METABOLIC COMPLICATIONS AND ASSOCIATED CARDIOVASCULAR DISEASE RISK POST LIVER TRANSPLANT

by

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As members of the DNP Project Committee, we certify that we have read the DNP project prepared by *Katrina Irene Peterson*, titled *Metabolic Complications and Associated Cardiovascular Disease Risk Post Liver Transplant* and recommend that it be accepted as fulfilling the DNP project requirement for the Degree of Doctor of Nursing Practice.

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ABSTRACT

Purpose: The purpose of this Doctor of Nursing Practice study was to investigate the prevalence of metabolic complications as well as recurrent or new-onset non-alcoholic fatty liver disease (NAFLD) and associated cardiovascular disease risk among liver transplant recipients.

Design: Retrospective, descriptive.

Setting: Local transplant program in San Antonio, Texas.

Sample: 41 liver transplant recipients transplanted between July 2016 and June 2017.

Methods: A health care record review using a data collection instrument created to profile cardiovascular disease risk up to one-year post-transplant.

Main Research Variables: Cardiovascular disease risk factors including blood pressure (BP), hemoglobin A1C, low-density lipoprotein, and body mass index, as well as NAFLD.

Additional Research Variables: Variables influencing NAFLD and cardiovascular disease risk such as etiology of liver disease, ethnicity, age, gender, family history, and immunosuppression medications.

Findings: Most data on metabolic complications and cardiovascular disease risk factors such as dyslipidemia and diabetes mellitus were not documented. Hypertension was prevalent at one-year post-transplant, and BPs were sub-optimally managed. New-onset or recurrent NAFLD following transplant only occurred in 12% of the sample. There were no documented cardiovascular disease related events within the first year following transplant.

Conclusions: Prevalence of metabolic complications as well as NAFLD among liver transplant recipients is important in the evaluation of cardiovascular disease risk to reduce related events and mortality following transplant but not commonly documented by the local transplant

program. Improved documentation and communication between Hepatology specialists and primary care providers is necessary for early recognition and appropriate medical management of post-transplant metabolic complications. Better control of BP may help reduce cardiovascular disease risk in the late post-transplant period. Prospective studies with larger sample sizes are needed to further investigate the prevalence of metabolic complications as well as NAFLD and associated cardiovascular disease risk among liver transplant recipients.

Key Words: cardiovascular disease risk; liver transplant; metabolic complications; non-alcoholic fatty liver disease

INTRODUCTION

This Doctor of Nursing Practice (DNP) study investigates the prevalence of metabolic complications among liver transplant recipients at a local transplant program in San Antonio, Texas. The study provides insight into the most recent practice guidelines on the appropriate medical management of obesity, dyslipidemia, diabetes mellitus, and hypertension as poor control can lead to an increased risk of cardiovascular disease and associated events following transplant. In addition, the prevalence of recurrent or new-onset non-alcoholic fatty liver disease (NAFLD) is explored as this disease coincides with the development of metabolic complications. The study data serves as a foundation for future improvement strategies to optimize the medical management of post-transplant metabolic complications. Early recognition and appropriate treatment of metabolic complications may help reduce the prevalence of recurrent or new-onset NAFLD as well as associated cardiovascular disease risk following transplant leading to an enhanced quality and quantity of life for liver transplant recipients.

Background Knowledge

Liver transplantation has become the leading treatment for patients diagnosed with acute liver failure and advanced liver disease or cirrhosis (Barnard, Konyn, & Saab, 2016; Pisano et al., 2016). Significant improvements in immunosuppression medications, screening of transplant candidates as well as donor organs, and surgical techniques since the time of the first human liver transplant have resulted in increased survival rates among liver transplant recipients (Barnard et al., 2016; Brunault et al., 2015; Haugen et al., 2018; Martin et al., 2014; Pisano et al., 2016; Song et al., 2014). Survival rates among this population have reached as high as over 90% and 80% at one- and five-years' post-transplant, respectively (Jimenez-Perez, Gonzalez-Grande,

Guzman, Trill, & Lopez, 2016; Organ Procurement and Transplant Organization, 2019). Thus, post-transplant metabolic complications and cardiovascular disease impacting longevity following transplant have gained increased attention.

Metabolic complications including obesity, dyslipidemia, diabetes mellitus, and hypertension are exceedingly prevalent following transplant and are associated with increased cardiovascular disease risk (Barnard et al., 2016; Brunault et al., 2015; Fussner et al., 2015; Glowczynska et al., 2018; Jimenez-Perez et al., 2016; Marjot et al., 2018; Pisano et al., 2016; Wang, Yu, & Chan, 2016). Estimated prevalence rates throughout the literature are outlined in Table 1 and surpass that of the general population making cardiovascular disease a leading cause of morbidity and mortality among liver transplant recipients (Barnard et al., 2016; Gallegos-Orozco & Charlton, 2017; Jimenez-Perez et al., 2016; Konerman et al., 2017).

TABLE 1. *Prevalence of cardiovascular disease risk factors in liver transplant recipients.*

Cardiovascular Disease Risk Factor	Estimated Prevalence
Hypertension	40% - 85%
Diabetes Mellitus	10% - 38%
Obesity	25% - 54%
Dyslipidemia	45% - 71%

Approximately 40% of deaths following transplant, not associated with allograft dysfunction, have been attributed to cardiovascular disease (Jimenez-Perez et al., 2016; Maurice & Manousou, 2018). Research by Fussner et al. (2015) further determined that 10.6% of liver transplant recipients developed a cardiovascular disease related event such as a myocardial infarction, stroke, peripheral vascular disease, or coronary artery disease within the first year following transplant. The number of cardiovascular disease related deaths has been shown to increase in the long-term and is noted to be over 20% at three-years of survival (Barnard et al.,

2016). Metabolic complications as well as NAFLD prior to transplant are considered risk factors highly associated with the development of cardiovascular disease related events following transplant (Jimenez-Perez et al. 2016; Pisano et al., 2016).

NAFLD is a manifestation of obesity, dyslipidemia, diabetes mellitus, and hypertension with a global prevalence rate of 25-30% (Chalasani et al., 2018; Haugen et al., 2018; Marjot et al., 2018; Martin et al., 2014; Mikolasevic et al., 2018). NAFLD is described as the presence of hepatic steatosis on either imaging or histology without any alternative suspicion for fat acquisition such as excessive alcohol consumption or steatogenic medications (Chalasani et al., 2018; Maurice & Manousou, 2018). NAFLD can be further categorized as non-alcoholic steatohepatitis (NASH) or non-alcoholic fatty liver (NAFL). Hepatocellular injury with or without the presence of fibrosis is characteristic of NASH whereas NAFL does not involve hepatocellular injury and is considered to be a non-aggressive disease process (Chalasani et al., 2018; Mikolasevic et al., 2018; Pan & Fallon, 2014). NASH can progress to advanced fibrosis or cirrhosis and significantly increase the risk for the development of hepatocellular carcinoma (Chalasani et al., 2018; Mikolasevic et al., 2018; Perumpail et al., 2017; Pisano et al., 2016).

NAFLD is predicted to become the leading etiology for liver transplantation in the near future and is strongly associated with cardiovascular disease (Chalasani et al., 2018; Haugen et al., 2018; Marjot et al., 2018). Liver transplant recipients with a NAFLD etiology have been noted to have higher rates of NAFLD recurrence following transplant (Barnard et al., 2016; Chalasani et al., 2018; Jimenez-Perez et al., 2016). Alarmingly, up to 40% of liver transplant recipients without a NAFLD etiology have been shown to develop NAFLD following transplant as well (Jimenez-Perez et al., 2016). Figure 1 highlights additional factors that increase the risk

of recurrent or new-onset NAFLD following transplant. Unfortunately, there are no definitive pharmacological therapies currently approved for the treatment of NAFLD (Hadi, Vettor, & Rosatto, 2018; Maurice & Manousou, 2018). Thus, early identification and appropriate management of modifiable risk factors such as obesity, dyslipidemia, diabetes mellitus, and hypertension are important in reducing new-onset or recurrent NAFLD following transplant (Barnard et al., 2016; Brunault et al., 2015; Jimenez-Perez et al., 2016).

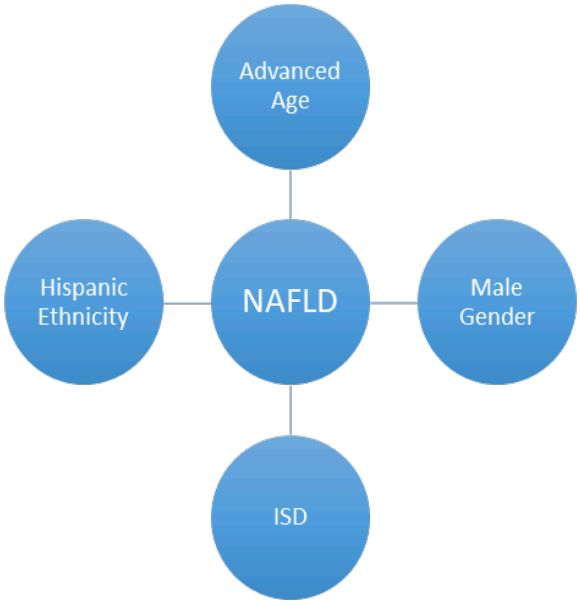

FIGURE 1. Additional risk factors influencing NAFLD. ISD = immunosuppression drugs.

Practice Guidelines for Metabolic Complications and NAFLD

Hypertension

Hypertension strongly correlates with the development of cardiovascular disease related events; thus, optimizing control is of vital importance in regard to long-term survival among liver transplant recipients (Barnard et al., 2016; Lucey et al., 2013; Whelton et al., 2017). Prior to transplant, the incidence of hypertension is low due to the high cardiac output as well as low

systemic vascular resistance and mean arterial pressure demonstrated in advanced liver disease or cirrhosis (Barnard et al., 2016; Jimenez-Perez et al., 2016). Liver transplantation quickly reverses this process with an estimated 40-85% of liver transplant recipients developing hypertension and 50% developing the condition within six months of surgery (Barnard et al., 2016; Jimenez-Perez et al., 2016). The hemodynamic changes as well as immunosuppression medications initiated at the time of transplant adversely influence the blood pressure of liver transplant recipients (Barnard et al., 2016; Jimenez-Perez et al., 2016; Lucey et al., 2013).

A target blood pressure of less than 130/80 mmHg is recommended for liver transplant recipients given their high risk of developing hypertension and associated cardiovascular events following transplant (Barnard et al., 2016; Jimenez-Perez et al., 2016; Lucey et al., 2013; Whelton et al., 2017). This target is also in concordance with the latest guidelines published by the American College of Cardiology and the American Heart Association. A systolic blood pressure greater than 130 mmHg or a diastolic blood pressure greater than 80 mmHg is classified as stage I hypertension and warrants lifestyle modifications and/or pharmacological therapies (Whelton et al., 2017). Lifestyle modifications include weight loss via healthy dieting and increased physical activity, smoking and alcohol cessation, and adherence to a low sodium diet (Barnard et al., 2016; Whelton et al., 2017). If lifestyle modifications are not effective in lowering blood pressure, then prescription medications are recommended to optimize control (Barnard et al., 2016; Jimenez-Perez et al., 2016; Lucey et al., 2013; Whelton et al., 2017).

Calcium channel blockers are the preferred anti-hypertensive medication for liver transplant recipients as they counteract vasoconstriction induced by immunosuppression medications such as calcineurin inhibitors (Barnard et al., 2016; Jimenez-Perez et al., 2016;

Lucey et al., 2013). Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are recommended for liver transplant recipients with uncontrolled hypertension as well as diabetes mellitus, proteinuria, and/or chronic kidney disease (Barnard et al., 2016; Lucey et al., 2013). However, these medications are felt to more beneficial when initiated in the late post-transplant period as low plasmin renin activity is demonstrated in the early post-transplant period (Barnard et al., 2016). If lifestyle modifications and pharmacological therapies are not successful at reducing blood pressure, then a quick steroid taper and/or lowering the dose of or changing immunosuppression medication is recommended as deemed appropriate (Barnard et al., 2016).

Dyslipidemia

Dyslipidemia like hypertension is uncommon prior to transplant due to the impaired hepatic function noted in advanced liver disease or cirrhosis (Barnard et al., 2016; Jimenez-Perez et al., 2016; Lucey et al., 2013). A high serum concentration of low-density lipoprotein (LDL) cholesterol is indicative of dyslipidemia and strongly associated with increased cardiovascular disease risk (Agarwal & Prasad, 2016; Grundy et al., 2018; Husing et al., 2016). Alarmingly, up to 71% of liver transplant recipients have been shown to develop dyslipidemia felt to be heavily influenced by the adverse cardiovascular effects of immunosuppression medications (Lucey et al., 2013). Additional risk factors for the development of dyslipidemia include impaired renal function, advanced age, increased body weight, hyperglycemia, and a family history of dyslipidemia (Barnard et al., 2016; Husing et al., 2016).

A target LDL of less than 130 mg/dL has been the standard recommendation for liver transplant recipients without additional risk factors (Agarwal & Prasad, 2016; Barnard et al., 2016; Husing et al., 2016; Jimenez-Perez et al., 2016). The latest guidelines by the American

College of Cardiology and the American Heart Association recommend a more aggressive approach to reducing cardiovascular disease risk by lowering the LDL to less than 100 mg/dL or even further to less than 70 mg/dL depending on the patient's risk for developing atherosclerotic cardiovascular disease events (Grundy et al., 2018). Initiation of a statin is recommended if improvement in LDL is unsuccessful with lifestyle modifications alone (Barnard et al., 2016; Jimenez-Perez et al., 2016; Grundy et al., 2018; Lucey et al., 2013). Pravastatin is highly recommended for liver transplant recipients with dyslipidemia as the medication does not become metabolized by the P450 cytochrome or interact with immunosuppression medications (Agarwal & Prasad, 2016; Barnard et al., 2016; Husing et al., 2016; Jimenez-Perez et al., 2016). Careful review of immunosuppression medications is of significant importance to determine if a change in medication would improve the LDL level (Barnard et al., 2016). Current use of corticosteroid therapy should also be reviewed and tapered as this medication increases cholesterol levels via acetyl coenzyme A carboxylase activity as well as the synthesis of fatty acids (Barnard et al., 2016; Jimenez-Perez et al., 2016).

Obesity

Obesity is now a national epidemic with a prevalence of nearly 40% affecting over 90 million people across the country (Centers for Disease Control and Prevention [CDC], 2018a). Furthermore, the latest obesity prevalence maps show all states to have over 20% of adults with obesity and seven states to have over 35% of adults with obesity (CDC, 2018b). The World Health Organization (WHO) (2019) defines obesity as a body mass index (BMI), a calculation that takes into account height and weight, of equal to or greater than 30 kg/m^2 to be consistent with obesity. Risk factors for obesity include dyslipidemia, hypertension, diabetes mellitus,

advanced age, and a family history of obesity (Barnard et al., 2016; Chalasani et al., 2018; Jimenez-Perez et al., 2016; Pan & Fallon, 2014). Obesity is highly prevalent among liver transplant recipients as well and associated with an increased risk of cardiovascular disease related events (Table 1).

Up to 30% of liver transplant recipients are noted to be obese prior to undergoing transplant (Barnard et al., 2016). The majority of these patients remain obese following transplant, and one-third of recipients who were previously at a normal weight develop obesity following transplant as well (Barnard et al., 2016). The aforementioned risk factors for obesity as well as corticosteroids initiated at the time of and following transplant play an essential role in weight gain (Barnard et al., 2016; Brunault et al., 2015; Jimenez-Perez et al., 2016). Thus, a rapid steroid taper is recommended to assist with weight loss. Lifestyle modifications including healthy dieting and increased physical activity are encouraged prior to and following transplant to reduce the risk of post-operative complications including the development of diabetes mellitus and NAFLD (Ayloo, Armstrong, Hurton, & Molinari, 2015; Barnard et al., 2016; Chalasani et al., 2018; Jimenez-Perez et al., 2016; Ratziu & Marchesini, 2016).

Diabetes Mellitus

According to the American Diabetes Association (ADA) (2018), 1.5 million people in the United States (US) are diagnosed with diabetes annually with the cost for diabetes health care estimated to be over 300 billion dollars. Diabetes mellitus is associated with poor outcomes following transplant as it significantly increases the risk for infection, acute rejection, renal dysfunction, cardiovascular disease related events, and overall mortality (Barnard et al., 2016; Einarson, Acs, Ludwig, & Panton, 2018; Jimenez-Perez et al., 2016). Diabetes mellitus is

estimated to be prevalent in nearly 40% of liver transplant recipients with a new-onset diabetes prevalence as high as 30% within the first year of transplant (Barnard et al., 2016). Factors influencing the development of diabetes mellitus following transplant include diabetes prior to surgery, metabolic syndrome, immunosuppression medications, advanced age, family history of insulin resistance, and recurrent hepatitis C or NAFLD (Barnard et al., 2016; Jimenez-Perez et al., 2016). Hepatitis C, NAFLD, and alcohol cause significant beta cell damage; thus, 90% of patients with advanced liver disease or cirrhosis develop glucose intolerance with 30% developing diabetes mellitus (Barnard et al., 2016).

A hemoglobin (Hgb) A1C target of less than 7% achieved through lifestyle modifications and/or pharmacological therapies is recommended following transplant (Barnard et al., 2016; Jimenez-Perez et al., 2016; Lucey et al., 2013). The latest guidelines by the American Association for the Study of Liver Diseases and the American Society of Transplantation recommend monitoring a HgbA1C level every three months following transplant (Lucey et al., 2013). However, updated management strategies advocate for more frequent monitoring of HgbA1C levels on a weekly basis for the first month and then at three, six, and 12 months following transplant due to the high risk of development of diabetes mellitus and associated cardiovascular disease related mortality among this population (Barnard et al., 2016). Thus, strict control via a corticosteroid taper, insulin use, and/or oral diabetic medications in liver transplant recipients with normal allograft function is recommended (Barnard et al., 2016; Jimenez-Perez et al., 2016). Lastly, careful consideration should be given to altering immunosuppression medication as calcineurin inhibitors, particularly Prograf, are associated with increased insulin resistance (Barnard et al., 2016; Jimenez-Perez et al., 2016; Lucey et al., 2013).

NAFLD

The rates of NAFLD are rising with increasing rates of obesity and diabetes mellitus (Chalasani et al., 2018). A liver biopsy continues to remain the gold standard for the diagnosis of NAFLD and staging of fibrosis (Chalasani et al., 2018; Gunn & Shiffman, 2018; Maurice & Manousou, 2018). However, a liver biopsy is an invasive procedure with associated serious risks such as infection, biopsy site pain, and hemorrhage and is not always feasible due to cost (Pan & Fallon, 2014; Wang et al., 2016). Non-invasive measurements of fibrosis and steatosis such as the FibroSure serum test, FibroScan, and liver elastography can help identify patients who may be at risk for significant disease (Chalasani et al., 2018). Imaging such as a liver ultrasound, computed tomography (CT) scan, and magnetic resonance imaging (MRI) can also detect fatty infiltration or hepatic steatosis but are unable to differentiate between NAFL and NASH. Thus, a liver biopsy is recommended in NAFLD patients with concern for NASH and/or advanced fibrosis or to exclude alternative etiologies for hepatic steatosis (Chalasani et al., 2018; Lindenmeyer & McCullough, 2017).

The medical management guidelines for NAFLD following liver transplantation reflect those for NAFLD prior to transplant (Chalasani et al., 2018). Optimizing control of hypertension, dyslipidemia, diabetes mellitus, and obesity are essential in the medical management of NAFLD (Barnard et al., 2016; Chalasani et al., 2018; Maurice & Manousou, 2018). As little as a 5-10% reduction in weight via healthy dieting and exercise has been shown to improve NAFLD as well as regress fibrosis (Chalasani et al., 2018; Maurice & Manousou, 2018). However, lifestyle modifications continue to remain a struggle for many patients and will not be adequate for those diagnosed with advanced liver disease or cirrhosis (Maurice & Manousou, 2018). The use of

vitamin E in patients with NAFLD has remained controversial as it has been associated with an increased risk of hemorrhagic stroke as well as prostate cancer and is not recommended in patients with diabetes or advanced liver disease (Hadi et al., 2018). Thus, there are currently no pharmacological therapies approved for the successful treatment of NAFLD although numerous studies are underway and significant pharmacological advances within the NAFLD realm are expected in the near future (Hadi et al., 2018; Lindenmeyer & McCullough, 2017; Maurice & Manousou, 2018).

Additional Risk Factors

Age, Gender and Ethnicity

Age, gender, and ethnicity have been shown to be significant risk factors for NAFLD (Chalasani et al., 2018; Pan & Fallon, 2014). The risk of NAFLD is felt to increase with age and is twice as prevalent in men versus women despite some conflicting research (Ballestri et al., 2017; Chalasani et al., 2018; Pan & Fallon, 2014). In addition, the Hispanic population has been found to be at a greater risk of developing NAFLD with more aggressive disease progression (Chalasani et al., 2018; Pan & Fallon, 2014). Both ethnic and gender differences among patients diagnosed with NAFLD are suspected to be related to a combination of environmental, genetic, and behavioral elements (Bertot & Adams, 2016; Chalasani et al., 2018; Pan & Fallon, 2014). Thus, age, gender, and ethnicity are additional factors that should be taken into consideration when assessing NAFLD risk prior to and following transplant.

Immunosuppression Medications

Liver transplant recipients typically require life-long immunosuppression following transplant to prevent rejection and preserve allograft function (Lucey et al., 2013; Song et al., 2014). Modern advances in immunosuppression medications have helped reduce the risk of rejection and associated mortality following transplant (Barnard et al., 2016; Brunault et al., 2015; Haugen et al., 2018; Martin et al., 2014; Pisano et al., 2016; Song et al., 2014). However, immunosuppression medications have been associated with an increased risk of infection, malignancy, and adverse cardiovascular profile (Moini, Schilsky, & Tichy, 2015). These variables as well as the time since surgery, etiology of liver disease, history of rejection, potential for pregnancy, and recipient co-morbidities influence immunosuppression regimen decisions (Lucey et al., 2013; Song et al., 2014).

Common immunosuppression medications include calcineurin inhibitors such as Prograf and cyclosporine, a mammalian target of rapamycin (mTOR) inhibitor such as Rapamune, corticosteroids such as Solu-Medrol and prednisone, and an anti-proliferative agent such as Cellcept (Barnard et al., 2016; Jimenez-Perez et al., 2016; Lucey et al., 2013; Moini et al., 2015; Song et al., 2014). Simulect is an immunosuppressive medication used as induction therapy in the immediate post-operative period along with intravenous Solu-Medrol to help prevent acute cellular rejection episodes. High doses of Solu-Medrol are tapered daily for the first week following transplant with transition to an oral prednisone taper. In addition, a calcineurin inhibitor and/or an anti-proliferative agent are typically initiated in the early post-transplant period and continued indefinitely thereafter as maintenance immunosuppression therapy (Moini et al., 2015).

Prograf is the preferred calcineurin inhibitor for maintenance immunosuppression therapy following transplant due to increased allograft survival and development of fewer acute cellular rejection episodes when compared with cyclosporine (Barnard et al., 2016; Moini et al., 2015). Furthermore, Prograf is associated with less adverse cardiovascular disease related complications and outcomes (Barnard et al., 2016; Fussner et al., 2015; Jimenez-Perez et al., 2016; Moini et al., 2015).

Calcineurin inhibitors induce vasoconstriction and steroids increase vascular resistance as well as cardiac contractility leading to worsening hypertension or new-onset hypertension following transplant (Barnard et al., 2016; Jimenez-Perez, 2016). However, hypertension is noted to be more prominent in cyclosporine compared with Prograf (Barnard et al., 2016; Jimenez-Perez, 2016). Cyclosporine, as well as Rapamune, can increase the risk of dyslipidemia by elevating serum lipid concentrations. Thus, Prograf-based immunosuppression is preferred unless liver transplant recipients develop significant renal dysfunction warranting a change to Rapamune therapy of which close monitoring of lipid levels is highly recommended (Barnard et al., 2016).

Calcineurin inhibitors and corticosteroids also inhibit insulin secretion leading to a greater risk of developing diabetes mellitus (Chalasani et al., 2018; Jimenez-Perez et al., 2016). Corticosteroids should be tapered quickly to improve hyperglycemia and hypertension as well as reduce weight gain often associated with the medication (Barnard et al., 2016; Chalasani et al., 2018). Careful review of immunosuppression medications as well as the cardiovascular profile of each liver transplant recipient is critical as regimens without calcineurin inhibitors or inadequate

doses of immunosuppression medications can significantly increase the risk for acute cellular rejection (Barnard et al., 2016).

Local Problem

A local transplant program in San Antonio, Texas, transplants patients with a variety of liver disease including NAFLD and is recognized as one of the top liver transplant programs in Texas due to its successful outcomes following liver transplantation (Methodist Physicians San Antonio, 2019). Liver transplant program-specific statistics across the country can be located via the Scientific Registry of Transplant Recipients. The website provides information regarding the number of listed candidates, outcomes while awaiting liver transplantation, details of the transplant recipients and donors, wait times on the list, and patient outcomes in regard to survival rates following surgery (Scientific Registry of Transplant Recipients, 2019). Unfortunately, program-specific data on the prevalence of metabolic complications as well as NAFLD following transplant is not readily available despite the increased cardiovascular disease risk among this population.

The local transplant program in San Antonio transplants patients with liver disease from all over Texas, which is now listed among the states with more than 30% of adults classified as obese (CDC, 2018). San Antonio is a major city located in south-central Texas and has continued to struggle with efforts to tackle metabolic complications, particularly obesity and diabetes mellitus, as an estimated 71% of adults have been classified as overweight or obese with one out of every eight (1:8) residents diagnosed with diabetes mellitus (City of San Antonio Metropolitan Health District, 2017). Furthermore, the city comprises of a predominantly Hispanic ethnicity (64%), which is a population that has been shown to be at an increased risk of

developing NAFLD with more aggressive disease progression (Data USA, 2017; Pan & Fallon, 2014). Thus, exploring the prevalence of metabolic complications and NAFLD following transplant in a community with significant risk factors for the development of cardiovascular disease is essential for the implementation of future strategies to reduce cardiovascular disease related mortality among liver transplant recipients.

Study Purpose

The purpose of this study is to investigate the prevalence of metabolic complications among liver transplant recipients at a local transplant program in San Antonio, Texas. Metabolic complications are prevalent following liver transplantation and associated with the development of recurrent or new-onset NAFLD as well as increased cardiovascular disease risk. Thus, the study will assess the prevalence of metabolic complications and NAFLD among the liver transplant recipients transplanted between July 2016 and June 2017, which is in concordance with the timeframes established by the Scientific Registry of Transplant Recipients. The data collected from this study will serve as a foundation for future improvement strategies to reduce the prevalence of metabolic complications as well as NAFLD following transplant in an effort to also reduce cardiovascular disease risk and improve the quantity and quality of life among liver transplant recipients.

METHODS

Study Design

This study involved a retrospective health record review of cardiovascular disease risk in patients with liver disease who underwent orthotopic liver transplantation performed by a local transplant program in San Antonio, Texas. The data collected were utilized to profile the

prevalence of metabolic complications as well as new-onset or recurrent NAFLD among liver transplant recipients transplanted between July 2016 and June 2017.

Sample and Setting

All adult patients age 18 or older with liver disease who underwent deceased donor liver transplantation at the local transplant program between July 1, 2016 and June 30, 2017 were included in this study. A total of 47 transplants occurred within this timeframe. Patients who underwent a combined liver-kidney transplantation (total of six patients) were excluded to provide a more accurate representation of the prevalence of metabolic complications and NAFLD among liver only transplant recipients. Thus, 41 charts were reviewed up to one-year post-transplant. None of the patients were excluded based on ethnicity or gender. Patients who did not survive one-year following surgery were also included and their cause of death listed.

Data Collection and Use

Data collection for this DNP study began upon approval by the local (Methodist Healthcare System) transplant program's Institutional Review Board (IRB) as well as the University of Arizona IRB (Appendix B & C). A data collection instrument was created based on the most updated practice guidelines and management strategies to profile cardiovascular disease risk among liver transplant recipients (Appendix A). Metabolic complications, such as hypertension, dyslipidemia, diabetes mellitus, and obesity, associated with an increased risk of cardiovascular disease as well as new-onset or recurrent NAFLD, were reviewed. Additional variables such as etiology of liver disease, ethnicity, age, gender, family history, and immunosuppression medications were included. All variables were obtained via retrospective review of health care records. The content validity of the data collection instrument was

supported by two doctorally prepared advanced practice nurses with expertise in cardiovascular and critical care. Data collection was completed at the local transplant program via review of electronic medical records. Meditech, Filebound, Velos, and Teleresults were the electronic programs accessed to review health care records of liver transplant recipients transplanted between July 1, 2016 and June 30, 2017. Study data were managed by the principal investigator and recorded electronically on an encrypted work computer provided by the local transplant program.

Study Risks

This study did not involve greater than minimal risk. Potential risks included breach of confidentiality and invasion of privacy. The collection of patients' private information was limited to that of which was necessary to achieve the study purpose as listed in the introduction. Electronic safeguards such as passwords, access privileges, encryption, and firewalls were implemented to minimize potential risks. Electronic records were only made available to the principal investigator, and private information was protected from improper use and disclosure via coding practices. The link between the patients' code and private information was stored on the encrypted computer used for data collection and permanently deleted once the study was completed. A confidentiality statement agreeing to protect the security of private information was signed as well. The collected data was permanently deleted from the encrypted computer per hospital protocol once data collection and data analysis were finalized.

Statistical Analysis

The International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) version 25 for Mac was utilized to analyze the data collected. Descriptive statistics

primarily involving frequency calculations were used to illustrate the prevalence of metabolic complications as well as new-onset or recurrent NAFLD among the liver transplant recipients selected for data collection.

RESULTS

Data Collection

Data collection occurred between September 26, 2018 and November 6, 2018. The medical records of 41 patients who underwent deceased donor liver only transplantation between July 1, 2016 and June 30, 2017 were reviewed up to one-year post-transplant. Metabolic complications such as hypertension, dyslipidemia, diabetes mellitus, and obesity as well as NAFLD were reviewed. Additional variables such as the etiology of liver disease, ethnicity, age, gender, family history, and immunosuppression medications were included. The collection of BMI, immunosuppression regimen, blood pressure, and prescription medications for co-morbidities at one-year post-transplant were obtained by review of the clinic visit note. Clinic visit dates varied depending on provider and clinic availability; thus, data at the clinic visit completed closest to the patient's one-year post-transplant date were reviewed. Data were subsequently entered into the IBM SPSS following collection to complete data analysis.

Sample Demographic and Survival Characteristics

Demographic and survival characteristics of the sample are listed in Table 2. The sample consisted of 25 (61%) men and 16 (39%) women with 17 (41%) documented as Hispanic and 24 (59%) documented as non-Hispanic in ethnicity. The mean age of liver transplant recipients was 55.24 with a standard deviation (SD) of 12.39, ranging from 24 years to 76 years of age. Only 38 of the 41 (93%) liver transplant recipients were alive at one-year post-transplant. The cause of

death for the three (7%) patients who did not survive one-year following transplant included septic shock with multi-organ failure, blast crisis with acute respiratory failure, and sudden cardiac death. Lastly, one patient did not continue to follow-up in clinic shortly after transplant as he moved out of state but continued to complete laboratory testing as directed.

TABLE 2. *Demographic and survival characteristics of patients (N=41).*

Demographic Characteristics			
Age			
	Mean (SD)	55.24 (12.39)	
	Range	24-76 years	
		Frequency	***Percent***
Gender			
	Men	25	61%
	Women	16	39%
Ethnicity			
	Hispanic	17	41%
	Non-Hispanic	24	59%
Survival Characteristics			
		Frequency	***Percent***
Alive at one-year post-transplant			
	Yes	38	93%
	No	3	7%

Etiology of Liver Disease

Etiology of liver disease was identified as NAFLD, other, or unknown (Table 3). There were five (12%) patients listed as having NAFLD. The diagnosis of NAFLD was confirmed on a liver biopsy performed prior to transplant or on explant. One patient with suspected NASH based on medical history as well as negative serologies for alternative causes of chronic liver disease and no definitive diagnosis noted on explant was marked as NASH etiology. The majority (81%) of the patients were noted to have alternative etiologies for liver disease including hepatitis C,

hepatitis B, primary biliary cholangitis, primary sclerosing cholangitis, amyloidosis, Alagille syndrome, and alcohol. Only three (7%) patients were marked as having an unknown etiology as they presented with acute or fulminant hepatic failure of unknown cause without a definitive diagnosis on explant.

TABLE 3. *Patients' etiology of liver disease (N=41).*

		Frequency	***Percent***
Etiology			
	NAFLD	5	12%
	Other	33	81%
	Unknown	3	7%

Immunosuppression

The immunosuppression regimen for liver transplant recipients at the local transplant program typically includes Simulect induction, intravenous Solu-Medrol taper with transition to oral prednisone, and intravenous Cellcept with transition to oral or no Cellcept. Immediate post-operative immunosuppression decisions are dependent upon history or evidence of active infection and development of significant bone marrow suppression or malignancy (Lucey et al., 2013; Moini et al., 2015). Of importance, prednisone was typically tapered off prior to or shortly after hospital discharge and was not included in the immunosuppression regimen at the time of transplant. Only one patient was noted to be on daily prednisone at one-year post-transplant. Prednisone was re-started by the patients' primary care provider due to concern for allograft dysfunction related to inadequate immunosuppression as the patient was not taking immunosuppression medications as directed. The immunosuppression medications recorded at the time of hospital discharge and one-year post-transplant included Prograf, Rapamune, and Cellcept (Table 4).

At the time of hospital discharge, 17 (42%) patients were on Prograf monotherapy, 23 (56%) patients were on Prograf and Cellcept, and one (2%) patient was on Rapamune and Cellcept. No patients were discharged on Rapamune monotherapy. Immunosuppression regimens at one-year post-transplant included 27 (71%) patients on Prograf monotherapy and two (5%) on Rapamune monotherapy. The number of patients on Prograf and Cellcept was seven (18%). Only one (3%) patient was on both Rapamune and Cellcept. Patients on Rapamune therapy at one-year post-transplant were noted to have significant renal dysfunction related to calcineurin nephrotoxicity or significant adverse reactions including tremors and altered mental status felt to be associated with calcineurin inhibitor use prompting a change in medication.

TABLE 4. *Patients' immunosuppression at time of transplant and one-year post-transplant.*

	Frequency	***Percent***
Immunosuppression at transplant (N=41)		
Prograf	17	42%
Prograf and Cellcept	23	56%
Rapamune and Cellcept	1	2%
Immunosuppression at one-year post-transplant (N=38)		
Prograf	27	71%
Rapamune	2	5%
Prograf and Cellcept	7	18%
Rapamune and Cellcept	1	3%
Other (Prograf and prednisone)	1	3%

History

Family History

The family history of each patient (Table 5) was obtained by review of hospital progress notes, outpatient clinic visit reports, history and physicals performed by hospitalists, and consultation reports completed by specialists. Notes that did not specify a family history of the

metabolic complication or a family history reported as “non-contributory” were regarded as unknown as “non-contributory” is generally not accepted as adequate documentation (Hughes, 2017). All 41 (100%) patients did not have a family history of obesity or dyslipidemia specified in the medical records. The majority of the patients, 27 (66%) and 32 (78%), did not have a family history of diabetes mellitus or hypertension specified in the medical records, respectively. Only 14 (34%) and nine (22%) patients had a recorded family history of type 2 diabetes and hypertension, respectively.

TABLE 5. *Patients' family history of metabolic complications (N=41).*

		Frequency	***Percent***
Family History			
	Obesity	-	-
	No Obesity	-	-
	Unknown	41	100%
	Dyslipidemia	-	-
	No Dyslipidemia	-	-
	Unknown	41	100%
	Type 2 Diabetes	14	34%
	No Type 2 Diabetes	-	-
	Unknown	27	66%
	Hypertension	9	22%
	No Hypertension	-	-
	Unknown	32	78%

Patient History

Each patient's medical history (Table 6) was obtained by review of hospital progress notes, outpatient clinic visit reports, history and physicals performed by hospitalists, and consultation reports completed by specialists. The BMI of each patient was calculated at the time of transplant and used to determine obesity prior to transplant (Table 7). The majority of patients

(56%) had a recorded history of hypertension prior to transplant. Only eight (20%) and 10 (24%) patients had a recorded history of dyslipidemia and type 2 diabetes prior to transplant, respectively.

TABLE 6. *Patients' history of metabolic complications (N=41).*

		Frequency	***Percent***
Patient History			
	Dyslipidemia	8	20%
	No Dyslipidemia	33	80%
	Type 2 Diabetes	10	24%
	No Type 2 Diabetes	31	76%
	Hypertension	23	56%
	No Hypertension	18	44%

Metabolic Complications

Obesity

BMI was reviewed at the time of transplant and at the clinic visit closest to one-year post-transplant (Table 7). The majority of the patients had a BMI of less than 30 kg/m^2 prior to (66%) and following transplant (59%). BMI at the time of transplant may have been lower than expected due to malnutrition often associated with chronic liver disease or cirrhosis (Chaney & Heckman, 2018). The number of patients with a BMI of less than 30 kg/m^2 decreased at one-year post-transplant due to four patients not surviving one-year or lost to follow-up after surgery. A total of 12 out of the 14 patients who were obese prior to transplant remained obese at one-year post-transplant. However, BMI at the time of surgery may have also been skewed due to the presence of ascites (Barnard et al., 2016). Three patients who were not obese prior to surgery were noted to have a BMI of greater than or equal to 30 kg/m^2 at one-year post-transplant. Only

two patients who were obese prior to transplant were able to lose weight to achieve a BMI of less than 30 kg/m^2 at one-year post-transplant.

TABLE 7. *Patients' BMI at time of transplant and one-year post-transplant.*

	Frequency	***Percent***
BMI at transplant (N=41)		
BMI ≥ 30 (kg/m^2)	14	34%
BMI < 30 (kg/m^2)	27	66%
BMI at one-year post-transplant (N=37)		
BMI ≥ 30 (kg/m^2)	15	41%
BMI < 30 (kg/m^2)	22	59%

Dyslipidemia

LDL levels closest to the time of transplant and at one-year post-transplant were reviewed (Table 8). The majority of patients (81%) did not have documented LDL levels prior to transplant. Eight patients had a recorded LDL level at the time of or prior to transplant with seven (17%) noted to have a LDL level of less than 130 mg/dL and only one (2%) noted to have a LDL level higher than 130 mg/dL. The patient who had a LDL level greater than 130 mg/dL at the time of transplant continued to have a LDL level greater than 130 mg/dL at one-year post-transplant and was not on statin therapy at either time point. There were six patients (16%) with a documented LDL level of less than 130 mg/dL at one-year post-transplant. However, the number of unknown LDL levels remained significantly high (82%) at one-year post-transplant and may not have accurately reflected the number of patients with abnormal or normal LDL levels. Only two patients (one with a history of dyslipidemia) were started on statin therapy with Lipitor following surgery and neither had a LDL level documented at one-year post-transplant.

TABLE 8. *Patients' LDL at time of transplant and one-year post-transplant.*

	Frequency	***Percent***
LDL at transplant (N=41)		
LDL > 130 mg/dL	1	2%
LDL < 130 mg/dL	7	17%
Unknown	33	81%
LDL at one-year post-transplant (N=38)		
LDL > 130 mg/dL	1	3%
LDL < 130 mg/dL	6	16%
Unknown	31	82%

Note. Percentages may not total 100 due to rounding.

Diabetes Mellitus

HgbA1C levels were reviewed at the time of transplant, weekly for the first month following transplant, and then at three, six, and 12 months following transplant (Table 9). The total number of patients at each time frame accounts for those who did not survive to one-year post-transplant and varies depending on time of death. Alarmingly, 56-100% of data were marked as unknown as no HgbA1C levels were documented in the available health records at the specified time frames despite 24% of patients recorded as having a history of type 2 diabetes prior to transplant.

HgbA1C was noted to be less than 7% among the majority of patients (42%) who had a documented level at the time of or prior to transplant. Of the 31 patients without a history of type 2 diabetes and not on medication prior to transplant, three were started on medication for hyperglycemia following surgery and continued on therapy for post-transplant diabetes at one-year post-transplant. HgbA1C was documented prior to transplant and at three- and six-months post-transplant for only one of these three patients. Furthermore, three of the 10 patients with a history of type 2 diabetes continued on treatment for diabetes at one-year post-transplant. Only

two of these patients had a documented HgbA1C level prior to or at the time of transplant and at week four as well as three- and six-months post-transplant. HgbA1C levels at one-year post-transplant were not documented for any patients who continued on therapy for diabetes at that time. Documented medications for the management of diabetes mellitus following transplant included pioglitazone, metformin, glimepiride, Tradjenta, Humalog and Lantus.

TABLE 9. *Patients' HgbA1C at time of transplant, three- and six-months post-transplant, and one-year post-transplant.*

	Frequency	***Percent***
HgbA1C at transplant (N=41)		
HgbA1C > 7%	1	2%
HgbA1C < 7%	17	42%
Unknown	23	56%
HgbA1C at one-week post-transplant (N=40)		
HgbA1C > 7%	-	-
HgbA1C < 7%	1	2%
Unknown	39	98%
HgbA1C at two-weeks post-transplant (N=40)		
HgbA1C > 7%	-	-
HgbA1C < 7%	1	2%
Unknown	39	98%
HgbA1C at three-weeks post-transplant (N=40)		
HgbA1C > 7%	-	-
HgbA1C < 7%	-	-
Unknown	40	100%
HgbA1C at four-weeks post-transplant (N=40)		
HgbA1C > 7%	-	-
HgbA1C < 7%	1	2%
Unknown	39	98%
HgbA1C at three-months post-transplant (N=40)		
HgbA1C > 7%	-	-
HgbA1C < 7%	4	10%
Unknown	36	90%

TABLE 9 – *Continued*

	Frequency	***Percent***
HgbA1C at six-months post-transplant (N=39)		
HgbA1C > 7%	1	3%
HgbA1C < 7%	2	5%
Unknown	36	92%
HgbA1C at one-year post-transplant (N=38)		
HgbA1C > 7%	-	-
HgbA1C < 7%	2	5%
Unknown	36	95%

Hypertension

Blood pressure was reviewed at the time of transplant and at the clinic visit closest to one-year post-transplant (Table 10). Only 12 (29%) of the 41 patients were documented to have a blood pressure greater than 130/80 mmHg at the time of transplant. However, a blood pressure of greater than 130/80 mmHg was documented in 24 (65%) patients at one-year post-transplant. The patients who did not survive one-year post-transplant or follow-up in clinic at one-year post-transplant were not included in the total at that time.

Approximately 54% (n=20) of patients were documented to be on anti-hypertensive medication at one-year post-transplant. Furthermore, 16 of the 23 patients with a history of hypertension prior to transplant and four of the 18 patients without a history of hypertension were documented to be on anti-hypertensive medication at one-year post-transplant. Alarmingly, 14 of the 20 patients on anti-hypertensive therapy were noted to have a blood pressure of greater than 130 mmHg systolic and/or 80 mmHg diastolic at their clinic visit closest to one-year post-transplant. Furthermore, five of the 14 patients with uncontrolled blood pressure had NAFLD prior to transplant. Only one patients' anti-hypertensive medication regimen was altered at the

clinic visit. Another patients' regimen was not changed due to the patient not taking anti-hypertensive medication the morning of the clinic visit. Further hypertensive management was documented as to defer to the primary care provider or specialist. In addition, 10 patients without a documented history of hypertension were noted to have a blood pressure of greater than 130 mmHg systolic and/or 80 mmHg diastolic at one-year post-transplant and were not on or started on therapy at that time. Documented anti-hypertensive medications included metoprolol, Coreg, lisinopril, losartan, hydrochlorothiazide, amlodipine, nifedipine, and propranolol.

TABLE 10. *Patients' blood pressure at time of transplant and one-year post-transplant.*

	Frequency	***Percent***
Blood pressure at transplant (N=41)		
BP > 130/80 mmHg	12	29%
BP < 130/80 mmHg	29	71%
Blood pressure at one-year post-transplant (N=37)		
BP > 130/80 mmHg	24	65%
BP < 130/80 mmHg	13	35%

NAFLD

The presence of NAFLD on imaging and liver biopsy was reviewed at the time of transplant and closest to one-year post-transplant (Table 11). A liver biopsy is generally performed within one week of surgery at the local transplant program in order to evaluate for early acute cellular rejection, alternative reasons for allograft dysfunction, or to assist with immunosuppression regimen decisions. Further biopsies as well as imaging are based upon allograft function and are an individualized decision per the transplant program's protocol (Lucey et al., 2013). Thus, the pathology of the most recent liver biopsy documented within one-year of transplant was reviewed as liver biopsies are not routinely performed at one-year post-transplant unless otherwise indicated. Doppler ultrasounds performed immediately following

transplant evaluate for potential vascular complications (Sanyal et al., 2014). Thus, Doppler ultrasounds were excluded from imaging reviewed for the presence of hepatic steatosis. Patients who did not survive to one-year post-transplant or who did not have imaging other than a Doppler ultrasound or further liver biopsies performed following transplant were marked as *Unknown*.

There were no patients with hepatic steatosis on imaging immediately following transplant. However, three patients developed fatty infiltration on imaging within one-year post-transplant. Of concern, one of the patients who developed fatty infiltration on imaging was the patient lost to follow-up. Only two patients had mild macrovesicular steatosis noted on liver biopsy pathology immediately following transplant. Both patients continued to display evidence of macrovesicular steatosis with one of the patients progressing to severe macrovesicular steatosis upon liver biopsy pathology closest to one-year post-transplant. Neither patients had evidence of steatohepatitis concerning for NASH or fibrosis noted on liver biopsy pathology reports. Fatty infiltration or hepatic steatosis was only noted on imaging closest to one-year post-transplant for the patient with macrovesicular progression. Lastly, two patients developed macrovesicular steatosis on liver biopsy closest to one-year post-transplant who did not have steatosis noted on liver biopsy or imaging immediately following transplant. Neither of these two patients had evidence of steatohepatits concerning for NASH or fibrosis noted on liver biopsy pathology.

TABLE 11. *Patients' with NAFLD at time of transplant and one-year post-transplant (N=41).*

NAFLD on Imaging	***Frequency***	***Percent***
At time of transplant		
Yes	0	0
No	24	59%
Unknown	17	41%
At one-year post-transplant		
Yes	3	7%
No	26	63%
Unknown	12	29%
NAFLD on Liver Biopsy	***Frequency***	***Percent***
At time of transplant		
Yes	2	5%
No	38	93%
Unknown	1	2%
At one-year post-transplant		
Yes	4	10%
No	27	66%
Unknown	10	24%

Note. Percentages may not total 100 due to rounding.

Cardiovascular Disease Risk

No cardiovascular disease related events such as myocardial infarction, stroke, peripheral vascular disease, or coronary artery disease were documented within the first year of transplant among the study sample. Only five (12%) patients were noted to have hepatic steatosis via imaging and/or liver biopsy following transplant. Thus, the risk factors for NAFLD as well as metabolic complications associated with increased cardiovascular disease risk were explored in these five patients. Of these, only one patient was noted to be over the age of 50 and four patients were men. Furthermore, two men were of Hispanic ethnicity and one had a liver disease etiology of NAFLD. The remaining patients had alternative etiologies for chronic liver disease. All patients were on the calcineurin inhibitor, Prograf, at one-year post-transplant. None of the

patients had a documented history of dyslipidemia and were not on medication prior to or following transplant for dyslipidemia. However, a LDL level following transplant was not documented on any of the patients.

The man over the age of 50 and of Hispanic ethnicity was noted to have a family as well as personal history of type 2 diabetes and hypertension requiring medications prior to transplant. No medications for hypertension or diabetes mellitus were noted at his clinic visit closest to one-year post-transplant. Blood pressure was normal at that time; however, a HgbA1C level was not documented. The patient was successful in losing 16 pounds of body weight since the time of transplant which may have contributed to improved blood pressure and possibly glucose control following transplant. Furthermore, liver biopsy pathology showed improvement from mild to minimal macrovesicular steatosis.

The man with a history of NAFLD and obesity prior to transplant was also successful in losing weight following transplant. He did not have a documented history of hypertension; however, he was noted to have hypertension at the time of and at one-year post-transplant. No anti-hypertensive medication was documented following surgery. Furthermore, the patient did not have a history of type 2 diabetes but was started on Lantus and Humalog following transplant which were ultimately discontinued. He was not on medications for hyperglycemia at his clinic visit closest to one-year post-transplant; however, a HgbA1C level was not documented to confirm glucose control. Despite weight loss, his liver biopsy pathology closest to one-year post-transplant showed mild macrovesicular steatosis.

Another man without a history of dyslipidemia, hypertension, diabetes mellitus, or obesity was noted to have minimal to mild macrovesicular and microvesicular steatosis

documented on liver biopsy pathology closest to one-year post-transplant. He developed steroid induced hyperglycemia following transplant but did not continue on insulin after hospital discharge. In addition, he was not on medication for diabetes mellitus, hypertension, or dyslipidemia at his clinic visit closest to one-year post-transplant. Blood pressure was normal at his clinic visit, and a HgbA1C level was not documented post-transplant. The patient was noted to have a significant weight gain of 37 pounds with a BMI of 32 kg/m^2 documented at one-year post-transplant which may have contributed to the development of post-transplant steatosis.

The woman with progression from minimal to severe macrovesicular steatosis upon liver biopsy pathology did have a history of obesity and hypertension prior to transplant. BMI decreased from 36 kg/m^2 to 31 kg/m^2 and blood pressure was well controlled on an anti-hypertensive medication at her clinic visit closest to one-year post-transplant. The patient did not have a documented history of diabetes mellitus but did require intravenous insulin following surgery. She did not continue on insulin therapy following hospital discharge and was not on medication at one-year post-transplant; however, a HgbA1C level was not documented to confirm glycemic control.

Lastly, the man of Hispanic ethnicity with fatty infiltration noted on imaging did not continue to follow-up in clinic shortly after transplant; however, he did continue to undergo laboratory testing to monitor liver function tests and immunosuppression levels. No history of obesity, hypertension, or dyslipidemia was documented. However, the patient did require intravenous insulin following transplant and was discharged home on Lantus as well as Humalog. A HgbA1C level was not documented after transplant. Unfortunately, the patient does

not have a BMI, blood pressure, or medications for co-morbidities documented either due to no longer following-up in clinic.

DISCUSSION

Summary of Findings

The electronic health care records of 41 transplant recipients who underwent liver only transplantation by a local transplant program in San Antonio, Texas, between July 1, 2016 and June 30, 2017 were reviewed up to one-year post-transplant. Of the 41 patients, three did not survive to one-year post-transplant and one was lost to follow-up with the program but did continue to undergo laboratory testing as directed. No cardiovascular disease related events such as myocardial infarction, stroke, peripheral vascular disease, or coronary artery disease were documented within the first year following transplant. A similar study by Fussner et al. (2015) demonstrated cardiovascular disease to be common following transplant with 10.6% of patients having developed a cardiovascular event within the first year of surgery. However, analysis on the prevalence of hypertension, diabetes mellitus, and hyperlipidemia was not explored as in this study (Fussner et al., 2015).

Studies have shown up to 71% and 30% of transplant recipients to develop dyslipidemia and diabetes mellitus within the first year of transplant, respectively (Barnard et al., 2016; Lucey et al., 2013). However, the majority of the patients in the present study did not have documented LDL or HgbA1C levels which are valuable markers indicative of increased cardiovascular disease risk (Agarwal et al., 2016; Barnard et al., 2016; Grundy et al., 2018; Husing et al., 2016). In the present study, the majority of the patients who were obese at the time of transplant remained obese at one-year post-transplant. Surprisingly, 66% of patients had a BMI of less than

30 kg/m^2 prior to transplant and 59% had a BMI of less than 30 kg/m^2 following transplant. Discrepancies in BMI in this study versus estimated prevalence rates may have been due to BMI not accounting for malnutrition as well as ascites associated with chronic liver disease or cirrhosis (Barnard et al., 2016; Chaney & Heckman, 2018). Thus, BMI at the time of transplant may not serve as a reliable measure of obesity prior to transplant. Review of hypertension provided the most comprehensive data as a blood pressure was documented at the time of transplant and at the clinic visit closest to one-year post-transplant on all patients who survived one-year post-transplant and continued to follow-up in clinic. In the present study, approximately 65% of patients were noted to have hypertension at one-year post-transplant which is in congruence with the estimated hypertension prevalence rate of 50% following 6 months of surgery (Barnard et al., 2016; Jimenez-Perez et al., 2016).

NAFLD is a manifestation of metabolic complications found to be common among liver transplant recipients (Chalasani et al., 2018; Haugen et al., 2018; Marjot et al., 2018; Martin et al., 2014; Mikolasevic et al., 2018; Patel, Berg, & Moylan, 2016). Approximately 30-60% of patients transplanted for NASH cirrhosis and 20-40% of patients without a NASH etiology of liver disease are estimated to develop NAFLD within a one- to five-year post-transplant period (Chalasani et al., 2018; Jimenez-Perez et al., 2016; Pais et al., 2016). A study by Hejlova et al. (2016) showed 26% of patients to have steatosis present on liver biopsy at one-year post-transplant. Thus, recurrent or new-onset NAFLD following transplant was not prevalent in this study as only five (12%) patients developed hepatic steatosis on imaging and/or liver biopsy following transplant with only one of the patients having a NAFLD etiology prior to transplant. None of the patients had evidence of NASH or fibrosis on liver biopsy pathology. Fortunately,

development of NAFLD following transplant typically yields a low risk of progression to advanced liver disease or re-current cirrhosis (Martin et al., 2014; Patel et al., 2016).

Additional risk factors such as male gender, Hispanic ethnicity, advanced age, and immunosuppression medications for the development of NAFLD and associated cardiovascular disease risk were explored with particular focus on the patients who developed NAFLD following transplant. All subjects were on the calcineurin inhibitor, Prograf, which is the preferred immunosuppression medication following transplant as it has been shown to increase allograft survival and demonstrate a less adverse cardiovascular profile (Barnard et al., 2016; Fussner et al., 2015; Jimenez-Perez et al., 2016; Moini et al., 2015). Of the five patients with hepatic steatosis on imaging and/or liver biopsy following transplant, 80% were of male gender which is consistent with studies showing NAFLD to be twice as prevalent in men versus women (Ballestri et al., 2017; Chalasani et al., 2018; Pan & Fallon, 2014). Only 40% of the patients with hepatic steatosis following transplant were of Hispanic ethnicity, and only one patient was noted to be over the age of 50. Thus, advanced age and Hispanic ethnicity in the present study did not correlate with an increased risk for developing NAFLD following transplant.

In summary, this study showed hypertension to be the most frequently documented metabolic complication that was prevalent among liver transplant recipients at one-year post-transplant and sub-optimally managed. The study failed to truly capture the prevalence of other metabolic complications and associated cardiovascular disease risk among the study population due to missing data, particularly in regard to LDL and HgbA1C levels. The prevalence of recurrent or new-onset NAFLD was low in this study and may be better captured in the late post-transplant period. Patients who developed hepatic steatosis following transplant did not have

evidence of NASH or fibrosis on liver biopsy pathology. The study sample consisted of a predominantly male population; however, the mean age was only 55 and patients were primarily of non-Hispanic ethnicity which were not considered risk factors for the development of NAFLD. Lastly, no cardiovascular disease related events were documented within the first year following transplant.

Limitations and Strengths

The study sample size was relatively small as the number of transplants during the July 2016 through June 2017 timeframe was lower than the 70 transplants performed by the local transplant program the prior year (Scientific Registry of Transplant Recipients, 2018). Only 41% of the patients were of Hispanic ethnicity which does not reflect the predominantly Hispanic community of San Antonio. In addition, only 12% of the patients in this study had a documented NAFLD etiology of liver disease prior to transplant. The low prevalence of Hispanic ethnicity and NAFLD may have been attributed to the transplant program performing transplants on patients from outside of San Antonio as well. Furthermore, there are two transplant programs located in San Antonio; thus, a future study encompassing data from both programs may better reflect the Hispanic community of San Antonio as well as the number of transplant recipients transplanted for NAFLD.

In the present study, patients' records were only reviewed up to one-year post-transplant. A long-term evaluation post-transplant may provide a more accurate depiction of metabolic complications and associated cardiovascular disease related mortality among the liver transplant recipients transplanted at this transplant program. Furthermore, the retrospective design of this study relied on available data documented within hospital progress notes, outpatient clinic visit

reports, history and physicals by hospitalists, and consultation reports by specialists to provide the patients' medical history and diagnoses as well as management strategies for post-transplant metabolic complications. Follow-up clinic visit dates at one-year post-transplant varied depending on clinic and provider availability which may have not accurately captured the prevalence of metabolic complications as well as recurrent or new-onset NAFLD within one-year of transplant. In addition, only laboratory testing performed at the local transplant program or via commercial laboratory testing centers ordered by the Hepatology and Transplant provider and scanned into the electronic medical record were available for review. Thus, HgbA1C and LDL levels performed through primary care providers or specialists as an outpatient may not have been accounted for if results were not requested or brought to the clinic by the patient. Missing data may have skewed the study outcomes and significantly underestimated the prevalence of metabolic complications and associated cardiovascular disease risk among liver transplant recipients at this transplant program.

In regard to study strengths, this is the first study to the author's knowledge that investigates the prevalence of metabolic complications as well as NAFLD and associated cardiovascular disease risk among liver transplant recipients at this transplant program in San Antonio, Texas. Furthermore, this study is one of few throughout the literature that investigates multiple research variables among liver transplant recipients including the prevalence of hypertension, diabetes mellitus, dyslipidemia, and obesity; additional risk factors such as age, ethnicity, gender, etiology of liver disease, family history, and immunosuppression medications; the prevalence of recurrent and new-onset NAFLD; and cardiovascular disease risk following transplant.

Implications for Advanced Practice Nursing

The prevention and adequate management of metabolic complications is crucial in reducing cardiovascular disease related events and increasing longevity among liver transplant recipients (Barnard et al., 2016). Although immunosuppression medications have helped lower the risk for acute cellular rejection and increase related survival, they are associated with the development of an adverse cardiovascular profile (Barnard et al., 2016; Brunault et al., 2015; Haugen et al., 2018; Martin et al., 2014; Moini et al., 2015; Pisano et al., 2016; Song et al., 2014). Age, ethnicity, and gender have also been shown to increase the risk for NAFLD and associated cardiovascular disease risk following transplant (Chalasani et al., 2018; Pan & Fallon, 2014). Thus, understanding the risk factors for metabolic complications, NAFLD, and cardiovascular disease as well as implementing appropriate practice guidelines and management strategies following transplant may help improve outcomes among liver transplant recipients.

Communication between Hepatology specialists and primary care providers is vital for the early recognition and appropriate management of post-transplant metabolic complications (Barnard et al., 2016). Coordination with a dietician and physical therapist may help promote lifestyle modifications via patient education as healthy dieting and increased physical activity have been shown to prevent and improve metabolic complications as well as NAFLD (Barnard et al., 2016; Chalasani et al., 2018; Maurice & Manousou, 2018; Patel et al., 2016). Immunosuppression decisions in collaboration with a pharmacist may also prove beneficial in reducing cardiovascular disease risk factors while maintaining adequate immunosuppression levels to prevent acute cellular rejection (Barnard et al., 2016). Thus, a multi-disciplinary approach is imperative to the successful implementation of the aforementioned strategies in an

effort to reduce the prevalence of metabolic complications as well as NAFLD and associated cardiovascular disease risk among liver transplant recipients.

Lastly, improved documentation is necessary to more accurately capture the prevalence of metabolic complications and associated cardiovascular disease risk among liver transplant recipients. Records of pertinent laboratory values and/or imaging should be requested and appropriately documented if testing is performed outside of the transplant program. Prospective studies are needed to further evaluate the prevalence of metabolic complications and associated cardiovascular disease risk among this population due to the missing data in this study.

Conclusions

Survival rates among liver transplant recipients have significantly improved particularly with modern advances in surgical techniques and immunosuppression medications (Barnard et al., 2016; Brunault et al., 2015; Haugen et al., 2018; Martin et al., 2014; Pisano et al., 2016; Song et al., 2014). However, metabolic complications such as hypertension, obesity, dyslipidemia, and diabetes mellitus as well as recurrent or new-onset NAFLD have become exceedingly prevalent following transplant and are associated with increased cardiovascular disease risk and related mortality (Barnard et al., 2016; Brunault et al., 2015; Fussner et al., 2015; Glowczynska et al., 2018; Jimenez-Perez et al., 2016; Marjot et al., 2018; Pisano et al., 2016; Wang et al., 2016). Additional factors influencing the development of NAFLD and associated cardiovascular disease risk include advanced age, male gender, Hispanic ethnicity, and immunosuppression medications initiated following transplant (Chalasani et al., 2018; Moini et al., 2015; Pan & Fallon, 2014). Thus, optimal management of modifiable risk factors is necessary to reduce cardiovascular disease risk.

Retrospective health care record review employed in this DNP study was an insufficient method for profiling cardiovascular disease risk due to missing data and, thus, inadequate to truly capture the prevalence of metabolic complications as well as NAFLD and associated cardiovascular disease risk among liver transplant recipients. Appropriate documentation of HgbA1C and LDL levels may prove beneficial in the assessment of post-transplant patients at risk for cardiovascular disease. Furthermore, better control of blood pressure may help reduce cardiovascular disease risk in the late post-transplant period. Findings from this DNP study serve as the foundation for future prospective studies to further investigate the prevalence of metabolic complications following transplant in an effort to prevent the development and optimize the medical management of hypertension, diabetes mellitus, dyslipidemia, and obesity as well as NAFLD and reduce associated cardiovascular disease risk among liver transplant recipients.

APPENDIX A:

DATA COLLECTION INSTRUMENT

CARDIOVASCULAR PROFILE OF LIVER TRANSPLANT RECIPIENTS

Data collection date (mm/dd/yy): _____

Patient's code number: _____

Transplant date (mm/dd/yy): _____

Age at date of transplant: _____

Etiology of liver disease:

NAFLD/Other/Unknown

Patient alive at 1-year post-transplant:

Yes/No

Ethnicity

Hispanic/Non-Hispanic/Unknown

Gender:

Male/Female

Immunosuppression:

At time of transplant:
Prograf/Rapamue/Cyclosporine/Cellcept/Other _____

At 1-year post-transplant:
Prograf/Rapamue/Cyclosporine/Cellcept/Other _____

Height and Weight:

At time of transplant – Date: _____
Height: _____ (in) or _____ (cm)
Weight: _____ (lbs) or _____ (kg)
BMI: _____ (kg/m^2)

BMI: > or = to 30 kg/m^2
Yes/No/Unknown

At 1-year post-transplant – Date: _____
Height: _____ (in) or _____ (cm)
Weight: _____ (lbs) or _____ (kg)
BMI: _____ (kg/m^2)

BMI: > or = to 30 kg/m^2
Yes/No/Unknown

Family history of obesity:
Yes/No/Unknown

Dyslipidemia:

Patient history of dyslipidemia:
Yes/No/Unknown

Family history of dyslipidemia:
Yes/No/Unknown

Fasting lipid panel closest to date of transplant – Date: _____
Low-density lipoprotein cholesterol: _____ mg/dL

LDL > 130 mg/dL
Yes/No/Unknown

On a lipid-lowering medication:
Yes/No/Unknown
If yes, specify name and dose: _____

Fasting lipid panel at 1-year post-transplant – Date: _____
Low-density lipoprotein cholesterol: _____ mg/dL

LDL > 130 mg/dL
Yes/No/Unknown

On a lipid-lowering medication:
Yes/No/Unknown
If yes, specify name and dose: _____

Diabetes Mellitus:

Patient history of diabetes:
Yes/No/Unknown

Family history of diabetes:
Yes/No/Unknown

HgbA1C closest to date of transplant – Date: _____
HgbA1C at week 1 post-transplant: _____
HgbA1C > 7%
Yes/No/Unknown

HgbA1C at week 2 post-transplant: _____
HgbA1C > 7%
Yes/No/Unknown

HgbA1C at week 3 post-transplant: _____
HgbA1C > 7%
Yes/No/Unknown

HgbA1C at week 4 post-transplant: _____
HgbA1C > 7%
Yes/No/Unknown

HgbA1C at 3 months post-transplant: _____
HgbA1C > 7%
Yes/No/Unknown

HgbA1C at 6 months post-transplant: _____
HgbA1C > 7%
Yes/No/Unknown

On a glycemic control medication at time of transplant:
Yes/No/Unknown
If yes, specify name and dose: _____

HgbA1C at 1-year post-transplant – Date: _____
HgbA1C > 7%
Yes/No/Unknown

On a glycemic control medication:
Yes/No/Unknown
If yes, specify name and dose: _____

Hypertension:

Patient history of hypertension:
Yes/No/Unknown

Family history of hypertension:
Yes/No/Unknown

At time of transplant – Date: _____
Systolic blood pressure: _____mmHg
Diastolic blood pressure: _____mmHg

BP >130/80 mmHg
Yes/No/Unknown

On an antihypertensive medication:
Yes/No/Unknown
If yes, specify name and dose: _____

At 1-year post-transplant – Date: _____
Systolic blood pressure: _____mmHg
Diastolic blood pressure: _____mmHg

BP >130/80 mmHg
Yes/No/Unknown

On an antihypertensive medication:
Yes/No/Unknown
If yes, specify name and dose: _____

NAFLD:

Liver biopsy at time of transplant – Date: _____
Evidence of NAFLD Yes/No/Unknown

Liver biopsy closest to 1-year post-transplant – Date: _____
Evidence of NAFLD Yes/No/Unknown

Imaging (CT/MRI/US) at time of transplant – Date: _____
Evidence of NAFLD Yes/No/Unknown

Imaging (CT/MRI/US) closest to 1-year post-transplant – Date: _____
Evidence of NAFLD Yes/No/Unknown

APPENDIX B:

METHODIST HEALTHCARE SYSTEM INSTITUTIONAL REVIEW BOARD (IRB)

APPROVAL LETTER

METHODIST HEALTHCARE
"Serving Humanity to Honor God"
www.SAHealth.com
INSTITUTIONAL REVIEW BOARD
FWA00000435
8109 Fredericksburg Road, 3rd Floor, San Antonio, TX 78229
Telephone: (210) 575-4918
Fax: (210) 575-0587
MHS IRB web site: https://sites.google.com/site/mhsirbsatx/

August 10, 2018

Katrina Peterson, MSN
6974 Oak Drive Apt. 1201
San Antonio, TX 78256

Re:	[1289067-1] Metabolic Complications and Associated Cardiovascular Disease Risk Post Liver Transplant
Site:	*[Methodist Specialty & Transplant Hospital; Texas Transplant Institute Liver Disease and Transplant Program (Liver Clinic)]*

Dear Ms. Peterson,

The above referenced study has been reviewed under expedited review (DHHS Regulation 45 CFR 46.110 and/or 21 CFR 56.110, as applicable). It is determined that this study meets minimal risk requirements as submitted. Provisions to protect the confidentiality of subjects have also been provided and are deemed appropriate and adequate measures for subject protection.

Expedited approval for the above referenced study is therefore granted **for a period of 12 (twelve) months, effective August 09, 2018,** per 45 CFR 46.110 Categories as described below:

- •**Category 5**: Research involving materials (data, documents, records or specimens) that have been collected solely for non-research purposes (such as medical treatment and/or diagnosis).

This Approval Includes:

- *Protocol version dated 8/07/2018*
- *Data Collection Tool*
- *MHS Fom P - Protocol Personnel Form*

*You are restricted to a maximum of **41 subjects (records).***

In accord with 45 CFR 46.116(d), the requirement to obtain and document informed consent is waived for this study. The waiver is granted after determining that:

1. The research involves no more than minimal risk to the subjects;
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. The research cannot practicably be carried out without the waiver; and

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4. Due to the nature of the study, status of the study subjects, data and manner in which data will be collected, it would not be appropriate to provide them with pertinent information after participation.

This approval expires August 9, 2019. A progress report must be submitted for continuing review and approved by the Board prior to that date. Failure to do so by this date will result in enrollment suspension. Further delay will result in study closure. A Progress Report form (and other forms needed for IRB submission) can be found in the library section of the Designer page on IRBNet.

RESPONSIBILITIES OF PRINCIPAL INVESTIGATOR:

1. Report to the MHS IRB any death of a subject whether Anticipated or Unanticipated and **whose cause is related** to the study or study procedures. The report must be submitted to the MHS IRB within ten (10) working days of the investigator becoming aware of the death;
2. Report promptly to the IRB any reportable severe adverse reactions or serious problems, per IRB Guidelines;
3. Report any significant findings that become known in the course of the research that might affect the willingness of subjects to continue to take part;
4. Ensure that only persons formally approved by the IRB enroll subjects;
5. Submit for review and approval by the IRB all modifications to the protocol or consent form(s) prior to the implementation of the change;
6. Submit a progress report for continuing review by the IRB. Federal regulations require that the IRB review on-going projects no less than one year from the approval date (progress report available in the Library in IRBNet); and
7. Notify the IRB in writing when the study has been completed and prepare a final report (Progress Report form).

If you have any questions, please contact the IRB Office or Tara Garcia at (210) 575-4918 or tara.garcia2@mhshealth.com. Please include your study title and reference number in all correspondence with this office.

"This document has been electronically signed in accordance with all applicable regulations, and a copy is retained within our records."

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APPENDIX C:

THE UNIVERSITY OF ARIZONA INSTITUTIONAL REVIEW BOARD (IRB)

APPROVAL LETTER

THE UNIVERSITY OF ARIZONA
Research, Discovery & Innovation

Human Subjects Protection Program

1618 E. Helen St.
P.O.Box 245137
Tucson, AZ 85724-5137
Tel: (520) 626-6721
http://rgw.arizona.edu/compliance/home

Date:	September 18, 2018
Principal Investigator:	Katrina Irene Peterson
Protocol Number:	1809938086
Protocol Title:	Metabolic Complications and Associated Cardiovascular Disease Risk Post Liver Transplant
Level of Review:	Administrative Review
Determination:	Approved
IRB of Record:	Methodist specialty and transplant hospital
Investigator at Site:	Katrina Peterson
IRB of Record Protocol Number:	1289067-1

Documents Reviewed Concurrently:

Data Collection Tools: *Data Collection Instrument.docx*
HSPP Forms/Correspondence: *Advisor Confirmation Email.pdf*
HSPP Forms/Correspondence: *Confirmation for Scientific Review and Department Review.pdf*
HSPP Forms/Correspondence: *Peterson Application for Human Research (2).pdf*
HSPP Forms/Correspondence: *Peterson List of Research Personnel.pdf*
Other: *Data Use Agreement.pdf*
Other: *Peterson_Resume2018.docx*
Other Approvals and Authorizations: *COI Certification Complete for 1809938086.msg*
Other Approvals and Authorizations: *Expedited Approval Letter.pdf*
Other Approvals and Authorizations: *Form H Waiver of Alteration of HIPAA Authorization.docx*
Other Approvals and Authorizations: *Form J Waiver or Alteration of Consent.docx*
Other Approvals and Authorizations: *Form P Research Personnel.doc*
Other Approvals and Authorizations: *HIPAA Waiver Approval (1).pdf*
Other Approvals and Authorizations: *Revised MHS IRB Initial Application.docx*
Protocol: *Research Protocol MHS.DOCX*

Regulatory Determinations/Comments:

- Methodist Healthcare Designated IRB of Record: When an institution is designated IRB of record, the UA IRB will not review the project.' The University of Arizona agrees that it will rely on the review, approval, and continuing oversight of the institution's IRB pursuant to the terms of the Institutional Review Board Authorization Agreement.

- The University of Arizona maintains a Federalwide Assurance with the Office for Human Research Protections (FWA #00004218).
- All documents referenced in this submission have been reviewed and are filed with the HSPP.
  The Principal Investigator should notify the IRB immediately of any proposed changes that affect the LOCAL protocol and report any LOCAL unanticipated problems involving risks to participants or others. Please refer to Guidance's *Investigators Responsibility after IRB Approval* and *Reporting Local Information*.
- All research procedures should be conducted according to the approved protocol and the policies and guidance of the IRB of record.

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