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Colorectal adenomas and MAFLD: a cross-sectional study in a Hispanic screening cohort

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Abstract

Aims: Prior evidence demonstrates an association between non-alcoholic fatty liver disease (NAFLD) and colorectal adenomas (CRA) risk. However, information using the new definition of the disease [i.e., metabolic dysfunction-associated fatty liver disease (MAFLD)] is scarce. We aimed to assess the relationship between MAFLD and CRA risk.

Methods: We conducted a cross-sectional study including patients from three university centers in Chile who underwent a colonoscopy for colorectal cancer screening and abdominal imaging study. We obtained sociodemographic and clinical data, and we performed univariate and multivariable regression analyses.

Results: In total, 895 patients were included; 42% were male, the mean age was 59.9 ± 9.3 years, and 37.8% (338) had CRA. Patients harboring polyps were predominantly males (48.2% *vs.* 38.2%, $P = 0.002$), older (61.6 ± 8.7 years *vs.* 58.9 ± 9.5 years, $P < 0.001$), and exhibited a higher body weight than controls [75 (66-88) kg *vs.* 72 (63-

82.3) kg, $P = 0.002$]. Fifty-six percent of patients showed hepatic steatosis in imaging studies and 54.4% met MAFLD diagnostic criteria. The adenoma detection rate was higher in the MAFLD group compared to controls (46.4% *vs.* 27.5%, $P < 0.001$). In the multivariable analysis, MAFLD was significantly associated with the presence of CRA (odds ratio = 2.32; 95%CI: 1.68-3.19, $P < 0.0001$). There were no statistically significant differences of histopathological characteristics of the adenomas according to the presence of MAFLD.

Conclusion: The present study shows that, in Chilean Hispanic subjects, MAFLD is associated with an increased risk of CRA. This information may be useful to design specific screening colonoscopy recommendations in MAFLD patients.

Keywords: MAFLD, colorectal adenoma, steatosis, adenoma detection rate, steatosis, steatohepatitis, fatty liver

INTRODUCTION

Colorectal cancer (CRC) is considered a public health priority since it is the third most common cancer with the second highest mortality worldwide. CRC was responsible for more than 9.6 million deaths in 2018[1]. Data from Latin America are also worrisome, as the burden of CRC in the region has increased in recent years[2]. In Chile, CRC is the second most frequent cancer and has exhibited a rise in incidence and mortality curves in recent years[3].

Most CRC cases (70%) follow the adenoma-carcinoma sequence where premalignant lesions are represented by colorectal adenomas (CRA)[4]. The rest of the cases develop through the "serrated pathway" or from dysplasia secondary to chronic inflammation in patients with inflammatory bowel disease[5]. Polyps are the clinical manifestation of altered cell proliferation processes that originate in the colorectal epithelium and are recognizable by endoscopic studies[6]. They are classified into those with no malignant neoplastic potential, such as inflammatory and hyperplastic polyps, and those that may originate a CRC, such as CRA. In addition, CRA can be classified into low- and high-risk lesions according to size, degree of dysplasia, and the presence of a villous component[7].

CRC can be prevented by controlling risk factors or through endoscopic resection of polyps[8]. Different screening methods to detect adenomas have been shown to reduce CRC incidence as well as CRC-associated mortality. These include non-invasive tools, based on testing for occult blood in the stools, and invasive procedures such as colonoscopy[9,10]. Current screening recommendations made by scientific societies are constantly being updated in light of new evidence. Of note, the recent rise of CRC in the younger population led to reducing the age to start screening from 50 to 45 years[11]. Other updates seek to ensure minimum standards of care that have shown benefit in reducing cancer rates in the intervals between colonoscopies, such as an adenoma detection rate (ADR) > 25%[12].

Nonalcoholic fatty liver disease (NAFLD) affects more than one-quarter of the adult population worldwide and is closely linked to underlying metabolic syndrome, obesity, and type 2 diabetes[13]. Several studies have shown that NAFLD is associated with increased incidence of multiple neoplasms, including hepatocarcinoma and breast cancer, among others[14]. In addition, NAFLD is also associated with an increased risk of CRA and CRC[15,16]. Thus, NAFLD constitutes an emerging risk factor for CRC.

A process of NAFLD renaming is ongoing and the term metabolic dysfunction-associated fatty liver disease (MAFLD) has been recently proposed[17]. This name change emphasizes metabolic dysfunction in NAFLD and suggests the implementation of positive diagnostic criteria[17,18]. Although NAFLD and MAFLD are not completely overlapping, most of the available knowledge on NAFLD could be extrapolated to MAFLD, but

more research is needed in this regard. Despite the notable impact of NAFLD in CRC, there are no data from Hispanic populations assessing the influence of MAFLD on the risk of CRA. In the present study, we explored the existence of an association between the presence MAFLD and the existence of CRA in patients attending to screening colonoscopy at three university centers in Chile.

METHODS

Ethical approval

This study was approved by the Institutional Review Board (Pontificia Universidad Católica de Chile, Santiago, Chile; ID: 210309004).

Data collection

We conducted a cross-sectional study including individuals from three university centers, which are part of the Healthcare Network of the Pontificia Universidad Católica de Chile School of Medicine: Red de Salud UC-CHRISTUS Hospital (Santiago, Chile), the Clínica UC San Carlos de Apoquindo (Santiago, Chile), and San Joaquín Medical Center (Santiago, Chile). All demographic information, clinical variables, laboratory results, imaging, and endoscopic and histological data were obtained from the institutional medical records by two independent observers (Villalón J and Villalón F), and disagreements were resolved by a third reviewer (Villalón A). We collected data between January 2018 and December 2020. We included patients older than 18 years, with no digestive symptoms, who underwent screening colonoscopy and an abdominal imaging study (i.e., abdominal ultrasound, abdominal computed tomography scan, or magnetic resonance imaging) in the 12 months before or after the index colonoscopy. We excluded all those with digestive symptoms (i.e., digestive bleeding, weight loss, recent change in intestinal transit time, *etc.*), with a prior diagnosis of cirrhosis or another chronic liver disease, with a personal history of CRC, resection of the large intestine, familial polyposis syndrome, or inflammatory bowel disease[19]. Colonoscopies without cecal intubation or suboptimal bowel preparation [i.e., Boston Bowel Preparation Scale (BBPS) score lower than 7], as defined by the operator, were also excluded[20].

We also recorded the following variables from the institutional electronic medical records: age at the time of colonoscopy, gender, weight (kg), waist circumference (cm), comorbidities (hypertension, diabetes, prediabetes, insulin resistance, dyslipidemia, sedentary lifestyle, obstructive sleep apnea-hypopnea syndrome, coronary heart disease, stroke, celiac disease, and family history of colorectal cancer), tobacco and alcohol consumption in the six months prior to colonoscopy, and medical therapy (including vitamin E, metformin, aspirin, and statins)[21-25]. The recorded comorbidities were selected to adequately diagnose MAFLD (hypertension, diabetes, prediabetes, insulin resistance, and dyslipidemia), and other conditions were chosen due to the potential association with a higher risk of CRA and CRC[26-29]. We considered the laboratory tests performed six months before or after the image. In addition, we calculated the FIB-4 score to estimate the presence or absence of liver fibrosis.

Colonoscopies with cecal intubation, BBPS score ≥ 7 points, and a withdrawal time greater than 6 min were considered as adequate quality studies. Colonoscopies were performed by either gastroenterologist endoscopists or surgeons. Initially, the presence or absence of polyps was described. Lesions were described by their morphology as pedunculated, sessile, or flat according to the Paris classification. We recorded polyp neoplastic appearance and size (according to the endoscopist's criteria). The number of lesions found was classified as single or multiple (≥ 1). The location of the lesions was described in relation to the splenic flexure, where the colon is considered proximal from the cecum to the ascending colon, up to the transverse colon including the flexure, and the rest as distal. All polyps were analyzed by pathologists and classified according to the histological criteria of the World Health Organization. In cases where more than one polyp

was found, the largest or the highest histological grade was described, the latter being the main criterion in dissenting cases. Colonoscopy findings allowed categorizing the study population into two groups (i.e., high-risk and low-risk groups). The high-risk group was defined by the presence of one or more adenomas ≥ 10 mm or the presence of an advanced adenoma (villous histology, high-grade dysplasia, or intramucosal cancer). Patients having CRA that did not meet these criteria were classified as having low risk of CRC. A colonoscopy without findings or with non-adenomatous polyps (i.e., inflammatory, hamartomatous, or hyperplastic polyps) was considered normal. In addition, we did not consider serrated polyps in the analyses.

The presence and degree of hepatic steatosis were evaluated by expert radiologists. Steatosis was defined, according to the radiological technique used, based on the classic criteria such as increased echogenicity and the visualization of intrahepatic vessels and the diaphragm on ultrasound, the lower attenuation of the liver parenchyma measured in Hounsfield units on CT scan, and the loss of hepatic signal in the opposed phase images in magnetic resonance imaging[30]. Finally, the diagnosis of MAFLD was made according to recently published criteria, which are based on evidence of steatosis by imaging or histology and the presence of diabetes, obesity, or at least two minor criteria of metabolic dysfunction[29].

Statistical analysis

We evaluated the distribution of continuous variables using the Kolmogorov-Smirnov test, age being the only variable with normal distribution expressed as the mean ± standard deviation. The rest of the variables were expressed as median and interquartile ranges. The differences between the two groups were analyzed with a *t*-student test for age and with a non-parametric test for the rest. The categorical variables were evaluated with the Chi-square test. A statistically significant difference was considered with a *P*-value < 0.05. The potential variables were analyzed using logistic regression. All significant laboratory tests were reassessed on a logarithmic scale to facilitate interpreting the results. A multivariable regression analysis was conducted to assess the association between MAFLD and CRA, adjusting for potential confounders[31]. We selected variables for multivariable analysis according to significance in the univariate analysis. We constructed three models, including all the significant variables (Model 1), clinical variables exclusively (Model 2), and including only those variables that resulted significantly in Model 1 or 2 to better predict presence of CRA (Model 3 or *fully predictive* model). We measured the goodness-of-fit for each model using the Hosmer-Lemeshow test. Finally, we used variance inflation factors to detect collinearity between variables. We used the statistical software SPSS (IBM Corp.) v24.0 to perform all the analyses.

RESULTS

In total, 12,833 colonoscopies were performed during the period analyzed in this study. Of those procedures, 1685 were screening studies with 958 having an abdominal imaging study in the 12 months before or after the index colonoscopy. Sixty-three patients were discarded because they did not meet inclusion criteria. The flow-chart of the study population enrolled in the final analysis is summarized in Figure 1.

In total, 895 patients were analyzed. The mean age was 59.9 ± 9.3 years and 58% were female. The median weight was 73 (65-84.5) kg, median waist circumference was 98 (93-110) cm, and 82% were overweight. Fifty-six percent (501) of patients had hepatic steatosis and 54.4% (487) met the MAFLD criteria. Ultrasound was the most widely available imaging method (74.4%) to establish the presence of steatosis [Supplementary Figure 1]. The degree of steatosis was quantified in 447 subjects with 58.4% of them having moderate to severe steatosis. Baseline characteristics of overall and each group are summarized in Table 1. Of note, 10.3% of patients were diabetic, 25.9% were active smokers, and 14.7% had a family history of CRC.

Table 1. Baseline characteristics of patients with and without colon adenomas

Variable	Total population (*n* = 895)	Absence of adenomas (*n* = 557)	Adenoma detection (*n* = 338)	*P*-value
General characteristic				
Age (years)	59.9 ± 9.3	58.9 ± 9.5	61.6 ± 8.7	< 0.0001
Male gender (%)	376 (42.0)	213 (38.2)	163 (48.2)	0.002
Weight (Kg)	73 [65-84.5]	72 [63-82.3]	75 [68-88]	0.002
Comorbidities (*n*, %)				
Diabetes	90 (10.3)	43 (7.9)	47 (14.2)	0.004
Prediabetes	120 (13.7)	69 (12.6)	51 (15.4)	0.243
Overweight	568 (82.0)	332 (77.8)	236 (88.7)	< 0.0001
Hypertension	362 (41.3)	214 (39.1)	148 (44.8)	0.095
Insulin resistance	143 (16.3)	87 (15.9)	56 (17)	0.789
Dyslipidemia	378 (43.2)	224 (41)	154 (46.7)	0.102
Sedentarism	338 (71.3)	198 (70.5)	140 (72.5)	0.623
OSAHS	45 (5.2)	31 (5.7)	14 (4.3)	0.346
Coronary artery disease	21 (2.4)	9 (1.7)	12 (3.6)	0.064
Ischemic stroke	11 (1.3)	3 (0.6)	8 (2.4)	0.016
Celiac disease	10 (1.2)	5 (0.9)	5 (1.5)	0.421
Family history CRC	123 (14.7)	69 (13.1)	54 (17.4)	0.086
Alcohol consumption	366 (45.9)	237 (47.6)	129 (43.1)	0.223
Smoking	213 (25.9)	121 (23.3)	92 (30.3)	0.028
Current therapies (*n*, %)				
Vitamin E	18 (2.1)	10 (1.8)	8 (2.4)	0.539
Metformin	192 (22.1)	110 (20.3)	82 (25.1)	0.100
Aspirin	79 (9.1)	44 (8.1)	35 (10.7)	0.201
Statins	246 (28.2)	141 (26)	105 (32)	0.055
Radiologic liver steatosis (*n*,%)	501 (56.0)	272 (48.8)	229 (67.8)	< 0.0001
MAFLD diagnosis (*n*, %)	487 (54.4)	261 (46.9)	226 (66.9)	< 0.001
Metabolic laboratory				
Total Cholesterol (mg/dL)	191 [163-216]	192 [165-215]	188 [159-217]	0.586
HDL-c (mg/dL)	52 [42-61]	52 [43-62]	50 [42-59]	0.331
LDL-c (mg/dL)	110 [87-133]	112 [88-133]	109 [85-133]	0.296
Triglycerides (mg/dL)	119 [88-166]	113 [83-162]	127 [95-176]	0.002
Fasting blood glucose (mg/dL)	95 [88-104]	94 [87-101]	98 [90-108]	< 0.0001
2-HPL glucose levels (mg/dL)	125 [97-167]	120.5 [96-145]	137 [109-170]	0.314
Glycosylated hemoglobin (%)	5.7 [5.4-6.0]	5.6 [5.4-5.9]	5.8 [5.5-6.1]	0.017
HOMA	3.1 [2.0-4.2]	2.9 [2.0-4.2]	3.4 [2.4-4.2]	0.151
General laboratory				
Hemoglobin (g/dL)	14.2 [13.3-15.1]	14.0 [13.2-15.1]	14.4 [13.4-15.3]	0.020
Platelets (× 106/ L)	240 [201-277]	240 [200-280]	240 [200-270]	0.819
Creatinine (mg/dL)	0.8 [0.7-1.0]	0.8 [0.7-0.9]	0.8 [0.7-1.0]	0.010
AST (U/L)	22 [18-26]	22 [18-26]	22 [18-27]	0.842
ALT (U/L)	23 [18-35]	23 [17-34]	24 [18-35]	0.246
-GT (U/L)	24 [17-38]	22 [16-36.5]	27 [18-40]	0.024
ALP (U/L)	81 [68-98]	80 [68-96]	83 [68-100]	0.470
Total bilirubin (mg/dL)	0.5 [0.4-0.7]	0.5 [0.4-0.7]	0.52 [0.39-0.72]	0.054
INR	1.0 [1.0-1.0]	1.0 [1.0-1.0]	1.0 [1.0-1.0]	0.181
Albumin (g/dL)	4.6 [4.4-4.8]	4.6 [4.4-4.8]	4.6 [4.4-4.8]	0.310
FIB-4	1.1 [0.9-1.5]	1.1 [0.9-1.5]	1.2 [0.9-1.5]	0.878
Withdrawal time (min)	12 [10-15]	11 [10-15]	14 [11-16]	< 0.001

OSAHS: Obstructive sleep apnea-hypopnea syndrome; CRC: colorectal cancer; MAFLD: metabolic dysfunction-associated fatty liver disease; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; HOMA: homeostatic metabolic model; ALT: aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio.

The median FIB-4 index was 1.1 (0.9-1.5). The median withdrawal time at colonoscopy was 12 min (10-15 min).

CRA were identified in 338 (37.8%) out of 895 patients. These patients were predominantly males (48.7% *vs.* 38.2% of patients without CRA, $P = 0.002$), older than patients without CRA (mean age 61.6 ± 8.7 years *vs.* 59.9 ± 9.3 years in those without CRA, $P < 0.001$), and had a higher body weight [75 (66-88) kg *vs.* 72 (63-

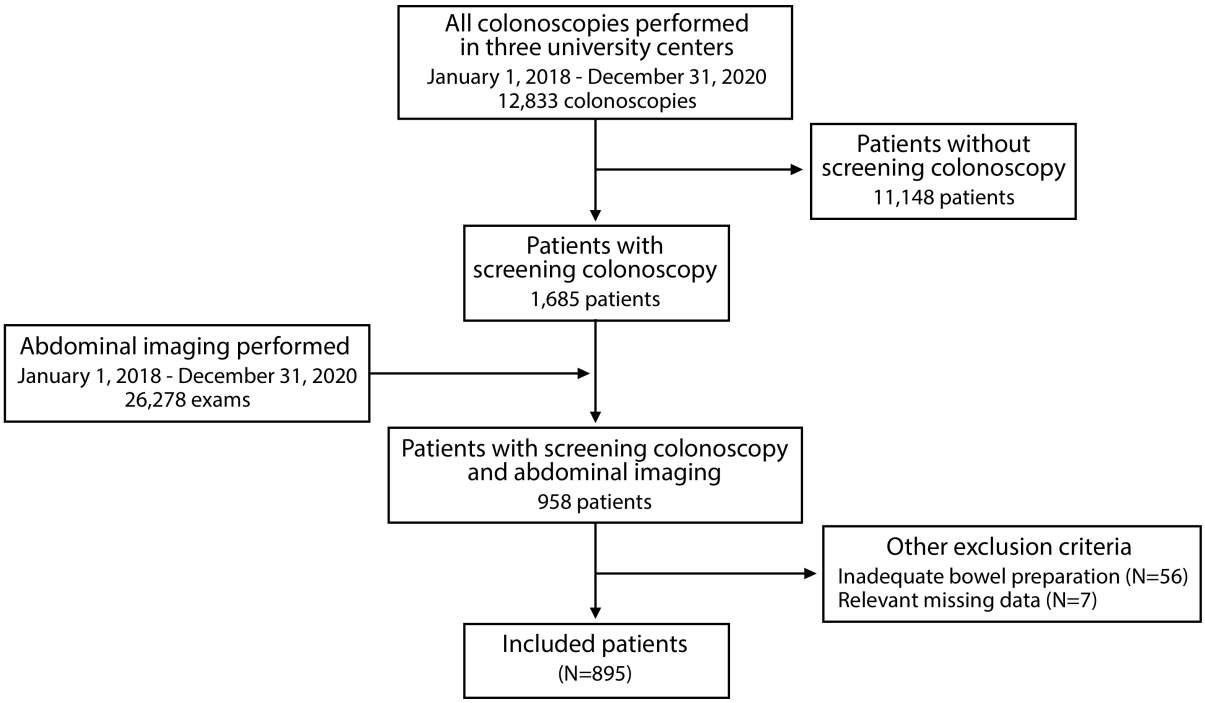

Figure 1. Patient selection process.

82.3) kg in patients without CRA, $P = 0.002$]. Furthermore, patients with CRA had a more frequent history of diabetes (14.2% *vs.* 7.9%, $P = 0.004$), ischemic stroke (2.4% *vs.* 0.6%, $P = 0.016$), and smoking (30.3% *vs.* 23.3%, $P = 0.028$) [Table 1]. The presence of MAFLD was significantly higher in patients with CRA (66.9% *vs.* 46.9%, $P < 0.001$). Serum triglycerides [127 (95-176) mg/dL *vs.* 113 (83-162) mg/dL, $P = 0.002$], fasting blood glucose [98 (90-108) mg/dL *vs.* 94 (87-101) mg/dL, $P < 0.001$], and glycosylated hemoglobin [5.8% (5.5%-6.1%) *vs.* 5.6% (5.4%-5.9%), $P = 0.017$] were also higher in the group with CRA. The colonoscopy withdrawal time was also significantly higher in patients with CRA [Table 1]. No differences were found with respect to FIB-4 or pharmacological therapies with incidence in fatty liver and CRC chemoprophylaxis [Table 1].

The general adenoma detection rate was 37.8%, and it was higher in the MAFLD group (46.4% *vs.* 27.5%, $P < 0.001$). We compared the histopathological differences of polyps according to the presence of MAFLD, and we did not identify differences regarding location, number, morphology, size, and malignancy of the colorectal polyps between the two groups [Table 2]. In addition, we did not identify differences in the characteristics according to the presence of MAFLD when we compared adenomas exclusively [Table 3]. No statistically significant association was found between the degree of hepatic steatosis and the presence of colorectal adenomas ($P = 0.458$) [Supplementary Table 1].

Finally, we conducted three multivariable analyses. The first model included age, sex, smoking, MAFLD criteria, overweight, diabetes, hemoglobin, triglycerides, fasting glucose, glycosylated hemoglobin, and creatinine. As result, we observed that the presence of MAFLD was associated with a higher risk of having CRA [odds ratio (OR) = 2.50; 95%CI: 1.24-5.04; $P = 0.011$] [Table 4]. Serum creatinine was also statistically associated with CRA in Model 1. The second model excluding laboratory tests demonstrated that MAFLD criteria, age, and male gender were associated with detection of CRA [Table 4]. The final model only included the significant variables of Models 1 and 2 and showed that MAFLD criteria better predicts the

Table 2. Comparison of location, number, morphology, size, and histology of the polyps between the MAFLD *vs.* non-MAFLD groups

Parameter	Total *n* = 439	MAFLD group *n* = 284 (64.7%)	Non-MAFLD group *n* = 155 (35.3%)	*P*-value
Location				0.398
Proximal colon	209 (47.6%)	142 (50%)	67 (43.2%)	
Distal colon	128 (29.2%)	79 (27.8%)	49 (31.6%)	
Right + left + rectum	102 (23.2%)	63 (22.2%)	39 (25.2%)	
Number				0.746
Single	200 (45.6%)	131 (46.1%)	69 (44.5%)	
Multiple	239 (54.4%)	153 (53.9%)	86 (55.5%)	
Morphology				0.301
Pediculated	36 (16.5%)	20 (14.2%)	16 (20.8%)	
Sessile	166 (76.1%)	113 (80.1%)	53 (68.8%)	
Flat	16 (7.4%)	8 (5.7%)	8 (10.4%)	
Size				0.238
< 10 mm	280 (80.5%)	187 (80.6%)	93 (80.2%)	
≥ 10 mm	68 (19.5%)	45 (19.4%)	23 (19.8%)	
Pathological features				
Non-adenoma	96 (21.9%)	54 (19%)	42 (27.1%)	0.743
Adenoma	338 (77%)	226 (79.6%)	112 (72.3%)	< 0.001
Non-advanced adenomas	270 (79.9%)	182 (80.5%)	88 (78.6%)	0.672
Advanced adenomas	68 (20.1%)	44 (19.5%)	24 (21.4%)	0.217
In-situ neoplasia	5 (1.1%)	4 (1.4%)	1 (0.6%)	0.471
Colorectal Cancer	0 (0%)	0 (0%)	0 (0%)	-

Table 3. Comparison of location, number, morphology, and size of adenomas between the MAFLD *vs.* non-MAFLD groups

Parameter	Total *n* = 338	MAFLD group *n* = 226	Non MAFLD group *n* = 112	*P*-value
Location				0.742
Proximal colon	173 (51.2%)	119 (52.6%)	54 (48.2%)	
Distal colon	79 (23.4%)	51 (22.6%)	28 (25.0%)	
Right + left + rectum	86 (25.4%)	56 (24.8%)	30 (26.8%)	
Number				0.631
Single	142 (42%)	97 (42.9%)	45 (40.2%)	
Multiple	196 (58%)	129 (57.1%)	67 (59.8%)	
Morphology*				0.128
Pediculated	32 (19%)	18 (15.9%)	14 (25.5%)	
Sessile	126 (75%)	90 (79.6%)	36 (65.5%)	
Flat	10 (6%)	5 (4.5%)	5 (9%)	
Size**				0.806
< 10 mm	220 (79.1%)	148 (78.7%)	72 (80%)	
≥ 10 mm	58 (20.9%)	40 (21.3%)	18 (20%)	
Adenoma detection rate	37.8%	46.4%	27.5%	< 0.001

*Available in 168 samples only. **Available in 278 samples only.

presence of CRA (OR = 2.32; 95%CI: 1.68-3.19; $P < 0.0001$). The main variables of univariate and multivariable analysis are summarized in Table 4.

DISCUSSION

NAFLD and the recently proposed related entity MAFLD have been linked to an increased risk of CRA detection[32]. In the present study, we examined whether MAFLD is a risk factor for the detection of CRA in screening colonoscopies in a sample of Chilean Hispanic patients as no data exist on the association of fatty liver and CRA in Latin-American patients. We found that MAFLD was significantly associated with a higher risk of having CRA with an OR of 2.50. This finding was consistent in different models. Moreover,

Table 4. The multivariable analysis to assess the colorectal adenoma risk

Variable	Univariate analysis			Multivariable analysis Model 1[a]			Multivariable analysis Model 2[b]			Multivariable analysis Model 3		
	OR	95%CI	*P*-value	OR	95%CI	*P*-value	OR	95%CI	*P*-value	OR	95%CI	*P*-value
Age	1.03	1.01-1.05	< 0.0001	1.01	0.97-1.04	0.701	1.05	1.03-1.07	< 0.001	1.03	1.01-1.05	< 0.0001
Male gender	1.53	1.17-2.01	0.002	1.56	0.70-3.50	0.276	1.81	1.28-2.57	0.001	1.56	1.06-2.30	0.025
Smoking	1.45	1.06-1.98	0.022	1.07	0.55-2.11	0.905	1.40	0.96-2.05	0.084	-	-	-
MAFLD criteria	2.24	1.70-2.96	< 0.0001	2.50	1.24-5.04	0.011	2.34	1.61-3.41	< 0.0001	2.32	1.68-3.19	< 0.0001
Overweight	2.30	1.48-3.58	< 0.0001	1.06	0.40-2.84	0.905	1.53	0.92-2.53	0.102	-	-	-
Diabetes	1.89	1.22-2.93	0.004	1.64	0.67-4.03	0.282	1.28	0.74-2.21	0.375	-	-	-
Ischemic stroke*	4.39	1.16-16.66	0.018	-	-	-	-	-	-	-	-	-
Creatinine (mg/dL)	1.77	1.11-2.81	0.016	3.93	1.25-12.39	0.019	-	-	-	1.07	0.59-1.94	0.826
Hemoglobin (g/dL)	3.66	1.26-10.64	0.017	0.73	0.05-9.87	0.813	-	-	-	-	-	-
Triglycerides (mg/dL)	1.38	1.10-1.73	0.005	0.93	0.59-1.49	0.771	-	-	-	-	-	-
Fasting blood glucose (mg/dL)	5.79	2.89-11.61	< 0.0001	2.66	0.47-14.94	0.266	-	-	-	-	-	-
Glycosylated hemoglobin (%)	1.42	1.06-1.89	0.018	0.95	0.55-1.63	0.841	-	-	-	-	-	-
Total bilirubin (mg/dL)	1.20	0.96-1.50	0.107	-	-	-	-	-	-	-	-	-
γ-GT (U/L)	1.16	0.99-1.37	0.070	-	-	-	-	-	-	-	-	-
Hosmer-Lemeshow test *P*-value**	-			0.745			0.182			0.548		

[a]Mean variance inflation factor = 1.56. [b]Mean variance inflation factor = 1.10. *Ischemic stroke was dropped out from the final models due to the low number of events. **A good model fit yields a *P* value > 0.05. γ-GT: Gamma-glutamyl transpeptidase; MAFLD: metabolic dysfunction-associated fatty liver disease.

the ADR in patients with MAFLD (46.4%) was significantly higher than that observed in patients without MAFLD (27.5%).

The risk of CRA and CRC is influenced by both genetic and environmental factors. Genetic predisposition and familial syndromes increase the risk strikingly, but, in clinical practice, the majority of CRC correspond to sporadic rather than familial cases. Modifiable risk factors for CRC include smoking, overweight, a sedentary lifestyle, and an unhealthy low-fiber diet with high content of red and processed meat[33]. Obesity and overweight are also known risk factors for CRC[34-36]. Pathophysiological links between obesity and CRC are complex and may be related to the altered metabolic milieu commonly present in obese patients[37].

Our findings are in agreement with available data on the association between MAFLD and CRA. Prior evidence using the diagnosis of NAFLD suggests that the association is consistent[16,38-40]. However, most of the published studies include Asian patients and few studies have been carried out in the western

population. Since the prevalence of NAFLD/MAFLD in Latin America is among the highest in the world[41], demonstrating its association with CRA is an important piece of evidence that can impact patient management. In our study, we did not find a significant association with an increased risk of advanced CRA according to the presence of MAFLD, which could be due to the low prevalence of these lesions in our study. Indeed, the incidence of CRC among individuals who undergo surveillance was lower than a prior Chilean study carried out during 2012-2015[42].

Although causality cannot be inferred from this study, the biological plausibility of the associations between MAFLD and CRA is generally accepted. Both conditions are related to unhealthy lifestyles including fructose-rich diets, processed meat consumption, sedentary habits, and the root cause of MAFLD, namely insulin resistance. Most of the proposed mechanisms that relate NAFLD and CRA, CRC, and other extrahepatic neoplasms suggest that the low-grade pro-inflammatory state generated by insulin resistance promotes neoplasia, but there are still a number of missing links[43]. Although insulin resistance was not associated with CRA in the present study, other conditions linked to insulin resistance, such as obesity, diabetes, and MAFLD, had a higher risk of CRA. This finding could be partially due to the progression from insulin resistance to diabetes or other conditions, with consequent cumulative damage. The potential dysregulation of bile acid metabolism has been suggested as one of the potential links based on data generated in mouse models[44-46], but more studies are needed.

The average age of patients included was 60 years or higher in the older population. This is attributable to the exclusive inclusion of patients who underwent screening colonoscopies. During the study period, the recommendations for surveillance of CRC in Chile were the onset of screening at 50 years[42]. Age is a key factor for the development of CRA as well as MAFLD, which could explain the high CRA rate and MAFLD prevalence identified in this study. On the other side, the most recent colorectal cancer screening guidelines recommend the onset of screening at 45 years[11]. From a public health perspective, the association between MAFLD and CRA could also modify the age of onset. Since other conditions (such as inflammatory bowel disease) have a high inflammation burden and long-term exposition[47], exposure over time could be necessary for patients with MAFLD to develop CRA and CRC. Future prospective studies are needed to elucidate this aspect and determine the best recommendations for surveillance.

The analysis of patients with colonoscopy performed only for screening purposes is one of the main strengths of the study. In addition, this is the first study on the Latin-American population that seeks to evaluate whether there is an association between colorectal adenomas and fatty liver disease associated with metabolic dysfunction. However, this study has some limitations. One of the most important ones is its retrospective nature, with the potential risk of lack of registry in some variables. Additionally, not all patients who underwent screening colonoscopy at these centers had abdominal imaging available, had different imaging methods, and the interval between both may also introduce risk of bias. In addition, withdrawal time was registered including the time of polypectomy, undoubtedly overestimating the relationship between withdrawal time and detection of CRA. Although a reverse association between MAFLD and CRA is plausible, it cannot be properly assessed in our study due to its nature. Even though this study demonstrated an association between MAFLD and the detection of CRA, it is unclear whether MAFLD could increase colorectal cancer risk.

In conclusion, the present study shows that Hispanic patients with MAFLD could be considered as a group with a high risk of presenting precursor lesions of colorectal cancer and that the ADR is significantly higher in this patient population. Thus, the presence of MAFLD should be taken into consideration when planning CRC screening strategies according to individual risk. We did not find statistically significant differences

regarding size, number, morphology, location, or risk histology in adenomas of patients with MAFLD *vs.* patients without demonstrated hepatic steatosis.

DECLARATIONS

Authors' contributions

Contributed to the conception and design of the study, acquisition of data, and analysis and interpretation of data: Villalón A, Fuentes-López E, Villalón J, Villalón F, Yañez B, Díaz LA, Candia R, Arrese M
Contributed to drafting the article or revising it critically for important intellectual content: Villalón A, Ayares G, Díaz LA, Arrese M, Arab JP
All authors approved the final version to be submitted.

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

This study was approved by the Institutional Review Board at the P. Univ. Catolica de Chile, Santiago, Chile (ID: 210309004). Individual informed consent waiver was granted by the local IRB.

Consent for publication

Not applicable.

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