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ORIGINAL ARTICLE

Upper and lower gastrointestinal diseases in liver transplant candidates

G. Gravante · D. Delogu · D. Venditti

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Abstract
Background The incidence and risk factors of gastrointestinal diseases in pre-liver transplant population are still a matter of debate. In a retrospective analysis, we addressed two questions: (1) Are there any lesions that occur at a higher prevalence than in the general population, and (2) are there patient characteristics that could predict their presence?
Materials and methods All asymptomatic patients that successfully entered the waiting list of liver transplantation were recorded. We also compared results with those obtained from a control group of non-cirrhotic patients undergoing screening for colorectal cancer. Main outcome measures were the incidence and description of upper/lower gastrointestinal findings after screening endoscopic examination.
Results We retrospectively evaluated from April 2004 to July 2007 a total of 80 liver transplant candidates. The most frequent pathologies were esophageal varices (71.2% of subjects), portal hypertensive gastropathy (51.2%), hemorrhoids (22.5%), and colonic polyps (18.7%). Comparison with 80 non-cirrhotic patients matched for age and sex demonstrated an increased frequency in the cirrhotic group of ulcerative colitis (6.2 vs 0%; p=0.02) and portal hypertensive colopathy (12.5 vs 0%; p=0.001) in non-cirrhotic of diverticulosis (10 vs 25%; p=0.01) and hemorrhoids (22.5 vs 40%; p=0.02). The univariate analysis showed no significant correlation between colonic polyps and patients' variables, except a mild correlation with age not confirmed at the multivariate analysis.
Conclusions The incidence of some benign gastrointestinal pathologies in liver transplant candidates is different from the asymptomatic population but not that of colorectal cancer or colonic polyps.

Keywords Colonoscopy · Esophagogastroduodenoscopy · Liver transplant · Cyrrhosis

G. Gravante · D. Venditti
Department of General Surgery, University of Tor Vergata,
via Montpellier 1,
Rome, Italy

D. Delogu
University "La Sapienza",
P. le Aldo Moro,
Rome, Italy

G. Gravante (✉)
via U. Maddalena 40/a,
00043 Ciampino, Roma, Italy
e-mail: ggravante@hotmail.com

Introduction

Data regarding the prevalence of upper and lower gastrointestinal pathology in liver transplant candidates are conflicting. Several studies have reported a prevalence of peptic ulcer disease in cirrhotic patients higher than in the general population [1–4], not confirmed by others [5–7]. The prevalence of hemorrhoids varied greatly, ranging from 25 to 63% of evaluated patients [8–10]. Many studies were biased by the presence of patients with dyspepsia and gastrointestinal hemorrhage, taking non-steroidal anti-inflammatory drugs (NSAIDS), or actively drinking alcohol [1, 5, 11]. Finally, very few studies reported endoscopic findings in both the upper and lower gastrointestinal tracts and their associations with clinical variables [12].

In the first months of 2004, colorectal cancer screening was introduced in our institution for liver transplantation candidates as a necessary examination to access the organ waiting list. Actually, all liver transplant candidates routinely undergo upper endoscopy for varices assessment,

whereas those older than 50 years are also investigated with colonoscopy for colorectal cancer screening according to current guidelines [13]. All our patients are abstinent from alcohol for at least 6 months, do not assume NSAID, and are asymptomatic. In this study, we conducted a retrospective analysis after more than 3 years of activity to study the prevalence of upper and lower gastrointestinal pathology in our pre-liver transplant population and address two questions: (1) Are there upper or lower gastrointestinal tract lesions that occur at a higher prevalence than that reported in the general population (with exception of portal hypertension- and liver-disease-related pathology), which should be endoscopically screened in liver transplant candidates; and (2) are there patient characteristics that predict the presence of these lesions?

Materials and methods

We recorded all asymptomatic patients evaluated for liver transplantation that successfully entered, according to their clinical condition, the waiting list. We excluded patients that were not able to enter it or those that underwent colonoscopy because of anemia, change of bowel movements, weight loss, and all symptoms that could be referred to a lower gastrointestinal tract pathology. We registered patients' data when all routine analyses and examinations necessary to enter the list were completed and when patients came to the hospital for their final evaluation. Furthermore, we selected from our database a control group composed of patients matched for age and sex that underwent screening colonoscopy for colorectal polyps during the same period of time. These patients were investigated in our institution by the same surgeon that screened cirrhotic patients (V.D.), reducing the chance of inter-observer variability.

Patients' baseline demographics (sex, age), clinical characteristics (etiology of liver diseases, child classification, ascitis, splenomegaly), and endoscopic findings (both upper and lower) were registered. We recorded all data in a prospective database (Excel) that was subsequently analyzed with Statistical Package for the Social Sciences (SPSS; see "Statistical analysis").

This study was designated to address two questions: (1) Are there lesions that occur at a higher prevalence than the general population (with the exception of portal hypertension- and liver-disease-related pathology), and (2) are there patient characteristics that could predict their presence? Primary outcomes were the incidence of colonic polyps and colorectal carcinomas, and eventual associations with patients' baseline demographics and/or clinical variables. Secondary outcomes were the description of other upper and lower gastrointestinal findings and their incidence.

Statistical analysis

All data analysis were performed using the SPSS Windows version 13.0 (SPSS, Chicago, IL, USA). The sample size calculation was based, assuming one of the lowest incidence reported, on literature for colorectal cancer in non-cirrhotic asymptomatic patients undergoing screening (1.8%) [19]. With this incidence, the predicted patients' drop-out rate was 15% of the subjects, the alpha value was $p=0.05$, the power was 80%, and the calculated sample size was 80 patients per group.

Descriptive statistics used for quantitative continuous variables (age) were mean and standard deviation after confirmation of normal distribution. Normality assumptions have been demonstrated with histograms, Q–Q plots, Skewness and Kurtosis, Kolmogorov/Smirnov, and Shapiro Wilk testings. The analysis between groups (cirrhotic vs normal patients) was conducted with the *t* test for continuous variables, or the chi-square or the Fisher test (if value within cells was inferior to 5) for categorical variables.

Univariate analysis was conducted with the Pearson chi-square test of association comparing colonic polyps, a categorical variable, with other categorical variables such as the demographics and clinical characteristics analyzed, and the other upper and lower endoscopic findings. If cells in the contingency table had fewer than five expected counts, the Fisher's exact testing was used. The point biserial correlation coefficient was used to compare colonic polyps with the continuous variables (age). Multivariate analysis was performed with the simple or multiple logistic regression method with variables found significant at the univariate analysis. These significant-associated variables were entered in the logistic predictive model. All *p* values were considered significant if inferior to 0.05.

Results

We followed the Consort criteria for the development and description of this study [14]. Data were collected at the Endoscopy Unit of the General Surgery Department of the University of Tor Vergata in Rome.

Screening colonoscopy for liver transplant candidates was introduced in our institution on April 2004. We excluded 97 patients (61 because they did not enter the list and 36 because they were symptomatic) and evaluated a total of 80 liver transplant candidates. All underwent both upper endoscopy to evaluate esophageal varices and a flexible colonoscopy to evaluate polyps/colorectal carcinomas. Descriptive statistics of baseline demographics, clinical characteristics, and endoscopic findings are summarized in Tables 1 and 2. The 80 non-cirrhotic patients

Table 1 Cirrothic patient demographics and clinical characteristics

	Number of patients (%)	
	Cirrhotic patients	Literature [18]
Total number of patients	80	–
Sex (male)	61 (76.2%)	56–72.5%
Age (years)	54 (±6.1)	49–52
Etiology of liver disease		
Hepatitis C	30 (37.5%)	17–52%
Alcohol	20 (25%)	27–36%
Hepatitis B	15 (18.7%)	6–10%
PBC/PSC	14 (17.5%)	10–11%
Cryptogenic	8 (10%)	9–16%
Caroli	6 (7.5%)	5%
Metabolic	2 (2.5%)	8%
Child		
A (5–6)	9 (11.2%)	27–34
B (7–9)	52 (65%)	49%
C (10–15)	19 (23.7%)	17–24%
Ascitis	46 (57.5%)	35%
Splenomegaly	67 (83.7%)	68%

(control group) had a mean age of 58±3 years, and 59 of them (73.7%) were males.

The most frequent pathologies found at upper endoscopy were esophageal varices (71.2% of the patients) and portal hypertensive gastropathy (51.2%). Varices were classified according to the Paquet's classification (Table 2) [15] and to the De Franchis classification [16]. According to the latter, 47 patients had small varices (58.7%), 7 large (8.7%), and 3 intermediate (3.7%). The most frequent pathologies found at colonoscopy were hemorrhoids (18 patients, 22.5%) and colonic polyps (15 patients; 18.7%). Eight patients had one, two, or multiple hyperplastic polyps and seven patients had adenomatous polyps. Among the seven patients with adenomatous polyps, three (42.9%) had a tubular adenoma with a mild dysplasia, and four (57.1%) had a tubulovillous adenoma with high dysplasia. No patients were found with colorectal carcinomas. Portal hypertensive colopathy was the third most frequent pathology found in the lower tract (ten patients; 12.5%). Two additional patients had some signs of congestive colopathy: one with a smooth and hard subepithelial cecal mass in which histology demonstrated diffuse edema of the lamina propria; the other an area of irregular mucosa 15 cm from the anal verge in which biopsies showed a lymphatic stasis.

Statistical analysis

All tests used for normality confirmation proved normal distribution of age. Comparison among patients with cirrhosis

Table 2 Endoscopic gastrointestinal findings for cirrhotic and non-cirrhotic patients and comparison with the literature data

	Our observations		Literature	
	Cirrhotic	Non-cirrhotic	Cirrhotic [18]	Non-cirrhotic [1, 2, 5, 17, 19–24]
Total number of patients	80	80	–	–
Esophageal varices	57 (71.2%)	–	64%	–
Degree of variceal severity				
1	26 (32.5%)		20.3%	
2	24 (30%)	-	33.8%	–
3	5 (6.2%)		9.5%	
4	2 (2.5%)		0%	
Esophagitis	5 (6.2%)	–	4.5–10%	8.5–15%
Hiatal hernia	4 (5%)	–	3%	50%
Portal hypertensive gastropathy	41 (51.2%)	–	28.4–61%	–
Gastritis	14 (17.5%)	–	7.5%	12–42.7%
Gastric polyps	3 (3.7%)	–	2%	0.4–0.8%
Gastric ulcer	2 (2.5%)	–	2%	1.1–2.2%
Duodenitis	9 (11.2%)	–	8%	10%
Duodenal ulcer	2 (2.5%)	–	3–7.8%	2%
Colonic polyps	15 (18.7%)	19 (23.7%)	30%	25%
Ulcerative colitis[a]	5 (6.2%)	–	3%	7.3/100,000
Portal hypertensive colopathy[a]	10 (12.5%)	–	3–48.5%	–
Diverticulosis[a]	8 (10%)	20 (25%)	15%	32–50%
Hemorrhoids[a]	18 (22.5%)	32 (40%)	21%	82%
Vascular ectasias	3 (3.7%)	–	3%	3%
Colorectal cancer	–	–	–	1–8.5%

[a] Diseases with a significant difference between cirrhotic and non-cirrhotic patients

vs those without demonstrated a significant increased frequency in the first group of ulcerative colitis (6.2 vs 0%; $p=0.02$) and portal hypertensive colopathy (12.5 vs 0; $p=0.001$) in the second group of diverticulosis (10 vs 25%; $p=0.01$), and hemorrhoids (22.5 vs 40%; $p=0.02$).

The univariate analysis showed that no significant correlation was found between colonic polyps and patients' baseline demographics and clinical variables ($p>0.05$), except a mild correlation with age (point biserial coefficient: 0.311; $p<0.05$) (Table 3). The multivariate simple logistic regression analysis did not confirm this association.

Discussion

Upper gastrointestinal tract findings

In our study, the prevalence of gastric ulcer disease was 2.5% (two patients), similar to that of the general population (1.1–2.2%) [17]. We did not record duodenal ulcers. Sacchetti [5] showed similar findings when they compared the prevalence of gastroduodenal ulcers in 142 cirrhotic patients with the control group. Rabinovitz et al. [2] in a group of 216 asymptomatic male cirrhotics undergoing preliver transplant evaluation found a 7.8% prevalence of duodenal ulcers. Siringo et al. found a prevalence of 20% in their asymptomatic patients with cirrhosis. However, their patients received routine NSAID [1].

Table 3 Univariate (bivariate correlational) analysis

	Correlation with colonic polyps	*p* Value
Sex	1.85	NS (0.318)
Age (years)	0.311	0.04
Etiology of liver disease		
Hepatitis C	0.982	NS (0.439)
Alcohol	0.062	NS (1)
Hepatitis B	2.325	NS (0.316)
HCC	2.325	NS (0.316)
PSC	*4.751*	NS (0.088)
PBC	0.241	NS (1)
Cryptogenic	2.747	NS (0.158)
Caroli	0.241	NS (1)
Child		
A (5–6)	1.286	NS (0.555)
B (7–9)	0.009	NS (1)
C (10–15)	0.857	NS (0.384)
Ascitis	0.938	NS (0.439)
Splenomegaly	0.085	NS (1)

Coefficient and validity of the association (p) for demographics and clinical characteristics as independent variables with colonic polyps (dependent variable) incirrhotic patients. All variables were analyzed with the Fisher's exact test, except for age, where the point biserial coefficient was used.

Table 4 Univariate (bivariate correlational) analysis

	Correlation with colonic polyps	p Value
Esophageal varices	0.815	NS (0.656)
Esophagitis	0.227	NS (1)
Hiatal hernia	0.466	NS (1)
Portal hypertensive gastropathy	0.611	NS (0.698)
Gastritis	0.306	NS (0.623)
Gastric polyps	4.605	NS (0.182)
Gastric ulcer	4.605	NS (0.182)
Duodenitis	1.805	NS (0.219)
Ulcerative colitis	0.497	NS (0.461)
Portal hypertensive colopathy	0.138	NS (0.566)
Diverticulosis	0.715	NS (1)
Hemorrhoids	0.029	NS (1)
Vascular ectasias	0.466	NS (1)

Coefficient and validity of the association (p) for endoscopic gastrointestinal findings as independent variables with colonic polyps (dependent variable) in cirrhotic patients. All variables were analyzed with the Fisher's exact test.

Previous studies have noted a high prevalence of gastritis and gastric erosions (42.7 and 29.6%) [3, 5]. However, it may be difficult to differentiate between portal hypertensive gastropathy and gastritis because biopsies were not performed. In our study, gastritis prevalence was found to be 17.5%, similar to that described by Zaman et al. [18] in liver transplant candidates (17.5%). Our incidence of esophagitis was lower than the one reported in that study (6.2 vs 10%).

Other upper gastrointestinal tract lesions were not present at a different frequency than in the general population, except for esophagogastric varices and portal hypertensive gastropathy that were higher in our series. The univariate analysis showed no significant associations between upper gastrointestinal tract lesions and patient characteristics (Table 4).

Lower gastrointestinal tract findings

The prevalence of hyperplastic polyps, adenomatous polyps, and of vascular ectasias did not appear to be different from the prevalence found in the control group and those described in the literature. On the contrary, diverticulosis and hemorrhoids had a significant lower incidence in cirrhotic patients than in normal asymptomatic subjects (Table 2). Such difference was also confirmed by the lower incidences of such diseases in published studies compared to our cirrhotic population [19–22]. All cases of ulcerative colitis and Crohn's disease were found among patients with primary sclerosing cholangitis. Colopathy was seen in only ten cases (12.5%), all verified histologically. Most previous studies reported a prevalence of colopathy of 52–84% [8, 9,

11] in cirrhotic patients. However, these were symptomatic and with some form of gastrointestinal bleeding. In two studies of asymptomatic cirrhotic patients, the prevalence was between 19.5 and 48.5% [10, 11]. Our patients had a lower incidence of colopathy (12.5%) and was not associated with the degree of liver dysfunction or portal hypertension, as in other studies [9, 11].

Several aspects of our work deserve special attention. Because of its retrospective nature, it is impossible to know if all patients were truly free of gastrointestinal complaints because each patient was not asked specifically about this. However, as noted earlier, these were "screening" endoscopies. Also, in a retrospective study, it is difficult to standardize the reporting of endoscopic findings. Efforts were made to review the endoscopic reports and, when possible, endoscopic pictures to assure a uniform interpretation. Finally, this study did not have a control population for the upper GI symptoms, as non-cirrhotic patients referred for gastroscopy were always symptomatic and required a diagnosis not screening. Therefore, prevalence rates obtained with gastroscopy in cirrhotic patients were compared directly with those reported in literature for asymptomatic patients.

Our study basically confirms previously published data and suggests that most upper and lower gastrointestinal tract lesions found in liver transplant candidates do not occur at a higher prevalence than that reported in the general population, with the exception of the portal hypertension, the liver-related pathology (esophagogastric varices, portal hypertensive gastropathy, or colopathy), and ulcerative colitis. No significant associations were found between these gastrointestinal tract lesions and patient characteristics. Therefore, the most rational endoscopic screening strategy in the pre-liver transplant population seems to be the upper endoscopy for the detection of esophagogastric varices in all patients (given their high incidence in this population) and colonoscopy for age-directed screening of colonic neoplasia, and for colitis/dysplasia screening in patients with primary sclerosing cholangitis, as suggested by current guidelines for colorectal cancer screening [13]. No specific risk factors for colorectal cancer seemed conferred by the cirrhotic status. However, we believe that these preliminary data should be confirmed by larger studies involving more patients.

Conclusions

The incidence of gastrointestinal pathologies in liver transplant candidates is not different from the asymptomatic normal population; exception is made for cirrhosis-specific complications (esophageal varices, portal hypertensive gastropathy, and colopathy) and ulcerative colitis. This study further adds value to previous findings that confirm the routine use of esophagogastroduodenoscopy for patients evaluated for liver transplantation and colonoscopy as indicated for screening by current guidelines [13].

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