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Nonalcoholic steatohepatitis is associated with a higher risk of advanced colorectal neoplasm

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Abstract

Background & Aims: Nonalcoholic fatty liver disease (NAFLD) is known to increase the risk of adenomatous colonic polyps. However, the role of screening colonoscopy in patients with biopsy-proven NAFLD in detecting advanced colorectal neoplasm is not clearly evidence-based. Therefore, we investigated whether the histological severity of NAFLD is associated with advanced colorectal neoplasm.

Methods: This study included patients ≥18 years old who underwent screening colonoscopy between 2013 and 2018 within a biopsy-evaluated prospective NAFLD cohort. Advanced colorectal neoplasm was defined as an adenomatous polyp greater than 10 mm in diameter and/or with villous histology and/or with high-grade dysplasia or adenocarcinoma.

Results: Among the 476 patients with clinically suspected NAFLD, 379 patients were diagnosed with biopsy-proven NAFLD and 97 patients had no evidence of NAFLD histologically, who were analyzed as healthy controls. The prevalence of advanced colorectal neoplasm was 11.1% (n = 53). Patients with advanced colorectal neoplasm had higher grade of steatosis (P = 0.004) and higher stage of hepatic fibrosis (P = 0.044) than those with normal colonoscopic findings or low-grade adenomatous polyp. Multivariable logistic regression analysis revealed that the presence of nonalcoholic steatohepatitis (NASH) was an independent risk factor for both colorectal polyp (odds ratio [OR], 2.08; 95% confidential interval [CI], 1.12-3.86; P = 0.020) and advanced colorectal neoplasm (OR, 2.81; 95% CI, 1.01-7.87; P = 0.049).

Conclusions: The presence of biopsy-proven NASH was significantly associated with an increased risk of advanced colorectal neoplasm among patients with NAFLD. This finding may alert physicians to conduct screening colonoscopy in patients with NASH to detect advanced colorectal neoplasm early.

KEYWORDS
colonoscopy, colorectal cancer, liver fibrosis, non-alcoholic fatty liver disease

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; CRC, colorectal cancer; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high sensitivity C-reactive protein; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; OR, odds ratio; SBP, systolic blood pressure; TG, triglycerides.

Yuri Cho and Soo-Kyung Lim contributed equally to this work.

1 | INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has become the most common form of liver disorders and may progress to nonalcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, or hepatocellular carcinoma.[1] Because the prevalence of NAFLD is increasing, metabolic syndrome with insulin resistance is becoming an important focus of research.[2] Similarly, colorectal cancer (CRC) is one of the most common forms of cancer, and some clinical studies have suggested that metabolic syndrome is an important risk factor for CRC.[3,4] Accordingly, the role of screening colonoscopy to identify the risk of developing CRC in patients with NAFLD is also of paramount importance as a component of a comprehensive therapeutic process.

NAFLD has a wide histological spectrum that ranges from simple steatosis to NASH. Within this spectrum, NASH with advanced fibrosis was shown to have higher morbidity and mortality resulting from liver-related outcomes, cardiovascular disease with type 2 diabetes mellitus, and malignancies such as CRC.[5,6] Recent studies using non-invasive diagnostic tools such as abdominal ultrasound to assess NAFLD, have shown an association between NAFLD and an increased risk of CRC.[7-9] However, the gold standard for diagnosis of NAFLD is liver biopsy. Thus, assessing the risk of CRC according to the histological severity of NAFLD would be valuable.

As the most common cause of chronic liver disease, NAFLD is likely to be associated with inflammation-mediated colorectal adenomatous polyp or colorectal neoplasm.[10,11] However, to date, few studies have shown the relationship between the histological severity of NAFLD and colorectal neoplasm.[12,13] In this prospective cohort study, we aimed to investigate the association between the histological severity of NAFLD and the prevalence of advanced colorectal neoplasm.

Keypoints

In this biopsy-assessed prospective nonalcoholic fatty liver disease (NAFLD) cohort study, the histological severity of NAFLD was strongly associated with advanced colorectal neoplasm. The presence of biopsy-proven nonalcoholic steatohepatitis was significantly associated with 2.8-fold increased risk of advanced colorectal neoplasm than those without histological findings of NAFLD. Patients with advanced colorectal neoplasm had higher grade of steatosis and higher stage of hepatic fibrosis than those with normal colonoscopic findings or low-grade adenomatous polyp.

2 | MATERIALS AND METHODS

2.1 | Patients and clinical assessment

We prospectively recruited consecutive 750 patients with clinically suspected NAFLD from the ongoing Boramae NAFLD registry (NCT 02206841) between January 2013 and November 2018. All patients underwent liver biopsy to evaluate the presence of NAFLD, histologically. The inclusion criteria for this study were as follows: (a) ≥18 years old, (b) bright echogenic liver on ultrasound scanning (liver hyperechogenicity compared to kidney and posterior attenuation),[14] and (c) unexplained high alanine aminotransferase (ALT) levels above the upper normal limit for men (30 IU/L) and women (19 IU/L) within the prior 6 months.[15] The following exclusion criteria were used: (i) hepatitis B or C virus infection, (ii) autoimmune hepatitis or primary biliary cholangitis, (iii) drug-induced liver injury or steatosis, (iv) Wilson disease or hemochromatosis, (v) excessive alcohol consumption (males >30 g/day, females >20 g/day),[16] (vi) diagnosis of malignancy within the prior year, (vii) family history of CRC in first-degree relatives, (viii) having an inherited syndrome (eg Lynch syndrome, Peutz-Jeghers syndrome, MYH-associated polyposis or familial adenomatous polyposis), (ix) past medical history of colorectal neoplasm, (x) inflammatory bowel disease, (xi) bowel symptoms (eg hematochezia, melena, or bowel habit change), (xii) patients who underwent polypectomy within the last 5 years, and (xiii) patients who declined to undergo colonoscopy. Among the eligible study participants, those with at least two of the following risk factors underwent liver biopsy: diabetes mellitus, central obesity (waist circumference ≥90 cm for men or ≥80 cm for women), a high level of triglycerides (TG) (≥150 mg/dL), a low level of high-density lipoprotein (HDL)-cholesterol (<40 mg/dL for men or <50 mg/dL for women), the presence of hypertension, insulin resistance, and clinically suspected NASH or fibrosis.[17]

A well-trained examiner recorded anthropometric measurements according to a consistent protocol. Body mass index was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured at the end of normal expiration, measuring at a midway between the lower rib margin and the iliac crest; the tape measure was placed completely around the waist in the horizontal position. Venous blood samples were drawn at the time of biopsy after a 12 hours overnight fasting, and plasma was separated immediately via centrifugation. The plasma glucose and lipid concentrations were measured enzymatically using the Hitachi Automatic Analyzer B2400 (Hitachi, Tokyo, Japan). Fasting insulin levels were measured using immunoradiometric assays (DIA source ImmunoAssays, Nivelles, Belgium). Insulin resistance was evaluated using the homeostasis model assessment of insulin resistance (HOMA-IR), as described previously.[18]

Diabetes mellitus was defined as fasting plasma glucose (FPG) levels ≥126 mg/dL, HbA1c levels ≥6.5% and/or treatment with antidiabetic medication(s) at the time of the survey. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg and/or the current use of anti-hypertensive medication(s). Smokers were defined as those who had smoked at least one cigarette per day during the previous year. Metabolic syndrome was defined as having at least three of the following (a)

waist circumference ≥90 cm (males) or 80 cm (females) in Asia, (b) TG ≥ 150 mg/dL, (c) HDL-cholesterol < 40 mg/dL (males) or 50 mg/dL (females), (d) SBP ≥ 130 mmHg or DBP ≥ 85 mmHg, and (e) FPG ≥ 110 mg/dL.[19]

This study was conducted in accordance with the provisions of the Declaration of Helsinki for the participation of human subjects in research and approved by the Institutional Review Board of Seoul National University Boramae Medical Center (IRB No. 30-2019-37). All subjects in the study cohort provided written informed consent.

2.2 | Colonoscopy examination

Among a total of 750 patients in the Boramae NAFLD registry, 476 patients (63.5%) underwent colonoscopy from January 2013 to November 2018 using a CF-H260 colonoscope (Olympus, Tokyo, Japan) by board-certified gastroenterologists who had performed more than 500 colonoscopies. All colonoscopies were performed for screening CRC or colorectal adenoma. For adequate bowel preparation, subjects were given 4 L of polyethylene glycol lavage solution. During colonoscopy, either intravenous midazolam and pethidine or pethidine alone was administered by the gastroenterologists according to participants' medical conditions. Colonoscope reaching the cecum, documented by a picture of ileocecal valve, was defined as a complete colonoscopic examination. All polypoid lesions were biopsied or removed and histologically assessed by experienced pathologists. All polypoid lesions were classified by number, size, and histological characteristics (tubular, tubule-villous, or villous adenoma; hyperplastic polyp; or sessile serrated or traditional serrated adenoma). Hyperplastic polyps, inflammatory polyps, or lipomas were not considered as colorectal adenomas. The grade of dysplasia was classified as low or high. The location and size of all detected colorectal lesions were documented (measured by biopsy forceps that expanded to ≥6 mm) by photographs. Advanced colorectal neoplasm was defined as an adenomatous polyp 10 mm or larger in diameter and/or with a feature of villous adenoma, and/or high-grade dysplasia or adenocarcinoma.[20]

2.3 | Liver histology

Percutaneous liver biopsy specimen, obtained using 16-gauge disposable needles, were fixed in 4% formalin, and embedded in paraffin. Adequate specimens, at least 20 mm in length and 3 mm thick, were stained with hematoxylin-eosin and Massson's trichrome. One experienced liver pathologist (JHK) assessed and reviewed all liver biopsy specimens.[21] Subjects with biopsies in which at least 5% of hepatocytes displayed macrovesicular steatosis, were diagnosed with NAFLD. Hepatic injury consisting of macrovesicular steatosis, lobular inflammation, and hepatocellular ballooning was defined as NASH according to Brunt et al's criteria.[22,23] Fibrosis was staged from 0 to 4, according to criteria of Kleiner et al.[24] Significant fibrosis was defined as ≥F2. Included patients had an NAFLD activity score (NAS) ranging from 0 to 8.

2.4 | Statistical analysis

Differences between groups were evaluated using the independent *t* test and analysis of variance (ANOVA). Categorical variables were compared using the chi-square test and Fisher's exact test. To investigate the associations of NAFLD and other risk factors with advanced colorectal neoplasm, binary logistic regression analysis was performed. Multivariate logistic regressions analysis, adjusted for age and sex, included clinically significant cofounders and variables selected from the results of the binary analysis: variable having a $P < 0.10$. If there was a positive co-linearity between the covariates, the most objective and easily applicable variable was selected as a representative variable for multivariate analysis. Each odds ratio (OR) is presented together with its 95% confidence interval (CI). All statistical analyses were conducted using STATA 13.0 (StataCorp, College Station, TX) and SPSS Statistics software version 23.0 (IBM Corporation, Armonk, NY). Significance was defined as $P < 0.05$.

3 | RESULTS

3.1 | Clinical characteristics of study population according to colonoscopic findings

A total of 476 patients with clinically suspected NAFLD (No-NAFLD, n = 97; NAFL, n = 194; and NASH, n = 185; by liver biopsy) underwent screening colonoscopy. Among 476 patients, 323 (67.9%) showed no evidence of colorectal polyps. The prevalence of low-grade colorectal adenomatous polyps and advanced colorectal neoplasm were 21.0% (n = 100) and 11.1% (n = 53), respectively. The baseline characteristics of the study population according to colonoscopic findings are shown in Table 1. Patients with advanced colorectal neoplasm had noticeable differences in age and the prevalence of hypertension, and metabolic syndrome compared with those who had normal colonoscopic findings or adenomatous polyps.

3.2 | Features of colorectal polyps

Comparing the number and location of colorectal polyps between patients with low-grade tubular adenoma and patients with advanced colorectal neoplasm, there were no significant differences in the number and location of polyps according to the category of colorectal polyps. Mean number of polyps found in colonoscopic studies was 3.0 ± 3.5 in patients with low-grade adenomatous colorectal polyp and 3.1 ± 2.2 in patients with advanced colorectal neoplasm, respectively. Ascending colon was found to be the most frequent location of both low-grade adenomatous colorectal polyp and advanced colorectal neoplasm (Table 2).

3.3 | Histological comparison of NAFLD according to the presence of low-grade tubular adenoma or advanced colorectal neoplasm

The mean NAS was 3.1 (±1.8) in patients with low-grade adenomatous colorectal polyp and 3.4 (±1.5) in those with advanced

TABLE 1 Clinical characteristics according to colonoscopic findings

	No colorectal adenoma (n = 323)	Low-grade tubular adenoma (n = 100)	Advanced colorectal neoplasm (n = 53)	Total (n = 476)	*P*-value
Age (years)	53.9 ± 12.7	59.0 ± 12.2	61.9 ± 12.5	55.9 ± 12.9	<0.001
Sex (male, %)	154 (47.7%)	55 (55%)	21 (39.6%)	230 (48.3%)	0.179
BMI (kg/m^2)	26.4 ± 3.7	27.0 ± 3.3	27.3 ± 3.2	26.6 ± 3.6	0.150
Diabetes mellitus	113 (35.0%)	41 (41%)	27 (50.9%)	181 (38.0%)	0.067
Hypertension	112 (34.7%)	49 (49%)	27 (50.9%)	188 (39.5%)	0.007
HOMA-IR	4.4 ± 3.8	4.2 ± 3.3	4.9 ± 4.2	4.4 ± 3.7	0.524
Adipose tissue IR	9.4 ± 7.8	9.7 ± 7.8	10.6 ± 9.8	9.6 ± 8.1	0.622
Waist circumference (cm)	90.3 ± 9.5	90.4 ± 8.7	93.3 ± 9.3	90.7 ± 9.3	0.098
Metabolic syndrome	149 (46.1%)	62 (62%)	31 (58.5%)	242 (50.8%)	0.033
Smoking	61 (18.9%)	24 (24%)	9 (17.0%)	94 (19.7%)	0.461
SBP (mmHg)	129.5 ± 16.7	133.5 ± 17.5	129.0 ± 17.8	130.3 ± 17.1	0.105
DBP (mmHg)	78.9 ± 12.0	82.7 ± 13.7	77.4 ± 11.2	79.5 ± 12.4	0.062
HDL-cholesterol (mg/dL)	47.7 ± 12.9	45.4 ± 12.7	47.8 ± 12.3	47.2 ± 12.8	0.282
LDL-cholesterol (mg/dL)	105.2 ± 35.6	101.5 ± 31.7	97.5 ± 30.2	103.4 ± 34.2	0.307
Total cholesterol (mg/dL)	183.3 ± 41.5	178.5 ± 44.0	171.2 ± 35.2	181.0 ± 41.5	0.115
Triglycerides (mg/dL)	148.7 ± 82.0	150.9 ± 87.8	142.9 ± 94.5	148.5 ± 84.5	0.854
FPG (mg/dL)	116.6 ± 37.2	113.2 ± 30.4	120.0 ± 32.9	116.3 ± 35.4	0.500
Albumin (g/dL)	4.1 ± 0.3	4.1 ± 0.4	4.0 ± 0.3	4.1 ± 0.3	0.135
AST (IU/L)	43.8 ± 32.9	44.0 ± 30.9	47.3 ± 34.4	44.2 ± 32.6	0.765
ALT (IU/L)	52.0 ± 43.7	46.4 ± 36.7	58.4 ± 63.4	51.6 ± 45.0	0.281
GGT (IU/L)	60.6 ± 74.6	81.4 ± 163.8	66.2 ± 76.1	65.6 ± 100.2	0.194
Total bilirubin (mg/dL)	1.1 ± 3.3	0.8 ± 0.4	0.8 ± 0.3	1.0 ± 2.7	0.711
Platelet (×10^3/μL)	224.3 ± 63.8	233.4 ± 64.5	206.4 ± 66.6	224.2 ± 64.5	0.058
PT (INR)	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	0.666
hsCRP (mg/dL)	0.2 ± 0.3	0.2 ± 0.4	0.3 ± 0.4	0.2 ± 0.3	0.381

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; PT, prothrombin time; SBP, systolic blood pressure.
The data are expressed as the means ± standard deviations.

TABLE 2 Number and location of colorectal polyps

	Low-grade tubular adenoma (n = 100)	Advanced colorectal neoplasm (n = 53)	*P*-value
Number of polyps	3.0 ± 3.5	3.1 ± 2.2	0.660
Location of polyp			
A-colon	32 (32%)	20 (37.7%)	0.392
T-colon	20 (20%)	10 (18.9%)	
D-colon	16 (16%)	3 (5.7%)	
S-colon	18 (18%)	11 (20.8%)	
Rectum	14 (14%)	9 (17.0%)	

Abbreviations: A-colon, ascending colon; D-colon, descending colon; S-colon, sigmoid colon; T-colon, transverse colon.

colorectal neoplasm, respectively. The distribution of histological steatosis grade differed significantly among the three groups, demonstrating higher grade of steatosis in patients with adenomatous colorectal polyp including advanced colorectal neoplasm (Table 3; $P = 0.004$). The distribution of histological fibrosis stage also differed significantly among the three groups; higher stage of fibrosis was observed more frequently in patients with advanced colorectal neoplasm ($P = 0.044$).

Among the patients without NAFLD, only 5% of patients had advanced colorectal neoplasm. Approximately, 12% and 13% of patients experienced advanced colorectal neoplasm among the patients with NAFL and NASH, respectively (Figure 1).

After stratified by age, only patients with NAFL or NASH developed advanced colorectal polyp among the patients aged <50 years, although the difference did not reach statistical significance because of the small number of subjects in each subgroup (Figure 2). Among the patients aged ≥50 years, the prevalence of low-grade tubular adenoma and advanced colorectal neoplasm in patients with NAFL or NASH were significantly higher than in those without NAFLD ($P = 0.003$ and $P = 0.05$, respectively).

3.4 | Risk factors associated with adenomatous colorectal polyp in the overall population

Risk factors for developing adenomatous colorectal polyps including advanced colorectal neoplasm are shown in Table 4. In the binary logistic regression analysis, univariate analysis suggested that age, the presence of diabetes mellitus, the presence of hypertension, lobular inflammation, the grade of hepatic steatosis, and the presence of NAFLD

TABLE 3 Histological characteristics according to the presence of low-grade tubular adenoma or advanced colorectal neoplasm

	No colorectal adenoma (n = 323)	Low-grade tubular adenoma (n = 100)	Advanced colorectal neoplasm (n = 53)	Total (n = 476)	*P*-value
Histological spectrum of NAFLD					
No NAFLD	77 (23.8%)	15 (15%)	5 (9.4%)	97 (20.4%)	0.029
NAFL	120 (37.2%)	50 (50%)	24 (45.3%)	194 (40.8%)	
NASH	126 (39.0%)	35 (35%)	24 (45.3%)	185 (38.9%)	
NAS	3.1 ± 1.9	3.1 ± 1.8	3.4 ± 1.5	3.1 ± 1.9	0.484
Steatosis grade					
0 (<5%)	76 (23.5%)	15 (15%)	5 (9.4%)	96 (20.2%)	0.004
1 (5-33%)	76 (23.5%)	40 (40%)	23 (43.4%)	139 (29.2%)	
2 (34-66%)	86 (26.6%)	25 (25%)	13 (24.5%)	124 (26.1%)	
3 (≥67%)	85 (26.3%)	20 (20%)	12 (22.6%)	117 (24.6%)	
Lobular inflammation					
0	87 (26.9%)	20 (20%)	7 (13.2%)	114 (23.9%)	0.136
1	190 (58.8%)	63 (63%)	36 (67.9%)	289 (60.7%)	
2	45 (13.9%)	15 (15%)	10 (18.9%)	70 (14.7%)	
3	1 (0.3%)	2 (2%)	0 (0%)	3 (0.6%)	
Portal inflammation					
Absent	129 (39.9%)	33 (33%)	17 (32.1%)	179 (37.6%)	0.521
Minimal	104 (32.2%)	34 (34%)	19 (35.8%)	157 (33.0%)	
Mild	55 (17.0%)	18 (18%)	8 (15.1%)	81 (17.0%)	
Moderate	21 (6.5%)	13 (13%)	5 (9.4%)	39 (8.2%)	
Severe	7 (2.2%)	1 (1%)	2 (3.8%)	10 (2.1%)	
Ballooning					
0	141 (43.7%)	46 (46%)	17 (32.1%)	204 (42.9%)	0.472
1	166 (51.4%)	49 (49%)	34 (64.2%)	249 (52.3%)	
2	16 (5.0%)	5 (5%)	2 (3.8%)	23 (4.8%)	
Fibrosis					
F0	102 (31.6%)	37 (37%)	8 (15.1%)	147 (30.9%)	0.044
F1	124 (38.4%)	31 (31%)	24 (45.3%)	179 (37.6%)	
F2	56 (17.3%)	17 (17%)	9 (17.0%)	82 (17.2%)	
F3	15 (4.6%)	9 (9%)	2 (3.8%)	26 (5.5%)	
F4	26 (8.0%)	6 (6%)	10 (18.9%)	42 (8.8%)	

Abbreviations: NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis.

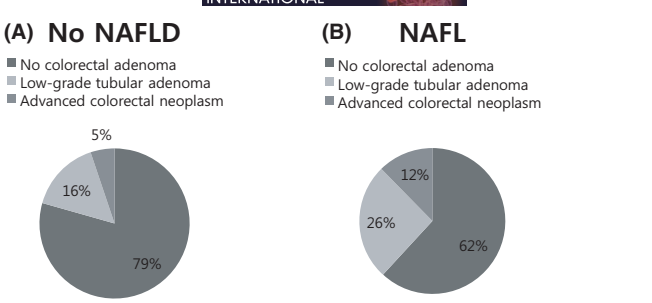

FIGURE 1 Prevalence of low-grade tubular adenoma and advanced colorectal neoplasm in patients with (A) no NAFLD, (B) NAFL, and (C) NASH. NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis

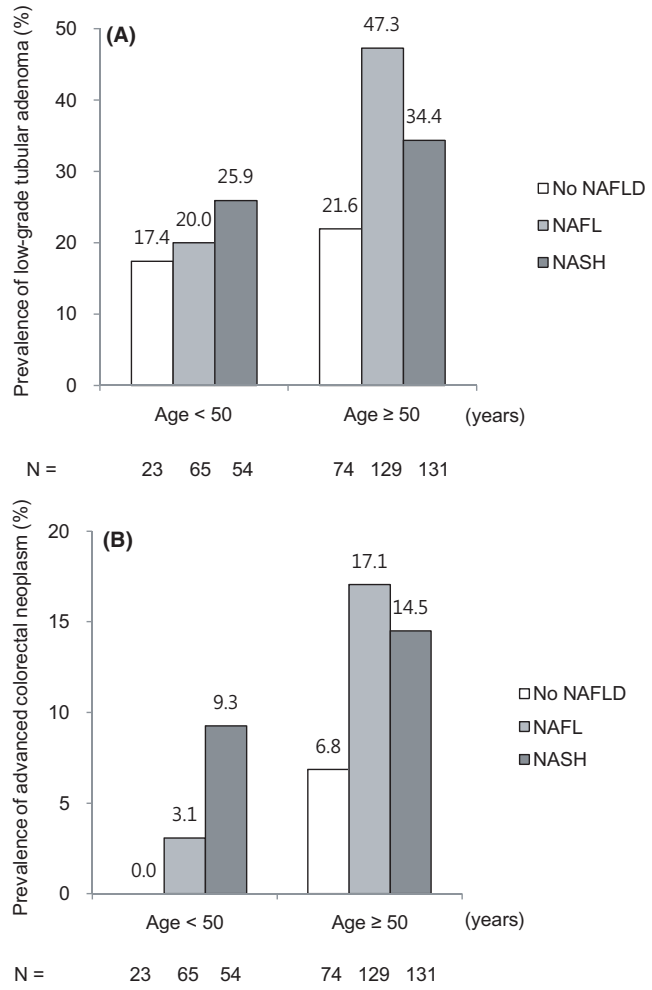

FIGURE 2 Prevalence of (A) low-grade tubular adenoma and (B) advanced colorectal neoplasm by age in patients with no NAFLD, NAFL, and NASH. NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis

were the risk factors for colorectal adenomatous polyp. Multivariate analysis included the presence of NAFLD due to the positive co-linearity with other histological findings including lobular inflammation and the grade of steatosis. In age-, sex-, the presence of hypertension and diabetes mellitus-adjusted multivariate analysis, the presence of NAFL (OR, 2.76; 95% CI, 1.51-5.06; P = 0.001) and the presence of NASH (OR, 2.08; 95% CI, 1.12-3.86; P = 0.020) were the independent risk factors for developing adenomatous colorectal polyp.

3.5 | Risk factors associated with advanced colorectal neoplasm in the overall population

Based on the binary logistic regression analysis of the risk factors for advanced colorectal neoplasm, univariate analysis demonstrated that age, the presence of diabetes mellitus, and the presence of NAFLD were significantly associated with advanced colorectal neoplasm (Table 5). According to the age-, sex-, and the presence of diabetes mellitus-adjusted multivariate analysis, the presence of NASH (OR, 2.81; 95% CI, 1.01-7.87; P = 0.049) was an independent risk factor for developing advanced colorectal neoplasm.

4 | DISCUSSION

In this biopsy-assessed prospective NAFLD cohort study, the prevalence of advanced colorectal neoplasm was strongly associated with the presence of NASH, and this association persisted after further adjustment for age, sex, and the presence of diabetes mellitus. Patients with hepatic steatosis were at higher risk of developing adenomatous colorectal polyp than were those without hepatic steatosis. Moreover, patients with biopsy-proven NASH were found to have 2.8-fold increased risk for developing advanced colorectal neoplasm than those without any histological finding of NAFLD.

Previous studies have focused on the relationship between colorectal polyp and NAFLD as assessed by non-invasive markers, abdominal ultrasonography or computed tomography.[7,9,20] The use of non-invasive diagnostic assessment of NAFLD may result in misclassification of NASH and over-diagnosis of NASH leading to biased or inflated study results. In addition, recent studies have compared the prevalence of colorectal polyp in NAFLD patients with that in healthy control subjects without consideration of the histological severity of NAFLD.[11,25] In contrast to the previous reports, our study evaluated the risk of advanced colorectal neoplasm in a large biopsy-evaluated NAFLD cohort and demonstrated that the presence of NASH was an independent risk factor for advanced colorectal neoplasm. Although liver biopsy is an invasive procedure, the confirmatory diagnosis of NASH is possible only by this invasive procedure. Moreover, our study revealed a histological evidence-based association between biopsy-proven NASH and advanced colorectal neoplasm.

Recent studies have suggested that insulin resistance, metabolic syndrome, obesity, type 2 diabetes mellitus, and dyslipidemia are closely related to a higher risk of colorectal adenomas and NAFLD is also

TABLE 4 Univariate and multivariate analyses for development of adenomatous colorectal polyp

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.04	1.02-1.06	<0.001	1.05	1.03-1.07	<0.001
Sex (male)	0.92	0.63-1.34	0.684	1.48	0.96-2.28	0.078
Diabetes mellitus	1.49	1.00-2.20	0.048	0.95	0.61-1.47	0.807
Antidiabetic drug use	1.18	0.71-1.96	0.536			
Hypertension	1.86	1.26-2.75	0.002	1.32	0.86-2.01	0.200
Antihypertensive drug use	2.33	1.43-3.78	0.001			
Statin use	0.74	0.45-1.24	0.253			
Smoking	1.18	0.73-1.90	0.493			
hsCRP	1.43	0.85-2.43	0.181			
HOMA-IR	1.01	0.96-1.06	0.825			
Lobular inflammation						
0	1		0.054[a]			
1	1.68	1.02-2.76	0.040			
2	1.79	0.93-3.44	0.080			
3	6.44	0.56-73.9	0.134			
Ballooning						
0	1		0.780[a]			
1	1.12	0.75-1.66	0.579			
2	0.98	0.38-2.50	0.965			
Steatosis grade						
0	1					
1-3	3.54	1.22-10.3	0.020			
Significant fibrosis						
F0-F1	1					
F2-F4	1.30	0.83-2.04	0.247			
Histological spectrum of NAFLD						
No NAFLD	1		0.001[a]	1		0.002[a]
NAFL	2.37	1.34-4.20	0.003	2.76	1.51-5.06	0.001
NASH	1.80	1.01-3.22	0.047	2.08	1.12-3.86	0.020

Abbreviations: 95% CI, 95% confidential interval; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high sensitivity C-reactive protein; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio.
[a]*P*-value for the test of trend of odds.

related to such factors.[13,26] NAFLD may precede and/or promote the development of metabolic syndrome.[1] Recent studies have shown a link between metabolic syndrome and the development of advanced colonic neoplasm.[27] From this bidirectional relationship, NAFLD might be associated with advanced colonic neoplasm. The mechanism by which NAFLD causes an increased risk of advanced colonic neoplasm is not fully understood. However, NAFLD represents a condition of profound insulin resistance and a proinflammatory state. Insulin and insulin-like growth factors may promote the development of advanced colonic neoplasm through their proliferative and anti-apoptotic effects.[28]

Fibrosis is a major histological harbinger of NAFLD prognosis because most studies have shown that the stage of fibrosis influences overall- and liver-related mortality among patients with NAFLD independently of the presence or severity of other histological features.[29] In the present study, the presence of NASH was correlated with the development of advanced colorectal neoplasm. Due to the uncertainty about the mechanism by which NASH is associated with an increased risk of advanced colonic neoplasm, further studies that evaluate the pathways leading from hepatic fibrosis to advanced colonic neoplasm are needed. Some studies proposed the roles of adiponectin, interleukin-6, tumor necrosis factor-α, leptin, and pro-inflammatory cytokines as relevant predictors of colorectal neoplasm.[30,31] Dysbiosis of gut microbiota, gut microbiota-medicated inflammation, and impaired mucosal immune function have been suggested as playing important roles in the

TABLE 5 Univariate and multivariate analyses for development of advanced colorectal neoplasm

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.05	1.02-1.08	<0.001	1.05	1.02-1.08	0.001
Sex (male)	0.67	0.38-1.20	0.181	0.94	0.50-1.75	0.833
Diabetes mellitus	1.81	1.02-3.22	0.042	1.13	0.61-2.09	0.705
Antidiabetic drug use	1.34	0.61-2.92	0.463			
Hypertension	1.69	0.95-3.00	0.173			
Antihypertensive drug use	1.50	0.65-3.46	0.344			
Statin use	0.97	0.44-2.10	0.928			
Smoking	0.81	0.38-1.73	0.592			
hsCRP	1.40	0.70-2.80	0.342			
HOMA-IR	1.04	0.97-1.11	0.288			
Lobular inflammation						
0	1		0.128[a]			
1	2.18	0.94-5.04	0.070			
2	2.55	0.92-7.04	0.071			
3	N/A	N/A	N/A			
Ballooning						
0	1		0.153[a]			
1	1.74	0.94-3.22	0.077			
2	1.05	0.23-4.85	0.953			
Steatosis grade						
0	1					
1-3	1.95	0.45-8.39	0.371			
Significant fibrosis						
F0-F1	1					
F2-F4	1.38	0.73-2.62	0.322			
Histological spectrum of NAFLD						
No NAFLD	1		0.001[a]	1		
NAFL	2.60	0.96-7.04	0.060			
NASH	2.74	1.01-7.43	0.047	2.81	1.01-7.87	0.049

Abbreviations: 95% CI, 0.195% confidential interval; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high sensitivity C-reactive protein; N/A, not available; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio.

[a]*P*-value for the test of trend of odds.

pathogenesis of NAFLD,[32] which might lead to developing advanced colorectal neoplasm. These possible mediators should be evaluated by further molecular studies in the future.

Hwang et al reported previously the first evidence of a relationship between NAFLD and an increased risk of colorectal adenomatous polyp.[20] An increased risk of NAFLD was also evident in patients with more adenomatous polyps. Untreated patients would suffer from these polyps progressing to CRC according to an adenoma-carcinoma sequence.

A more recent study that assessed NAFLD severity by non-invasive tools, including Fibrosis-4 index and NAFLD fibrosis score, also revealed an association between NAFLD severity and colorectal neoplasm; however, the diagnostic accuracy of these non-invasive methods is questionable.[7,25] Furthermore, some of patients with NAFLD identified by these non-invasive tools indeed may have been misdiagnosed with NAFLD because they were not diagnosed by liver biopsy, which is a gold standard of the diagnosis of NAFLD.[33,34] Therefore, the diagnostic accuracy of non-invasive tools in those studies was potentially limited. Objective detection of NAFLD would be necessary for confirmation of those findings.

In the present study, NASH was associated with a higher risk of advanced colorectal neoplasm and these results suggested the

benefit of CRC screening in NAFLD patients. Several features of our approach differed from those of other studies. First, our study included only biopsy-proven NAFLD patients. Using a reference tool for diagnosis of NAFLD, we could more accurately evaluate the evidence-based relationship of NAFLD and advanced colorectal neoplasm than non-invasive tool-based studies. Second, in contrast to the previous studies that also used liver biopsy as a diagnostic tool, our study was able to characterize in greater detail the histological features of patients with NAFLD by grading histological findings, including lobular inflammation, hepatocellular ballooning, and fibrosis severity. By considering detailed histological features in our analysis, we could obtain more complex information about the association between the histological severity and characteristics of NAFLD and the development of advanced colorectal neoplasm. Third, we have adjusted for the potential confounders which may affect the development of colorectal adenomatous polyps, such as age, sex, and metabolic risk factors. Thus, we could better describe the relationship between the histological severity of NAFLD and the risk of advanced colorectal neoplasm.

The limitation of this study is that the detection of colorectal polyps is prone to intra- as well as inter-observer variation. Despite our experienced examiners who performed colonoscopy, intra- and inter-observer variations could affect the detection of colorectal polyps. Although our initial cohort included more than 750 biopsy-proven NAFLD patients, only 476 patients underwent colonoscopy, which might produce a selection bias in our study. To overcome this limitation, we are currently building another multicenter, prospective cohort in Korea and will soon perform an extended study for external validation. Second, given the known association between diabetes mellitus and colorectal adenomas,[35,36] the presence of diabetes mellitus might act as a confounding factor. To minimize the confounding effect, we have performed multivariate analyses for developing of adenomatous colorectal polyp or advanced colorectal neoplasm including diabetes mellitus as a covariate. Since this study is a cross-sectional study, proving whether NAFLD by itself is a predictor of colorectal neoplasm may be difficult. The mechanism linking NAFLD to colorectal neoplasm is not yet completely understood. NAFLD represents a condition of insulin resistance and pro-inflammatory state. Insulin or insulin-like growth factors may promote the development of CRC. In the present study, we have adjusted for the presence of diabetes mellitus to prove that the presence of NASH is an independent risk factor for developing advanced colorectal neoplasm. Given the high prevalence of NAFLD, performing a screening colonoscopy in all patients with NAFLD may not be feasible due to limited resources. However, for the patients with biopsy-proven NASH, the need for screening colonoscopy is more compelling due to a higher risk of advanced colorectal neoplasm.

In conclusion, NASH may be an independent risk factor for advanced colorectal neoplasm. Understanding the sequential progression from colorectal adenoma to CRC according to the histological spectrum of NAFLD and recommendations to perform screening colonoscopy in patients with NASH are important and useful messages for clinicians. Therefore, further studies are needed to better understand the pathophysiology of NAFLD associated with advanced colorectal neoplasm, the benefit of early screening of advanced colorectal neoplasm in NASH patients, the effect of genetic traits on the development of NASH and advanced colorectal neoplasm, and the impact of NAFLD treatment on the modulation of the risk of advanced colorectal neoplasm.

CONFLICT OF INTEREST

The authors declare that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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