Increased risk of colorectal polyps in patients with non-alcoholic fatty liver disease undergoing liver transplant evaluation

Birju D. Bhatt, Thresiamma Lukose, Abby B. Siegel, Robert S. Brown Jr, Elizabeth C. Verna

Center for Liver Disease and Transplantation, Columbia University College of Physicians and Surgeons, New York, NY, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Elizabeth C. Verna, MD, MS. Assistant Professor of Medicine, Center for Liver Disease and Transplantation, Division of Digestive and Liver Diseases, Columbia University College of Physicians and Surgeons, 622 West 168th St., PH 14-105K, New York, NY 10032, USA. Email: ev77@columbia.edu.

Background: Screening colonoscopy is a standard part of the liver transplant (LT) evaluation process. We aimed to evaluate the yield of screening colonoscopy and determine whether non-alcoholic fatty liver disease (NAFLD) was associated with an increased risk of colorectal neoplasia.

Methods: We retrospectively assessed all patients who completed LT evaluation at our center between 1/2008-12/2012. Patients <50 years old and those without records of screening colonoscopy, or with greater than average colon cancer risk were excluded.

Results: A total of 1,102 patients were evaluated, 591 met inclusion criteria and were analyzed. The mean age was 60 years, 67% were male, 12% had NAFLD and 88% had other forms of chronic liver disease. Overall, 42% of patients had a polyp found on colonoscopy: 23% with adenomas, 14% with hyperplastic polyps and with 1% inflammatory polyps. In the final multivariable model controlling for age, NAFLD [odds ratio (OR) 2.41, P=0.001] and a history of significant alcohol use (OR 1.69, P=0.004) were predictive of finding a polyp on colonoscopy. In addition, NAFLD (OR 1.95, P=0.02), significant alcohol use (OR 1.70, P=0.01) and CTP class C (OR 0.57, P=0.02) were associated with adenoma, controlling for age.

Conclusions: Screening colonoscopy in patients awaiting LT yields a high rate of polyp (43%) and adenoma (22%) detection, perhaps preventing the accelerated progression to carcinoma that can occur in immunosuppressed post-LT patients. Patients with NAFLD may be at a ~2 fold higher risk of adenomas and should be carefully evaluated prior to LT.

Keywords: Colon cancer; screening; cirrhosis; liver transplant (LT); non-alcoholic fatty liver disease (NAFLD)

Introduction

Colorectal cancer (CRC) is the third most common cancer and the third leading cause of cancer-related death in the United States (1). Risk-based screening, including in individuals over the age of 50 in the absence of other known risk factors, has been advocated (2-8). Obesity, and associated metabolic syndrome manifestations including diabetes have now been associated with increased CRC risk in epidemiologic studies,

and increased risk of polyps by ~1.5-6.2-fold (9-17). While the mechanism of this association is uncertain, perturbations in cytokine and hormone levels (e.g., IGF and adipokines) have been implicated (9,18,19).

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver disease which includes steatosis, non-alcoholic steatohepatitis (NASH) and fibrosis/cirrhosis. It represents the hepatic manifestation of the metabolic syndrome. NAFLD is now estimated to impact 10-46% of the

population in the United States (20-24) and is projected to become the leading indication for LT in the next decade (25-28). Extrahepatic complications of NAFLD (29) and in particular, an association between NAFLD and colorectal polyps have been suggested by a limited number of studies without histologic confirmation of NAFLD.

Given the increased risk of malignancy with post-LT immunosuppression (including CRC) (30) and the limited supply of organs, age-appropriate CRC screening with colonoscopy is a standard part of the evaluation for solid organ transplant, including liver transplant (LT) (31). Because the metabolic syndrome and its associated diseases (obesity, diabetes, hypertension and hyperlipidemia) are common in the transplant population, and the proportion of patients in transplant evaluation with NAFLD is projected to rise, we assessed the yield of screening colonoscopy in the transplant evaluation process and hypothesized that patients with NAFLD-related end stage liver disease would have a higher prevalence of colonic polyps than those in LT evaluation for other types of liver disease.

Patients and methods

Patients

This is a retrospective single center cohort study of all adult patients evaluated for LT between January 1, 2008 and December 31, 2012. Patients were excluded if they were less than 50 years old at LT evaluation, or had above average risk for CRC, including inflammatory bowel disease (IBD) (7,32), a history of multiple/recurrent adenomatous polyps (7,33), a significant family history of colon cancer (7,34), known cancer-predisposing gene alteration or a prior history of solid organ transplant (35,36). In addition, patients with HIV infection (37,38), a prior personal history of cancer (39,40), or with no colonoscopy report available for review were excluded.

Study design and definitions

All patients 50 years or older are required to have a screening colonoscopy within 5 years of LT evaluation, and records of this exam are included in the LT evaluation documentation for review. Records of prior colonoscopies and pathology reports were also reviewed when available. All lesions found on colonoscopy were recorded, including number, location (right, transverse or left colon) and size of each polyp. Polyps were classified as adenomatous (tubular, tubulovillous, villous, or serrated), hyperplastic or inflammatory based

upon pathology reports. Dysplasia and evidence of invasive carcinoma were also noted when present.

The primary outcomes of our study were the presence of any polyp on screening colonoscopy and the presence of an adenomatous polyp. Only patients with histology available for review were included in the analysis of risk factors for adenoma.

The primary predictor evaluated was the diagnosis of NAFLD-related end stage liver disease. This was defined as biopsy proven [either with liver biopsy in the pre-LT period or on explant when available, (n=50), or clinically in patients with cryptogenic cirrhosis and NAFLD risk factors (n=18)]. We used clinical criteria for some patients because explants with cirrhosis often obscure underlying features of NAFLD. Sensitivity analyses were performed including only patients with biopsy-proven disease. Additional predictors tested included the presence of diabetes, hypertension, hyperlipidemia, the metabolic syndrome (defined as the presence of obesity and two associated comorbidities), age, toxic exposures (including significant alcohol or tobacco use), and characteristics of liver disease including etiology, MELD and Child-Turcotte-Pugh class. The study was approved by the Columbia University Institutional Review Board.

Statistical analysis

Baseline characteristics and outcomes of colonoscopy were compared between patients with and without NAFLD with student t-test or Rank sum (continuous variables), or chi-square (categorical variables) as appropriate. We used multiple logistic regression analysis to identify predictors of (I) any polyp on colonoscopy and (II) an adenomatous polyp. A backwards elimination approach was utilized in multivariable modeling, considering parameters with $P<0.2$ in the initial multivariable model and sequentially removing non-significant predictors. Age was included in all final models given the known significant impact of age on CRC risk. Sensitivity analyses were performed excluding those patients without biopsy-proven NAFLD (18/68, 26%) and those without colon polyp histology available for review (61/248, 24%).

Results

Patient characteristics

A total of 1,102 adult patients were evaluated for LT in the study period, 320 (29%) were excluded due to age less than 50, 44 (4%) due to higher than average risk of CRC,
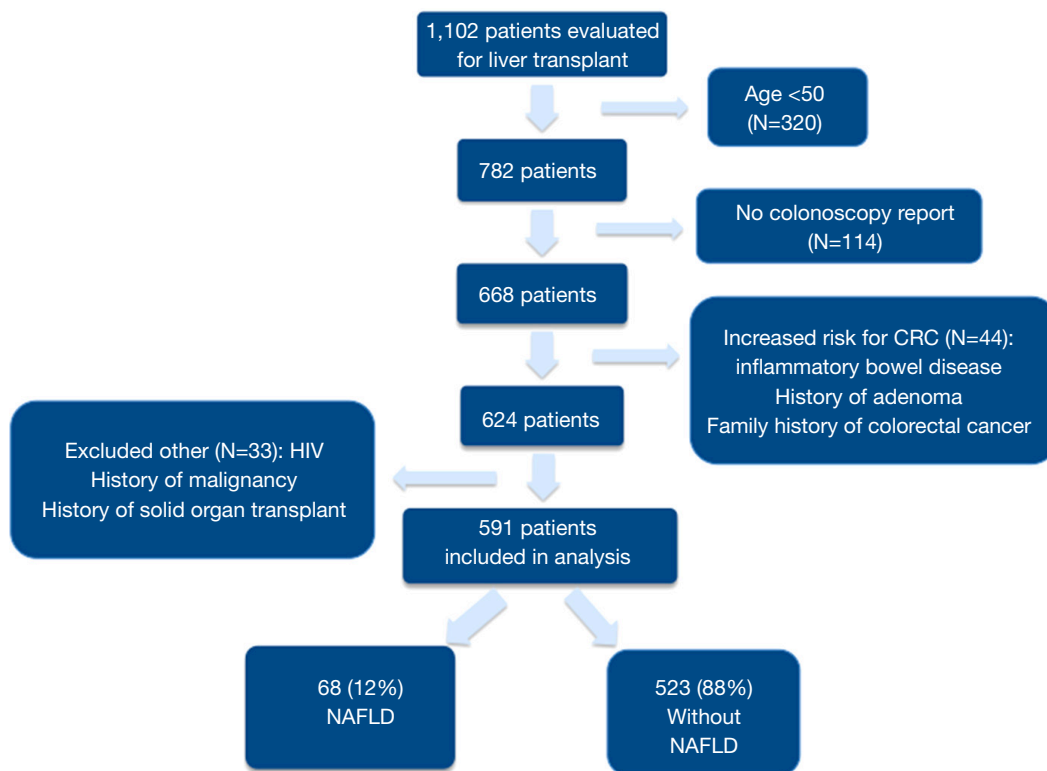
Figure 1 Flow diagram of patient population included in the final analysis. NAFLD, non-alcoholic fatty liver disease.

21 (2%) due to HIV, 6 (0.5%) due to prior malignancy, 6 (0.5%) due to prior solid organ transplant and 114 (10%) for a lack of colonoscopy report available for review (*Figure 1*). Thus, 591 patients were included in the final analysis: 68 (12%) with NAFLD and 523 (88%) without NAFLD. Baseline characteristics including the degree of liver disease severity were generally similar between the NAFLD and non-NAFLD groups (*Table 1*). When compared to the non-NAFLD group, patients with NAFLD were older (mean age 62.5 *vs.* 59.5 years, P≤0.001), had a higher body mass index (BMI) (31.6 *vs.* 29.1, P≤0.001), were more likely to be obese (57% *vs.* 29%, P≤0.001), and to have comorbidities such as diabetes (71% *vs.* 28%, P≤0.001), hypertension (46% *vs.* 33%, P=0.05), coronary artery disease (31% *vs.* 9%, P≤0.001) and the metabolic syndrome (29% *vs.* 6%. P≤0.001). Any history of significant alcohol intake (9% *vs.* 37%, P≤0.001) and tobacco (32% *vs.* 49%, P=0.02) use were less common in the NASH patients.

Colonoscopy findings

Overall, 248 (42%) patients had any polyp found on colonoscopy: 133 (23%) were adenomas, 81 (14%) were hyperplastic and 7 (1%) were inflammatory (*Table 2*). There were very few patients with dysplasia (2%) and no patients with invasive carcinoma. Other findings included hemorrhoids in 59%, diverticulosis in 29%, rectal varices in 7%, and vascular ectasia in 3%.

Association between NAFLD and colorectal polyps

Patients with NAFLD were significantly more likely to have a polyp found on colonoscopy than those without NAFLD (59% *vs.* 40%, P=0.003) (*Figure 2*). In addition, NAFLD patients were more likely to have multiple polyps, with 15% *vs.* 8% having more than 2 polyps encountered (P=0.04, *Table 2*). In univariate analysis (*Table 3*), significant predictors of finding a polup included NALFD [odds ratio (OR) 2.16, P=0.003]. a significant history of alcohol use (OR 1.47, P=0.03), and the presence of diabetes (OR 1.46, P=0.03). The presence of the metabolic syndrome was not significantly predictive (OR 1.37, P=0.27). In multivariable analysis controlling for age, NAFLD (OR 2.42, P=0.001), and alcohol use (OR 1.69, P=0.004), remained the only significant predictors of encountering a polyp. In particular, polyps

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Table 1 Patient demographics

Variables	NAFLD (N=68)	Non-NAFLD (N=523)	P value
Age, mean	62.5	59.5	<0.001
Male gender [%]	42 [62]	356 [68]	0.30
BMI, mean	31.6	29.1	<0.001
Obese (BMI ≥30)	39 [57]	153 [29]	<0.001
Race/ethnicity [%]			0.12
Non-Hispanic White	46 [68]	270 [52]	
Hispanic	9 [13]	105 [20]	
African American	3 [4]	35 [7]	
Asian	4 [6]	42 [8]	
Other/unknown	6 [9]	71 [14]	
Etiology of liver disease [%]			—
NAFLD	68 [100]	—	
HCV	—	266 [51]	
HBV	—	37 [7]	
Alcohol	—	113 [22]	
AIH/PSC/PBC	—	57 [11]	
Other	—	50 [10]	
HCC [%]	19 [28]	168 [32]	0.49
Medical comorbidities [%]			
Metabolic syndrome	20 [29]	33 [6]	<0.001
Diabetes mellitus	48 [71]	145 [28]	<0.001
Hypertension	31 [46]	175 [33]	0.05
Coronary artery disease	21 [31]	48 [9]	<0.001
Significant alcohol use [%]			<0.001
Recent	0 [0]	9 [2]	
Former	6 [9]	184 [35]	
Never	62 [91]	330 [63]	
Tobacco use [%]			0.02
Current	3 [4]	56 [11]	
Former	19 [28]	202 [39]	
Never	46 [68]	265 [51]	
Intravenous drug use [%]			0.01
Current	0 [0]	1 [0.2]	
Former	2 [3]	86 [16]	
Never	66 [97]	436 [83]	
Listed for liver transplant [%]	53 [78]	420 [80]	0.65
Transplanted [%]	37 [54]	260 [50]	0.47
MELD, mean	15.1	14.5	0.58
CTP score, median	8.0	8.1	0.89

Table 1 (*continued*)

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Variables	NAFLD (N=68)	Non-NAFLD (N=523)	P value
CTP class [%]			0.29
A	18 [26]	161 [31]	
B	35 [51]	217 [41]	
C	15 [22]	145 [28]	
Portal hypertension [%]			
Esophageal varices	45 [66]	321 [61]	0.44
Hepatic encephalopathy	36 [53]	276 [53]	0.98
Ascites	39 [57]	295 [56]	0.88
Spontaneous bacterial peritonitis	3 [4]	16 [3]	0.55
Laboratory values*, mean			
Albumin (g/dL)	3.3	3.2	0.86
Hemoglobin (g/dL)	11.6	11.9	0.26
INR	1.4	1.4	0.54
AFP (ng/mL)	92.6	54.0	0.34
Creatinine (mg/dL)	1.3	1.2	0.40
Bilirubin (mg/dL)	3.6	3.7	0.96
Platelets (10^3/uL)	101.1	111.8	0.23

*, all laboratory values are at the time of presentation for listing; NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; INR, international normalized ratio; AFP, alpha fetoprotein; MELD, model for end stage liver disease; CTP, child turcotte pugh score.

in the right (29% *vs.* 16%, P=0.01) and transverse (18% *vs.* 9%, P=0.03) segments of the colon were significantly more common in NAFLD patients (*Figure 3*). In sensitivity analysis excluding patients without histologically confirmed NAFLD (n=18) or those without available polyp histology (n=61), NAFLD remained a significant predictor of polyps in univariate (OR 2.44, P=0.003 and OR 1.97, P=0.009, respectively) and multivariable analyses (OR 2.68, P=0.002 and OR 2.08, P=0.007, respectively).

Association between NAFLD and colorectal adenoma

NAFLD patients were also more likely to have an adenomatous polyp than those without NAFLD (32% *vs.* 21%, P=0.04). In univariate analysis, significant predictors of finding an adenoma included NAFLD (OR 1.95, P=0.02), a significant history of alcohol use (OR 1.70, P=0.01), and CTP class C status (OR 0.57, P=0.04) (*Table 3*).

Table 2 Findings on colonoscopy			
Variables	NAFLD (N=68)	Non-NAFLD (N=523)	P value
Any polyp [%]	40 [59]	208 [40]	0.003
Adenoma	22 [32]	111 [21]	0.04
Inflammatory	3 [4]	4 [1]	0.01
Hyperplastic	11 [16]	70 [13]	0.53
Unknown pathology	9 [13]	52 [10]	0.40
Location [%]*			
Right	20 [29]	85 [16]	0.01
Left	22 [32]	126 [24]	0.20
Transverse	12 [18]	47 [9]	0.03
Adenoma location [%]*			
Right	9 [13]	46 [9]	0.25
Left	10 [15]	54 [10]	0.27
Transverse	7 [10]	32 [6]	0.21
Polyp size			
Largest polyp (mm), median [IQR]	5.5 [5-8]	5.0 [3-8]	0.09
No. >1 cm [%]	6 [20]	33 [23]	0.70
Adenoma size			
Largest adenoma, median [IQR]	5.0 [5-8]	5.0 [3-10]	0.27
No. >1 cm [%]	5 [20]	24 [31]	0.53
Number [%] with			0.001
4 polyps	5 [7]	12 [2]	
3 polyps	5 [7]	27 [5]	
2 polyps	3 [4]	52 [10]	
1 polyp	27 [40]	117 [22]	
Dysplasia [%]	1 [1]	8 [2]	0.97
Invasive carcinoma [%]	0 [0]	0 [0]	1.0
Other findings [%]			
Hemorrhoids	42 [62]	306 [59]	0.61
Diverticulosis	26 [38]	147 [28]	0.08
Rectal varices	3 [4]	37 [7]	0.41
Vascular ectasia	1 [1]	18 [3]	0.39

*, patients may have more than one polyp or adenoma location if there is more than one encountered; NAFLD, non-alcoholic fatty liver disease.
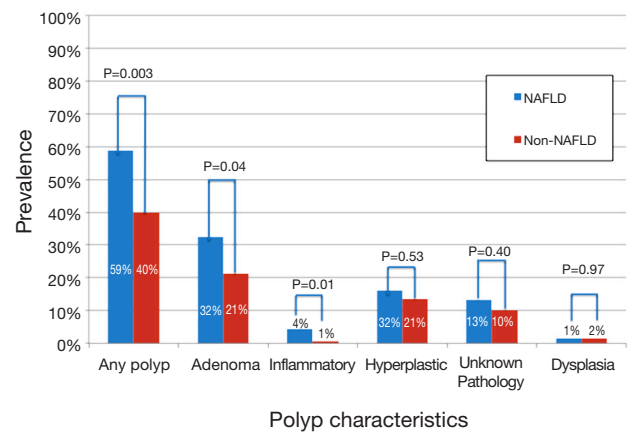

Figure 2 The prevalence of polyps by polyp type and liver disease etiology (NAFLD compared to non-NAFLD). NAFLD, non-alcoholic fatty liver disease.

The presence of diabetes (OR 1.15, P=0.45) or the metabolic syndrome (OR 1.4, P=0.29) were not predictive of adenoma. In multivariable analysis controlling for age, NAFLD (OR 1.95, P=0.02), and alcohol use (OR 1.73, P=0.01) were associated with a greater risk of adenomatous polyps and CTP class C status remained protective against adenoma (OR 0.54, P=0.03). In a sensitivity analysis excluding patients without biopsy confirmed NAFLD (n=18), NAFLD remained similarly predictive of adenomas in univariate (OR 1.71, P=0.10) and multivariable (OR 1.79, P=0.08) analyses though did not reach statistical significance possible due to decreased power.

Discussion

Our study demonstrates that polyps (42%), and specifically adenomatous polyps (23%), are common among average risk LT candidates undergoing screening colonoscopy, comparable to the average detection rates for adenomatous polyps in the general population (20-32%) (41-44). These rates of polyp and adenoma detection are also consistent with recent findings in the cirrhotic pre-LT population (49% and 29%, respectively) (41,45). In addition, polyps and adenomatous polyps are more common in patients with NAFLD than in those with other forms of end stage liver disease. In adjusted models, NAFLD patients had a ~2.5-fold higher risk of polyps and a ~2-fold higher risk of adenomatous polyps compared to non-NAFLD patients.

Previous literature suggests an association between colorectal neoplasia and the metabolic syndrome and

Table 3 Unadjusted and adjusted predictors of a polyp or an adenoma on colonoscopy

Predictor	Polyp				Adenoma			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
NAFLD	2.16 (1.29-3.62)	0.003	2.42 (1.42-4.11)	0.001	1.95 (1.09-3.47)	0.02	1.95 (1.09-3.48)	0.02
Age (per year)	1.02 (0.99-1.05)	0.18	1.02 (0.99-1.05)	0.29	1.02 (0.99-1.06)	0.20	1.02 (0.98-1.05)	0.32
Hispanic ethnicity	1.12 (0.74-1.71)	0.59			0.91 (0.56-1.48)	0.72		
African American	0.80 (0.40-1.57)	0.51			0.63 (0.23-1.54)	0.31		
BMI	0.99 (0.97-1.02)	0.60			0.99 (0.95-1.02)	0.49		
Obesity (BMI ≥30)	0.95 (0.67-1.35)	0.78			0.95 (0.63-1.43)	0.80		
Albumin	1.26 (0.99-1.61)	0.06			1.16 (0.87-1.54)	0.33		
Hgb	0.99 (0.92-1.07)	0.84			1.01 (0.92-1.10)	0.89		
INR	0.97 (0.76-1.24)	0.81			0.99 (0.73-1.33)	0.93		
Creatinine	1.04 (0.90-1.21)	0.59			1.00 (0.84-1.19)	0.97		
Total bilirubin	0.98 (0.96-1.01)	0.25			0.98 (0.94-1.02)	0.25		
Platelets	1.00 (0.998-1.00)	0.31			1.00 (0.998-1.00)	0.24		
Meld score	0.98 (0.96-1.01)	0.16			0.98 (0.95-1.00)	0.10		
CTP score	0.94 (0.88-1.01)	0.10			0.91 (0.84-1.0)	0.05		
CTP class								
A	– (–)	—			– (–)	—	– (–)	—
B	0.87 (0.59-1.28)	0.49			1.04 (0.67-1.63)	0.85	0.98 (0.63-1.54)	0.93
C	0.69 (0.45-1.07)	0.10			0.57 (0.35-0.92)	0.04	0.54 (0.31-0.94)	0.03
Diabetes	1.46 (1.03-2.06)	0.03			1.17 (0.78-1.75)	0.45		
HTN	1.11 (0.79-1.57)	0.53			1.32 (0.89-1.97)	0.17		
Coronary artery disease	0.81 (0.49-1.37)	0.44			0.95 (0.52-1.75)	0.87		
Alcohol use	1.47 (1.04-2.08)	0.03	1.69 (1.19-2.42)	0.004	1.70 (1.12-2.58)	0.01	1.73 (1.14-2.62)	0.01
Tobacco	1.04 (0.75-1.45)	0.80			1.17 (0.79-1.72)	0.43		
HCC	0.98 (0.69-1.40)	0.93			0.91 (0.60-1.38)	0.66		
HCV	0.81 (0.58-1.12)	0.20			0.93 (0.63-1.37)	0.71		
Portal hypertension	1.35 (0.80-2.26)	0.26			1.18 (0.64-2.20)	0.59		

NAFLD, non-alcoholic fatty liver disease; INR, international normalized ratio; Hgb, hemoglobin; BMI, body mass index; HTN, hypertension; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; CTP, child turcotte pugh score.

its components, including diabetes mellitus and obesity (9-13,15-17,46-50). In one series, a 5 unit increase in BMI increased the risk of colorectal adenoma by as much as 19% (51). In our study, NAFLD was a much stronger predictor of polyps than the metabolic syndrome or diabetes. Several large retrospective studies and meta-analyses have recently demonstrated similar associations in adjusted analyses between NAFLD and polyps, adenomas and even CRC on screening colonoscopy (46-48,52-54), though these studies used predominantly imaging-based NAFLD diagnostic criteria. In one previous small series of younger patients in the US with histologically proven NAFLD, there was no difference in the prevalence of polyps, though NAFLD patients had a greater number of adenomas encountered (55).

Wong *et al.* performed perhaps the most detailed analysis with two cohorts, including patients with magnetic resonance spectroscopy evidence of steatosis, those with biopsy-proven NASH, and controls (46). Overall, in adjusted analysis, NAFLD was associated with a 3-fold higher risk of advanced colorectal neoplasms. Interestingly, this association was most strongly observed in patients with NASH as opposed to those with simple steatosis.
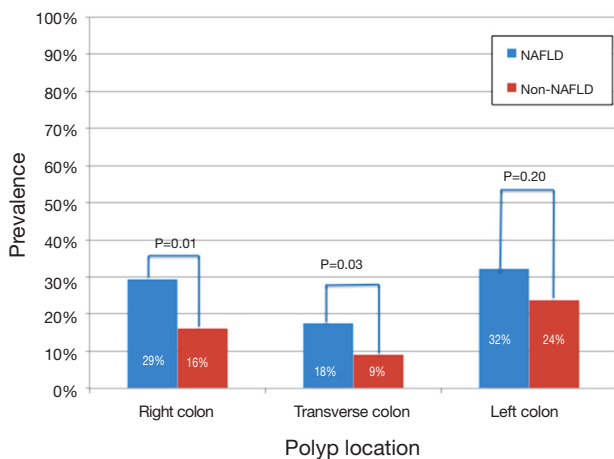
Figure 3 The prevalence of polyp by location and liver disease etiology (NAFLD compared to non-NAFLD). NAFLD, non-alcoholic fatty liver disease.

Given that all the patients in our cohort had end stage liver disease requiring transplantation. It is likely that the vast majority of these patients did have NASH, rather than simple steatosis. In addition, as in our study, those with biopsy-proven NAFLD were more likely to have polyps or adenomas on colonoscopy.

We found the greatest difference in polyps was in right and transverse areas of the colon. This was also found in Wong *et al.* cohort of NASH patients, as well as in a recent large study of patients with cirrhosis undergoing pre-LT screening colonoscopy (46). A similar pattern has been well described in patients with primary sclerosing cholangitis (PSC) and IBD, thought possibly to be due to alterations in bile salt metabolism (56). The reasons for this association specifically with proximal lesions deserve additional investigation.

The mechanism of the observed association between NAFLD and colorectal polyps is not completely understood. It is possible that elevations in insulin and pro-inflammatory cytokines such as insulin-like growth factor in NAFLD patients may promote neoplastic growth of the colonic mucosa (57). In addition, reduced levels of adiponectin are seen in NAFLD patients (58,59), which has been associated with increased risk of colorectal adenomas (60), and may also contribute to this association. In addition, the postulated role of the intestinal microbiome in the pathogenesis of both NAFLD (61-65) and CRC (66-69) may suggest a common pathway putting patients at risk for both diseases, and additional investigation in this area is

warranted.

We also found that patients with a history of significant alcohol exposure were at higher risk of polyps. In adjusted models, patients with prior heavy alcohol use were at ~1.7-fold higher risk of polyps or adenomatous polyps compared to those without a significant alcohol history. This finding is supported by previous literature, possibly due to an increase in reactive oxygen species and acetaldehyde contributing to mucosal hyper-regeneration (70). Those that do use alcohol tend to have earlier presentation of premalignant lesions in the colon (71). PSC was not associated with polyp risk in our cohort, despite previous reports of this association (72,73). The lack of association with PSC may be due to the exclusion of patients with a diagnosis of IBD, and the small number (10) of PSC patients included.

Unexpectedly, CTP class C status was associated with a significantly decreased risk of specifically adenomatous polyps in our cohort. It is uncertain whether this reflects a true decrease in rate of adenomas in patients with severe chronic liver disease, or whether it reflects a decreased detection rate due to poor prep or change in colonoscopic technique in this severely ill patient population. Additional studies are needed to confirm this finding.

Our study is limited by the retrospective study design and the lack of colonoscopy and pathology reports in a limited number of patients. However, even in adjusted analysis, the magnitude of association between NAFLD and polyps or adenomas was very similar in sensitivity analyses excluding those without pathology. In addition, given the variation in colonoscopy reports, we were unable to reliably extract data on prep quality, withdrawal times or overall adenoma detection rates for the individual colonoscopists.

In conclusion, screening colonoscopy in patients awaiting LT detects a high rate of polyps and adenomas. The presence of NAFLD and a history of significant alcohol use were highly predictive of encountering polyps and adenomas, even after controlling for traditional risk factors such as advanced age. Proximal lesions were particularly common in NAFLD patients, indicating that full colonoscopy may be the preferred screening strategy in this population and that deferral of the procedure until after transplant may not be advisable. It is uncertain whether these findings together the similar previously reported data warrant a change in the screening guidelines for NAFLD patients, or how NAFLD and the metabolic syndrome impacts post-LT rates of malignancy and therefore post-LT screening protocols.

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Acknowledgements

None.

Footnote

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