ORIGINAL ARTICLE

Evaluation of Clinical Characteristics and Outcomes of Postoperative Infections in Living Liver Donors

Running title: Infections in living liver donors

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ABSTRACT

Aim: To analyze developing infections after living donor hepatectomy (LDH) in living liver donors (LLDs).

Methods: Demographic and clinical charecteristics of 1106 LLDs were retrospectively analysed in terms of whether postoperative infection development. Therefore, LLDs were divided into two group: with (n=190) and without (n=916) antimicrobial agent use.

Results: The median age was 29.5 (min-max: 18-55). A total of 257 (23.2%) infection attacks (min-max: 1-8) was developed in 190 (17.2%) LLDs. The patients with infection that were longer intensive care unit (ICU) and hospital stays, higher hospital admissions, emergency transplantation, invasive procedures for ERCP, PTC biloma and abscess drainage, and the presences of relaparatomies and transcystic catheters. Infection attacks derived from a 58.3% hepatobiliary system, 13.2% urinary system, 6.6% surgical site and 5.8% respiratory system. The most common onset symptoms were fever, abdominal pain, nausea and vomiting. A total of 125 positive results was detected from 77 patients with culture positivity. The most detected microorganisms from the cultures taken are Extended-Spectrum β-lactamases (*ESBL)* producing *Klebsiella pneumonia* (16.8%) and *Escherichia coli* (16%), Methicillin-Resistant *Staphylococcus aureus* [(*MRSA)* (9.6%)], Methicillin-susceptible *Staphylococcus aureus* [(*MSSA* (9.6%)] and *Pseudomonas aeruginosae* (8.8%), respectively. The average number of ICU hospitalization days was 3±2 (min 1-max 30, IQR:1) and hospitalization days was 14±12 (min 3-max 138, IQR: 8). All infection attacks were successfully treated. No patients died due to infection or another surgical complication.

Conclusion: Infections commonly observed infected biloma, cholangitis and abscess arising from the biliary system and other nosocomial infections are the feared complications in LLDs. These infections should be managed multidisciplinary without delay and carefully.

Keywords; living donor liver transplantation, living donor hepatectomy, infections in donors, antimicrobial therapy for infections in living liver donors.

INTRODUCTION

Living donor liver transplantation (LDLT) has increased dramatically in recent years as an alternative due to the growing need for liver transplantation (LT) and a shortage of available cadaveric donor organs. Therefore, LDLT has become a viable and tolerable option over the years due to its acceptable results (1). The most important advantages of living liver donors (LLDs) when compared with cadaveric donors shows that the transplant process can be performed in the early stages of liver diseases. The biggest concern about LDLT especially in western contries is the donor safety. The most important principle that should not be compromised in donor hepatectomy is never to risk the donor (2).

Potential living liver donor (LLD) candidates should be carefully evaluated in details in terms of possible intraoperative and postoperative complications (3). The risks associated with living donor hepatectomy (LDH) include both short- and long-term health risks from the surgical procedure, infections, organ dysfunction and psychological problems. Most common surgical complication after LDH are infections, hernia, bleeding, blood clots, wound complications and, in rare cases, mortality. Despite the standardized surgical techniques even where there is a high volume transplantation centers, biliary complications and infections that follows LDH has been reported to be the major cause of morbidity after LDLT. Morbidity after LDH is estimated to be high with the rates ranging between 0-67% (4). The most common complication in the early postoperative period is atelectasis, followed by an intra-abdominal collection (3.6%) requiring drainage, pulmonary embolism (1.8%), bile leakage (1.8%) and secondary infections, respectively (5). Biliary, pulmonary, and infectious problems are predictable complications with more serious issues and donor death being very rare (6).

Most of the infections primarily originated from the hepatobiliary system, and the most common sites of other infection sources are described in the literature of surgical site, pulmonary and urinary tract (7). Unfortunately, the existing data are still very limited to a better understanding of the clinical characteristics and outcomes of the developing infections in LLDs (8). Although the number of LDLT increases day by day in our country, however, the studies that included a single-centered and a large number of patients involving the risk factors and clinical outcomes of infections in LLDs have not been reported yet (9). In the current study, we aimed to analyze the risk factors, microbiological culture results, antimicrobial treatment modalities and the outcomes in LLDs who were followed-up in our medical center due to the developing infections after the surgery.

MATERIAL AND METHODS

Study design

Demographic and clinical characteristics of 1106 LLDs candidate who underwent LDH for LDLT between October 2015 and October 2020 were prospectively collected and retrospectively analysied. These patients' data, including demographic characteristics, onset symptoms, results of the biochemical and microbiological tests and radiological imaging, the treatments received and their outcomes, were collected from the daily Infectious Diseases consultation records, nurse treatment observation forms and pharmacy drug outputs were also collected. This study was obtained from the Inonu University Non-Interventional Ethics Committee (Approval No: 2020/668).

Surgical Procedure

LLD candidates meeting the preoperative donor evaluation criteria were intubated using the standardized anaesthesia technique. Laparotomy was performed using a midline incision from xyphoid to 1 cm above the umbilicus and transverse incision extending from the umbilicus to the right flank region (reverse L incision). Firstly, hepatoduodenal ligament dissection was performed and portal vein (right or left), hepatic artery (right or left) and bile duct junction were exposed. Then cholangiography was performed through the cystic duct to see the entire biliary tree anatomy. Vascular and biliary structures were divided according to which lobe of the liver was to be removed, and remnant stumps were sutured. The liver graft obtained was delivered to the recipient' team to be implanted in the recipient. Cholangiography was performed again to see the structure of the remnant biliary structure. A drain was placed in the hepatectomy lodge to drain the surgical area. All LLDs were followed up in the ICU for a few days in the postoperative period (10).

Definitions

The definition of infections were based on the criteria of the Centers for Disease Control and Prevention (CDC). Clinical suspicion of infection was considered when one or more of the following were present: clinical symptoms (such as fever, jaundice, abdominal pain, nausea, vomiting, dysuria, pollakiuria, cough, and hypoxemia), leucocytosis, neutrophilia, elevate in C-reactive protein (CRP) and procalcitonin (PCT), relevant radiological findings and at least one positive culture from any body fluid. Infections were classified according to the anatomic site (e.g, respiratory, hepatobiliary, surgical site and urinary tract) (11).

Postoperative follow-up: Microbiology, Laboratory and Radiological Studies

Following the operation, all LLDs were taken to ICU, donors without indication were quickly extubated within the first day, and oral nutrition was switched, central venous and urinary catheters were removed. Blood and urine cultures of all LLDs were routinely taken as soon as they were admitted to ICU. LLDs with no suspicion and/or signs of infection were administered with 1 g intravenous ampicillin/sulbactam therapy every four hours within 24 hours for prophylaxis (12). Sputum, abscess, drain (within 24 hours), wound cultures was studied with gram staining, if there were clinical findings suggesting pneumonia, bile leakage, biloma and purulent drainage from the surgical site. Patients who did not indicate the reason for ICU were quickly taken into the clinics.

Bacteriological studies

Blood culture samples were collected and incubated in the BACT / ALERT 3D (BioMérieux, France) automated blood culture system. Positive blood culture and other samples were cultured on 5% sheep blood agar, Eosin Methylene Blue (EMB) agar and chocolate agar they were incubated for 18-24 hours at 35-37°C temperature. Breeding bacterial colonies were selected and identified with classic bacteriological analyses. General characteristics of the bacterial colonies that purely grew after incubation were determined by colony morphology, Gram staining, and catalase test. Also, the bacterial colonies were identified by "Matrix-Assisted Laser Desorption/Ionization time of flight, Mass Spectrometry" (MALDI-TOF MS) (BioMerieux, France). *In vitro* antimicrobial susceptibility tests were determined by Kirby-Bauer disc diffusion and gradient diffusion method. The antimicrobial susceptibility test was evaluated based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. *Staphylococcus aureus* ATCC 29213 and *Escherichia coli* ATCC 25922 strains were used as a standard (13).

Blood and Serum Parameters

Complete Blood Count (CBC; haemoglobin, total white blood cells (WBC), and the counts of neutrophils, lymphocytes, and platelets), coagulation parameters (INR) and serum biochemistry (creatinine, albumin, liver enzymes, total bilirubin and direct bilirubin) were measured daily, CRP and PCT were measured weekly twice routinely.

Statistical Analysis

The data collected were given as a median, minimum, maximum, interquartile range (IQR), and count (percentages). Normal distribution was checked with the Kolmogorov-Smirnov test. Quantitative data were analyzed with Mann-Whitney U test. Qualitative data were analyzed with the Pearson Chi-Square Test, Yates corrected Chi-Square Test, and Fisher Exact test where appropriate. IBM SPSS Statistics 25.0 program was used for other analysis and $p < 0.05$ was considered statistically significant.

RESULTS

The median age of 1106 LLDs was 29.5 (min-max= 18-55, IQR= 11.3). Four hundred twenty-eight (38.7%) patients were female, 678 (61.3%) patients were male. The mean BMI was 24.1 ± 3.5 (min-max=14.4-37.1, IQR= 4.73). Eighty-six (7.78%) LDHs were performed in emergency conditions, 1020 (92.22%) LDHs were performed in elective conditions. Left liver lobe from 90 (8.2%) LLDs, left lateral segment from 185 (16.7%) and right lobe 831 (75.1%) were removed. Nine hundred forty-seven (85.6%) of the LLDs were relatives of various degrees with the recipient, while 159 (14.4%) were altruistic donors. The average number of ICU hospitalization days of LLDs was 3±2 (min-max=1-30, IQR=1) and the average number of hospital hospitalization days was 14±1 (min-max= 3-138, IQR= 8).

The patients with infection; It was found statistically significant that there were patients with longer intensive care unit (ICU) and hospital stays, higher hospital admissions, emergency transplantation, invasive procedures for ERCP, PTC biloma and abscess drainage, and the presences of relaparatomies and transcystic catheters ($p < 0.05$). Donor age, gender, body mass index (BMI), blood groups, type of graft received, and the degree of relatives of the LLDs to the recipient was not statistically significant ($p > 0.05$). All infection attacks were successfully treated, and none of LLDs died due to infection or other complications. These factors in LLDs are summarized in Table 1.

A total of 257 infection attacks (min-max=1-8) developed in 190 (17.2%) LLDs. Infection attacks in the order of frequency of the systems; 58.3% derived from the hepatobiliary system (cholangitis, intraabdominal abscess, infected biloma and pancreatitis), 13.2% from the urinary system (cystitis, pyelonephritis and urosepsis), 6.6% from the surgical site, and 5.8% from the respiratory system. The mean antimicrobial therapy time was calculated as 9.1±11.3 days (min-max=1- 89, IQR: 7) for the treatment of infection attacks. One hundred ninety-five (75.9%) attacks were treated with monotherapy, 46 (17.9) attacks with two antimicrobials, and 16 (6.2%) attacks with three antimicrobial agents. The distribution of attacks according to the sites of infection and antimicrobial treatment preferences are summarized in Table 2.

In the treatment of infection attacks with monotherapy, piperacillin / tazobactam in 69 (26.8%) attacks (min-max=5-24, median=8.3 days), 54 (21.0%) attacks ertapenem (min-max=5-12, median= 7.7 days), and 30 (11.7 %), meropenem (min-max=6-17, median= 10 days) was preferred. The mean treatment durations for two or three antimicrobial drug combinations were longer (10.5% and 12.8% respectively). Antimicrobial preferences and treatment durations for infection attacks are summarized in Table 3.

One hundred ninety LLDs who had clinical findings such as fever, abdominal pain, nausea and vomiting, dysuria, pollakiuria, cough and sputum production, and increased WBC, CRP and PCT values were initiated on antimicrobial therapy due to infection. The most common reasons for the initiation of antimicrobial therapy were the presence of symptoms such as fever, abdominal pain, nausea and vomiting accompanied by elevated CRP and PCT. A total of 125 positive results were detected from blood, urine, abscess, drain, sputum and catheter cultures sent on different dates from 77 LLDs with culture positivity. In LLDs with no culture positive, the decision of the cessation antimicrobial therapy was decided according to laboratory parameters, radiological and clinical findings. The most detected microorganisms growing in taken cultures as *ESBL-producing K. pneumonia* (16.8%), *ESBL-producing E. coli* (16%), *MRSA* (9.6%), *MSSA* (9.6%) and *P. aeruginosae* (8.8%), respectively. Microorganisms growing in the cultures were indicated and they are summarized in Table 4.

The daily hemogram and biochemical parameters of all LLDs, CRP and PCT values were measured twice a week with or without signs of infection. Changes in the course of WBC, CRP and PCT values of LLDs with infection attacks were statistically significant compared to LLDs without infection ($p < 0.05$). The course of laboratory parameters of all LLDs are summarized in Table 5.

DISCUSSION

This is the first clinical research study that included single-center and wide-scale LLDs, which evaluates for the development of infections following LDH. Our current study emphasizes that the patients with infection that there were longer intensive care unit (ICU) and hospital stays, higher hospital admissions, emergency transplantation, invasive procedures for ERCP, PTC biloma and abscess drainage, and the presences of relaparatomies and transcystic catheters. The majority of infection attacks originate from the hepatobiliary system. The most grown microorganisms in cultures are generally Multidrug-Resistant (MDR) and gram-negative microorganisms known as nosocomial microorganism. Before the initiation of antimicrobial therapy, relevant cultures must be taken. Combined antimicrobial therapy is not mandatory for the treatment of infection attacks, but with monotherapy, it could be treated successfully. As a result of the timely initiation of an effective antimicrobial treatment accompanied by invasive radiological interventions when necessary, the chances of success were greatly increased.

Biliary complications constitute the majority cause for morbidity following the LDH (14). Even with standardization of surgical technique in high-volume centres, the reported incidence of biliary complications after living liver donation ranges from 1.9% to 14.3% (15). Although there are many studies involving biliary complications that were developed in long-term follow-up of LLDs after donor hepatectomy operation, a large-scale and single-center study that examines the infections in detail has not been reported yet (16). In the current study, we analyzed all aspects of LLD infections, all of which were operated in one center and then followed up.

Since the right lobe LDH is a major procedure and it carries a high morbidity risk, LLDs should be healthy to reduce the risk of complications (17). In our study, 75.1% of LLDs had their right lobe harvested, and we found that this process was not a factor that increased the risk of biliary complications and infections. Braun et al. (18) reported in his recent systematic review that the overall complications post donor hepatectomy at 8.1-50% with the incidence of biliary complications rates were approximately 2-18%. Pamecha et al. (15) reported a biliary complication rate of only 2.5% in their study on LLDs from India. Guler et al (19) stated the major complication rate in male LLDs especially those with a BMI of >25 kg/m2 was higher if the remnant liver volume was <32,5%.

The effect of age on LLD and recipient outcomes after LDLT remains unclear. Their previous study involving 150 LLDs showed that the complication rate was similar in LLDs of >50 years and ≤50 years old (20). Findings from the A2ALL study group and other single center studies describe a 38–44% complication rate for right lobe donors, typically occurring in the first postoperative year with almost half presented while the LLDs are still in the hospital. The most common significant complications include bile leak, pleural effusion, and infection (21). We observed that the patients with infection were longer intensive care unit (ICU) and hospital stays, higher hospital admissions, emergency transplantation, invasive procedures for ERCP, PTC biloma and abscess drainage, and the presences of relaparatomies and transcystic catheters. Additionally, it was observed that the age, gender and body mass index of the donor, different blood groups, type of graft taken and the degree of proximity to the recipient were not associated with the development of infection. All of the infection attacks developed in the first postoperative year, reports from six countries in high volume demonstrate the safety of the donor operation. In this report, it was emphasized that 25-33% of LLDs developed at least one complication. In the same study, the rate of infection was found to be 13% (22). In our study, the rate of patients who developed infection was found to be 17.17%. The reason for the higher rate of infection can be considered to be the result

of the inclusion of more patients in this study and the longer follow-up. Infectious complications related to donor hepatectomy surgery occur in 9–19% of LLDs, including hepatobiliary infections, bloodstream infections, urinary tract infections, wound infections and pneumonia. According to a national survey in Japan, 244 postoperative infectious complications were reported in 12% of LLDs (228/1853). The frequency of infectious complications was significantly higher in LLDs of the right liver graft than in those of left-sided grafts (23).

The selection of antimicrobial treatment depends on the patient's immune status, intraoperative events, recent or recurrent hospitalization, and donor infections at the time of liver graft procurement while it has been tailored in accordance with the colonization of the LLDs, recently, it was characterised by the prevalence of MDR gram-negative bacilli. Patients are at the highest risk of acquiring infections during the first postoperative month (24). In our study, the most common complaints of LLDs who developed infection were fever, abdominal pain, nausea and vomiting. In particular, the symptoms of LLDs who developed urinary infection or pneumonia at the time of admission were similar to the normal patient population, but according to our results, we did not make mention of an increased incidence of urinary infection and pneumonia in LLDs. It can be considered that the cause of this is as a result of the effectiveness of ampicillin/sulbactam prophylaxis applied to LLDs in the perioperative period.

In LLDs, even if relieved by biliary manipulations such as stenting and/or dilation, most of the infections originate from the hepatobiliary system. The infections emerge with clinical symptoms such as fever, jaundice, or right upper quadrant pain (25). In our study, 58.3% of infection attacks were sourced by the hepatobiliary system (cholangitis, intraabdominal abscess, infected biloma and pancreatitis). Nosocomial MDR gram-negative microorganisms predominate an infections originating from the hepatobiliary system (26). Particularly high mortality rates, in the range of approximately 35–70%, are reported for patients developing infections with MDR microorganisms, such as ESBL-producing or carbapenem-resistant *Enterobacteriaceae*. The improvements in prevention, early diagnosis and management of infections in the early period after LDLT are thus undoubtedly necessary to further improve patient outcomes (27). We found that *ESBL-producing K. pneumonia* and *ESBL-producing E. coli* has emerged as the most commonly detected microorganisms. Monotherapy (piperacillin/tazobactam and ertapenem, respectively) was preferred for 75.8% attacks in empirical treatment and antimicrobial treatment based on culture results, and an average of 9.11 days of treatment was applied to attacks. Our study showed that gram-negative nosocomial microorganisms, especially *ESBL-producing* and *P. aeruginosae*, should be included in the selection of empirical treatment at the initiation of antimicrobial treatment, infection attacks can be effectively and successfully treated with monotherapy, and even combined therapies are not needed much. However, before the initiation of treatment, relevant cultures must be taken, and antimicrobial treatment must be revised if necessary, according to the culture results. Our blood culture positivity rate was found to be 6.96% and this rate was consistent with other studies in the literature as mentioned above. Serum CRP, PCT concentrations and high leucocytes levels are well-established systemic inflammation markers utilized for diagnosing postoperative infectious episodes in LLDs. Although several reports focused on clinical utility of these inflammatory markers in LLDs, data on their diagnostic accuracy, optimal cut-offs and factors influencing their changes in the first days after donor hepatectomy are scarce. However, high levels of CRP-PCT and leucocytosis may be used for the initially exclusion of the diagnosis of infectious complications in the immediate period after donor hepatectomy (28). In our study, leukocytes, CRP

and PCT levels in patients with an infection attack regressed to normal levels, improvement in clinical findings and negative culture were found.

As a result of the timely initiation of effective antimicrobial treatment accompanied by invasive radiological and/or surgical interventions when necessary, the chances of success are greatly increased. It should be kept in mind that in the selection of empirical antimicrobials, the chances of success in treatment with monotherapy are high, but the antimicrobial drug to be started must include gram-negative microorganisms of nosocomial origin and the relevant cultures must be taken before treatment. Figiel et al. (29) reported that the risk of early death among live liver donors in the United States is 1.7 per 1000 donors. Mortality of LLDs did not differ from that of healthy, matched individuals over a mean of 7.6 years including 4111 living liver donors in follow-ups 17 years (30). It was observed that our LLDs with an infection attack had higher hospital admissions, ICU and hospitalization days, more surgical complications and patients who underwent more invasive procedures. All infection attacks in LLDs were successfully treated and the patients were discharged with healing. No LLD patient died due to infection or other complications.

CONCLUSION

LDLT is now an acceptable option in most countries due to a lack of cadaveric donors. Donor safety should always be prioritized and close follow-up of LLDs should be made especially for infections that may develop in the first postoperative month. It should be kept in mind that most infectious complications can often arise from the hepatobiliary system, and the infection treatment process should be managed as multidisciplinary without delay, and carefully. However, more clinical studies involving in LLDs, multicenter and wide-scale are needed.

Declarations

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Conflict of Interest Statement

The authors declare to have no conflict of interests.

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Data availability statement

The findings data of this study are available from the corresponding author upon reasonable request.

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Final revision: Kutlu R, Isık B, Bayindir Y, Yilmaz S.

Table legends

Table 1. Risk factors for infection development in living liver donors

Table 2. Distribution of attacks according to the sources of infection and antimicrobial treatment preferences

Table 3. Antimicrobial therapy preferences and total therapy durations

Table 4. Microorganisms growing in cultures

Table 5. The course of laboratory parameters of all living liver donors

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