PREDICTIVE FACTORS OF INTENSIVE CARE LENGTH OF STAY IN LIVER TRANSPLANT RECIPIENTS

by

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SIGNED: __Lynn A. Rowe_____

DEDICATION

This dissertation started as a pipe dream that I never thought would happen. But now, five years later, I proudly present my research to improve the care of our patients. However, without the support of my husband Bill, this would not have been possible. This is for my mom and dad, who were always willing to lend a helping hand, and to my grandmother who died before I began this journey but believed that I could do anything I put my mind to. I say thank you.

After more than five years of work, I understand the next phase of my professional journey is to improve patient care through my dedication to research. With this focus, I believe that I can make a difference. So for this next phase of my journey, the following quote will show how to measure my success.

The most difficult thing is the decision to act, the rest is merely tenacity.

The fears are paper tigers.

You can do anything you decide to do.

You can act to change and control your life: and the procedure, the process, is its own reward.

Amelia Earhart, aviator

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ABSTRACT

The purpose of this study was to evaluate liver transplant recipient factors associated with postoperative complications leading to longer intensive care unit (ICU) length of stay which in turn may increase hospital morbidity and mortality. A retrospective, correlational design was developed with a sample of 230 participants. Data were collected for liver transplant recipients over a four-year period (June 2007-December 2011) from the electronic medical record and the transplant database. T test and binary logistic regression were used to assess for the factors predictive of ICU complications, ICU length of stay (LOS), hospital length of stay (HLOS), and overall morbidity and mortality. Data were collected from three time periods: preoperatively, intraoperatively, and postoperatively. The factors identified as statistically significant were cold ischemic time, lowest intraoperative glucose, postoperative four-hour blood urea nitrogen (BUN), Postoperative Day 1 (POD 1) hematocrit, postoperative lowest systolic blood pressure, and fresh frozen plasma (FFP) transfusions. Mortality occurred in 1 recipient in the > 9-day ICU stay group, and 7 deaths were noted in the > 19-day hospital LOS group. Age of recipients who died was 48-59 (6 males, 2 females), with 7 Caucasian and 1 Other. Comorbidities of these deceased recipients were diabetes and obesity with MELD scores of 18-45. Complications experienced by recipients included: 6 with renal failure, 2 with sepsis, 3 with graft dysfunction, and 1 with cerebral edema. Findings from this study showed factors that impact ICU LOS, HLOS, and mortality, including BUN, glucose, and hematocrit. Implications for practice are that these factors should be closely monitored in the pre-, intra-, and postoperative time periods to reduce risks of complications to transplant recipients. Future research should include further evaluation of the factors associated with poor transplant outcomes, including glucose, continuous

renal replacement therapy (CRRT) use, age, and gender. Nurse researchers must continue to strive to understand the pathophysiological mechanism of liver disease to reduce ICU complications ultimately to improve the care and outcomes of liver transplant recipients while reducing ICU LOS and HLOS.

CHAPTER 1 INTRODUCTION

Overview

Liver transplantation is associated with a high incidence of postoperative complications, leading to longer intensive care unit (ICU) and hospital length of stay (LOS) and increased hospital morbidity and mortality. Understanding the causes of liver transplantation and the variables that affect the incidence of postoperative complications will help in the design of programs to lessen the incidence of postoperative complications.

Liver and biliary disease affects all ages of people in the United States. Today, more than 30 million Americans (1 in 10) have a diagnosis of chronic liver disease or cirrhosis (American Liver Foundation, 2014). Liver disease has been identified as the 10th-leading cause of death in the United States, accounting for 44,677 deaths from liver disease and 25,192 as a result of end-stage liver disease (ESLD), the final stage of liver failure (Al-Khafaji & Huang, 2011; W. R. Kim, Brown, Terrault, & El-Serag, 2002; NIH, 2004). The epidemiology of liver disease, specifically incidence, is difficult to determine due to the long latency period between the patient's disease occurrence and its detection (W. R. Kim et al., 2002). Liver and biliary disease have multifactorial etiologies, including alcohol use/abuse, genetics, infectious agents, metabolic disturbances, and toxins (C.-T. Huang, Lin, Chang, & Lee, 2011; Stilley et al., 2010; Washburn, Meo, Halff, Roberts, & Feng, 2009). The most common liver diseases are: viral hepatitis, alcoholic and nonalcoholic fatty liver disease, autoimmune and metabolic liver disease, and drug-induced liver injury. Symptoms of liver disease include fatigue, muscle weakness, nausea, poor appetite and weight loss, fluid retention, predisposition to bleeding and infection,

depression, anxiety, and often physical disability that limits the recipients' ability to work (NIH, 2004).

ESLD is the result of any disease that alters function of either the hepatocyte or excretory function within the biliary system. ESLD complications include recurrent intractable ascites, variceal hemorrhage, and refractory encephalopathy leading to complete liver failure (Al-Khafaji & Huang, 2011; Manzarbeitia & Smith, 2003).

Acute liver failure (ALF) encompasses (1) acute chronic hepatic failure, (2) late-onset hepatic failure, and (3) fulminant failure and is considered a gastrointestinal emergency. The clinical criteria for diagnosis of ALF include (1) a coagulation abnormality (international normalized ratio [INR] greater than 1.5) with a mental alteration or encephalopathy; (2) presence of cirrhosis; and (3) any illness that causes acute liver failure with a duration of less than 26 weeks (Shenoy, 2006).

Liver transplantation to treat liver disease began in the 1960s and was considered an experimental procedure. By 1983, the National Institutes of Health (NIH) determined liver transplantation to be clinically accepted as a definitive therapy and resource-intensive intervention for patients experiencing ESLD (Manzarbeitia & Smith, 2003; Verdonk, van den Berg, Sloof, Porte, & Haagsma, 2007; Wertheim, Petrowsky, Saab, Kupiec-Weglinski, & Busuttil, 2011). Indication for liver transplantation are autoimmune diseases, drug-mediated (e.g., acetaminophen overdose) thrombotic complications or vascular complication, viral hepatitis, infectious processes, malignancy, metabolic disorders, and trauma (Shenoy, 2006). Contraindications are multisystem organ failure, sepsis, uncontrolled or extrahepatic malignancy, irreversible brain damage, or unresponsive cerebral edema: defined as an intracranial pressure

(ICP) value greater than 50 mm Hg and cerebral perfusion pressure (CPP) less than 40 mg/dL (Shenoy, 2006).

Despite the success of liver transplantation, one challenge is the availability of donor organs. Nationwide, a reduction in donors is noted, from 7,017 in 2006 to 6,608 in 2010. This reduction in donors has resulted in a waiting list in excess of 12,230 patients. Despite the large number of patients on the waiting list, there were only 6,319 transplant recipients over the same 5-year range. As of July 21, 2010, the number of patients on the waiting list had grown to 16,647; unfortunately, donor numbers remain unchanged (Wynn & Alexander, 2011). Impaired function paired with the recipients' poor health and complications intra- and postoperatively result in suboptimal postoperative outcomes. Complications arising after transplantation may include biliary complications (atresia, leaks), hepatic artery thrombosis, portal vein thrombosis, and bleeding, often resulting in surgical re-exploration (Wertheim et al., 2011). If a transplant is a result of cirrhosis, additional complications that have demonstrated increase morbidity and mortality include portal arterial hypertension, varices, ascites, and portosystemic encephalopathy (W. R. Kim et al., 2002). Causes of death in the postoperative period include sepsis (50.7%), cancer (14.2%), cardiac arrest (8.2%), graft failure (5%), intracranial hemorrhage (3.7%), and multisystem failure (2.7%; Zand et al., 2011). Strategies to help reverse these complications include intubation (endotracheal, laryngeal mask) with mechanical ventilation and administration of blood, plasma, and platelet transfusions (Feltracco et al., 2011; S. Lee et al., 2013). Administration of benzodiazepines and mannitol reduces increased intracranial pressure. Adverse events due to the recurrence of the underlying liver disease, the recipients' nonadherence to the medical plan, continuation of smoking, alcohol consumption, and non-

adherence to immunosuppressant therapy all impact morbidity and mortality (Stilley et al., 2010). Improvement in morbidity and mortality is a result of improvements in the technical skill of the surgeon, donor selection, and prevention of complications (Shenoy, 2006).

Despite the increased success of liver transplantation, the underlying liver disease of recipients places a significant strain on the health care system. Recipients who receive organs from high-risk donors (extended criteria donors) have longer LOS and higher medical costs (Alkofer et al., 2006). Extended criteria donors are donors aged 60 or older, or greater than 50 years old with at least two of the following conditions: hypertension by history, hypernatremia exceeding 155 mEq/L, serum creatinine > 1.5 mg/dl, cause of death from a cerebrovascular accident, cold ischemia time over 12 hours, and organs retrieved after cardiac death. Annual medical costs for liver transplants exceed $1 billion in personal health care (physician visits, prescriptions, laboratory testing) with direct costs (hospital stay, surgical costs, and immunosuppressant agents) of a liver transplant estimated at $1.6 billion (NIH, 2004). Transplant costs include hospitalization, professional fees, and prescriptions, with an additional $2.4 billion dollars calculated for other medical care (care unrelated to transplant procedure and postoperative period). Liver transplantation is identified as the highest cost Medicare-approved procedure, with costs expected to increase proportionally to the increasing insurance premiums, decreases in Medicare spending, and increases in Medicaid patient volumes (Axelrod et al., 2011).

Costs of liver transplantation are driven by the severity of liver disease and length of stay in the intensive care unit (ICU) post transplantation. Length of stay (LOS) is an indirect measure of resources needed within the ICU and is directly related to recipients' complications

(Merion et al., 2010). Historically, hospital length of stay (HLOS) averages 33-64 days, with the post-transplant period consisting of 7 to 10 days of the total hospital stay (Kramer & Zimmerman, 2011; Showstack et al., 1999). Reports indicate that ICU stays within the last decade have decreased by an average of 3.9 days (standard deviation [*SD*] of 5.1 days), with a mortality rate of 8% (Kramer & Zimmerman, 2011). This reduction in ICU LOS is variable. If the transplant recipient does not experience any complications in the postoperative period, ICU LOS is 16 days (*SD* = 14.1 days). However, if complications are experienced, ICU LOS averages 45 days (Merion et al., 2010; Moreno & Berenguer, 2006). If a recipient receives a transplant and was previously in the ICU, the recipient's LOS may range from 25.0 to 56.8 days (Merion et al., 2010), with average daily costs of $1,900-$2,300 (Norris, Jacobs, Rapoport, & Hamilton, 1995). Total ICU costs account for approximately 20-30% of total hospital costs, with total hospital expenditures of $145,776-$287,432 per case. These costs are calculated without the professional expenses and individual transplant center fees (Alban, Nisim, Ho, Nishi, & Shabot, 2006). Post-discharge medical costs for the first year post transplantation average approximately $203,000 per recipient (Showstack et al., 1999; Smith et al., 2009; Whiting, Martin, Zavala, & Hanto, 1999). The first-year costs cover only the surgical intervention because post-transplant medications (immunosuppression regimen, steroids, and antibiotics) are covered by the pharmaceutical companies. After the first year, these costs will increase due to the development of complications or hospital readmissions.

Problem Statement

Prediction and prevention of complications from liver transplant are a source of improvement in care of the liver transplant recipient in the ICU, but few studies have analyzed the preoperative, intraoperative, and postoperative factors that result in longer ICU LOS. Additional gaps exist in the research related to the identification of donor and recipient factors that drive hospital LOS, and the resulting morbidity and mortality within the ICU in the immediate post-transplant period (Saner et al., 2008).

Purpose

The purpose of this study was to evaluate liver transplant recipient factors associated with postoperative complications leading to longer ICU LOS with increased hospital morbidity and mortality.

Specific Aims

Three aims have been identified for this dissertation proposal.

Specific Aim 1: Determine factors in the preoperative, intraoperative, and postoperative period that predict ICU complications (bleeding, sepsis, graft dysfunction, acute renal failure, cerebral edema, and prolonged mechanical ventilation).

Specific Aim 2: Determine the predictive factors of liver recipients in the preoperative, intraoperative, and postoperative period as they relate to ICU and hospital length of stay.

Specific Aim 3: Describe the relationship of ICU complications with intensive care length of stay, hospital length of stay, and mortality.

Significance of the Study

Nursing researchers must continue to strive to understand the pathophysiologic mechanisms of liver disease to improve the care and outcomes of liver transplant recipients (W. R. Kim et al., 2002). Knowledge of pathophysiologic mechanisms allows for the identification of characteristics of recipients that require alternative medical strategies to better predict and/or prevent common postoperative complications. These predictions may reduce a recipient's ICU LOS and HLOS and ultimately improve the morbidity and mortality associated with solid organ transplantation (Stilley et al., 2010).

Operational Definitions

Throughout this research study, the following definitions are used:

1. Acute renal failure: Identified by physician documentation of reduced function, no urine output, requiring assistance of dialysis or continuous renal replacement therapy (CRRT). An acute increase of the serum creatinine level from baseline in the postoperative period.
2. Bleeding: Acute decrease in hemoglobin to at least 8.0 gm/dL that requires at least one unit of red blood cell transfusion in 24 hours or as identified by physician documentation of bleeding.
3. Cerebral edema: The excess accumulation of water in the intra- and/or extracellular spaces of the brain (Jha, 2003). For this study, cerebral edema was defined as a change in level of consciousness that is caused by the presence of hepatic encephalopathy graded using the West Haven criteria as documented by the treating transplant physicians.

4. Child-Pugh score: A score with value in the prognosis of patients with cirrhosis. Scores are calculated using total serum bilirubin, serum albumin, INR, presence of ascites, and presence of encephalopathy (Durand & Valla, 2005; Wunsch, Zawada, Mróz, Salamonik, & Milkiewicz, 2008). Interpretation of results is somewhat subjective but breaks down into three classes: Class A (5-6 points), Class B (7-9 points), and Class C (10-15 points). The higher the points, the more severe the disease state, and higher associated mortality rate (Durand & Valla, 2005).
5. Deceased donor: A deceased individual who agreed to donate a specific organ.
6. End-stage liver disease (ESLD): Final stage of liver disease characterized by the abnormality of liver synthetic and excretory functions, with clinical symptoms of ascites, variceal hemorrhage, hepatic encephalopathy, and renal impairment (Cox-North, Doorenbos, Shannon, Scott, & Curtis, 2013).
7. Graft dysfunction: Immunological failure leading to loss of liver function during the first week post transplant. Graft dysfunction was identified as graft failure based on physician documentation of graft failure or the presence of elevated liver enzymes above baseline, with elevated total bilirubin levels and continued presence of coagulopathy and encephalopathy (Moreno & Berenguer, 2006).
8. Hepatic encephalopathy (HE): Complication of liver failure resulting in progressive but potentially reversible conditions from mild alteration of cognitive and motor function to coma and death (Eroglu & Byrne, 2009).
9. ICU complications: Complications are those conditions experienced by the liver transplant recipient postoperatively while in the ICU. These complications include:

bleeding, sepsis, graft dysfunction, acute renal failure, cerebral edema, and prolonged mechanical ventilation.

10. Intraoperative time period: Time beginning with the initiation of anesthesia and ending with the end of anesthesia delivery and exit from the operating room.
11. Liver failure: Rapid deterioration of liver function, demonstrating the clinical presentation of coagulopathies and an altered mental status, as a result of multiple medical conditions, including cirrhosis, drug overdose, hepatitis B or C, hepatocellular carcinoma, portal vein thrombosis, and Wilson disease (Sood, 2011).
12. Outcomes: Outcomes of the study specifically of interest are the development of complications (bleeding, infection, graft failure, rejection, and prolonged ventilator time) and increased ICU and hospital LOS.
13. Postoperative Day 1: Includes all laboratory data collected within the first 24 hours post liver transplantation surgery.
14. Postoperative time period: Period that starts with recipient's arrival in the ICU post transplant until transfer to the next level of care. Laboratory data were collected four hours postoperatively and through Postoperative Day 1.
15. Preoperative time period: Period that starts upon admission to the hospital until the patient is transferred to the operating room. Laboratory data for this time period were collected 12 hours prior to surgery because this was when baseline laboratory tests were ordered.
16. Prolonged mechanical ventilation time: Transplant recipients requiring greater than 24 hours of mechanical ventilation in the postoperative period.

17. Renal dysfunction: Defined as a creatinine level greater than 1.8 mg/dL, an increased base creatinine greater than 50%, or a glomerular filtration rate (GFR) below 30 milliliters per minute (Benten, Staufer, & Sterneck, 2009).
18. Respiratory failure: Loss of the ability to ventilate adequately or to provide sufficient oxygen to the blood and systemic organs. Four types exist: hypoxemic, hypercapnic, perioperative, shock (Melanson, 2014). These conditions would include development of atelectasis, pleural effusion, and poor compliance as a result of edema in the chest wall or high intra-abdominal pressure. Eleven percent of liver transplant recipients develop respiratory failure and require mechanical ventilation support (C.-T. Huang et al., 2011).
19. Sepsis: ICU complication that is the result of an inflammatory and procoagulant response to infection that causes microvascular changes. This condition was identified through physician notes and the presence of a diagnosis of infection with systemic inflammatory response syndrome (SIRS) criteria, elevated or low white blood cell counts, tachycardia, respiratory rate (greater than 20/minute), and evidence of organ dysfunction (Burdette, 2014).
20. Transplant recipient: Patient who has received a solid organ transplant. Within this study, the organs were livers from deceased donors.

CHAPTER 2 REVIEW OF THE LITERATURE

Introduction

This chapter provides the state of the science addressing the pathophysiological conditions associated with liver failure and the accompanying need for liver transplantation. The literature review identifies common themes representing five categories: predictive tools, outcomes (physiologic, recipient, and donor variables, including type of death), length of stay (hospital, ICU), postoperative ICU complications (bleeding, cerebral edema, graft dysfunction, acute renal failure, sepsis, and prolonged mechanical ventilation), and costs. Each category has three time periods: preoperative, intraoperative, and postoperative.

A literature review was performed using the search engines Google Scholar, Cochrane Review, the clinical evidence-based medicine (EBM) search (general and surgical), and OVID/Medline. Search terms used included liver transplantation, deceased donor, length of stay, mechanical ventilation, prediction, postoperative complications in transplantation, and ICU. The search dates for the literature review were January 1, 1990, to November 15, 2011. Most of the identified studies used retrospective data collection methods. A secondary literature search was performed with dates from December 1, 2011 to May 30, 2014 after data were analyzed to determine if additional literature could be found to support the researchers' findings.

Background and Significance

Between 1996 and 2008, 250,000 transplants were performed, with approximately 10,000 for the treatment of acute and chronic ESLD (Alban et al., 2006; Ford, Sakaria, & Subramanian, 2010). Between 2008 and 2012, more than 65,000 liver transplants were performed, with 57,000 completed on adults and 8,700 children (SRTR, 2012; Wynn & Alexander, 2011). Indications for

liver transplantation include alcohol-induced injury, autoimmune diseases, cryptogenic cirrhosis, hepatocellular cancer, and infection (Mailey et al., 2009; Rajiv, 2005).

Within the United States, ESLD is the 12th-leading cause of death but 7th-leading cause of death in people between the ages 25 and 64 (Cox-North et al., 2013). Common complications in liver transplant recipients include ascites, hepatic encephalopathy, hypotension, hypoxia, ischemia, renal impairment, surgical problems (e.g., clots, graft dysfunction), and side effects of the immunosuppressive medications that increase the risk of graft rejection (Moreno & Berenguer, 2006).

A recipient's survivability postoperatively is influenced by the complexity of preexisting diseases and the development of postoperative complications. These complications often precipitate a prolonged LOS, translating into increased cost and risk of death (Mailey et al., 2009; Smith et al., 2009). Despite post-transplant complications increasing the cost of liver transplantation, little research has focused on the effect of complications on total resource use and patient outcomes, offering an opportunity for researchers to study this issue in more depth (Siddiqui et al., 2008; Smith et al., 2009).

An estimated 10% of patients with advanced liver disease require some surgical intervention, including transplantation in the last two years of their lives (Koffron & Stein, 2008; Malik & Ahmad, 2009). Therefore, clinical evaluations pre-transplant must include need, urgency, and technical feasibility of the surgery, paired with physical assessments, diagnostic testing (laboratory/radiology), and predictive scores (e.g., MELD). Stravitz et al. (2007) argued that it is impossible to predict recovery or death for patients experiencing acute liver failure without the intervention of transplantation. Ferraz-Neto et al. (2008) identified standardized tools

in the pretransplant period that must be used to assess the clinical conditions present in the liver recipient may predict postoperative complication risks. Ioannidis and Tzoulaki (2010) suggested that predictive tools must be unambiguous, favor benefit-to-risk ratios, and be inexpensive and convenient for use in the clinical setting. Common predictive tools in the transplant literature are Child-Pugh and Model of End-Stage Liver Disease (MELD) score, mortality predictive model (MPM), sequential organ function assessment (SOFA), and Survival Outcomes Following Liver Transplantation (SOFT; Durand & Valla, 2005; Dutkowski, De Rougemont, Müllhaupt, & Clavien, 2010; Lemeshow et al., 1993). Each of these tools determines patient risk of death while awaiting transplantation but has not been useful in the prediction of long-term transplant mortality (Year 1, 3, and 5 post liver transplant). This study uses the MELD and Child-Pugh score to measure the severity of recipient illness based on preoperative mortality risk and will analyze the ability of the resulting scores to predict postoperative complications and the effect on the recipients' ICU LOS.

Model of End-Stage Liver Disease (MELD)

MELD was first introduced in 2002 to assist in prioritization of organs based on clinical urgency (Foxton et al., 2010; Tenório et al., 2010). MELD has been shown to be valid as a measure predicting mortality of patients on the liver transplant waiting list but fails to predict long-term outcomes in the postoperative period (Attia et al., 2008; Tenório et al., 2010). Despite MELD implementation, a continued reduction in donor organs has led to an increase in recipient deaths that has been associated with increased patient severity of illness and availability of less-ideal donors (H.-C. Huang, Lee, & Huo, 2009). Three variables define the MELD score: serum bilirubin, serum creatinine, and INR; these are used to calculate an acuity or urgency score

(Bucuvalas, Campbell, Cole, & Guthery, 2006; Guo et al., 2010; Tenório et al., 2010). The formula for calculation is: MELD = 3.8 [Ln serum bilirubin (mg/dL)] + 11.2 [Ln INR] + 9.6 [Ln serum creatinine (mg/dL)] + 6.4 (Kamath et al., 2001; Oberkofler et al., 2010; Tenório et al., 2010). MELD scores range from 0 to 40, with higher scores indicating increased disease severity. However, for standardization in organ allocation, the cutoff for a MELD score is 40 (Oberkofler et al., 2010).

Validation for the MELD score was demonstrated with the concordance ("c") statistic that yields high accuracy according to risk in the short term (3 months) with values of 0.8 (Table 1). The concordance "c" statistic, also known as the area under the curve (AUC) is used to report prognostic effects of variables studied. This statistic is determined by the ranks of predicted probabilities or discrimination and compares them to the ranks in individuals with and without the disease of interest, known as sensitivity (Cook, 2008). Normal range is from 0.5 (no predictive ability) to 1 (perfect discrimination). Within any study a c statistic between 0.8 and 0.9 is anticipated, ensuring accuracy of the results. If the calculated results are greater than 0.7 the data are useful (Kamath et al., 2001). Sensitivity, specificity, and negative and positive predictive values are calculated to measure the effect on a specific population.

MELD sensitivity is 77.8%-92.7%, with a specificity of 69%-92.7%, positive predictive values of 70%, and negative predictive values of 95%, making it clinically superior to the Child-Pugh score for prediction of mortality which is used in prediction of liver disease mortality in patients with cirrhosis (Chatzicostas et al., 2003; Kamath et al., 2001; Okonkwo, Nwosu, & Bojuwoye, 2011; Soliman et al., 2011).

MELD score is used by medical teams to identify patients at high risk of death preoperatively, which has improved the organ allocation process (NIH, 2004). Strengths of the MELD score are that it is a simple, objective measure of disease severity with a continual scale and the ability to predict short-term mortality risk while accurately predicting 30-month survival (Bernardi, Gitto, & Biselli, 2011; Wunsch et al., 2008). Weaknesses of the MELD are the inability to capture endpoints for prioritization in hepatocellular carcinoma and portopulmonary hypertension patients and that the MELD underscores patients with malnutrition, hyponatremia, and male gender (Bernardi et al., 2011). Due to the severity of liver disease, it is suggested that hyponatremia (excluded from the current calculation) should be included in the MELD calculation to improve the predictive validity in both the pre- and postoperative period (H.-C. Huang et al., 2009).

Child-Pugh Score

Child-Pugh is a descriptive, prognostic indicator used to evaluate the prognosis of patients with cirrhosis (Durand & Valla, 2005). Laboratory values used in calculating this score are total serum bilirubin, serum albumin, INR, ascites, and the presence of encephalopathy (Durand & Valla, 2005; Wunsch et al., 2008). Interpretation of results is broken down into three classes: Class A (5-6 points), Class B (7-9 points), and Class C (10-15 points). Higher points equate to a higher severity of disease with higher mortality rates (Durand & Valla, 2005). Limitations to this score are its arbitrary cutoff of values and that each variable has equal weight. This equality may result in either an overestimation or underestimation of the severity of illness. Despite these scores predicting mortality while patients are on the waiting list, they have not

been able to predict transplant outcomes with certainty (H. J. Kim & Lee, 2013). Despite these limitations, the Child-Pugh score is the only tool easily used at the bedside.

Each score (MELD and Child-Pugh) has been validated using the concordance or c statistics in four patient populations, including hospitalized patients, non-cholestatic ambulatory patients, primary biliary cirrhosis, and chronic cirrhosis (Angermayr et al., 2003). Studies focused on cirrhosis yield the closest results, with Child-Pugh demonstrating a sensitivity of 66.7-91% specificity 76%-90%, positive predictive value 33%, and negative predictive value 97.1% (Chatzicostas et al., 2003; Soliman et al., 2011).

Table 1

C Statistic for MELD and Child-Pugh and One-, Three- and Five-Year Mortality Prediction in Cirrhosis

Patient type	MELD	Child-Pugh
Hospitalized patients	0.87	0.84
Ambulatory patients with noncholestatic cirrhosis	0.80	Nd
Primary biliary cirrhosis (PBC)	0.87	Nd
Cirrhosis	0.78	0.76

Limitations to both predictive scores are that these tools have only shown efficacy in the pre-transplant period for prediction of complications and mortality for transplantation; no consistency is seen with predicting complications in the postoperative period, and neither showed efficacy in predicting complications in the ICU setting (Borrows, 2010; Chung, Kirkpatrick, Kim, Scudamore, & Yoshida, 2000; Guo et al., 2010).

Predictive Physiological Factors

Predictive scores such as those obtained from MELD and Child-Pugh are only one factor to determine liver transplant recipients' perioperative risks. Wigg, Gunson, and Mutimer (2005) have identified pretransplant predictive variables that impact HLOS. Recipient factors include age, gender, number of days in the ICU (pre- and postoperatively), presence of sepsis, ascites, and laboratory alterations, including an elevated bilirubin, creatinine, and INR (Wigg, Gunson, & Mutimer, 2005). Patkowski et al. (2009) and others identified additional recipient, operative, and physiological factors that affect outcomes. Operative factors included total operative time (greater than 6 hours), methods used, total cold ischemic time, intraoperative hyperglycemia, and large variability of glucose values (blood glucose 250-330 mg/dL) throughout the operative period (Patkowski et al., 2009); also, the administration of greater than 10 units of red blood cells (RBC), 15 units of fresh frozen plasma (FFP), and the donor type (deceased or living; Bucuvalas et al., 2006; Stahl, Kreke, Malek, Schaefer, & Vacanti, 2008). Physiological factors identified were ascites, cachexia, cardiovascular alterations (tachycardia, hypotension), coagulopathy, encephalopathy, hepatic edema, and neurological complications (cerebral edema; Patkowski et al., 2009). Four additional factors found to predict patient risk in the literature were the type of health insurance (Medicare, Blue Cross, etc.), intubation for greater than four hours postoperatively, primary indication for the transplant surgery, and race (Whiting et al., 1999). A study by Aduen et al. (2009) using only physiological data, comparing older (over age 70) and younger patients (less than age 60), reported that the presence of comorbid conditions can predict success of liver transplantation. Patients with ESLD as a comorbid condition have a poor prognosis and increased ICU LOS (Bruns et al., 2014; C.-S. Wong et al., 2010).

Patkowski et al. (2009) and others demonstrated factors predictive of postoperative complications within the total HLOS, but these require further exploration to address how these impact the ICU LOS (Lewsey, Dawwas, Copley, Gimson, & Meulen, 2006). Immediate post-transplantation complications belong to four categories: graft function (dysfunction/rejection), surgical technique (hemorrhage, vascular, biliary tract complications), infections (bacterial, fungal, and viral), and multisystem complications (cardiovascular, neurological, electrolyte/metabolic, renal, and pulmonary; Siddiqui et al., 2008). Complications in the postoperative period require the care of specialized physicians to treat the complications and reduce the recipient's risk of death (Alban et al., 2006; Faenza et al., 2005; Perry et al., 2011; Saner et al., 2008; Schumann, Hudcova, Bonney, & Cepeda, 2010).

Graft Dysfunction/Rejection

Graft function alterations can occur anytime in the postoperative period. Graft dysfunction relies on intrinsic hepatic cell recovery and reflects donor factors, recipient’s acuity, and the perioperative course (Feltracco et al., 2011; Niemann & Kramer, 2011). A recipient's acuity inversely correlates to graft survival, but accounts for only 30% of the variability in total survival post liver transplant (Niemann & Kramer, 2011). Primary graft dysfunction/failure results in the recipient's death or need for retransplantation in the first seven postoperative days.

Symptoms of liver graft dysfunction include a significant change in mental status secondary to the development of encephalopathy, with an occurrence rate of 5% to 10% (Moreno & Berenguer, 2006). Symptoms of encephalopathy are often paired with an elevated bilirubin greater than 10 mg/dl, acidosis, and a prothrombin time greater than or equal to 17 seconds (Deschenes, Belle, Krom, Zetterman, & Lake, 1998). Late graft dysfunction occurs

during the follow-up period and is related to the recipient's preexisting disease (hepatitis, biliary disease, autoimmune liver disease, or chronic rejection). Within 5-10 years post transplant, 10-40% of patients transplanted for hepatitis C will have disease recurrence and progress to cirrhosis requiring retransplantation. Hepatitis C recipients with graft dysfunction who require retransplantation decompensate quickly in the postoperative period and represent a higher morbidity and mortality than recipients who experience graft failure during their initial or primary transplant surgery (Perry et al., 2011; Zucker, 2009). Failure to receive a new organ after decompensation results in a recipient's death within months (Benten et al., 2009).

Rejection is a complication identified in 30% of liver transplant recipients. Rejection is categorized into three clinical types: hyperacute, acute, and chronic; each is based on the timeframe for development of symptoms (Eksteen & Neuberger, 2008). Hyperacute (caused by hemorrhagic necrosis) is rare but results in rapid graft destruction, with parenchymal necrosis occurring within minutes of organ implantation. Acute or cellular rejection occurs up to three months post transplant and presents as bile duct damage and inflammation of liver venules. Chronic or ductopenic rejection reveals a vanishing bile duct syndrome that generates a persistent inflammation causing progressive cholestasis and liver dysfunction (Eksteen & Neuberger, 2008). Fortunately for liver recipients, rejection is uncommon because of the liver's immune tolerance. Tolerance is achieved through lymphocytes, including natural killer T cells, CD_8 and CD_4 cells; each facilitates an anti-inflammatory immune response to the new organ by reducing parenchymal destruction (Eksteen & Neuberger, 2008). Treatment goals in rejection focus on the reduction of parenchymal damage through specific drug interventions based on recipients’ clinical presentation and biopsy result. This treatment includes immunosuppression

therapy (prednisone, tacrolimus, mycophenolate mofetil) titrated to preserve T cell function and reduce rejection risk (Eksteen & Neuberger, 2008).

Surgical Complications

Surgical complications include hemorrhage and vascular or biliary dysfunction. Surgical technique accounts for 26% of postoperative complications, with the most significant complications related to arterial thrombosis of the hepatic artery. Hemorrhage occurs in up to 20% of recipients in response to preoperative coagulopathy, intraoperative bleeding, and poor function of clotting factors postoperatively, including platelet consumption and sequestration following graft reperfusion (Feltracco et al., 2011). Hemorrhage is commonly observed in the first 48 hours post-transplant, resulting in a 15% re-exploration rate (Moreno & Berenguer, 2006; Warner et al., 2011). Monitoring for bleeding requires serial assessment of hemoglobin/hematocrit, prothrombin time, and INR. Treatment requires administration of blood products, including RBC, FFP, platelets, and often vitamin K. Reversal of the preexisting coagulopathy is done slowly to prevent additional thrombotic complications (Feltracco et al., 2011; McCauley, Thiel, & Puschett, 2014).

Vascular complications present as venous or arterial thrombosis. Venous thrombosis is the result of preoperative portal thrombosis, and stenosis is the result of the venous anastomosis presenting with persistent ascites and bleeding. Treatment includes surgical thrombectomy and prophylactic use of heparin or warfarin (Feltracco et al., 2011). Arterial thrombosis occurs in 5-10% of recipients as a result of poor arterial flow, preservation injury, and hypercoagulability. If the thrombosis occurs in the hepatic artery, symptoms may include hemodynamic instability, hepatic failure, portal hypertension, coagulopathy, and marked elevation of aminotransferases,

with the potential for acute liver failure or graft loss, requiring revascularization or retransplantation (Feltracco et al., 2011).

Biliary complications are secondary to the use of deceased donor organs and occur in 10-50% of transplant recipients (Foley et al., 2011). Biliary complications include ischemia (ischemic cholangiopathy, leakage from the common bile duct requiring placement of a biliary or T tube), and an obstruction caused by duct stones, abscess, biloma or biliary sludge (a mixture of microscopic particulate that precipitates in bile containing calcium and sodium crystals; Feltracco, Carollo, Barbieri, Pettenuzzo, & Ori, 2013; Siddiqui, 2014). Cold ischemic time begins with the clamping of the donor aorta until anastomosis of the organ in the recipient. Research indicates that the longer the cold ischemic time the greater the likelihood of graft loss as a result of ischemic cholangiopathy (Foley et al., 2011; Stahl et al., 2008). Assessing for biliary complications is achieved through measurement of white blood cell levels, serial direct and total bilirubin, albumin, aminotransferase (ALT), and alkaline phosphatase (AST; Feltracco et al., 2011). Treatment is an endoscopic or percutaneous dilatation, placement of stents, and surgical re-exploration (Feltracco et al., 2011). Outcomes of the recipient are poor when biliary complications occur and may result in retransplantation or death (Foley et al., 2011).

Infection

Post transplantation, recipients' primary cause of death is infection. Infection is time-sensitive and defined by the presence of preexisting illness, intraoperative course, and use of immunosuppressant therapy (Niemann & Kramer, 2011; Park et al., 1989). Infections are identified in 20-40% of ESLD patients within the ICU; 80% are bacterial and 20% viral (Siddiqui et al., 2008). Prolonged ICU stays result in colonization of recipients with multi-drug-

resistant bacteria, including candida, cytomegalovirus, enterococcus faecium, enterococcus faecalis, staphylococcus aureus, methicillin susceptible staph aureus, and vancomycin-resistant enterococcus (Findlay et al., 2011; S.-O. Lee, Kang, Abdel-Massih, Brown, & Razonable, 2011; Siddiqui et al., 2008). Postoperatively, a patient may experience several episodes of infection, with approximately one-third occurring in the abdomen as bacterial peritonitis or urinary tract infections (UTIs; Sun, Cacciarelli, & Singh, 2010). UTIs occur in 21% of the cases but account for more than half of the deaths in transplant recipients (Faenza et al., 2005; Moreno & Berenguer, 2006).

Within the postoperative period, the source of infection is often unclear. Two theories surround the source of infection: (1) the donor is the source and (2) it is the result of activation of latent bacteria within the recipient in response to immunosuppression therapy. Regardless of the infectious source, treatment is the same and begins in the immediate postoperative period with the introduction of broad-spectrum antibiotics until bacterial-specific antibiotics can be initiated (S.-O. Lee et al., 2011).

Infections occurring 6 months post transplantation often mimic the infections present in the community. Respiratory and urinary tract sources are identified as the most common infection sources, followed by cytomegalovirus-associated infections and opportunistic infections like tuberculosis and lymphoproliferative disorders. Based on an increased morbidity associated with infections, a prevention strategy is immunizations for the influenza and pneumococcus virus with inactivated/attenuated viruses for each recipient (Benten et al., 2009).

Multisystem Complications

Multisystem complications include cardiovascular, neurologic, electrolyte/metabolic, renal, and respiratory dysfunction post liver transplant. Cardiovascular complications are a result of lost vasomotor tone, preexisting left ventricular hypertrophy, and low systemic vascular resistance (SVR) that sustain for approximately three weeks postoperatively and include hypotension (systolic blood pressure less than 90), arrhythmias (tachycardia), myocardial infarction, and high cardiac output states (cardiac output greater than eight liters/minute; Niemann & Kramer, 2011; Saner et al., 2008). Cardiovascular stability is measured by hemodynamic values, including a mean arterial pressure (MAP) greater than 70 mm Hg, central venous pressure (CVP) of 6 to 10 mm Hg, and normalized oxygen status with saturations greater than 94% (Al-Hamoudi, Alqahtani, Tandon, Ma, & Lee, 2010). Hemodynamic alterations experienced by the acute liver failure patient result in severe circulatory failure or death in 70% of transplant recipients (Rajiv, 2005).

Pulmonary arterial hypertension (PAH) is a complication with a mortality of 15% within 1 year of diagnosis and is the result of a hyperdynamic circulatory state and volume overload in ESLD (Ayoub, 2011). Diagnostic criteria include a pulmonary artery pressures (PAP) greater than or equal to 25 mm Hg, peripheral vascular resistance (PVR) of 240 dynes/s/cm, a pulmonary capillary wedge pressure (PCWP), and potential presence of a thrombus in the pulmonary vessels (Bozbas & Eyuboglu, 2011). PAH with a PAP greater than 50 mm Hg is a contraindication to transplantation. Intraoperatively, PAH is managed through the initiation of hemodialysis, use of nitrous oxide for optimization of right ventricular function, milrinone to decrease preload, and vasopressors (Neo-Synephrine, vasopressin) to sustain blood pressure and

systemic vascular resistance (SVR; Ayoub, 2011). If this condition is present postoperatively, PAP values between 35-50 mm Hg are associated with a mortality rate of 50%, and if PAP values are greater than 50 mm Hg, 100% mortality (Ayoub, 2011).

Neurological

The most common complications in the ICU setting are disorientation, agitation, and confusion, which lessen as liver function improves (Moreno & Berenguer, 2006). Neurological complications are a direct result of acute liver failure and may include seizures (drug-induced), encephalopathy, cerebrovascular events, intracranial hypertension, and cerebral edema (Aduen et al., 2009; Faenza et al., 2005). Seizures occur in response to hypoglycemia, uremia, intracranial hemorrhages, and preexisting comorbidities (Frontera & Kalb, 2011). Seizures may occur in response to changes in electrolytes (hyponatremia), drug toxicity (prograf, cyclosporine), or other metabolic disturbances (Feltracco et al., 2011).

Hepatic encephalopathy (HE) is a metabolic disturbance associated with varying degrees of brain edema as a result of neurotoxicity of ammonia, inflammatory cytokines, and oxidative stress (Eroglu & Byrne, 2009). HE is defined using the West Haven criteria (Table 2). West Haven criteria use four grades to describe mental status, clinical manifestation, psychiatric symptoms, and cerebral edema development (Eroglu & Byrne, 2009; Ferenci et al., 2002; Frontera & Kalb, 2011).

Grade 1: the patient has minimal awareness of surroundings, a short attention span, variable sleep abnormalities, and altered mood. Grade 2: the patient has lethargy, disorientation to time. Slurred speech is present with asterixis. Asterixis is an arrhythmic flexion movement of the hands and the outstretching of arms with wrist dorsiflexion (Gokula & Khasnis, 2003).

Grade 3: the patient demonstrates somnolence, acute confusion, and disorientation to place.

Grade 4: the patient has the inability to communicate via verbal, oral, or eye response, paired with eventual progression to a comatose state.

Table 2

West Haven Criteria for Hepatic Encephalopathy

HE Grade for Mental Status	Clinical Manifestations	Psychiatric Symptoms	Edema Development
Grade 1	Minimal awareness, short attention span, sleep abnormalities, altered mood	Euphoria/depression	25-35%
Grade 2	Lethargy, disorientation to time, inappropriate behavior, slurred speech and asterixis.	Irritability, personality changes	25-35%
Grade 3	Somnolence and confusion, disorientation to place, positive Babinski sign, no asterixis	Anxiety, paranoia, anger or rage	65-75%
Grade 4	Unable to communicate with verbal or noxious stimuli. Comatose	Coma	Greater than 75%

HE may lead to an increased risk of aspiration, increasing carbon dioxide (CO_2) leading to cerebral edema (Frontera & Kalb, 2011). Cerebral edema and intracranial hypertension require close ICU monitoring, with the potential for an intraventricular drain and administration of osmotic diuretics (e.g., mannitol; Stravitz et al., 2007). Treatment of intracranial hypertension or cerebral edema is achieved by the use of mechanical ventilation, sedation, and treatment of pain and anxiety using agents like midazolam, fentanyl, and dexmedetomidine (Frontera & Kalb, 2011). Treatment goals with intracranial hypertension/cerebral edema are the prevention of

coughing, agitation, and ventilator asynchrony. If none of the goals are possible, hyperventilation and barbiturate coma may be indicated (Frontera & Kalb, 2011). Failure of this treatment may result in a recipient's deterioration to a comatose state, brain herniation, or death (Detry, De Roover, Honore, & Meurisse, 2006).

Electrolyte/Metabolic

Electrolyte imbalances are affected by pretransplant nutrition and intraoperative events. Pretransplant, these imbalances represent lost muscle mass and the inability of the liver to control glucose metabolism (Faenza et al., 2005; Schumann et al., 2010). The most common electrolyte alterations are hypo/hyperkalemia, hypocalcemia, hypophosphatemia, hyponatremia, hypo/hyper glycemia, and hypomagnesemia (Feltracco et al., 2011). Hyponatremia (serum sodium < 130 mmol/L) is a life-threatening abnormality in response to altered renal function and volume resuscitation with crystalloids. Measuring sodium, blood urea nitrogen (BUN), and creatinine and their alterations may help predict some common postoperative complications that result in longer ICU LOS (Luu, 2014; Okada et al., 2013). Treatment postoperatively for these alterations include increasing sodium intake, promoting intravascular mobilization, and restoring oncotic pressure through diuretic and albumin administration (Feltracco et al., 2011).

Renal complications are multifactorial and a result of preexisting renal dysfunction, intraoperative hemorrhage, venous clamping for organ removal, hypotension, nephrotoxic antibiotics, and graft dysfunction (Moreno & Berenguer, 2006; Sedra & Strum, 2011; Zand et al., 2011). Renal dysfunction is defined as a creatinine level greater than 1.8 mg/dL, an increased base creatinine greater than 50%, or a glomerular filtration rate (GFR) below 30 milliliters per minute (Benten et al., 2009). Renal dysfunction ranges from impairment to acute failure and is

diagnosed in one-third of liver transplant candidates. Risk factors for renal complications include recipient age, cytomegalovirus infections, need for fluid resuscitation, intraoperative transfusions of multiple units of blood or fresh frozen plasma and intra- or postoperative dialysis (Contreras et al., 2002). During the postoperative period, renal dysfunction re-occurs or is diagnosed usually between postoperative day 2 and 4 with a mortality rate of 28-90% (Bellomo et al., 2004; Findlay et al., 2011; Northup et al., 2010). Stage 3 to 5 renal insufficiency produces glomerular filtration rates of 30-60 milliliters per minute in 35% of recipients within five years post transplantation (Zand et al., 2011). Monitoring for this complication requires daily BUN and creatinine measures (Agrawal & Swartz, 2000; Liu & Schiano, 2007; Moreno & Berenguer, 2006).

Dialysis or CRRT initiation is based on the degree of renal dysfunction, fluid balance, metabolic abnormalities, and need for more space for blood and parenteral nutrition (Findlay et al., 2011). Feltracco et al. (2011) reported that 8-17% of recipients will need CRRT. Continuous venovenous hemofiltration (CVVH) is the method of CRRT used to manage fluid shifts, rapid adjustment to electrolytes, and osmotic therapy (Frontera & Kalb, 2011; Zand et al., 2011). The goal of intraoperative CVVH is to maintain a euvolemic or zero balance state. CVVH use may result in the complications of acidosis, hyperkalemia, and volume management increase morbidity and mortality throughout the perioperative period (Sedra & Strum, 2011). Metabolic acidosis begins with the excision of the recipient's organ as a result of cross-clamping of the large vessels, especially in the presence of renal dysfunction. Management of acidosis is achieved through adjustment of the dialysate bicarbonate levels and close monitoring of arterial blood gases every 30 minutes for bicarbonate and pCO_2 levels.

Hyperkalemia occurs during reperfusion of the recipient's organ and requires close monitoring of electrocardiogram and fluids used for resuscitation. Hypovolemia intraoperatively increases the risk of renal failure in the postoperative period, with a central venous pressure (CVP) less than 5 mm Hg. Euvolemia results in increased need for blood and other fluids, with the goal of maintaining a CVP of 7-10 mm Hg. Finally, dialysis use in the intra- and postoperative period is associated with a 39% survival rate five years post liver transplant while recipients that did not receive dialysis or develop renal complications had a survival rate of 51% (Sedra & Strum, 2011; Zand et al., 2011). Controlling for postoperative renal dysfunction requires close monitoring by the ICU intensivist to control blood pressure and blood glucose levels, avoid nephrotoxic drugs, and reduce use of calcineurin inhibitors (Benten et al., 2009). Many transplant centers further reduce the risk of renal dysfunction through the administration of combination immunosuppressant therapies of Tacrolimus, CellCept, and glucocorticoids. These drug combinations aim to keep drug trough levels low to reduce their nephrotoxic potential (Benten et al., 2009).

Respiratory complications are responsible for the greatest morbidity and mortality post organ transplantation (Antonelli et al., 2000). Specific causes include the presence of pleural effusions, intrapulmonary vascular disorders, smoking, respirator muscle wasting in the pretransplant period, fluid resuscitation and blood loss during abdominal surgery, and total surgical time (Bozbas & Eyuboglu, 2011). Hypoxemia is a result of a hypoventilation state present in 20% of recipients on the waiting list due to the presence of hepatopulmonary syndrome, which in the postoperative period leads to adult respiratory distress syndrome (ARDS). Symptoms associated with hypoxia include progressive dyspnea, finger clubbing,

cyanosis, and hyperventilation (Bozbas & Eyuboglu, 2011). Liver transplant surgery decreases a recipient's ventilation capacity in response to anesthetic agents, reperfusion injury, intraoperative corticosteroid administration, and surgical times greater than 6 hours (C.-T. Huang et al., 2011; Lui et al., 2002; Moreno & Berenguer, 2006; Murthy, 2008). Pneumonia, subclinical pulmonary edema (occurs in 50% of recipients within 24 hours) and ARDS are due to the presence of ascites pretransplant and fluid overload postoperatively related to crystalloid and blood product administration (Feltracco et al., 2011; Murthy, 2008; Razonable et al., 2011). Respiratory complications require endotracheal intubation and mechanical ventilation, increasing a recipient's risk of infection and graft dysfunction (S. Lee et al., 2013; Sun et al., 2010).

Focused interventions are aimed at optimizing cardiac output, avoiding fluid overload, and reducing pulmonary congestion, achieved with noninvasive ventilation or mechanical ventilation with rapid weaning and removal, early ambulation, and fluid balance maintenance (Feltracco et al., 2011; Oberkofler et al., 2010). Noninvasive ventilation is continuous, positive pressure ventilation delivered without an invasive airway. Noninvasive ventilation decreases frequency of intubation and is often initiated as a frontline treatment in low-risk recipients or used immediately following an early extubation to facilitate weaning (Feltracco et al., 2011; Findlay et al., 2011; Lui et al., 2002). Antonelli et al. (2000) exhibited mechanical ventilation with low tidal volumes resulting in four days of ventilator time with noninvasive methods and five days with standard endotracheal intubation (Niemann & Kramer, 2011). Both groups demonstrated similar time on positive pressure ventilation, but the ICU stay dropped from 10 to 7 days, potentially reducing complications (Feltracco et al., 2011). If prolonged ventilation is anticipated postoperatively, strategies must be used to decrease lung injury, including low tidal

volumes (6 milliliters/kilogram of ideal body weight), increased respiratory rate, and increased amounts of positive end expiratory pressure (PEEP) to decrease atelectasis. High PEEP (greater than 10 mm Hg) use results in a reduction of liver outflow volumes and increase venous stasis that may cause hemodynamic compromise. If respiratory failure progresses, the use of prone therapy and high-frequency oscillatory ventilation may be needed, but little evidence is available on its efficacy in this patient population (Feltracco et al., 2011). Preventing intubation and prolonged ventilation reduces a recipient's risk of nosocomial pneumonia, increased congestion due to the liver graft, and morbidity (Feltracco et al., 2011; Sellares et al., 2011; Williams et al., 2010).

Length of Stay (Intensive Care/Hospital)

Length of stay (LOS) is an indirect, objective measure to calculate needed resources and correlates to hospital costs associated with complications in the postoperative period (Bucuvalas et al., 2006; Washburn et al., 2009). LOS relates to the severity of illness before and after liver transplantation (Williams et al., 2010). Average HLOS for liver transplants is between 33 and 64 days, with 7 to 10 days representing the post-transplantation period (Showstack et al., 1999; Whiting et al., 1999). Patients with high MELD scores (> 40) have an ICU LOS twice that of patients with MELD scores less than 40 (Bucuvalas et al., 2006). Prolonged LOS is defined as an ICU admission lasting 5 to 14 days. Only 2 to 11% of ICU patients experience a prolonged LOS, but these account for 25-45% of total ICU days (Arabi, Venkatesh, Haddad, Shimemeri, & Malik, 2002; K. H. Lee, Martich, Boujoukos, Keenan, & Griffith, 1996; Williams et al., 2010). LOS has been linked to the type of donor organ. Two types of donors exist in transplantation: living and deceased. Deceased donor liver transplants (DDLT) will be the focus of this

dissertation. Deceased organs that are a result of anoxia, stroke, head trauma, or central nervous system tumors increase a recipient's risk of developing graft dysfunction and increase mortality (Singhal, Sheng, Drakos, & Stehlik, 2009). DDLT recipients have significant hospital resource use pretransplantation and less in the first year due to improvements in treatment and prevention of complications (Merion et al., 2010). These complications include infection (41%), biliary leaks (32%), surgical re-exploration (25%), pleural effusion (20%), biliary stricture (17%), ascites (14%), pulmonary edema (12%), intra-abdominal abscess (9%), gastrointestinal bleed (8%), intra-abdominal bleeding, hernia (6%), hepatic artery thrombosis (6%), portal vein thrombosis (3%; Olthoff et al., 2005). Hospitalization is a result of limited physiological reserves of the recipient and worsening of liver failure, translating into ICU stays postoperatively between 9 and 14.1 days (Findlay et al., 2011). National transplant data reveal that, if complications occur, hospital LOS can extend to 45 days, with the ICU stay averaging 7.6 to 17.0 days (Findlay et al., 2011). Patkowski et al. (2009) demonstrated a two-and-a-half times higher risk of death when ICU LOS exceeded 10 days, whereas Watt and coworkers (2010) identified ESLD as a late predictor of ICU death.

Cost

Liver transplantation is expensive, with ICU LOS accounting for 20-30% of total hospital costs (Washburn et al., 2009). Based on an average ICU stay of nine days at $1,500/day an ICU cost of $13,500 was calculated (Buchanan et al., 2009). Increased ICU costs are further broken down into three donor and four recipient factors. Donor factors are age, body weight, and gender, whereas recipient factors are age, male gender, number of previously transplanted organs, and MELD score (Tenza et al., 2009; Washburn et al., 2009). Patients with low MELD scores (6-14)

average hospital costs of $145,000, and those with MELD scores of 28-40 have an average cost of $333,300 (Buchanan et al., 2009; Foxton et al., 2010). Daily ICU costs range from $1,501 to $1,639 per day or $5,065-$25,332 per ICU LOS (Norris et al., 1995; Noseworthy, Konopad, Shustack, Johnston, & Grace, 1996; Welton, Meyer, Mandelkehr, Fakhry, & Jarr, 2002). Adding to costs is the recipient's funding (private insurance [e.g., Blue Cross] or self-pay [e.g., Medicare/Medicaid]). Recipients with Medicare/Medicaid have longer LOS in the postoperative period when compared to traditional insurance providers (Bucuvalas et al., 2006). Unfortunately, payment from all insurers does not break down payment into specific ICU and hospital costs. Instead, hospital costs are based on diagnostic groups (liver failure, transplantation, sepsis) with capitated payments. This payment structure explains the variability of cost between transplant centers and recipients (Bucuvalas et al., 2006). Maximizing reimbursement is achieved using clinical pathways for specific disease management profiles along with transfer to a step-down unit to provide care as soon as clinically possible (Welton et al., 2002).

Understanding predictive factors for prolonged ICU stays will enable clinicians to determine appropriate discharge plans with treatment goals that will decrease patient risk, reduce ICU stays, and potentially prevent readmission to the ICU post transplant (Gruenberg et al., 2006; Levy et al., 2001). The future of liver transplantation requires alternative management for chronic liver disease and identification of gaps in care of recipients focusing on reducing the impact of postoperative complications while simultaneously reducing ICU LOS and cost (Perry et al., 2011; Watt, Pedersen, Kremers, Heimbach, & Charlton, 2010).

CHAPTER 3 THEORETICAL FRAMEWORK

Introduction

The literature review identified factors affecting liver transplant recipients' outcomes. This chapter will focus on development and explanation of a theoretical model to link the various physiological factors to improvements in transplant outcomes. The theoretical framework used in developing the proposed research includes an original physiology model by Merkel et al. (2000) and a modified version of the model for use in identifying factors of liver transplant recipients that predict development of ICU complications, ICU and HLOS, and morbidity/mortality rates. Nurses develop knowledge through the use of concepts and empiric phenomena that generate improvements in evidence-based practice and clinical effectiveness (Rodgers, 1989; Rycroft-Malone et al., 2002). Within ICU nursing, conceptual models link to practice guidelines for use in developing concrete, theoretical knowledge. Ideally, nurses' knowledge of physiological and psychological responses paired with technology strengthens the usefulness of guidelines for use in practice (Fawcett et al., 1987; Walker & Avant, 2005). The theoretical framework focuses on predictive factors of postoperative ICU complications and their effect on ICU LOS in liver transplant recipients.

University of Arizona Concept Model

The University of Arizona Conceptual Model of Injury Mechanisms and Related Responses developed by Merkle et al. (2000; Figure 1) describes physiological processes and their effect on patient outcomes. Concepts identified within the model are altered health conditions, responses (individual), interventions, response modifications, and outcomes. Altered health conditions are disease, injuries, and life events with the potential for negative effects on an

individual or group. Responses are consequences of the interventions and an individual's response based on biological, psychological, cultural, and sociological factors. Interventions are actions performed by nurses or other health care professionals minimizing injury and disease progression to positively affect health outcomes. Response modifications include factors that may influence the response, including age or genetic makeup. Outcomes are the result of altered health condition. Outcomes may be a response to an individual event or a result of interventions and individual responses.

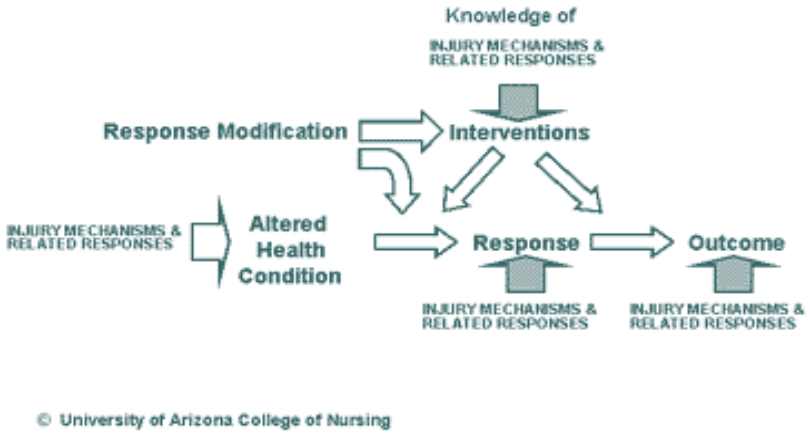

Figure 1. Conceptual model: Injury mechanisms and related responses to the management of altered health conditions

Model Relationships

In the model, altered health conditions (disease, injury) include individual biological, psychological, cultural, or sociological responses. These responses produce “outcomes” (Merkle et al., 2000). Two factors that may change an individual’s response to an altered health condition are “response” (person’s age or genetic makeup) and “interventions” (nursing and other health professional actions to minimize injury and positively impact health outcomes), which together

are labeled “response modifications." Adapting this model to the liver transplant recipient enhances prediction of ICU complications and their outcomes on transplant recipients in the postoperative period. Five core concepts within the modified model are altered health status, focused intervention/measurements, response to intervention, response modification, and outcomes. Within the model, arrows represent relationships and potential causality of concepts in relation to each other.

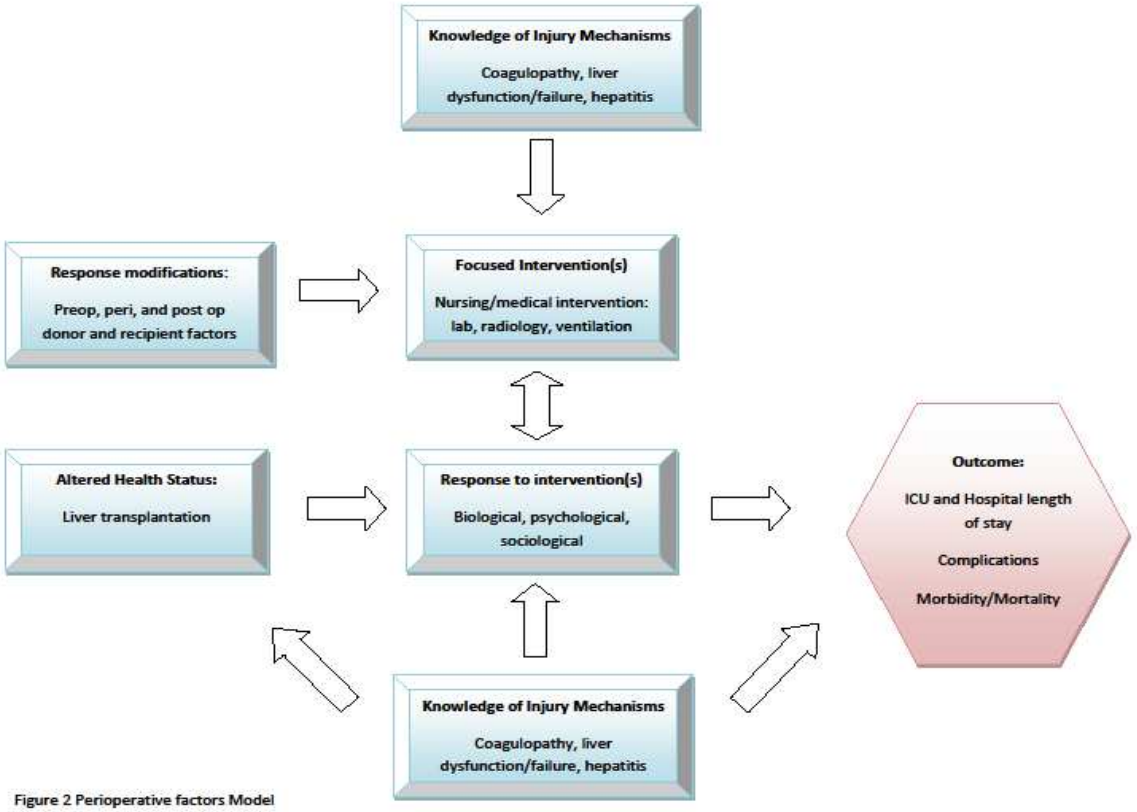

Figure 2. Perioperative factors that predict postoperative outcomes in liver transplant recipients

Modified Model Concepts

Concepts in the modified model include recipient factors that may shape post-liver transplant outcomes. Altered health status refers to clinical conditions that lead to a change in a patient's disease state. The alterations are any physiological condition that results in liver failure (e.g., acetaminophen overdose, cirrhosis, coagulopathy, hepatic encephalopathy, and viral hepatitis). Focused interventions are interventions/clinical measurements identified by physicians, nurses, and the interdisciplinary care team used to treat the symptoms of organ dysfunction as a result of the underlying pathology of the recipients' clinical condition (e.g., cirrhosis, encephalopathy). Measurements include diagnostic and laboratory testing, such as ultrasound, computerized tomography (CT) scan, liver function tests, coagulation panels, immunosuppressant protocols, and mechanical ventilation. Evaluation of these interventions results in a positive or negative response by the recipient (Sidani & Braden, 1998). Responses to intervention describe any biological, psychological, and sociological factors that drive a recipient's outcome. Biological factors are laboratory results and clinical symptoms that reveal rejection, consisting of an elevated white blood cell counts, ascites, eosinophilia, increased bile drainage, and fever. Psychological factors include quality of life both pre- and postoperatively, compliance to medication regimen, and resolution of encephalopathy to eradicate confusion. Sociological factors include social support from family and community. For this initial research, the factors of interest are the biological factors and their impact on a recipient's development of ICU complications and their effect on ICU LOS.

Response modifications are time-driven factors that predict recipient outcome post liver transplantation and the focused interventions set by the health care team. The foci of this

research are the preoperative, intraoperative, and postoperative time periods and encompass the diagnosis of the alteration in the recipient's health condition until hospital discharge. This period involves recipient factors (age, genetic makeup, diagnosis requiring transplant, evidence of coagulopathy, encephalopathy, and hemodynamic stability). Outcomes focus on identifying the effects of ICU complications experienced by a transplant recipient and include episodes of bleeding, infection (sepsis), normalization of liver function, graft dysfunction, acute renal failure, cerebral edema, and prolonged mechanical ventilation. The end outcomes are complication development, ICU and hospital LOS, and morbidity/mortality. Table 3 identifies each of the model’s concepts with their definitions and measures within the current study.

Table 3

Model Concept Definitions

Model Concept	Definition of Concepts	Measurable Variables
Knowledge of injury mechanism	Underlying physiological changes in liver failure	Diagnosis for transplant (e.g., hepatitis, cirrhosis, acute liver failure, hepatic encephalopathy)
		Pathophysiology of liver failure
Altered health condition	Liver failure/End-stage liver disease requiring transplantation	Diagnosis of patient with liver failure, hepatitis (reason for transplant)
		Model of end-stage liver disease (MELD) score, Child-Pugh score
Focused interventions	Nursing and medical interventions/measurements including laboratory and radiology studies and use of mechanical ventilation	Chest x-ray, prothrombin time (PT), partial prothrombin time (PTT), international normalized ratio (INR), medication administration, blood, and blood product administration, dialysis
Response modifications	Perioperative factors	Pre: age, sex, weight, diagnosis, medical history
		Intra: blood pressure, cold/warm ischemic time, total surgery time, length of mechanical ventilation, vasopressor use, glucose values
		Post: laboratory data, ventilator time
Response to interventions	Biological, psychological, and sociological factors	Biological (improvement or worsening of clinical variables) listed under interventions.
Outcomes	Expected results of using this model to define reasons for an increased ICU LOS.	Development of complications (bleeding, infection [sepsis], rejection, renal failure, cerebral edema)
		ICU and hospital LOS
		Morbidity/mortality rates

Modified Model Relationships

Relationships are statements with structurally interrelated concepts in a proposed theory (Chinn & Kramer, 2008). These relationships define the direction, strength, and quality of the interrelationships between concepts and define the empirical world they represent (Chinn & Kramer, 2008; Jacox, 1974). Statements describe, explain, prescribe, or predict the relationships between concepts as defined below (Meleis, 2007; Walker & Avant, 2005). Knowledge of injury mechanisms focuses on comorbidities and is the basis of all prescribed interventions aimed at maximizing the recipient's health prior to transplantation. The altered health status can be both positive and negative, as the recipient undergoes transplantation. Altered health status to response to intervention includes the perioperative interventions affecting the outcome of transplant surgery and the experience within the ICU. Recipient factors identified within this period help direct interventions by the health care team to prevent complications and alleviate risk throughout the transplant hospitalization.

Response modifications to focused intervention are factors needing evaluation to identify their role in the recipient’s development of the altered health condition. These factors and focused interventions are continually monitored for their effect (positive or negative) and may be modified to decrease ICU and hospital LOS. Focused intervention to recipient response to intervention covers the time from the recipient's arrival in the ICU until transfer to a lower level of care (progressive care or medical unit) or hospital discharge. Focused interventions offered by the health care team may include immunosuppressant therapy, steroid administration, dialysis, and mechanical ventilation requiring constant monitoring. Recipient responses to specific interventions to outcomes identify the patient’s response that consists of biological (clinical

symptoms), psychological (quality of life, mental status), and sociological factors (family, social support) that determine a recipient's ability to manage their postoperative course (ICU to hospital discharge). Monitoring of recipient responses may result in modifications to various interventions when ICU complications occur to ensure safety of the recipient and transplanted graft.

Strengths and Limitations of the Model

Strengths of the model are its ability to look at multiple factors over time that can influence a recipient's outcomes post liver transplant. This model allows exploration of the progression of liver dysfunction/failure of liver transplant recipients and the identification of factors that may directly impact their outcomes in the postoperative period. Despite the global focus of the historical model, several limitations are present. The model is based on human physiological responses. Its initial use was to describe cancer intervention (specifically methotrexate) response; later, it was used in various other physiological conditions, but it is untested in the transplant population. Data are available within the medical record; however, due to documentation standards, some data may not be available at prescribed intervals as expected (e.g., laboratory test results, MELD score), making it difficult for comparisons between time periods for recipients or their placement into a specific phase in the model. The final limitation is the inability to separate ICU-specific factors from hospital factors because many factors are present throughout the hospital stay.

Summary

The proposed model will be used to identify factors that alter both ICU and hospital outcomes for liver transplant recipients. The model may identify screening and ICU clinical

practices that can be modified to provide a more holistic plan of care for recipients experiencing an altered health status. Interventions can be tailored based on the identified potential for complications in all phases of the transplant process. These factors may provide insight into possible modifications to nursing practice for improved liver transplant outcomes.

CHAPTER 4 METHODS

Design

A retrospective, correlational design was used for the study to look at the nature of relationships or associations of preoperative, intraoperative, postoperative factors and their impact on ICU LOS, HLOS, and development of ICU complications in patients undergoing liver transplantation.

Sample and Setting

The study took place in a single transplant center in a 1,100-bed, tertiary care hospital in Central Florida. The sample was obtained using a convenience sampling method, with 230 liver transplant recipients that experienced a postoperative ICU stay. Inclusion criteria were liver transplant recipients over age 18 with an ICU stay from June 1, 2007, to October 31, 2011. Exclusion criteria included liver transplant recipients under the age of 18 or recipients who received a combined organ transplant (e.g., kidney/liver, liver/pancreas) at time of their initial transplant surgery.

Procedure

Human Subject Protection

Institutional Review Board (IRB) approval was obtained from the University of Arizona along with the Office of Research Administration (ORA) review and IRB at the study facility prior to study initiation.

Data Collection

Data for the study were obtained from the electronic medical record (EMR) of the liver transplant recipients from June 1, 2007-October 31, 2011. The electronic medical record is

housed on the Cerner® system and through the OTTR database housed within the transplant center. Factors related to the four types of complications commonly associated with the liver recipient in the postoperative period were collected. These include (1) graft function: dysfunction (2) surgical: hemorrhage, vascular, biliary tract complications, (3) infectious: bacterial, fungal, and viral, sepsis and (4) systemic: cardiovascular, neurological, electrolyte/metabolic, renal, and pulmonary (Patkowski et al., 2009; Smith et al., 2009). Each of these complications has distinct factors that are present within the pre-, intra-, and postoperative time period. Each of these specific factors is displayed in Table 4.

Table 4

Factor Definition for Data Collection

Factors	Definition/time frame	Code
Demographic/Preoperative		
Age	Age range	Actual ages of recipients
Sex	Male or Female	1 = Male 2 = Female
Race	Ethnicity of recipient	1 = African American, 2 = Asian, 3 = Caucasian, 4 = Hispanic, 5 = Other
Weight (on admission)	Actual weight	Weight in kilograms
Diagnosis for transplant	Diagnosis for transplant	1 = hepatitis C, 2 = hepatitis other, 3 = hepatic cancer, 4 = Tylenol overdose, 5 = cirrhosis, 6 = nonalcoholic sclerosing hepatitis (NASH), 7 = other
Medical history	Select history that increase risk of complication based on literature	1 = renal failure, 2 = diabetes, 3 = hypertension, 4 = obesity
Insurance	Type of insurance coverage	1 = Medicare, 2 = Medicaid, 3 = Private insurance
MELD Score	Calculated score for risk of mortality	Calculated Score
Ejection Fraction (EF)	Measure of ventricular function	Value in percent
Sodium (Na)/Potassium (K) Blood Urea Nitrogen (BUN) Creatinine (creatinine) Glomerular filtration rate (GFR) Glucose (Gluc)/Albumin (Alb) Total bilirubin (T. bili) Prothrombin (PT)/Partial thromboplastin time (PTT) International normalized ratio (INR) White blood cell count (WBC) Hemoglobin (Hgb)/Hematocrit (Hct)/Platelet (Plt)	Laboratory testing done 12 hours prior to surgical intervention	Value
Intraoperative Period		
Highest and lowest systolic blood pressure (SBP)	Highest and lowest blood pressure readings	Values
Oxygen saturation (Sats)	Average saturation during surgery	Average of all values

Factors	Definition/time frame	Code
Vasopressor	Vasopressors used during surgery	1 = Yes, 2 = No
Pulmonary artery pressure (PAP)	Systolic and diastolic pressure of the ventricles per pulmonary artery catheter	Actual values expressed as a fraction (20/10)
# units of Red blood cell transfusions (RBC) # units of fresh frozen plasma (FFP) # units of platelet transfusions (Plt)	Number of specified transfusions	Actual number of transfusions received by each product (RBC, FFP, Plt)
Continuous renal replacement therapy (CRRT)	Continuous dialysis modality used throughout surgery	1 = Yes, 2 = No
Total surgery time	Time from start of case on surgery record until end of surgery per surgeon's notation	Total documented surgery time in hours and minutes.
Cold ischemic time (CIT)	Time from end of circulation to reestablishment of blood flow	Time expressed in minutes
Warm ischemic time (WIT)	Time from organ reimplantation to reestablishment of blood flow	Time expressed in minutes
Immunosuppression medication	Drugs used to initiate immunosuppression	1 = Simulect, 2 = Solu-Medrol, 3 = Thymoglobulin
Glucose values (highest/Lowest)	Glucose values highest and lowest during the transplant	Value
Thromboelastography (TEG) values Platelet/Fibrinogen	Lowest platelet count and fibrinogen during surgery collected by TEG	Value
Postoperative period		
Bleeding/acute? Renal failure Graft dysfunction Sepsis/Cerebral edema	Complication experienced	1 = Yes, 2 = No
Prolonged mechanical ventilation	Greater than 24 hours of mechanical ventilation	Actual time of mechanical ventilation

Factors	Definition/time frame	Code
Sodium (Na)/Potassium (K) Blood urea nitrogen (BUN)/Creatinine (creatinine) Glomerular Filtration rate (GFR) Glucose (Gluc)/Albumin (Alb) Total bilirubin (T. bili) Prothrombin (PT) Partial thromboplastin time (PTT)/Internationalized normalized ratio (INR) Hemoglobin (Hgb) /Hematocrit (Hct)/Platelet (Plt)	Laboratory values collected 4 hours and 24 hours post transplant	Values at 4 and 24 hours.
Ventilator time (total hours)	Time patient on mechanical ventilation post transplant from intubation to extubation based on physician documentation	Time expressed in hours and minutes
Intensive care Unit LOS	Total time recipient spends in the ICU post transplant	Total time expressed as days.
Hospital LOS	Total time recipient hospitalized for transplant	Total time expressed as days

Outcomes

Each of the outcomes has been identified in the literature as a potential contributor to the long-term success of a liver transplantation recipient's transplanted organ. Outcome variables obtained from recipients were collected to support the three study aims including:

Specific Aim 1: Determine factors in the preoperative, intraoperative and postoperative time period that predict ICU complications (bleeding, sepsis, graft dysfunction, acute renal failure, cerebral edema, and prolonged mechanical ventilation).

Specific Aim 2: Determine the predictive factors of liver recipients in the preoperative, intraoperative, and postoperative period as they relate to ICU and hospital length of stay.

Specific Aim 3: Describe the relationship of ICU complications with ICU length of stay, hospital length of stay, and mortality.

Each of these aims focuses on the prevention of ICU complications. ICU complications are defined as conditions that occur in the postoperative period that may hinder a transplant recipient's outcome. ICU complications include: bleeding, acute graft dysfunction, sepsis, cerebral edema, prolonged ventilator time, and acute renal failure as defined in chapter 1.

Data Analysis Plan

After data collection was completed, SPSS Pack 21.0 was used to perform the data analysis. Central tendency was used for age, HLOS, and ICU LOS. Frequencies were used to describe general characteristics of the sample, including age, sex, ethnicity, and MELD score at the time of transplant. Descriptive statistics was used for demographics, laboratory data (Table 5), and recipient factors that increase postoperative risk. Logistic regression was used to identify factors that affect outcomes for both the ICU LOS and HLOS based on predicted national averages (Trochim & Donnelly, 2008). Multiple regressions were used to compare the ICU LOS and HLOS to the identified physiological factors. The dependent variable was the ICU LOS and the independent variables were preoperative, intraoperative, and postoperative factors listed in (Table 4).

CHAPTER 5 RESULTS

Results

Sample Demographics

The sample was a convenience sample of 247 liver transplant recipients admitted to an ICU postoperatively. Seventeen patients were excluded (15 due to exclusion criteria and 2 due to an inability to access the electronic medical record) resulting in a final sample of 230 subjects. Demographic characteristics of the study sample are presented in Table 5.

Table 5

Sample Characteristics

Variable	Data Category	Frequency (N)	Percentage (%)
Age	22-74 (Mean 55.3 ± 9.285)	230	(100)
Sex	Male	144	(62.6)
	Female	86	(37.4)
Ethnicity	Caucasian	154	(67.0)
	Hispanic	55	(23.9)
	African American	9	(3.9)
	Asian	6	(2.6)
	Unknown	6	(2.6)
Medical history	No history of below diagnosis	94	(40.9)
	Hypertension	78	(33.9)
	Diabetes	69	(30)
	Obesity	27	(11.7)
	Renal Failure	17	(7.4)
Transplant diagnosis	Hepatitis (B, C)	136	(59.2)
	Cirrhosis	65	(28.2)
	Graft failure	7	(3.0)
	Other	17	(7.3)
	Cholangitis	5	(2.1)
Insurance	Private insurance	127	(55.2)
	Medicare	52	(22.6)
	Medicaid	45	(19.6)
	Self-pay	6	(2.6)
Discharge location	Home	199	(86.5)
	Rehabilitation	14	(6.1)
	Long term care/Skilled facility	8	(93.5)
	Expired	8	(3.5)
Other	Ventilator time	Mean 59:48:10 hr	3:13-1800:00 hr
	ICU length of stay	Mean 9.35 days	2-145 days
	Hospital length of stay	Mean 19.12 days	5-145 days

The sample consisted of 230 patients, of whom 62.6% were male (*n* = 144) and 37.4% female (*n* = 86). The age range was 22-74, with the mean age of 55.27 ± 9.29 years. Ethnicity is representative of patients within the transplant center: Caucasians (*n* = 154, 67.0%), Hispanic (*n* = 55, 23.6%), African Americans *n* = 9, 3.9%), Asians (*n* = 6, 2.6%), and unknown (*n* = 6, 2.6%). Comorbid conditions that may affect a patient's outcome include the presence of diabetes (*n* = 69, 30%), hypertension (*n* = 78, 33.9%), obesity (*n* = 27, 11.7%), renal failure

(*n* = 17, 7.4%). The remaining 94 subjects in the sample did not have any of the listed comorbid factors (*n* = 94, 40.9%). Multiple diagnoses for transplant were identified including: hepatitis (*n* = 136, 59.2%), cirrhosis (*n* = 65), graft failure (*n* = 7, 3.0%) cholangitis (inflammation of bile duct; *n* = 5, 2.1%) and other conditions including hemochromatosis, nonalcoholic steatohepatitis, Osler-Weber-Rendu syndrome, primary biliary sclerosis, and Wilson disease (*n* = 17, 7.3%).

The type of insurance carried by the potential recipient may limit procedures or specialists available to treat liver disease. This limit may extend to access to transplantation. The insurance types were broken down into private insurance (*n* = 127, 55.2%), Medicare (*n* = 52, 22.6%), Medicaid (*n* = 45, 19.6%) and self-pay (*n* = 6, 2.6%).

Subjects were discharged to home (*n* = 199, 86.5%), long-term care facilities (*n* = 8, 3.5%), rehabilitation facilities (*n* = 14, 6.1%), or expired (*n* = 8, 3.5%). Complications experienced by the transplant recipient included bleeding (*n* = 32, 13.9%), renal failure (*n* = 68, 29.6%), graft dysfunction (*n* = 44, 19.1%), sepsis (*n* = 14, 6.1%) and cerebral edema (*n* = 2, 0.9%). Ventilator time ranged from 3.22 hours to 1800 hours, with a mean of 59.80 hours ± 155 hours 46 minutes. Prolonged mechanical ventilation time according to transplant literature is greater than 24 hours (Razonable et al., 2011). ICU LOS ranged 2-145 days, with a mean of 9.35 ± 12.93 days. HLOS ranged 5-145 days, with a mean of 19.12 ± 18.11 days.

The analysis divided the sample into two groups to better analyze the ICU complications based on recipient LOS in both the ICU (greater than or less than 9 days) and hospital (greater or less than 19 days). Additionally, factors included in the analysis were divided into three time periods (preoperative, intraoperative, and postoperative) for ease of analysis. This strategy allowed for factors to be identified in each time period and location to develop specific

interventions to improve recipient outcomes. These time periods are defined within the hospital's protocols for assessment and treatment of liver transplant recipients.

1. Preoperative factors included demographic factors as well. Grouping this way allows for better delineation of sample description and identification of the role of comorbidities in the development of complications and their role in the postoperative period. Preoperative factors included age, sex, race, weight, insurance, ejection fraction, MELD score, Na, K, BUN, creatinine, GFR, glucose, total bilirubin, PT, PTT, INR WBC, HGB, Hct, and Plt. Analysis of factors for the preoperative time period included n = 226 due to missing data.
2. Intraoperative factors included pulmonary artery systolic pressure, pulmonary artery diastolic pressure, systolic blood pressure, systolic diastolic pressure, oxygen saturations, vasopressor use, packed RBC transfusion, FFP transfusion, platelet transfusion, CRRT, surgery time, cold ischemic time, warm ischemic time, induction medications, glucose (high and low), and thromboelastrography (TEG; platelet, fibrinogen). Analysis of factors in the intraoperative time period utilized an n = 217 due to missing data.
3. Postoperative factors include the complications of bleeding, acute renal failure, graft dysfunctions, sepsis, cerebral edema, and prolonged ventilation time. Additional factors broken into two additional time periods (4 hours post surgery and Postoperative Day 1) Na, K, BUN, creatinine, GFR, glucose, albumin, total bilirubin, PT, PTT, INR, Hgb, Hct, Plt, creatinine. Analysis performed on factors in the postoperative time period utilized an n = 225 due to missing data.

Analysis for each time period controlled for MELD. Controlling for MELD allowed standardization of the sample based on preoperative risk of death during transplantation. Missing

values that were identified in the database were reviewed, and missing factors were removed from the logistic regression model. Factors included in the analysis were based on previous literature including the comorbidities of diabetes, hypertension, renal failure (C.-T. Huang et al., 2011; Malik & Ahmad, 2009) and the specific laboratory data were based on practice guidelines of the study transplant center that were identified for each of the complications (i.e. Hemoglobin, INR, BUN, Creat, etc.). One main reason for missing data was that recipient's and electronic record were incomplete often based on the fact the study bridged the initial transition from a paper to electronic medical record (inpatient) resulting in frequently mismatched results. An additional factor was the addition of the OTTR database that also had incomplete data fields that could not be verified by other records.

Specific Aim 1: Determine factors in the preoperative, intraoperative, and postoperative time period that predict ICU complications (bleeding, sepsis, graft dysfunction, acute renal failure, cerebral edema, and prolonged mechanical ventilation).

Data were analyzed using binary logistic regression comparing all perioperative factors with the development of postoperative complications (Table 6).

Table 6

Factor Significance by ICU Complication

Postoperative Complication	Preoperative, Intraoperative, Postoperative Factors	Complication Yes/No	Mean	Standard deviation	Odds Ratio	95% Confidence Interval	*p* value
Bleeding (n=38, 13.9%)	Pre: BUN	Yes	18.969	12.275	1.039	1.023-1.164	0.008
		No	23.131	17.021			
	Intra: None	N/A	N/A	N/A	N/A	N/A	N/A
	Post: 4-hour sodium	Yes	141.0	4.142	0.827	0.705-0.970	0.020
		No	139.06	4.423			
	POD 1 hemoglobin	Yes	9.703	2.221	1.458	1.086-1.957	0.012
		No	10.755	1.955			
Acute renal failure (n=68, 29.6%)	Pre: Creatinine	Yes	1.568	0.988	0.346	0.169-0.708	0.004
		No	1.164	0.905			
	Intra: CRRT						
		Yes	1.82	0.384	0.166	0.036-0.773	0.022
	TEG fibrinogen	No	1.98	0.135			
		Yes	118.99	51.502	1.007	1.001-1.014	0.031
	Post: 4-hour INR	No	153.96	85.706			
		Yes	2.176 C	0.634	4.238	1.236-14.352	0.022
	POD 1 lowest glucose	No	1.994	0.412			
		Yes	167.40	54.405	0.992	0.985-0.999	0.020
		No	155.40	51.632			
Graft dysfunction (n=44, 19.1%)	Pre: Age	Yes	53.70	9.697	1.051	0.000	0.039
		No	56.01	9.156			
	Intra: Warm ischemic time	Yes	0:33	0:08	.999	0.998-1.000	0.009
		No	0:30	0:07			
	Post: None	N/A	N/A	N/A	N/A	N/A	N/A
Sepsis (n=14, 6.1%)	Pre: Age	Yes	59.07	7.760	0.880	0.000	0.019
		No	55.34	9.345			
	BUN	Yes	34.714 C	27.370	0.932	0.880-0.987	0.017
		No	21.764	15.292			
	Creatinine	Yes	1.122	0.678	7.522	1.228-46.059	0.029
		No	1.294	0.962			
	Intra: FFP transfusion	Yes	8.64 C	7.732	0.804	0.660-0.980	0.031
		No	4.83	4.829			
	Warm ischemic	Yes	0:27	0:06	1.002	1.000-1.005	0.031

	Time	No	0:30	0:07			
	Post: 4-hour	Yes	25.43	21.295	0.873	0.180-199.307	0.013
	BUN	No	19.62	11.698			
Cerebral	Pre: None	N/A	N/A	N/A	N/A	N/A	N/A
edema (n=2,	Intra: None	N/A	N/A	N/A	N/A	N/A	N/A
0.9%)	Post: None	N/A	N/A	N/A	N/A	N/A	N/A
Prolonged	Pre: BUN	<24 hours	19.292	13.0863	1.026	1.002-1.052	0.034
Ventilator		>24 hours	27.355	19.597			
time	Intra: Lowest	<24 hours	100.62	23.515	1.032	0.000-1.032	< .0005
(n=137, 63%)	glucose	>24 hours	121.23	108.907			
	Post: POD 1	<24 hours	138.25	3.745	1.217	0.006-1.192	0.003
	sodium	>24 hours	140.35	4.252			
	POD 1	<24 hours	10.881	1.959	0.742	0.587-0.991	0.042
	hemoglobin	>24 hours	10.220	2.054			

Note *$p \leq 0.05$. POD 1 = Postoperative Day 1.

An association was defined as factors having a p value < 0.05. With multiple outcome measures there is mixed evidence about adjusting the level of the p value based on the analysis of large data sets (Feise, 2002). Adjustment of the p values to reduce the risk of type 1 errors due to the large number of variables entered into the analysis. Evidence recommends that researcher must balance statistical significance with the magnitude of the effect compared to other research (Feise, 2002). Based on the fact that the studied factors are a combination of what has been identified in research and the facilities practice adjustment to the p value is not necessary. Instead, the odds ratio, confidence intervals, and researchers experience with transplant care will determine if the statistically significant factors have clinical significance or not. Within each table factors that are statistically significant are marked with an asterisk while those clinically significant are marked with a C.

Bleeding

Bleeding was experienced by 38 or 13.9% of the recipients out of a total of 230 recipients. Results demonstrated three factors that were associated with a risk of bleeding. The preoperative factor (*n=226*) that was associated with bleeding was BUN ($p = 0.008$). With a BUN mean of 18.969 mg/dL ± 12.275 mg/dL bleeding is noted however, a BUN with a mean of 23.131mg/dL ± 17.021 mg/dL did not experience bleeding complications. Intraoperatively ($n = 217$), no significant factors were associated with bleeding. Postoperatively ($n = 225$), the significant factors were four-hour sodium ($p = 0.020$) and POD 1 hemoglobin ($p = 0.012$). Recipients with bleeding had a four hour sodium mean of 141.0 mEq/L ± 4.142 mEq/L those without bleeding had a four hour sodium mean of 159.06 mEq/L ± 4.423 mEq/L. POD 1 hemoglobin mean was 9.703 gm/dL ± 2.221gm/dL with bleeding but without bleeding the POD 1 hemoglobin mean is 10.755 gm/dL ± 1.955 gm/dL. Normal hemoglobin value range is 13.8-17.2 gm/dL for men and 12.1-15.1 gm/dL in women.

Acute Renal Failure

Acute renal failure was experienced by 68 or 29.6% of recipients. Five factors significantly associated with the complication of acute renal failure were: creatinine, CRRT use, TEG fibrinogen, four hour INR, POD 1 lowest glucose. Preoperatively, creatinine was significant ($p = 0.004$). If acute renal failure presents the mean creatinine is 1.568 mg/dL± 0.988 mg/dL without acute renal failure the creatinine mean is 1.164 mg/dL ± 0.905 mg/dL. Intraoperatively, the significant factors were CRRT use ($p = 0.022$) if acute renal failure present CRRT mean is 1.82 ± 0.384 treatments but without acute renal failure the CRRT mean is 1.98 ± 0.135 treatments and TEG fibrinogen ($p = 0.031$) with acute renal failure the TEG fibrinogen

mean is 118.99 g/L ± 51.502 g/L or without acute renal failure the TEG fibrinogen mean is 153.96 g/L ± 85.706 g/L. Postoperatively, the identified factors were four-hour INR ($p = 0.022$) and POD 1 lowest glucose ($p = 0.020$). With acute renal failure the INR mean is 2.176 ± 0.634 without renal failure INR mean is 1.994± .412. POD 1 lowest glucose ($p = 0.020$) in the presence of acute renal failure had a mean of 167.40 mg/dL ± 54.405 mg/dL, without acute renal failure the lowest glucose mean was 155.40 mg/dL ± 51.632 mg/dL.

Graft Dysfunction

Graft dysfunction was experienced by 44 or 19.1% of recipients. Age and mean warm ischemic time were identified as significant for graft dysfunction. In the preoperative time period, age was a significant predictor of graft dysfunction ($p = 0.039$). When graft dysfunction was present, the mean age of recipient was 53.70 ± 9.697 years but without graft dysfunction the mean age was 56.01 ± 9.156 years. Intraoperatively, warm ischemic time was significant ($p = 0.009$) with graft dysfunction the mean warm ischemic time was 0:33 minutes ± 0:08 minutes without graft dysfunction the mean warm ischemic time was 0:30 minutes ± 0:07 minutes. Postoperatively, no significant factors were noted for graft dysfunction.

Sepsis

Sepsis was experienced by 14 or 6.1% of recipients. Significant factors for sepsis include age, BUN, FFP transfusions, warm ischemic time, and four hour BUN. Factors preoperatively include age ($p = 0.019$), with sepsis the mean age was 59.07 ± 7.760 without sepsis the mean age was 55.34 ± 9.345. BUN ($p = 0.017$) with sepsis has a mean BUN of 34.714 mg/dL ± 27.370 mg/dL without sepsis the mean BUN was 21.764 mg/dL ±15.292 mg/dL, and creatinine ($p = 0.029$) with sepsis mean creatinine was 1.122 mg/dL ± 0.678 mg/dL without sepsis mean

creatinine was 1.294 mg/dL ± 0.962 mg/dL. Intraoperatively, significant factors were FFP transfusions ($p = 0.031$) with sepsis the mean FFP transfusion volume was 8.64 units ± 7.732 units without sepsis the mean FFP transfusion volume was 4.83 units ± 4.829 units. Warm ischemic time ($p = 0.031$) with sepsis mean warm ischemic time was 0:27 minutes ± 0:06 minutes, without sepsis the mean warm ischemic time was 0:30 minutes ± 0:07 minutes. Postoperatively, the identified factor was four-hour BUN ($p = 0.013$) with sepsis the mean four hour BUN was 25.43 mg/dL ± 21.295 mg/dL or without sepsis the mean four hour BUN was 19.62 mg/dL ± 11.698 mg/dL.

Cerebral Edema

Cerebral edema was experienced by 2 or 0.9% of recipients. No pre, intra or postoperative factors were associated with cerebral edema.

Prolonged Mechanical Ventilation

The majority of recipients 137 or 63% experienced prolonged mechanical ventilation of greater than 24 hours. Preoperatively, the significant factor was BUN ($p = 0.034$) with prolonged ventilator time the mean BUN was 27.355 mg/dL ± 19.597 mg/dL without prolonged ventilation the mean BUN was 19.292 mg/dL ± 13.08mg/dL. Intraoperatively, the significant factor was lowest glucose ($p \leq 0.0005$) with prolonged ventilation the mean lowest glucose was 121.23 mg/dL ± 108.907 mg/dL without prolonged ventilation the lowest glucose mean was 100.62 mg/dL ± 23.515 mg/dL. Postoperatively, factors included POD 1 sodium ($p = 0.003$) with prolonged ventilation mean POD 1 sodium was 140.35 mEq/L± 4.252 mEq/L, without prolonged ventilation the mean POD 1 sodium was 138.25 mEq/L ± 3.745 mEq/L and hemoglobin with a

(p = 0.042). With prolonged ventilation the mean hemoglobin was 10.220 g/L $\pm$ 2.054 g/L without prolonged ventilation mean hemoglobin was 10.881 g/L $\pm$ 1.959 g/L.

Specific Aim 2: Determine the predictive factors of liver transplant recipients in the preoperative, intraoperative, and postoperative period as they relate to ICU and hospital length of stay.

Using binary logistic regression, ICU LOS was a dependent variable. MELD score was used as a control variable to equalize the disease severity between recipient groups (< 9 day and > 9 day LOS; Bernardi et al., 2011; Butt et al., 1998). The first section begins with analysis of preoperative factors that impact ICU LOS (Tables 7-9).

Table 7

Preoperative Factors Impacting Recipient ICU Length of Stay

Preoperative Factor	Length of stay 0-9.0 or 9.0+	Mean	Standard Deviation	Odds Ratio	95% Confidence Interval	*p* value
Age				0.993	0.946-1.041	0.786
Sex: Male	0-9.0 9.0+			4.879	1.855-12.832	0.001*
Race: Caucasian				0.341	0.047-2.493	0.289
Race: Hispanic				0.115	0.013-1.015	0.052
Race: African American				0.145	0.007-2.880	0.203
Race: Asian				<0.0005	0.000	0.999
Insurance: Medicare				2.864	0.199-41.193	0.439
Insurance: Medicaid				3.481	0.239-50.758	0.362
Insurance: Private insurance				1.276	0.099-16.441	0.852
Sodium (mEq/L)				1.022	0.943-1.107	0.594
Potassium (mEq/L)	0-9.0 9.0+	4.12 4.01	.664 .522	0.442	0.222-0.879	0.015*
Blood urea nitrogen (mg/dL)				1.008	0.981-1.036	0.563
Creatinine (mg/dL)				0.718	0.393-1.311	0.281
Glucose (mg/dL)				1.005	0.997-1.012	0.118
Prothrombin time (Seconds)				1.012	0.973-1.052	0.566
International normalized ratio				0.837	0.561-1.268	0.413
WBC ($x10^9$/L)				1.110	0.989-1.246	0.076
Hemoglobin (g/L)				0.953	0.630-1.442	0.819
Hematocrit (g/L)				0.898	0.751-1.073	0.236
Platelet ($x10^9$/L)				0.973	0.994-1.006	0.973
Albumin (U/L)				1.097	0.639-1.472	0.706
Total bilirubin (mmol/L)				0.834	0.975-1.032	0.848

Preoperative factors that were significant for ICU LOS were sex ($p = 0.001$) and potassium ($p = 0.015$). With a LOS < 9 days the mean potassium value was 4.125 mEq/L $\pm$.664 mEq/L but with a LOS > 9 days the mean potassium was 4.010 mEq/L $\pm$ 0.522 mEq/L.

Table 8

Intraoperative Factors Significant for ICU Length of Stay

Intraoperative Factor	Length of stay 0-9.0 / 9.0+ days	(n)	Mean	Standard Deviation	Odds Ratio	95% Confidence Interval	*p* value
Highest systolic blood pressure (mmHg)					0.984	0.956-1.016	0.336
Lowest systolic blood pressure (mmHg)					0 .993	0.955-1.038	0.837
Highest diastolic blood pressure (mmHg)					1.038	0.997-1.081	0.067
Lowest diastolic blood pressure (mmHg)					1.002	0.933-1.058	0.844
Pulmonary artery systolic pressure (mmHg)	0-9.0 days 9.0+ days	174 49	25.62 29.71	5.822 6.076	1.093	1.002-1.187	0.045*
Pulmonary artery diastolic pressure (mmHg)					1.089	0.988-1.210	0.084
Saturations %					1.693	0.640-3.972	0.331
Red blood cell transfusion (#)					1.125	1.000-1.261	0.051
Platelet transfusion (#)					1.011	0.818-1.257	0.899
Fresh frozen plasma transfusion (#)					1.0811	0.948-1.242	0.235
Vasopressor utilization					0.827	0.298-2.341	0.733
Continuous renal replacement therapy					0.774	0.142-4.124	0.754
Surgical time (total hours)					1.000	1.000-1.000	0.973
Cold ischemic time (Hr)	0-9.0 days 9.0+ days	178 52	5:41 5:59	1:40 2:06	1.000	1.000-1.000	<0.0005*
Warm ischemic time (Min)					1.001	1.000-1.002	0.187
Induction medications used					<0.0005	0.000	1.000

Highest glucose (mg/dL)					0.997	0.987-1.007	0.516
Lowest glucose (mg/dL)	0-9.0 days 9.0+ days	178 52	102.94 129.54	25.060 143.505	1.018	1.001-1.037	0.040*
TEG platelet count ($x10^9$/L)	0-9.0 days 9.0+ days		62.62 69.79	45.398 80.766	1.008	1.001-1.016	0.026*
TEG fibrinogen count (g/L)					0.998	0.992-1.003	0.392

Intraoperative factors that were significant for ICU LOS included pulmonary artery systolic pressure ($p = 0.045$) with LOS < 9 days the mean pulmonary artery systolic pressure is 25.62 mmHg$\pm$ 5.822 mmHg, greater than 9 days the mean pulmonary artery systolic pressure is 29.71 mmHg $\pm$ 6.076 mmHg, cold ischemic time ($p \leq 0.0005$) with LOS < 9 days mean cold ischemic time is 5:41 hours $\pm$ 1:40 hours with LOS > 9 days mean cold ischemic time is 5:59 hours $\pm$ 2:06 hours, lowest glucose ($p = 0.040$) with LOS < 9 days mean glucose is 102.94 mg/dL $\pm$ 25.060 mg/dL, with LOS > 9 days mean lowest glucose is 129.54 mg/dL $\pm$ 143.505 mg/dL, and TEG platelet count ($p = 0.026$) with LOS < 9 days the mean TEG platelet count is 62.62 $x10^9$/L $\pm$ 45.398 $x10^9$/L with LOS > 9 days mean TEG platelet count is 69.79 x 10^9/L $\pm$ 80.766 $x10^9$/L.

Table 9

Postoperative Factors Significant for ICU Length of Stay

Postoperative Factor	Length of stay 0-9/ 9.0+ days	(n)	Mean	Standard Deviation	Odds Ratio	95% Confidence Interval	*p* value
4-hour							
sodium (mEq/L)					1.087	0.941-1.254	0.256
potassium (mEq/L)					0.918	0.500-2.153	0.922
blood urea nitrogen (mg/dL)	0-9 days 9.0+days	178 52	19.22 22.54	10.536 17.528	1.110	1.020-1.208	0.015*
creatinine (mg/dL)					0.532	0.123-1.971	0.317
glucose (mg/dL)					0.997	0.989-1.005	0.490
prothrombin time (seconds)					1.392	0.325-5.959	0.655
international normalized ratio					0.121	0.000-49372.928	0.748
hemoglobin (g/L)					0.700	0.393-1.099	0.109
hematocrit (g/L)	0-9 days 9.0+ days	178 52	31.101 32.096	5.2969 4.8944	1.263	1.031-1.547	0.024*
platelet count ($x10^9$/L)					1.002	0.992-1.012	0.725
albumin (U/L)					1.630	0.550-1.794	0.251
total bilirubin (mmol/L)					0.972	0.844-1.177	0.972
POD 1							
sodium (mEq/L)					0.972	0.844-1.177	0.417
potassium (mEq/L)					0.636	0.242-1.671	0.359
blood urea nitrogen (mg/dL)					0.938	0.875-1.005	0.072
creatinine (mg/dL)					0.758	0.224-2.569	0.657
glucose (mg/dL)	0-9 days 9.0+ days	177 52	162.51 146.88	53.194 49.293	0.990	0.982-1.000	0.047*
prothrombin time (seconds)					1.052	0.803-1.377	0.715
international normalized ratio					1.379	0.167-11.39	0.765

Postoperatively, the significant factors ICU LOS included four-hour BUN ($p = 0.015$) with LOS < 9 days mean BUN was19.22 mg/dL ± 10.536 mg/dL with LOS > 9 days BUN mean was 22.54 mg/dL ± 17.528 mg/dL. The next factor is four-hour hematocrit ($p = 0.024$) with LOS < 9 days four hour hematocrit mean was 31.101 g/L ± 5.2969 g/L with LOS > 9 days four hour hematocrit mean was 32.096 g/L ± 4.8944 g/L, POD 1 glucose ($p = 0.047$) with LOS < 9 days mean POD 1 glucose was 162.51 mg/dL ± 53.194 mg/dL and LOS > 9 days mean POD 1 glucose was 146.88 mg/dL ± 49.29 mg/dL, POD 1 hemoglobin ($p = 0.033$) with LOS < 9 days mean was 10.583 g/L ± 1.9329 g/L and LOS > 9 days was 10.713 g/L ± 2.3122 g/L, and POD 1 hematocrit ($p = 0.037$) mean with LOS < 9 days was 32.229 g/L ± 21.8857 g/L with LOS > 9 days mean was 30.854 g/L ± 6.5050 g/L.

Further analysis for this specific aim focused on the preoperative, intraoperative, and postoperative factors that affect hospital LOS. The second binary logistic regression model used the same pre, intra and postoperative factors but used hospital LOS instead of ICU LOS as the dependent variable (Tables 10-12).

Table 10

Preoperative Factors Significant for Hospital Length of Stay

Preoperative Factor	HLOS <19/>19 days	(n)	Mean	Standard deviation	Odds Ratio	95% Confidence Interval	*p* Value
Age					1.015	0.969-1.056	0.596
Sex: Male					1.792	0.793-4.048	0.161
Race: Caucasian					2.344	0.296-18.591	0.420
Race: Hispanic					1.459	0.173-12.311	0.729
Race: African American					3.957	0.321-48.828	0.283
Race: Asian					3.004	0.096-94.086	0.531
Insurance: Medicare					0.433	0.043-4.365	0.478
Insurance: Medicaid					1.637	0.175-15.316	0.666
Insurance: Private insurance					0.892	0.100-7.977	0.627
Sodium (mEq/L)					0.991	0.920-1.068	0.818
Potassium(mEq/L)	<19 days >19 days	157 73	4.129 4.034	.652 .600	0.476	0.250-0.904	0.023*
Blood urea nitrogen (mg/dL)					1.027	1.000-1.058	0.052
Creatinine (mg/dL)					0.477	0.486-1.401	0.461
Glucose (mg/dL)					1.003	0.996-1.009	0.388
Prothrombin time (seconds)					1.009	0.974-1.046	0.612
International normalized ratio					0.529	0.830-1.101	0.529
WBC ($x10^9$/L)	<19 days >19 days	157 73	5.244 7.364	2.251 5.174	1.149	1.005-1.314	0.042*
Hemoglobin (g/L)					0.951	0.597-1.513	0.873
Hematocrit (g/L)					0.882	0.745-1.055	0.174
Platelet ($x10^9$/L)					0.999	0.994-1.004	0.588
Albumin (U/L)					1.407	N/A	0.148
Total bilirubin (mmol/L)					1.001	0.973-1.030	0.939

Preoperative factors that were significant for HLOS were potassium (p = 0.023) with HLOS < 19 days mean potassium level was 4.129 mEq/L $\pm$ 0.652 mEq/L, with a WBC count (p = 0.042) of 5.244 ($x10^9$/L) $\pm$ 2.251 ($x10^9$/L). For recipients with HLOS > 19 days the mean potassium was 4.034 mEq/L $\pm$0.600 mEq/L, with a WBC count mean of 7.364 $x10^9$/L $\pm$ 5.174 $x10^9$/L.

Table 11

Intraoperative Factors Impacting Hospital Length of Stay

Intraoperative Factors	HLOS <19/>19 days	(n)	Mean	Standard Deviation	Odds Ratio	95% Confidence Interval	*p* Value
Highest systolic blood pressure (mmHg)					0.996	0.971-1.026	0.895
Lowest systolic blood pressure (mmHg)	<19 days	153	83.31C	12.104	1.049	1.001-1.098	0.044*
	>19 days	71	86.03	11.774			
Highest diastolic blood pressure (mmHg)					1.018	0.980-1.057	0.361
Lowest diastolic blood pressure (mmHg)					0.957	0.900-1.019	0.169
Pulmonary artery systolic pressure (mmHg)					1.071	0.989-1.160	0.092
Pulmonary artery diastolic pressure (mmHg)					1.020	0.927-1.121	0.688
Oxygen saturations (%)					1.933	0.768-4.869	0.235
Red blood cell transfusions (#)					1.056	0.949-1.175	0.317
Platelet transfusions (#)					1.115	0.896-1.386	0.330
Fresh frozen plasma transfusions (#)	<19 days	157	3.85	3.925	1.143	1.007-1.296	0.039*
	>19 days	73	7.66	6.299			
Vasopressor utilization					0.805	0.301-2.156	0.666
Continuous renal replacement therapy (treatments)					0.600	0.099-3.660	0.580
Surgical time (minutes)					1.000	1.000-1.000	0.288
Cold ischemic time (hours)					1.000	1.000-1.000	0.980
Warm ischemic time (minutes)					1.001	1.000-1.002	0.194
Induction medication					<0.0005	0.000	1.000
Highest glucose (mg/dL)					0.998	0.988-1.007	0.638
Lowest glucose (mg/dL)	<19 days	157	100.93	22.545	1.031	1.013-1.050	0.001*
	>19 days	73	126.21	122.406			
TEG platelet count	<19 days	156	63.40	42.159	1.011	1.003-1.019	0.010*

($x10^9$/L)	>19 days	72	66.10	76.872			
TEG fibrinogen count ($x10^9$/L)					1.000	0.994-1.005	0.876

Intraoperative factors identified as significant for HLOS were lowest systolic blood pressure (p = 0.044) with HLOS < 19 days systolic blood pressure mean is 83.31$\pm$ 12.104 mmHg with HLOS > 19 days mean systolic pressure is 86.03 mmHg $\pm$ 11.774 mmHg. FFP transfusions (p = 0.039) with HLOS < 19 days mean FFP transfusion is 3.85 units $\pm$ 3.925 units and > 19 days mean FFP transfusions was 7.66 units $\pm$ 6.299 units. The lowest glucose value (p = 0.001) with HLOS < 19 days mean lowest glucose was 100.093 $x10^9$/L $\pm$ 22.545 $x10^9$/L with HLOS > 19 days mean lowest glucose is 126.21mg/dL $\pm$ 122.406 mg/dL and TEG platelet count (p = 0.010) with HLOS < 19 days mean TEG platelet count is 63.40 $x10^9$/L $\pm$ 42.159 $x10^9$/L with HLOS > 19 days the TEG platelet count mean is 66.10 $x10^9$/L $\pm$ 76.872 $x10^9$/L.

Table 12

Postoperative Factors Impacting Hospital Length of Stay

Postoperative Factor	HLOS <19/>19 days	(n)	Mean	Standard Deviation	Odds Ratio	95% Confidence Interval	*p* value
4-hour							
sodium (mEq/L)					0.993	0.881-1.130	0.907
potassium (mEq/L)					1.042	0.550-1.976	0.899
blood urea nitrogen (mg/dL)	< 19 days	157	17.97	9.313C	1.055	1.013-1.099	0.010*
	>19 days	72	24.27	16.770			
creatinine (mg/dL)					1.141	0.461-2.825	0.775
glucose (mg/dL)					1.000	0.992-1.007	0.908
prothrombin time (seconds)					1.018	0.288-3.603	0.977
INR					0.665	0.000-51305.617	0.943
hemoglobin (g/L)					0.648	0.383-1.096	0.106
hematocrit (g/L)	< 19 days	157	31.133	5.2785	1.256	1.022-1.567	0.031*
	>19 days	73	31.740	5.0866			
platelet count ($x10^9$/L)					1.005	0.995-1.015	0.325
albumin (U/L)					0.810	0.457-1.436	0.471
total bilirubin (mmol/L)					1.014	0.865-1.189	0.860
POD 1							
sodium (mEq/L)					1.068	0.935-1.218	0.333
potassium (mEq/L)	< 19 days	157	4.422	.5407	0.357	0.148-0.883	0.026*
	>19 days	73	4.143	.4841			
blood urea nitrogen (mg/dL)					0.990	0.971-1.009	0.284
creatinine (mg/dL)					0.722	0.332-1.570	0.411
glucose (mg/dL)					1.005	0.998-1.013	0.180
prothrombin time (seconds)					1.021	0.885-1.178	0.779
INR					1.326	0.559-3.146	0.523
hemoglobin (g/dL)					2.142	0.572-8.019	0.258
hematocrit (g/dL)					0.764	0.480-1.216	0.256
platelet count ($x10^9$/L)					0.999	0.984-1.013	0.860
albumin (U/L)					1.073	0.749-1.397	0.886
total bilirubin (mg/dL)					1.039	0.890-1.214	0.625

Postoperative factors significant for HLOS less than 19 days were four-hour BUN (p = 0.010) with mean BUN of 17.97 mg/dL ± 9.313 mg/dL, four hour hematocrit (p = 0.031) with a mean of 31.1333g/dL ± 5.2785 g/dL and POD 1 potassium (p = 0.026) with a mean of 4.422 mEq/L ± 0.5407 mEq/L. When the HLOS is greater than 19 days the mean BUN is 24.27 mg/dL ± 16.770 mg/dL, four hour hematocrit with a mean of 31.740 g/dL ± 5.0866 g/dL and POD 1 potassium with a mean of 4.143 mg/dL ± 0.4841 mg/dL.

Specific Aim 3: Describe the relationship of ICU complications with ICU LOS, HLOS, and mortality.

Analysis of ICU LOS used binary logistic regression and a sample of n = 228 (Table 13). This analysis investigated complications for liver transplantation recipients who had an ICU stay of less than 9 days and those with an ICU stay of more than 9 days. For recipients having an ICU stay less than 9 days prolonged ventilator time (>24 hours) was a significant factor (p = 0.002). For recipients with an ICU stay greater than 9 days, the significant complications included graft dysfunction (p = 0.001) sepsis ($p \leq 0.0005$) and prolonged ventilator time (> 24 hours; p = 0.002).

Table 13

Results of Binary Logistic Regression for Complications and ICU Length of Stay

Complications	Odds Ratio	95% Confidence Interval	*p* value
Bleeding	1.403	0.526-3.741	0.499
Renal failure	1.901	0.819-4.413	0.135
Graft dysfunction	4.312	1.801-10.326	0.001*
Sepsis	13.767	3.287- 57.667	<0.0005*
Cerebral edema	N/A	N/A	N/A
Prolonged Ventilator time	3.646	1.584- 8.395	0.002*

Note. ICU LOS > 9 days.

Analysis of HLOS used binary logistic regression with a sample of $n = 228$ (Table 14). This analysis looked at complications for liver transplantation recipients with a HLOS less than and greater 19 days. For recipients with a HLOS < 19 days prolonged ventilator time was significant with ($p \leq 0.0005$). Recipients with HLOS of more than 19 days, the significant factors were bleeding ($p = 0.046$), renal failure ($p = 0.027$), graft dysfunction ($p \leq 0.0005$), and prolonged ventilator time ($p \leq 0.0005$).

Table 14

Results of Binary Logistic Regression for Complications and Hospital Length of Stay

Complications	Odds Ratio	95% Confidence Interval	*p* Value
Bleeding	2.875	1.019- 8.117	0.046*
Renal failure	2.636	1.117- 6.223	0.027*
Graft dysfunction	7.150	2.831- 18.056	<0.0005*
Sepsis	32.282	5.007-208.121	<0.0005*
Cerebral edema	N/A	N/A	0.999
Prolonged Ventilator time	4.717	2.083- 10.684	<0.0005*

Note HLOS greater than 19 days.

Analysis of overall mortality (8/230 or 3.48%) post liver transplant was completed comparing recipients who expired and those who experienced an ICU complication (regardless of LOS). No recipient deaths were associated with either ICU time period. HLOS less than 19 resulted in only 1 recipient death while HLOS greater than 19 resulted in 7 recipient deaths (Table 15).

Table 15

Results of Binary Logistic Regression Comparing ICU Complications and Mortality

Complications	Odds Ratio	95% Confidence Interval	*p* Value
Bleeding	<0.0005	<0.000- N/A	0.998
Renal failure	11.735	0.871-158.165	0.064
Graft dysfunction	5.370	0.697- 41.348	0.107
Sepsis	22.189	1.372- 358.909	0.029*
Cerebral edema	78.188	1.679- 3641.168	0.026*
Ventilator time	3.227	0.253- 41.113	0.367

Based on analysis, the factor significant for ICU complications and mortality were: sepsis ($p = 0.029$) and cerebral edema ($p = 0.026$). Additional descriptive analysis of those recipients who died revealed that all deaths occurred in the > 9 day ICU LOS and > 19 HLOS groups. Age range of recipients who died was 48-59 consisting of 6 males and 2 females. Race of each recipient revealed 7 Caucasian and 1 other. Comorbidities present in these recipients included diabetes, obesity or none had MELD scores of 18-45. Finally, of all the ICU complications 6 recipients had renal failure, 2 with sepsis, 3 with graft dysfunction and 1 with cerebral edema.

CHAPTER 6 DISCUSSION

Discussion

Bleeding

Coagulopathy is a universal concern in patients with acute liver failure. Coagulopathy presents with an inadequate synthesis of clotting factors paired with platelet abnormalities, peaking 2-5 days postoperatively (Pyleris, Giannikopoulos, & Dabos, 2010; Thorat & Lee, 2013). Preoperatively, the only significant variable associated with bleeding was BUN. BUN is an unusual find for bleeding because it is associated with renal function or is a symptom of the preexisting malnutrition in this time period. Elevated BUN may also be an indication of persistent dehydration in the preoperative time period that will require a more aggressive management strategy. Based on the identified means, it would appear that BUN is clinically significant since values are elevated above normal range (7-20 mg/dL) by a minimum of 3-5 mg/dL. This value warrants closer observation in conjunction with the direction of the creatinine which with an increase supports worsening renal failure, persistent hypovolemia or if BUN is unrelated. With worsening renal failure, a reduction occurs in erythropoietin production (Manzarbeitia, 2014). Reduction of erythropoietin is the result of inflammatory cytokines suppression of erythropoietin in hepatocytes but also renal production of erythropoietin (Vasilopoulos et al., 2000). This response is important since the liver is the primary extrarenal producer of erythropoietin. Reduction of erythropoietin reduces the circulating blood volume that could lead to anemia and if paired with systemic hypoxia will worsen the anemia (Vasilopoulos et al., 2000). Additional reasons for an elevation in BUN can be in response to an active bleed secondary to digested blood, secondary to a gastric bleed a source of urea or the elevation may

be in response to dehydration (Contreras et al., 2002). Goldaracena et al. (2013) identified that, in the preoperative period, certain laboratory values may not be normal and require close observation, including the hemoglobin, hematocrit, platelet count, and prothrombin time, because these may indicate a low-grade disseminated intravascular coagulation which can be more severe based on persistent hypovolemic state (Olcese, 2013). Intraoperatively, no significant factors were identified for liver transplant recipients at risk for bleeding.

Postoperatively, factors that were significant for bleeding were four-hour sodium and POD 1 hemoglobin. Alterations intraoperatively, including bleeding, transfusions, and fluid resuscitation, are often related to total volume of blood products administered. Alterations in the four-hour sodium may be related to both the volume and the age of blood products administered. (Uvizl, Klementa, Adamus, & Neiser, 2011) identified that the older the blood and the larger the volume transfused, the higher the glucose and sodium levels measured in the blood. The age of RBC units was not monitored in this study to validate this finding. POD 1 hemoglobin was significant for bleeding. Low hemoglobin values (7.4 to 8.5 mg/dL) were a result of dilutional coagulopathy, presence of active bleeding, acute renal failure or sepsis (Goldaracena et al., 2013; Olcese, 2013).

Acute Renal Failure

Based on the national transplant database, long-term renal failure occurs 3-12 months post transplant in response to hepatorenal syndrome, immunosuppressant medication toxicity (cyclosporine, tacrolimus, steroids), and preexisting hypertension (Contreras et al., 2002). Additional factors for developing renal failure include surgical re-exploration and the intraoperative use of immunosuppressant medications (Feltracco et al., 2011). Medications

administered to all recipients in this study included steroids upon initiation of the surgical procedure and were sustained in the postoperative period. Additional immunosuppression is administered as part of the transplant protocol (tacrolimus or cyclosporine) but was not evaluated for each recipient, only the intraoperative medications for induction were reviewed due to their potential impact on organ dysfunction in the immediate ICU period.

Preoperatively, the factor associated with renal failure was creatinine. This is clinically significant if the creatinine is already above normal ranges in the preoperative setting indicating an already compromised recipient but based on analysis creatinine were just marginally elevated in the preoperative period (1.5-1.7 mg/dL). Creatinine is a reflection of renal and liver function, and in the preoperative state these values may be compromised if the recipient's liver failure includes portal hypertension. The creatinine may also be affected by increased age and the presence of muscle wasting often seen in liver transplant recipients secondary to preexisting malnutrition (Lerma, 2014). It is not uncommon for liver failure patients to experience simultaneous renal failure as a result of hepatorenal syndrome that may result in a kidney transplant after the liver transplant (Fagundes & Gines, 2012).

Intraoperatively, the significant results for acute renal failure include the use of CRRT and fibrinogen. During this time, fibrinogen values are abnormal due to the consumption of fibrinogen in response to poor liver function. CRRT is an indication that renal function is impaired and waste clearing is ineffective. Often, CRRT is started preoperatively but is more often initiated in the operating room as a way to manage fluid volume in patients with impaired renal function. Literature does not define specific criteria for either initiation or discontinuation of CRRT other than the general requirement for removal of waste products in a recipient was

hemodynamically unstable (Douthitt et al., 2012; Townsend et al., 2009). For this study CRRT was determined to be necessary when the physicians needed a slow fluid removal process and then needed a procedure to manage fluid volume during the actual transplant (Douthitt et al., 2012). CRRT usage is the result of either preoperative renal failure or intraoperative fluid overload. For recipients with preexisting renal failure, CRRT is the most efficient way to manage fluid shifts in the intraoperative period. CRRT is effective in managing of electrolytes and fluid volumes but may lead to a false sense of stabilization of kidney function because BUN and creatinine levels are controlled. If fluid management is a significant concern in the operating room, CRRT will often be continued for additional days in the ICU, increasing HLOS. Use of CRRT intraoperatively may lead to dialysis postoperatively to assist with fluid volume management and support new onset renal failure. Use of CRRT in transplantation pretransplant and then intraoperatively have demonstrated an association with increased mortality rates (pre 65%, post 30%; Contreras et al., 2002; L. Wong et al., 2005), increased risk of infection, reduced graft survival, and prolonged ICU stays (Abbasy et al., 2010; L. Wong et al., 2005).

Postoperatively, the four-hour INR with a mean of 2.176 $\pm$0.634 and POD 1 lowest glucose with a mean of 54.405 $\pm$ 0.992 mg/dL were identified as significant factors for the development of renal failure. Elevation of INR is both statistically and clinically significant. Elevation of INR is an indication that the preexisting coagulopathy has not resolved and increased risk of bleeding is possible requiring additional transfusions of RBC and FFP. This increased transfusion volume may lead to fluid volume overload that requires the use of dialysis in the postoperative period. Resolution of INR elevation may take several days due to the transplanted organ needing to initiate production of the necessary clotting factors to reverse the

coagulopathy. Failure to reverse the coagulopathy paired with any renal failure increase the recipients' risk of developing an ICU complication. Glucose abnormalities are multifactorial. First serve as an indication of sustained gallbladder dysfunction, often present prior to liver dysfunction which decreases lymphatic flow and reducing gluconeogenesis (MedicineNet, 2014) while increasing metabolic demands on the newly transplanted liver (Luu, 2014). Additionally, low glucose is a result of reduced hepatic glucagon stores. Blood glucose levels are not directly related to renal failure but can be linked to the presence of hepatorenal syndrome often present in liver recipients which reduces the efficiency of the liver and kidney to filter and excrete glucose from the body (Schumann et al., 2010). If blood glucose remains elevated damage to the vascular components of the kidney can occur requiring further dialysis intervention and potentially kidney transplantation if failure is not reversed. Interventions that may improve the existing renal failure include improving fluid resuscitation and only replacing the specific fluids lost (normal saline, dextrose, RBC transfusions, etc.). Fluid resuscitation is a common postoperative occurrence and accounts for the frequency of laboratory testing, hemodynamic monitoring for the first 48 hours post transplant. Fluid resuscitation is necessary to ensure that kidney functioning returns to baseline or is stabilized in the postoperative period.

Graft Dysfunction

Graft dysfunction was experienced by 19.1% of the recipients in the postoperative period and is dependent on donor, recipient, and operative factors (Briceno & Ciria, 2010). Preoperatively, age was a significant factor for predicting graft dysfunction. Advanced age was associated with a high risk for transplantation. Despite this risk there has been no federal regulation on maximum age of recipient but individual transplant centers have attempted to

mitigate these risks by developing rules for transplantation based on “physiologic age.” One key feature of age is that the older the patient is when diagnosed with biliary cirrhosis or hepatocellular carcinoma, the higher their mortality (Lipshutz et al., 2007; Marino et al., 1995). Lipshutz (2007) identified that longevity has led to a higher incidence of liver disease in older patients 65-74 years of age. Higher mortality rates in recipients may be related to the development of the complications of aging specifically coronary artery disease and infection with possible progression to sepsis (Bruns et al., 2014; Lipshutz et al., 2007).

Despite research indicating older age (> 65 year old) recipients have a higher risk for graft dysfunction (Aduen et al., 2009; Rook & Rand, 2011). This study demonstrated that recipients experiencing graft dysfunction were younger (55-64) compared to the literature of over 65 years of age. When looking at the literature, episodes of graft failure are lower in donors younger than age 45, but doubles between age 45 and age 65 (Marino et al., 1995). The difference of results in this study and the literature is primarily due to the age of the recipients within the transplant center and their comorbid conditions. An additional factor that may also be the reason for age being younger was the use of deceased donors altering the makeup of the recipient pool.

Intraoperatively, warm ischemic time was significant in predicting graft dysfunction. Warm ischemic time, “anastomosis time,” is the ischemia of rewarming from the time the organ is removed from ice (preservation solution) until it is reperfused with the recipient's blood (Halazun, Al-Mukhtar, Aldouri, Willis, & Ahmad, 2007). During this time, the liver has potential for injury as catecholamines are flushed through the vasculature creating an increased cellular metabolic demand that exhausts the organ's oxygen and nutrients potentially worsening organ

ischemia (Brennan, Lunsford, & Kuo, 2010; Stiegler et al., 2013). The longer the warm ischemic time (ischemia peaks at > 100 minutes), the more likely the recipient's graft will sustain a poor outcome (Halazun et al., 2007). In this study, the average warm ischemic time was 30 ± 7 minutes, well below ischemic peak values in the literature. One explanation of this variation in time for warm ischemic time is due to the transplant centers use of only deceased donor organs. This donor type often results in long ischemic time due to donor cause of death and organ procurement techniques (Stiegler et al., 2013). Current research is looking at ways to reduce this ischemic time. No recommendation has been noted for a standard warm ischemic time forcing research to try approaches focused on the benefit of preconditioning organs to limit the progression of cellular injury associated with low oxygen supply and nutrient delivery during these ischemic periods (Berrevoet, Schafer, Vollmar, & Menger, 2003).

Additional cause of graft dysfunction identified by Pillai and Levitsky (2009) is the administration of induction medications or preoperative immunosuppressive regimen. This regimen consists of medication used to keep the recipient’s immune system from rejecting the new organ while simultaneously allowing immunological control of infection (Pillai & Levitsky, 2009). The medications used in liver transplantation include Solu-Medrol, Muromonab-CD3 (OKT3), Tacrolimus, and Cyclosporine. In the transplant center in the present study, the immunosuppression medication included a 500 mg bolus of intravenous Solu-Medrol administered during the cross-clamp period prior to the recipient’s organ is removed. One complication of immunosuppressive regimens is their potential to cause toxicity in the transplanted organ, worsening graft dysfunction, often resulting in longer ICU stays (Pillai & Levitsky, 2009). Prevention of graft dysfunction is achieved through daily monitoring of the

immunosuppressant agents via therapeutic drug level monitoring. Drug level monitoring, standard in the postoperative period, allows practitioners to adjust doses of each of the immunosuppressant medications to minimize toxic effects. This monitoring if accompanied by graft dysfunction may increase a recipients' HLOS. Within this study therapeutic drug monitoring was not closely monitored for the purposes of this study. Postoperatively, no factors were identified that predicted graft dysfunction.

Sepsis

Sepsis is a complication often experienced by ICU patients postoperatively due to compromised immune systems (Aberg, Makisalo, Hockerstedt, & Isoniemi, 2011). Sepsis is the generalized, inflammatory and procoagulant response to infection (S.-O. Lee et al., 2011). Sepsis induces organ failure, resulting in microvascular changes. These changes are precipitated by the release of inflammatory cytokines and the inhibition of fibrinolysis, causing endovascular injury that often progresses to organ death (Aberg et al., 2011; Perri & Fumagalli, 2008). Kaido and coworkers (2012) studied sepsis in solid organ transplants and identified that infection post liver transplant is the most frequent cause of morbidity and cause of hospital death. Within this study both renal failure and sepsis had the highest frequency followed by graft dysfunction and cerebral edema as complications that resulted in a recipients' death.

Preoperatively, the significant factors for developing sepsis were age, BUN, creatinine. Age is an independent predictor if acute renal failure is identified (McCauley et al., 2014). Within this study age was not seen as a predictor of acute renal failure but was a predictor for sepsis and graft dysfunction. No other direct link has been demonstrated in the literature, but there is reference to the effect that donor age has, including reduced liver weight and flow, which

may result in a recipient having a delay in regeneration of the transplanted liver. An altered BUN is often linked to renal dysfunction, but in a low perfusion state such as sepsis is more likely the reflection of wasting of parenchymal tissue within the kidney. Low perfusion states and the resulting anaerobic metabolism results in an elevation of the BUN. BUN will return to baseline as the ischemic state is resolved. This baseline BUN value may not be reached until the recipient is post hospitalization. Despite controlling for MELD, the creatinine values were a significant factor in sepsis. This supports Oberkofler (2010) and McCauley et al., (2014) claim that suggests renal failure results in increased mortality and increased HLOS (Kirnap et al., 2014). Creatinine represents the hydration and overall function of the renal system. Dehydration with an elevated creatinine and the recipients' comorbidities of liver failure will be worsened if sepsis develops. Dehydration must be monitored closely in the intraoperative period to ensure it does not impair the hemodynamic stability of the recipient during surgery. When dehydration is identified early it can be slowly treated to minimize the fluid and electrolyte shifts that will occur and could lead to complications postoperatively i.e. cardiac dysrhythmias.

Intraoperatively, factors identified as significant for sepsis included FFP transfusions and warm ischemic time. The presence of sepsis often requires FFP transfusions to correct the coagulopathies present at the time of transplant. FFP results in the development of multiple organ dysfunction due to its potential for volume overload and sepsis, but may be the only way to replace the necessary complex coagulation factors to reverse the ongoing coagulopathy (Meybohm, Zacharowski, & Weber, 2013; Weber et al., 2013).FFP transfusions in sepsis are both statistically and clinically significant since the continued transfusion need may indicate a worsening of sepsis or a symptom of graft dysfunction and potentially other organ failure

indicating a worsening of the initial septic event. Warm ischemic time , prolonged or shortened, causes an increased cellular metabolic demand that increases ischemic injury that may result in poor graft outcomes (Halazun et al., 2007).Within this study ischemic times are shorter than what is in literature and may be related to the transplantation of deceased donor organs and distance of recovery for these donor organs. Additionally recipient selection may impact this time based on comorbidities and preoperative stability.

Postoperatively, the factor that appeared significant in predicting sepsis was four-hour BUN. Appearance of an elevated BUN postoperatively may signal an ongoing anaerobic metabolism based on vascular changes caused by the transplant and potential sepsis condition. Vascular changes include vasodilation causing fluid leakage from the intravascular space, impairment of fibrinolysis, procoagulant state, and inflammation of endothelium that impairs microvascular flow which causes hypoperfusion of the transplant liver (Schouten, Wiersinga, Levi, & Der Poll, 2008). This value will need to be continually monitored because it may also indicate additional organ dysfunction that may be a result or even cause of a septic event. With sepsis organs often develop a hypoperfused state and anaerobic metabolism. Anaerobic metabolism results in muscle wasting and increased organ dysfunction that may take a few days to develop. Key interventions for a hypoperfused state are to reestablish blood pressure to support organ function.

Cerebral Edema

Cerebral edema is a rare complication. Cerebral edema is the excess accumulation of water in the intra- and/or extracellular spaces of the brain that occurs within 24-96 hours of developing cerebral ischemia or alterations to cerebral space due to increased fluid in response to

a decrease in albumin (Blei, 2007; Jha, 2003). Cerebral edema exists as a preexisting surgical factor in relation to the severity of liver failure and presents with symptoms of encephalopathy. Postoperatively this condition will resolve as liver function improves. There were no identified factors that were predictive of developing cerebral edema during any of the three time periods evaluated.

Prolonged Ventilator Time

A prolonged ventilator time in the transplant literature is defined as ventilation for greater than 24 hours (C.-T. Huang et al., 2011; Razonable et al., 2011). Ventilator times in this study ranged 3.2 hrs-1800 hours and were often seen in conditions with long surgical times which did not appear as significant factors for any ICU complication. Statistics show that in general 5-10% of surgery patients experience pulmonary complications that often require prolonged mechanical ventilation (C.-T. Huang et al., 2011). Common risk factors for pulmonary complications and need for mechanical ventilation in liver transplant recipients include MELD score, presence of impaired or failed kidneys, hepatopulmonary syndrome, preoperative ventilator support, preexisting diabetes, and deceased donor source for transplant (Feltracco et al., 2013).

Preoperatively, factors associated with ventilator time included BUN. An elevated BUN here is a reflection of malnutrition commonly found preoperatively in liver failure paired with fluid alterations in a state of reduced renal function. Malnutrition results in the alteration to BUN due to the amount of protein in the recipients' diet. An elevated BUN represents a high protein diet which might be present in end stage liver disease to help reduce body fat or increase a recipients energy however if inadequate fluid intake is also present may lead to additional increases in BUN as renal function is impaired by amount of protein that must be filtered. Health care professionals should focus on maintenance of fluid volume to reduce any additional renal dysfunction and prevent pulmonary complications secondary to fluid overload either from general fluid resuscitation or administration of blood products.

Intraoperatively, an increased mechanical ventilation time in ICU was associated with lowest intraoperative glucose values. Low glucose intraoperatively is usually a result of poor

nutrition preoperatively. During this same time period, cold ischemic time is experienced and is the period immediately before the liver is removed. The longer the void, the less glycogen available to maintain normal glucose levels in the body, so the diaphragm does not have proper nutrition.

The last factor found significant for a prolonged ventilator time was lowest intraoperative blood glucose (40 gm/dL). This factor appeared to be a reflection of the high metabolic needs of the system during these types of surgeries. Failure to maintain blood glucose (normal range 80-150 mg/dL) will reduce the energy available to the diaphragm to function properly (Okada et al., 2013). This reduced energy to the diaphragm will result in the muscles weakening, reducing the ability to extubate the recipient at the completion of the surgical period. This low blood glucose may be the result of the poor nutritional state that often accompanies liver failure as well as the result of the surgical intervention. Shifts in blood glucose values are the result of the removal of the diseased liver and the glucose shift from the diseased organ to the blood stream. Blood glucose values will stabilize as the new liver begins to function in the immediate post transplant period. Additionally the variable blood glucose levels were based on preexisting nutritional state of recipient and treatment interventions of the medical team.

Postoperatively, the factors that were significant for prolonged ventilator time were POD 1 sodium and hemoglobin. Alterations to sodium, above or below 135-145 mEq/L, were found by Bruns (2014) to be a predictor of mortality at 90 days in transplant recipients. Sodium alteration, within the same range as Bruns study are a result of fluid loss and administration of blood products, paired with potential alterations to renal function within this study. The last factor predictive of a prolonged ventilator time is an alteration to hemoglobin values.

Postoperatively lower hemoglobin values are a result of fluid volume and administration of blood products both intra and postoperatively. Administration of blood products impact the amount of oxygen available for the respiratory system specifically providing adequate oxygenation to maintain diaphragmatic function necessary to facilitate removal from mechanical ventilation.

Specific Aim 2: Describe the association of recipients' factors in the preoperative, intraoperative, and postoperative period as they relate to ICU and hospital length of stay.

ICU Length of Stay

ICU LOS was dichotomized into less than and greater than 9 days. Preoperatively, two factors that increased ICU LOS were sex and potassium. As with many of the complications of liver recipients, these two factors are a result of some preexisting conditions of the recipient. Bruns (2014) identified that females, with higher MELD scores, have higher mortality rates and longer LOS compared to other recipients. For this study, demographics were different from Burns with a larger male population than female but each had high MELD scores. However, the females did have longer ICU stays (2-145 days) and higher MELD but due to the small study sample cannot conclude that all female recipients will have a longer LOS but it does appear with the total sample that the identified comorbidities do play a role in extending ICU LOS. Male sex was both statistically and clinically significant and may be based on the large volume of recipients or their underlying history that places them at risk but will need further evaluation to determine which factors place them at a higher risk.

High potassium, value over 4.0 mEq/L, preoperatively had a significant association with ICU LOS. Elevated potassium in the preoperative period were attributed to the recipients'

comorbidities, presence of malnutrition (Rook & Rand, 2011). Malnutrition in liver failure patients is multifactorial. Factors include decreased intake, metabolic alteration, increased beta adrenergic actively and malabsorption of fats. Malnutrition is due to the inability of the liver to produce bile to breakdown fats causing poor absorption of fat needed for body functions. Failure to absorb fats in turn may lead to zinc deficiency leading to anorexia. A second issue is the inability to synthesize and store of glycogen so carbohydrates cannot be utilized for energy and muscle function. Along with malnutrition in these recipients is the potential for coagulopathies. In the presence of coagulopathy, an elevated potassium level may indicate a condition marked with bleeding or the presence of hemolyzed cells. An additional reason for elevated potassium values may be the presence of renal failure preoperatively. Management of these values can be corrected through the use of intravenous fluids, diet adjustments, and ultimately dialysis if necessary. This condition may predispose a patient to complications related to fluid overload or cardiac arrhythmias intraoperatively that may cause an increased LOS. Within this study dialysis was the only intervention required for fluid overload, not for arrhythmia management. These recipients did have a prolonged hospital and ICU LOS.

Intraoperatively, the identification of an elevated pulmonary artery pressure indicates a high volume of fluid in the pulmonary space that needs redistribution back into the extracellular space (Al-Hamoudi et al., 2010; Glauser, 1990). To directly measure the effect of this volume, a pulmonary artery catheter was used but the preexisting hepatopulmonary hypertension causing values to be falsely elevated but can assist with trending of fluid shifts. Use of a pulmonary artery catheter for the ongoing monitoring of fluid volume requires a longer ICU stay because this catheter is only used in the ICU at the study transplant facility. If a pulmonary artery catheter

is not used, the surgeon will need to focus closer on patient assessment for fluid overload using chest x-rays, ventilator pressure (if indicated), and urine output. In this study, pulmonary artery catheters were used on all recipients along with physical assessments and x-rays to assess volume trends. No data was collected regarding specific interventions based on the pulmonary artery catheter values. The pulmonary artery catheter is a tool used for trending of fluid volumes, but there are concerns about the invasiveness of the device, and risk of infection.

Cold ischemic time also was associated with increased ICU LOS because this period results in an absence of blood flow to the transplant organ that may lead to a prolonged organ dysfunction extending coagulopathy. Reduced blood flow may also worsen the hepatopulmonary edema that could lead to increased fluid in the abdomen (ascites) which could result in failure of the kidneys and pulmonary failure. Cold ischemic time is experienced by all transplant recipients however there are no studies that compare outcomes based on cold ischemic time. Additionally because the study utilized a center that utilized only deceased donor organs some of the results may not be replicated in other centers that do living related or partial organ surgeries since cold ischemic time is not experienced.

Another factor predictive of increased ICU LOS is low intraoperative blood glucose. Pre-surgical blood glucoses in this study ranged from 50-103 mg/dL. National guidelines recommend general surgical glucose levels to be 80-150 mg/dL but no specific recommendation in the transplant literature (Okada et al., 2013). The blood glucose value drops even lower when the liver is removed, requiring an increased supply of dextrose. Failure to maintain steady states of blood glucose in the operative period may increase existing encephalopathy and acidosis, delay in wound healing potentially prolonging a recipients' recovery.

Hypoglycemia is a temporary condition as a result of the removal of the liver intraoperatively in the anhepatic phase (Halazun et al., 2007). This removal causes a sudden increase in blood glucose levels as a result of the release of glycogen stored in the donor organ being released when the liver is manipulated and implanted into the recipient, resulting in hyperglycemia (>200 mg/dL) that occurs prior to the end of surgery and into POD 1. Variability of the glucose triggers suggests the need to closely manage glucose throughout surgery since this variability can impact the healing potential of the recipient postoperatively. In addition prevention of hypoglycemia will help reduce any cerebral dysfunction in response to these low glucose values along with inflammatory response (Okada et al., 2013). Management of this condition involves the use of intravenous insulin to prevent hypoglycemia, which would impair organ function. There is no specific goal for glucose values in the liver transplant population outside Okada levels of 80-150 mg/dL. However based on findings from the NICE-SUGAR study the goal is adjusted to $\leq$ 150 mg/dL but to date is not mandated when looking at transplant outcomes (Okada et al., 2013).

Additional significant factors that predict ICU LOS include RBC transfusion and TEG platelet counts. The number of RBC transfusions is a reflection of preexisting coagulopathy with acute bleeding and TEG platelet counts are a reflection of intraoperative interventions to correct the coagulopathy (RBC, FFP transfusions). If the hemoglobin and hematocrit values remain low secondary to the preexisting coagulopathy may impact the ability of the health care team to stabilize the patient in the postoperative period.

Postoperatively, factors that influence ICU LOS include: four-hour BUN, POD 1 glucose, hemoglobin, and hematocrit. Alterations in sodium and BUN in the 4-hour timeframe may be

related to fluid management intraoperatively but is most likely related to a reduction in kidney function. If kidney function is reduced it may be early to see any change in creatinine especially since values were slightly elevated preoperatively (1.3-1.5 mg/dL) and the full impact of the fluid volume will not be evident for up to 24 hours. Each of the laboratory values (sodium, potassium, and BUN) reflect kidney function and efficiency of fluid volume management. The elevation of the four hour BUN is both statistically and clinically significant with BUN ranging normally from 5-20 mg/dL. This may be a reflection of acute renal failure but may more likely related to the presence of hepatorenal syndrome and suspected dehydration that untreated could lead to permanent renal failure. Low hemoglobin and hematocrit in the postoperative period are a result of the interventions during surgery, including the administration of blood products and intravenous fluids. If the liver begins to function immediately as expected, these blood levels will return to normal with minimal intervention; however, if liver function is delayed results in the continued need for blood transfusions to maintain adequate oxygen levels to support cellular metabolism. Within the postoperative period these values are used to manage blood product administration but hospital protocol does utilize liver function to also follow liver function graft function. LOS will be impacted if hemoglobin values do not stabilize and require additional transfusions that may warrant an active bleed that needs re-exploration.

POD 1 glucose alteration is a result of the replacement of the liver in response to the administration of steroids intraoperatively and postoperatively to reduce the risk of rejection. Glucose values will stabilize as liver function improves and minimal dosing of steroids is achieved. Ongoing discussion exists in the diabetes literature about the extent of interference steroids have on blood glucose levels. Instead of the focus on the actual values the focus should

be switched to reduce the inflammatory response that if allowed to continue may cause functional disorders of the liver, kidney and vascular endothelium (Okada et al., 2013).

Hospital Length of Stay

HLOS was dichotomized into less than and greater than 19 day groups. Preoperatively, WBC count, potassium, and hematocrit were significant predictors of an increased hospital LOS. Elevated WBC may indicate an infection that may result in a septic state or at minimum a systemic inflammatory response that may require pre- and post-surgical management to reduce the risk of additional organ dysfunction. Often the transplant population's surgery is held until infection is identified and controlled. This delay in identification of the suspected infection may result in the recipients transplant delayed resulting in a longer HLOS with many of these days attributed to the pre-transplant period. If the transplant is delayed due to the inability to identify the specific infection the recipient's risk of ICU complications are increased in the postoperative period. Infection risk is related to the administration of steroids, at the start of the transplant and continued into the postoperative period. Steroid use causes a decrease in the recipient's immune response to prevent it from attacking the new organ, but also reduces the immune system's ability to fight infection. Common sources of infection with recipients both pre and postoperatively are abscesses, pneumonia, and pulmonary edema which could result in the development of sepsis which will increase the recipients HLOS (Feltracco et al., 2013; C.-T. Huang et al., 2011). Intraoperatively, four factors were predictive of HLOS including, lowest systolic blood pressure, FFP transfusion, lowest glucose, and TEG platelet count. These factors reflect the continued coagulopathy present in the preoperative period. The biggest concern with coagulopathy is the stabilization of the factors postoperatively. Stabilization includes the close

monitoring of fluid shifts, episodes of hypoglycemia, and any new or additional bleeding that is slow to resolve. Stabilization can be further compromised due to the presence of a low systolic blood pressure (<90 mmHg) for a prolonged period of time. This hypotension creates a state of hypoperfusion that may alter the vasculature of the transplanted organ seen as a decreased osmotic pressure of the vasculature resulting in leaking of fluid into the interstitial space, increasing the recipients' risk of sepsis. Due to the time needed for stabilization for the new liver and its continued coagulopathy, a prolonged HLOS is expected and may impact mortality if any ICU complications are experienced within the postoperative period.

Postoperatively, factors that impact HLOS include four-hour BUN, hematocrit, and POD 1 potassium. As in the intraoperative period, alterations in sodium, potassium, and BUN are related to the fluid status of the recipient and often a result of intraoperative interventions like CRRT, transfusion administration and potential hemolysis that may occur with laboratory draws. BUN is statistically and clinically significant since the value is twice as high in the postoperative period in comparison to the preoperative period and may indicate worsening of organ dysfunction secondary to hypoperfusion. This hypoperfusion results in anaerobic metabolism and muscle wasting that is exacerbated by the inability to correct pre-existing malnutrition in the preoperative period. Close monitoring of laboratory data is crucial postoperatively due to the rapid fluid shifts that result in electrolyte changes that affect cardiac and brain function. These effects include cardiac dysrhythmias due to potassium changes and encephalopathy and acidosis with sodium alterations. Alterations in hematocrit are in response to ongoing coagulopathy of liver disease, fluid status (dehydration causing hemoconcentration) or transfusions, excessive

fluid intake (dilutional anemia), or in response to reduced erythropoietin production in the presence of renal failure.

Specific Aim 3: Describe the relationship of ICU complications with ICU length of stay, hospital length of stay, and mortality.

The ICU LOS period analysis included 228 subjects that were dichotomized into two groups: less than and greater than 9 days. Using binary logistic regression, no complications were identified as significant for the development of an ICU complication in the < 9 day group. However, in the > 9 day group, recipients experienced graft dysfunction ($p = 0.001$) sepsis (<0.0005). Lee et al. (2013) identified that graft dysfunction and sepsis were associated with aggravation of the original disease paired with an infectious complication. Graft dysfunction can also be a result of intraoperative factors, such as prolonged warm ischemic times, technical complications, and immunosuppressant medications. The goal was to stabilize the organ through adjustments to immunosuppression to allow for the recipient to mount an immune response to fight off infection while still providing enough suppression to prevent rejection of the transplanted liver.

The last factor that was seen as significant for ICU LOS was prolonged mechanical ventilation ($p = 0.002$). Reasons for prolonged ventilator time include complications in the ICU or preexisting conditions such as post-transplant infection, post-transplant cardiac event, and hepatitis (Smith et al., 2009). Additional causes of prolonged mechanical ventilation include fluid volume overload or reduced erythropoietin levels secondary to acute renal failure. Low levels of erythropoietin result in decreased hemoglobin levels decreasing amount of oxygen being carried on an RBC that can be released and utilized by the cells of the diaphragm and

pulmonary vascular bed that can lead to hypoxia and hypoxemia that requires increased mechanical ventilation support.

HLOS (n = 228) was dichotomized into two groups less than and greater than 19 days. Recipients with HLOS > 19 days had significant findings for the following ICU complications: bleeding, acute renal failure, graft dysfunction, sepsis, and prolonged ventilator time. Acute renal failure at this point was a preexisting complication that has not been corrected post transplantation may require a kidney transplant to correct. Graft dysfunction after the initial ICU stay is considered to be prolonged graft dysfunction and will require ongoing monitoring and titration of immunosuppressant medication. If the graft dysfunction does not improve, it may result in the need for another transplant but will require a closer look at reasons for the initial graft loss.

Sepsis was in response to a preexisting condition that worsens with the introduction of immunosuppressant medications or the development of an infection based on surgical course, like pneumonia. Regardless of cause, it is essential to reduce immunosuppressant medications to minimum doses to assist the immune response and the administration of organism-specific antibiotics. Use of antimicrobial agents might improve the sepsis but could lead to renal failure if organism resistant or requires a long clinical course.

The last complication is prolonged ventilator time. This complication was related to prolonged encephalopathy, high MELD scores, graft dysfunction, and hemodynamic instability post transplant (Wu, Rastogi, & Zheng, 2012). Within this study prolonged ventilator time was related to fluid balance, low hemoglobin, and hematocrit, resulting in low oxygen perfusion of

the diaphragm. Transplant graft dysfunction increases HLOS as a result of an altered level of consciousness experienced when encephalopathy is not resolved.

Mortality rates were 3.48% in liver transplant recipients with long HLOS. Mortality in liver transplants is often based on preexisting comorbidities or ICU complications. Within this study the causes of death (may be experienced by more than 1 recipient) in the expired recipients included: renal failure (3 recipients); sepsis with renal failure (1 recipient); graft dysfunction (1 recipient); renal failure and graft dysfunction (2 recipients); and sepsis and cerebral edema (1 recipient).

Limitations of the Study

There are limitations to the study. The retrospective design is a limitation because of the potential for incomplete data collection. Throughout the data collection phase, this limitation was identified despite the use of two electronic databases, resulting in some data variables being excluded (missing values) from statistical analysis, requiring adjustments to the statistical tests. Using a manual data collection process from two databases, there was the potential for data to be transcribed incorrectly. A double check of data entry into the data collection tool was completed, and some missing values were noted. Analysis of data was completed by dividing the sample into two groups: ICU days < 9 days or > 9 days and HLOS < 19 days or > 19 days. Factors were divided into three time periods: preoperative, intraoperative, and postoperative. These time periods followed the process for the transplant center for monitoring patients but also how laboratory work was ordered and how it was represented in the literature, suggests a process of “trending” to identify complications earlier. An additional data analysis strategy was to attempt to stratify participants using the MELD score, unfortunately the MELD score does not represent

all potential comorbidities of the recipient so may not have controlled for all the severity of illness. Additionally, the choice of using only a deceased donor transplant center may reduce the ability to generalize findings to other transplant centers because most use both living and deceased donors, which involve slightly different acuities and outcomes. The last limitation was for the transplant center to merge their separate databases to improve consistency of data collection and retrieval for recipient data.

Study Implications

Findings from this study identified trends in individual factors, including age, sex, BUN, glucose, transfusion volumes, warm ischemic times, and sodium levels, that warrant closer observation throughout the entire transplantation period to reduce development of complications while improving recipient outcomes. An example would be a patient that experiences diabetes preoperatively should have their blood sugar measured closely and treated in the operating room with insulin due to the wide swings in blood glucose intraoperatively (range 50-1125 mg/dL). No national standard is identified for what blood glucose ranges should be or standard intervention to use in the liver transplant recipient. This gap in the literature supports future study of glucose values throughout the transplant period to develop a standard practice that will reduce patient risks for transplantation related to blood glucose results. Postoperatively, glucose range was 72-383mg/dL, again with little standardization of interventions. Unfortunately, from these research data, it was not possible to determine if there was a trend with treatments because only average values were collected, not and treatment interventions. Maintenance of glucose values is important in the postoperative period. This is often difficult with the utilization of steroids that augment glucose levels that could increase wound healing time and further suppresses the

recipients' immune response. Additionally, maintenance doses are usually achieved on day 5 but if graft dysfunction is prolonged or a rejection episode is noted, steroid doses remain high until the acute inflammation slows down and the organ is functioning normally. Instability of blood glucose values and the frequent adjustments to immunosuppressant medications lead to delays in discharge. Delays in discharge, supports research to look at a standard of care for blood glucose management in the perioperative transplant period to reduce recipient risks and long term complications.

Implications for Education. The close evaluation of diagnostic/laboratory results at each phase of the perioperative period identified factors that should be highlighted when educating staff about care of the transplant recipients. These include trending data specifically glucose, BUN, Creat, to anticipate the potential complications of acute renal failure, sepsis, and graft dysfunction. The chemistry values require the nurse to better understand the physiology of BUN and creatinine in relation to end stage liver disease and hepatorenal syndrome specifically the importance of proper assessment of fluid status and interventions to resolve the ongoing dehydration.

Implications for Practice. Clinicians need to be aware of laboratory test level changes pre-, intra-, and postoperatively and their association with HLOS, ICU LOS, and mortality. For the clinician determining baseline and trends will allow for the clinician to predict complications as variation to the testing changes throughout the transplant period. To assist with this monitoring standard, concise pre- and postoperative order sets are available that list laboratory draws with frequency and order sets for nursing care like diet, wound care, and ambulation but may require adjustments based on the study findings. Education by the transplant center should

focus on improving recipients' health by reducing risk factors and comorbidities (i.e., heart disease, hypertension, or selection criteria for donor organs).

Implications for Future Research. This study identified some pre, intra, and postoperative factors that should be investigated further. These include glucose, CRRT, age, and sex. These factors should be evaluated to confirm if they are predictive or associated with poor outcomes. Based on current evidence supporting an update to the MELD score should be explored since this researcher believes the addition of sodium should be included in the calculation to improve its ability to predict the mortality of potential liver recipients (W. Kim et al., 2008; Manka et al., 2013). This research could include the validation of a screening tool used in the outpatient setting or even hospital-based screening that augments the MELD score to predict complications (additional mortality screening; Clemente et al., 2013).

A closer look at the prevention and treatment of coagulopathies inherent in liver failure is another potential research direction. Prevention strategies may include updated criteria for administration of RBC's beyond current hospital standards and then the potential to develop bloodless surgeries or at least blood alternatives to reduce the immune complications current blood potentiates (Goldaracena et al., 2013; Weber et al., 2013). Hospitals have general guidelines for transfusions. Within the transplant facility, transfusions should be recommended when hemoglobin is < 7 mg/dL and patient is symptomatic, unless they are a bypass patient, then 8 mg/dL is the accepted transfusion parameter. Additional parameters from the hospital protocol are to transfuse platelets an active bleed must be present and platelet count must be less than 50,000 x 10^9/L, and for transfusion of plasma an INR > 2 as seen in liver failure. Within this transplant center, due to coagulopathies identified, recipients may be excluded from these guidelines since the cause of

the abnormalities is a failed liver and not evidence of acute bleeding in the system. The results could yield a standard of laboratory testing and transfusion numbers, reducing unnecessary blood work and overuse of blood products. This modified transfusion protocol might also help reduce the set number of transfusion products available preoperatively (i.e., 10 units RBC, 5 PLT, 5 FFP). Reducing these products can help to reduce costs of the liver transplant (Goldaracena et al., 2013).

Another complication that should be further evaluated is the practice of prolonged mechanical ventilation in the liver transplant recipient. Based on the data revealing prolonged mechanical ventilation effects outcomes makes it essential to develop weaning protocols specific to use in liver transplants. Finally, since this study was done at a transplant facility that only performed deceased donor organs, the study should be repeated in a facility that performs living and deceased donor liver transplants to determine if the same conclusions can be drawn in a different population. All of these potential topics for research will help build the database for liver recipients for both living and deceased donor sources to have a more standard method of caring for this population and may assist in reducing ICU and HLOS.

Conclusion

Identification of factors that impact a liver transplant recipient's outcome is necessary for the success of a transplant program. Preoperatively, attention needs to be paid to factors including age, BUN, creatinine, and potassium. This might include improved screening tools to better predict surgical risk in addition to the traditional use of MELD score. Intraoperatively, sodium levels, glucose values, use of CRRT, cold/warm ischemic time, and transfusions should be closely observed to assist in development of a standard of care to prevent hypoperfusion of the transplanted organ as evidenced by the development of acute renal failure and sepsis in the

post liver transplant recipient. Postoperatively, the focus should be on standardization of care specifically related to laboratory studies, transfusions and medication administration (steroids, immunosuppressants). The factors of interest are sodium, BUN, hemoglobin, and glucose. Each should be evaluated for its role in a recipients' outcome. Better understanding of these recipient factors may lead to reductions in ICU complications, mortality rates as well as decreased ICU and HLOS.

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