

Impact of pre-transplant infection management on the outcome of living-donor liver transplantation in Egypt

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Background and aim: Liver transplantation (LT) has emerged as an established therapeutic option for patients with chronic liver disease. Patients with end-stage liver disease are at high risk of infection with multidrug-resistant organisms, which may affect the outcome of LT. The aim of this study was to evaluate the impact of pre-transplant infection on the outcome of living-donor LT.

Methods: Prospective follow-up was done for 50 patients with chronic liver disease who had had LT performed from September 2013 to December 2017. We divided patients into group 1 (patients who had had infection within 3 months before transplantation with adequate treatment [n=20]), and group 2 (patients without infection [n=30]). Both groups were followed for 4 months post-operatively.

Results: Patients with high Model for End-Stage Liver Disease scores were more susceptible to infection pre- and post-operatively, and chest infection was the most common infection pre-transplant. There were no significant statistical differences regarding hospital and ICU stay and post-operative course between the groups, but the mortality rate was higher in group 1 (40%) than in group 2 (23.3%), and the causes of mortality in the group 1 were mainly due to medical causes (infections and sepsis, 75%) versus 28.6% in group 2.

Conclusion: Liver-cell failure and concomitant infection 3 months before LT with adequate treatment had no significant statistical differences regarding hospital, ICU stay, or medical complications, but post-operative infection and mortality rate were more frequent in group 1 and the causes of mortality were mainly medical.

Keywords: hepatitis C virus, cirrhosis, steatosis, chronic liver disease, liver transplantation, outcome

Introduction

Liver transplantation (LT) is considered as an established therapeutic option for patients with acute and chronic liver failure and hepatocellular carcinoma.¹ It evolved as a highly effective approach to treat many end-stage liver disease (ESLD) cases that had had no treatment before LT.² Patients with liver cirrhosis are more susceptible to infections, due to alterations in gut microbiota, intestinal barrier dysfunction, genetic predisposition, and immunodysfunction.³ Being immunocompromised, they are predisposed to develop bacterial infections and sepsis, due to endothelial alterations, leukocyte dysfunction, bacterial translocation, and iatrogenic factors.⁴ Patients with severe ESLD and a high Model for End-Stage Liver Disease (MELD) score are at increased risk of infections in the period before

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and after LT.⁵ Infection could be with multidrug-resistant microorganisms, which can have an adverse impact on outcomes after LT.⁶ Also, acute-on-chronic liver failure may develop as sequela of a superimposed bacterial infection or sepsis.⁷ Egypt has an increasing number of patients with chronic LDs and LDs, due to the high prevalence of hepatitis C virus among the population, with an increasing need for LT.^{8–14} In our study, we aimed to assess the impact of the presence of pre-transplant infections and treatment on the outcome of living-donor LT (LDLT).

Methods

This study was based on a prospective follow-up that was performed for 50 patients with chronic liver-cell failure who had had LT performed between September 2013 and December 2017 at a major tertiary-care hospital. The study was conducted in accordance with the Declaration of Helsinki. Patients were categorized to two groups: group 1, which comprised patients who had had infection within 3 months before LT with adequate treatment, and group 2, which comprised only patients who did not show any evidence of infection before transplantation. A pre-transplant infection was any infection that occurred within 3 months prior to LT, and was diagnosed by clinical, laboratory (eg, blood, ascites, sputum, stool, urine, and swabs), and/or imaging (eg, chest X-ray, ultrasonography, and computed tomography) findings. The commonest pre-transplant infections were chest infections, spontaneous bacterial peritonitis (SBP), urinary tract infections (UTIs), nasal infections, bacteremia, skin and soft-tissue infections, meningitis, and gastroenteritis.

Patients who had one of high or suboptimal temperature, tachycardia (heart rate >100 beats/minute), tachypnea (respiratory rate >20 breaths/minute), leukocytosis (white blood cells $>11,000/\text{mm}^3$) or leukopenia (white blood cells $<4,000/\text{mm}^3$) had pan-cultures and sensitivity (urine, stool, ascites, nasal swab, blood, sputum) performed. Chest infection was considered by the presence of progressive opacity on chest X-ray with fever, leukocytosis, purulent sputum, newly developed or worsening cough, tachypnea, tachycardia, crepitations detected at auscultation, and/or arterial oxygen desaturation. UTI was defined as the presence of dysuria, frequency and/or urgency, and pyuria. SBP was defined as the presence of ascitic polymorphonuclear neutrophilic count >250 cells/ mm^3 , regardless of culture results. Skin and soft-tissue infections, including cellulitis and necrotizing fasciitis, were defined as

erythema and hotness or pus collection in the affected skin. Nasal infection was defined as hyperemic mucosa of the nostril with positive swab culture, including fungal and bacterial infections. Bacteremia was defined as positive blood culture with or without primary source of infection.

All patients with diagnosed bacterial or fungal infections started antibiotic or antifungal treatment that was then adjusted based on culture and sensitivity results. A pre-transplant bacterial infection was considered adequately treated and the patient regarded as a candidate for LT when manifestations of infection had disappeared, with normalization or improvement of laboratory and/or imaging findings that had previously indicated bacterial infection, as well as achieving negative culture and sensitivity tests at least 2 weeks before operation.

Most patients were admitted at two days pre-transplantation. Postoperatively, they were admitted to the ICU for 5 days till stabilization, transferred to the ward for 1–2 weeks, then discharged for outpatient follow-up. Follow up was performed weekly for the first 3 months to detect any complications, such as infections, renal impairment, immunosuppressant side effects, graft dysfunction, biliary stricture, and neurological abnormalities. Follow-up of patients include history-taking, general examination, and laboratory investigations, including complete blood count, complete liver profile, renal function, and trough levels of immunosuppressants. As for prophylaxis for postoperative bacterial and fungal infections, a combination of imipenem, metronidazole, trimethoprim–sulfamethoxazole and fluconazole was started immediately before operation and continued for 1 week postoperatively.

The immunosuppressive regimen consisted of long-term therapy with tacrolimus (Tac; the dose was modified according to the patient's trough serum level) and steroids that were gradually withdrawn and ended by the end of the third postoperative month. Tac was replaced by cyclosporin A in patients with adverse effects from Tac. Patients were followed for 4 months post-operatively to compare outcomes between the two groups. We compared patients according to their hospital and ICU stays, post-operative complications, including both medical (infection, sepsis, renal impairment, DIC, chest complications, cardiac complications, neurological complications), and surgical complications (hemorrhage, biliary complications, intra-abdominal collections, excisional hernia), percentage of mortalities, and causes of death.

Data were collected, coded, translated to English to facilitate data manipulation, double-entered into Microsoft Access, and analysis performed using SPSS 18 with Windows 7. Simple descriptive analysis is in the form of numbers and percentages for qualitative data, arithmetic means as central tendency measurement, SD as measure of dispersion for quantitative parametric data, and inferential statistical tests. For quantitative parametric data, we used paired *t*-tests in comparing two dependent quantitative data. As for qualitative data, χ^2 was used to compare two or more variables. Bivariate correlations were used to test associations between variables. $P \leq 0.05$ was considered the cutoff value for significance.

Results

Fifty patients received adult-to-adult LDLT during the study (42 men and eight women). Their median age was 47.1 (18–65) years. Patients were categorized as those with pre-transplant infection (group 1, $n=20$) and those without pre-transplant infection (group 2, $n=30$). Demographic, laboratory and clinical features were comparable between the groups. Chronic LD due to hepatitis C virus was the most commonly encountered indication for transplantation (Table 1). All cases were right-lobe grafts. A total of 29 pre-transplant-infection episodes were found in the 20 LDLT recipients. Among these patients, nine (45%) experienced one episode of pre-transplant infection, while eleven patients experienced two or more episodes. Pre-transplant-infection entities were chest infection ($n=10$), nasal mucosal infection ($n=8$), UTI ($n=6$), SBP ($n=4$), and gastroenteritis ($n=1$). All patients with pre-transplant infection received effective antibiotic therapy and were considered eligible for LT from 2 weeks after cure from infection (Table 2).

Concerning outcomes after LT, no significant difference was found in length of hospital or ICU stay, and both groups had comparable post-operative courses regarding medical complications (35% for group 1 versus 30% for group 2). These included rejection and post-transplant-infection rates. Higher MELD score in group 1 than group 2 was the only causative factor potentially contributing to the development of postoperative complications and infections. There was one case of poor graft function related to “small-for-size syndrome”. There were severe biliary complications in ten cases: four developed biliary leak and anastomotic stricture, four biliary stricture and biliary leak, three biliary leak, and

Table 1 Demographic, clinical, and laboratory features of the studied group

	Mean	Normal range	SD
Age	47.1		± 9.7
MELD score	16.2		± 3.9
INR	1.5	(1–1.2)	± 0.37
TLC (cells/mm ³)	4.8×10^3	(4–11)	± 2.12
CRP (mg/L)	10.25	(0–6)	± 11.38
Albumin (g/dL)	2.66	(3.5–5.5)	± 0.66
Creatinine (mg/dL)	0.93	(0.6–1.2)	± 0.35
Bilirubin (mg/dL)	3.7	(0.3–1)	± 2.8
ESR (mm/h)	38.8	(0–15)	± 25.8
	n		%
Sex			
Male	42		84
Female	8		16
Child–Pugh score			
A	6		12
B	14		28
C	30		60
Indication for LT			
HCV-CLD	40		80
HBV-CLD	2		4
AIH-CLD	4		8
Cryptogenic CLD	4		8
Patients who had HCC	13		26

Abbreviations: MELD, Model for End-Stage Liver Disease; INR, international normalized ratio; TLC, total lymphocyte count; ESR, erythrocyte-sedimentation rate; LT, liver transplantation; HCV, hepatitis C virus; CLD, chronic liver disease; AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma.

one epigastric biloma. The mortality rate was higher in group 1 (eight patients, 40%) than in group 2 (seven patients, 23.3%), and causes of mortality in group 1 were mainly medical (mainly infections and sepsis) in six (75%) versus two patients (28.6%) in group 2 ($P=0.03$). However, these results did not show statistically significant differences (Table 3). Finally, eleven post-transplant-infection episodes occurred in eight patients (six [30%] in group 1 and two [6.6%] in group 2, $P=0.027$). These episodes and pathogens are detailed in Table 4. Intra-abdominal infections were the most frequently encountered post-transplant infection, of which *Enterococcus* spp. were the leading pathogens.

Discussion

We observed 29 pre-transplant-infection episodes that developed in 20 patients (40%) of the total patients studied. Also,

Table 2 Descriptive analysis of episodes of pre-transplant infection (n=29) found in 20 living-donor liver-transplant recipients

	n	%
Infection		
Present	20	40
Absent	30	60
Type of infections		
Chest	3	15
UTI	3	15
Nasal	3	15
Chest and nasal	3	15
Chest and UTI	2	10
SBP	2	10
Chest, nasal, and SBP	1	5
Chest and SBP	1	5
UTI and nasal	1	5
Gastroenteritis	1	5
Frequency of infection by site		
Chest	10	50
Nasal	8	40
UTI	6	30
SBP	4	20
Gastroenteritis	1	5
Time of last infection prior to operation		
Less than 1 month	2	10
1–2 months	14	70
2–3 months	4	20

Abbreviations: UTI, urinary tract infection; SBP, spontaneous bacterial peritonitis.

we observed that patients with higher MELD scores (17.2) were those who mostly developed infection in the pre-transplantation period. This was similarly to Sun et al¹⁵ and Reddy et al,⁵ who mentioned that high MELD score and severe ESLD were associated with increasing susceptibility to infections before and after LT.

Chest infection was the most common pre-transplant infection, followed by nasal infection, UTI, SBP, and lastly gastroenteritis. According to Fernandez et al, the most common infections in cirrhotic patients are SBP (25%), UTI (20%), pneumonia (15%), bacteremia following a therapeutic procedure, cellulitis, and spontaneous bacteremia.¹⁶ In 2014, Thévenot et al reported that chest infection was the most common infection in cirrhotic patients, followed by UTI.¹⁷ However, these results disagreed with Garcia-Tsao, who reported that SBP was the most common infection to occur in pre-transplant patients.¹⁸ Also, they disagreed with Lin et al, who found that UTI was the most common infection to occur

in their study of 54 pre-transplant patients.¹⁹ We found that SBP prevalence in our ascitic patients was 18%. This coincided with Garcia-Tsao, who noted that SBP in hospitalized cirrhotic patients with ascites was 10%–30%. Postoperatively, we found that patients in group 1 were more susceptible to infection (30%) than group 2 (6.6%).¹⁸ The most common types of infection were intra-abdominal infection, chest infection, bloodstream infection, nasal infection, necrotizing fasciitis, and maxillary sinusitis.

Patients with liver-cell failure and concomitant infections within 3 months before LT and who received adequate treatment showed no significant statistical differences regarding hospital or ICU stay and had a comparable post-operative course regarding medical complications (35% for group 1 versus 30% for group 2). Patients were followed for 4 months post-operatively to compare outcomes between the groups. Patients with ESLD are predisposed to infection with multidrug-resistant microorganisms that can have an adverse impact on outcome after LT.⁶ Lin et al¹⁹ suggested that adequately treated pre-transplant infections do not significantly affect clinical outcomes, including post-transplant fatality in recipients in adult-to-adult LDLT, and there was no significant difference found in length of post-transplant ICU stay, 1-year survival, graft rejection, or post-transplant-infection rates between the groups.

Our recorded mortality rates were higher in group 1 (eight patients, 40%) than group 2 (seven patients, 23.3%), and the causes of mortality in group 1 were mainly medical in six patients (75%) versus two (28.6%) in group 2, but these results were of no statistical significance. Regarding mortality due to sepsis, this was more frequent in group 1 (62.5%) than group 2 (42.8%). Bertuzzo et al²⁰ reported that bacterial infection 1 month before LT was related to a higher rate of infection after transplantation, but did not lead to a worse outcome. Also, Hara et al²¹ reported that 20 patients who underwent LDLT with an infection 1 month before transplant had a lower 1-year post-transplant survival rate than patients without infection (65% versus 86%, respectively).

The main limitation of this study was the small sample and limited follow-up. Studies on larger populations with more prolonged follow-up are needed to support or refute the results of this study.

In conclusion, liver-cell failure and concomitant infection 3 months before LT with adequate treatment showed no significant statistical differences regarding hospital/ICU stay or medical complications. However; postoperative

Table 3 Post-operative course of both groups

	Group 1 (n=20)		Group 2 (n=30)		P-value
	n	%	n	%	
Hospital stay (days)	19.6±6.1		23±10.1		0.185
ICU stay (days)	8.2±5.6		7.1±3.3		0.403
Complications					
• Yes	11	55.0	19	63.3	0.349
• No	9	45.0	11	36.7	
Surgical complications					
• Yes	3	15.0	9	33.3	0.720
• No	17	85.0	23	66.7	
Medical complications					
• Yes	8	35	10	30	0.902
• No	13	65	20	60	
Infection	6	30	2	6.6	0.027
Mortality	8	40	7	23.3	0.208
Mortality causes					
• Medical	6	75	2	28.6	0.132
• Surgical	2	25	5	71.4	

Notes: Group 1: patients with treated infections. Group 2: patients without infection.

Table 4 Episodes of post-transplant infection (n=11) found in eight living-donor liver-transplant recipients

Infection category	Organisms	Episodes
Chest infection	<ul style="list-style-type: none"> • <i>Escherichia coli</i> and streptococci • <i>Acinetobacter</i> and <i>Klebsiella pneumoniae</i> 	16.6% (2/12)
Bloodstream infections	<ul style="list-style-type: none"> • <i>E. coli</i> • Enterococci 	16.6% (2/12)
Intra-abdominal infections	<ul style="list-style-type: none"> • Enterococci • <i>Staphylococcus aureus</i> and Gram-negative bacilli, ESBL strain • <i>E. coli</i> — enterococcus 	25% (3/12)
Nasal infection	• <i>Streptococcus saprophyticus</i>	8.3% (1/12)
Necrotizing fasciitis	• <i>Streptococcus</i> and <i>Staphylococcus aureus</i>	8.3% (1/12)
Maxillary sinusitis	• <i>Streptococcus aureus</i> pneumonia	8.3% (1/12)
Wound infection	• <i>E. coli</i>	8.3% (1/12)

infection and mortality rates were more frequent in this special category of patients.

Ethics and consent

Participants provided written informed consent, and the study was approved by the Tanta University Faculty of Medicine Research Ethical Committee.

Disclosure

The authors report no conflicts of interest in this work.

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