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Colonoscopy findings in liver transplantation candidates

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ABSTRACT – Background – Mandatory colonoscopy in liver transplantation (LT) candidates is recommended but still controversial. **Objective –** To investigate the frequency of colonoscopy lesions in order to support colorectal cancer (CRC) screening in a real-world pre-LT cohort. **Methods –** Retrospective study conducted at a single-center included 632 subjects who underwent pre-transplantation colonoscopy. **Results –** Median age was 56.9 years (yr.) old (82.3% were ≥50 yr.). Primary sclerosing cholangitis (PSC) occurred in 4.6%. Colonoscopy was abnormal in 438 (69.3%) by detection of polyps (37.7%), vascular changes (29.9%), diverticulosis (18.4%), inflammatory bowel disease features (5.2%) and CRC (0.6%). Histology was available in 66.8% of polyps: hyperplastic (47.8%), low-grade dysplasia (56.6%) and high-grade dysplasia (3.8%). High-risk adenomas occurred in 8.2% of the 594 subjects evaluated. Individuals ≥50 yr. were more likely to present abnormal colonoscopy and polyps. High-grade dysplasia and CRC were only found in individuals ≥50 yr. Patients with high-risk adenomas were more likely to be ≥50 yr. – there was no association between high-risk adenomas detection and liver disease etiology or PSC diagnosis. **Conclusion –** Most LT candidates presented abnormal colonoscopy examination, especially by polyps presence. All cases of high-grade dysplasia and CRC occurred in patients ≥50 yr., regardless of disease etiology.

Keywords – Liver transplantation; colonoscopy; colorectal cancer; dysplasia; polyps.

INTRODUCTION

Colonoscopy is recommended as part of the standard screening for neoplastic lesions in patients who are candidates for liver transplantation (LT) according to international guidelines[1,2], although the prevalence of colorectal cancer (CRC) in LT candidates is still unclear. The frequency of premalignant lesions, such as high risk adenomas, vary from 5% to 14%[3-6] in this population, and their removal is recommended, since immunosuppressive therapy after LT can potentially accelerate progression to CRC.

Previous studies have reported that cirrhotic patients and LT candidates are more likely to develop polyps, adenomas and high risk pre-malignant lesions than the overall population[4,7,8]. However, this association is still divergent in the literature[5,9,10] and most studies present remarkable limitations such as usage of sigmoidoscopy[10], small patient sample and inclusion criteria of age >45 or >50 years old[11-13]. Therefore, it is still uncertain if end-stage liver disease patients would benefit from referral to colonoscopy and at what age, since it can be a high risk procedure in this group.

The aim of this study is to evaluate the frequency of abnormal colonoscopy findings in LT candidates of a Brazilian referral center, as well as to report the observed lesions and to investigate its association with age and cirrhosis etiology.

METHODS

Study design and patients

A retrospective study was performed at the Liver Transplantation Outpatient Clinic, *Hospital das Clínicas da Universidade Federal de* Minas Gerais, Brazil. We selected 632 patients evaluated for LT eligibility who received colonoscopy assessment between January 2008 and November 2016. At our institution, LT candidates ≥50 years routinely undergo screening colonoscopy[1,2]. Also, patients with risk factors for CRC, such as inflammatory bowel diseases, primary sclerosing cholangitis (PSC) or family history of colonic neoplasia were submitted to colonoscopy at any age, as advised by guideline recommendations[1,2]. In cases of fulminant hepatitis, colonoscopy is not required.

This study was approved by the institution's Ethics Committee (CAAE 37895220.0.0000.5149). Informed consent was waived due to the retrospective design of the study. All procedures performed were in accordance with the 1964 Helsinki declaration.

Clinical characteristics at the time of colonoscopy including sex, age, liver disease etiology and diagnosis of concomitant schistosomiasis infection or hepatocellular carcinoma were collected. Liver disease etiology was classified as: ethanolic, chronic hepatitis C and B, cryptogenic, autoimmune liver disorders (i.e., autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis) and other causes (i.e., nonalcoholic steatohepatitis, hemochromatosis, Budd-Chiari syndrome and alpha-1-antitrypsin deficiency).

Data of the colonoscopy procedure was recorded, including presence of polyps, tumors, diverticulosis, features of inflammatory bowel disease (IBD) and vascular changes. Vascular changes included hemorrhoids, angiodysplasia and portal hypertension colopathy. If histopathological study was available, polyps were

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classified according to their histological characteristics, grade of dysplasia (i.e., low or high) and presence of CRC. High risk adenomas were defined as presence of any of the following features: (i) high-grade dysplasia, (ii) presence of three or more adenomas, (iii) adenomas ≥1 cm, or (iv) villous histologic subtype[14]. Histopathological study was not available in all cases due to the retrospective nature of the study. Also, in the following situations biopsy was unavailable: patients with coagulopathy or severe thrombocytopenia, small lesions non suggestive of CRC, loss of the tissue sample after resection or if the material was insufficient to pathological analysis. All patients with CRC received proper treatment.

Statistical analysis

Statistical analysis was performed using SPSS 23.0 software (IBM, USA). Data are expressed as mean ± standard deviation for normally distributed continuous variables, as median and interquartile range (IQR) when distribution was skewed, or as absolute number and percentage for qualitative variables. Missing data were handled by pairwise deletion. Continuous variables distribution was assessed by the Shapiro-Wilk test. Student's *t*-test or non-parametric test (i.e., Mann-Whitney U-test) were used to compare quantitative data, as appropriate. Chi-square test or Fisher's exact test were used for comparison of categorical data, as appropriate. All tests were two-tailed and *P*-values <0.05 were considered significant.

RESULTS

Cohort comprised 632 patients. The study population was 69.8% male, median age was 56.9 (IQR 51.3–62.1) years old and 82.3% were ≥50 years old. Liver disease etiology frequency was: ethanolic (36.1%), chronic hepatitis C (27%), cryptogenic (20.8%), autoimmune liver disorders (10.3%, from those 44.6% was PSC), other causes (7.9%) and chronic hepatitis B (4.5%). Other baseline characteristics are presented in TABLE 1. Patients were separated in two groups according to their age (<50 yr. vs ≥50 yr.).

Colonoscopy examination presented abnormal findings in 438 (69.3%) subjects, as described: polyps in 238 (37.7%), vascular changes in 189 (29.9%), diverticulosis in 116 (18.4%), IBD features in 33 (5.2%) and CRC in 4 (0.6%) individuals. Histopathological examination was available in 159 (66.8%) of the polyps. From those, hyperplastic polyps were observed in 76 (47.8%), low-grade dysplasia in 90 (56.6%) and high-grade dysplasia in 6 (3.8%). From the total cohort of 632 patients, high risk adenomas occurred in 49 of the 594 subjects evaluated (8.2%) – 38 individuals did not have histopathology exam available, so they could not be classified. Colonoscopy macroscopic and microscopic findings are expressed in TABLE 2.

When comparing individuals <50 yr. vs ≥50 yr. (TABLE 3), we found no differences between sex (male 66% vs 71%, respectively, *P*=0.203) and availability of polyps histopathology (83.3% vs 64.6%, *P*=0.698). Patients ≥50 yr. were more likely to present hepatocellular carcinoma (18.5% vs 8.0%, *P*=0.007), abnormal colonoscopy examination (73.7% vs 49.1%, *P*<0.001), portal hypertension colopathy (32.1% vs 19.6%, *P*=0.009), diverticulosis (21.3% vs 4.5%, *P*<0.001) and polyps (41.2% vs 21.4%, *P*<0.001), when compared to those <50 yr. Polyps were present in 24 (21.4%) of the patients <50 yr., and 20 (83.3%) of those had histopathology exam available; whereas polyps were found in 214 (41.2%) of the participants ≥50 yr., and histopathology exam was available in 139

TABLE 1. Cohort baseline demographic and clinical characteristics.

Variable	Total cohort (n=632)
Male sex n (%)	441 (69.8)
Age	
Median	56.9 (51.3–62.1)
≥50 yr. n (%)	520 (82.3)
Range of age n (%)	
<45 yr.	66 (10.4)
45–50 yr.	46 (7.3)
50–55 yr.	142 (22.5)
55–60 yr.	157 (24.8)
60–65 yr.	138 (21.8)
≥65 yr.	83 (13.1)
Liver disease etiology n (%)	
Ethanolic	228 (36.1)
Chronic hepatitis C	171 (27.0)
Chronic hepatitis B	28 (4.5)
Cryptogenic	131 (20.8)
Autoimmune liver disorder	65 (10.3)
PSC	29 (4.6)
Other causes	50 (7.9)
Associated hepatosplenic schistosomiasis	21 (3.3)
Hepatocellular carcinoma	105 (16.6)

Yr.: years old; PSC: primary biliary cholangitis.

TABLE 2. Cohort colonoscopy macroscopic and microscopic data.

Variable n (%)	Cohort (N=632)
Normal examination	194 (30.7)
Abnormal examination	
Colorectal cancer	4 (0.6)
IBD features	33 (5.2)
Vascular changes	189 (29.9)
Diverticulosis	116 (18.4)
Polyp	238 (37.7)
Polyps	
Available polyp histopathology	159 (66.8)
Hyperplastic polyp	76/159 (47.8)
Low-grade dysplasia	90/159 (56.6)
High-grade dysplasia	6/159 (3.8)
High risk adenomas	49/594 (7.8)

IBD: inflammatory bowel disease.

TABLE 3. Comparison between clinical and histopathological data of patients < 50 vs ≥ 50 years old.

Variable n (%)	Patients <50 yr. (n=112)	Patients ≥50 yr. (n=520)	*P*-value
Male sex	74 (66.1)	367 (70.6)	0.203
Liver disease etiology			
Ethanolic	31 (27.6)	197 (37.8)	0.040*
Hepatitis C	22 (19.6)	149 (28.6)	0.052
Hepatitis B	5 (4.5)	23 (4.4)	>0.999
Cryptogenic	17 (15.2)	114 (21.9)	0.110
Autoimmune liver disorder	33 (29.5)	32 (6.1)	<0.001*
PSC	20 (17.9)	9 (1.7)	<0.001*
Other causes	8 (7.1)	42 (8.1)	0.740
Associated hepatosplenic schistosomiasis	2 (1.8)	19 (3.7)	0.317
Hepatocellular carcinoma	9 (8.0)	96 (18.5)	0.007*
Normal examination	57 (50.9)	137 (26.3)	<0.001*
Abnormal examination			
Colorectal cancer	0 (0)	4 (0.8)	0.003*
IBD features	15 (13.4)	18 (3.5)	<0.001*
Vascular changes	22 (19.6)	167 (32.1)	0.009*
Diverticulosis	5 (4.5)	111 (21.3)	<0.001*
Polyp	24 (21.4)	214 (41.2)	<0.001*
Polyps			
Available polyp histopathology	20/24 (83.3)	139/214 (64.6)	0.698
Hyperplastic polyp	7/20 (35.0)	69/139 (49.6)	0.220
Low-grade dysplasia	15/20 (75.0)	75/139 (53.9)	0.075
High-grade dysplasia	0/20 (0)	6/139 (4.3)	0.025*
High risk adenomas	3/109 (2.7)	46/485 (9.5)	0.020*

IBD: inflammatory bowel disease. $P<0.05$ was considered significative (*).

(64.6%) of those. All patients with high-grade dysplasia (4.3%) or CRC (0.8%) were ≥50 yr. (FIGURE 1).

The group of patients with high risk adenomas had a mean age of 57.2 (±5.9) yr. Those who presented high risk adenomas, when compared to subjects without high risk adenomas, were more likely to be ≥50 yr. (93.9% vs 80.6%, *P*=0.021), and to show absence of vascular changes (83.7% vs 69.2%, *P*=0.033). Only three individuals <50 years old presented high-risk adenomas, which were incidental findings in all cases, since there was no known risk factor for their occurrence. There was no difference between frequency of liver disease etiology (*P*=0.678), PSC diagnosis (*P*=0.155), ≥45 yr. vs <45 yr. (*P*=0.115) and sex (*P*=0.566).

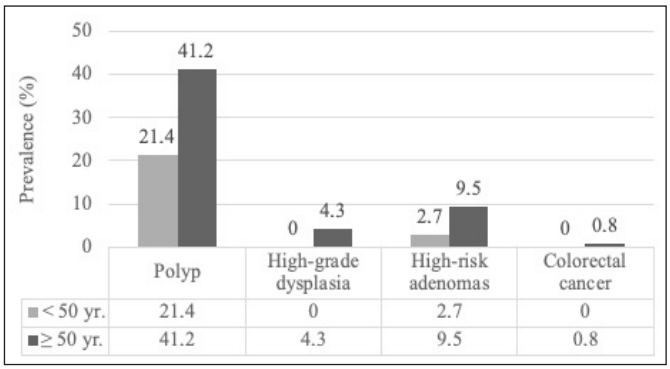

FIGURE 1. Colonoscopy prevalence of polyps and colorectal cancer in liver transplantation candidates with <50 vs ≥50 years old.

DISCUSSION

This study demonstrated that abnormal findings on colonoscopy are common in LT candidates. The most frequent abnormality was the presence of polyps. Cohort's frequency of high risk adenomas was 7.8%, and CRC was found in four patients (i.e., 0.6%). Patients ≥50 yr. were more likely to present abnormal colonoscopy, polyps, high-grade dysplasia and CRC than those <50 yr. In fact, all patients with high-grade dysplasia or CRC were ≥50 yr.

In absolute terms, Brazil is the country that most performs LT in Latin America, although organ donation availability is far below the demand due to the increasing population and inadequate donor organ supply[15]. Thus, selecting adequate LT candidates is extremely relevant for public health, and for this purpose cancer screening is required for eligibility assessment, since extrahepatic cancer can be a contraindication for LT, besides that the immunosuppressive post-transplantation therapy is associated with malignancies development[16-18]. Since CRC incidence is known to be increased after solid organ transplantation[19], including LT patients[20], colonoscopy is recommended for all LT candidates aged 50 years or older or having PSC[1,2].

In end-stage liver disease patients, colonoscopy is a high-risk invasive procedure, with potential morbimortality, besides high cost[21]. Although the procedure has not demonstrated relevant intraoperative complications in a previous cross-sectional study[6], further prospective investigation has shown that after colonoscopy there was an increased risk for renal failure and gastrointestinal bleeding especially in advanced liver disease patients[5]. Therefore, the reconsideration of current guidelines has been suggested and alternative colorectal screening strategies have been proposed[5].

In order to support future recommendations, previous studies have described the frequency of abnormal findings in LT candidates' colonoscopy[3-6,9-13]. The prevalence of polyps ranged from 19–46% in these studies, while high-grade dysplasia was detected in 2–5%[3,9], high risk adenoma in 5–14%[3-6] and CRC in 0–4%[3,5,6,9,10,12,13]. Our cohort presented similar results which corroborated previous studies. However, the previous studies presented remarkable limitations, as follows: examination with only sigmoidoscopy[10], selection criteria of LT candidates 45 or 50 years and older[11-13], lack of detailed polyp histopathological description[6,10,12] and small patients sample[3,9-13]. Our study presented a larger cohort sample and the selected patients were all submitted to total colonoscopy per protocol, which assured reliability to our findings, compared to previous investigations.

A recent study evaluated colonoscopic screening in LT candidates in Egypt[22]. Authors observed polyp prevalence of 8.7%, of which 4.2% were adenomas. Moreover, prevalence of adenoma was significantly higher in patients ≥50 yr. Our study found a higher prevalence of polyps than described in that study and corroborated the finding that being ≥50 yr. is associated with a higher risk of polyp detection.

It is noteworthy that PSC diagnosis was not associated with the occurrence of high risk adenomas in our study, however this might have been observed because PSC patients undergo early colonoscopy examination in order to search for or assess remission of IBD. Thus, early treatment of previous intestine lesions may have an impact on polyps prevalence in those patients.

All high-grade dysplasia adenomas and CRC were observed in subjects ≥50 yr., which can suggest that screening subjects older than 50 yr. may be an adequate strategy. Further studies should compare colonoscopic screening between ≥50 yr. and ≥45 yr. by specific methodology design in order to clarify if LT candidates would benefit from earlier colonoscopic examination. Also it is important to consider the benefits of screening compared to the potential harms of performing an invasive exam in a cirrhotic patient, most of the times decompensated. Although our study did not evaluate data on colonoscopy side effects or complications, our findings on the prevalence of pre-neoplastic lesions was relevant, since high frequency of abnormal findings can support colonoscopy performance.

To the best of our knowledge, this is the first study that investigated colonoscopy findings in LT candidates screening in the Brazilian population. CRC and the adenoma-carcinoma sequence are multifactorial and influenced by lifestyle, genetic and environmental factors, thus its occurrence is heterogeneous around the world[23]. Thereby, investigating the Brazilian population is relevant in order to support future guidelines recommendations. In fact, CRC is the second most incident cancer in both sex in our study geographical region in Brazil, excluding non-melanoma skin cancer[24].

There are limitations to this study. The investigation design was retrospective, data collection was based on patient records and the study did not enroll liver healthy controls. Moreover, there was a considerable lack of histopathological data regarding polyps examination for reasons previously described, although there was no statistical difference between available biopsy samples in <50 yr. and ≥50 yr. Missing data may have reduced statistical power of our study, but pairwise deletion was performed in order to avoid selection bias and keep the population representative. Lastly, in Brazil CRC surveillance in the general population is recommended to be performed after 50 yr. old, so this can have an impact on data analysis in the population studied.

In conclusion, most LT candidates presented abnormal colonoscopy examination, especially by polyps presence. There was a considerable frequency of high-grade dysplasia and CRC in our cohort, which were all detected in patients ≥50 yr. These findings suggest that CRC screening should be performed in LT candidates with 50 yr. or older and colonoscopy might be an adequate strategy for detecting high-risk pre-malignant and malignant lesions. Further investigation by prospective and controlled studies is needed to better analyze the CRC screening in LT candidates.

Authors' contribution

Osório FMF and Lima AS designed the study; Osório FMF, Maia LG and Rodrigues RAT collected data; Osório FMF, Nardelli MJ, Penna FGC and Lima AS analyzed data; Osório FMF and Nardelli MJ wrote the paper; Penna FGC and Lima AS critically reviewed the manuscript for intellectual content; all authors approved the final version of the manuscript.

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Osório FMF, Nardelli MJ, Maia LG, Rodrigues RAT, Penna FGC, Lima AS. Achados da colonoscopia em candidatos a transplante hepático. Arq Gastroenterol. 2022;59(1):35-9.

RESUMO – Contexto – Colonoscopia mandatória em candidatos a transplante hepático (TH) é recomendada, mas ainda é controversa. **Objetivo –** Investigar a frequência de lesões detectadas pela colonoscopia para endossar o *screening* de câncer colorretal (CCR) em uma coorte pré-TH de mundo real. **Métodos –** Estudo retrospectivo conduzido em um centro único que incluiu 632 indivíduos submetidos a colonoscopia pré-TH. **Resultados –** Idade mediana foi 56.9 anos (82,3% eram ≥50 anos). Colangite esclerosante primária (CEP) estava presente em 4.6%. Colonoscopia foi anormal em 438 (69,3%) por: detecção de pólipos (37,7%), alterações vasculares (29,9%), diverticulose (18,4%), características de doença inflamatória intestinal (5,2%) e CCR (0,6%). Histologia estava disponível em 66,8% dos pólipos: hiperplásicos (47,8%), displasia de baixo grau (56,6%) e displasia de alto grau (3,8%). Adenomas de alto risco ocorreram em 8,2% dos 594 indivíduos avaliados. Indivíduos ≥50 anos eram mais prováveis de apresentar colonoscopia anormal e pólipos. Displasia de alto grau e CCR foram encontrados somente em indivíduos ≥50 anos. Pacientes com adenoma de alto risco eram mais prováveis de ter ≥50 anos – não houve associação entre a detecção de adenomas de alto risco e a etiologia da hepatopatia ou o diagnóstico de CEP. **Conclusão –** A maioria dos candidatos a TH apresentaram achados anormais na colonoscopia, principalmente pela presença de pólipos. Todos os casos de displasia de alto grau e CCR ocorreram em pacientes ≥50 anos, independente da etiologia da hepatopatia.

Palavras-chave – Transplante hepático; colonoscopia; câncer colorretal; displasia; pólipos.

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