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Gastrointestinal perforation in liver transplantation recipients: risk factors analysis from a 10-year retrospective study with an international multicenter survey about management strategies

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Keywords

Liver transplantation · Liver transplantation outcomes · Liver transplantation complications · Liver, transplantation recipients · Gastrointestinal perforation

Abstract

Risk factors for gastrointestinal (GI) perforations in adult liver transplantation (LT) recipients have never been deeply investigated, as well as their management. The aim of this study is to report a single-center 10 years' experience about GI perforations after LT, focusing on risk factors and management strategies according to an international survey involving expert transplant surgeons. Data regarding all consecutive patients undergoing liver transplantations from January 2009 until December 2019 in a single institution were retrospectively collected. Risk factors for GI perforation were investigated. A web survey about the management of gastrointestinal perforations was conducted among worldwide transplantation centers. On 699 adult liver transplantations performed in our center, 20 cases of GI perforations were found, with an incidence of 2.8%. A previous abdominal surgery was found to be the only risk factor ($p = 0.01$). Ninety-day mortality was 75%. According to the survey, a more conservative treatment was suggested in case of gastric and duodenal perforations (consisting in a direct suture or an external drain), while a more aggressive treatment was adopted for ileal or colic perforation (stoma with or without resection). The W value for inter-personal agreement was 0.41. Despite rare, GI perforations in LT recipients can represent a life-threatening complication. Surgical management can be challenging and depends on both the site of perforation and the clinical conditions of the patient.

Introduction

Liver transplantation is considered the best available treatment for end-stage liver disease, as well as for some metabolic and neoplastic pathologies [1]. However, several complications can adversely affect short- and long-term outcomes [2–4]. Gastrointestinal (GI) perforations after LT have been reported as rare but life-threatening complications, and data regarding their incidence in adult recipients are scarce in the literature. Bacterial sepsis is a major cause of mortality after LT. Similarly, peritonitis caused by a bowel perforation is an even more dramatic event in immunocompromised patients [5].

The first report about GI perforations in LT recipients was written by the group of Dr. Starzl in 1979, describing a high mortality rate [6]. Similarly, GI perforations have been reported after kidney and heart transplantations with poor outcomes, especially in cases of colonic perforation with gross peritonitis [7–9]. Such complication is more frequent after LT in pediatric patients for biliary atresia than in adults [10], and possible risk factors have been suggested in pediatric population, including treatment with high-dose steroids, previous laparotomy, prolonged surgery, subsequent re-laparotomy, and portal vein clamp time [11–13]. However, there are no studies that investigate risk factors for GI perforation in adults LT recipients. To counterbalance the well-known difficulty of the clinical diagnosis of peritonitis in such patients, and the gravity of this complication, it is fundamental to try to identify all possible risk factors in order to prevent its occurrence.

Early diagnosis can be difficult because of the large doses of immunosuppressants that often produce atypical clinical features by stopping the inflammatory response [14]. GI perforations may occur at any point in the gastrointestinal tract. Furthermore, in LT recipients, parameters

such as immunosuppression state, impaired metabolic function, surgical stress, and ICU stay, add more and more challenges to the management of perioperative GI perforations. In this scenario, worldwide experienced transplant surgeons' opinions and management procedures were investigated.

The aim of this study is to evaluate risk factors for gastrointestinal perforation in LT recipients and speculate possible management strategies.

Materials and methods

Study design and patients' selection

This is a monocentric observational retrospective study. The study was approved by the local Institutional Review Board (IRB #2019-01-234) and reporting was made according to STROCCS guidelines [15].

Data regarding consecutive adult LT recipients undergoing single liver transplantation or liver–kidney transplantation between 1st January 2009 and 31 December 2019 were retrospectively collected from the institutional database of Montpellier University Hospital. Patient's demographics, intraoperative characteristics (operation time, portal vein clamp time, number of red blood cells units transfused, cold and warm ischemia time), postoperative outcomes, hospitality status and hospital stay data were collected. Data regarding Child–Turgot–Pugh (CTP) score, MELD score, morbidity and mortality were also recorded.

Patients' management

The management of transplanted patients was carried out according to Montpellier University Hospital protocols. After LT, all the patients moved to the transplantation Intensive Care Unit (ICU). Induction therapy consisted of intravenous corticosteroids immediately post-transplant for several days, until when the shift to oral corticosteroids was possible. Other modalities of induction therapy could be used for patients at higher immunological risk (re-transplantation for rejection, immune-mediated liver disease, simultaneous liver–kidney; highly sensitized). The cornerstone of maintenance IS therapy were the CNIs, with tacrolimus (TAC) being preferred over cyclosporine. Antiproliferative agents, such as mycophenolic acid (MMF), were used during the in hospital stay, to lower the toxicity of CNI therapy, usually in combination with lower dose CNI therapy.

In case of diagnosis of a possible cause of sepsis, the dose of both corticosteroids and calcineurin inhibitors was reduced to the minimal effective dose, as soon as the diagnosis was made. The therapeutical strategies were always decided after a multidisciplinary decision-making process, involving anesthesiologists, hepatologists, surgeons. Indication to surgery was given based on clinical, laboratoristic and radiological elements. The type of surgery was decided according to both clinical and intraoperative findings: in case of stable patients, absence or low degree of peritoneal contamination, and proximal GI perforation, a more conservative strategy was adopted.

International survey

An online survey on Google Forms, named “Management of GI perforations during the postoperative course of a liver transplantation: an international survey”, was created and suggested to medium- and high-volume transplant centers (> 50 LT per year) in Western Europe, USA and ASIA, excluding our own center [1]. In the survey, questions about ideal surgical treatment were proposed according to the site of perforation (esophageal, gastric, small bowel and colon). In particular, treatment was divided into conservative (direct suture or placing a drain/T tube in the perforation/endoscopy) or non-conservative (resection and anastomosis or resection plus stoma or just a stoma). Participants had different options that were either non-conservative or conservative. Questions were based on the absence of a septic shock and on the possibility to give a single unique answer according to GI perforation location and patients’ clinical status.

The time frame for two rounds of this survey spanned from January 2020 to June 2020 (including a first round between January and March and a second one between April and June to reach more centers as possible). The inter-expert agreement was computed after both rounds using Intra-class Kendall’s W Coefficient.

Statistical analysis

The categorical data were described by frequencies and percentages, whereas continuous data by mean \pm standard deviation (SD) or median \pm inter-quartile range (IQR) depending on whether they have a normal distribution. Categorical variables were compared using the χ^2 test or Fischer exact test, while the distribution of continuous variables was compared by applying Student’s *t* test or Mann–Whitney test, when appropriated.

The primary endpoint was the incidence of perforation after adult liver transplantation. Univariate and multivariate analyses were performed with a *p* value set to 0.05, via backward logistic regression.

The statistical analysis was conducted using the SPSS software (version 26.0).

Results

Patients’ and surgeries’ characteristics

Six hundred and ninety-nine adult liver transplantations were performed between January 2010 and December 2019. Mean age was 53.1 years, and the 74% of the recipients were male. Regarding the underlying liver diseases, 44% of LT recipients had alcoholic cirrhosis, 20% HCV-related cirrhosis, and 4% HBV-related end-stage liver disease. All available data about patients and surgeries are shown in Table 1. Twenty cases of gastrointestinal perforations were found, with an incidence of 2.8%. A history of previous abdominal open surgery was the only factor significantly associated with the development of a gastrointestinal perforation (*p* 0.01). Univariate analysis about possible risk factors and LT recipient details are shown in Table 1. All details about perforated patients and their management are shown in Table 2A, B.

Table 1 Patients' and surgeries' characteristics

	Without GIP <i>N</i> =679	With GIP <i>N</i> =20	<i>p</i> value
Age, mean (SD)	53,5 (13)	53 (11)	0.90
Sex, male (%)	504 (74)	16 (80)	0.55
BMI, mean (SD)	26,1 (3.9)	24.2 (2.9)	0.60
Liver status			
Cirrhosis, <i>n</i> (%)	649 (95)	20 (100)	0.27
Non-cirrhotic, <i>n</i> (%)	30 (5)	0	
Cirrhosis etiology			
Alcoholic	305 (45)	6 (25)	0.08
HBV	24 (5)	1(5)	0.50
HCV	131 (18)	8 (35)	0.07
Others	225 (32)	5 (25)	0.44
Child-Pugh score, (%)			
A	142 (21.8)	1 (5)	0.07
B	177 (27.5)	5 (25)	0.83
C	326 (51.7)	14 (70)	0.07
MELD score, median (IQR)	18 (15)	16 (10)	0.95
MELD > 20, <i>n</i> (%)	365 (52)	12 (60)	0.52
HCC, <i>n</i> (%)	194 (28)	8 (40)	0.12
Previous abdominal surgery, (%)	227 (33)	12 (60)	0.01
Previous OLT, (%)	42 (6.1)	3 (15)	0.11
Operation time, mean (SD)	450 (125)	445 (137)	0.91
Estimated intraoperative ascites, mean in cc (SD)	2204 (3038)	2757 (3579)	0.87
Intraoperatively transfused RBC units, median (IQR)	5 (6)	5 (7)	0.67
Mean portal clamp time, (SD)	88.3 (37.5)	72.3 (57.5)	0.16
CMV infection, (%)	29 (4)	1 (5)	0.52

GIP gastrointestinal perforations, *HCC* hepatocellular carcinoma, *HBV* Hepatitis B virus, *HCV* Hepatitis C virus, *MELD* model for end-stage liver disease, *OLT* orthotopic liver transplantation, *CMV* cytomegalovirus, *SD* standard deviation, *IQR* inter-quartile range

Statistically significant *p*-values are highlighted in bold

Gastrointestinal perforations

Perforations were diagnosed after a median delay of 12 days (IQR25-75 7–21). The involved organ was the stomach in 4 cases, duodenum in 6 cases, small bowel in 4 cases and colon in 6 (Table 2). For 7 patients, an aggressive strategy was performed, with a colic resection plus stoma, and an ileal resection followed by anastomosis in one case. Twelve patients underwent a more conservative surgery: 8 received a peritoneal washing and the insertion of a drain (either T tube or Petzer type) into the duodenal or jejunal perforation in order to externally drain and to obtain a mature fibrous tract. Four patients underwent a direct suture to treat gastric perforations. Details about patients' managements are shown in Table 2A. One patient died before the possibility to receive the surgical procedure. Ninety-day mortality was 75% (Fig. 1), significative higher than the 21% observed in the non-perforated LT recipients ($p < 0.0001$). In particular, 4/7 resected patients died within 90 days (57%), while 9 died in the conservative treated group (75%).

In all the LT recipients with gastrointestinal perforation, immunosuppressive therapy was not discontinued. The dose of corticosteroids and calcineurin inhibitors was reduced to the minimal effective dose, as soon as the diagnosis was made. No cases of graft rejection among the perforated patients were encountered.

Table 2 A Characteristics and management of perforated LT recipients. B OLT data about perforated patients

A Characteristics and management of perforated LT recipients							
Patient number	Previous surgery*	Immunosuppressive regimen	Locations of the perforation	Time between LT and diagnosis	Treatment	Cause of death	Time to death
1		CCS+Tacrolimus+MMF	Stomach	9	Suture		
2	Appendectomy; cholecystectomy	CCS+Tacrolimus+MMF	Transverse colon	14	Resection+stoma	Sepsis with MOF	58
3		CCS+Tacrolimus+MMF	Transverse colon	12	Resection+stoma	Kidney failure	21
4	Distal gastrectomy; cholecystectomy	CCS+Tacrolimus+MMF	Duodenum	12	Peritoneal washing+T tube to externally drain	Respiratory distress	40
5	Appendectomy	CCS+Tacrolimus+MMF	Right colon	5	Resection+stoma	Sepsis with MOF	63
6		CCS+Tacrolimus+MMF	Stomach	10	Suture		
7	Appendectomy; cholecystectomy	CCS+Tacrolimus+MMF	Ileum	6	Resection+side to side ileal anastomosis	Sepsis with MOF	68
8	Cholecystectomy; OLT	CCS+Tacrolimus+MMF	Duodenum	12	Peritoneal washing+T tube to externally drain	Respiratory distress	74
9	Wedge liver resection; cholecystectomy	CCS+Tacrolimus+MMF	Transverse colon	0	Resection+stoma		
10	Wedge liver resection; OLT	CCS+Tacrolimus+MMF	Duodenum	36	Peritoneal washing+Petzer tube to externally drain	Sepsis with MOF	57
11	Nephrectomy; appendectomy; OLT	CCS+Tacrolimus+MMF	Duodenum	23	None	Sepsis with MOF	23
12		CCS+Tacrolimus+MMF	Right colon	11	Resection+stoma	Sepsis with MOF	38
13		CCS+Tacrolimus+MMF	Jejunum	8	Peritoneal washing+T tube to externally drain	Sepsis	54
14		CCS+Tacrolimus+MMF	Right colon	7	Resection+stoma	Sepsis with MOF	31
15	Cholecystectomy	CCS+Tacrolimus+MMF	Jejunum	0	Peritoneal washing+T tube to externally drain		
16	Left lateral sectionectomy	CCS+Tacrolimus+MMF	Stomach	8	Suture		
17		CCS+Tacrolimus+MMF	Jejunum	31	Peritoneal washing+T tube to externally drain	Sepsis	50
18	Wedge liver resection; OLT	CCS+Tacrolimus+MMF	Duodenum	36	Peritoneal washing+Petzer tube to externally drain	Sepsis with MOF	74
19		CCS+Tacrolimus+MMF	Duodenum	49	Peritoneal washing+T tube to externally drain	Respiratory distress	89
20	Left hepatectomy	CCS+Tacrolimus+MMF	Stomach	16	Suture	Sepsis with MOF	42

B OLT data about perforated patients					
Patient number	Cold ischemia time	Warm ischemia time	Hepatectomy time	Clamping time	Operation time
1	360	50	130	65	374
2	320	35	140	80	390
3	480	45	120	90	553
4	311	50	125	60	375

Table 2 (continued)

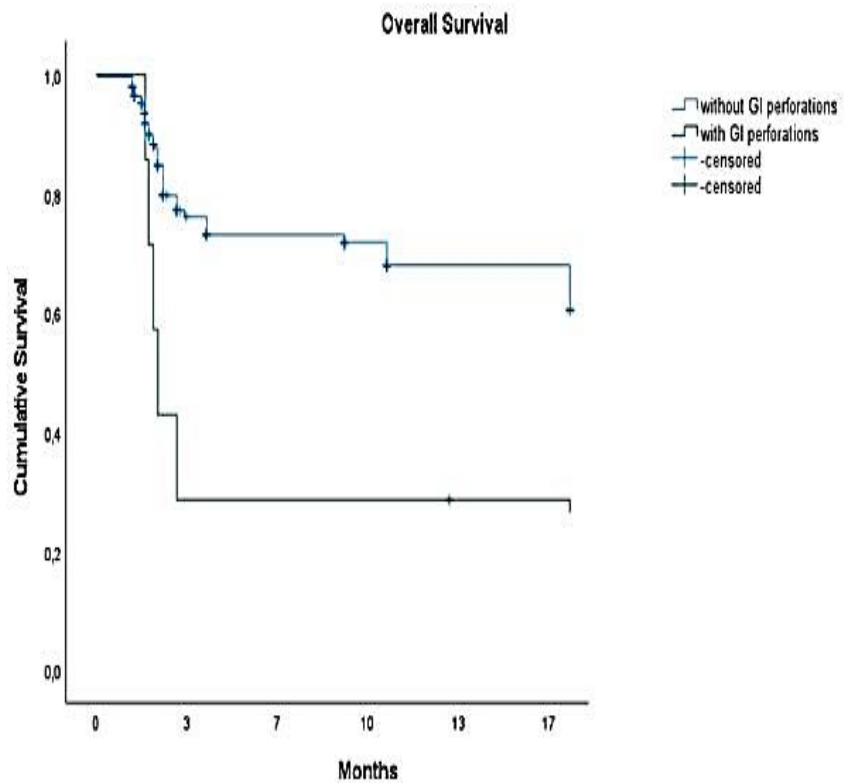
B OLT data about perforated patients

Patient number	Cold ischemia time	Warm ischemia time	Hepatectomy time	Clamping time	Operation time
5	420	50	208	75	482
6	385	35	135	45	420
7	275	120	150	44	325
8	501	140	238	156	510
9	300	52	47	70	338
10	415	65	180	68	480
11	450	135	214	90	560
12	423	90	150	55	480
13	345	67	90	100	495
14	430	70	89	72	444
15	400	63	73	45	275
16	410	88	150	57	430
17	440	28	90	60	310
18	550	120	200	118	750
19	390	55	135	32	403
20	439	105	69	65	460

OLT orthotopic liver transplantation, CCS corticosteroids, MMF mycophenolate mofetil, MOF multi-organ failure

*Only laparotomic surgeries (including previous OLT) have been investigated, and have been here reported

Fig. 1 Survival in liver transplantation recipients with and without a GI perforation



International survey

A total of 38 participants answered the online survey: 23 from France, 5 from Italy, 3 from the UK, 2 from Spain, 2 from Germany, 1 from Australia, 1 from South Korea and 1 from the USA (Fig. 2).

About esophageal perforations, 30% of the surgeons choose the direct suture as the ideal treatment, followed by a 25% of surgeons choosing endoscopic stenting and 25% drainage; only the 20% of surgeons voted for an aggressive strategy. Similarly, for gastric perforations, the 70% of transplant surgeons voted the direct suture as the ideal treatment. The preferred treatment option for duodenal perforation was found to be the positioning of a T tube to externally drain the perforation. On the contrary, for small bowel and colonic perforations the highest part voted for a more aggressive surgical strategy (79% and 76%, respectively). The full results of the survey can be found in Fig. 3.

The overall *W* value for inter-personal agreement was 0.41, showing a moderate agreement.

Discussion

This is the first study to investigate the possible risk factors for GI perforations in a wide adult LT recipients' population. Our results from 10 years' experience in a high volume center show an incidence of GI perforations after LT of 2.8%, with a 75% of 90-day mortality. A previous laparotomic surgery was found to be the only risk factor for developing this life-threatening complication (p 0.01). Regarding the type of previous surgery, only the laparotomies were included in the analysis, excluding abdominal wall surgeries that did not open the abdominal cavity, as well as laparoscopic procedures.

Xiong et coll. reported a series of 187 adult LT with an incidence of 6 GI perforations and a mortality of 50%, without analysis of risk factors or different management options according to the site of perforation [14]. Similarly, other 2 papers from Middle and Eastern Asia experiences show a superimposable incidence and mortality rate, within a population of less than 300 LT [16, 17].

Different possible etiological factors have been advocated in previous studies, especially in pediatric populations, without any statistical analysis. Corticosteroid therapy with its pharmacodynamics can play a role because of an impaired wound healing, a decrease mucosal turn over, and an atrophy of Peyer's patches and lamina propria with thinning of the bowel wall [18]. However, in our study, we could not analyze its association with perforation, since its use was routinary within the induction therapy for all the transplanted patients in our center. Similarly, the possible role of other immunosuppressive agents was not investigated, since there were some lacking data for some of the 699 LT recipients. However, almost all the LT recipients in our hospital received a combination of CCS with Tacrolimus plus MMF at the beginning of the hospital stay, until the shift to the only Tacrolimus for the domiciliary maintenance therapy. This was the antirejection regimen followed by all the perforated patients, as well.

The duration of portal clamping was found to be another risk factor by Soubrane et al., in a study involving a pediatric population [11]. However, our data did not confirm such hypothesis in our experience on adult patients. Furthermore, other possible risk factors were investigated, such as the quantity of ascites, the number of intraoperative transfusions, the operation time, and the liver status

stratification based on the Child–Pugh and the Meld score. Anyway, no differences were found between the two populations.

Fig. 2 Country of origin of the transplant surgeons answering the survey

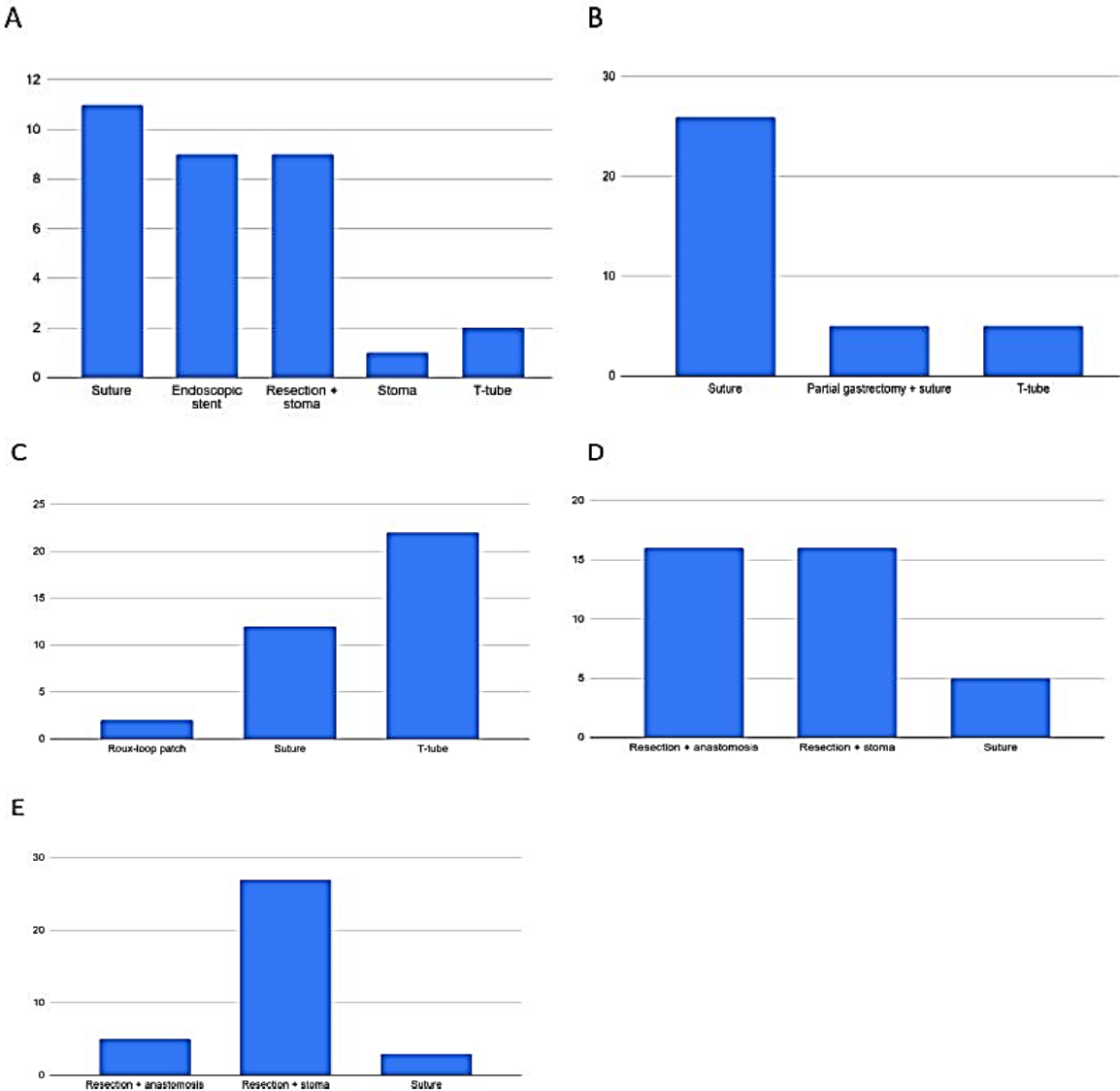
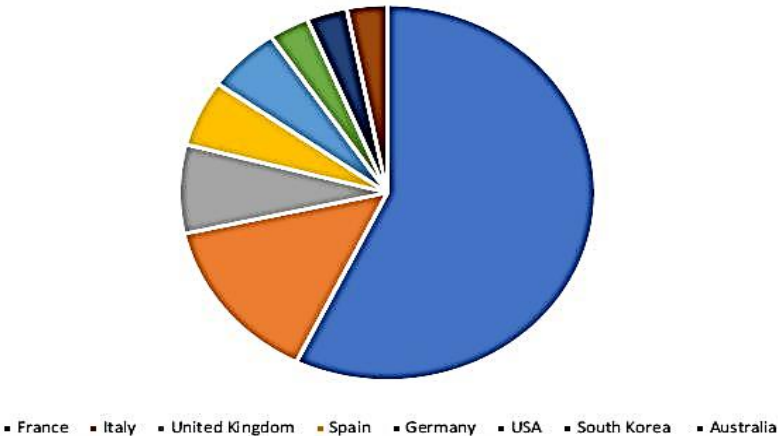


Fig. 3 International survey about management of GI perforation in LT recipients according to the involved organ. **A** Esophageal perforation management. **B** Gastric perforation management. **C** Duodenal perforation management. **D** Small bowel perforation management. **E** Colonic perforation management

CMV has also been reported to be associated with GI perforations in LT recipients, maybe linked to a primary intestinal infection mechanism with subsequent ulceration and perforation [19, 20]. Herein, one patient in the perforated group was found to be positive for CMV serology, with no difference when compared to the other group (p 0.52). Our 90-day mortality for the patients with GI perforation was as high as 75%, confirming the results from previous literature. Main reasons of such a poor prognosis can be found probably in the immunosuppressed condition of LT recipients, carrying a high septic risk. Furthermore, the delay between the onset of digestive perforation and diagnosis can be very long in immunosuppressed patients. Therefore, also the consequent treatment can be delayed. The suppression of the inflammatory response can hide signs and symptoms of peritonitis, with an inverse correlation between the time from initiation of immunosuppressant therapy and the expressions of the signs and symptoms of the abdominal disease [21]. Furthermore, several common medical conditions may be responsible for infectious diseases in transplanted patients mimicking acute abdomen, so the timeline from the initiation of immunosuppressive therapy may be helpful in the differential diagnosis [22].

Regarding the clinical results according to different patients' management in our experience, there was a slightly lower mortality in the patients treated by a more radical surgery (resection or stoma). Nonetheless, the difference is not significant: the conservative first operation group consists of mainly duodenal perforations, for which a radical surgery may be technically challenging or considered too aggressive in such conditions. Perforation can occur in any part of the gastrointestinal tract, and different treatment options have been proposed according to clinical conditions and perforation site (primary repair, resection-anastomosis, resection and stoma, and loop stoma formation) [23]. In our study, GI perforation was more common in duodenum and colon. Furthermore, the site of perforation had a significant impact on the overall survival of patients in previous studies: Barut et al. reported the lowest overall survival for duodenal and colonic perforations [24]. In any case, we strongly suggest an aggressive strategy in case of contamination of the abdominal cavity, when technically possible, with a resection plus stoma.

The uncertainty in management strategy and the lack of wide experiences in literature in such frail patients constituted the rationale of the international survey. In our clinical experience, dealing with postoperative perforations lead to face both the possibility of a late diagnosis and the gravity of this complication in a postoperative and immunosuppressive setting, can lead to different approaches, leading to a multidisciplinary discussion to find the possible solution. The inquiry was sent to high-volume (> 50 LT per year) LT centers in Western Europe, USA and ASIA, obtaining 39 answers. As appears in our survey results, there is a moderate concordance about the type of strategy to act, with regard to the perforation site. The strategies can be summarized to a more conservative and direct surgery for proximal perforation, because of a lower grade of contamination, as well as of the technical possibility of stenting/suture. Furthermore, according to our experience, duodenal drainage seems to be more technically feasible of a resection, especially in LT recipients. Finally, the high contamination grade of bowel perforation leads to most answers suggesting resections or stoma formations. However, it must be emphasized that the scenario proposed in the survey is certainly too simplistic compared to the real-life situation that can arise in the management of a transplant patient. In particular, we focused on the treatment based only on the site of perforation, and not on the several other variables possibly present in such difficult situations, to simplify answers and their analysis.

This study has several limitations. First, the retrospective design did not allow to adequately investigate all the possible risk factors for developing GI perforation. A multivariate analysis was not performed because backward selection was not possible, since only one factor was shown to be associated in the univariate analysis. Finally, the role of the immunosuppressive protocols was not deeply investigated, as well as the possible role of different perioperative and surgical techniques. At the same time, our cohort was the widest published so far, and the highlighted risk factor is known to be a risk factor of GI perforations also for other surgeries, giving strength to our result.

In conclusion, GI perforations in LT recipients confirm to be a rare complication but can represent a life-threatening condition with a high mortality rate. Surgical management can be challenging and depends on the site of perforation.

Author contributions

All the authors made substantial contributions to the conception or design of the work, the drafting the work and the final approval.

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None.

Data availability

The data that support the findings of this study are available from the corresponding author [FP], upon reasonable request.

Declarations

Conflict of interest

The authors declare that they have no conflict of interest. Nothing to disclose. Ethical approval and Informed consent This study involving human beings was conducted according to WMA declaration of Helsinki. It was approved by the local Institutional Review Board (IRB #2019-01-234), informed consent was obtained.

Research involving human participants and/or animals

The research was conducted according to WMA declaration of Helsinki, after obtaining approval from institutional review board (IRB #2019-01-234).

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