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ORIGINAL ARTICLE

Surgical site infections in liver transplantation in the era of multidrug-resistant bacteria

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ABSTRACT

BACKGROUND: Surgical site infection (SSI) is the major complication in orthotopic liver transplantation (LT). It is of prime importance to assess the incidence of infections in liver transplants and to analyze the risk factors associated with morbidity and mortality.

METHODS: Between 2014 and 2019, we performed a retrospective cohort study at the Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. The liver transplant procedure and its related infections were examined in 4 timepoints, both prior and post-surgery. Multiple random-intercept Poisson regression models with robust variance were fitted to calculate the adjusted risk ratios (RR) and the 95% confidence intervals (CI) according to selected recipient and donor variables.

RESULTS: We included in the analysis 249 transplants (in 241 patients). The SSIs (mostly due to *S. aureus*, *E. faecium*, and *K. pneumoniae*) were 7 (2.8%) in the days following LT, increasing to 61 (24.5%) within the first month after LT, and declining to 35 (14.1%) between 31 and 60 days, and to 19 (7.6%) afterwards. The factors associated with increased risk of infection were age (RR=1.17 per 10 years, CI: 0.99-1.38), BMI (RR=1.04 per BMI Unit, CI: 0.99-1.08), donor age (RR=0.88 per 10 years, CI: 0.78-0.98), re-interventions (30 infections, RR=2.02, CI: 1.21-3.38) and the Roux-en-Y approach (25 infections, RR=2.75, CI: 1.47-5.15).

CONCLUSIONS: The risk of infection occurred mainly in the first two months after LT. Important determinants were age and BMI, donor age, reinterventions, and Roux-en-Y procedure. Our study suggests that these factors should be assessed when performing LT.

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KEY WORDS: Surgical wound infection; Liver transplantation; Risk factors.

The complexity and long duration of the surgical act in LT are the major causes of SSIs. Surgical site infection (SSI) is defined by the US Centers for Disease Control and Prevention (CDC) as an infection that occurs within 30 days of the operation or within one year if the implant has been left in place and the infection is considered secondary to the operation. Deep incisional

SSI infection is defined by its occurrence within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation.[1, 2] The CDC classified surgical site infections as superficial (limited to the skin and subcutaneous tissue), deep (involving the fascial and muscle layers) or organ-space infections (extending beyond fascia and muscle layer).[3, 4] LT patients are particularly susceptible to healthcare-associated infections compared with patients undergoing other types of solid transplants.[2] SSI is the most common hospital acquired infection, with an incidence after LT that ranges from 8 to 37%.[3, 5, 6] Infections in liver-transplanted patients are a significant cause of morbidity and play a decisive role in the survival of this group of patients.[7] Most of these infections occur in the period immediately after transplantation. In 95% of cases the agent responsible is bacteria, and it is currently estimated that about 14.3% of infections are caused by multidrug-resistant microorganisms (MDRO).[5] LT is a therapy for patients with acute or chronic liver damages. In Europe 7940 liver transplants were performed in 2019, 1179 of which in Italy.[8] Results have improved considerably, particularly in the last two decades, compared to the beginning of the transplantology-era thanks to the advance in surgical techniques, improved immunosuppression and better preoperative attention, including the prophylaxis of infections. For these reasons patient survival rate is 86.8% at 1 year and 75% at 5 years (Italian average).[8] Many factors are involved on the onset of infections in liver-transplanted patients: complexity of surgical techniques, comorbidities, general pretransplant clinical conditions (*e.g.*, poor nutrition, bleeding), surgical reoperation, acute rejection, hospital admissions before transplantation, intraoperative blood transfusions, use of invasive equipment (*e.g.*, extracorporeal circulation, mechanical ventilation) and long-term vascular devices, high Model for End-stage Liver Disease (MELD) Score, prolonged surgical time, prolonged cold ischemia time, type of immunosuppression, high Body Mass Index (BMI) and several other factors.[3] The most common infections affecting LT patients after the procedure involve the surgical wound, the abdominal cavity, the biliary tract, the lungs and the bloodstream.[3] In previous studies[3] SSIs after LT have been associated with increased mortality, higher readmission rates and higher costs. Recently, the emergence of MDRO raised concerns and increased awareness, leading to changes in management of SSI after LT. Recently, the percentage of SSIs has been used by regulatory centers as a measure of the quality of care and several studies have appeared on the incidence and impact of these infections.[3] Considering our 20-years' experience in the field of LT, our aim was to assess the rate of SSI in LT patients both in the pre- and post-transplant follow-up period. Moreover, we intended to focus the study mainly on MDRO, whose incidence appears to increase in immune deficient settings.[9]

Materials and methods

We performed a retrospective cohort study at the General Surgery and Liver Transplant Centre in a University Hospital (Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy). The study was approved by the ethics committee of the Comitato Etico Milano Area 2 Protocol n.0027112 24 May 2022. All patients undergoing LT from January 1, 2014, to December 31, 2019 have been evaluated. The exclusion criteria were: patients under 18 years of age, Child-Pugh Score (CPS) equal or less than A5, and late retransplants (over 6 months since the first transplant due to prolonged immunosuppressive therapy). The definition criteria of SSI adopted here are similar to those of CDC, in order to better assess the course of SSIs observed in our patients. In agreement with other studies, we also considered late deep infections.[10] We considered 4 timepoints: 1) T0, within 48 hours after LT; 2) T1, within the first month; 3) T31, between 31 and 60 days after transplantation; and 4) T61, from 61 to 90 days post-transplant. The choosing of these time-references was dictated by the need to identify as many risk factors as possible, including those related to the recipient, and those related to surgical intervention and immunosuppressive therapy. On each time point, cultural samples (*e.g.*, wound swabs, exudates, purulent material, biopsy and necrotic tissue)

were collected from the surgical site, assessing the number of bacteria present at those time points and how frequently individual bacteria were present. Only clinically evident infections were considered (wound infections, intraperitoneal abscesses, hepatic abscesses, cholangitis) and not colonization. Follow-up was interrupted 90 days after LT. At every time point, we analyzed the risk factors associated with morbidity (and mortality). Moreover, we considered the incidence of individual bacteria in relation to different risk factors. In our study, the medical history, laboratory results, donor information card (Nord Italia Transplant program [NITp]), operating room documentation and electronic medical records (especially hospital discharge cards) were analyzed by computer application for each of the 4 timepoints. The database includes sex, age, date of patient assignment, date on the list, date of transplant, liver disease, Child-Pugh Score and Model of End-stage Liver Disease (MELD) scores at the time of the transplantation, duration of surgery, duration of hospitalization, Intensive Care Unit (ICU) period days, results of wound culture, type of culture buffer, presence of possible other infections (*e.g.*, respiratory, urinary), moment of onset of infection, possible presence of hepatocarcinoma, type of graft (whole or split), type of donor, donor age, Body Mass Index, CRP test, possible presence of rejection, extracorporeal circulation (if performed or not), type of surgical technique (standard, Belghiti, Piggy-back), vacuum assisted closure therapy (if performed or not), type of transplant (single or combined), surgical reoperation, ischemia cold time, total ischemia time, Roux-en-Y choledochojejunostomy or duct-to-duct anastomosis, type of immunosuppressant discharge drug (FK 506, CyA or other), possible presence of diabetes mellitus at time of discharge, recipient status (alive or dead), cause of death (sepsis), eventual sepsis before LT, creatinine at the time and after 3 days of transplantation, glucose, INR (International Normalized Ratio) and bilirubin at the time of transplantation.

Statistical analysis

Categorical and continuous variables were analyzed with the Chi-squared and the Wilxoxon Rank-Sum (Mann-Whitney) Test. Therefore, the continuous data were compared with *t*-test (Table I). We first evaluated the risk of infections separately at the four time points (T0: just after LT; T1: 1 to 30 days after LT; T31: 31 to 60 days after LT; and T61: 61 to 90 days after LT). Then we analyzed the four periods together by selecting the variables of interest a priori or associated with infection risk at univariate analyses. Given that the outcome (infections) was examined four time, to consider within-patients correlation we fitted multiple random-intercept Poisson regression models with robust variance to calculate risk ratios (RR) and 95% confidence intervals (CI) according to the selected recipient and donor variables.[11, 12] Analyses were performed with Stata 17 (2021; Stata Corp., College Station, TX, USA).

Results

We analyzed 330 consecutive liver transplants on adult recipients (>18 years) from deceased donors performed at the General Surgery and Liver Transplants Centre of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, from 1 January 2014 to 31 December 2019. Patients with CPS≤A5, liver cirrhosis, and late liver re-transplantations (over 6 months after the first transplantation) were excluded, leaving 249 liver transplantations (8 patients underwent an early re-transplantation) to be analyzed. Patient characteristics are summarized in Table II. They included 178 men and 71 women, mostly aged 50 years or more. Post-viral hepatitis was the most frequent reason for LT. Patients with hepatocellular carcinoma (HCC) were almost 40%. Most of the LT were performed using a whole graft. The principal surgical technique for the caval reconstruction was side-to-side anastomosis (Belghiti). As of December 31, 2019, 28 patients were dead, 3 were lost in the follow-up and 218 were alive. Of the 28 deceased patients, 5 died from confirmed sepsis and 6 from probable septic state. SSIs were only 7 (2.8%) within 48 hours after LT, increasing to 61 (24.5%) within the first month after surgery, and then declining to 35 (14.1%) between 31 and 60 days, and to 19 (7.6%) from 61 to 90 days (P<0.001). On

TABLE I.—*Statistical significance of multidrug-resistant germs with respect to continuous risk factors.*

Time	T0			T1		
Infection	No	Yes	P	No	Yes	P
	Mean±SD	Mean±SD		Mean±SD	Mean±SD	
Age patient	53.1±34.6	53.6±9.2	0.960	53.2±34.5	53±12	0.292
Age donor	59±22.6	57±9.9	0.165	59±22.6	58±36.8	0.109
Rec. tot.	29±5.6	22±0.7	0.090	30±5.6	27±23.3	0.183
Rec. uti.	5±1.4	2±1.4	0.254	5±1.4	3.9±0.7	0.079
MELD	18±9.9	17±7.8	0.866	18±9.9	17.5±14.8	0.115
Red blood cells	6±2.8	5±0.7	0.490	6±2.8	6.1±7.1	0.800
Fresh frozen plasma	11±11.3	10±1.4	0.520	11±11.3	11±7.1	0.939
Platelets	0±0.7	0±0.7	0.393	0±0.7	0.3±1.4	0.022
Isch. cold	502.5±49.5	497±26.2	0.179	500±49.5	510.3±217.1	0.298
Isch. tot	551.2±35.3	553±43.8	0.072	551±35.3	552.5±157	0.078
Surg time	492±48.8	480±48.1	0.501	489±48.8	499±187.4	0.103
BMI	25.2±1.9	25±2.6	0.963	25±1.9	24.5±2	0.621
Gluc. olt.	120±32.5	103±11.3	0.334	120±32.5	115.8±9.2	0.481

SD: standard deviation; Rec tot.: days of recovery; rec ICU: days of recovery in Intensive Care Unit; MELD: Model of End-stage Liver Disease; Cold isch.: time of cold ischemia time in minutes; Tot isch.: time of total ischemia in minutes; Surg time: time of surgical operation in minutes; BMI: Body Mass Index; Gluc. olt.: glucose at the time of transplantation.

TABLE II.—*Baseline and clinical characteristics of the cases analyzed in the study.*

Characteristics	N. patients	%
Total	249	100%
Sex		
Male	178	71.5%
Female	71	28.5%
Age (years)	Mean: 53.1; SD=11.4	
<40	32	12.8%
40-49	37	14.9%
50-59	96	38.5%
60+	84	33.7%
Disease		
Urgent	14	5.6%
Alcoholic hepatitis	42	16.9%
Post-viral	132	53.0%
Cholestatic	18	7.2%
Atresia	1	0.4%
Autoimmune	1	0.4%
Budd Chiari	2	0.8%
Metabolic	27	10.8%
Other	12	4.8%
HCC		
No	155	62.3%
Yes	94	37.7%
Child Pugh		
Cp A	35	14.1%
Cp B	86	34.5%
Cp C	102	41.0%
No-Cp	26	10.4%
Graft		
Whole	245	98.4%
Split	4	1.6%
Liver/Kidney	7	2.8%
Retransplantations	11	4.4%
Donor		
Male	143	57.4%
Female	106	42.6%
Age donor (years)	Mean: 59; SD=18	
Mismatch (sex)		
No	86	34.5%
Yes	163	65.5%
Δ Age D/R>10 years		
No	92	36.9%
Yes	157	63.0%
Reinterventions		
No	223	89.6%
Yes	26	10.4%
Roux-en-Y		
No	233	93.6%
Yes	16	6.4%
Immunosuppressive therapy		
Cya	38	15.3%
Other	6	2.4%
Fk 506	205	82.3%
Surgical technique		
Belghiti (LL)	219	87.9%
Standard (TT)	29	11.6%
Piggy-back (TL)	1	0.4%
Donor		
Optimal	66	26.5%
Standard	179	71.9%
Marginal	4	1.6%
Meld score	Mean: 18.0; SD=9.2	
Ischemia time (minutes)		
Cold	Mean: 502; SD=120	
Total	Mean: 551; SD=116	
Surgical time (minutes)	Mean: 491; SD=100	
BMI (kg/m^2)	Mean: 25.2; SD=4.1	
Days of hospitalization		
Total	Mean: 29; SD=21.0	
ICU	Mean: 5; SD=6.5	
Follow-up		
Alive	217	87.1%
Lost	3	1.2%
Dead	29	11.6%

HCC: hepatocarcinoma; MELD: Model of End-stage Liver Disease; BMI: Body Mass Index; ICU: Intensive Care Unit; urgent: hepatic trauma, early retransplantation (primary non function, hepatic artery thrombosis).

(To be continued)

T31		P	T61		P
No	Yes		No	Yes	
Mean±SD	Mean±SD		Mean±SD	Mean±SD	
52.8±34.6	55±0.7	0.835	52.6±34.6	59.4±10.6	
59.3±22.6	57±7.1	0.147	59±22.6	59.3±11.3	0.559
30.1±5.6	23.8±9.2	0.047	29.5±5.6	26.4±2.1	0.490
4.8±1.	3.1±2.8	0.052	4.4±1.4	5.9±2.1	0.066
18.1±9.9	17.4±6.7	0.965	18.0±9.9	17.4±13.4	0.089
6.2±2.8	5.0±1.4	0.295	6.0±2.8	6.3±1.4	0.704
11.5±11.3	9.9±0.7	0.072	11.3±11.3	11.6±4.2	0.913
0.3±0.7	0.3±0.7	0.574	0.3±0.7	0.4±0.7	0.981
504±49.5	492.4±16.3	0.774	501.6±49.5	510.8±96.2	0.568
553.6±35.3	537.5±10.6	0.863	550.3±35.3	563.9±99.7	0.294
495.2±48.8	469.3±36.8	0.351	493.6±48.8	466.7±19.8	0.239
25.3±1.9	24.4±1.56	0.564	25.2±1.9	24.6±2.6	0.522
118.7±32.5	123.2±125.2	0.273	118.5±32.5	129.1±24.7	0.541

the basis of culture samples results, poli-bacterial infection was found at T0 in 6/249 patients (0.4%), at T1 in 12/249 patients (4.8%), at T31 in 7/249 patients (2.8%) and at T61 in 5/249 patients (2.0%); infection with isolation of one bacterium was at T0 in 6/249 patients (2.4%), at T1 in 49/249 patients (19.7%), at T31 in 28/249 patients (11.2%), at T61 in 14/249 patients (5.6%). Similar results are reported in other studies.[3] In our study, the most frequent MDROs found in culture samples were methicillin resistant *Staphylococcus aureus* (MRSA), particularly at T1 (2.8%), Vancomycin-resistant *Enterococcus faecium* (VRE=1.6%) and Carbapenemase-producing *Klebsiella pneumoniae* (KPC=4.0%). Statistical significance in SSIs has been demonstrated in all time points only for the following risk factors: biliary reconstruction on a Roux-en-Y (T0: P<0.001; T1: P<0.001; T31: P=0.001; T61: P=0.007) and reinterventions (T0: P<0.001; T1: P=0.007; T31: P=0.046; T61: P=0.002) (Table III). In the continuous variables, using the *t*-test, it has been shown statistical significance at T1 for the number of platelets transfused during LT (P=0.022); at T31 both for the entire duration of hospital stay related to transplantation (P=0.047) and for the duration of the stay in the Intensive Care Unit (P=0.052) (Table I). On multivariate analysis, it was confirmed the statistical significance of hepaticojejunal reconstruction and re-operations as predisposing factors for the development of infections. Considering infections in the 4 timepoints together, at univariate analyses we found that several variables, except for sex, were positively associated with infection risk, while donor age was negatively associated (the older the donor age, the lower the risk for the recipient as proved by statistical evidence, the causes are unknown). On multivariate analysis, association with recipient age, BMI, donor age, reinterventions, and Roux-en-Y hepaticojejunal reconstruction were confirmed, while the effect of ischemia and surgical time appeared to be attenuated (Table IV).

Discussion

Infections are the primary cause of morbidity and mortality in solid organ transplants. Liver transplants are more prone than other types of solid organ transplants to infections due to both the complex and prolonged surgery and the access to the epatobiliary system.[13] This study describes a retrospective cohort of liver transplant recipients enrolled for 6 years and followed up for 3 months. In this retrospective study we found that the SSIs occurred in 61/249 patients, and the current incidence of SSIs is 24.5% in the first month. According with other study, the first month after LT is confirmed as having the highest incidence of infections.[14] Previous studies performed in other centers reported the incidence of SSI after

TABLE III.—*Number and percentage of patients with SSIs: correlation with multi-resistant germs at different time periods according to selected variables.*

Risk factors	T0			T1			T31			T61		
	N.	%	P	N.	%	P	N.	%	P	N.	%	P
Sex												
Female	3	4.2	0.394	20	28.2	0.395	11	15.5	0.680	4	5.6	0.454
Male	4	2.2		41	23.0		24	13.5		15	8.4	
Age (years)												
<40	2	6.2	0.420	8	25.0	0.892	3	9.4	0.781	2	6.2	0.628
40-49	0	0.0		10	27.0		5	13.5		2	5.4	
50-59	2	2.1		21	21.9		13	13.5		6	6.2	
>60+	3	3.6		22	26.2		14	16.7		9	10.7	
Disease												
Urgent												
No	12	85.7		10	71.4		11	78.6		12	85.7	
Yes	2	14.3	0.008	4	28.6	0.715	3	21.4	0.414	2	14.3	0.334
ETOH												
No	41	97.6		32	76.2		37	88.1		38		
Yes	1	2.38	0.853	10	23.8	0.909	5	11.9	0.660	4	9.5	0.660
Viral hepatitis												
No	130	98.5		104	78.8		117	88.6		123	93.2	
Yes	2	1.5	0.189	28	21.2	0.200	15	11.4	0.194	9	6.8	0.608
Cholestatic												
No	18	100.0		8	44.4		12	66.7		17	94.4	
Yes	0	0.0	0.454	10	55.6	0.001	6	33.3	0.015	4	9.5	0.612
Atresia												
No	0	0.0		0	0.0		1	100.0		1	100.0	
Yes	1	100.0	<0.001	1	100.0	0.079	0	0.0	0.685	0	0.0	0.773
Autoimmune												
No	1	100.0		1	100.0		1	100.0		1	100.0	
Yes	0	0.0	0.865	0	0.0	0.568	0	0.0	0.685	0	0.0	0.773
Budd-Chiari												
No	2	100.0		1	50.0		2	100.0		2	100.0	
Yes	0	0.0	0.809	1	50.0	0.400	0	0.0	0.566	0	0.0	0.683
Metabolic												
No	26	96.3		21	77.8		23	85.2		25	92.6	
Yes	1	3.7	0.766	6	22.2	0.771	4	14.8	0.904	2	7.4	0.963
Other												
No	12	100.0		11	91.7		10	83.3		11	91.7	
Yes	0	0	0.546	1	8.3	0.182	2	16.7	0.790	1	8.3	0.925
HCC												
No	91	96.8		75	79.8		80	85.1		86	91.5	
Yes	3	3.2	0.777	19	20.2	0.221	14	14.9	0.767	8	8.5	0.684
Child-Pugh												
A	1	2.9	0.372	7	20.0	0.493	6	17.1	0.857	2	5.7	0.282
B	1	1.2		21	24.4		10	11.6		8	9.3	
C	3	2.9		29	28.4		15	14.7		5	4.9	
No child-Pugh	2	7.7		4	15.4		4	15.4		4	15.4	
Type of graft												
Whole	7	2.9	0.732	61	24.9	0.251	35	14.3	0.415	19	7.8	0.562
Split	0	0.0		0	0.0		0	0.0		0	0.0	
Sex donor												
Female	4	3.8	0.429	25	23.6	0.773	11	10.4	0.150	6	5.7	0.313
Male	3	2.1		36	25.2		24	16.8		13	9.1	
Mismatch												
No	5	3.1		37	22.7		29	17.8	0.020	4	4.6	
Yes	2	2.3	0.736	24	27.9	0.364	6	7.0	0.020	15	9.2	0.198
Delta age >10 years												
No	2	2.2		26	28.3		14	15.2		7	7.6	
Yes	5	3.2	0.641	35	22.3	0.291	21	13.4	0.687	12	7.6	0.992

(To be continued)

TABLE III.—*Number and percentage of patients with SSIs: correlation with multi-resistant germs at different time periods according to selected variables (continues).*

Risk factors	T0			T1			T31			T61		
	N.	%	P	N.	%	P	N.	%	P	N.	%	P
Reinterventions												
No	2	0.9		49	22.0		28	12.6		13	5.8	
Yes	5	19.2	<0.001	12	46.1	0.007	7	26.9	0.046	6	23.1	0.002
Immunosuppression												
CYA	3	7.9	0.115	14	36.8	0.044	9	23.7	0.171	6	15.8	0.102
FK 506	4	1.9		44	21.5		25	12.2		13	6.3	
Other	0	0.0		3	50.0		1	16.7		0	0.0	
Roux-en-Y												
No	4	1.7		51	21.9		27	11.6		15	6.4	
Yes	3	18.7	<0.001	10	62.5	<0.001	8	50.0	0.001	4	25.0	0.007
Single or combined												
Only liver	7	2.9	0.648	59	24.4	0.799	34	14.0	0.986	19	7.8	0.440
Liver/kidney	0	0.0		2	28.6		1	14.3		0	0.0	
Caval anastomosis												
Belghiti (LL)	7	3.2	0.611	57	26.0	0.039	32	14.6	0.025	17	7.8	0.946
Standard (TT)	0	0.0		3	10.3		2	6.9		2	6.9	
Piggyback (TL)	0	0.0		1	100.0		1	100.0		0	0.0	
Type of donor												
Marginal	0	0.0	0.589	0	0.0	0.451	1	25.0	0.611	0	0.0	0.249
Standard	4	2.2		43	24.0		23	12.8		11	6.1	
Optimal	3	4.5		18	27.3		11	16.7		8	12.1	

Urgent: hepatic trauma, early retransplantation (primary non function, hepatic artery thrombosis).

TABLE IV.—*Risk of infection with multiresistant germs at any time periods according to selected variables; results of univariate and multivariable random-intercept Poisson regression models with robust variance.*

Variables	N.	%	Crude RR	95% CI	Adjusted RR	95% CI
Sex						
Female	38	13.3	1.00	Reference	1.00	Reference
Male	84	11.8	0.88	0.58-1.33	0.82	0.55-1.21
Age (decades)	122		1.12	0.90-1.38	1.17	0.99-1.38
BMI (kg/m^3)	122		1.05	1.00-1.09	1.04	0.99-1.08
Donor age (decades)	122		0.91	0.82-1.02	0.88	0.78-0.98
Ischemia (hours)	122		1.11	1.00-1.22	1.05	0.96-1.16
Surgical time (hours)	122		1.18	1.07-1.31	1.03	0.87-1.21
Cholestatic forms						
No	105	11.4	1.00	Reference	1.00	Reference
Yes	17	23.6	2.08	1.26-3.42	1.53	0.79-3.01
Reinterventions						
No	92	10.3	1.00	Reference	1.00	Reference
Yes	30	28.8	2.80	1.77-4.42	2.02	1.21-3.38
Roux-en-Y						
No	97	10.4	1.00	Reference	1.00	Reference
Yes	25	39.1	3.75	2.45-5.76	2.75	1.47-5.15

RR: Risk Ratio; CI: confidence interval.

LT as being between 8 and 37%.[3, 5, 6] As it was done in other studies, we also prolonged the observation to 90 days after LT to capture late onset infections.[3] Our study also included the analysis of the bacteria most commonly isolated, and their correlation with risk factors. Among the Gram-positive bacteria, the most frequent is *Staphylococcus aureus*, both in T0 (0,4%), T1 (8,8%), and T31 (6,4%). Also, *Enterococcus faecium* has been frequent in T1 (1,6%). In another study,[15-19] percentages of the isolated bacteria are higher for MRSA. In this study, the most frequent Gram-negative germ was KPC in T1 (4,0%), as in other studies.[17, 20] However, an effective comparison

with other research is difficult to perform due to a different count of isolates species, different site of infections (not only SSIs) and different time frames. Risk factors for SSIs after LT are more related to surgical conditions arising from transplantation than to risk factors at the time before the transplant. A variable proportion of patients in the 4 timepoints considered have been infected with multisensible bacteria. Statistical significance has been demonstrated in all 4 time points only for the following risk factors: biliary reconstruction on a Roux-en-Y[21] and abdominal reinterventions.[14, 22-39] Choledoco-jejunal anastomosis, which is mainly used in cholestatic diseases, is particularly associated with a higher risk of bacterial infections and candidiasis than choledoco-choledoco anastomosis. This type of biliary anastomosis can cause bacterial and fungal upward migration and recurrent cholangitis. This risk factor has been observed in other studies.[10, 40-44] Surgical interventions on the jejunum increase bacterial contamination with increased infectious risk.[10] Antifungal prophylaxis is not recommended for patients at low risk due to possible toxicity and can select resistant strains;[7, 45] on the contrary, prolonged antibiotic prophylaxis (>2 days) is recommended in cases where choledoco-jejuanal anastomosis is performed.[10] Both one event and the other lead to possible contamination of the surgical field, the first for the possible spread of germs from the intestinal lumen during surgical maneuvers, the second for the long-term exposure of the surgical field to possible environmental contaminants. In our case the reinterventions were: retransplantation, laparotomy with abdominal cavity toilet, wound revision, vascular suture repackaging, wall synthesis, hepatic artery thrombectomy hepatic artery thrombectomy in order to prevent hepatic abscesses formation,[46] drainage of abdominal collections, distal splenopancreasectomy, ileal resection. Only abdominal reinterventions were considered. Both elective and emergency procedures and major and minor procedures are included in this category. In addition, reinterventions are also carried out for infectious conditions already present that may also locally spread or at a systemic level (sepsis) due to the immunosuppressive therapy used after transplantation. Immunosuppressive agents not only increase infections but also mask the inflammatory response, making an early detection more challenging.[47] In our center, the antimicrobial prophylaxis is carried out with cephalosporins of first generation (cefazolin 2 grams intraoperative at the time of the skin incision; re-dosing if the procedure lasts more than 8 hours). In our department is proven to be effective in preventing multi-sensitive germ infections. In our unit, to prevent SSIs, a bacterial screening is carried out both in the donor and in the recipient prior to transplantation; however, laboratory limitations often prevent the availability of complete information at the time of the transplant. Infections caused by MDRO require specific pharmacological treatment, calibrated on the antimicrobial susceptibility testing and on the clinical condition of patients and organ function (*e.g.*, kidney failure). Excessive use of antibiotics may select more resistant organisms which may cause infection in the recipient; therefore, it is important to reduce the duration of therapy to a minimum, especially when empirical therapy is used in the absence of clinical symptoms or when microbiological evidence documenting the presence of the infection is lacking.[48] In this study has been observed that patients on antibiotic therapy have a worse prognosis. This may be partially since patients on antibiotic therapy are in worse clinical conditions, but it should also be considered that antibiotic therapy creates resistance. Patients which underwent a vacuum-assisted closure therapy also have a worse prognosis: this therapeutic remedy is used where traditional medications, associated or not associated with systemic antibiotic therapy, are not effective in controlling superficial, but often deep infections. Such method has an impact on the length of hospitalization. It is our belief that it is not possible to standardize the therapeutic and preventive strategy of MDRO infections in LT. The identification of risk factors could help to minimize their development. Risk factors assessment is an important step for early detection of infections.[49]

Conclusions

Although the increasingly advanced therapies used in the fight against infections have reduced

the number of deaths, SSIs are still a challenging problem to solve, because antibiotics, although in most cases represent valuable therapeutic tools, can sometimes lead to the emergence of MDRO. It will be crucial to evaluate novel therapeutic strategies and to improve surgical techniques by seeking to minimize the number of reinterventions which, as it has been amply demonstrated in this study, they are the main cause of SSIs. Another parameter to be considered is the Roux-en-Y reconstruction which also plays an important role as a triggering factor for the development of infections: in these cases, it is necessary to assess precautionary strategies to prevent their development. Further studies and evaluations will be necessary before an effective and generalizable strategy can be defined, partly due to the extreme variability of patient characteristics and risk factors.

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