G Chir Vol. 40 - n. 6 - pp. 463-480
November-December 2019

review

Intensive care unit outcomes following orthotopic liver transplantation: single-center experience and review of the literature

C. DAMASKOS[1*], A. KASKANTAMIS[2*], N. GARMPIS[1*], D. DIMITROULIS[1], D. MANTAS[1], A. GARMPI[3], S. SAKELLARIOU[4], A. ANGELOU[5], A. SYLLAIOS[6], A. KOSTAKIS[7], E. LAMPADARIOU[8], I. FLOROS[9], K. REVENAS[10], E.A. ANTONIOU[1]

SUMMARY: **Intensive care unit outcomes following orthotopic liver transplantation: single-center experience and review of the literature.**

C. DAMASKOS, A. KASKANTAMIS, N. GARMPIS, D. DIMITROULIS, D. MANTAS, A. GARMPI, S. SAKELLARIOU, A. ANGELOU, A. SYLLAIOS. A. KOSTAKIS, E. LAMPADARIOU, I. FLOROS, K. REVENAS, E.A. ANTONIOU

Background/Aim. *Orthotopic Liver Transplantation (OLT) is the treatment of choice for patients with end stage liver disease, acute liver failure, hepatocellular carcinoma and metabolic disorders. As a result of improvement in surgical and anesthesiological skills, advanced understanding of transplant immunology and better critical care management of complications, patients survive longer after liver transplantation. It has been gradually achieved one-year survival rates of 80-90%. During the early post-operative period, all patients undergoing OLT are admitted to the intensive care unit, as they need a management of both preexisting patient's conditions and post-operative complications, usually due to either adverse intra-operative or post-operative events. The purpose of this review is the detailed recording, understanding and interpretation of immediate post-operative complications occurred in patients undergoing OLT, in intensive care unit. This could help to improve patient's treatment and reduce the incidence of complications, with further reduction of morbidity-mortality and cost. We also present our experience from the first 32 OLT patients from Liver Transplantation Unit of Laiko General Hospital, the only Liver Transplantation Unit in Athens.* Materials and methods. *This literature review was performed using the MEDLINE database. The key words were; Orthotopic liver transplantation; intensive care unit; post-operative complications; outcomes. One hundred-sixteen articles published in English until 2018 were used. We also use all the results from our 32 patients from our Liver Transplantation Unit during the period 07/2006 to 07/2009.* Results. *All patients undergoing OLT admitted to the intensive care unit for a period of time, depending on the occurrence of post-operative complications. The incidence of primary failure ranges between 2-14%, whereas post-operative bleeding ranges between 7-15%. The treatment is usually conservative, although surgical repair may need in 10-15%. Acute renal failure post-operative is not an infrequent problem too, and has been reported to occur in 9% to 78% of cases. Acute rejection normally occurs 7-14 days after OLT. Additionally, the delay of the weaning from mechanical ventilation in the immediate post-operative period could increase the complications. Infectious complications are quite common almost from the first post-operative day in intensive care unit.* Conclusions. *Prolonged intensive care stay could increase the complications post-operative Infectious complications, renal and respiratory impairment are among the most common causes of early post-transplant morbidity and mortality.*

KEY WORDS: Orthotopic - Liver - Transplantation - Intensive - Care - Unit - Post-operative - Complications - Outcomes.

Research on the possibility of orthotopic liver transplantation (OLT) began in 1956 by Cannon, with relevant experiments in dogs. The first human OLT was performed by Dr. Thomas Starzl in The University of Colorado, Denver, United States, in March 1963 (1). This patient died, as four other patients transplanted in Boston and Paris did, during the next two years. However, in July 1967 T. Starzl performed the first OLT with longer than a year postoperative survival (2). Despite the development of viable surgical techniques, OLT remained experi-

[1] Second Department of Propedeutic Surgery, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[2] Department of Anesthesiology, Ygeia Hospital, Athens, Greece
[3] First Department of Propedeutic Internal Medicine, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[4] First Department of Pathology, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[5] Health Center Alexandras, Athens, Greece
[6] First Department of Surgery, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[7] Biomedical Research Foundation (IIBEA), Academy of Athens, Athens, Greece
[8] Department of Anesthesiology, Laiko General Hospital, Athens, Greece
[9] Intensive Care Unit, Laiko General Hospital, Athens, Greece
[10] Department of Radiology, Laiko General Hospital, Athens, Greece

* These authors contributed equally

Corresponding author: Dr Christos Damaskos, e-mail: x_damaskos@yahoo.gr

mental procedure through the 1970s, with an approximately 15% first-year survival rate.

The introduction of cyclosporine in human cadaveric transplantation by Sir Roy Calne, Professor of Surgery Cambridge in 1979, markedly improved patients' outcomes (3). During the 1980s, OLT became a widely accepted method for a plethora of liver diseases. In June 1983, a Consensus Development Conference Statement, National Institute of Health (NIH) of USA, stated that OLT is the treatment of choice for patients with end stage liver disease (4). Improvement of surgical and anesthesiological skills, advanced understanding of transplant immunology and better critical care management of complications contributed in achieving longer survival after liver transplantation; one-year survival rates of 80-90% have been gradually achieved. Usually, all patients undergoing OLT are admitted to the intensive care unit (ICU) during the early postoperative period. OLT patients need both their preexisting conditions and post-operative complications to be addressed in ICU, usually due to either adverse intraoperative events or post-operative ones.

Indications for orthotopic liver transplantation

OLT is indicated for most causes of acute or chronic liver disease. Cirrhosis accounts for more than 80% of transplantations performed in adults, with hepatitis C and alcohol abuse being the second most common diagnoses (5). Other indications include the cholestatic liver disorders (primary biliary cirrhosis, primary sclerosing cholangitis, biliary atresia in children), chronic hepatitis (hepatitis B, autoimmune hepatitis), metabolic disease (Wilson Disease, non alchoholic steatoepatitis), fulminant hepatic failure and non-metastatic hepatocellular carcinoma (HCC) in cirrhosis. Major pediatric indications for OLT include biliary atresia and metabolic liver disease. Non-metastatic primary hepatic malignancies - mainly hepatomas - are considered as an ideal indication for OLT. Other treatments for HCC patients (such as resection, percutaneous alcohol ablation, chemotherapy and embolization) have not significantly improved survival rates (6). According to the Milan Criteria, acceptable tumor dimensions for patients with HCC under consideration for OLT are those with a single lesion less or equal to 5cm, or, if multiple, 3 or fewer lesions with the largest < 3cm in diameter (8).

Yao *et al.* presented data on expansion of the Milan Criteria for OLT for HCC to a single lesion <6.5cm or up to 3 lesions with none >4.5cm and with total tumor diameter < 8 cm. In this study of 168 patients followed for at least six months after OLT, the 5-year recurrence free survival rate exceeded 88%. However, most liver transplant centers still use the Milan Criteria (9).

Kim et al. reviewed the outcome of patients transplanted for hepatitis B in the US using the UNOS (United Netword of Organ Sharing) database. With the development of hepatitis B immune globulin (HBIG) and subsequently the use of lamivudine, researchers suggested that the liver transplantation era should be divided into three periods: pre-HBIG (before 1991), HBGI (1991-1996) and HBGI + lamivudine (1997-present). They reported that patient survival increased with each ensuing era, resulting in no difference in survival for patients transplanted for hepatitis B virus (HBV) infection, as compared with other indication for OLT when HBGI + lamivudine was used for HBC recurrence prophylaxis (10).

Brandsaeter et al. reported long term follow up and outcomes in 255 Nordic patients with primary sclerosing cholangitis waitlisted for OLT from 1990 to 2000. 87% of patients underwent transplantation and 13% died awaiting OLT. One in five patients was found to have hepatobiliary malignancy at transplantation and those with cholangiocarcinoma fared the worst, with 5-year survival at only 28% (11).

Complications of orthotopic liver transplantation

The severity of surgery and the pathology of recipients predispose to a significant number of post-liver transplantation complications (12) (Figure 1). There are frequent complications on both the graft and the organs of the recipient. The most common complications are described in the following paragraphs.

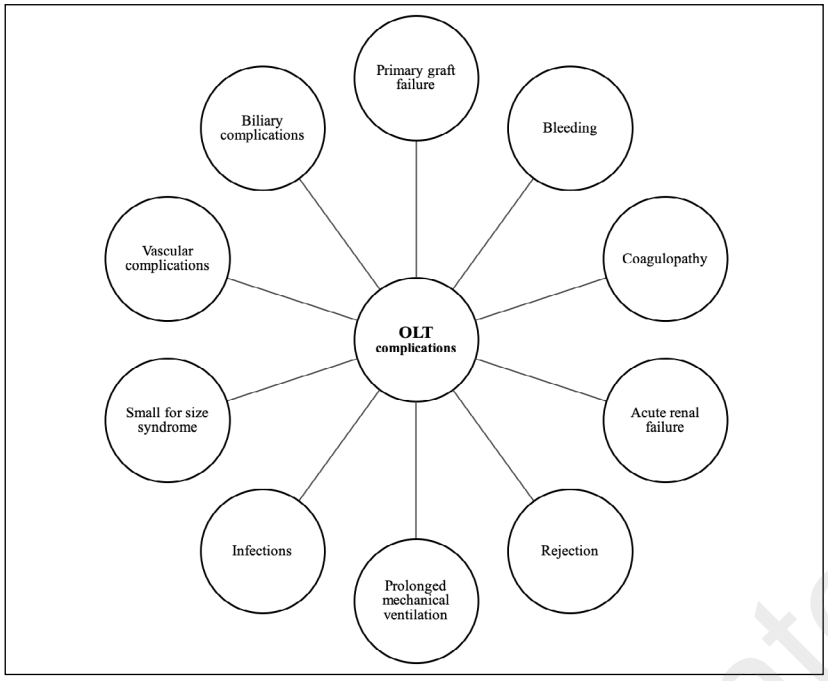

Figure 1 - Post-operative complications occurred in patients undergoing orthotopic liver transplantation, in intensive care unit.

Primary graft failure

Primary graft failure is characterized by the incapacity of the new graft to maintain the recipient's metabolic homeostasis. It is associated with high percentage of mortality without an emergency re-transplantation. The incidence of primary liver failure ranges between 2-14% (13). The signs of graft dysfunction including significant Central Nervous System (CNS) changes, coma, serious coagulopathy, oliguria, jaundice, hypoglycemia, increase of liver transaminase (often greater than 5000 U\L), Factor V (< 10%) and prothrombin time < 20% (14).

Post-operative bleeding and coagulopathy

Poor graft function, imperfect hemostasis, slippage of a tie, hypersplenism, hypocalcemia and dilution may lead to bleeding that necessitates transfusion or surgical re-exploration. During the first post-operative hours, intra-abdominal and wound "oozing" may also be the result of heparine release from the implanted graft along with hyperfibrinolysis (15-17). The risk of bleeding is increased by thrombocytopenia, mainly caused by platelet activation - consumption and sequestration following graft reperfusion and platelet–associated immunoglobulin M and immunoglobulin A antibody production. Other causes of thrompocytopenia include viral infection, cytomegalovirus-induced hematophagic histiocytosis and treatment with antiviral therapy. Thrombocytopenia usually regresses within two weeks, but it sometimes lasts longer due to persistent splenomegaly (18-20). The postoperative incidence of bleeding ranges between 7-15%. The treatment is usually conservative and surgical repair is needed in 10-15% (12).

Acute renal failure

The occurrence of acute renal failure (ARF) in patients undergoing OLT is associated with reduced patient and graft survival not only in the perioperative period but also in the longer term (21, 22), with reports of 10% progressing to end-stage renal failure (23). ARF reduces patient survival and leads to increased health care costs because of increased ICU and hospital stays (21, 22). Furthermore, increasing evidence supports the fact that even relatively minor deteriorations in renal function not requiring continuous veno-venous hemodiafiltration (CVVHDF) are associated with inferior renal outcomes in longer term; this underlines the importance of the early identification of individuals at risk and the need to identify preventative strategies (21, 22). Unfortunately, there are no uniform guidelines on the optimal timing when CVVHDF should be initiated

(23). Post-OLT ARF is not an infrequent problem and has been reported to occur in 9% to 78% of cases (22-26). This marked variability in the reported incidence rates can be predominantly attributed to the different underlying etiologies and definitions of ARF used. Definitions of acute kidney injury (AKI) have varied, and only relatively recently has a consensus definition based on the Risk, Injury, Failure, Loss, and End Stage Kidney Disease (RIFLE) criteria have been introduced (Table 1) (27). This staging system has been modified by the Acute Kidney Injury Network (AKIN) to define AKI as a rise in serum creatinine levels within a 48-hour time frame and also stresses the importance of even relatively small rise in serum creatinine levels (27, 28) (Table 1). More recently, the *Kidney Disease: Improving Global Outcomes Group* has taken elements from both the RIFLE and AKIN definitions. The etiology of post-OLT AKI can be multifactorial, as these patients are quite often critically ill in the perioperative period. Renal insults can occur during septic episodes or periods of hemodynamic instability and hypovolemia due to intraoperative blood loss (29, 30). Vasodilatation at anesthesia induction can also result in pre-renal failure or ischemic injury (29, 30). The initiation of renal support remains a clinical decision. Fluid overload and electrolyte disturbances are the most common trigger factors (Table 2) (31), and they are followed by metabolic acidosis rather than urea and creatinine level itself (32).

Rejection

Acute cellular rejection following OLT has decreased in incidence with the use of potent immunosuppressive agents, but it still affects 15 to 25 % of OLT recipients (33, 34). In liver transplantation, hyperacute rejection, although described, is quite

TABLE 1 - RISK, INJURY, FAILURE, LOSS, AND END STAGE KIDNEY DISEASE (RIFLE) SCORING SYSTEM FOR ACUTE KIDNEY INJURY.

AKI Stage	Serum Creatinine Criteria	Urine Output Criteria
Risk (AKIN-1	Serum creatinine > 0.3 mg/dL or Serum creatinine > 150%-200% above the baseline	<0.5ml/kg/hour for > 6hours
Injury (AKIN-2)	Serum creatinine > 200%-300% above the baseline	<0.5ml/kg/hour for >12 hours
Failure (AKIN-3)	Serum creatinine > 300% above the baseline or Serum creatinine > 4.5 mg/dL with an acute rise > 0.5 mg/dL	<0.3ml/kg/hour for 24 hours or anuria for 12 hours

AKI: Acute Kidney Injury; AKIN: Acute Kidney Injury Network

TABLE 2 - INDICATIONS GENERALLY USED TO START RENAL REPLACEMENT TRANSFUSION IN PATIENTS WITH ACUTE KIDNEY INJURY AFTER ORTHOTOPIC LIVER TRANSPLANTATION IN STANDARD CLINICAL PRACTICE.

Biochemical Indications
- Refractory hyperkalemia > 6.5 mmol/L
- Serum urea > 30 mmol/L
- Refractory metabolic acidosis (pH : 7.1)
- Refractory electrolyte abnormalities: hyponatremia or hypernatremia and hypercalcemia
Clinical Indications
- Urine output < 0.3 mL/kg for 24 hours or absolute anuria for 12 hours
- AKI with primary graft non function or multiple organ failure
- Refractory volume overload
- End organ damage: pericarditis, encephalopathy, neuropathy, myopathy, and uremic bleeding
- Creation of intravascular space for plasma and other blood product infusions and nutrition

RRT: Renal Replacement Trasfusion; AKI: Acute Kidney Injury

rare (35). Early acute cellular rejection mostly occurs within 90 days of the liver transplantation. Early acute rejection episodes do not adversely affect graft or patient outcomes, except in patients transplanted for hepatitis C virus, who demonstrate worse outcomes in the setting of bolus glucocorticoid therapy (36). Late cellular rejection episodes are often associated with low blood cyclosporine or tacrolimus concentrations and have been associated with reduced graft survival (37). Ramjii et al. reported late acute rejection (after more than 180 days) occurred in 97 of 415 patients (23%). Most (73%) responded to pulse intravenous steroids, while 5% were steroid-resistant. Late rejection appeared to be less likely in those who underwent transplantation for a viral etiology (38). Soin et al. reported that in a series of 717 liver transplantation recipients, 7.5% had at least one episode of late acute rejection. Most occurred within the first year, but some were seen as late as one to six years (39). Thus, the term "acute" seems inappropriate for describing this type of rejection. In a cohort of 762 consecutive adult liver transplantation recipients, Wiesner et al. reported that 490 (64%) developed at least one episode of rejection, most occurring during the first six weeks after transplantation. Approximately 20% of these patients developed a second rejection episode within one year of transplantation (40).

In addition to low blood levels of immunosuppressive therapy, several other risk factors for acute cellular rejection have been identified. In the study discussed above, independent variables associated with acute cellular rejection within 42 days of transplantation included lower recipient age, fewer human leukocyte antigen (HLA)-DR matches, cold ischemia time of at least 15 hours, and donor age of at least 30 years (40). Some variables associated with early allograft dysfunction have been described as indicators of poor long-term graft and patient survival; these include donors older than 50 years, cold ischemia time greater than 15 hours, donor pre-procurement acidosis, and recipient prothrombin time or bilirubin that remains steadily elevated (41). It has been suggested that in some cases, donor-specific HLA alloantibodies (DSAs) have the ability to persist after liver transplantation and potentially contribute to both acute cellular rejection and allograft injury (42).

A low incidence of cellular rejection was observed in patients transplanted for alcoholic liver disease, while patients transplanted for autoimmune diseases had higher rates of rejection. Nutritional status may play a role in the development of acute cellular rejection. In a multivariate analysis of pre-transplant patient characteristics, depleted mid-arm muscle circumference was associated with the absence of acute rejection (43). Cytomegalovirus genotype gB1 infection is associated with an increased rate of acute rejection (44). The identification of additional clinical risk factors may permit a more individualized approach to immunosuppressive therapy.

A variety of clinical signs and symptoms may be observed in patients with rejection, and include fever, malaise, abdominal pain, hepatosplenomegaly, and rarely, increasing ascites. However, none of these is specific for rejection (45).

Acute cellular rejection is generally suspected based upon the development of hepatic biochemical test abnormalities, which may include elevations of some or all of the following: serum aminotransferases, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), and bilirubin levels. However, these abnormalities are neither sensitive nor specific for distinguishing acute cellular rejection from other causes of hepatic allograft dysfunction and do not correlate with the severity of the rejection episode (46-48).

Liver histology remains the gold standard for the diagnosis of acute cellular rejection. Figure 2 describes the histologic findings of acute cellular rejection. Despite its utility, liver biopsy carries a small risk of complications in liver transplantation recipients. One study found a 1.8% rate of significant complications after each biopsy in this setting, including an increased rate of sepsis (49). In another report, infectious complications of liver biopsy were associated with the presence of biliary strictures and biliary anastomosis by choledochojejunostomy (50).

Prolonged mechanical ventilation

Weaning of the mechanical ventilator is the gradual withdrawal of ventilation support through utilization of a variety of ventilator modes, periods of total spontaneous ventilation, and appropriate rest periods for muscle unloading (51). The risks of prolonged mechanical ventilation include infections

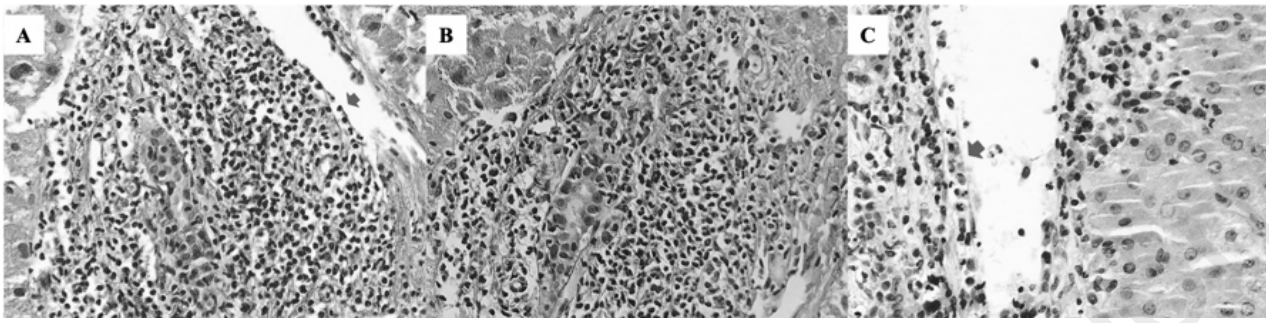

Figure 2 - Portal tract lesions in acute liver allograft rejection. A) Portal tract with dense mixed, lympocytic predominant inflammatory infiltrate. Interlobular bile duct with cholangitis (arrow). Portal vein showing subendothelial inflammatory infiltration with lifting of the endothelium (endothelitis) (arrowhead) (HE X100); B) Interlobular bile duct showing moderate infiltration by inflammatory cells, particularly lymphocytes and focal disruption of the basement membrane (HEX200); C) Portal vein showing a mixed subendothelial inflammatory infiltration, with lifting and focal disruption of endothelial cells (endothelitis) (HEX200).

(ventilator associated pneumonia), muscle deconditioning and tracheal injury. Evidence shows that prolonged mechanical ventilation is associated with increased mortality (52). Candidates for tracheostomy are patients who fail in multiple weaning attempts, those who continue to present with poor mental status and those who experienced prolonged respiratory failure. Neelakanta et al. retrospectively compared 18 patients who immediately extubated after the operation to 17 patients who underwent delayed extubation (immediate extubation was defined as extubation in the operating room) (53). Immediate extubated patients had often a lower pH and higher arterial carbon dioxide partial pressure in comparison with those patients who had a late extubation. In a retrospective study from 2 centers, Mandell et al. reported that 41 out of 173 patients were extubated immediately at the end of the operation, and only 2 patients required re-intubation (54). To qualify for early extubation, patients needed a good donor liver function and an alveolar - arterial oxygen gradient less than 150 mmHg. Patients with a successful OLT and receiving less than 10 units of packed red blood cells, extubated early. Their length stay in the ICU was reduced and the overall cost was also substantially reduced. Biancofiore et al. retrospectively studied 168 patients who had undergone OLT (181 procedures in all). One hundred fifteen patients (64%) were extubated within 3 hours of surgery, whereas 19 more patients were extubated within 8 hours (55). The identified risk factors for delayed extubation are presented on Table 3. After examining OLT procedures between 1999 and 2004, they updated their data: they found that 207 out of 354 patients (58.5%) were extubated immediately at the end of the procedure. They also reported that in the last 2 years of the study, 82.5% of their patients were extubated at the end of surgery. The best predictor of extubation success was a Model for End - Stage Liver Disease (MELD) score less than 11 (56). Anesthetic management may also contribute to the success of early extubation (57). In a randomized study, the use of short - acting anesthetic and analgesic agents instead of longer acting agents was associated with significantly shorter times to extubation (58). Although the majority of post OLT patients are candidates for early weaning and extubation, this is not possible for some. Weaning for these patients should follow the best practices identified for all ICU patients. Among the identified parameters (Table 3), frequency / tidal volume ratio is the most well studied one. Yang and Tobin found that rapid shallow breathing, as measured by the frequency/ tidal volume ratio, was the most accurate predictor of weaning failure. A frequency/ tidal volume ratio over 100 breaths / minute / L meant that weaning failure was likely to occur (59). Specific techniques used for weaning assessment have been studied. Esteban et al. compared 4 methods of weaning patients from mechanical ventilation in a randomized, prospective, multicenter study involving 546 patients. They reported that spontaneous breathing trials (SBTs) once daily were superior to intermittent mandatory ventilation and pressure support ventilation methods and were just as efficacious as multiple SBTs. On this basis, they recommended that all mechanically ventilated patients be weaned with SBTs once daily. Most ICU patients require sedation to tolerate mechanical ventilation, yet there is increasing evidence that sedation results

TABLE 3 - PREDICTORS OF SUCCESSFUL VENTILATOR WEANING.

Predictors
Respiratory rate
Tidal volume
Minute ventilation
Maximal inspiratory force
Frequency / tidal volume ratio

in an increased duration of mechanical ventilation (60). The same organizational issues that limit the evaluation of patients for ventilator weaning affect the sedation process. Likewise, it is difficult for patients to tolerate SBTs if they are over-sedated. Kress et al. randomized 128 ICU patients to daily sedation interruption (the intervention group) or the usual physician - led treatment (the control group). Daily sedation interruption led to a significant reduction in the duration of mechanical ventilation (from 7.3 to 4.9 days) and reduced the length of the ICU stay (from 9.9 to 6.4 days). Studies by Kress and Girard have demonstrated that protocol driven ventilator and sedation weaning can result in a reduced duration of mechanical ventilation without additional costs or complications (61). These authors recently collaborated on a randomized prospective trial combining paired sedation and ventilator protocols (61, 62). They randomized 336 patients to either a combination of daily sedation interruption and an SBT or routine sedation management with a daily SBT (the control group). The combination of the two interventions led to significant reduction in the duration of mechanical ventilation, the length of the ICU and hospital stays, and the one-year mortality. The findings of the aforementioned trials suggest that the current standard of care in any ICU should include both daily SBTs and daily sedation interruption (63-65).

Infectious complications

It has been calculated that more than half of patients will develop an infection during the first year after OLT (66-68) and many of these infections will require care in the ICU. The risk of infection is generally determined by the intensity of the exposure to infectious agents in the hospital environment, the community settings and the state of immunosuppression. During the first postoperative month, most infections are related to surgical issues and hospitalization (67). With potential breaks in areas of high microbial loads (i.e., the gastrointestinal tract), the exposure to infectious pathogens during prolonged hospitalization, the presence of urinary and vascular catheters, and the occasional need for prolonged ventilatory support predispose OLT patients to nosocomial bacterial and fungal infections during the first post-OLT month (64). The urgent nature of some OLT procedures (i.e., those for fulminant hepatic failure) diminishes the available time for optimizing patients for OLT, and this may further increase their risk (67). Fulminant hepatic failure per se is particularly associated with an increased risk of opportunistic viral and fungal superinfections.

Abdominal re-exploration surgery (for re-transplantation, abdominal bleeding, biliary leaks and vascular thrombosis) and the type of biliary anastomosis (eg, choledochojejunostomy) increase the risk of bacterial and fungal infections as well (67, 68).

Bacterial and fungal wound infections, urinary infections, bloodstream infections, pneumonia and *Clostridium difficile*-associated diarrhea are common during this period (69). Carbapenem - resistant *Klepsiella pneumonia* infections are very severe often associated with relevant morbidity (70).

Prolonged and complicated surgical procedure and the volume of blood loss directly correlate with mortality and the risk of infection after OLT. Wound infections, pneumonia, peritonitis, cholangitis, urinary and catheter-related infections, *Clostridium difficile* colitis, and liver abscesses are similar to the hospital-acquired infections observed in other surgical patients (71). Coagulase-negative and coagulase-positive *Staphylococci*, *Enterococci*, anaerobes, and Gram-negative bacteria such as *Escherichia coli*, *Enterobacter* species, and *Pseudomonas aeruginosa* are common in surgical-site infections (72). Pneumonia after OLT is usually caused by Gram-negative bacilli, *Enterobacter* species, *Serratia marcescens* and methicillin-susceptible or methicillin-resistant *Staphylococcus aureus. Enterococci* are frequent pathogens, and infections with vancomycin resistant *Enterococci* (VRE) have become a troublesome complication. Risk factors for VRE bacteremia include Roux-en-Y choledochojejunostomy, biliary strictures, prolonged ICU stay, and Cytomegalovirus (CMV) infection (73).

The risk of infections after OLT is reduced by standard perioperative antibacterial prophylaxis. The early administration of effective empirical antimicrobial therapy is crucial in the management of infections after OLT, and for this, knowledge of the local antibiogram profile of the hospital is essential. No single agent is widely recommended for peritransplant antibacterial prophylaxis, although third-generation cephalosporins are preferred. Despite prevention efforts, infected bilomas, intra-abdominal abscesses, and surgical site infections caused by drug susceptible and drug-resistant bacteria (eg, *Staphylococcus aureus*, coagulase-negative *Staphylococci*, *Enterococci*, gram-negative bacilli, and anaerobic organisms) and fungi (eg, *Candida albicans*) may occur (74-77). The clinical manifestations of these infections vary widely and include fever, leukocytosis, erythema, purulent draining, and dehiscence of surgical wounds; in severe cases, these infections can lead to bacteremia and sepsis, which would require care in the ICU. These early-onset infections often lead to prolonged hospitalization, which further increases the risk of nosocomial and ventilator-associated pneumonias, catheter-associated urinary tract and bloodstream infections, and antibiotic-related *C. difficile*-induced diarrhea (74).

Surveillance cultures or other methods such as polymerase chain reaction (PCR) are used to identify infections before their clinical manifestation. Surveillance using rectal swab and stool specimens can be employed to identify colonization with drug-resistant bacteria such as vancomycin-resistant Enterococci in an effort to interrupt nosocomial transmission (75).

Herpes simplex virus (HSV) reactivation disease is the most common opportunistic viral infection during this early period, although antiviral prophylaxis (with acyclovir or ganciclovir) has markedly reduced its incidence (78). If left untreated, a reactivated HSV infection can progress from limited orolabial ulcerative lesions to disseminated multiorgan infections (eg, fulminant hepatitis) with high morbidity and mortality rates. Latent or unrecognized active infections involving the donor or recipient liver (eg, *Histoplasma capsulatum*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Toxoplasma gondii*, and *Mycobacterium tuberculosis*) can manifest with severe atypical disease during the early period after OLT (79-81). The prevention of infections is essential in the management of all OLT recipients. Initially, a broad-spectrum antibacterial therapy is recommended for the treatment of bacterial sepsis and other infectious syndromes requiring admission to the ICU. Resuscitation and hemodynamic management should follow the guidelines for early goal-directed therapy, which are discussed in detail in the accompanying review of critical care for the pre-transplantation patient. These infections should be treated aggressively with antimicrobial therapy and guided by susceptibility tests (82), as these infections have been associated with poor allograft and patient survival (83). It is important to control the source of the infection, and thus the drainage of infected fluid collections (eg, infected hematomas and abscesses), the debridement of surgical infections, and the removal of infected vascular and urinary catheters is essential (82, 83).

Postoperative infection is one of the most common complications in liver transplant recipients. Gram-negative bacteria, especially *Enterococcus faecium* and *Escherichia coli*, is the predominant bacterial pathogens and *Candida albicans* is the most common fungal pathogen (84). Post-operative bile leakage is an independent risk factor for bacterial infection. Patients with post-operative bile leakage suffered from longer abdominal drainage, which may increase the risk of intra-abdominal and wound infection (85). Additionally, bile leakage can cause biloma that often progress to an infected abscess (86). It is interesting that patients' age over 45 years was a risk factor for postoperative bacterial infection to occur. Nayaranan et al. suggested patients' age over 42 years was significantly associated with a poor long-term survival (87). This finding suggested the incidence of post-operative bacterial infection may be increased with the increasing of recipient age. John et al. suggested pre-transplant diabetes was associated with increased post-operative morbidity and mortality (88). Recently, Ling et al. confirmed preexisting diabetes was not a contraindication for liver transplantation, as well controlled diabetes does not increase the risk of post-operative complication. After transplantation, the administration of immunosuppressive agents, including cyclosporine, steroids and tacrolimus, may cause post-operative hyperglycemia (89). Ata et al. confirmed postopera-

tive hyperglycemia was the most important risk factor for surgical site infection in general surgery patients (90). Rueda et al. reported hyperglycemia would increase the risk for and severity of pneumonia among non-diabetic patients (91). Prolonged ICU stay and hyponatremia were associated with post-operative bacterial infection. Mnatzaganian et al. confirmed the incidences of bloodstream and urinary infections of patients in ICU were higher than those in regular ward (92). Suljagic et al. confirmed the incidence of nosocomial bloodstream infection of ICU patients was higher than non-ICU patients (93). Stormont et al. confirmed hyponatremia was associated with pneumonia (94). Zilberberg et al. suggested hyponatremia was associated with worsened clinical outcomes among patients with pneumonia (95). Although the relationship between massive RBCs transfusion and bacterial infection was well established in previous studies, there was little information of the correlation of massive RBCs transfusion and fungal infection. Broad-spectrum antibiotics might lead to dysbacteriosis and increase fungal infection (96).

Small for size syndrome

This syndrome is described in patients receiving a split liver or a partial liver graft from a live donor. Clinical signs include delayed synthetic function, poor bile production, cholestasis, sepsis infections, including (97, 98). Supportive care of multiorgan failure and of infections are critical for patients' survival.

Vascular complications

Hepatic artery thrombosis (HAT) is the most frequent vascular complication after OLT that range 4-12% in adults and 40% in children (Figure 3A). Risk factors are the discrepancy between the donor artery and the native vessel, the prolonged ischemia of the graft and ABO incompatibility (99). Poor arterial inflow, artery avulsion during anastomosis and hypercoagulability are all considered risk factors, as well (12). In early HAT, graft is endangered, while in late HAT, the graft is usually safe, but bile ducts complications occur. Clinical signs are moderate increase in liver enzymes, bile links, biliary stenosis or ischemia, recurrent bacteremia, or fulminant hepatic necrosis (100, 101). Diagnosis is set by either ultrasound Doppler examination or digital subtraction angiography. Treatment is open or endovascular revascularization, and if these fail, urgent re-transplantation is necessary (101, 102).

Hepatic artery stenosis is the second most frequent complication that an average range 5% during the first quarter near the anastomosis. If not treated, may lead to hepatic artery thrombosis and progressive ischemia of the graft with liver failure, biliary stenosis, sepsis and graft rejection. Treatment options include surgical repair or transluminal balloon angioplasty (101).

Portal vein stenosis and thrombosis are not frequent after OLT and occur in 1-3% of cases (Figure 3B). It is caused by technical problems, coagulation disorders, and pre-operative poor inflow (12). Clinical signs are portal hypertension, liver failure, ascites and edema. Treatment options include percutaneous transhepatic angioplasty with or without stenting, and surgical repair with either venous bypass or thrombectomy. Coagulation is necessary in those cases where recurrence of portal vein thrombosis is expected (101).

Vena cava stenosis appears in approximately 1% of all cases. Clinical signs are pleural effusions, hepatomegaly, ascites and edema. Treatment of this complication is balloon angioplasty with or without stenting (101).

Biliary complications

Biliary complications are a common consequence of necrosis at the surgical anastomosis, technical errors or biliary tract ischemia (103). Remains a common cause of morbidity in rate of 5-30% after OLT and mortality up to 10%. The frequency of biliary complications is higher during the first months after OLT and decreases at first year. These complications include extensive bile leaks, anastomotic stenosis (Figure 4), gallstone (cholelithiasis), cholangitis and functional disorders of sphincter di Oddi. During the first postoperative month, the most frequent complication is bile leakage. The absence of bile outflow through a drain, an increase of cholestatic enzymes, and leucocytosis are indicative of a biliary complication. Ultrasound scanning, percutaneous cholangiography and abdominal CT scans may show ductal dilation or bile collection (104). Bile leakage can be addressed wither conservatively or

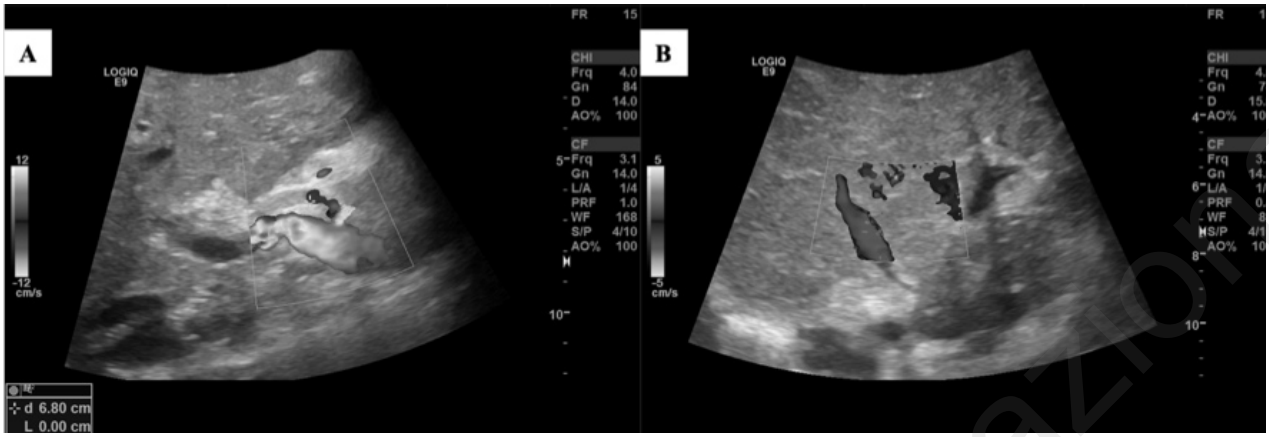

Figure 3 - Ultrasound findings of vascular thrombosis of liver graft. A) Hepatic artery thrombosis; B) Portal vein thrombosis.

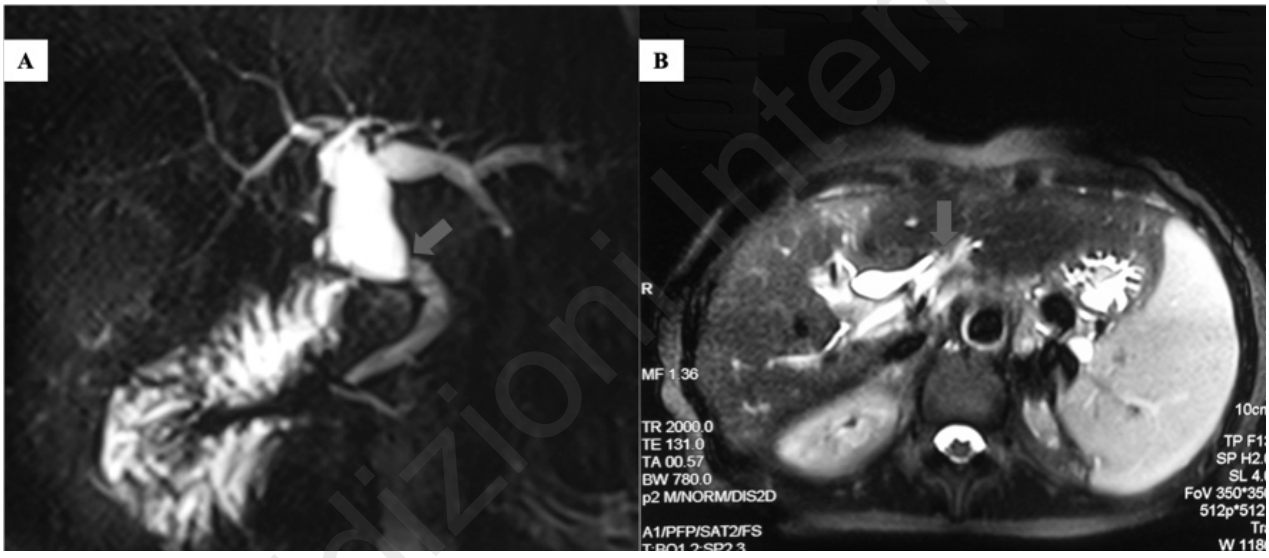

Figure 4 - Imaging findings of common bile duct anastomotic stenosis. A) Cholangiography; B) Computed tomography.

surgically. Treatment options include endoscopic-retrograde cholangio-pancreatography (ERCP) with biliary stenting or percutaneous transhepatic cholangiography (PTC) with external drainage, or surgical repair (105).

Our experience

The Liver Transplantation Unit of Laiko General Hospital of Athens, undertook 32 OLTs in the period from 07/2006 to 07/2009; 36 months. Transplantation patients were predominantly males (25 males; 7 females). Mean age was 51.2 years. Figure 5 and Tables 4, 5, and 6 show the basic clinical characteristics of patients and their respective primary cause to undergo transplantation.

In this study, all patients were transferred to the ICU intubated, aiming in early weaning from mechanical ventilation and extubation under carefully controlled conditions. Mean stay in ICU was 15.9 days and four patients had to be readmitted in the ICU (12.5%). Our center's length of stay (LOS) in the ICU exceeded what is currently reported in the literature, especially data coming from centers of expertise that have already minimized ICU LOS or have adopted fast-track protocols (106-109). Criteria for early extubation were patient to be normothermic, haemodynamically stable, needing FiO2 <50% and maintaining satisfactory gas exchange as

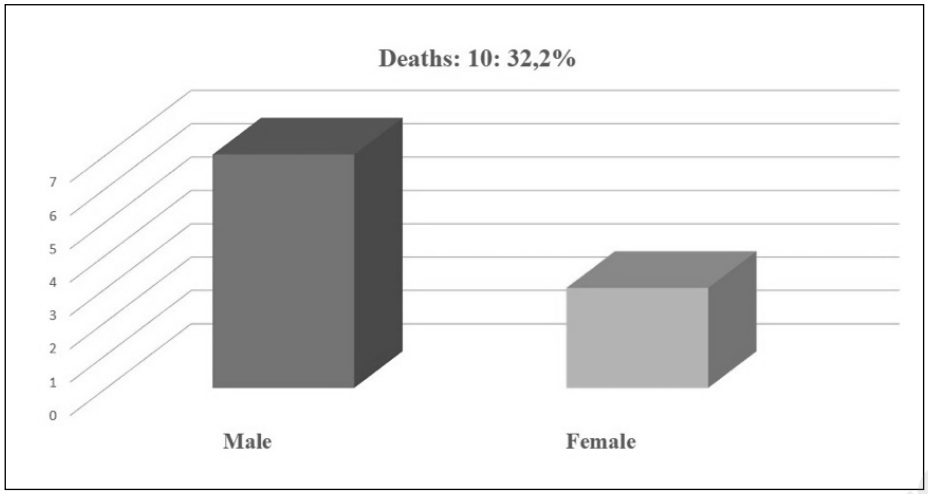

Figure 5 - Results of the Transplant Unit of Athens General Hospital 'Laikon'.

TABLE 4 - CLINICAL CHARACTERISTICS OF PATIENTS OF THE TRANSPLANT UNIT OF ATHENS GENERAL HOSPITAL 'LAIKON'.

Total patients		**Age** R: 25-71 y					**Sex**	
		≤ 35Y	*36-45Y*	*46-55Y*	*56-65Y*	*66Y ≥*	*M*	*F*
N	32	6	4	8	11	3	25	8
N%	100	19	13	25	34	9	78,2	21,8

N: number; R: range; Y: years; M: male; F: female

TABLE 5 - PRIMARY CAUSE TO UNDERGO TRANSPLANTATION FOR PATIENTS OF THE TRANSPLANT UNIT OF ATHENS GENERAL HOSPITAL 'LAIKON'.

Disease	**N**	**N%**
HCC + HCV	6	19
HCC + HBV	5	16
Alcoholic cirrhosis	5	16
HBV	4	13
Primary biliary cirrhosis	4	13
Primary sclerosing cholangitis	3	9
Acute liver insufficiency	3	9
Cryptogenic cirrhosis	2	6

HCV: Hepatitis C virus; HBV: Hepatitis B virus

reported by Arterial Blood Gase (ABG) checks, without electrolytes unbalance, or hemorrhage. Decreased urine output and/or renal failure were not taken under consideration in order to extubate the patient or not, as the patient could be supported with CVVHDF.

Nine patients (28%) were extubated during the first 3 post-operative days, ten patients (31%) between the 4th and 7th post-operative days, and five patients (16%) between 10th and 16th post-operative days. Two patients were re-intubated; one on the 6th post-operative day due to respiratory infection and acute respiratory failure, the other on the 11th post-operative day due to acute pulmonary edema. The second patient was readmitted to the ICU.

Samples of respiratory secretions wedged in the distal airway that were collected with non-bronchoscopic techniques (through the endotracheal tube or tracheostomy) isolated *Acinetobacter baumanii* in five patients (15.6%), *Pseudomonas aeruginosa* in four (12.5%), *Klebsiella pneumonia* in three (9.4%), *Candida albicans* in two (6.25%) and *Staphylococcus aureus* in two (6.25%) patients. (Table 7) Blood samples isolated *Klebsiella pneumoniae* in one patient (3.1%), *Carbapenemase-producing Klebsiella pneumonia* (*KPC*) in one patient (3.1%) and *Klebsiella pneumoniae verona integrin-encoded metallo-β-lactamase* (VIM) in one (3.1%) patient. Cultures from removed Central Venous Catheter (CVC) tips isolated *Klebsiella Pneumoniae* in two patients (6.25%), methicilline-resistant *Staphylococcus aureus* (MRSA) in one (3.1%), *Staphylococcus aureus* in one patient (3.1%), *Pseudomonas aeruginosa* in one patient

TABLE 6 - RESULTS OF THE TRANSPLANT UNIT OF ATHENS GENERAL HOSPITAL 'LAIKON'.

Complication	N	N%	Post OLT day	Cause
Re-intubation	1	6	6	Respiratory infection
	1		11	Acute pulmonary edema
Urgent reoperation	1	6	1	Intraabdominal hemorrhage
	1		13	Obstructive ileus
Acute renal failure	7	22		
Septic shock	1	9	5	
	1		13	
	1		23	
Urgent retransplantation	1	3	9	Thrombosis of the right hepatic artery

(3.1%), and *Acinetobacter baumanii* in one (3.1%) patient. Cultures of wound specimens isolated *Klebsiella pneumoniae* in one patient (3.1%), *Staphylococcus aureus* in one (3.1%), and Acinetobacter baumanii in one patient (3,1%). Cerebrospinal fluid (CSF) cultures isolated with Acinetobacter Baumanii and Staphylococcus Aureus in one patient each. Cultrures of plural effusion fluid was potisive for VIM in one patient (3.1%). Four patients (12.5%) had positive urine cultures; two (6.25%) for *Escherichia coli* and two (6.25%) for *Enterococcus spp*. One patient (3.1%) had positive stool culture for *Proteus mirabilis*. Out of the 32 patients, 25 had a positive culture for one or more of the above-mentioned microbes. As a result of these infections, three liver transplant recipients (9.4%) died from septic shock on 5th, 13th and 23th days, respectively. Culture results from our patients follow what is already described in existing literature, both in types of microbes and in infection rates.

Seven patients (21.9%) presented with postoperative surgical complication. Three patients (9.4%) developed a stenosis of the vascular anastomoses without clinical significance urging for surgical solution. A patient with a good postoperative outcome, underwent urgent re-transplantation, because of thrombosis of the right hepatic artery and liver ischemia on the 9th postoperative day. Eventually the patient died because of infarcts in the spleen and septic shock. Three patients (9.4%) had postoperative hemorrhage and had to undergo laparotomy. On the first day after OLT, one of them underwent urgent reoperation due to intra-abdominal hemorrhage; no single source of bleeding was found, but diffuse oozing from the surgical field was present. Bleeding control was performed in the other two cases. The 9.4% incidence of early postoperative bleeding and reoperation in our center is marginally lower than the reported 10% (12). One patient (3.1%) underwent exploratory laparotomy for obstructive ileus on 13th post-operative day with satisfactory outcomes.

Twelve patients (37.5%) experienced confusion, disorientation, seizures, delirium and or encephalopathy during the postoperative period. All of these patients received proper antipsychotic, anticonvulsive or sedative medication and symptoms gradually resolved. It is important to mention here, that all patient in the list had pre- transplant psychiatric and neurological assessment and post-transplant psychiatric and neurological follow up.

No strokes occurred in the liver recipients. In our center, neurological complications were minimal and transient without permanent and/or grave alteration of the patient's preoperative neurological status.

One patient (3.1%) presented with primary transplant dysfunction, while five more (15.6%) had light to moderate acute graft rejection during their staying in ICU.

All patients had normal preoperative renal function. Postoperatively, seven patients (22%) had AKI and were supported with CVVHDF. Twenty-one patients had decreased urine output and received diuretics, resulting in restoring good diuresis. Six of these patients (18.8%) developed ascites and nine

TABLE 7 - RESULTS OF POSITIVE CULTURES FOR VARIOUS SPECIMENS OF THE TRANSPLANT UNIT OF ATHENS GENERAL HOSPITAL 'LAIKON'.

Pathogen	**Specimen source**								**Total positive cultures for given microbe**
	Airway secretions	Blood	Tips of Central Venous catheters	Wound	Cerebrospinal fluid (CSF)	Urine	Stool	Pleural effusion	
Acinetobacter baumanii	5		1	1	1				**8**
Pseudomonas aeruginosa	4	1	1						**6**
Klebsiella pneumonia	3		2	1					**6**
Carbapenemase-producing Klebsiella pneumonia (KPC)		1							**1**
Klebsiella pneumoniae verona integron–encoded metallo-β-lactamase (VIM)		1						1	**2**
Candida spp	2								**2**
Staphylococcus aureus	2		1	1	1				**5**
methicilline-resistant Staphylococcus aureus (MRSA)			1						**1**
Escherichia coli						2			**2**
Enterococcus spp						2			**2**
Proteus mirabilis							1		**1**
Total positive cultures for given type of specimen	**16**	**3**	**6**	**3**	**2**	**4**	**1**	**1**	**36**

had to undergo temporary dialysis. Upon their discharge from hospital, all patients had a gradual but complete recovery of their renal function to normal. The number of our patients who require renal replacement therapy or temporarily dialysis are approximately equal to the number reported by other centers of similar expertise as ours (110).

More than half the patients' group (53.1%) had a complication from the respiratory system, something that is expected and well reported in OLT (111). Twelve patients (37.5%) had pleural effusion, nine (28.1%) had atelectasis, three (9.4%) had pulmonary oedema, and one (3.1%) had pneumothorax. Two of these patients (6.25%) had a chest tube placed and four (12.5%) had to be re-intubated. The clinical meaning of respiratory complications in OLT is great, as these are mortality predictor factors for liver recipients (112). Our results are on the high end the reported range of respiratory complications (35-50%) and expected to be improved as our center gains more experience (113).

Finally, fourteen patients (43.8%) were tachycardic with low blood pressure and received inotropes and vasoconstrictors. Only one patient (3.1%) presented with hypertension, which resolved after receiving the indicated antihypertensive medication. Since cardiovascular complications are related to high postoperative morbidity and mortality, our results are satisfactory as they are within the reported results from other centers (114, 115). Further improvement of these numbers is essential as it will further improve the outcomes and it can be reached by implementing preoperative optimization techniques or by using prediction models (114, 116). Table 8 summarizes the postoperative complications of the Liver Transplantation Unit of 'Laikon' General Hospital of Athens.

TABLE 8 - POSTOPERATIVE COMPLICATIONS OF THE TRANSPLANT UNIT OF ATHENS GENERAL HOSPITAL 'LAIKON'.

Complication	Number of patients	%
Surgical	7	21.9%
Infectious	25	78.1%
Primary graft dysfunction	1	3.1%
Neurological	12	37.5%
Graft rejection	5	15.6%
Gastrointestinal	2	6.3%
Renal	21	65.6%
Dialysis	9	28.1%
Cardiovascular	15	46.9%

Conclusions

The patient's management is very important in ICU because of various complications. Issues related to infectious, organ rejection, renal disease, weaning from mechanical respiration and biliary complications. Despite advances in OLT morbidity and mortality due to infectious complications remains a major problem. The risk of infections and type of infections differ based upon the time after OLT, although with changes in immunosuppressive agents over time and the institution of prophylaxis for various infections, the timeline of infection has been altered to some extent.

Ethics approval and consent to participate

This retrospective single center case study was approved by the local ethics committee of the Laiko General Hospital, Athens, Greece, and followed the ethical guidelines of Declaration of Helsinki from 1975. The ethics committee waived informed consent because of the retrospective design.

Consent for publication

All patients have given a written consent.

Availability of data and material

All presented data are available and can be requested from the Authors.

Acknowledgements

EAA would like to thank everyone who participated and supported the Liver Transplantation Unit of Laiko General Hospital, during the period 07/2006 to 07/2009.

References

1. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. Homo transplantation of the liver in humans. Surg Gynecol Obstet. 1963;117:659-676.
2. Starzl TE, Groth CG, Brettschneider L, Penn I, Fulginiti VA, Moon JB, Blanchard H, Martin AJ Jr, Porter KA. Orthotopic homotransplantation of the human liver. Ann Surg. 1968;168:392-414.
3. Calne RY, White DJ, Thiru S, Evans DB, McMaster P, Dunn DC, Craddock GN, Pentlow BD, Rolles K. Cyclosporin A in patients receiving renal allografts from cadaver donars. Lancet. 1978;2:1323-1327.
4. Liver Transplantation. NIH Consens Statement. 1983;4:1-15.
5. Seaberg EC, Belle SH, Beringer KC, Schivins JL, Detre KM. Liver transplantation in US from 1987-1998: Updated results from Pitt-UNOS Liver Transplant Registry. Clinical Transplant. 1998:17-37.
6. Bruix J. Treatment of hepatocellular carcinoma. Hepatology. 1997;25:259-262.
7. Dimitroulis D, Damaskos C, Valsami S, Davakis S, Garmpis N, Spartalis E, Athanasiou A, Moris D, Sakellariou S, Kykalos S, Tsourouflis G, Garmpi A, Delladetsima I, Kontzoglou K, Kouraklis G. From diagnosis to treatment of hepatocellular carcinoma: An epidemic problem for both developed and developing world. World J Gastroenterol. 2017;23:5282-5294.
8. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334:693-699.
9. Yao FY, Kinkhabwala M, La Berge J, Bass NM, Kerlan R, Roberts JP. The impact of expansion of conventional tumor criteria and pre-operative locoregional treatments on survival following liver transplantation for hepatocellular carcinoma: Results from two centers [abstract]. Hepatology. 2003;38:157A.
10. Kim WR, Poterucha JJ, Ishitani MB, Dickson ER. Outcome of liver transplantation for hepatitis B in the US. Hepatology. 2003;38:526A.
11. Brandsaeter B, Isoniemi H, Broomé U, Olausson M, Bäckman L, Hansen B, Schrumpf E, Oksanen A, Ericzon BG, Höckerstedt K, Mäkisalo H, Kirkegaard P, Friman S, Bjøro K. Liver transplantation for primary sclerosing cholangitis; predictors and consequences of hepatobiliary malignancy. J Hepatol. 2004;40:815-822.
12. Moreno R, Berenguer M. Post-liver transplantation medical complications. Annals Hepatol. 2006;5:77-85.
13. Uemura T, Randall HB, Sanchez EQ, Ikegami T, Narasimhan

G, McKenna GJ, Chinnakotla S, Levy MF, Goldstein RM, Klintmalm GB. Liver retransplantation for primary nonfunction: analysis of a 20-year single-center experience. Liver Transpl. 2007;13:227-233.
14. Nissen N, Colquhoun S. Graft failure: etiology, recognition and treatment. In: Busuttil R, Klintmalm G, eds. Transplantation of the Liver. 2nd ed. Philadelphia, PA: Elsevier, 2005:915-926.
15. Wang SC, Shieh JF, Chang KY, Chu YC, Liu CS, Loong CC, Chan KH, Mandell S, Tsou MY. Thromboelastography-guided transfusion decreases intraoperative blood transfusion during orthotopic liver transplantation: randomized clinical trial. Transplant Proc. 2010;42:2590-2593.
16. Gala B, Quintela J, Aguirrezabalaga J, Fernández C, Fraguela J, Suárez F, Gómez M. Benefits of recombinant activated factor in complicated liver transplantation. Transplant Proc. 2005;37:3919-3921.
17. Lodge JP, Jonas S, Jones RM, Olausson M, Mir-PallardoJ, Soefelt S, Garcia-Valdecasas JC, McAlister V, Mirza DF; rFVIIa OLT Study Group. Efficacy and safety of repeated perioperative doses of recombinant factor in liver transplantation. Liver Transpl. 2005;11: 973-979.
18. Pereboom IT, Lisman T, Porte RJ. Platelets in liver transplantation: friend or foe? Liver Transpl. 2008;14:923-931.
19. Kim J, Yi NJ, Shin WY, Kim T, Lee KU, Suh KS. Platelet transfusion can be related to liver regeneration after living donor liver transplantation. World J Surg. 2010;34:1052-1058.
20. Gopal PB, Kapoor D, Raya R, Subrahmanyam M, Juneja D, Sukanya B. Critical care issues in adult liver transplantation. Indian J Crit Care Med. 2009;13:113-119.
21. Barri YM, Sanchez EQ, Jennings LW, Melton LB, Hays S, Levy MF, Klintmalm GB. Acute kidney injury following liver transplantation: definition and outcome. Liver Transpl. 2009;15:475-483.
22. Foxton MR, Al-Freah MA, Portal AJ, Sizer E, Bernal W, Auzinger G, Rela M, Wendon JA, Heaton ND, O'Grady JG, Heneghan MA. Increased Model for End-Stage Liver Disease score at the time of liver transplant results in prolonged hospitalization and overall intensive care unit costs. Liver Transpl. 2010;16:668-677.
23. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, Boanta A, Gerß J, Meersch M. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. JAMA. 2016;315:2190-2199.
24. Bahirwani R, Reddy KR. Outcomes after liver transplantation: chronic kidney disease. Liver Transpl. 2009;15(Suppl 2):S70-S74.
25. O'Riordan A, Wong V, McQuillan R, McCormick PA, Hegarty JE, Watson AJ. Acute renal disease, as defined by the RIFLE criteria, post-liver transplantation. Am J Transplant. 2007;7:168-176.
26. Lebron Gallardo M, Herrera Gutierrez ME, Seller Perez G, Curiel Balsera E, Fernandez Ortega JF, Quesada Garcia G. Risk factors for renal dysfunction in the postoperative course of liver transplant. Liver Transpl. 2004;10:1379-1385.
27. Ferreira AC, Nolasco F, Carvalho D, Sampaio S, Baptista A Pessegueiro P, Monteiro E, Mourão L, Barroso E. Impact of RIFLE classification in liver transplantation. Clin Transplant. 2010;24:394-400.
28. Ostermann M, Joannidis M. Acute kidney injury 2016: diagnosis and diagnostic workup. Crit Care. 2016;20:299.
29. Pham PT, Pham PC, Wilkinson AH. Management of renal dysfunction in the liver transplant recipient. Curr Opin Organ Transplant. 2009;14:231-239.
30. Goren O, Matot I. Update on perioperative acute kidney injury. Curr Opin Crit Care. 2016;22:370-378.
31. Gibney N, Cerda J, Davenport A, Ramirez J, Singbartl K, Leblanc M, Ronco C. Volume management by renal replacement therapy in acute kidney injury. Int J Artif Organs. 2008;31:145-155.
32. Davenport A, Farrington K. Dialysis dose in acute kidney injury and chronic dialysis. Lancet. 2010;375:705-706.
33. Maluf DG, Stravitz RT, Cotterell AH, Posner MP, Nakatsuka M, Sterling RK, Luketic VA, Shiffman ML, Ham JM, Marcos A, Behnke MK, Fisher RA. Adult living donor versus deceased donor liver transplantation: a 6-year single center experience. Am J Transplant. 2005;5:149-156.
34. Gruttadauria S, Vasta F, Mandalà L, Cintorino D, Piazza T, Spada M, Verzaro R, Gridelli B. Basiliximab in a triple-drug regimen with tacrolimus and steroids in liver transplantation. Transplant Proc. 2005;37:2611-2612.
35. Choudhary NS, Saigal S, Bansal RK, Saraf N, Gautam D, Soin AS. Acute and Chronic Rejection After Liver Transplantation: What A Clinician Needs to Know. J Clin Exp Hepatol. 2017;7:358-366.
36. Samonakis DN, Germani G, Burroughs AK. Immunosuppression and HCV recurrence after liver transplantation. J Hepatol. 2012;56:973-983.
37. Adams DH, Neuberger JM. Patterns of graft rejection following liver transplantation. J Hepatol. 1990;10:113-119.
38. Ramjii A, Yoshida EM, Bain VG, Kneteman NM, Scudamore CH, Ma MM, Steinbrecher UP, Gutfreund KS, Erb SR, Partovi N, Chung SW, Shapiro J, Wong WW. Late acute rejection after liver transplantation: The Western Canada experience. Liver Transpl. 2002;8:945-951.
39. Soin AS, Rasmussen A, Jamieson NV, Watson CJ, Friend PJ, Wight DG, Calne RY. CsA levels in the early post transplant period predictive of chronic rejection in liver transplantation? Transplantation. 1995;59:1119-1123.
40. Wiesner RH, Demetris AJ, Belle SH, Seaberg EC, Lake JR, Zetterman RK, Everhart J, Detre KM. Acute hepatic allograft rejection: incidence, risk factors and impact on outcome. Hepatology. 1998;28:638-645.
41. Bennett-Guerrero E, Feierman DE, Barclay GR, Parides MK, Sheiner PA, Mythen MG, Levine DM, Parker TS, Carroll SF, White ML, Winfree WJ. Preoperative and intraoperative predictors of postoperative morbidity, poor graft function and early rejection in 190 patients undergoing liver transplantation. Arch Surg. 2001;136:1177-1183.
42. Taner T, Stegall MD, Heimbach JK. Antibody-mediated rejection in liver transplantation: current controversies and future directions. Liver Transpl. 2014;20:514-527.
43. Bathgate AJ, Hynd P, Sommerville D, Hayes PC. The prediction of acute cellular rejection in orthotopic liver transplantation. Liver Transpl Surg. 1999;5:475-479.
44. Rosen HR, Cortless CL, Rabkin J, Chou S. Association of cytomegalovirus genotype with graft rejection after liver transplantation. Transplantation. 1998;66:1627-1631.
45. Suriawinata AA, Thung SN. Liver Pathology: An Atlas and Concise Guide. Springer, 2011.
46. Abraham SC, Furth EE. Receiver operating characteristic analysis of serum chemical parameters as tests of liver transplant rejection and correlation with histology. Transplantation.

1995;59:740-746.
47. Williams JW, Peters TG, Vera SR, Britt LG, van Voorst SJ, Haggitt RC. Biopsy-directed immunosuppression following hepatic transplantation in man. Transplantation. 1985;39:589-596.
48. Henley KS, Lucey MR, Appelman HD, Baliga P, Brown KA, Burtch GD, Campbell DA Jr, Ham JM, Merion RM, Turcotte JG. Biochemical and histopathological correlation in liver transplant: the first 180 days. Hepatology. 1992;16:688-693.
49. Bubak ME, Porayko MK, Krom RA, Wiesner RH. Complications of liver biopsy in liver transplant patients: increased sepsis associated with choledochojejunostomy. Hepatology. 1991;14:1063-1065.
50. Larson AM, Chan GC, Wartelle CF, McVicar JP, Carithers RL Jr, Hamill GM, Kowdley KV. Infection complicating percutaneous liver biopsy in liver transplant recipients. Hepatology. 1997;26:1406-1409.
51. Keegan MT, Kramer DJ. Perioperative care of the Liver Transplant patient. Crit Care Clin. 2016;32:453-473.
52. Feltracco P, Carollo C, Barbieri S, Pettenuzzo T, Ori C. Early respiratory complications after liver transplantation. World J Gastroenterol. 2013;19:9271-9281.
53. Neelakanta G, Sopher M, Chan S, Pregler J, Steadman R, Braunfeld M, Csete M. Early tracheal extubation after liver transplantation. J Cardiothorac Vasc Anesth. 1997;11:165-167.
54. Mandell MS, Lockrem J, Kelley SD. Immediate tracheal extubation after liver transplantation: experience of two transplant centers. Anesth Analg. 1997;84:249-253.
55. Biancofiore G, Romanelli AM, Bindi ML, Consani G, Boldrini A, Battistini M, Filipponi F, Mosca F, Vagelli A. Very early tracheal extubation without predetermined criteria in a liver transplant recipient population. Liver Transpl. 2001;7:777-782.
56. Masior Ł, Grąt M, Krasnodębski M, Patkowski W, Figiel W, Bik E, Krawczyk M. Prognostic Factors and Outcomes of Patients After Liver Retransplantation. Transplant Proc. 2016;48:1717-1720.
57. Biancofiore G, Bindi ML, Romanelli AM, Boldrini A, Bisà M, Esposito M, Urbani L, Catalano G, Mosca F, Filipponi F. Fast track in liver transplantation: 5 years' experience. Eur J Anaesthesiol. 2005;22:584-590.
58. Findlay JY, Jankowski CJ, Vasdev GM, Chantigian RC, Gali B, Kamath GS, Keegan MT, Hall BA, Jones KA, Burkle CM, Plevak DJ. Fast track anesthesia for liver transplantation reduces postoperative ventilation time but not intensive care unit stay. Liver Transpl. 2002;8:670-675.
59. Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. N Engl J Med. 1991;324:1445-1450.
60. Esteban A, Frutos F, Tobin MJ, Alia I, Solsona JF, Valverdu I, Fernández R, de la Cal MA, Benito S, Tomás R, Carriedo D, Macias S, Blanco J. A comparison of four methods of weaning patients from mechanical ventilation. N Engl J Med. 1995;332:345-350.
61. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med. 2000;342:1471-1477.
62. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, Jackson JC, Canonico AE, Light RW, Shintani AK, Thompson JL, Gordon SM, Hall JB, Dittus RS, Bernard GR, Ely EW. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomized controlled trial. Lancet. 2008;371:126-134.
63. Burns KE, Adhikari NK, Keenan SP, Meade M. Use of non-invasive ventilation to wean critically ill adults off invasive ventilation: meta-analysis and systematic review. BMJ. 2009;338:b1574.
64. Squadrone V, Coha M, Cerutti E, Schellino MM, Biolino P, Occella P, Belloni G, Vilianis G, Fiore G, Cavallo F, Ranieri VM; Piedmont Intensive Care Units Network (PICUN). Continuous positive airway pressure for treatment of postoperative hypoxemia: a randomized controlled trial. JAMA. 2005;293:589-595.
65. Razonable RR, Findlay JY, O'Riordan A, Burroughs SG, Ghobrial RM, Agarwal B, Davenport A, Gropper M. Critical Care Issues in Patients After Liver Transplantation. Liver Transpl. 2011;17:511-527.
66. Blair JE, Kusne S. Bacterial, mycobacterial, and protozoal infections after liver transplantation —part I. Liver Transpl. 2005;11:1452-1459.
67. Razonable RR, Paya CV. Liver transplant patients. In: Cohen J, Powderly WG, Opal SM, eds. Infectious Diseases. Vol 1. 3rd ed. London, United Kingdom: Mosby Elsevier Science; 2010:848-852.
68. Kusne S, Blair JE. Viral and fungal infections after liver transplantation—part II. Liver Transpl. 2006;12:2-11.
69. Rogala BG, Malat GE, Lee DH, Harhay MN, Doyle AM, Bias TE. Identification of Risk Factors Associated With Clostridium difficile Infection in Liver Transplantation Recipients: A Single–Center Analysis. Transplant Proc. 2016;48:2763-2768.
70. Mazza E, Prosperi M, Panzeri MF, Limuti R, Nichelatti M, De Gasperi A. Carbapenem-Resistant Klepsiella Pneumoniae Infections Early After Liver Transplantation: A Single-Center Experience. Transplant Proc. 2017;49:677-681.
71. Falagas ME, Snydman DR, Griffith J, Ruthazer R, Werner BG. Effect of cytomegalovirus infection status on first-year mortality rates among orthotopic liver transplant recipients. Ann Intern Med. 1997;126:275-279.
72. Zhong ZQ, Luo AJ, Wan QQ, Ye QF. Pseudomonas Infection Among Liver Transplant Recipients: A Clinical Analysis of 15 Cases. Transplant Proc. 2016;48:2130-2134.
73. Gearhart M, Martin J, Rudich S, Thomas M, Wetzel D, Solomkin J, Hanaway MJ, Aranda-Michel J, Weber F, Trumball L, Bass M, Zavala E, Steve Woodle E, Buell JF. Consequences of vancomycin-resistant Enterococcus in liver transplant recipients: a matched control study. Clin Transplant. 2005;19:711-716.
74. Dubberke ER, Riddle DJ. Clostridium difficile in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S35-S40.
75. Garzoni C. Multiply resistant gram-positive bacteria methicillin resistant, vancomycin-intermediate and vancomycin-resistant Staphylococcus aureus (MRSA, VISA, VRSA) in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S41-S49.
76. Pappas PG, Silveira FP. Candida in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S173-S179.
77. Van Delden C, Blumberg EA. Multidrug resistant gram negative bacteria in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S27-S34.
78. Zuckerman R, Wald A. Herpes simplex virus infections in solid organ transplant recipients. Am J Transplant. 2009;9(Sup-

pl 4):S104-S107.
79. Kotton CN, Lattes R. Parasitic infections in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S234-S251.
80. Proia L, Miller R. Endemic fungal infections in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S199-S207.
81. Singh N, Forrest G. Cryptococcosis in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S192-S198.
82. Rice JC, Safdar N. Urinary tract infections in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S267-S272.
83. Al-Hasan MN, Razonable RR, Eckel-Passow JE, Baddour LM. Incidence rate and outcome of gram-negative bloodstream infection in solid organ transplant recipients. Am J Transplant. 2009;9:835-843.
84. Lee SO, Kang SH, Abdel-Massih RC, Brown RA, Razonable RR. Spectrum of early-onset and late-onset bacteremias after liver transplantation: implications for management. Liver Transpl. 2011;17:733-741.
85. Liu CL, Fan ST, Lo CM, Wong Y, Ng IO, Lam CM, Poon RT, Wong J. Abdominal drainage after hepatic resection is contraindicated in patients with chronic liver diseases. Ann Surg. 2004;239:194-201.
86. Vazquez JL, Thorsen MK, Dodds WJ, Quiroz FA, Martinez ML, Lawson TL, Stewart ET, Foley WD. Evaluation and treatment of intraabdominal bilomas. AJR Am J Roentgenol. 1985;144:933-938.
87. Narayanan Menon KV, Nyberg SL, Harmsen WS, DeSouza NF, Rosen CB, Krom RA, Wiesner RH. MELD and other factors associated with survival after liver transplantation. Am J Transplant. 2004;4:819-825.
88. John PR, Thuluvath PJ. Outcome of liver transplantation in patients with diabetes mellitus: a case-control study. Hepatology. 2001;34:889-895.
89. Ling Q, Xu X, Wei Q, Wei X, Wang Z, Zhou L, Zheng S. Impact of preexisting diabetes mellitus on outcome after liver transplantation in patients with hepatitis B virus-related liver disease. Dig Dis Sci. 2011;56:889-893.
90. Ata A, Lee J, Bestle SL, Desemone J, Stain SC. Postoperative hyperglycemia and surgical site infection in general surgery patients. Arch Surg. 2010;145: 858-864.
91. Rueda AM, Ormond M, Gore M, Matloobi M, Giordano TP, Musher DM. Hyperglycemia in diabetics and non-diabetics: effect on the risk for and severity of pneumococcal pneumonia. J Infect. 2010;60:99-105.
92. Mnatzaganian G, Galai N, Sprung CL, Zitser-Gurevich Y, Mandel M, Ben-Hur D, Gurman G, Klein M, Lev A, Levi L, Bar-Lavi Y, Zveibil F, Simchen E. Increased risk of bloodstream and urinary infections in intensive care unit (ICU) patients compared with patients fitting ICU admission criteria treated in regular wards. J Hosp Infect. 2005;59:331-342.
93. Suljagić V, Cobeljić M, Janković S, Mirović V, Marković-Denić L, Romić P, Mikić D. Nosocomial bloodstream infections in ICU and non-ICU patients. Am J Infect Control. 2005;33:333-340.
94. Stormont JM, Waterhouse C. Severe hyponatremia associated with pneumonia. Metabolism. 1962;11:1181-1186.
95. Zilberberg MD, Exuzides A, Spalding J, Foreman A, Jones AG, Colby C, Shorr AF. Hyponatremia and hospital outcomes among patients with pneumonia: a retrospective cohort study. BMC Pulm Med. 2008;8:16.
96. Quan F, Liu G, Wang L, Wang X. Investigation of pulmonary infection pathogens in neurological intensive care unit. Ther Clin Risk Manag. 2011;7:21-25.
97. Alamo JM, Gómez MA, Pareja F, Martínez A, López F, Romero E, Barrera L, Serrano J, García I, Bernardos A. Morbidity and mortality in liver retransplantation. Transplant Proc. 2006;38:2475-2477.
98. Rudow DL, Goldstein MJ. Critical care management of the liver transplant recipient. Crit Care Nurs Q. 2008;31:232-243.
99. Crippin J. Pathogenesis/pathology of organ dysfunction. In: Norman DJ, Suki WN, eds. Primer on Transplantation. Mt Laurel, NJ: American Society of Transplant Physicians. 1998:321-327.
100. Bellido CB, Martínez JM, Gómez LM, Artacho GS, Diez-Canedo JS, Pulido LB, Acevedo JM, Bravo MA. Indications for and survival after liver retransplantation. Transplant Proc. 2010;42:637-640.
101. Feltracco P, Barbieri S, Galligioni H, Michieletto E, Carollo C, Ori C. Intensive care management of liver transplanted patients. World J Hepatol. 2011;3:61-71.
102. Abdullah MS, Al-Waili NS, Baban NK, Butler GJ, Sultan L. Postsurgical psychosis: case report and review of literature. Adv Ther. 2006;23:325-331.
103. Duailibi DF, Ribeiro MAF. Biliary complications following deceased and living donor liver transplantation: A Review. Transplant Proc. 2010;42:517-520.
104. Koffron A, Stein JA. Liver transplantation: indications, pretransplant evaluation, surgery and posttransplant complications. Med Clin North Am. 2008;92:861-888.
105. Wojcicki M, Milkiewicz P, Silva M. Biliary tract complications after liver transplantation: a review. Dig Surg. 2008;25:245-257.
106. Echeverri J, Goldaracena N, Singh AK, Sapisochin G, Selzner N, Cattral MS, Greig PD, Lilly L, McGilvray ID, Levy GA, Ghanekar A, Renner EL, Grant DR, McCluskey SA, Selzner M. Avoiding ICU Admission by Using a Fast-Track Protocol Is Safe in Selected Adult-to-Adult Live Donor Liver Transplant Recipients. Transplant Direct. 2017;3:e213.
107. Stratigopoulou P, Paul A, Hoyer DP, Kykalos S, Saner FH, Sotiropoulos GC. High MELD score and extended operating time predict prolonged initial ICU stay after liver transplantation and influence the outcome. PLoS One. 2017;12:e0174173.
108. Bulatao IG, Heckman MG, Rawal B, Aniskevich S, Shine TS, Keaveny AP, Perry DK, Canabal J, Willingham DL, Taner CB. Avoiding stay in the intensive care unit after liver transplantation: a score to assign location of care. Am J Transplant. 2014;14:2088-2096.
109. Taner CB, Willingham DL, Bulatao IG, Shine TS, Peiris P, Torp KD, Canabal J, Nguyen JH, Kramer DJ. Is a mandatory intensive care unit stay needed after liver transplantation? Feasibility of fast-tracking to the surgical ward after liver transplantation. Liver Transpl. 2012;18:361-369.
110. Papadopoulos S, Karapanagiotou A, Kydona C, Dimitriadis C, Theodoridou T, Piperidou M, Imvrios G, Fouzas I, Gritsi-Gerogianni N. Causes and incidence of renal replacement therapy application in orthotopic liver transplantation patients: our experience. Transplant Proc. 2014;46:3228-3231.
111. Feltracco P, Carollo C, Barbieri S, Pettenuzzo T, Ori C. Early respiratory complications after liver transplantation. World J Gastroenterol. 2013;19:9271-9281.
112. Aydin C, Otan E, Akbulut S, Karakas S, Kayaalp C, Karagul S, Colak C, Gonultas F, Yilmaz S. Postoperative Pulmonary Complications After Liver Transplantation: Assessment of Risk

Factors for Mortality. Transplant Proc. 2015;47:1488-1494.
113. Levesque E, Hoti E, Azoulay D, Honore I, Guignard B, Vibert E, Ichai P, Antoun F, Saliba F, Samuel D. Pulmonary complications after elective liver transplantation-incidence, risk factors, and outcome. Transplantation. 2012;94:532-538.
114. VanWagner LB, Ning H, Whitsett M, Levitsky J, Uttal S, Wilkins JT, Abecassis MM, Ladner DP, Skaro AI, Lloyd-Jones DM. A point-based prediction model for cardiovascular risk in orthotopic liver transplantation: The CAR-OLT score. Hepatology. 2017;66:1968-1979.
115. Pisano G, Fracanzani AL, Caccamo L, Donato MF, Fargion S. Cardiovascular risk after orthotopic liver transplantation, a review of the literature and preliminary results of a prospective study. World J Gastroenterol. 2016;22:8869-8882.
116. Froghi F, Koti R, Gurusamy K, Mallett S, Thorburn D, Selves L, James S, Singh J, Pinto M, Eastgate C, McNeil M, Filipe H, Jichi F, Schofield N, Martin D, Davidson B. Cardiac output Optimisation following Liver Transplant (COLT) trial: study protocol for a feasibility randomised controlled trial. Trials. 2018;19:170.