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GASTROINTESTINAL BLEEDING AFTER LIVER TRANSPLANTATION[1]

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Abstract

To investigate the causes of gastrointestinal bleeding (GIB) and its impact on patient and graft survival after liver transplantation (OLTx), adult patients among the first 1000 consecutive OLTx under Tacrolimus comprised our study population. Of 834 patients who comprised our population, 74 had at least one bleeding episode, and 760 patients had no GIB. Patients with GIB had their bleeding episodes analyzed and those without GIB were used as controls. The mean age, gender, and UNOS status were similar in both groups. Endoscopy was done in 73 patients with GIBand yielded a diagnosis in 60 (82.2%) who had a single (n=39) or multiple (n=21) GIB episodes. In the remaining 13 (17.8%) patients, the bleeding source was not identified. Ulcers (25) were the most common diagnosis, followed by enteritis (23), portal hypertensive lesions (15), RY bleeds (6), and miscellaneous (25). The majority (73%) of the GIB episodes occurred during the first postoperative trimester. The patient and graft survival were statistically lower in the GIB group compared with the rest. The adjusted relative risk of mortality and graft failure were increased by bleeding. In summary, endoscopy identified the source of GIB after OLTx in most cases. The cumulative incidence of GIB was 8.9% for the study period. Ulcers were the most common cause of GIB. The onset of gastrointestinal bleeding after liver transplantation carried a decreased patient and graft survival.

INTRODUCTION

Despite refinements in surgical techniques, the incidence of complications after liver transplantation remains significant. This reflects the degree of physical illness of the recipients as well as the technical demands of the operation (1–6). Bleeding is one of the operative (7) and postoperative (8,9) complications reported after liver transplantation. Although postoperative bleeding has been described in a variety of clinical situations (8–17), the incidence and significance of gastrointestinal bleeding (GIB) after liver transplantation have yet to be determined.

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The onset of bleeding during (7) and after (9) transplantation increases early mortality, particularly when there are multiple episodes of bleeding or when the source of bleeding is not known. These patients are often subject to repeated surgical explorations (8,9). Bleeding from lesions associated with portal hypertension after liver transplantation has been reported as a sign of thrombosis in the portal system (8,10,11 18). In these studies, no reference is made to the histological status of the grafts at the time of bleeding, or whether or not portal hypertension represented graft dysfunction. There is also a lack of information on the long term outcome, the causes, and the precise incidence and impact of gastrointestinal bleeding on liver transplant recipients. Therefore, the aim of our study was to further define the incidence and the causes of gastrointestinal bleeding after liver transplantation, and to assess its impact on patient and graft survival.

PATIENTS AND METHODS

Patients

The records of the first 1000 consecutive primary liver transplants performed since the introduction of Tacrolimus were retrospectively reviewed. Only adult (>18 years old) patients were included. The patients were stratified according to UNOS classification (status 4 and 3, patients out of the hospital with limited activity; status 2, patients in the hospital; status 1, patients in the intensive care unit). Demographic data was collected, including: age, etiology of liver disease, the number, source, and timing of the bleeding episodes (as determined by endoscopic, operative, angiographic, or nuclear medicine reports), the number of transplants, and the causes of patient and graft loss.

The diagnosis of gastrointestinal bleeding was confirmed with existing diagnostic operative, endoscopic, and/or radiological tests. For the purpose of this retrospective study, we adhered to the following criteria:

- Bleeding episode: presence of hematemesis and/or melena, with or without hemodynamic instability, that required evaluation and testing. Available diagnostic procedures were considered part of the same bleeding episode if they were performed within the same 24 hour period.
- Diagnostic endoscopy: reports that unequivocally described: i) active bleeding (i.e., varices, ulcers, mucosal lesions, etc.) or signs of recent bleeding (i.e. adherent clots); ii) blood in the gastrointestinal lumen and endoscopic evidence of portal hypertension (esophageal and/or gastric) with no other findings or active bleeding were classified as bleeding from portal hypertension; iii) bleeding mucosal lesions described using endoscopic terms of “esophagitis”, “gastritis”, or “duodenitis” were classified separately as ‘enteritis’ if there were no descriptions that would specifically described them as portal hypertensive lesions; iv) presence of blood in the small intestine without evidence of ulcers, enteritis, or portal hypertension in patients with Roux-en-Y (RY) anastomosis were considered “possible RY bleeds” unless the source was directly visualized at endoscopy. v) endoscopic evidence of ‘enteritis’ and serological (early or late CMV antigens), or histological (inclusion bodies, specific immunoperoxidase staining, or PCR) evidence of CMV infection at the time of the bleeding episode were classified as CMV enteritis.
- Non-diagnostic endoscopy: reports in which the signs of bleeding were not present, regardless of the nature of the endoscopic findings, including: i) portal hypertension without active bleeding or blood; ii) lack of luminal blood in patients with RY anastomosis; iii) mucosal lesions (erosions or ‘enteritis’) with no signs of bleeding; iv) ulcers without active bleeding, clots, visible vessels, or signs of recent bleeding.

The findings during the diagnostic and/or therapeutic endoscopic interventions were recorded for each patient during each bleeding episode and subsequently classified according to diagnosis.

Immunosuppression

The primary immunosuppression was Tacrolimus, as previously reported in this group of patients (19).

Statistics

Continuous variables are presented as the mean ± standard error, and categorical variables as proportions. The standard two-sample t-test was used to test differences between means, while differences in proportions were tested using Pearson's chi-square or Fisher's Exact test, if expected frequencies were less than five. The Wilcoxon Rank Sum test, a nonparametric equivalent to the standard two-sample t-test, was used for highly skewed data.

The cumulative risk of the first episode of a GI bleed was computed using the Kaplan-Meier (Product-Limit) method. Risk estimates were calculated as 1-S(t), where S(t) is the cumulative probability of being event-free at time *t*.

Patient survival was calculated from the date of liver transplantation until death, and primary graft survival from the date of liver transplantation until first retransplantation or death. Survival curves were generated using the method of Feuer et al. (20) and compared by the Mantel-Byar chi-square test (21). This method produces a graphical representation of survival associated with a time dependent covariate. That is, the method compares survival for those patients who already had a GI bleed at time *t* to those who have never had a GI bleed and are still alive at time t. The choice of t is arbitrary. We chose 90 days, since the majority of cases (73%) occurred in this interval (see Results section). Cox's proportional hazards model was used to compute the relative risk (RR) of mortality for GI bleed, and 95% confidence intervals. The variable GI bleed was incorporated into Cox's model as a time-dependent covariate. Multivariate Cox regression was used to adjust the RR for UNOS status at time of transplantation, recipient age, gender, and etiology of liver disease.

Survival according to the cause of GIB was calculated from the date of first episode of GIB until death. The date of GIB was used as a reference date because the timing of the first episode was statistically similar for the different causes. Survival curves were generated using the Kaplan-Meier (Product-Limit) method and compared by the log-rank test.

All tests were two-tailed. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Among the first 1000 OLTx performed between August of 1989 and December of 1992, there were 834 adults. The mean age was 49.9 (range 18.1 to 76.2) years. The mean follow-up was 47.9 (range 27.7 to 67.9) months. There were 330 (39.6%) women and 504 (60.4%) men. The UNOS classification prior to liver transplantation was status 4 or 3 in 120 (14.4%), status 2 in 321 (38.5%), and status 1 in 393 (47.1%) patients. The causes of liver disease in these patients included postnecrotic cirrhosis (25% viral, 3% autoimmune, and 1% drug-induced and miscellaneous), alcoholic liver disease (23%), primary biliary cirrhosis (10%), cryptogenic cirrhosis (9%), primary liver tumors (9%), sclerosing cholangitis (7%), and other diagnoses (13%).

Patients were excluded from the study if they had an unconfirmed diagnosis of blood loss (n=18), or if the source of blood loss was non-gastrointestinal (GI) (n=3). A total of 74/834

(8.9%) patients were identified who had at least one bleeding episode (range 1 to 5) from a GI source. The age, gender, and UNOS status of the 74 patients with GIB were similar to the ones in the 760 patients without GIB (table 1), who therefore were used as a reference group in the survival analysis (figures 1 to 3). The etiology of the liver disease was similar in both groups (table 1).

Overall causes of bleeding

Of the 74 patients with GIB, endoscopy was declined in one case. This patient had hematemesis, decreased hematocrit, and was managed conservatively. In three patients with RY biliary reconstruction, endoscopy was not performed during the first bleeding episode and a presumed diagnosis of bleeding RY was given. These three patients subsequently had other episodes of bleeding with endoscopic evaluations (tables 2 and 3). In the remaining 70 patients, endoscopy was performed during the initial and subsequent bleeding episodes (table 3). There were 108 bleeding episodes evaluated with endoscopy (94 upper endoscopies and 22 colonoscopies, range of 1 to 4 procedures per bleeding episode). Therefore, including the patient who declined endoscopy, there were 109 bleeding episodes in the entire group (table 3).

In 21 patients (including the 3 without initial endoscopic examination) there were multiple (one or more) bleeding episodes. In 39 patients, there was a single bleeding episode with an identified source at endoscopy. In 13 other patients, the source was not found despite endoscopy (table 2). Therefore, endoscopic evaluation yielded a diagnosis in 60/70 (85.7%) patients. The overall causes of bleeding according to episode are listed in table 3. Bleeding from ulcers was the most common diagnosis, followed by non-CMV enteritis (table 3), portal hypertensive lesions (tables 3 and 4), bleeding RY anastomosis (tables 3 and 5), and miscellaneous (table 3).

Time of bleeding

The first (or only) bleeding episode occurred during the first three months after OLTx in 54 (73%) patients, from 3 months to 1 year in 9 (12%) patients, and after the first year in 11 (15%) patients. The cumulative incidence of bleeding at one year was 8%. A second bleeding episode occurred in 21 cases (at 268 ± 57 POD), a third episode in 11 cases (at 337 ± 87 POD), a fourth episode in 2 cases (at 828 ± 443 POD), and a fifth episode in 1 case (at 1272 POD). No significant differences (p=0.3147) were found in the median -range- time to bleeding in non-diagnostic bleeds (23 -2 to 591- days), single bleeds (26 -1 to 1306- days), or multiple bleeds (88 -2 to 885- days).

Although more frequent during the first three months, bleeding from ulcers and enteritis was also seen during the late postoperative follow-up (see below). In the case of bleeding from portal hypertension, bleeding occurred either before POD 12 or after POD 270 (table 4). All RY bleeds occurred during the first three months after OLTx (table 5).

Bleeding from ulcers

There were 25 bleeding episodes from bleeding diagnosed in 23 patients. Two patients had two bleeding episodes; the first had a gastric ulcer that bled at POD 82 and 116; the second also had a gastric ulcer at pod 140 and 1272. Active bleeding (with or without clots) was described in 9 episodes, of which a therapeutic intervention was performed in 7 cases [injection therapy alone (n=3), with heater probe (n=1) or bicap electrocautery (n=1), and bicap electrocautery alone (n=2)]. Adherent clots without active bleeding were described in 4 episodes, and pigmented lesions in 1 episode (none treated). A visible vessel with clot was described in 1 episode (treated with injection therapy). Unspecified “stigmata of bleeding” was described in the remaining 10 episodes (one treated with injection therapy).

Helicobacter pylori was not described in any of the pathology reports of 11 (44%) cases in which a biopsy was obtained. Although information on the use of steroids in these patients was previously available (19), there was insufficient data on the use of non-steroidal antiinflammatory drugs to further characterize these ulcers. Neither of the two patients with recurrent bleeds had any therapeutic intervention. Multiple ulcers were described in: four patients with gastric ulcers (2 ulcers in 3 patients and 3 ulcers in 1 patient); one patient with two duodenal ulcers; and three patients with esophageal ulcers (2 ulcers in 2 patients and 3 ulcers in 1 patient). The description of the size or location (i.e., antrum vs. corpus) of these ulcers was generally imprecise. Ulcers were also described in 10 patients with bleeding from other sources and although they were clearly described as non-bleeding additional endoscopic details were insufficient to further classify them. The median time to bleeding from ulcers was 22 (range 5–1306) days when they were the only source of bleeding and 129 (2–885) days when they occurred with other bleeding lesions, a non-significant difference (p=0.172). Most (52%) episodes of bleeding from ulcers occurred during the first three months, 16% occurred from the first trimester to one year, and 32% episodes occurred after one year. In 6 patients, ulcers were found within the first two postoperative weeks. The number of retransplants after the GIB in these 23 patients was 5 (22%), and the number of deaths was 10 (43%).

Bleeding from enteritis

There were 26 episodes of bleeding diagnosed in 25 patients. Histological sampling was performed in 13/26 (50%) of these episodes. One biopsy (colon) showed CMV inclusion bodies, and another (stomach) was positive for CMV by PCR. These two patients were classified in the miscellaneous group as having CMV enteritis (table 3). Therefore, there were 24 bleeding episodes in 23 patients with non-CMV enteritis. The median time to bleeding from enteritis was 57 (range 1–531) days when they were the only source of bleeding and 60 (2–760) days if they occurred with other bleeding lesions (p=0.87). Most (46%) episodes occurred during the first three months, 38% occurred from the first trimester to one year, and 16% after one year. Five patients had bleeding within the first 2 postoperative weeks. The number of retransplants after the GIB in these 25 patients was 10 (40%), and the number of deaths was 10 (40%).

Bleeding from portal hypertension

Thirteen patients had bleeding from portal hypertensive lesions (varices, gastropathy, or both). Two groups of patients could be identified according to the time of bleeding (table 4). In seven patients, the bleeding occurred within the first 12 POD and all of them had portal hypertension (PHT) prior to OLTx (one required early retransplantation and another died after the bleed). In six other patients, the bleeding occurred after POD 270. Three (50%) of them required retransplantation (two after the bleeding episode), and three (50%) died. Patients requiring retransplantation were found to have cirrhosis (n=2) or HA thrombosis (n=1) with other graft findings such as acute rejection or hepatic necrosis (table 4).

The bleeding was controlled with sclerotherapy (sodium morrhuate) in three patients, and one of them subsequently underwent band ligation.

Additionally, PHT was described in 17 patients who bled from sources other than their portal hypertensive lesions. The graft histology in these patients after the endoscopic diagnosis of PHT also showed significant abnormalities ranging from hepatitis to cirrhosis (data not shown). The number of retransplants after the GIB in these 17 patients was 4 (23%), and the number of deaths was 5 (29%), respectively. Therefore, when bleeding (n=13) and non-bleeding PHT (n=17) were considered together, the postbleeding retransplantation rate was 7/30 (23%), and the mortality rate was 9/30 (30%).

Bleeding Roux-en-Y anastomosis

Clinical suspicion of RY bleeding existed in 10 patients (table 5). Exploratory laparotomy was performed in 7 cases of whom 6 were found to have active bleeding. Bleeding scans (n=2), but not angiography, were positive when performed before surgery (table 5). Endoscopy revealed luminal blood but failed to identify the precise source of bleeding at the anastomosis in 7 cases. Therefore, these endoscopies were classified as either non-diagnositic or as 'possible RY' bleeds in the diagnostic group with multiple bleeds (table 2 and 5). The mean time of bleeding was 21 (range 3–87) days after OLTx. The rates of retransplantation and mortality were 40% and 30% respectively.

Miscellaneous causes of bleeding

Bleeding from Mallory-Weiss tears, hemobilia (hepatic artery pseudoaneurysm, and post-liver biopsy), colonic polyps, hemorrhoids, AVMs, and trauma from nasogastric tubes occurred in 2 cases each. Additionally, in 4 bleeding episodes, endoscopy revealed the presence of blood in the gastric (n = 2) or small intestinal (n=2) lumen without a specific source. None of these patients had RY reconstructions. The remaining bleeding diagnoses occurred only once (table 3). Only three therapeutic interventions were recorded in this group (two for AVMs and one for a bleeding colonic polyp).

Survival analysis

The overall primary patient and graft survival (Kaplan-Meier) in patients with GIB was lower ($p < 0.00001$) than the patients with no GIB. Since most of the bleeding episodes occurred during the first three months after OLTx, the Mantel-Byar chi-square test showed a lower ($p<0.00001$) survival (figures 1a and 1b) in patients who had a GIB within the first three months compared to those patients who never had a GIB and survived to 3 months (see Statistical Analysis section). The adjusted relative risk (RR) of patient mortality for GIB was 4.2 (95% CI = 2.9–6.0). The adjusted RR of graft failure for GIB was 3.4 (95% CI = 2.3–4.9).

Patients with no identifiable sources of GIB at endoscopy (n=13) and with no endoscopy (n=1) fared better than patients with specific endoscopic diagnoses. Multiple bleedings had worse (log rank, p=0.3557) outcome than single bleeds (figure 2). Survival in patients bleeding from a single source (i.e., ulcers only) was better than in patients in which the sources were multiple (i.e., ulcers and others), although the differences did not reach statistical significance (figure 3). There were no significant differences in survival (p=0.364, log rank) between the various types of bleeding lesions (ulcers vs. enteritis vs. portal hypertensive lesions).

The outcome of bleeds occurring in the first three postoperative months showed an adjusted RR of mortality of 2.91 (95% CI = 1.86–4.55), and of primary graft failure of 2.47 (95% CI = 1.55–3.93). The outcome of bleedings occurring from 4 to 12 months showed an adjusted RR of mortality of 7.84 (95% CI = 3.80–16.19), and of primary graft failure of 8.80 (95% CI = 4.24–18.23). The outcome of bleedings occurring after the first year showed an adjusted RR of mortality of 26.84 (95% CI = 10.47–68.84), and of primary graft failure of 18.84 (95% CI = 6.23– 52.26).

DISCUSSION

The occurrence of bleeding has long been recognized as a complication following liver transplantation (8). Some of the reported sources of blood loss in recipients of liver transplants are vascular anastomotic leaks (8,9), persistent coagulopathy (8,9), hemobilia (8,13), viral (CMV and EBV) gastroduodenitis (9,12), RY anastomotic bleeds (9,7), esophageal perforations (8,12), and PHT due to splenic (11,18) or portal (8,10) vein thrombosis, and various other vascular complications (9,15).

The presence of gastrointestinal bleeding is not an infrequent indication for initiating a diagnostic (8) or therapeutic (14) endoscopic evaluation in liver transplant recipients. Bleeding from a RY anastomosis during the first two weeks has been attributed to incomplete hemostasis of the mucosa at the jejunojejunostomy site, facilitated by the reabsorption of the sutures, poor nutritional status, presence of PHT, and use of immunosuppressants (9). Gastrointestinal blood loss after the first postoperative weeks has been attributed to cytomegalovirus gastroenteritis (9), and more infrequently to other interventions such as liver biopsy (13). Some other reports have described esophageal perforations (8,12), and PHT due to splenic (11 18) or portal (8, 10) vein thrombosis in the early postoperative period. The onset of bleeding from PHT has been mentioned as a sign of thrombosis in the splachnic vascular territory (8,10,11,18) but not as a sign of graft dysfunction. Otherwise, there is no information about other gastrointestinal sources of blood loss in these patients. With the exception of RY bleeds (14), the gastrointestinal sources of bleeding had not been analyzed in the previous studies. Furthermore, although patients with gastrointestinal bleeding had been reported as having an increased morbidity (8), the survival of patients with OLTx complicated by gastrointestinal bleeding has not been fully determined.

In the present study, we analyzed the early and late causes of gastrointestinal bleeding after liver transplantation. We studied 834 adults from the first 1000 patients treated with Tacrolimus since preliminary data on survival and other adverse events in these patients was already available (19). No statistical differences in terms of age, gender, and UNOS status prior to transplantation were seen between patients with and without GIB. The diagnoses of the pre-transplant liver disease were also similar in these two groups. In the majority of cases, an accurate clinical diagnosis of GIB existed since only 3 patients were found not to have had GIB after reviewing their records. Endoscopy was declined in one case, and was not performed initially in 3 others. Therefore, there were endoscopic reports available for analysis in the majority of the bleeding episodes. In most of these patients, endoscopy was the diagnostic intervention. Although the terms “gastritis”, “duodenitis”, etc., are of histologic nature and require biopsy, we created the group ‘enteritis’ to separate these from the other groups, despite the lack of histological confirmation. In contrast with previous observations (18), the most common bleeding lesions found in these patients were ulcers, followed by hemorrhagic enteritis and portal hypertensive lesions in a similar way as described in non-transplant patients (22). RY bleeds were confirmed in 6 cases and probably existed in an additional 4, making it the fourth most common diagnosis. Non-bleeding ulcers, enteritis, and portal hypertensive lesions were also seen in 10, 28, and 17 bleeding episodes respectively, in conjunction with other diagnoses.

The incidence of bleeding was highest during the first postoperative trimester for the entire group. Bleeding from ulcers and enteritis also occurred after the first trimester. In the case of bleeds from portal hypertensive lesions, two distinct periods were seen: early bleeding most likely representing lack of resolution of preoperative PHT, and late bleeding representing de novo PHT. Bleeding from RY anastomosis was an early postoperative event.

In patients who had bleeding ulcers, the data on the incidence of *Helicobacter pylori* infection was not sufficient to characterize them. Details on the use of non-steroidal anti-inflammatory drugs, tests for detecting helicobacter pylori, or other risk factors for peptic ulcer disease were insufficient to allow further classification. Seven of the nine patients with actively bleeding ulcers underwent therapeutic intervention during the endoscopy. In the other two not receiving treatment, there was recurrence of the GIB. Most ulcers without active bleeding but with clots, visible vessels, or other stigmata of bleeding did not have therapeutic intervention. This probably reflects the lack of uniform consensus on endoscopic treatments in these type of ulcers that existed at the time in which the bleeds took place.

In patients bleeding from enteritis, histologic data was not available in most cases. There were only two patients in which CMV was identified as the pathogen, yielding a rate that is low compared to previous reports (9). The etiology of the enteropathy in the other cases remained undetermined, although there were no recurrences of bleeding and no antiviral therapy was administered.

In patients bleeding from portal hypertensive lesions, the rate of graft failure and retransplantation was high (up to 50%). Overall, the onset of PHT, (with or without bleeding) reflected poor graft function based on the findings at histology, ranging from hepatitis to cirrhosis.

In the present series of patients, bleeding from RY anastomosis was addressed surgically in 6 cases. In three other cases, the source of bleeding was not visualized endoscopically, but they subsided with conservative management. In one case, endoscopy and laparotomy failed to reveal the source of bleeding (table 5).

According to the survival analysis, bleeding with an identified source at endoscopy carried a worse prognosis than bleeding with no source, and multiple bleeding episodes carried worse survival than single bleeding episodes. With respect to diagnosis, ulcers, enteritis, or PHT, when they were the only source of bleeding, had better outcome than if they occurred with other lesions. However, none of these differences reached statistical significance.

The time in which GIB took place influenced the outcome, with worse survival for GIB episodes occurring after the first postoperative year regardless of etiology. Bleeding from portal hypertensive lesions was seen with graft dysfunction by histological criteria. Whether ulcers and enteritis also reflected graft dysfunction is unknown since, unlike patients bleeding from portal hypertensive lesions, most of these cases had no liver biopsies.

In summary, the results of this study show ulcers as the most common cause of gastrointestinal bleeding after liver transplantation, followed by hemorrhagic enteritis, portal hypertensive lesions, and RY bleeds. The patient and graft survival when gastrointestinal bleeding was present were worse than in patients without bleeding. Early bleeding from PHT was seen with graft dysfunction but probably represented persistent pre-transplant PHT. Late bleeding from PHT was seen with a significant rate of graft dysfunction and loss, retransplantation, and death. Multiple episodes and sources of bleeding were associated with poor patient survival. Attempts at characterizing the nature (peptic vs. non-steroidal vs. stress) of the gastrointestinal ulcers after liver transplantation seem justified since they are a common cause of GIB, and the evaluation may affect the therapeutic options offered to these patients. In the present study, the nature of the hemorrhagic mucosal lesions described as enteritis remains undefined. It is possible to speculate that they could also be a sign of graft dysfunction. Histological sampling to determine the nature of the enteritis and to exclude CMV or other viral pathogens needs to be considered whenever biopsies can be safely obtained. Evidence of portal hypertension during endoscopy should prompt a thorough functional assessment of the liver graft since it seems to be associated with a significant rate of graft dysfunction and failure.

In conclusion, gastrointestinal bleeding after liver transplantation seems to be an indicator of poor patient and graft survival. Late postoperative bleeding appears to be particularly ominous.

ABBREVIATIONS

ACR	Acute cellular rejection
AVM	Arteriovenous malformation

C-J	Choledocho-jejunum
CA	Carcinoma
CMV	Cytomegalovirus
DIC	Disseminated intravascular coagulation
DU	Duodenal ulcer
EBV	Epstein Barr virus
EU	Esophageal ulcer
EV	Esophageal varices
GIB	Gastrointestinal bleed
GU	Gastric ulcer
GV	Gastric varices
HA	Hepatic artery
HCC	Hepatocellular carcinoma
Hep	Hepatitis
J-J	Jejuno-jejunum
MW	Mallory-Weiss
NG	Nasogastric
OLTx	Orthotopic liver transplant
PBC	Primary biliary cirrhosis
PCR	Polymerase chain reaction
PHT	Portal hypertension
PHTG	Portal hypertensive gastropathy
POD	Postoperative day
RY	Roux-en-Y
SB	Small bowel
UNOS	United Network for Organ Sharing

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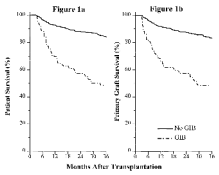

Figure 1.
Survival of patients **(1a)** and grafts **(1b)** with gastrointestinal bleeding (GIB) during the first postoperative trimester compared to patients with no GIB ($p < 0.00001$ Mantel-Byar chi square test, see text for details).

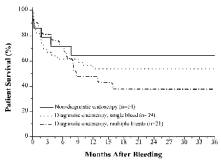

Figure 2.
Survival after liver transplantation in patients with gastrointestinal bleeding according to the type of endoscopy.

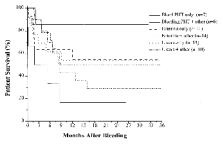

Figure 3.
Survival after liver transplantation in patients with gastrointestinal bleeding according to the source of bleeding.

Table 1

Characteristics of 834 patients prior to liver transplantation.

	Patients without GIB (n=760)	Patients with GIB (n=74)	p value
Age (years)	49.9 ± 0.4	50.1 ± l.5	0.53
Gender (female/male)	305 (40.1%)/455 (59.9%)	25 (33.8%)/49 (66.2%)	0.28
UNOS status			0.51
1	354 (46.6%)	39 (52.7%)	
2	294 (38.7%)	27 (36.5%)	
3 and 4	112 (14.7%)	8 (10.8%)	
Cause of liver disease			0.64
Postnecrotic(viral, autoinmune, drugs)	215 (28%)	26 (35%)	
Alcoholic	170 (22%)	18 (24%)	
Primary biliary cirrhosis	79 (10%)	4 (5%)	
CryPtogenic Cirrhosis	74 (10%)	6 (9%)	
Liver tumors (HCC, CholangioCA., etc.)	65 (9%)	7 (9%)	
Primary Sclerosing Cholangitis	57 (8%)	3 (4%)	
Others[a]	100 (13%)	10 (14%)	

[a] Congenital or genetic liver disease, Budd-Chiari, secondary biliary cirrhosis, etc.

Table 2

Findings and diagnoses in 73 patients with gastrointestinal bleeding who had endoscopy.

NON DIAGNOSTIC ENDOSCOPY	DIAGNOSTIC ENDOSCOPY				
(n=13)	**Single episode(n=39)**		**Multiple episodes (n=21)**		
Findings	**Findings**		**First episode**	**Second episode**	**Third episode**
Candida Esophagitis	DU	(6)	GV	PHTG	PHTG[a]
Diverticulosis	Gastritis (1CMV)	(5)	Possible RY	Esophagitis	
Antritis, internal and external hemorrhoids	GU	(4)	EV + GV	Internal hemorrhoids	
EV, gastritis, duodenitis, rectal varices	Colitis (1 CMV)	(3)	Oversewn GU	Colon biopsy	
Gastritis, duodenitis	EV	(3)	No endoscopy	Colitis	
EV, gastric ulcer, PHTG, colon polyps	EU	(3)	DU	Ulcerative colitis	
EV, antritis	PHTG	(2)	No endoscopy	Psuedom. colitis	SB bleed
EV, colon polyps	NG tube trauma	(2)	GU	EV	
Possible RY, esophagitis, gastritis	Duodenitis	(2)	Gastritis	Duodenitis	AVM colon
Possible RY, gastritis, duodenitis	MW tear	(2)	Gastritis	GU	SB obstruction[b]
Possible RY, EV,	Duodenal perforation	(1)	Pyloric ulcer	GU	SB bleed
Possible RY, colitis	Ileitis/Pouchitis	(1)	Gastritis	Hemobilia	
Possible RY	Rectal polyp	(1)	EV	DU	Gastritis
	EV + PHTG	(1)	Gastritis	Internal hemorrhoids	DU
	GV + PHTG	(1)	GV	MW tear	
	AVM (stomach)	(1)	Gastritis	GU	
	SB bleed	(2)	No endoscopy	Gastritis	Petechiae in colon
			Colon polyps	Esophagitis	GU
			Colitis	PHTG	
			Possible RY	Gastritis	Colonic perforation
			SB bleed	Colitis (proctitis)	Intussusception

More than 3 bleeding episodes:

[a] Esophageal ulcers;

[b] Hemobilia, Gastric ulcer.

Table 3

Overall causes of gastrointestinal bleeding (by episode) in 74 patients.

Group	Findings or Source of bleeding	Number	Total
Bleeding episodes without endoscopy	Endoscopy declined by patient	1	
	See tables 2 and 5	3	4
Bleeding episodes with endoscopy and no diagnosis	See tables 2 and 5		13
Bleeding episodes with endoscopy and diagnosis			
Ulcers	Gastric ulcer	11	
	Duodenal ulcer	10	
	Esophageal ulcer	4	25
Enteritis	Gastritis	12	
	Colitis	6	
	Duodenitis	3	
	Esophagitis	2	
	Ileitis	1	24
Portal Hypertension	Esophageal Varices	5	
	Portal hypertensive gastropathy	5	
	Gastric Varices	2	
	Combination	3	15
RY bleed and other bleeds	See tables 2 and 5	2	2
Miscellaneous	CMV enteritis, AVMs, hemobilia, colon polyps, hemorrhoids, trauma from nasogastric tube, small bowel (undetermined), gastric cavity (undetermined), MW tears.	2 each	
	Intussusception, colonic perforation, SB obstruction, colon biopsy, ulcerative colitis, jejunal bleed, petechiae in colon, duodenal perforation	1 each	26
TOTAL BLEEDING EPISODES			109

Table 4

Liver histology in 13 patients with bleeding and portal hypertension.

Patient	Bleeding pod	Bleeding source	Cause of re-OLTx	Graft biopsy/explant
1	Intra-op	PHTG	---	---
2	2	EV	---	Graft biopsy: No evidence of chronic liver disease
3	3	PHTG	---	Graft biopsy: No evidence of chronic liver disease
4	5	GV	1. Non- function	Graft explant 1: Early ACR, severe necrosis
			2. Non- funtion	Graft explant 2: Early ACR, severe necrosis
5	9	EV	---	Graft biopsy:. No evidence of chronic liver disease
6	11	EV+GV	HA thrombosis	Graft explant: HA thrombosis with infarction, bile obstruction with biloma
7	12	EV+PHTG	---	Graft biopsy: Treated active cellular rejection
8	270	EV		Graft biopsy: Portal inflammation, focal lobular reactivity, low grade hepatits
9	279	PHTG	Cirrhosis	Graft explant: Cirrhosis, giant cell formation, ductular proliferation, hepatitis
10	340	EV	1. Non- funtion	Graft explant 1: Massive hepatic necrosis
			2. HA thrombosis	Graft explant 2: Mild ACR, diffuse infarction, necrosis of HA wall
11	349	GV	---	Graft biopsy: Mild ACR, duct damage and loss, hepatocyte swelling, cholangitis
	365	PHTG		
	380	PHTG		
12	708	GV+PHTG	Cirrhosis, Hepatitis B	Graft explant: Active micronodular cirrhosis.
13	750	EV	---	Graft biopsy: Active micronodular cirrhosis, increased bile stasis, mild ACR

Table 5

Diagnostic evaluation on patients suspected of having bleeding from RY anastomosis.

Patient	Bleeding POD	Endoscopy	Angiography	Bleeding Scan	Therapeutic Intervention	Site of bleeding
1	9	Done[a]	Not done	Done; **positive**	Laparotomy	J-J anastomosis
2	4	Done[b]	Done; negative	Done; **positive**	Laparotomy	J-J anastomosis
3	87	Not done	Not done	Not done	Laparotomy	J-J anastomosis
4	35	Done[a]	Done; **positive**	Not done	Laparotomy	C-J anastomosis
5	8	Not done	Not done	Not done	Laparotomy	Mesentery of RY limb
6	10	Not done	Not done	Not done	Laparotomy	RY anastomosis[c]
7	11	Done[a]	Not done	Not done	Not done	---
8	3	Done[a]	Not done	Not done	Not done	---
9	35	Done[b]	Done; negative	Not done	Laparotomy	Not determined
10	4	Done[a]	Not done	Not done	Not done	---

Classified as:

[a] non-diagnostic endoscopy or

[b] multiple bleeding episodes.

[c] Unspecified source.