We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Management of Patients with Liver Transplantation in ICU

Areti Karapanagiotou, Achillefs Pitsoulis, Maria Vasileiou and Nikolaos Voloudakis

Abstract

Liver transplantation constitutes the most effective and indispensable treatment of end-stage liver disease (ESLD). Major advances in surgical techniques, anesthesiological management, postoperative care, immunosuppression, and diagnostic approach have led to increased overall survival of patients. Postoperative care poses a great challenge since detrimental occurrences that need prompt treatment may affect the graft or distant organ functionality. Adequate graft function is strongly associated with distant organ restoration and rapid patient recovery. In the ICU setting, the main focal points are hemodynamic stabilization, coagulation and electrolyte disturbances correction, respiratory support, early weaning from mechanical ventilation, and evaluation of graft functionality. It is of paramount importance to facilitate early graft recovery, recognize and promptly treat systematic complications and life-threatening sequelae, and individualize treatment protocols considering graft quality, donor's and recipient's health status, and potential co-morbidities. To achieve those goals, technological advancements in continuous patient monitoring, graft functionality, and its metabolic reserves must be assimilated and implemented in the ICU.

Keywords: liver transplantation, post-liver transplantation intensive care, immediate postoperative management, complications, infections prophylaxis, early postoperative complications

1. Introduction

In the past years, liver transplantation (LT) has made leaps and evolved from an endeavor in specialized centers to a worldwide definitive and gold standard treatment of the end-stage liver disease (ESLD), acute liver failure, and various cancer types [1, 2].

The advances in perioperative management, including the improvement of surgical techniques, preservation solutions, perioperative management, and monitoring, as well as advances in immunosuppression and postoperative care have led not only to an increased number of transplantations but also to better outcomes [2]. According to recent studies in the United Kingdom, the 1- and 5-year survival rate for liver transplant recipients has reached 92 and 80%, respectively [3]. However, there are still certain challenges in LT. Scarcity of allografts and disparity between supply and demand has led the transplantation community to expand the donor pool by utilizing split grafts, allografts from living donors after cardiac death and including marginal donors of older age and with extended steatosis [4].

Additionally, recipients are sicker, given that priority of graft allocation is based on higher MELD scores, older and with co-morbidities such as metabolic syndrome, cardiac disease, and diabetes mellitus [5, 6]. Postoperative liver transplant patient care requires careful accounting of the recipient's pre-existing pathophysiology, intraoperative events, and donor's quality. Moreover, the implanted liver represents a unique biological entity that has undergone physiological changes and has to adapt to a new environment. This donor-recipient interaction is the key of a successful transplantation [7].

The intensivist's role is essential as a multifaceted approach is critical for optimal transplantation outcomes. The main hurdles to tackle are early recognition and immediate treatment of the hemodynamic and metabolic disorders, restoration of intravascular volume, avoidance of coagulation disorders, optimization of organs function affected by hepatic failure, prophylaxis and treatment of infections, early enteral nutrition, and evaluation of graft function. Technological advances offer the possibility of continuous cardiovascular and allograft function monitoring facilitating improved endpoint results.

2. General principles

The aim of immediate postoperative support is the adequate O_2 supply to tissues and graft by ensuring hemodynamic stabilization, fluid balance, restoration of diuresis, optimal ventilation, and supporting graft function. It should be noted that graft recovery depends primarily on the intrinsic hepatocyte recovery capacity and secondly on optimizing liver hemodynamics and preventing venous stasis.

3. Hemodynamic stabilization and monitoring

The primary goal of hemodynamic monitoring is to prevent inadequate cardiac filling and the subsequent tissue hypoperfusion, and also to avoid overloading leading to congestion of the lungs and sinusoids and hence allograft dysfunction [8]. The intravascular volume, cardiac output (CO), and systematic vascular resistance (SVR) are important parameters vital in determining the success of a LT. The treatment becomes even more complicated when renal and/or heart failure, portopulmonary hypertension, or hepatopulmonary syndromes are also present [9].

Successful management of patients with end-stage liver disease (ESLD) requires a complete understanding of their hemodynamic profile that is often characterized by high cardiac output (CO) with decreased systemic vascular resistance, depleted intravascular volume, and compensatory tachycardia with concomitant renal vasoconstriction and dilutional hyponatremia, due to excessive production of vasodilators during the development of hepatic failure [10]. Following LT, vasodilation and hyperdynamic circulation remain until the graft begins to function and excretes excess vasodilatory agents that are almost completely restored after 6 months [11].

Upon the arrival of a liver transplant recipient in the ICU, advanced monitoring, which estimates CO and volume status, additionally to standard hemodynamic monitoring, that is electrocardiogram, pulse-oximetry, and invasive blood pressure, are deemed essential [12].

Hemodynamic depression may be the result of hypovolemia, prolonged reperfusion syndrome, cardiac dysfunction, either caused by pre-existing or emerging ischemic cardiomyopathy, and metabolic disorders such as acidosis, hypocalcaemia, hypothermia, vasodilation due to sepsis, or graft dysfunction.

The assessment of the intravascular volume is of vital importance given that volume status can be affected by contradictory factors such hypovolemia or hypervolemia, both detrimental for graft and patient survival. Restoring volume status, a continually dynamic parameter, and achieving optimal CO are crucial in order to maintain the delicate balance between preload optimization and avoidance of pulmonary edema [13].

Hypovolemia, possibly due to continued bleeding, occult or overt, inadequate fluid replacement and/or loss in the third space, can lead to reduced preload and CO and hence hypoperfusion resulting in additional lesions in the newly transplanted liver [14]. The aim is to replace the intravascular fluid and maintain the circulating blood volume. There is still controversy over the type of fluids administered, with crystalloids gaining ground against the colloids (hydroxyl ethyl starches), which have been associated with renal injury and increased mortality in critically ill patients [15], a conclusion that is not supported by convincing evidence in LT. Nevertheless, the appropriate crystalloid should be carefully selected taking into account its special characteristics and based on its metabolism, electrolyte composition, pH and osmolarity, and considering patients' status [16]. Albumin (Alb) administration as a replacement fluid has been a matter of debate. In some centers, a large amount of Alb is exogenously administered following the LT to support circulatory stability. Moreover, a concentration of 25 g/L is considered necessary for the immunosuppressive drugs to be effective [17]. Beneficial properties were attributed to Alb in recent studies; whereas, postoperative hypoalbuminemia has been linked to the development of acute kidney injury (AKI) [18]. It has been found that during LT there is translocation of Alb, probably to the interstitial space, which persists until the third postoperative day and whose role has not been clearly clarified [19]. Certain centers choose to replace two-thirds of the required fluids with crystalloids and one-third of drain losses with albumin [14]. Although, blood and blood products transfusion strategies vary between institutions, it is considered that postoperative hematocrit (Hct) values, ranging between 25 and 30%, are safe for adequately transporting O_2 to the new graft [14]. The rational use of blood products depends on the monitoring of the coagulation mechanism. Whole-blood viscoelastic tests, such as thromboelastogram (TEG) and rotational thromboelastometry (ROTEM), that illustrate each step of thrombus formation and fibrinolysis are useful tools to guide transfusions and drug administration (anti-fibrinolytics, coagulation factors) [20, 21] by limiting the number of transfusions, as there has been an association between them and increased morbidity/mortality, prolonged stay in the hospital, postoperative sepsis, increased risk of acute rejection, and hepatic artery thrombosis [22–24].

Hypervolemia occurs either from intraoperative over-resuscitation or coexistence of renal dysfunction. It can result in capillary leak syndrome with loss of fluids in the third space, further congestion and graft edema due to vascular permeability disorder, caused by ischemia/reperfusion injury (I/R) that is more pronounced in grafts with higher preservation injury, greater steatosis, or in older donors [7, 25]. Studies also indicate that massive administration of fluids and blood is a risk factor for complications of the respiratory system postoperatively and is correlated with increased mortality [26]. On the contrary, conservative resuscitation strategy and negative fluid balance during the first three postoperative days, if hemodynamic stability has been achieved, act protectively. Codes et al. [27] concluded that a continuous positive balance in the first 4 days after surgery correlates with the development of AKI and the need for renal replacement therapy (RRT). Goal directed therapy (GDT) strategy, which has been successfully applied in major surgical interventions, is proposed. It aims at maintaining an adequate supply of O_2 to the end organs by a bundle of measures including fluid titration in conjunction with blood transfusions as well as administration of vasopressors and/or inotropic agents [28]. The hemodynamic

targets are predefined and specific variables are used to control fluid adequacy, improvement of CO, and tissue perfusion. GDT has beneficial effects compared to liberal fluid administration, reducing postoperative ileus, mechanical ventilation time, and respiratory system complications, as it has been indicated in relevant, although limited, studies [29]. Jiang et al. [30] suggests the individualization of fluid administration in the perioperative period as an optimal recovery strategy. They estimated that transfusions >100 ml/kg and fluid balance ≤−14 ml/kg during the first postoperative days result in prolonged mechanical ventilation, extubation time, and ICU stay. Prudent use of vasopressor agents is proposed since they increase arterial tone and improve perfusion pressure avoiding overload. Noradrenaline (0.01–1 μg/kg/min) with mixed α-β-adrenergic effects is most commonly administered to maintain CO and organ perfusion. Vasopressin (0.5–0.6 U/h) and terlipressin (1.5 μg/kg/h) have also been used in recent years because of their modifying effect on visceral circulation, where approximately 37% of the total blood volume is located in cirrhotic patients, and of their ability to reduce pressure in the portal vein [31, 32].

Since there has been no consensus on hemodynamic monitoring in LT yet, there is a number of invasive and noninvasive CO monitors available in order to evaluate hemodynamic fluctuations (**Table 1**) [13, 36].

The pulmonary artery (PAC) catheter has traditionally been used for hemodynamic monitoring in LT. It provides the possibility of measuring the CO by the thermodilution method, which is considered the gold standard, but also the cardiac

Monitors	Principle	Advantages	Limitations
PAC	Thermodilution	Accurate continuous measures of CO Direct measures of PAP and RVEDVI Gold standard in POPH	Invasive CVP, PCWP static pressures measurement Unreliable indicators of volume status, SV and fluid responsiveness
PiCCO	Pulse contour analysis	Less invasive Continuous CO, SV measures ITBVI, EVLWI, PPV, SVV Reliable indicators of fluid responsiveness	Need for recalibration in marked changes of SVR Inaccurate CO measures in Child-Pugh Band C stages in cirrhosis Requires sinus rhythm and certain ventilator setting
LiDCO	Pulse contour analysis	Continuous CO, SV measures comparable to PAC measures PPV, SVV Indicative of volume status	Calibration with lithium Inaccurate CO measures in Child-Pugh Band C stages in cirrhosis
FlowTrac/Vigileo	Pulse contour analysis	No need for calibration Continuous CO, SV measures PPV, SVV, indicative of volume status	Not reliable in hyperdynamic circulation with very low SVR
TEE	Ultrasound, Doppler	Less invasive Direct visualization of cardiac function and volume status	Advanced training is required Risk of rupture in 3rd or 4th grade of esophageal varices

Table 1.
Hemodynamic monitoring in LT.

filling pressures, the CVP, and especially the PCWP for assessing the preload [33]. Numerous studies have shown that static preload measurements are indirect markers of the end diastolic volume and have a poor predictive value for fluid management, improvement of hepatic perfusion, and recovery guidance [34]. Although still under debate, current data favor the use of a modified pulmonary artery catheter, with an incorporated heating coil, that provide continuous measurement of CO (CCO) and right ventricular end diastolic volume (RVEDV) as the more reliable preload indicator. Patients with portopulmonary hypertension are highly benefited from PAC, as it is the method of choice for measuring and monitoring pulmonary artery pressures intraoperatively and directly postoperatively [13, 35].

In recent years, interest has shifted to the dynamic parameters and expanding data yielded from existing monitoring of blood pressure to assess the CO, the preload and the afterload. There is technology available to accurately analyze pressure waveforms and sufficient knowledge to generate algorithms that are interpreted by the complex pulse wave morphology [36, 37].

The PiCCO system (Pulsion Medical System, Munich, Germany) uses the method of transpulmonary thermodilution, single indicator technique, and arterial pulse contour analysis which by means of an algorithm can continuously calculate CO and preload markers: global end diastolic volume (GEDVI), extra vascular lung water index (EVLWI), and intrathoracic blood volume index (ITBVI) which is considered a reliable preload indicator in LT. In transplant patients, the CO measurements deriving from the PiCCO system are consistent with those of PAC [38, 39].

Furthermore, this system offers the capability of functional hemodynamic monitoring by detecting the changes in left ventricular pulse volume caused by changes in preload due to mechanical ventilation. Stroke volume variation (SVV) and pulse pressure variation (PPV) have been used successfully to assess the intravascular volume and fluid responsiveness in critically ill patients [12, 13, 40]. Certain LT studies have concluded that the SVV is a better indicator for RVEDVI than CVP, while a SVV greater than 9% is an indicator of low RVEDVI which means fluid responsiveness [41, 42]. However, there are always limitations deriving from the presence of arrhythmia and mechanical ventilation settings.

The LiDCO system (LiDCO Plus, Cambridge, United Kingdom) is similar to the PiCCO system, but in its case the lithium indicator dilution technique is applied in order to calibrate the arterial waveform analysis algorithm [40].

The Flowtrac/Vigileo system (Edwards Lifesciences, Irvine, CA United States) is a special energy converter that links the arterial line with a CO monitor and uses arterial waveform analysis with an algorithm for real-time CO measurement in conjunction with patient demographics without the need for calibration. However, a poor correlation has been found between findings of waveform analysis CO when compared to PAC thermodilution, mainly in patients with cirrhosis B and C according to Child-Pugh classification [43, 44]. Biais et al. came to the same conclusion, using the recent third generation, FloTrac system, pointing out that there was great discrepancy in cases of significantly low SVR [45, 46].

In recent years, the use of transesophageal echocardiography (TEE) has been gaining ground not only because it is considered a noninvasive method, but also because it provides the ability to directly visualize the contractility of the left and right heart, preload status, and differential diagnosis of various pathological conditions such as pulmonary embolism, pleural, or pericardial effusion [47]. The CO can be estimated with measurements of flow across the cardiac valve, left ventricular outflow tract, or the flow in the main pulmonary artery. The ability to instantly display real-time preload is considered its biggest advantage. The functional application of TEE is limited by the risk of rupture of the third or fourth grade esophageal varices, but it is considered a reliable hemodynamic monitoring method when used by experienced intensivists [12, 13].

4. Liver allograft function

Assessment of graft function is necessary and is performed by combining clinical parameters, laboratory values, and imaging examinations. The first positive signs of adequate function of the new liver can be evident by the correction of metabolic acidosis, coagulation disturbances, hemodynamic stabilization, and temperature normalization in addition to diuresis restoration. Continuous monitoring in the postoperative period is required for the immediate recognition of early, subtle findings of graft dysfunction which necessitate aggressive treatment. Traditionally, the evaluation of liver function involves static and dynamic tests [48].

Static tests include hematology, coagulation, and biochemistry blood tests, in order to evaluate the main liver functions. The hepatic enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which rather indicate hepatocyte necrosis, display a rise postoperatively reaching their peak during the first 2 days before they finally start decreasing. Their elevation is attributed to preservation injuries and/or prolonged cold ischemia time (CIT). A persisting elevated value raises concerns about liver function and requires further investigation. The canalicular enzymes γ-glutamyl transferase and alkaline phosphatase increase after day four and usually five-fold before their decline begins. The synthetic function of the liver is evaluated by the prothrombin time or international normalized ratio (INR), which estimate the production of coagulation factors by the liver. Bilirubin levels define the liver excretory function while its metabolic function is assessed by glucose and lactate levels. A resistant to the treatment hypoglycemia is an indicator of graft dysfunction. The levels of lactates should also be carefully considered, if increased, due to the fact that such result may derive from peripheral tissue hypoxia.

The dynamic tests express the ability of the liver to metabolize or excrete certain substances. The lidocaine conversion to monoethylglycinexylidide metabolite (MEGX test) assesses the metabolic capacity and the liver blood flow [48, 49].

The indocyanine green (ICG) clearance test is routinely used in several centers. The functional activity of the graft is assessed by ICG dye administration, which is almost exclusively eliminated from the liver into the bile without undergoing enterohepatic circulation. Its removal from the blood depends on the hepatic blood flow, parenchymal cell function, and biliary excretion. It is expressed as half-life time, blood clearance, or plasma disappearance rate (ICG-PDR) smaller than 15% associated with a higher rate of primary dysfunction [50]. The bedside ultrasound imaging methods with hepatic blood vessel Doppler examination are usually performed on the day of surgery or on the first postoperative one in order to evaluate the patency of the hepatic artery, the portal vein, and the hepatic vein. It is particularly useful in the presence of intraoperative technical difficulties or when there is graft dysfunction, with a view to identify vascular abnormalities that could be treated [51].

Recovery of the graft is a combination mainly of the severity of the recipient's condition, donor quality, intraoperative events, perioperative hemodynamic stability, and preservation injuries, while adequate blood flow to the organs and prevention of venous stasis in the new liver have to be ensured (**Table 2**) [49]. On the other hand, the risk of poor outcome is increased in case of ESLD-associated syndromes and co-morbidities coexistence, especially in sicker patients, as estimated by the MELD score [4, 7].

Donor quality has a major impact on the graft function since the use of marginal donors is now commonplace [4]. The prolonged time of cold ischemia for more than 12 h increases ischemia reperfusion injuries. Macrosteatosis greater than 30% reduces tolerances in such injuries, while the risk of rejection and PNF is increased. Grafts from donors older than 60 years of age are considered to be of higher risk for PNF or exhibit delayed recovery mainly owing to cholestasis, whereas grafts from donors older than 75 show reduced liver regeneration capacity [52–54].

Donor related	Recipient related	Intraoperative events	Allograft related
Donor age Macrovesicular steatosis >30% High dose of vasopressors Hypernatremia Prolonged ICU stay Prolonged CIT Donation after cardiac death	ESLD-associated syndromes Pretransplant HD/renal dysfunction Cardiovascular disease BMI < 18.5 kg/m²	Massive transfusion Reperfusion syndrome High vasopressors dose	I/R Injury Graft inflow (Right HF, Hepatic vein stenosis/thrombosis) Graft outflow (Hepatic artery and portal vein patency) Small-for-size syndrome

Table 2.
Factors related to graft function.

Nevertheless, the results in the literature are contradictory; and in 2016, the donors older than 65 years old reached a percentage of 20.7%. In a recent study, Gilbo et al. concluded that older grafts can be safely used in older recipients without endangering their survival, if the remaining risk factors have been minimized [55]. The best practice for graft allocation is the use of scores that include donor and recipient data, such as the survival outcomes following liver transplantation (SOFT) and/or the BAR-score, which offer excellent prognostic ability for survival after transplantation and could lead to the final decision on using or rejecting the graft [56].

5. Ventilatory support and weaning from mechanical ventilation

The intraoperative use of short-acting anesthetics and neuromuscular blocking agents allows a prompt recovery of consciousness and facilitates the rapid release from mechanical support and early extubation (EE), which can occur in the operating theater or within the first three postoperative hours and is associated with shorter ICU and hospital stay. In a recent meta-analysis comparing early versus conventional extubation, the authors report a reduction in re-intubation rate, morbidity, respiratory complications, incidence of graft dysfunction, and ICU/hospital stay [57–59]. In a study published by Taner et al., it was exhibited that early extubation failed only in 1.90% of patients when performed on selected cases. According to these researchers, patients with HCC and low MELD score are appropriate candidates for EE [60].

Prolonged mechanical ventilation (MV) remains a critical risk factor for infections development, especially ventilator-associated pneumonia, tracheal trauma, prolongation of neuromuscular recovery, graft venous congestion due to positive intrathoracic pressures, and reduced venous return to the inferior vena cava and hepatic veins [61, 62]. It has also been correlated by Yuan et al. with the recipient's age, female gender, preoperative need for renal replacement therapy (RRT), ascites, higher MELD score, prolonged cold ischemia, and the number of transfusions [62].

Emphasis is placed on the fact that optimal selection criteria and timing of EE have not been clearly defined yet. Patients with encephalopathy, marked hypoxemia, obesity (BMI > 30), severe hemodynamic instability, pulmonary edema, cardiac or renal dysfunction, and multiple transfusions are not indicated for EE. The personalized and selective approach is likely to be the best strategy with a focus on avoiding delayed extubation, preserving hemodynamic stabilization, and ensuring graft functionality [63].

The criteria of weaning from MV applied to liver transplanted patients in ICU conform to those of the rest patient groups [64]. Distinct sequelae may often arise

from ESLD-related disorders such as encephalopathy, massive transfusions, graft dysfunction, preoperative nutrition disorders, volume overload, and postoperative respiratory complications including pulmonary edema, pleural effusions, or pneumonia. During MV, lungs and liver allograft interaction should be taken into account with the aim of improving oxygenation without impairing the outflow of the liver graft. Implementation of daily withdrawal of sedation combined with spontaneous breathing trial facilitates weaning from MV [63].

Acute respiratory distress syndrome (ARDS), one of the prominent respiratory complications following LT, is usually attributed to reperfusion syndrome, substantial blood loss and transfusions, prolonged operation time, and early postoperative infections and sepsis. Lung-protective ventilator strategies with low tidal volumes (6 ml/kg IBW), higher respiratory rate, and positive end-expiratory pressure (PEEP) are recommended to limit lung injury from shear forces and atelectasis [64]. There is debate about optimum PEEP in LT since some consider that higher PEEP values impair venous return and visceral blood flow leading to hepatic edema. Evaluation of transpulmonary pressure has been proposed to optimize PEEP titration [65]. Saner et al. concluded that PEEP up to 15 cm H_2O affects neither blood flow to the liver, nor flow and velocity in the hepatic artery, right hepatic vein, and portal vein [66]. In refractory ARDS and persistent hypoxia, prone positioning, high frequency ventilation, and extracorporeal membrane oxygenation support have been utilized as rescue therapy [67–69].

There are certain syndromes related to ESLD characterized by severe hypoxemia which require special management in the ICU such as hepatopulmonary syndrome and portopulmonary hypertension.

Hepatopulmonary syndrome is caused by intrapulmonary capillary dilatation that leads to hypoxemia and shortness of breath. LT is considered the treatment of choice; however, in most cases, severe hypoxemia might persist for a 6–12 months period. In the ICU, fluids should be managed carefully and lung-protective strategies should be employed during MV. In persistent hypoxemia, high frequency ventilation and/or venovenous extracorporeal membrane oxygenation is recommended. Some authors suggest early extubation and the immediate application of noninvasive ventilation with high-inspired fraction of oxygen [70, 71].

Portopulmonary hypertension resulting from pulmonary vasoconstriction due to portal hypertension requires prevention of hypoxemia, maintaining oxygen saturation >90% and correcting factors involved such as acidemia, arrhythmia, and anemia. Administration of diuretics and/or renal replacement therapy is advised if volume overload cannot be avoided. MV can both compromise venous return from the allograft and increase pulmonary vascular resistance through alveolar overdistension; therefore, lung-protective ventilation is considered to be the most appropriate strategy. The use of pulmonary vasodilators, that can be both administered IV such as epoprostenol and orally, via nasogastric tube, such as phosphodiesterase V inhibitor or nonselective endothelin receptor antagonist, is recommended during ICU stay [71].

6. Immunosuppression

Advances in immunosuppression have greatly impacted the survival of patients following LT. The initial endpoint was to prevent rejection; but in recent years, the interest has also been shifted to avoiding long-term complications from immunosuppressant agents and relapsing of the disease. In spite of the latest developments in this field, most centers commence immunosuppression with calcineurin inhibitors (CNIs) and corticosteroids with or without an anti-proliferative agent depending on protocols [72, 73].

Calcineurin inhibitors: Tacrolimus and cyclosporine inhibit calcineurin by impairing interleukin-2 (IL-2) transduction. Used as first-line immunosuppressant, tacrolimus is considered 100 times more potent than cyclosporine, and is superior in graft and patient survival with fewer acute and steroid-resistant rejection episodes. The main side effect is nephrotoxicity, while hypertension, hyperkalemia, uremic hemolytic syndrome, and neurotoxicity have lesser incidence [72]. Corticosteroids are important both in the initial immunosuppressive therapy and in the treatment of acute rejection.

Mycophenolate mofetil has been widely used as an adjuvant and alternative immunosuppressive agent. It is a potential inhibitor of B- and T-cell proliferation. It is mainly utilized when a dose reduction or discontinuation of CNI is demanded due to certain adverse effects such as nephrotoxicity and neurotoxicity [72].

Mammalian target of rapamycin (mTor) inhibitors, sirolimus, and everolimus, prevent B- and T-cell proliferation prompting the cell to arrest at G1 to S phase of the cell cycle. Although accounted for wound healing delay incidents, they can be administered as primary and rescue immunosuppression therapy with the advantages of being renal sparing as well as reducing the need for high doses of steroids. The newer IL-2 receptor-blocking antibody preparations daclizumab (Zenapax) and basiliximab (Simulect) are often used to initiate immunosuppression and avoid CNIs, and can also play a part in steroid-resistant rejection [72].

7. Infection prophylaxis

Prevention of infections is a major problem as they are the leading cause of death following LT [74]. The most common ones in the immediate postoperative period are of bacterial or fungal origin and include bloodstream, catheter related, surgical site, pulmonary, urinary tract, *Clostridium difficile* infections, and intra-abdominal collections. The identification of risk factors and the stratification of patients according to them determine the prophylactic perioperative antimicrobial treatment [75, 76]. Antimicrobial chemoprophylaxis 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 patients, recently characterized by a prevalence of multidrug-resistant Gram-negative bacilli [76, 77]. Other recipient-related risk factors are malnutrition, re-operation, acute liver failure, biliary complications, and the existence of postoperative catheters, lines, and drains. Antibiotics right before surgery cover Gram-negative bacteria (*Pseudomonas* sp., *Enterobacter* sp., and *Klebsiella* sp.), Gram-positive organisms (*Staphylococcus aureus*), fungi, and viruses according to the center protocols and their epidemiology. Antifungal prophylaxis is administered to higher risk patients determined by factors such as renal dysfunction with a need for RRT, re-transplantation, multiple transfusions, prolonged ICU stay, colonization by *Candida*, and graft rejection incidents with administration of high doses of corticosteroids. In many centers, azoles or liposomal amphotericin are used [76–78]. Siddique et al. reported that the rate of post-transplant infections was 24.5% with no difference between deceased and living donors; however, mortality was higher in bacterial infections in deceased donor recipients [79].

Herpes family viral infections, due to immunosuppression mainly by administration of T-cell-specific agents, are adequately treated with acyclovir. Ganciclovir or valganciclovir is sufficient for CMV seronegative recipients with CMV-seropositive grafts, or after rejection treatment. In case of suspected infection during hospitalization, broad spectrum antimicrobial therapy is administered and reviewed according to cultures results [75].

8. Nutritional support in liver transplant recipients

Post-LT nutritional support in ICU is an essential adjunct to transplant recovery. Malnutrition, which characterizes many patients with ESLD being evident at rates of up to 80%, deteriorates with the progression of liver failure, and affects the patients' outcome [80]. On the other hand, it is associated with prolonged ICU and hospital stay, infections, respiratory complications, graft impairment, and mortality. Sarcopenia, defined as severe muscle wasting, is also a determining factor of the outcome, and it can be easily diagnosed with bioelectrical impedance. Patients with cirrhosis often present carbohydrate, fat, and protein disorders, characterized by elevated levels of aromatic amino acids and methionine while lowering plasma levels of branched-chain amino acids are detected [81, 82]. The immediate postoperative energy demands are increased, especially in patients with a high MELD score [82]. Factors such as operational stress, release of catabolic hormones, administration of immunosuppressants, mainly corticosteroids, as well as ICU factors including mechanical ventilation and hemodialysis, contribute to increased metabolic needs. For the above reasons, the aim is to ensure adequate intake of protein and calories in addition to protein breakdown protection [81]. An increase in nonprotein calories, estimated at 25–35% kcal/kg per day, is recommended when indirect calorimetry is not available. It should always be in accordance with the metabolic and inflammatory status, and it should be reviewed in hemodynamically unstable patients [83]. Due to elevated protein catabolism, it is necessary to obtain 1.5–2 g/kg of protein. Enteral nutrition (EN) has the edge over the parenteral one, assisting in maintaining intestinal integrity, by supporting the diversity of the microbiome, and helping the immune and metabolic response. The rapid onset of EN even 12 h after LT is recommended by some authors. It has been reported to reduce viral infections and contribute to a better N_2 balance. If postoperative encephalopathy remains, the amount of protein intake is not reduced but the type of nutrition is altered by the addition of branched-chain amino acid (BCCA) enriched formulae, while the administration of immunonutrition remains under discussion. Frequent screening of electrolytes is required to prevent and correct disorders, while re-feeding syndrome is also considered a risk factor for these disorders [83].

9. Renal dysfunction

Renal impairment is a very common complication after LT. Its presence ranges from 19 to 64%. Even with the application of the RIFLE and AKIN criteria, the percentage reaches from 39 to 54% [84, 85]. In cases of living donors, acute kidney injury (AKI) has been estimated at around 23% [86]. AKI occurrence is complex and multifactorial in origin, depending on the existence of the preoperative hepatorenal syndrome as well as various intraoperative and postoperative factors. High MELD score, perioperative transfusions, hemodynamic instability, vasoactive agents, graft dysfunction, infections, and nephrotoxic agents are mainly accountable for renal function deterioration [87]. Systematic evaluation of renal function is required with close monitoring of urine output, fluid balance, and hemodynamic parameters [18]. The treatment is mainly supportive and includes: restoring CO with sufficient preload for optimization of renal perfusion, administering loop diuretics, and efforts to avoid nephrotoxic agents. Renal replacement therapy is recommended in cases of volume overload, electrolyte disturbances, and acidemia in an attempt to avoid pulmonary edema and hepatic congestion. Immunosuppressants, antibiotics, and contrast agents are commonplace nephrotoxic agents. The dosage of CNIs should be minimized or they should be converted into mTOR inhibitors combined with anti-proliferative agents. In ICU, CVVDHF is the renal replacement therapy of choice and favors the outcome of patients [88].

10. Primary graft dysfunction

Primary graft dysfunction (PGD) is a major complication after LT and is associated with prolonged hospital and ICU stay jeopardizing graft viability, being responsible for its high rejection rates as well as higher mortality and morbidity. It describes different degrees of graft impairment which begins intraoperatively, divided into early or initial poor function (IPF) and primary nonfunction (PNF) [89–91]. IPF represents the clinical phenotype of severe ischemia-reperfusion injury due to various donor and/or recipient-related factors. Expanding the criteria to marginal donors has increased the use of allografts with a higher likelihood of initial malfunction. It affects the survival of both graft and patient, whether the transplant comes from living or deceased donors. Dysfunction may be transient and possibly reversible with appropriate supportive treatment. There are no clear definitions, nevertheless, there are suggested scores, such as MEAF and LGrAFT, that could help in early detection and classification of early hepatic impairment [92, 93]. On the contrary, PNF is a catastrophic injury characterized by hepatic necrosis, aminotransferase elevation, coagulation disorders, lactate elevation, hemodynamic instability, persistent hypoglycemia, and respiratory and renal failure with an incidence ranging from 0.9 to 7%. The treatment is immediate re-transplantation. There are certain risk factors related to donors, recipients, intraoperative events, and allograft preservation [91] (**Table 2**).

11. Rejection

Acute cellular rejection (ACR), usually mediated by T-cells, has decreased in recent years with the use of improved potent immunosuppressants, but still ranges from 15 to 25% and usually occurs 7–14 days after surgery [94]. Hyperacute liver rejection is controversial, but undoubtedly early accelerated rejection occurs in the first 7 days and is associated with preformed antibodies. Risk factors include adequacy, type, and level of immunosuppression, underlying immune disease, biliary complications, certain transplant-related features such as donor-negative recipient-positive CMV mismatch, sex mismatch with a female donor. ACR is not significantly associated with long-term graft failure unless it concerns HCV-positive patients in which case it may result in corticosteroid-resistant rejection and graft loss. Early ACR is associated with better graft outcomes [95]. It is even hypothesized that such activation of the immune system may be beneficial and may induce a degree of tolerance. Manifestations of ACR include elevated levels of aminotransferase, alkaline phosphatase, bilirubin, and fever in later stages. Hepatic artery or portal vein thrombosis, biliary leak, CMV infection, and delayed graft function should be excluded. Diagnosis is finally confirmed by percutaneous liver biopsy prior to initiation of treatment, which depends on patient severity and current immunosuppression [94]. Cyclosporine is converted to tacrolimus or the sub-therapeutic levels of tacrolimus are increased and/or mycophenolate mofetil is added. In moderate to severe ACR, high doses of corticosteroids, usually methyl-prednizolone, are administered as a first-line medicine in a dose ranging from 500 to 1000 mg for 1–3 days depending on the center protocol [94].

12. Cardiac complications after LT

Cirrhotic cardiomyopathy (CCM) is defined as cardiac dysfunction in patients with cirrhosis characterized by a blunted contractile responsiveness to stress and/or diastolic dysfunction and electrophysiological abnormalities in the absence of known cardiac disease [96]. Diagnostic features include a reduced ejection

fraction (EF), an E/A ratio < 1, and electrocardiographic abnormalities such as a prolonged QTc interval. Diagnostic approaches involve transthoracic ultrasound, dobutamine stress echocardiography (DSE), as well as cardiac magnetic resonance (CMR). The concept of "ventriculo-arterial coupling" (VAC) has recently been suggested as a means of assessing cardiac function in ESLD. The VAC (ratio of ventricular elastance to arterial elastance) is measured conventionally by ultrasound and has been correlated with prognosis. Moreover, cardiac biomarkers such as troponin and brain natriuretic peptide (BNP) are deemed early markers [97].

It is difficult to define the exact impact of CCM due to the fact that its clinical course is usually silent, especially in early stages, due to the profound vasodilatation in cirrhosis and offloading of the left ventricle. It only becomes apparent in conditions of stress and increased afterload. LT is a cause of significant cardiovascular stress since there are marked variations in preload and afterload, cardiac workload increases and the existing underlying cardiac dysfunction may become overt heart failure during LT or several days postoperatively. Complete recovery has been recorded at 6 months [98].

Cardiac dysfunction and pulmonary edema are encountered in almost half of the patients within a week after LT. They have been identified as the third most important cause of mortality during the first year following the surgery. High MELD score and AKI have been considered as risk factors. Early diagnosis can prevent acute onset or deterioration of heart failure. An empirical and supportive therapeutic approach is applied which includes optimization of volume status and cardiac monitoring via echo and/or PAC [99, 100].

Prevalence of coronary artery disease (CAD) in cirrhosis reaches 5–26% and has been associated with poor prognosis. It has been correlated with a number of cardiac adverse events: myocardial infraction, arrhythmias, and cardiac death. LT can be postponed in cases with known CAD for medical optimization and/or revascularization [99, 100].

13. Neurological complications

Neurological complications (NC) are still common after LT with a 15–30% incidence rate. In recipients from living donors, this percentage does not exceed 20% [101, 102]. Major neurologic complications immediately postoperatively include alterations of consciousness, seizures, hepatic encephalopathy, CNI neurotoxicity, cerebrovascular complications, central nervous system infections, and central pontine myelinolysis (CPM) [103]. They can delay recovery and make immunosuppression and patient management difficult. Rapid patient recovery requires daily evaluation of mental status and neurological assessment in the ICU.

Immunosuppression-related neurotoxicity can range from headaches and convulsions to posterior reversible encephalopathy (PRES). Immunosuppressants have the potential to reduce the seizure threshold that is enhanced by electrolytic disorders mainly hypomagnesaemia and hypophosphatemia. CNIs are mainly implicated while incidents of PRES have been reported even in treatment with sirolimus. The treatment is conservative involving reduction of dosage and/or interchange with CNI-sparing regimens. Neurotoxicity of corticosteroids can be manifested either in the form of convulsions or myopathy and behavioral disorders [103].

Post-transplant encephalopathy is responsible for 12% of NC. It relates closely to metabolic disorders, CNS infections and/or septic encephalopathy, cerebrovascular events, history of severe encephalopathy, and graft dysfunction [78]. Seizures are one of the most common postoperative neurological consequences and may be the effect of various factors, mainly drug toxicity and metabolic disorders. Correction of underlying causes and administration of anti-convulsive medicines are the appropriate treatment.

Central pontine myelinolysis (CPM) represents a serious complication, with a low incidence of approximately 1–3.5% that may affect the postoperative course of patients. It has been associated with large fluid shift and rapid correction of prolonged hyponatremia. The indicated treatment is supportive and requires careful correction of severe hyponatremia (serum Na <125 mEq/L), which is encountered in approximately 17% of patients with ESLD, using sodium chloride and adjusting Na serum values to 8–10 mEq/L per day [104, 105].

14. Ischemia reperfusion injury

Ischemia-reperfusion injury is related with the degree of transaminitis and primary and/or delayed graft dysfunction. Mitochondria are more prone to I/R injuries with subsequent alterations that can lead to dysfunction or even to necrosis of hepatocytes following LT. Alternatively, machine reperfusion has been proposed to preserve the donor organ. It promises to restore energy balance, extend preservation time while offering the ability to "test" the organ performance [106, 107].

15. Postoperative surgical complications

15.1 Early surgical complications

In the early postoperative period, according to Parikh et al., 79.3% of patients are present with at least one complication with 62.8% of the recipients suffering severe

Complications	Diagnosis-treatment	Therapeutic approach
Abdominal bleeding	Anastomosis site Graft surface Diffusion bleeding	Re-operation
Biliary Complications	Biloma, Hemobilia Bile leaks Anastomosis necrosis Anastomotic stricture	ERCP, PTC, MRCP EUS-guided approach HIDA Digital Cholagiography or Surgical re-intervention

Table 3.
Immediate surgical complications after LT.

Vascular complications	Diagnosis	Treatment
Hepatic artery thrombosis (HAT) 2.9%	DUS, CT Angiography	Emergent revascularization (endovascular or surgical) or re-LT
Hepatic artery stenosis (HAS) 1–2%	DUS, CT Angiography	Endovascular intervention or surgical HA revision
Hepatic artery rupture (HAR) 0.64%	Angiography None in emergency	Emergent surgical hemostasis and surgical repair
Portal vein thrombosis (PVT) 5%	DUS, CT (portal phase) Venography	Surgical revision Endovascular intervention or re-LT
Portal vein stenosis (PVS) 2%	DUS, CT (portal phase) Venography	Endovascular intervention

Table 4.
Vascular complications after LT.

complications. The incidence of those related to surgical techniques range from 5 to 10% and can be categorized into abdominal bleedings, vascular complications, and biliary complications. Treatment can be determined by the severity of each case and its spectrum includes simple surgical interventions, or even re-transplantation. The main complications are illustrated in **Tables 3** and **4** along with diagnostic and therapeutic approaches [108, 109].

16. Conclusions

LT has been established as the gold standard treatment for patients with ESLD and following successful postoperative course, organs previously affected return to normal functionality in due time. Postoperative ICU stay is often imperative, especially in cases of adverse events during operation, delayed cardiovascular resuscitation, utilization of marginal donors, and distant organ dysfunction. Early recognition, evaluation, and treatment of hemodynamic instability, distant organ complications, impaired graft functionality, and use of optimal immunosuppressive agents are of paramount importance.

Prompt recognition and treatment of life-threatening sequelae following LT in addition with optimal management of immunosuppression are keys to successful postoperative care and have led to improved overall survival although recipients are in relatively worse condition and the use of marginal donors is more widespread.

Furthermore, overall survival of LT patients has improved dramatically in recent years due to the formation of LT specific centers and medical teams, which follow each patient from admission to the donor list up to the operation itself as well as during their postoperative course. Therefore, according to the authors, the creation of LT specific ICUs that provide a postoperative continuation of excellency in managing the intricacies of those patients is paramount. Those units will not only provide prompt treatment in cases of a complication but will also act as additional reinforcement against postoperative infections.

Author details

Areti Karapanagiotou[1,2]*, Achillefs Pitsoulis[2], Maria Vasileiou[2] and Nikolaos Voloudakis[3]

1 Intensive Care Unit "Hippokratio" Hospital, Thessaloniki, Greece

2 Intensive Care Unit "G. GENNHMATAS" Hospital, Thessaloniki, Greece

3 Second Surgical Department AUTH, Thessaloniki, Greece

*Address all correspondence to: aretikarapan@gmail.com

References

[1] Zanripar A, Busutil R. Liver transplantation: past, present and future. Nature Reviews. Gastroenterology & Hepatology. 2013;**10**(7):434-440. DOI: 10.1038/nrgastro.2013.88

[2] Adam R, Karam V, et al. 2018 annual report of the European liver transplant registry (ELTR) – 50-year evolution of liver transplantation. Transplant International. 2018;**31**(12):1293-1317

[3] Neuberger J. Liver transplantation in the United Kingdom. Liver Transplantation. 2016;**22**:1129-1135

[4] deLemos AS, Vageti PA. Expanding the donor Pool in liver transplantation: Extended criteria donors. Clinics in Liver Disease. 2013;**2**(4):156-159

[5] Karapanagiotou A, Kydona C, et al. Impact of the model for end-stage-liver-disease (MELD) score in Creece. Transplantation Proceedings. 2014;**46**(9):2312-2315

[6] Asrani S, Kamash P. Model for end-stage liver disease score and MELD exceptions 15 years later. Hepatology International. 2015Jul;**9**(3):346-354

[7] Markin N, Ringenberg K, et al. 2018 clnical update in liver transplantation. Journal of Cardiothoracic and Vascular Anesthesia. 10 Feb 2019. pii: S1053-0770(19)30106-5. DOI: 10.1053/j.jvca.2019.02.004

[8] Kramer D, Siegal E, et al. Perioperative management of the liver transplant recipient. Critical Care Clinics. 2019;**35**:95-105

[9] Utako P, Emyoo T, et al. Clinical outcomes after liver transplantation for hepatorenal syndrome: A systematic review and meta-Analysis. BioMed Research International.

24 May 2018;**2018**:5362810. DOI: 10.1155/2018/5362810. eCollection 2018

[10] Hori T, Ogura Y, et al. Systemic hemodynamics in advanced cirrhosis: Concerns during perioperative period of liver transplantation. World Journal of Hepatology. 2016;**8**(25):1047-1060

[11] Al-Hamoudi W, Alqahtani S, et al. Hemodynamics in the immediate post-transplantation period in alcoholic and viral cirrhosis. World Journal of Gastroenterology. 2010;**16**(5):608-612

[12] Singh S, Nasa V, et al. Perioperative monitoring in liver transplant patients. Journal of Clinical and Experimental Hepatology. 2012;**2**:271-278

[13] Rudnick MR, DeMarchi L, et al. Hemodynamic monitoring during liver transplantation: A state of the art review. World Journal of Hepatology. 2015;**7**(10):1302-1311

[14] Feltracco P, Barbieri S, et al. Intensive care management of liver transplanted patients. World Journal of Hepatology. 2011;**3**(3):61-71

[15] Zarychansky R, Abou-Setta AM, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation. A systematic review and meta-analysis. JAMA. 2013;**309**(7):678-688

[16] Arshed S, Pinsky M, et al. Applied physiology of fluid resuscitation in critical illness. Critical Care Clinics. 2018;**34**:267-277

[17] Mukhtar A, Masry EL, et al. The impact of maintaining normal serum albumin level following living related liver transplantation: Does serum albumin level affect the course? A pilot study. Transplantation Proceedings. 2007;**39**:3214-3218

[18] Sang BH, Bang JY, et al. Hypoalbuminemia within two postoperative days is an independent risk factor for acute kidney injury following living donor liver transplantation: A propensity score analysis of 998 consecutive patients. Critical Care Medicine. 2015;**43**(12):2552-2561

[19] Amouzanden M, Nowak G, et al. Albumin mass balance and kinetics in liver transplantation. Critical Care. 2018;**22**:152-162

[20] Clevenger B, Mallett S, et al. Transfusion and coagulation management in liver transplantation. World Journal of Gastroenterology. 2014;**20**(20):6146-6158

[21] Zamper R, Amorim T, et al. Association between viscoelastic tests guided therapy with synthetic factor concentrates and allogenic blood transfusion in liver transplantation: A before-after study. BMC Anesthesiology. 2018;**18**:198

[22] Lisman T, Potre R. Rebalanced hemostasis in patients with liver disease: Evidence and clinical consequences. Blood. 2010;**116**(6):878-885

[23] Cywinski J, Alster J, et al. Prediction of intraoperative transfusion requirements during orthotopic liver transplantation and the influence on postoperative patient survival. Anesthesia and Analgesia. 2014;**118**:428-437

[24] Dunn LK, Thiete RH, et al. Duration of red blood cell storage and outcomes following Orthotopic liver transplantation. Liver Transplantation. 2012;**18**:475-481

[25] Keegan M, Cramer D, et al. Perioperative care of the liver transplant patient. Critical Care Clinics. 2016;**32**:453-473

[26] Carrier FM, Chasse M, et al. Effects of perioperative fluid management on postoperative outcomes in liver transplantation: A systematic review protocol. Critical Care. 2018;7:180-186

[27] Codes L, De Souza YG, et al. Cumulative positive fluid balance is a risk factor for acute kidney injury and requirement for renal replacement therapy after liver transplantation. World Journal of Transplantation. 2018;**8**(2):44-51

[28] Jin J, Lu D, et al. Clinical and economic impact of goal directed fluid therapy during elective gastrointestinal surgery. Perioperative Medicine. 2018;7:22-30

[29] Reydelle L, Blasco V, et al. Impact of goal-directed therapy protocol on postoperative fluid balance in patients undergoing liver transplantation; a retrospective study. Annales Françaises d'Anesthésie et de Réanimation. 2014;**33**:e47-e54

[30] Jiang GQ, Chen P, et al. Individualized peri-operative fluid therapy facilitating early phase recovery after liver transplantation. World Journal of Gastroenterology. 2012;**18**(16):1981-1986

[31] Wagener G, Gubitosa G, et al. Vasopressin decreases portal vein pressure and flow in the native liver during liver transplantation. Liver Transplantation. 2008;**14**:1664-1670

[32] Mukhtar A, Dabbous H, et al. Modulation of splanchnic circulation: Role in perioperative management of liver transplant patients. World Journal of Gastroenterology. 2016;**22**(4):1582-1592

[33] Hori T, Yamamoto C, Yagi S, et al. Assessment of cardiac output in liver transplantation recipients. Hepatobiliary & Pancreatic Diseases International. 2008;7:362-366

[34] Kumar A, Anel R, Bunnell E, et al. Pulmonary artery occlusion pressure

and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. Critical Care Medicine. 2004;**32**:691-697

[35] Feltracco P, Biancofiore G, et al. Limits and pitfalls of haemodynamic monitoring systems in liver transplantation surgery. Minerva Anestesiologica. 2012;**78**:1372-1384

[36] Krenn CG, De Wolf AM. Current approach to intraoperative monitoring in liver transplantation. Current Opinion in Organ Transplantation. 2008;**13**:285-290

[37] Samgkum L, Liu G, et al. Minimally invasive or noninvasive cardiac output measurement: An update. Journal of Anesthesia. 2016;**30**(3):461-480. DOI: 10.1007/s00540-016-2154-9

[38] DellaRocca G, Costa MG, et al. Preload and haemodynamic assessment during liver transplantation: A comparison between the pulmonary artery catheter and transpulmonary indicator dilution techniques. European Journal of Anaesthesiology. 2002;**19**:868-887

[39] Monnnet X, Teboul JL. Transpulmonary thermodilution: Advantages and limits. Critical Care. 2017;**21**(1):147

[40] Teboul JL, Saugel B, et al. Less invasive hemodynamic monitoring in critically ill patients. Intensive Care Medicine. 2016;**42**:1350-1359

[41] Su BC, Tsai YF, et al. Stroke volume variation derived by arterial pulse contour analysis is a good indicator for preload estimation during liver transplantation. Transplantation Proceedings. 2012;**44**:429-432

[42] Kim SH, Hwang GS, et al. Is stroke volume variation a useful preload index in liver transplant recipients? A

retrospective analysis. International Journal of Medical Sciences. 2013;**10**:751-757

[43] Biancofiore G, Critchley LA, et al. Evaluation of an uncalibrated arterial pulse contour cardiac output monitoring system in cirrhotic patients undergoing liver surgery. British Journal of Anaesthesia. 2009;**102**:47-54

[44] Krejci V, Vannucci A, et al. Comparison of calibrated and uncalibrated arterial pressure-based cardiac output monitors during orthotopic liver transplantation. Liver Transplantation. 2010;**16**:773-782

[45] Biais M, Nouette-Gaulain K, et al. Cardiac output measurement in patients undergoing liver transplantation: Pulmonary artery catheter versus uncalibrated arterial pressure waveform. Anesthesia & Analgesia. 2008;**106**:1480-1486

[46] Camporota L, Beale R. Pitfalls in haemodynamic monitoring based on the arterial pressure waveform. Critical Care. 2010;**14**:124

[47] Dalia A, Flores A, et al. A comprehensive review of transesophageal echocardiography during orthotopic liver transplantation. Journal of Cardiothoracic and Vascular Anesthesia. 2018;**32**:1815-1824

[48] Sakka SG. Assessing liver function. Current Opinion in Critical Care. 2007;**13**:207-214

[49] Fedovarious A, Charlton M. Abnormal liver tests after liver transplantation. Clinics in Liver Disease. 2016;**7**(4):73-79

[50] Sun Y, Yu L, et al. Predictive value of indocyanine green plasma disappearance rate on liver function and complications after liver transplantation. Medical Science Monitor. 2018;**24**:3661-3669

[51] Ren J, Zheng BW, et al. Application of contrast-enhanced ultrasound after liver transplantation: Current status and perspectives. World Journal of Gastroenterology. 2016;**22**(4):1607-1616

[52] Roullet S, Defaye M, et al. Liver transplantation with old grafts: A ten-year experience. Transplantation Proceedings. 2017;**49**:e2135-e2143

[53] Lué A, Solanas E, et al. How important is donor age in liver transplantation? World Journal of Gastroenterology. 2016;**22**(21):4966-4976

[54] Alamo JM, Olivares C, et al. Donor characteristics that are associated with survival in liver transplant recipients older than 70 years with grafts. Transplantation Proceedings. 2013;**45**(10):3633-3636

[55] Gilbo N, Jochmans I, et al. Age matching of elderly liver grafts with elderly recipients does not have a synergistic effect on long-term outcomes when both are carefully selected. Transplantation direct. 2019;**5**:e342

[56] Boecker J, Czigany Z, et al. Potential value and limitations of different clinical scoring systems in the assessment of short- and long-term outcome following orthotopic liver transplantation. PLoS One. 2019;**14**(3):e0214221

[57] Mandell MS, Stoner TJ, et al. A multicentre evaluation of safety of early extubation in liver transplant recipients. Liver Transplantation. 2007;**13**:1557-1563

[58] Rao JH, Zhang F, et al. Effects of multimodal fast-track surgery on liver transplantation outcomes. Hepatobiliary & Pancreatic Diseases International. 2017;**16**:364-369

[59] Li J, Wang C, et al. Immediate versus conventional postoperative tracheal extubation for enhanced recovery after liver transplantation IPTE versus CTE for enhanced recovery after liver transplantation. Medicine. 2018;**97**:45-55

[60] Taner CB, Willingham DL, et al. Is a mandatory intensive care unit stay needed after liver transplantation? Feasibility of fast-tracking to the surgical ward after liver transplantation. Liver Transplantation. 2012;**18**:361-369

[61] Razonable R, Findlay J, et al. Critical care issues in patients after liver transplantation. Liver Transplantation. 2012;**17**:511-527

[62] Yuan H, Tuutte-Newhall J, et al. Prognostic impact of mechanical ventilation after liver transplantation: A national database study. American Journal of Surgery. 2014;**208**(4):582-590

[63] Lui J, Spaho L, et al. Intensive care of pulmonary complications following liver transplantation. Journal of Intensive Care Medicine. Nov 2018;**33**(11):595-608

[64] Tobin MJ, Jubran A. Weaning from mechanical ventilation. In: Tobin MJ, editor. Principles and Practice of Mechanical Ventilation. 3rd ed. Chapter 58. The McGraw-Hill Companies, Inc.; 2013. pp. 1307-1351. ISBN: 978-0-07-173626-8

[65] Wu X, Zheng R, et al. Effect of transpulmonary pressure-guided positive end-expiratory pressure titration on lung injury in pigs with acute respiratory distress syndrome. Journal of Clinical Monitoring and Computing. 2019. DOI: 10.1007/s10877-019-00267-2

[66] Saner F, Steven O, et al. How far can we go with positive end-expiratory pressure (PEEP) in liver transplant patients? Journal of Clinical Anesthesia. 2010;**22**:104-109

[67] Jaber S, Lescot T, et al. Effect of noninvasive ventilation on tracheal

re-intubation among patients with hypoxemic respiratory failure following abdominal surgery: A randomized clinical trial. JAMA. 2016;**315**:1345-1353

[68] Lee KW, Cho CW, et al. Extracorporeal membrane oxygenation support for refractory septic shock in liver transplantation recipients. Annals of Surgical Treatment and Research. 2017;**93**(3):152-158

[69] Combes A, Pesenti A, et al. Is extracorporeal circulation the future of acute respiratory distress syndrome management? American Journal of Respiratory and Critical Care Medicine. 2017;**195**(9):1161-1170

[70] Cosardereli_oglou C, Cosar AM, et al. Hepatopulmonary syndrome and liver transplantation: A recent review of the literature. Journal of Clinical and Translational Hepatology. 2016;**4**:47-53

[71] Aldenkortt F, Aldenkortt M, et al. Portopulmonary hypertension and hepatopulmonary syndrome. World Journal of Gastroenterology. 2014;**20**(25):8072-8081

[72] Jadiowiec C, Taner T. Liver transplantation: Current status and challenges. World Journal of Gastroenterology. 2016;**22**(18):4438-4445

[73] Pillai AA, Levitsky J. Overview of immunosuppression in liver transplantation. World Journal of Gastroenterology. 2009;**15**:4225-4231

[74] Baganate F, Beal E, et al. Early mortality after liver transplantation: Defining the course and the cause. Surgery. 2018;**116**:58-69

[75] Clark NM, Scott JC, et al. Infectious complications in liver transplantation UpToDate. Available from: http://www.uptodate.com/contents/infectious-complications in- liver-transplantation [Accessed: 01-October-2018]

[76] Karapanagiotou A, Cydona C, et al. Infections after orthotopic liver transplantation in the intensive care unit. Transplantation Proceedings. 2012;**44**:2748-2750

[77] Weiss E, Dahmani S. Early-onset pneumonia after liver transplantation: Microbiological findings and therapeutic consequences. Liver Transplantation. 2010;**16**:1178-1185

[78] Fernandez T, Gardiner P. Critical care of the liver transplant recipient. Current Anesthesiology Reports. 2015;**5**:419-428. DOI: 10.1007/s40140-015-0133-6

[79] Siddique O, Siddique A, et al. Effects of infection on post-transplant outcomes: Living versus deceased donor liver transplants. Journal of Clinical Experimental Hepatology. 2018;**4**(1):28-34

[80] Anastácio LR, Correia MI. Nutrition therapy: Integral part of liver transplant care. World Journal of Gastroenterology. 2016;**22**(4):1513-1522

[81] Arabi YM, Casaer MP, et al. The intensive care medicine research agenda in nutrition and metabolism. Intensive Care Medicine. 2017;**43**:1239-1256

[82] Fereira LG, Anastacio LR, et al. Assessment of nutritional status of patients waiting for liver transplantation. Clinical Transplantation. 2011;**25**:248-254

[83] Kaido T, Ogura Y. Effects of post-transplant enteral nutrition with an immunomodulating diet containing hydrolyzed whey peptide after liver transplantation. World Journal of Surgery. 2012;**36**:1666-1671

[84] Karapanagiotou A, Cydona C, et al. Acute kidney injury after orthotopic liver transplantation. Transplantation Proceedings. 2012;**44**:2727-2729

[85] Karapanagiotou A, Dimidriadis C, et al. Comparison of RIFLE and AKIN criteria in the evaluation of the frequency of acute kidney injury in post-liver transplantation patients. Transplantation Proceedings. 2014;**46**:3222-3227

[86] Hilmi I, Damian D, et al. Acute kidney injury after orthotopic liver transplantation using live donor versus cadaveric donor grafts: A propensity score-matched analysis. Liver Transplantation. 2015;**21**(9):1179-1185

[87] de Haan JE, Hoorn EJ, de Geus HRH. Acute kidney injury after liver transplantation: Recent insights and future perspectives. Best Practice & Research. Clinical Gastroenterology. 2017;**31**:161-169

[88] Papadopoulos S, Karapanagiotou A, et al. Causes and incidence of renal replacement therapy application in orthotopic liver transplantation patients: Our experience. Transplantation Proceedings. 2014;**46**:3228-3231

[89] Chen XB, Xu MQ. Primary graft dysfunction after liver transplantation. Hepatobiliary & Pancreatic Diseases International. 2014;**13**:125-137

[90] Neves DB, Rusi MB, et al. Primary graft dysfunction of the liver: Definitions, diagnostic criteria and risk factors. Einstein. 2016;**14**(4):567-572

[91] Xie Q, Zheng S. Risk factors for primary non-function after liver transplantation. HPB. 2018;**20**(2):S789-S790

[92] Pareja E, Cortes M, et al. A score model for the continuous grading of early allograft dysfunction severity. Liver Transplantation. 2015;**21**:38-46

[93] Agopian VG, Halander-Locke MP, et al. Evaluation of early allograft function using the liver graft assessment following transplantation risk score model. JAMA Surgery. 2018;**153**(5):436-444

[94] Dogan N, Husing-Kabar A, et al. Acute allograft rejection in liver transplant recipients: Incidence, risk factors, treatment success, and impact on graft failure. The Journal of International Medical Research. 2018;**46**(9):3979-3990

[95] Shindoh J, Akamatsu N, et al. Risk factors for acute liver allograft rejection and their influences on treatment outcomes of rescue therapy in living donor liver transplantation. Clinical Transplantation. 2016;**30**:880-896

[96] Liu H, Jayakumar S, et al. Cirrhotic cardiomyopathy: Implications for Liver Transplantation. Liver Transplantation. 2017;**23**:826-835 ASLD

[97] Shin WJ, Song JG, Jun IG, et al. Effect of ventriculo-arterial coupling on transplant outcomes in cirrhotics: Analysis of pressure-volume curve relations. Journal of Hepatology. 2017;**66**:328-337

[98] Carvalho MVH, Kroll PC, et al. Cirrhotic cardiomyopathy: The liver affects the heart Braz. Journal of Medical and Biological Research. 2019;**52**(2):e7809

[99] Kwon HM, Hwang GS, et al. Cardiovascular dysfunction and liver transplantation. Korean Journal of Anesthesiology. 2018;**71**:85-91

[100] Nicolau-Raducu R, Gitman M, et al. Adverse cardiac events after orthotopic liver transplantation: A cross-sectional study in 389 consecutive patients. Liver Transplantation. 2015;**21**:13-21

[101] Živković SA. Neurologic complications after liver transplantation. World Journal of Hepatology. 2013;**5**(8):409-416

[102] Saner FH, Gensicke J, et al. Neurologic complications in adult living donor liver transplant patients: An underestimated factor. Journal of Neurology. 2010;**257**:253-258

[103] Li C, Jin H, et al. Clinical analysis of neurological complications following liver transplantation. Biomedical Research. 2017;**28**(6):2471-2474

[104] Lening C, Agorian V, et al. Incidence, etiology, and outcomes of altered mental status in the perioperative setting of liver transplantation. The Neurohospitalist. 2018;**8**(3):124-128

[105] Karapanagiotou A, Kydona C, et al. The effect of hyponatremia on the outcome of patients after orthotopic liver transplantation. Transplantation Proceedings. 2012;**44**:2724-2726

[106] Cerera C, Narsalla D, et al. Normothermic machine preservation of the liver: State of the Art. Current Transplantation Reports. 2018;**5**:104-110

[107] Watson C, Jochmans I. From "gut feeling" to objectivity: Machine preservation of the liver as a tool to assess organ viability. Current Transplantation Reports. 2018;**5**:72-81

[108] Tan-Tam C, Segedi M, et al. Surgical complications of liver transplantation. AME Medical Journal. 2018;**3**:107-114

[109] Meek J, McDougal J, et al. Use of a mechanical thrombectomy device to treat early hepatic artery thrombosis after orthotopic liver transplant. Radiology Case Reports. 2018;**13**:522-526