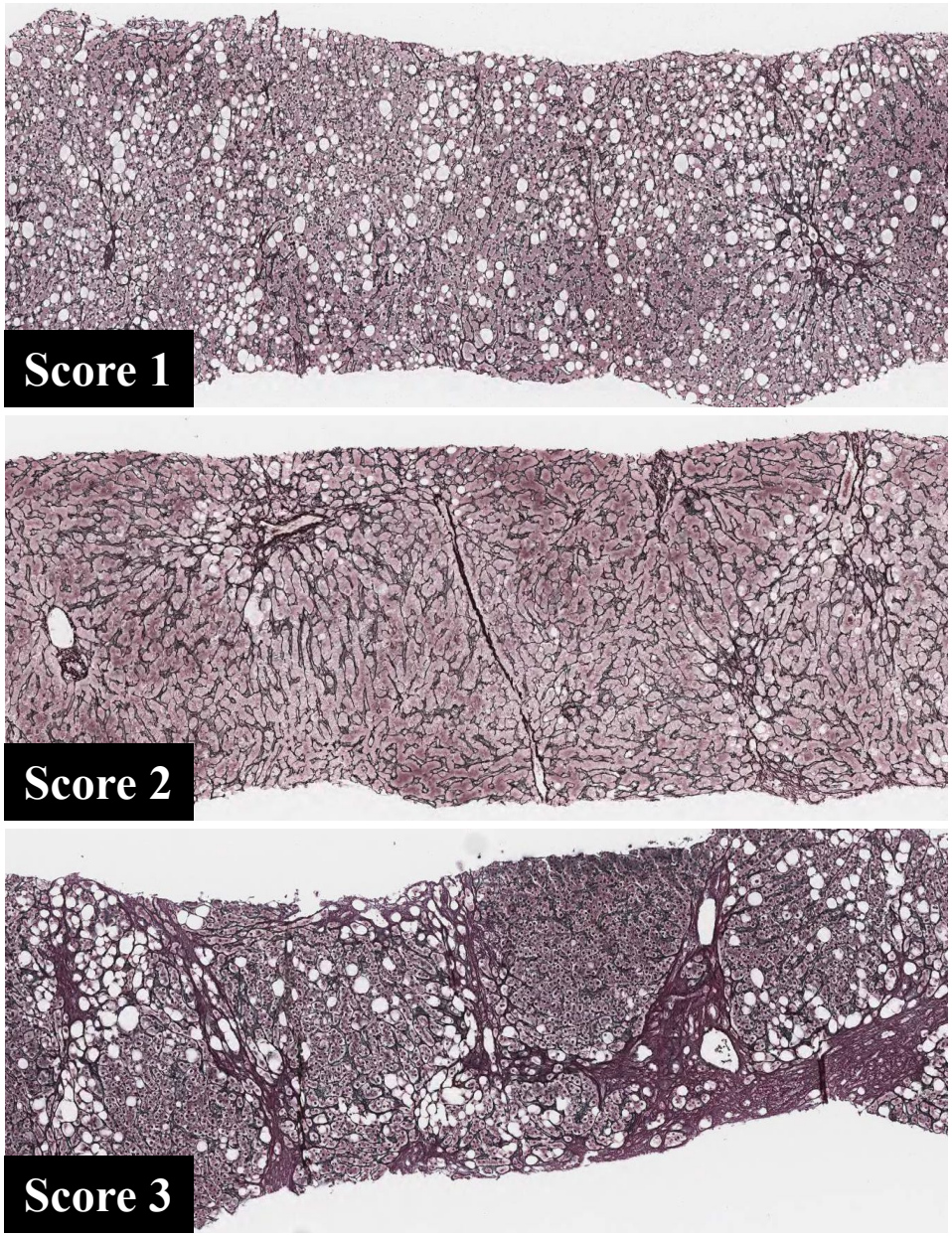

Fig.1. Pericellular fibrosis scores

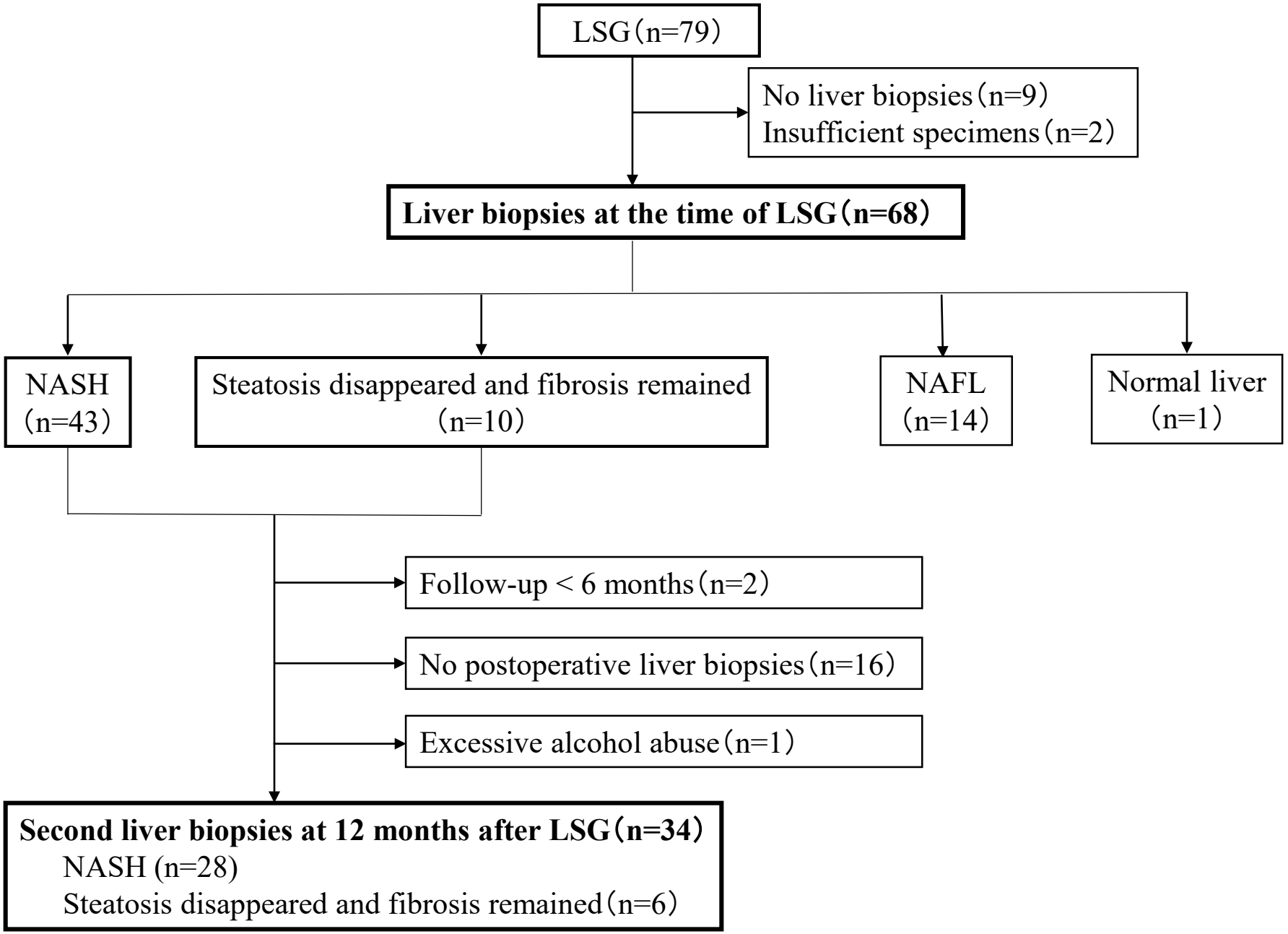

Fig.2. Flowchart of eligible patients included in the study

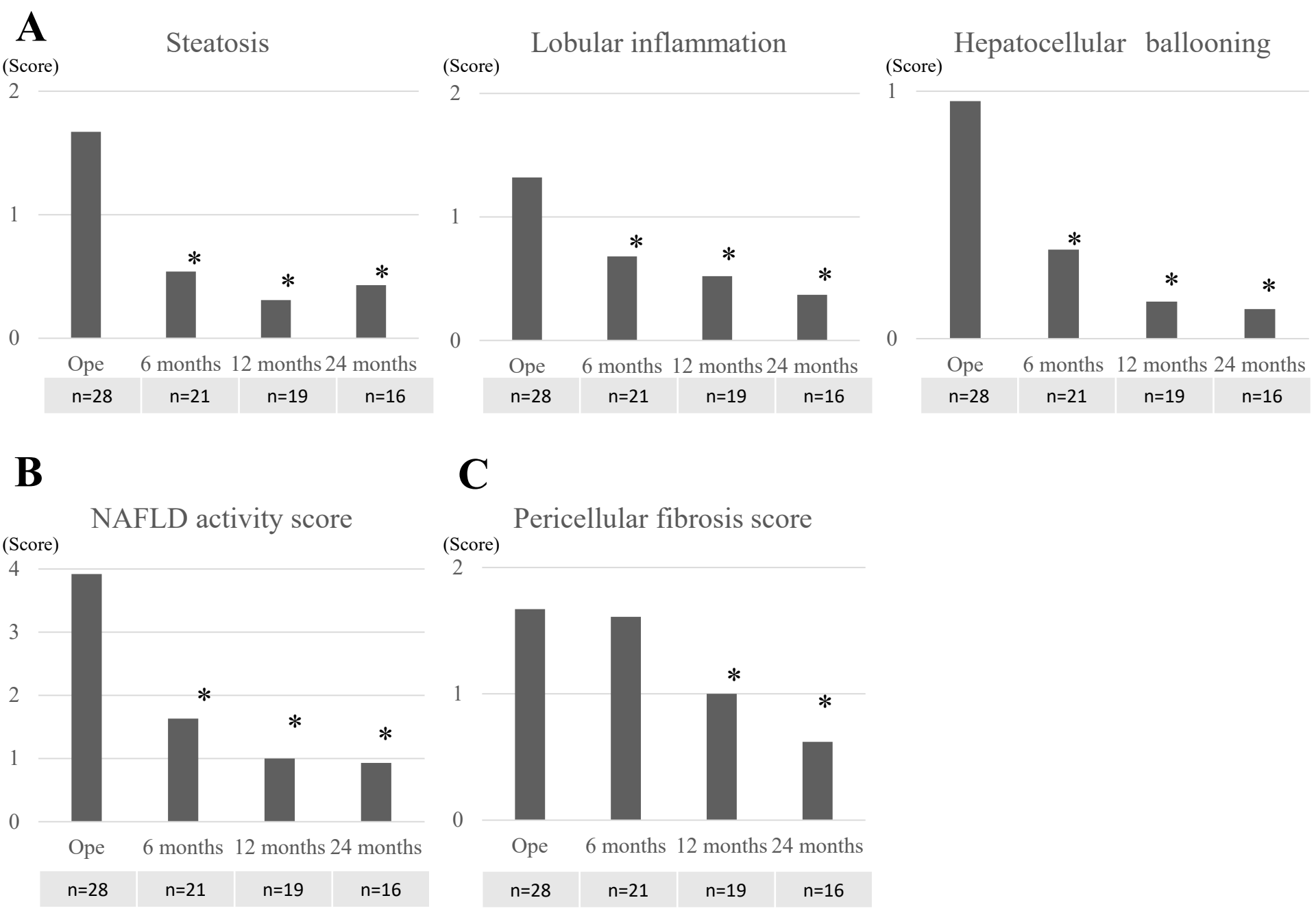

Fig.3. Changes in histologic features at 6, 12, and 24 months after LSG in NASH patients

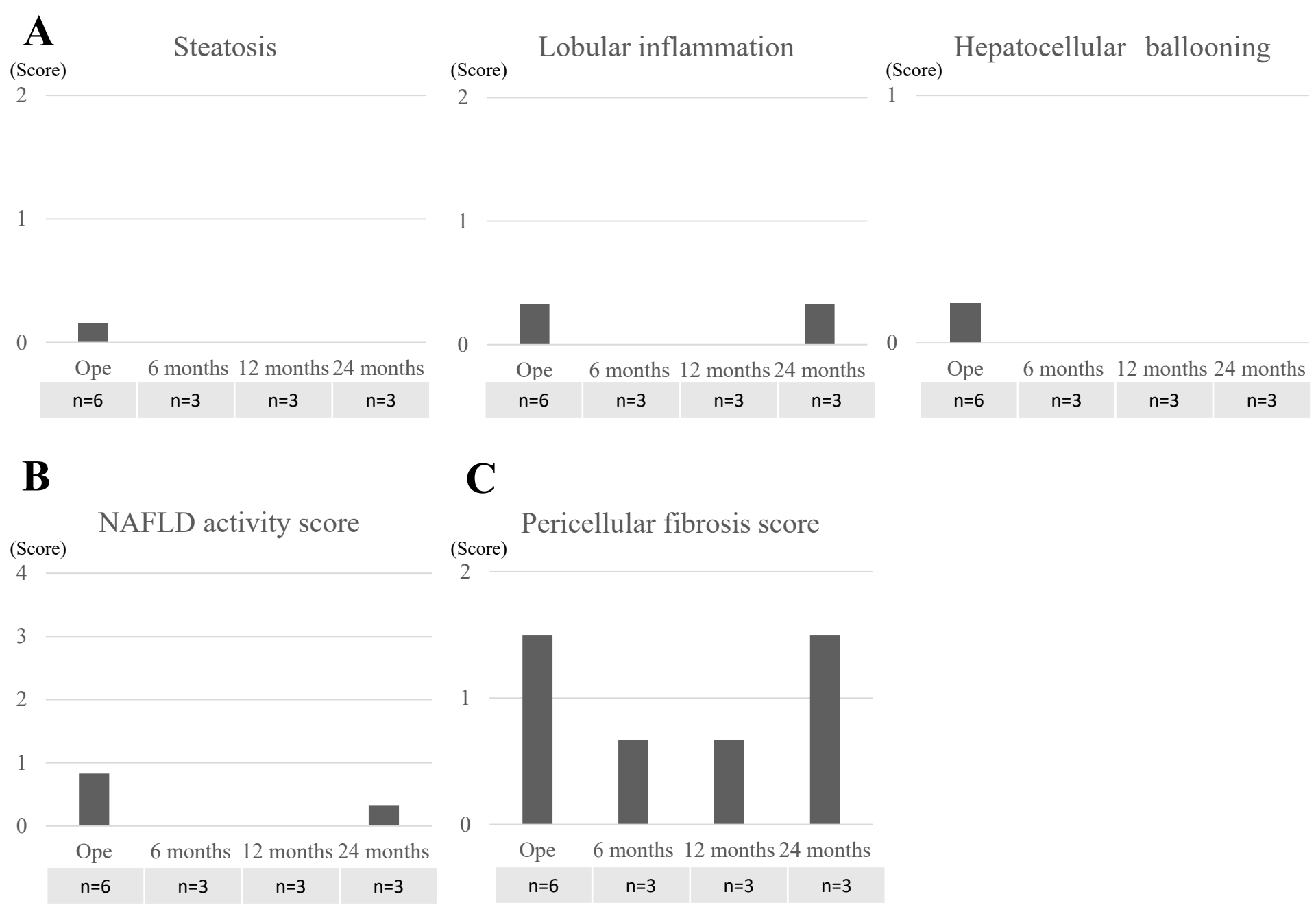

Fig.4. Changes in histologic features at 6, 12, and 24 months after LSG in the patients with fibrosis but without steatosis