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ASSESSING MALNUTRITION IN LIVER DISEASE PATIENTS BEING EVALUATED FOR TRANSPLANT USING THE NUTRITION FOCUSED PHYSICAL EXAM

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ASSESSING MALNUTRITION IN LIVER DISEASE PATIENTS BEING
EVALUATED FOR TRANSPLANT USING THE NUTRITION FOCUSED
PHYSICAL EXAM

THESIS

A thesis submitted in partial fulfillment of the requirements for the degree of Master of
Science in Nutrition and Food Systems in the College of Agriculture, Food and
Environment at the University of Kentucky.

By

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2018

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ABSTRACT OF THESIS

ASSESSING MALNUTRITION IN LIVER DISEASE PATIENTS BEING EVALUATED FOR TRANSPLANT USING THE NUTRITION FOCUSED PHYSICAL EXAM

Patients with liver disease have an increased risk for malnutrition because of side effects of the disease. The Nutrition Focused Physical Exam (NFPE) was developed for nutrition professionals to aid physicians in a nutrition-based diagnosis of malnutrition. The purpose of this study was to examine the NFPE for its validity in liver disease patients being evaluated for transplant. In addition, the NFPE was used to assess incidence and severity of malnutrition in end stage liver disease patients and compare these results to already developed malnutrition tools such as the Patient Generated-Subjective Global Assessment (PG-SGA), Triceps Skinfolds (TSF), Mid-Arm Circumference (MAC), Lumbar Index, and Total Psoas Muscle Area (TPA). The NFPE was found to be highly correlated with PG-SGA results. There was a weak correlation between the NFPE and the TSF, MAC, and Lumbar Index/TPA, except when comparing the bottom 25% quartile of the Lumbar Index to severe malnutrition using the NFPE. This resulted in a moderate correlation. The odds-ratio for hospital admission based on malnutrition and severe malnutrition were both extremely high (14.571, 18.857 respectively). These preliminary results reinforce the significance of the NFPE and the need for additional studies using this tool.

KEY WORDS: Cirrhosis, Malnutrition, Nutrition Focused Physical Exam, Transplant, PG-SGA

Madison Hilgendorf
July 17, 2018

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Chapter 1: Introduction

End stage organ disease and organ transplantation, is rapidly growing. According to the *United Network for Sharing Organs*, better known as *UNOS*, there has been a 19.8% increase in growth of organ transplants since 2012.[1] This is mainly due to an increase in deceased donors and changes in medical criteria that would have previously resulted in clinicians declining the use of an organ. Since the first organ transplant occurred in 1954, over 700,000 people have received transplants offering an extension on life in the U.S. [1, 3] Liver transplantation for end stage liver disease (ESLD), is a major section of this population. ESLD affects 1 in 10 Americans, or roughly 30 million Americans.[3] The most common causes of liver disease are from the hepatitis virus, heavy alcohol use, non-alcoholic fatty liver disease (NAFLD), liver cancer, and autoimmune diseases. Patients with NAFLD, liver cancer, and cirrhosis from the hepatitis virus are rising in number, and may be related to the obesity epidemic, previous non-screening of blood products for the hepatitis virus, and drug use in the U.S. [3]

End stage liver disease can lead to many health complications such as ascites/edema which may require paracentesis or draining, decline in kidney function, encephalopathy or confusion, enlarged blood vessels, infection, or decline in respiratory function.[3] A common complication of end stage liver disease is malnutrition, which can greatly affect a patient's quality of life outcomes.[4-8] Malnutrition is common in patients with liver disease because of their increased metabolic demands, side effects of the disease such as malabsorption, and changes in eating habits such as decreased appetite or nausea. [4, 9, 10] Additionally, mild to moderate malnutrition is common in chronic disease such as organ failure, due to the continuous level of inflammation.[11]

This mild to moderate degree of malnutrition can advance to severe malnutrition if it is left unrecognized or untreated.[12]

Malnutrition is prevalent in 15-60% of the adult patient population, but many of the methods used to assess malnutrition are expensive, unreliable, or have limitations.[12] The range for prevalence of malnutrition varies widely due to the differences in patient population and tools used to assess malnutrition. Some tools are very in-depth, while others are simply based on appetite and weight loss. Common tools used to assess for malnutrition are protein levels (albumin and prealbumin), malnutrition screening tools which use a questionnaire, or anthropometric measurements such as triceps skin folds (TSF), mid-arm circumference (MAC), and hand-grip strength.[11, 12] These tools can be affected by medical conditions and inter-observer reliability. These tools can be expensive to conduct, leading to inconsistent and potentially unreliable malnutrition diagnoses.

In 2012, the Academy of Nutrition and Dietetics (AND) and the American Society for Parenteral and Enteral Nutrition (ASPEN) released a Consensus Statement on the identification and documentation of malnutrition in the adult population.[12] According to White et al. (2012), “there is currently no universally accepted approach to the diagnosis and documentation of adult malnutrition.” White et al. (2012) in conjunction with AND and ASPEN, developed a set of parameters and characteristics for qualified nutrition professionals to aid physicians in a nutrition-based diagnosis of malnutrition. Thus, the Nutrition Focused Physical Exam (NFPE) was created for assessing malnutrition in all of the adult patient population. (See Appendix B)

Problem Statement

The focus of this study is to use the Nutrition Focused Physical Exam (NFPE), developed by the Academy of Nutrition and Dietetics and American Society for Enteral and Parenteral Nutrition, to identify and assess the severity of malnutrition in end stage liver disease patients being evaluated for transplant. In addition, the NFPE will be studied for its validity and effectiveness in this specific patient population.

Purpose

According to a recent literature search, only one published study has assessed malnutrition using the NFPE.[13] This study was conducted in head and neck cancer patients and the results may not apply to all patient populations. More studies need to be conducted using the NFPE to determine its use in different adult patient populations. This study will use the NFPE to assess incidence and severity of malnutrition in ESLD patients and compare these results to already developed malnutrition tools.

Research Questions

1. How does the NFPE relate to current tools such as Patient Generated-Subjective Global Assessment (PG-SGA), Triceps Skinfolds (TSF), Mid-Arm Circumference (MAC), and Lumbar Index/Psoas Muscle Area in End Stage Liver Disease Patients?
2. How prevalent is malnutrition in ESLD patients using the NFPE for diagnosis?
3. How does malnutrition diagnosed using the NFPE relate to patient outcomes?

Research Hypotheses

1. There is a positive correlation between the NFPE and current tools such as PG-SGA, MAC, TSF, and the Lumbar Index/Psoas Muscle Area, when assessing malnutrition in ESLD patients.
2. Malnutrition is prevalent in at least half of all ESLD patients using the NFPE for diagnosis.
3. ESLD patients with a malnutrition diagnosis using the NFPE are more likely to result in a patient outcome such as hospital admission, decompensation, listing for transplant, transplant, and death.

Justification

Malnutrition may be prevalent in “ 65-90% of patients with cirrhosis, and in up to 100% in patients waiting for liver transplantation”. [14] Many side effects of ESLD, such as ascites, may mask the incidence and severity of malnutrition in these patients when using available methods such as BMI and weight loss. [4, 9, 10] There has been some success in previous studies using hand grip strength, MAC, SGA, and TST. However, there are still limitations to using these methods. [10, 15]

AND and ASPEN developed the NFPE in 2011. The tool shows promise to be used successfully in many adult patient populations to assess the incidence and severity of malnutrition. However, to our knowledge, there has only been one published study to date that used the NFPE to assess malnutrition in the adult population. The NFPE is intended to be an affordable, simple, and reliable method for assessing malnutrition and

can be used in a variety of patient populations. Therefore, it is imperative to conduct more research using the NFPE to assess malnutrition in multiple populations, including those with ESLD, and hopefully, establishing this tool as a “gold standard” for assessing malnutrition.

Chapter 2: Literature Review

Introduction:

Malnutrition in ESLD patients is a widespread issue that can lead to many health complications and poor outcomes in this patient population. Many studies evaluated ESLD and the role of malnutrition.[6, 8-10, 14, 16-18] However, there are many limitations to these studies, mainly due to the tools used to assess malnutrition. At this point in time, there is no “gold standard” tool that is cheap, easy to use, and valid for assessing malnutrition. The purpose of this study is to look at ESLD patients being evaluated for transplant, and to assess for malnutrition using the NFPE. Liver disease diagnosis and a patient’s MELD (model for end stage liver disease) score will also be examined in ESLD patients and will be compared to the NFPE results.

End Stage Liver Disease

The most common causes of ESLD are Hepatitis B and C, acute liver failure, autoimmune hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease/nonalcoholic steatohepatitis, hepatocellular carcinoma, primary biliary cirrhosis, and primary sclerosis cholangitis.[2, 3] There are other causes of ESLD, but they are not as commonly seen. Table 1 (see below) provides a summary of these diseases.

Table 1: Summary of Common Liver Disease Diagnoses[2, 3]

Type of Liver Disease	Cause of Liver Disease	At Risk Populations/Risk Factors	Treatment/Cure
Hepatitis B and C	Hepatitis is a virus that can be transmitted through bodily fluids (semen, blood, and vaginal secretions)	<ul style="list-style-type: none"> • IV drug use • Unprotected sex • Body piercings • Tattoos • Incarceration 	<ul style="list-style-type: none"> • Hepatitis can be cured spontaneously by the body and through pharmaceuticals. • There is currently a vaccine for Hepatitis B, but not for Hepatitis C. • When a patient with the hepatitis virus fails treatment, or waits too long to seek treatment, it can lead to liver damage and ultimately liver failure. This can only be treated with transplant.
Acute Liver Failure	Drug overdose (acetaminophen), drug toxicity/reaction, herbal supplements, viruses, cancer, metabolic diseases	<ul style="list-style-type: none"> • High acetaminophen use • Herbal use • Cancers with high risk of liver metastasis development • Liver Cancer • Metabolic Disorders 	<ul style="list-style-type: none"> • Medications to reverse poisoning • Transplant
Autoimmune Hepatitis	Immune system attacks liver cells causing inflammation and damage	<ul style="list-style-type: none"> • Women between the ages 15-40 • Other autoimmune diseases 	<ul style="list-style-type: none"> • Suppress immune system with steroids or other immunosuppressant drugs • Transplant
Alcoholic Liver Disease	Alcohol abuse	<ul style="list-style-type: none"> • Alcoholics • Those with long history of frequent alcohol use 	<ul style="list-style-type: none"> • Alcohol cessation • Transplant
Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis	Build-up of fat cells in the liver	<ul style="list-style-type: none"> • Obesity • Diabetes • High cholesterol • Unhealthy diet 	<ul style="list-style-type: none"> • Healthy diet and exercise • Weight loss if overweight/obese • Transplant
Hepatocellular Carcinoma	Liver Cancer	<ul style="list-style-type: none"> • Pre-existing cirrhosis • Long term hepatitis virus 	<ul style="list-style-type: none"> • Resection • Chemoembolization • Ablation • Treatment of hepatitis or underlying cirrhosis • Transplant
Primary Biliary Cirrhosis	Destruction of intrahepatic bile ducts leads to build	<ul style="list-style-type: none"> • Women • Middle age 	<ul style="list-style-type: none"> • Symptom management with medications • Transplant

Table 1: Summary of Common Liver Disease Diagnoses (continued) [2, 3]

	up of bile and scar tissue, damaging the liver.	adults • Genetics	
Primary Sclerosis Cholangitis	Blocked bile ducts due to scar tissue and inflammation leads to buildup of bile, damaging the liver.	• Men • Genetics • Exact cause unknown	• Symptom management with medications and surgery • Transplant
Other (less common)	Wilson's Disease, Hemochromatosis, Alpha-1 Anti-trypsin Deficiency, Undetermined cause, etc.	• Genetics • Lifestyle	• Treatment based on disease. • Transplant

ESLD has many different causes and components to its development. The most common indication that liver disease has reached end stage or organ failure, is the development of decompensation.[16] The development of decompensation in liver disease occurs when there is diffuse scarring in the liver and it loses its ability to fully function.[3, 10] Decompensation in liver disease results in various health issues such as hepatocellular carcinoma (HCC), ascites that may require frequent paracentesis (LVP) or drainage, esophageal varices (EV), hepatorenal syndrome (HRS), jaundice, hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP) and kidney insufficiency. While decompensation is a useful indicator of ESLD, many patients do not develop these symptoms until later in the disease. Therefore, clinicians have developed additional tools and resources, such as MELD Score and Child-Turcotte-Pugh Score, to assess the severity of ESLD in transplant patients.

MELD Score and Liver Disease

Until 2001, the tool used to assess the severity of liver disease for organ allocation was the Child-Turcotte-Pugh Score (CTP). Using clinic measurements such as: albumin, prealbumin, and prothrombin time lab values, and the subjective evaluation of the degree

of ascites and encephalopathy, CTP was used to determine the overall severity of the liver disease.[16] Mayo Clinic developed the model for end stage liver disease (MELD) in 2000. MELD was used in patients undergoing the transjugular intrahepatic portosystemic shunt (TIPS) procedure as a tool to predict survival.[19] In 2002, *UNOS* adapted the MELD for use in predicting the 3-month mortality of patients awaiting liver transplant. Switching from CTP to MELD score decreased mortality on the waiting list 15% and wait time from 656 to 300 days.[16] In the study conducted by Ahmad, Downey, Akoad, and Cacciarelli (2007), they found that Veterans were transplanted faster after switching to MELD score for listing, and there was an increase in prioritization of sicker patients for transplant on the waiting list.[20] The drastic improvement in wait time and decreased mortality on the waiting list, is why MELD scores are now seen as superior to CTP in ESLD patients.

One reason that MELD score is favored for transplant listing is that objective data, instead of subjective data like that used in CTP is used to create the score. A score from 6-40 is used to rate the severity of illness. This is calculated based on bilirubin, prothrombin time, and creatinine lab values.[16, 21] These scores can vary as patient's liver function improves or worsens. *UNOS* uses this MELD score to prioritize organs to sicker patients. The higher the score, the more likely a patient is to be transplanted. According to Leise et al. (2011), a MELD score ≥ 15 has a favorable benefit-risk ratio for transplant and patients with a MELD > 10 should be referred for liver transplant. While the MELD score has been shown to decrease liver transplant wait time and improved mortality while waiting on the list, there are still drawbacks to the scoring system. One of the major drawbacks of the score, is the missing components of nutritional and functional

status.[22] With malnutrition being so widespread in this patient population, it is important to determine how malnutrition and MELD are related as a potential indicator for mortality in ESLD patients waiting for transplant. Limited research with a broad array of malnutrition assessment tools makes consistent evaluation difficult. One aspect of this study is to find if there is a correlation between MELD score and degree of malnutrition in ESLD patients using the recently developed NFPE.

Malnutrition in Liver Disease

Malnutrition in liver disease is extremely common due to many factors. According to Strasser & Vidot (2011), malnutrition may be prevalent “in 65-90% of patients with cirrhosis, and in up to 100% in patients waiting for liver transplantation.” Malnutrition in ESLD patients has been shown to further complicate their health, by increasing their risk of developing infections, ascites, hepatorenal syndrome, and hepatic encephalopathy.[9, 14] Understanding the mechanisms and causes of the development of malnutrition in cirrhosis patients is key in their prevention and diagnosis.

Malnutrition in ESLD patients is recognized as a form of undernutrition or inadequate intake of nutrients, which can be influenced by a variety of factors. Often, resulting in muscle and fat loss, nutrient deficiencies, and poor outcomes. Those with ESLD have common nutrition-related side effects that include decreased appetite, early satiety due to ascites, abdominal pain with possible nausea and bloating caused by decreased gastric motility of indigestion, and impaired absorption secondary to portal hypertension and cholestatic liver disease.[10, 17] Impaired absorption from liver disease prevents the body from completely absorbing nutrients or foods ingested or decreases the

ability to use the nutrients consumed as adequately as the body should. These patients also have increased calorie and protein needs due to their hypermetabolic state.[17]

The hypermetabolic state in ESLD, as a result of chronic inflammation, promotes the breakdown of proteins and causes an increase in energy expenditure.[17] The release of pro-inflammatory cytokines and alcohol intake leads to a hypermetabolic state resulting in poor appetite and anorexia.[9, 17] Anorexia, hypermetabolism, and nutrition-related side effects from liver disease are important components in the development of malnutrition.

Patients with ESLD are often prescribed different diets based on their diagnosis, weight, presence of decompensation, and level of muscle and fat loss. These diets are tailored for specific patient needs to help with symptom management and to prevent future side effects as the liver disease progresses. A low sodium, high protein diet is the general recommendation for liver disease patients to reduce ascites/edema development and prevent protein catabolism or breakdown.[10] As ascites increases or appetite decreases, patients are recommended to eat small, frequent meals and include a bedtime snack to increase calorie and protein intake, thus preventing long periods of fasting. Patients with a diagnosis of NASH or NAFLD are recommended to lose weight, while consuming adequate amounts of protein due to the catabolic state of their cirrhosis.[10] Adhering to these diets can be challenging for patients, and may play a role in the development of malnutrition.

Nutrition-related side effects and hypermetabolism, are not the only factors that drive a patient's malnutrition. The nature of the recommended diet for patients with cirrhosis itself can also make it difficult to meet nutritional goals. Maintaining adequate

nutrition while following a low sodium diet is especially difficult for ESLD patients.[14] Decreased palatability of food without salt and limited number of food options that are high in calories and protein but low in sodium can make it difficult for patients to maintain a satisfactory nutritional status, especially without the help of nutrition expert. A decreased intake of foods and impaired absorption may lead to micronutrient deficiencies such as zinc and magnesium, which can lead to taste changes (metallic, foul, rancid) and further decrease their intake.[9]

It is also still commonplace for practitioners to recommend patients follow a low protein diet for encephalopathy prevention, even though this was found to be inaccurate, and can be detrimental to a patient's nutritional status.[14, 23] In a randomized study conducted by Cordoba et al. in 2004, there was no difference seen in development and course of encephalopathy between normal protein and low protein diet groups. Furthermore, higher protein catabolism was seen in the patients on the low protein diet, providing further evidence of why protein should not be restricted in this population.[24] Even with evidence to the contrary, many clinicians still recommend cirrhotic patients follow a low-protein diet, either from misinformation or lack of knowledge surrounding current research, further complicating their health.

Protein needs are high in ESLD patients. Their hypermetabolic state leads to an increased breakdown of protein, while complications from cirrhosis can lead to increased protein losses in ascites, during paracentesis, and in blood loss from varices.[10, 17] The decrease in liver function itself, can also lead to decreased protein stores. Cirrhotic livers produce an insufficient amount of protein and have reduced capacity to store proteins in the liver. A continual decreased intake of protein in liver disease, can drive the body into

a metabolic state comparable to starvation.[10, 14] Even an overnight fast without protein can throw the body into this “starvation” mode due to the cirrhotic liver’s decreased glycogen reserves. These decreased glycogen reserves cause the body to create energy through gluconeogenesis and lipolysis.[14]

When the body uses these alternate sources of fuel, amino acids are pulled from the muscle for gluconeogenesis, and fat stores are used for lipolysis.[17] This leads to muscle wasting and fat loss that is commonly seen in end stage cirrhotic patients. The presence of decompensation also increases the risk of developing malnutrition in liver disease patients.[10] The nutrition-related side effects we commonly see in these patients, the decreased function of the liver, inability to meet nutritional needs from decreased appetite and dietary restrictions, and the high calorie and protein needs all contribute to the weight loss, muscle loss, and fat loss seen in ESLD patients. This contributes to, an increased risk of developing malnutrition.

Previous studies have used different methods to assess the degree of malnutrition in liver patients. The Subjective Global Assessment (SGA) and anthropometric measures such as BMI and weight loss/gain, mid-arm muscle circumference (MAMC), mid-arm circumference (MAC), triceps skin fold (TSF), hand grip strength with dynamometer, and blood protein levels are all common tools that have been used to assess the degree of malnutrition in liver patients.[10, 17] Anthropometrics such as BMI and weight loss/gain is especially hard to use as an evaluator of malnutrition due to the large volume of ascites that is typically found in ESLD patients. NASH/NAFLD patients are typically obese and signs of muscle loss can be masked.[9, 10] Merli et al. (2011) and Johnson et al. (2013) discussed how measuring protein stores/levels, such as albumin and prealbumin as

indicators of nutritional status, have been used in previous studies but can be unreliable in ESLD patients. This is due to the already decreased production of proteins in the liver and their response to inflammation. While protein stores, BMI, and weight changes have limitations when assessing malnutrition in liver disease patients, there are some tools that are fairly useful and can be used in this population.

The SGA, MAMC, MAC, TSF, and hand grip strength have been relatively successful in previous studies for evaluating malnutrition in liver disease patients, but still have limitations.[9, 14, 15, 17] MAMC, MAC, and TSF can be good tools to use in ESLD because they are not affected by ascites and edema, but there could be inter- and intra-observer variability if they are not properly trained. Alveres-Da Silva & Silveira (2005), compared hand grip strength, SGA, and nutritional index derived from lab values and TSF, and determined that hand grip strength can be a reliable measure, but none of these assessment tools can be considered a “gold standard” alone. A simple, cheap, and more effective method needs to be developed. The purpose of this study is to explore newly developed malnutrition assessment tools in the search of this “gold standard”.

Lumbar Index and Muscle Loss

Sarcopenia, or loss of muscle mass, is frequently an issue in chronic illness such as ESLD. Muscle loss is often the result of poor nutritional status or malnutrition, a common characteristic in cirrhosis patients, and is often used to assess the severity of malnutrition. Measuring nutritional status is often unreliable or subjective. Therefore, research into measuring sarcopenia with objective tools, such as CT scans, has become of

recent interest. These tools are especially useful in this patient population due to ascites and fat mass potentially masking evidence of muscle loss.

A study conducted by Durand et al. (2014) looked at the muscle thickness of the psoas muscle to assess for sarcopenia. This muscle is in the lumbar region of the spine and was studied at the level of the umbilicus. The psoas muscle has been shown to correlate to whole body muscle mass, and is relatively easy to see on scans, making it an ideal measure of muscle loss.[25] This study examined psoas muscle thickness in ESLD patients waiting for transplant. Decreased psoas muscle thickness were shown to be predictive of mortality, independent of MELD score, while on the waiting list. Durand et al. (2014), also found this to be true in the patients with lower MELD scores (<25) who also had refractory ascites. This is especially important because of the role of MELD and ascites in the ESLD patient. Assessing muscle loss in these patients is often difficult due to their ascites, and MELD scores do not always accurately reflect mortality risk because they lack a nutritional component. MELD scores were also shown to underestimate mortality risk in this study and refractory ascites was believed to be a component in the development of muscle loss in these patients.[25] However, there are limitations to using this tool to assess muscle loss or sarcopenia. These scans are not low in cost, they can be affected by osteoporosis or spinal fractures, and they are not as easy to frequently reassess in a patient as a MELD score. While this tool is not perfect, it is very useful as an objective tool for measuring sarcopenia in ESLD patients.

In the study conducted by Montano-Loza et al. (2012), sarcopenia was studied as a predictor of mortality compared to MELD scores. The patients used in this study were being evaluated for transplant. All patients underwent a routine CT scan as part of their

evaluation. The third lumbar (L3) vertebrae was studied on these scans for sarcopenia using a skeletal muscle index (SMI).[22] The results of this study showed no correlation between sarcopenia and MELD, CTP, or albumin levels in these patients. A higher mortality rate was found in the patients with sarcopenia and was related to sepsis-related death instead of death from liver failure. When using tools such as MELD/CTP as sole indicators of mortality in ESLD patients, without including nutritional or functional status, there may be an underestimation in a patient's risk of mortality.[22] Montano-Loza et al. (2012) notes that CT scans are considered the "gold standard" for diagnosing sarcopenia, but including measurements of muscle function, such as hand-grip strength, should be used in the assessment of sarcopenia. These results demonstrate how sarcopenia can be used to predict mortality. In addition, sarcopenia could be beneficial in determining MELD scores, which could potentially lead to a more accurate reflection of mortality risk in ESLD patients.

In a recent study conducted in the U.K., sarcopenia and malnutrition were assessed and compared to MELD scores in ESLD patients to predict post-transplant outcomes. Nutritional status and degree of malnutrition were assessed using the validated Royal Free Hospital Global Assessment (RFH-GA), a tool that is similar to the SGA, that is used frequently in the U.S. This assessment includes subjective and objective measures including MAC, TSF, hand grip strength, BMI, and dietary intake.[8] CT scans were taken to evaluate L3, including the psoas muscle, and were used in the L3-psoas muscle index (L3-PMI) as a means of comparison. L3-PMI was found to be "positively correlated with dry weight, BMI, MAC, TSF, handgrip strength, RFH-GA, and MELD" in this study. However, there was a wide variance in L3-PMI in patients with similar

MELD scores.[8] This shows how nutritional status is not reflected in MELD scores, but can be an important predictor of mortality and outcomes. In addition, there was no correlation found between MELD and RFH-GA scores. Pre-transplant RFH-GA was associated with worse outcomes and survival, independent of MELD scores.[8] Kalafetelia et al. (2016) also found that malnutrition and sarcopenia were independent predictors for post-transplant complications, such as prolonged mechanical ventilation, longer LOS in ICU and hospital, increased rate of infections, and mortality 1-year after transplant. RFH-GA even had a stronger correlation with determining post-transplant outcomes, than L3-PMI.[8] This shows the importance of using nutritional assessments in predicting post-transplant complications. Using valid nutrition assessments such as RFH-GA, with objective tools used to determine muscle loss such as L3-PMI, can improve the mortality prediction of MELD scores in ESLD patients. An easy, reliable, and valid tool that encompasses both of these aspects, needs to be developed for use in calculating MELD scores to better predict 3-month mortality in cirrhosis patients waiting for transplant.[8]

Recognizing sarcopenia in ESLD patients, is important for their course of treatment and reduction of complications associated with malnutrition. However, CT scans are extremely expensive, are not feasible for all populations, are not practical to use as a frequent tool to monitor sarcopenia, and may be inferior to an overall nutritional status, especially as a predictor of post-transplant outcomes. The need for a valid, reliable, all-encompassing tool, is important for prevention and reduction of transplant outcomes in ESLD patients.

Nutrition Focused Physical Exams

In 2012, AND and ASPEN formed an international work group assisted by the European Society for Parenteral and Enteral Nutrition (ESPEN) to standardize markers and characteristics of malnutrition. AND and ASPEN later released a consensus statement for identifying and assessing malnutrition.[12] Today, there is no “gold standard” for identifying malnutrition in the adult patient population. The resources we have vary widely. Often, they are subjective. This leads to intra-observer variability. They may also not be specific enough to use between different adult population groups. When AND and ASPEN released their updated characteristics to detect and diagnose malnutrition, inflammation, illness vs. environment, and physical characteristics were added to aid in diagnosis. According to White et al. (2012), to identify malnutrition, two of the six proposed characteristics need to be present and the characteristics can be distinguished between non-severe and severe. These characteristics are located below in Table 2. These characteristics should be assessed upon admission and routinely throughout patient’s admission/care and should be used to aid physician in diagnosis of malnutrition. These characteristics have not been validated and will be updated as research is conducted.

Table 2: NFPE: Clinical Characteristics to Identify and Support a Diagnosis of Malnutrition[26]

Clinical Characteristic	Malnutrition in the context of acute illness or injury		Malnutrition in the context of chronic illness		Malnutrition in the context of social or environmental circumstances							
	Non-severe (moderate) malnutrition	Severe Malnutrition	Non-severe (moderate) malnutrition	Severe Malnutrition	Non-severe (moderate) malnutrition	Severe Malnutrition						
Energy Intake	<75% of estimated energy requirement for > 7 days	< 50% of estimated energy requirement for ≥ 5 days	< 75% of estimated energy requirement for ≥ 1 month	< 75% of estimated energy intake for ≥ 1 month	< 75% of estimated energy requirement for ≥ 3 months	£ 50% of estimated energy requirement for ≥ 1 month						
Interpretation of Weight Loss	%	Time	%	Time	%	Time	%	Time	%	Time	%	Time
	1-2	1 week	>2	1 week	5	1 month	>5	1 month	>5	1 month	>5	1 month
	5	1 month	>5	1 month	7.5	3 months	>7.5	3 months	>7.5	3 months	>7.5	3 months
	7.5	3 months	>7.5	3 months	10	6 months	>10	6 months	>10	6 months	>10	6 months
					20	1 year	>20	1 year	>20	1 year	>20	1 year
Physical Findings												
Body Fat	Mild	Moderate	Mild	Severe	Mild	Severe	Mild	Severe	Mild	Severe	Mild	Severe
Muscle Mass	Mild	Moderate	Mild	Severe	Mild	Severe	Mild	Severe	Mild	Severe	Mild	Severe
Fluid Accumulation	Mild	Moderate to Severe	Mild	Severe	Mild	Severe	Mild	Severe	Mild	Severe	Mild	Severe
Reduced Grip Strength	N/A	Measurably Reduced	N/A	Measurably Reduced	N/A	Measurably Reduced	N/A	Measurably Reduced	N/A	Measurably Reduced	N/A	Measurably Reduced

Since the consensus statement was released, there has been very little research using the newly defined malnutrition characteristics. In 2016, Mulasi et al. conducted a study using the new consensus criteria in head and neck cancer patients who were undergoing cancer treatment. They compared the criteria to other nutrition tools such as the Subjective Global Assessment (SGA) and bioimpedance methodology to assess for muscle loss. The bioimpedance methodology is relatively new and is still being studied for validity.[13] The individuals in this study were assessed with the consensus characteristics, SGA, and bioimpedance before chemoradiotherapy (CRT) treatment, at three weeks after beginning treatment, during the last week of treatment, and one and three months after completion of treatment. There was no significant difference found

between diagnosis of malnutrition between consensus criteria and SGA. They found good sensitivity (94%), and moderate specificity (43%). However, there were limitations to this study. There was a very small population in this study (n=19), it was a single-center study, and only one participant was female. Many of the components of the NFPE were validated through other nutrition tools in this study. More research needs to be conducted using validated tools to compare to the physical findings section of the NFPE.

Conclusion

The purpose of this study is to address the gap in knowledge concerning the Nutrition Focused Physical Exam (NFPE) such as limited research using the NFPE and its use in ESLD patients. Additionally, the study will test the validity and reliability of the NFPE by comparing current, valid, objective tools such as PG-SGA, TST, MAC, and the Lumbar Index/Psoas Muscle identified through CT scans. Each of these tools will be used to diagnose malnutrition and will be compared against the NFPE results. In addition, this tool will be used to identify and assess the severity of malnutrition in ESLD patients being evaluated for transplant. The findings of this study will examine the NFPE to determine if it's a valid tool for assessing malnutrition in ESLD patients.

Chapter 3: Methods

Study Design:

This was a human based, non-intervention, cross-sectional study, for the assessment of incidence and severity of malnutrition in end stage liver disease patients being evaluated for transplant. Malnutrition was determined using multiple tools including the Subjective Global Assessment (SGA), mid-arm circumference (MAC), triceps skin fold (TSF), Lumbar Index, Psoas muscle mass, and the Nutrition Focused Physical Exam (NFPE). These results will be compared to liver disease diagnosis and model for end stage liver disease (MELD) score. After receiving approval by the University of Kentucky's IRB panel, the study was conducted. The study is summarized and described below.

1. The research team obtained consent from patients who are deemed appropriate for transplant evaluation.
2. The liver transplant team's scheduling coordinators randomly assigned the liver transplant dietitian evaluations between the Registered Dietitians (RD) in the clinic.
3. A RD completed all patient assessments during their initial consult, including NFPE, SGA, MAC, and TST.
4. Following a CT scan completed during the patient's initial clinic evaluation, the research team completed Lumbar Index and Psoas Muscle Area assessments.
5. The research team maintained contact with the patients' nurse coordinators for three-month endpoints, such as incidence of death, listing for transplant, transplant, development of decompensation, or hospital admissions.

Subject Recruitment:

Patients were referred to clinic for transplant evaluation from outside providers. Potential patients were identified from their regularly scheduled clinic visit for liver transplant evaluation. After a full discussion of the research to be conducted, consent was obtained by the research team before data was collected for the study. Normal protocol was followed with all patients regardless of their participation in the study.

Patients in this study were required to have end stage liver disease and deemed appropriate for liver transplant evaluation. They also had to attend a nutrition evaluation as part of the standard evaluation process. Patients were excluded from this study if a patient did not complete the necessary consent form, attend nutritional evaluation as part of their standard evaluation process, or wish to be part of the research study.

Measurements and Procedures:

All research assessments and procedures were taken during patient's regularly scheduled clinic visit with a RD for liver transplant evaluation. Medical history, MELD, medications, and demographics were taken from patient's charts or during the visit.

Research assessments and procedures are listed below.

- 1. Nutrition Focused Physical Exam (NFPE):** The RD administered a physical exam to assess for muscle loss, fat loss, energy intake, weight loss, fluid accumulation (related to malnutrition), and hand grip strength. Muscle loss and fat loss are determined using the *Nutrition Focused Physical Exam Pocket Guide* (2015) guidelines and RD's clinical judgement. Two of the six

characteristics are needed to make a diagnosis of malnutrition, and can be used to determine severe vs. non-severe malnutrition.[26] Patients were sitting upright during assessment and a RD measured for fat loss/muscle in various parts of the body by gentle touch and manipulation. If any areas of body needed for assessment were unable to be accessed due to clothing, injury, edema, or pain, the RD did not assess the area. Energy intake was evaluated by asking questions on appetite, average % of meals consumed, and duration that patient has been eating in this manner. Weight loss was calculated based on dry weights (if available) per patient or by chart review. Hand grip strength was assessed using a dynamometer in both hands. Patient squeezed the dynamometer with as much strength as possible in each hand, being careful to only squeeze once for the measurement. Each measurement was recorded to the nearest pound or kilogram.

- 2. Patient Generated-Subjective Global Assessment (PG-SGA):** The PG-SGA is a validated tool that expands on the original SGA and was chosen over the SGA due to the more extensive range of nutrition symptoms and physical assessment. The PG-SGA assessment data was completed by the RD with the help of the patient. Data in the assessment includes: weight changes, dietary intake, gastrointestinal symptoms, functional capacity, physical examination of fat and muscle loss, edema related to malnutrition, and ascites related to malnutrition. The physical examination of fat and muscle loss is very similar to the NFPE, including gentle touch and manipulation of the same body areas, and did not need to be repeated. Results from the physical exam were used for

both NFPE and PG-SGA. If any areas of body needed for assessment were unable to be accessed due to clothing, injury, edema, or pain, the RD did not assess the area.

3. **Triceps Skin Fold (TSF):** The RD located the site midway between the acromial (shoulder) and elbow. The skin fold was grasped as a vertical fold on the posterior midline and pulled it away from the muscle. Millimeters of the skin fold were assessed. If measurements were below the “normal” range, patients were considered to have malnutrition. The following ranges were considered normal. [27]
 - Male: 12.5-7.3 mm
 - Female: 16.5-9.9 mm
4. **Mid Arm Circumference (MAC):** The circumference was measured at the mid-point between the shoulder and the elbow. The circumference was assessed for muscle mass. If measurements were below the “normal” range, patients were considered to have malnutrition. The following ranges were considered normal.[27]
 - Male: 29.3-17.5 cm
 - Female: 28.5-17.1 cm
5. **Lumbar Index:** Patients being evaluated for liver transplant received a CT scan as part of their transplant evaluation. The Lumbar Index is total muscle surface area at L3 and was evaluated for muscle loss. If measurements were below the “normal” range, patients were considered to have sarcopenia. The following ranges were considered normal.[5]

- Males: $\leq 52.4 \text{ cm}^2/\text{m}^2$
- Females: $\leq 38.5 \text{ cm}^2/\text{m}^2$

6. Psoas Muscle Area: Patients being evaluated for liver transplant received a CT scan as part of their transplant evaluation. Psoas muscle surface area at L3 was evaluated for muscle loss. If measurements were below the “normal” range, patients were considered to have sarcopenia. The following ranges were considered normal.

- Males: $< 545 \text{ mm}^2/\text{m}^2$
- Females: $< 385 \text{ mm}^2/\text{m}^2$

7. Additional data collected: The RD asked additional questions and collected data on whether the patient is consuming protein supplements at home and if they have had previous diet education pertaining to their liver disease. Albumin levels were also recorded and drawn as part of the patient’s routine lab work for their transplant evaluation.

Analysis:

Results of the nutrition assessment and radiological data were analyzed by a member of the research team. Data was analyzed by the research team using SPSS software version 24 (IBM Inc., Armonk, NY, USA). Data was assessed for normal distribution, incomplete data, and inaccurate data. Means were compared using the Mann-Whitney Test. A Spearman’s rho test was conducted to assess for correlation between the different malnutrition tools. A Fisher’s Exact test was used to compare malnutrition to patient characteristics such as disease, decompensation, and outcomes

such as decompensation, listing for transplant, hospital admission, transplant, and death.

An additional logistic regression test was ran to investigate the relationship between hospital admissions and malnutrition. A p-value of 0.05 or less was determined to be significant.

Chapter 4:

Results

Thirty-one patients undergoing liver transplant evaluation and who met inclusion criteria, participated in this research study. The majority of the participants were male (77%) and caucasian (96.8%). The median age was 54 years old, with the youngest participant at 29 years old and the oldest 69 years old. The median BMI was 28.8, with a range of 15.8-43.9. The median MELD score was (18± 6.63) and albumin level (g/dL) was (2.7±1.3). These patient characteristics are shown below in Table 3.

Table 3: Age, Sex, Race, MELD, BMI, and Albumin Level Characteristics of Study

Sample

	<i>n</i>	%	Median	Std. Deviation	Min	Max
Age	-	-	54	9.9	29	69
Sex	Male	24	77.4%	-	-	-
	Female	7	22.6%	-	-	-
Race	Caucasian	30	96.8%	-	-	-
	African-American	1	3.2%	-	-	-
MELD	-	-	18	6.63	7	34
BMI	-	-	28.8	6.62	15.8	43.9
Albumin (g/dL)	-	-	2.7	0.73	1.3	4.0

Table 4: Diagnosis and Decompensation in Study Sample

	<i>n</i>	%
Diagnosis		
Autoimmune Hepatitis	1	3.2%
Cryptogenic	3	9.7%
Alcohol	15	48.4%
Hepatitis C	2	6.4%
NASH	10	32.3%
Secondary Diagnosis		
None	27	87.1%
HCC	3	9.7%
Autoimmune Hepatitis	1	3.2%
Decompensation		
Ascites	30	96.8%
Esophageal Varices	22	71%
Hepatic Encephalopathy	19	61.3%
Large Volume Paracentesis	21	67.8%
Hepatorenal Syndrome	3	9.7%
Spontaneous Bacterial Peritonitis	3	9.7%
Acute Kidney Injury	1	3.2%
Hepatopulmonary Syndrome	1	3.2%
Chronic Kidney Disease	5	16.1%

The majority of these patients either had a diagnosis of alcohol related cirrhosis (48.4%) or NASH cirrhosis (32.3%). Only four patients had a secondary diagnosis such as HCC ($n=3$) or autoimmune hepatitis ($n=1$). Almost every single patient had a history of ascites ($n=30$), and more than half of all patients had history of esophageal varices, hepatic encephalopathy, or large volume paracentesis. Nearly one-third of the patients had some form of cirrhosis-related kidney dysfunction such as hepatorenal syndrome (HRS), acute kidney injury (AKI), or chronic kidney disease (CKD). Table 4 contains these and further diagnoses.

When examining the association between MELD score and cirrhosis diagnosis, there was a higher median MELD score seen in cryptogenic cirrhosis patients than alcohol (ETOH) and NASH patients, but there was a wide variability in MELD scores in each cirrhosis group. Autoimmune hepatitis and Hepatitis C patient groups were excluded

from this analysis due to their small number size ($n=1$ and $n=2$, respectively). The results are show in Figure 1 below.

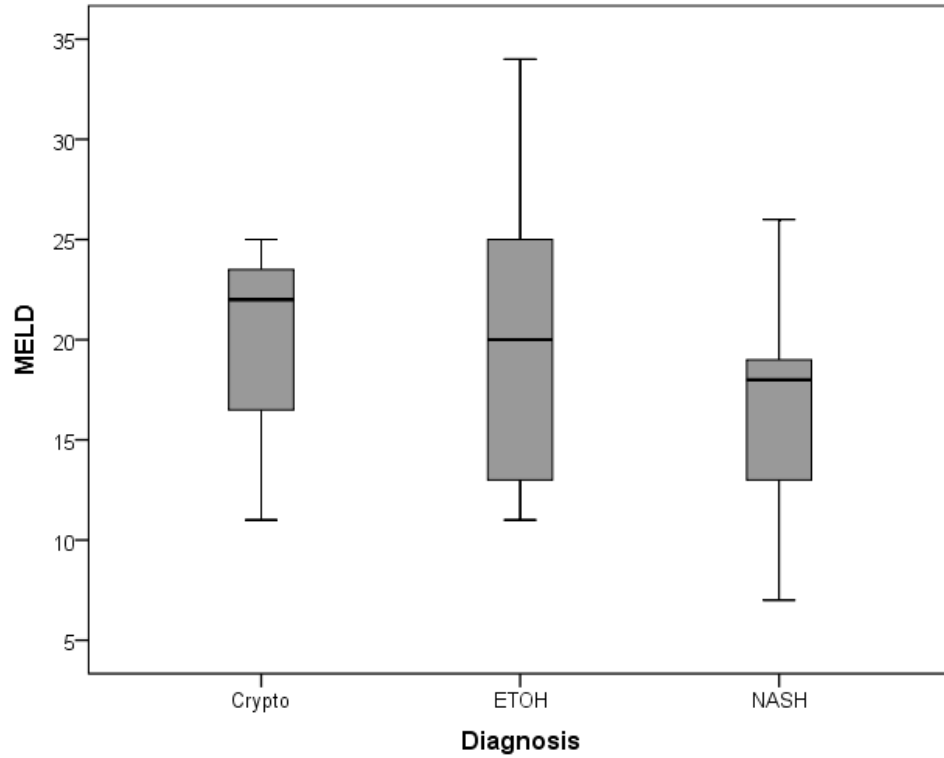


Figure 1: MELD Score and Cirrhosis Diagnosis

When examining data on nutrition related variables, only (32.3%) of the patients endorsed “good” appetite, while the rest noted fair, poor, or no appetite at all. However, over half of all patients (67.8%) stated that they had some sort of weight loss prior to evaluation. The median percent body weight loss was ($10.8\% \pm 9.64$), with the highest amount of percent weight loss at (32.6%). In addition, only 12 patients (38.7%) indicated that they consumed some sort of protein supplement on a regular basis. Furthermore, roughly one-third of these patients (35.5%) had never had any type of nutrition-related diet education. Table 5 shows these results.

Table 5: Nutrition Related Variables in Study Sample

Variable	<i>n</i>	%	Median	Std. Deviation	Min	Max
Appetite						
Good	10	32.3%	-	-	-	-
Fair	13	41.9%	-	-	-	-
Poor	7	22.6%	-	-	-	-
None	1	3.2%	-	-	-	-
Protein Supplement	12	38.7%	-	-	-	-
Previous Diet Education	20	64.5%	-	-	-	-
Weight Loss	21	67.8%				
% Weight Loss	-	-	10.8	9.64	0	32.6

NFPE Diagnosis of Malnutrition and Patient Characteristics:

Table 6: Comparison of NFPE Diagnosis of Malnutrition with Decompensation, Patient Outcomes, MELD score, and Albumin levels.

		NFPE Diagnosis of Malnutrition				
		No (n = 7)	Moderate (n = 12)	Severe (n = 12)	p-value	
Diagnosis	Autoimmune	0 (0.0%)	0 (0.0%)	1 (8.3%)	0.027*	
	Cryptogenic	0 (0.0%)	0 (0.0%)	3 (25.0%)		
	Alcohol	4 (57.1%)	6 (50.0%)	5 (41.7%)		
	Hepatitis C	2 (28.6%)	0 (0.0%)	0 (0.0%)		
	NASH	1 (14.3%)	6 (50.0%)	3 (25.0%)		
Decompensation	Ascites	6 (85.7%)	12 (100.0%)	12 (100.0%)	0.226	
	EV	7 (100.0%)	7 (58.3%)	8 (66.7%)	0.210	
	HE	5 (71.4%)	9 (75.0%)	5 (41.7%)	0.255	
	LVP	4 (57.1%)	8 (66.7%)	9 (75.0%)	0.884	
	HRS	1 (14.3%)	1 (8.3%)	1 (8.3%)	1.000	
	SBP	0 (0.0%)	1 (8.3%)	2 (16.7%)	0.776	
	AKI	0 (0.0%)	0 (0.0%)	1 (8.3%)	1.000	
	HP	0 (0.0%)	1 (8.3%)	0 (0.0%)	1.000	
	CKD	1 (14.3%)	0 (0.0%)	4 (33.3%)	0.082	
Outcomes	Decompensation	-	-	-	0.899	
	Listing	2 (28.6%)	4 (33.3%)	5 (41.7%)		
	Hospital Admission	1 (14.3)	6 (50.0%)	11 (91.7%)		0.002*
	Transplant	0 (0.0%)	3 (25.0%)	1 (8.3%)		0.413
	Death	0 (0.0%)	0 (0.0%)	3 (25.0%)		0.106
MELD		14.00 (13.00- 27.00)	17.00 (12.25- 19.75)	21.50 (14.25- 25.75)	0.432	
Albumin (g/dL)		2.80 (2.40- 3.60)	2.70 (2.43- 3.43)	2.15 (2.00- 3.05)	0.382	
* indicates statistically significant						

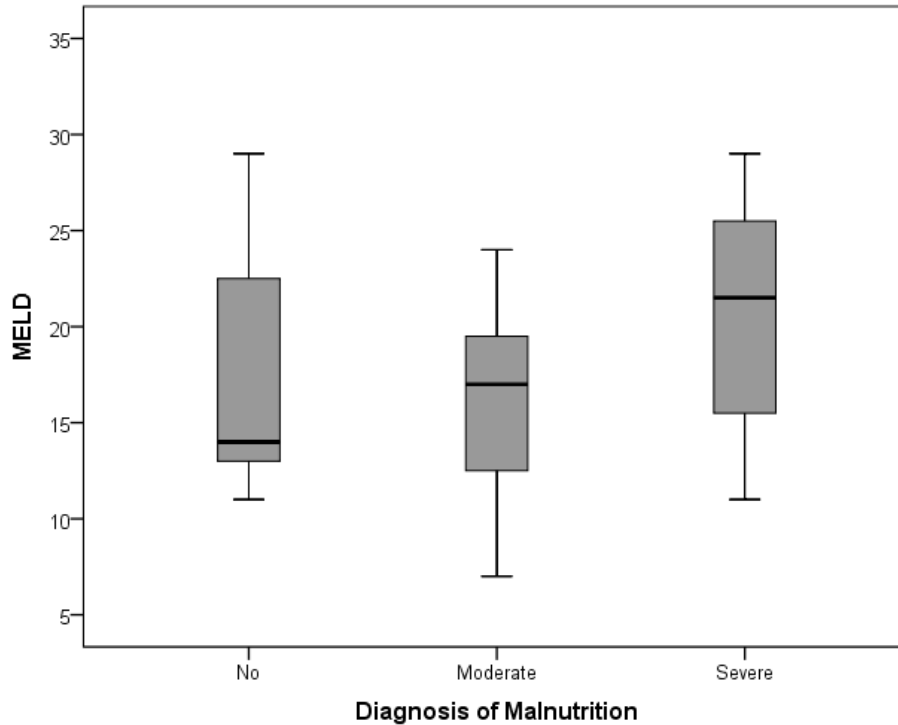


Figure 2: MELD Score and Malnutrition
(In the moderate group, the highest MELD was excluded from the plot as an outlier)

Based on the dietitian-conducted NFPE, 24 patients had a malnutrition diagnosis of moderate or severe malnutrition. The results of the NFPE were then compared to cirrhosis diagnosis, decompensation, patient outcomes, MELD score, and albumin level. As a result of the small sample size ($n=31$), a Fisher's Exact Test was used for analysis in the majority of variables. A Mann-Whitney test was used when comparing albumin and MELD scores. There was no relation between types of decompensation, MELD score, or albumin levels and malnutrition ($p > 0.05$). However, higher median MELD scores were found in those with malnutrition than those without. Median MELD score also increased with severity of malnutrition. While albumin levels were not found to be significantly associated with malnutrition, the median albumin levels were higher in the group without malnutrition compared to those with malnutrition (2.80, 2.70 and 2.15 respectively). In

addition to this, albumin levels decreased as severity of malnutrition increased (Table 6). In comparison, disease diagnosis was found to be significantly related to malnutrition ($p = 0.027$). Lastly, when comparing malnutrition to patient outcomes, only hospital admission was found to be significantly associated with malnutrition ($p = 0.002$).

Additional analyses were conducted comparing presence of malnutrition and severe malnutrition to hospital admissions due to the high level of significance found in a previous analysis. A logistic regression analysis was conducted for each, and was adjusted for age, gender, and albumin levels. The odds-ratio for hospital admission based on malnutrition and severe malnutrition were both extremely high (14.571, 18.857 respectively) and were found to both be significant ($p < 0.05$). Caution is warranted in interpreting these results, as the small sample size and increased variation, leads to wide confidence intervals. Table 7 and 8 reflect these results.

Table 7: Hospital Admission and Malnutrition

Binary Logistic Regression on Hospital Admission							
	B	S.E.	Wald	Sig.	OR	95% C.I. for OR	
						Lower	Upper
Malnutrition	2.679	1.170	5.245	.022*	14.571	1.472	144.280
Constant	-1.792	1.080	2.752	.097	.167		
The variables age, gender and ALB were eliminated from the model after model selection. *Indicates statistical significance							

Table 8: Hospital Admission and Severe Malnutrition

Binary Logistic Regression on Hospital Admission							
	B	S.E.	Wald	Sig.	OR	95% C.I. for OR	
						Lower	Upper
Severe Malnutrition	2.937	1.148	6.549	.010	18.857	1.989	178.796
Constant	-.539	.476	1.284	.257	.583		
The variables age, gender and ALB were eliminated from the model after model selection. *Indicates statistical significance							

Comparison of NFPE to Additional Assessment Tools

Table 9: Malnutrition Compared to Additional Tools

Correlation		Malnutrition		
NFPE Results		N (n = 7)	Y (n = 21)*	Spearman's rho
Based on TPA		2 (28.6%)	12 (57.1%)	0.247
Based on L3 SMI		6 (85.7%)	19 (90.5%)	0.067
Less than 25% of L3		0 (0.0%)	7 (33.3%)	0.333
		N (n = 7)	Y (n = 24)	Spearman's rho
SGA stage	A	5 (71.4%)	0 (0.0%)	0.669
	B	2 (28.6%)	13 (54.2%)	
	C	0 (0.0%)	11 (45.8%)	
TSF-I		1 (14.3%)	5 (20.8%)	0.069
MAC-I		0 (0.00%)	0 (0.00%)	-
*3-missing CT L3 SMI represents Lumbar Index				

Table 10: Severe Malnutrition Compared to Additional Tools

Correlation		Severe Malnutrition		
NFPE Results		N (n = 19)	Y (n = 9)*	Spearman's rho
Based on TPA		7 (36.8%)	7 (77.8%)	0.382
Based on L3 SMI		16 (84.2%)	9 (100.0%)	0.238
Less than 25% of L3		2 (10.5%)	5 (55.6%)	0.486
		N (n = 7)	Y (n = 24)	Spearman's rho
SGA stage	A	5 (26.3%)	0 (0.0%)	0.760
	B	13 (68.4%)	2 (16.7%)	
	C	1 (5.3%)	10 (83.3%)	
TSF-I		3 (15.8%)	3 (25.0%)	0.114
MAC-I		0 (0.00%)	0 (0.00%)	-
*3-missing CT L3 SMI represents Lumbar Index				

In addition to the NFPE, multiple additional tools were used to assess malnutrition in this study for comparison, including the Lumbar Index, psoas muscle area, PG-SGA, TSF, and MAC. Three participants did not have a CT scan as part of their evaluation, and their data was excluded for the CT/NFPE comparison portion of the analysis. After using the CT scans to assess for sarcopenia, fourteen patients were shown to have sarcopenia based on total psoas muscle area (TPA) and twenty-five participants

were found to have sarcopenia using the Lumbar Index. There were six participants who had a TSF below normal limits, which was considered malnourished. All participants had a MAC that was found to be within normal limits, and therefore considered without malnutrition. Out of the thirty-one participants, twenty-six participants were found to have some degree of malnutrition (Stage B or C) based off of the PG-SGA, and eleven of those participants were found to have severe malnutrition (Stage C). Tables 9 and 10 shows how each of the malnutrition assessment tools compared to the NFPE results.

A Spearman's rho test (r_s) was used to assess strength and direction of correlation between each of these tools and the NFPE. A diagnosis of malnutrition versus no malnutrition using the NFPE, was compared against whether or not malnutrition was found using the TPA, L3 SMI, TSF, PG-SGA, and MAC. An additional analysis was run comparing patients who had severe malnutrition using the NFPE, to the lowest quartile measurements of TPA, L3 SMI, and TSF and Stage C of the PG-SGA. There was a strong, positive correlation ($r_s = 0.669$) between NFPE malnutrition and PG-SGA classified malnutrition. This correlation was increased ($r_s = 0.760$) when comparing severe malnutrition using the NFPE to PG-SGA classified severe malnutrition (Stage C). When comparing TPA and L3 SMI to NFPE classified malnutrition, there was a very weak correlation between each test, except when comparing the bottom 25% quartile of the L3 SMI to severe malnutrition using the NFPE. This resulted in a moderate correlation ($r_s = 0.486$) between the two measures. An additional test was completed to compare L3 SMI measurements to NFPE malnutrition diagnosis. Table 11 reflects these results. There was a significant ($p = 0.027$) association between L3 SMI and NFPE

diagnosis of malnutrition. However, there was no correlation seen between L3 SMI and severe malnutrition.

Table 11: L3 SMI and NFPE Malnutrition Diagnosis

L3 SMI (cm²/m²)			
Malnutrition			
	N (n = 7)	Y (n = 21)†	p-value
Mean ± S.D.	45.01 ± 10.25	34.29 ± 10.23	0.027*
Median (Q1, Q3)	46.72 (36.82, 48.99)	35.80 (29.78, 39.83)	0.385
Severe Malnutrition			
	N (n = 19)	Y (n = 9)†	p-value
Mean ± S.D.	38.91 ± 8.48	32.87 ± 15.04	0.357
Median (Q1, Q3)	37.57 (32.29, 43.16)	31.46 (24.73, 45.69)	1.000
†3-missing CT			

Chapter 5: Discussion

Malnutrition is a very common medical condition that is seen in a variety of settings. It can greatly affect patient outcomes and is often hard to diagnosis and assess. This is mainly due to the wide variety of methods and techniques available, many of which are often unreliable or inconsistent.[12] In 2012, the NFPE was developed for dietitians to aid physicians in a nutrition-based diagnosis of malnutrition. Since its development, there have been very few research studies using the NFPE.[13]

One particular setting that assessment of malnutrition is increasingly difficult, is in patients with cirrhosis or ESLD. These patients are at high risk for developing malnutrition due to a variety of disease-related side effects such as ascites, nutritional deficiencies, and increased metabolic demand. The quest for a reliable and valid tool for assessing malnutrition in ESLD, is an ever-growing topic in research.[4-10, 15, 17, 18, 22, 25, 28, 29] The purpose of this study was to assess malnutrition in ESLD patients being evaluated for transplant. It is important to assess malnutrition in this patient population because of the effect malnutrition has on mortality and pre/post-transplant outcomes. ESLD patients have an increased of developing malnutrition and aggressive nutrition intervention can greatly affect patient outcomes. This study assessed malnutrition using a variety of tools and methods such as NFPE, Lumbar Index, TPA, MAC, and TSF. The NFPE is advantageous over other tools because of how simple, quick, and inexpensive the tool is compared to others and can be easily repeated. In addition, the NFPE can be especially beneficial in this patient population since other previously studied tools either were too expensive or unreliable in ESLD patients.

Malnutrition was also examined in its relation to ESLD diagnosis, MELD, decompensation, patient outcomes, and lab values.

Malnutrition Prevalence

Malnutrition was found in 77% of this patient population using the NFPE, in comparison to 84% using PG-SGA, 19.3% using TSF, 50% using TPA, and 89.3% using L3 SMI. These results reflect the high incidence of malnutrition in this patient population and the wide variability in malnutrition diagnosis, mainly due to the lack of a standardized, all-encompassing tool. However, many of these tools were correlated with each other in determining malnutrition. These relationships will be further discussed in the following sections.

Appetite changes and weight loss was also found in the majority of participants. Both are risks factor for developing malnutrition. In comparison, less than half of these patients were using protein supplements to supplement their decreased intake, and over a quarter of this population had never had a previous diet education. This is alarming considering the overwhelming occurrence of malnutrition in this patient population and the prevalence of factors like decompensation that can greatly affect nutritional intake. Especially since poor nutritional status is linked to poor outcomes before and after transplant.[4-6, 8, 9] This indicates a need for earlier nutrition intervention to assist with symptom management and proper nutrition therapy for ESLD patients.

Malnutrition and Liver Disease

The relationship between the NFPE diagnosed malnutrition and ESLD diagnosis, decompensation, and patient outcomes was also examined in this study. ESLD diagnosis was found to be significantly associated with malnutrition diagnosis in this patient population. There were not enough participants to determine which diagnosis was linked to an increased risk of malnutrition. A larger sample size may further examine if certain ESLD diagnoses increase the risk of developing malnutrition.

Although there was a significant association between ESLD diagnosis and malnutrition, there were no decompensation characteristics that were linked to development of malnutrition. However, a larger sample size may find an association between specific decompensation symptoms and incidence of malnutrition.

Additionally, albumin levels, a common tool used to previously diagnose malnutrition, had no significant correlation with the NFPE malnutrition diagnosis. While median albumin levels were found to be higher in non-malnourished patients, there was still a wide variation in albumin levels for each malnutrition category. Albumin is not a reliable indicator of nutritional status, which is also reflected in these results.

Similar to the albumin results, higher median MELD scores were shown in those with malnutrition versus those without. This could reflect the increased risk of developing malnutrition as ESLD worsens or the possibility that the presence of malnutrition worsens ESLD. While MELD has been found to be a good tool to predict mortality in ESLD patients, it does not reflect additional factors that affect mortality such as malnutrition. Possible future studies using a MELD score with a malnutrition component should be considered.

Malnutrition using the NFPE was also compared to patient outcomes such as transplant listing, decompensation, hospital admission, transplant, and death. Only hospital admissions were found to be correlated with a malnutrition diagnosis. There was also an extremely high odds-ratio for hospital admission, which increased with the severity of malnutrition. Patients with a diagnosis of malnutrition were roughly 1,400% more likely to be admitted to the hospital, and roughly 1,900% more likely with a diagnosis of severe malnutrition. However, due to the small patient population, this data is limiting. More research will need to be conducted to evaluate this relationship. If similar results are found in future studies, this could signify the importance of an earlier nutrition intervention, including the RD screening for malnutrition and more aggressive nutrition care, to prevent negative patient outcomes such as hospital admissions.

PG-SGA

Previous studies have used SGA to assess malnutrition in cirrhosis patients with positive results. While the SGA and PG-SGA are not the exact same tool, the PG-SGA is an expanded version of the SGA. In this study, the NFPE was found to be strongly correlated with the PG-SGA in both diagnoses of malnutrition and severity of malnutrition. In addition, the PG-SGA in this study, provided similar results to those that were seen with the SGA in cirrhotic patients in other studies. [6, 15] In these previous studies, malnutrition determined by the SGA, was also associated with poor patient outcomes. This study found similar results when examining the role of NFPE identified malnutrition and hospital admissions.

These results strengthen the NFPE as a valid tool to assess malnutrition in ESLD patients. Additionally, the NFPE is a quick, simple tool compared to the PG-SGA and can be conducted in a variety of settings. The PG-SGA relies heavily on patient recall which could possibly skew results and could be inaccurate depending on literacy level or patient understanding. In comparison, the NFPE is completed by a trained RD and patient recall is only a small portion of the exam. The NFPE also relies heavily on the physical exam, while the physical exam is only a small part of the PG-SGA. More research will need to be conducted with the NFPE to study its validity.

TSF and MAC

TSF and MAC are standardized tools that have been used to assess malnutrition in many studies involving cirrhotic patients. In this study, there were no patients that had a MAC below normal limits to indicate malnutrition. Malnutrition was indicated in six patients using TSF parameters. Both of these tools under-diagnosed malnutrition compared to the NFPE and PG-SGA. This indicates that the TSF and MAC may not be reliable tools to assess malnutrition in ESLD patients. The majority of this population were overweight or obese, likely skewing the effectiveness of these tools. A larger sample size may collaborate these results.

L3 SMI and TPA

Overall, sarcopenia was found in the majority of the patients in this study after examining the TPA and L3 SMI. In comparison to the NFPE, there was a poor correlation between most of the studies and the NFPE diagnosed malnutrition. However,

moderate correlation was found between severe malnutrition using the NFPE and the lowest quartile of the L3 SMI. It is likely that the correlation between these tests would increase with a larger sample size. The mean L3 SMI was also found to be significantly associated with malnutrition diagnosis. These are promising results. If the NFPE is found to be a valid tool to measure sarcopenia, the ability to diagnose malnutrition in this patient population would be substantially altered. Since sarcopenia is often masked in these patients due to ascites and edema this would be of great benefit to those making assessments. As with the previously discussed tools, future studies with larger sample sizes, will need to be conducted.

Conclusion

In conclusion, malnutrition is a consistent problem in most patient populations. There have been numerous tools used over the years used to diagnose malnutrition, but many of these tools have been found to be unreliable and inconsistent. The need for a standardized tool that encompasses a variety of measures and can be used in all patient populations, has been ever-growing. In 2012, the NFPE was developed for dietitians to aid physicians in a nutrition-focused malnutrition diagnosis. However, there have been very few research studies using this NFPE to assess malnutrition.

Based on the results of this study, the validity of this tool is very promising. The validity of the NFPE was examined by comparing its results to other malnutrition tools. The NFPE has been shown to correlate with other tools such as the invasive L3 SMI measure for sarcopenia and the PG-SGA/SGA, which has been validated in other studies. In addition, the NFPE diagnosed malnutrition was found to be significantly associated

with hospital admissions. Due to the small patient population of this study, more research will need to be conducted to support these results.

Sample size and number of patients without malnutrition were limitations to this study. The majority of the patients examined were white and males, therefore limiting the generalizability of the results. The NFPE was also limited in this study from inability to collect data on all physical locations due to ascites, clothing, or injury. There was also likely inaccuracy in assessing weight status and energy intake due to patient recall. While there were many limitations in this study, the use of multiple malnutrition tools for comparison was a strength in this study. These tools were comprised of both objective and subjective tools which was another strength. Additionally, inclusion/exclusion criteria and patient randomization between RDs limited possible biases. Lastly, comparing NFPE-diagnosis to patient outcomes showed the benefits of using this tool.

These preliminary results reinforce the significance of the NFPE and the need for additional studies using this tool. The NFPE also stresses the importance of the RD in the medical field, and how an earlier dietitian screening and intervention could improve patient outcomes, such as reduced hospital admissions, reduced incidence and severity of malnutrition, and decreased risk of mortality, especially in patients with ESLD. Furthermore, using MELD score to predict mortality in ESLD patients needs to be re-evaluated. As compared to previous research, MELD is not associated with liver disease diagnosis or incidence of malnutrition. However, adding a nutritional component to MELD scoring could potentially improve the accuracy of mortality risk and prioritization of transplant patients on the wait list. More research using the NFPE will need to be

conducted in not only ESLD patients, but other patient populations, before the NFPE can be considered the “gold standard” for diagnosing malnutrition.

Appendix A: List of Abbreviations

Abbreviation	Explanation
AND	Academy of Nutrition and Dietetics
ASPEN	American Society for Parenteral and Enteral Nutrition
CTP	Child-Turcotte-Pugh Score
ESLD	End Stage Liver Disease
EV	Esophageal Varices
HCC	Hepatocellular Carcinoma
HE	Hepatic Encephalopathy
HRS	Hepatorenal Syndrome
L3 PMI	Lumbar Psoas Muscle Index
L3 SMI	Lumbar Index
LVP	Large Volume Paracentesis
MAC	Mid-Arm Circumference
MAMC	Mid-Arm Muscle Circumference
MELD	Model for End Stage Liver Disease
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
NFPE	Nutrition Focused Physical Exam
PG-SGA	Patient Generated-Subjective Global Assessment
RFH-GA	Royal Free Hospital Global Assessment
RD	Registered Dietitian
SBP	Spontaneous Bacterial Peritonitis
SGA	Subjective Global Assessment
TIPS	Transjugular Intrahepatic Portosystemic Shunt

TSF	Triceps Skin Folds
UNOS	United Network for Organ Sharing

Appendix B: NFPE: Clinical Characteristics to Identify and Support a Diagnosis of Malnutrition[26]

Clinical Characteristic	Malnutrition in the context of acute illness or injury				Malnutrition in the context of chronic illness				Malnutrition in the context of social or environmental circumstances			
	Non-severe (moderate) malnutrition		Severe Malnutrition		Non-severe (moderate) malnutrition		Severe Malnutrition		Non-severe (moderate) malnutrition		Severe Malnutrition	
Energy Intake	<75% of estimated energy requirement for > 7 days		< 50% of estimated energy requirement for ≥ 5 days		< 75% of estimated energy requirement for ≥ 1 month		< 75% of estimated energy intake for ≥ 1 month		< 75% of estimated energy requirement for ≥ 3 months		£ 50% of estimated energy requirement for ≥ 1 month	
Interpretation of Weight Loss	%	Time	%	Time	%	Time	%	Time	%	Time	%	Time
	1-2	1 week	>2	1 week	5	1 month	>5	1 month	>5	1 month	>5	1 month
	5	1 month	>5	1 month	7.5	3 months	>7.5	3 months	>7.5	3 months	>7.5	3 months
	7.5	3 months	>7.5	3 months	10	6 months	>10	6 months	>10	6 months	>10	6 months
					20	1 year	>20	1 year	>20	1 year	>20	1 year
Physical Findings												
Body Fat	Mild	Moderate	Mild	Severe	Mild	Severe	Mild	Severe				
Muscle Mass	Mild	Moderate	Mild	Severe	Mild	Severe	Mild	Severe				
Fluid Accumulation	Mild	Moderate to Severe	Mild	Severe	Mild	Severe	Mild	Severe				
Reduced Grip Strength	N/A	Measurably Reduced	N/A	Measurably Reduced	N/A	Measurably Reduced	N/A	Measurably Reduced				

Appendix C: Summary of Common Liver Disease Diagnoses[2, 3]

Type of Liver Disease	Cause of Liver Disease	At Risk Populations/Risk Factors	Treatment/Cure
Hepatitis B and C	Hepatitis is a virus that can be transmitted through bodily fluids (semen, blood, and vaginal secretions)	<ul style="list-style-type: none"> • IV drug use • Unprotected sex • Body piercings • Tattoos • Incarceration 	<ul style="list-style-type: none"> • Hepatitis can be cured spontaneously by the body and through pharmaceuticals. • There is currently a vaccine for Hepatitis B, but not for Hepatitis C. • When a patient with the hepatitis virus fails treatment, or waits too long to seek treatment, it can lead to liver damage and ultimately liver failure. This can only be treated with transplant.
Acute Liver Failure	Drug overdose (acetaminophen), drug toxicity/reaction, herbal supplements, viruses, cancer, metabolic diseases	<ul style="list-style-type: none"> • High acetaminophen use • Herbal use • Cancers with high risk of liver metastasis development • Liver Cancer • Metabolic Disorders 	<ul style="list-style-type: none"> • Medications to reverse poisoning • Transplant
Autoimmune Hepatitis	Immune system attacks liver cells causing inflammation and damage	<ul style="list-style-type: none"> • Women between the ages 15-40 • Other autoimmune diseases 	<ul style="list-style-type: none"> • Suppress immune system with steroids or other immunosuppressant drugs • Transplant
Alcoholic Liver Disease	Alcohol abuse	<ul style="list-style-type: none"> • Alcoholics • Those with long history of frequent alcohol use 	<ul style="list-style-type: none"> • Alcohol cessation • Transplant
Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis	Build-up of fat cells in the liver	<ul style="list-style-type: none"> • Obesity • Diabetes • High cholesterol • Unhealthy diet 	<ul style="list-style-type: none"> • Healthy diet and exercise • Weight loss if overweight/obese • Transplant
Hepatocellular Carcinoma	Liver Cancer	<ul style="list-style-type: none"> • Pre-existing cirrhosis • Long term hepatitis virus 	<ul style="list-style-type: none"> • Resection • Chemoembolization • Ablation • Treatment of hepatitis or underlying cirrhosis • Transplant
Primary Biliary Cirrhosis	Destruction of intrahepatic bile ducts leads to build	<ul style="list-style-type: none"> • Women • Middle age 	<ul style="list-style-type: none"> • Symptom management with medications • Transplant

	up of bile and scar tissue, damaging the liver.	adults • Genetics	
Primary Sclerosis Cholangitis	Blocked bile ducts due to scar tissue and inflammation leads to buildup of bile, damaging the liver.	• Men • Genetics • Exact cause unknown	• Symptom management with medications and surgery • Transplant
Other (less common)	Wilson's Disease, Hemochromatosis, Alpha-1 Anti-trypsin Deficiency, Undetermined cause, etc.	• Genetics • Lifestyle	• Treatment based on disease. • Transplant

Appendix D: Age, Sex, Race, MELD, BMI, and Albumin Characteristics of Study

Sample

	<i>n</i>	%	Median	Std. Deviation	Min	Max
Age	-	-	54	9.9	29	69
Sex						
Male	24	77.4%	-	-	-	-
Female	7	22.6%	-	-	-	-
Race						
Caucasian	30	96.8%	-	-	-	-
African-American	1	3.2%	-	-	-	-
MELD	-	-	18	6.63	7	34
BMI	-	-	28.8	6.62	15.8	43.9
Albumin (g/dL)	-	-	2.7	0.73	1.3	4.0

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