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Assessing Doppler-Derived Pressure Gradients and Liver Echogenicity to Predict Liver Disease

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COLLEGE OF HEALTH SCIENCES

This is to certify that the doctoral dissertation by

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Abstract

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DHSc., Nova Southeastern University, 2006

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Abstract

Liver disease causes an estimated 36,000 deaths in the United States each year. Currently, to detect liver disease, an invasive biopsy is required. Other, less invasive diagnostic alternatives are needed. The purpose of this study was to assess the efficacy of a modified form of sonographic screening, including portal, hepatic, and splenic venous pressure, hepatic venous waveform analysis, portal vein diameter, and echogenicity of liver parenchyma in predicting liver disease. The study was based on conversion of a velocity measurement to a pressure gradient, allowing a fluid comparison between known catheterization venous pressures and sonographic Doppler-derived pressure gradients. This study was a secondary data analysis of a data set from 546 patients who received abdominal sonograms at a medical facility in the western United States between March 2010 and December 2010. The dependent variable was liver disease and the independent variables were ECHOGRADE, hepatic venous waveform (HVW), splenic vein pressure gradient (SVPG), modified portal vein pressure gradient (MPVPG), and hepatic vein pressure gradient (HVPG). Logistic regression was used to analyze the data. ECHOGRADE, HVW, and MPVPG in males were found to be statistically significant in detecting liver disease, supporting the theoretical framework and thus documenting a novel use of Doppler for the detection of liver disease. The social change significance of these results is to provide clinicians with an alternative, noninvasive method of diagnosing early liver disease before it progresses into chronic liver disease. With earlier detection, severe adverse health outcomes leading to irreversible liver cirrhosis may be avoided.

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Dedication

I dedicate this work to my dear husband, Roger, for supporting my countless hours of study and giving up our time together. To my children, Adam, Vincent, and Allison, for their love and support along the way. To my parents, Bill and Fayette, for teaching me that no goal is too high, and for my friends, Susan, Jen, and Debby, who never allowed me to give up. And finally, to my wonderful sonography staff for helping collect the sonographic data for the study.

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Chapter 1: Introduction to the Study

Background

Chronic liver disease and liver cirrhosis are major public health problems worldwide. In 2004, these conditions were associated with nearly 40,000 deaths and a cost of at least $1.4 billion for medical services in the United States alone (Centers for Disease Control and Prevention [CDC], 2009). Chronic liver disease caused by hepatitis, alcoholism, or nonalcoholic fatty liver disease (NAFLD) is a major health problem that results in increased morbidity and greater expenditures of health dollars (CDC, 2005). The condition has been associated with 20% to 30% of all cases of cirrhosis (CDC, 2009). Early detection of liver fibrosis, which is the precursor for liver cirrhosis, is important to the selection of treatment strategies, as well as to predicting overall prognosis. The gold standard for assessing liver fibrosis is a liver biopsy; however, this procedure is invasive and carries risks (Goodman, 2007). Complications of liver biopsy may include bleeding, pneumothorax, and possible perforation of other organs such as the colon or gallbladder (Herrine & Friedman, 2005). Due to their invasive nature, liver biopsies are both costly and time-consuming. According to the CDC (2008), about 70,000 cases of liver biopsy result in complications each year, but this number likely represents only a fraction of cases occurring. The estimated cost per biopsy ranges between $2,000 and $7,000, depending on the biopsy method, use of ultrasound guidance, and complication (Rockey, Caldwell, Goodman, Nelson, & Smith, 2009). Despite the limitations of liver biopsy, the procedure remains the gold standard, for lack of better alternatives to assess the severity of liver fibrosis (Bonekamp, Kamel, Solga, &

Clark, 2009). Alternative noninvasive tests might predict the chronic progression of liver disease so clinicians need not rely on liver biopsy alone.

The ideal noninvasive marker should accurately detect the presence or absence of significant disease. High sensitivity, specificity, and accuracy would be required of the marker. It must also be readily accessible, available, and reproducible, with low interlaboratory or intraobserver variability, and must demonstrate applicability to liver disease of various etiologies (Bonekamp et al., 2009). Current noninvasive methods of measuring liver fibrosis include serum markers (Castéra, Forns, & Alberti, 2008) and transient elastography (TE), also known as Echosens FibroScan® (Bonekamp et al., 2009). Serum markers increase with acute liver disease and cannot always distinguish between acute and chronic disease (Obrador et al., 2006). Elastography has decreased sensitivity in obese patients (Castéra et al., 2008). The objective of this study was to develop a noninvasive sonographic screening method that included portal, hepatic, and splenic venous pressure; portal vein diameter; and the echogenecity of liver parenchyma for use in predicting the existence of chronic liver disease, even for patients who are moderately obese (body mass index [BMI] < 35). The development of a noninvasive method holds potential for social change because detecting the presence of liver fibrosis before the patient becomes chronically ill allows for earlier treatment options (Castéra et al., 2008).

Understanding the disease burden of viral hepatitis requires awareness of the chronic sequelae of hepatitis infection, which can range from asymptomatic chronic infection to chronic hepatitis (Heymann, 2004), cirrhosis (Nelson & Williams, 2007), and

primary liver cancer (Galfione, Kronforst, & Conlon, 2007). A healthy liver serves several functions including the synthesis of proteins; the processing of amino acids, carbohydrates, lipids, and vitamins; the detoxification of pollutants; and the secretion of endogenous waste products into bile (Galfione et al., 2007). In essence, the liver acts as a filter, with architecture similar to a sponge when of normal status. When the liver tissue becomes fibrotic, these processes malfunction, leading to liver failure (Nicolau, Bianchi, & Vilana, 2002). The texture of a fibrotic liver is nodular.

Fibrosis is associated with difficulty in the portal vein, preventing the liver from functioning normally. In response to these circulatory difficulties, the portal vein dilates to deliver increased blood flow to the damaged liver. With advanced liver fibrosis (cirrhosis), blood flow can reverse because it is easier for the blood to find another path to the inferior vena cava rather than course through the cirrhotic liver. This condition is portal hypertension (Hagen-Ansert, 2006). Cirrhosis can cause liver failure, portal hypertension, esophageal varices, ascites, and hepatic encephalopathy (Heymann, 2004). Liver changes can manifest with sustained hepatitis C (HepC) infection, including fatty infiltration, a condition in which the individual hepatocytes fill with fat and subsequently become fibrotic with cirrhosis (Bonekamp et al., 2009).

Etiology and Epidemiology of Hepatitis

Acute Hepatitis

Hepatitis refers to an inflammation of the liver (Heymann, 2004). Causal factors include infectious agents (Angulo, 2002), drugs (W. M. Lee, 2003), or toxins/toxicants (W. M. Lee, 2003). The function of the liver in healthy individuals is to produce clotting

factors, cholesterol, plasma proteins, and glycogen (Heymann, 2004). Additionally, the liver detoxifies drugs and stores fat-soluble vitamins (W. M. Lee, 2003). Hepatitis compromises the ability of the liver to perform these functions and damages liver cells. Individual hepatocytes in the liver, once inflamed, can become swollen and unable to function (W. M. Lee, 2003). Illnesses associated with liver inflammation range from mild to life threatening and can be acute or chronic (Hagen-Ansert, 2006).

Symptoms of acute hepatitis typically include acute jaundice, dark urine, anorexia, malaise, extreme fatigue, and right upper quadrant tenderness (Galfione et al., 2007). HepC is a precursor for hepatocellular carcinoma (HCC; Hagen-Ansert, 2006). Many viruses have been associated with hepatitis, including the hepatitis A, B, C, D, and E viruses (CDC, 2009). The following sections describe the epidemiology and etiology of hepatitis.

Hepatitis C Virus

The hepatitis C virus (HCV) that causes HepC is a spherical, enveloped, ribonucleic acid member of the *Flaviviridae* family and is approximately 50nm in diameter (Heymann, 2004). HCV is associated with a moderate to high mortality rate as well as a high risk of chronic illness (Heymann, 2004). Measuring the burden of HCV requires information on hospital utilization and mortality related to chronic hepatitis, cirrhosis, and liver cancer, as well as data from cancer registries (National Cancer Institute [NCI], 2010). According to the National Foundation for Infectious Disease (as cited in NCI, 2010), HCV is responsible for approximately 8,000 to 10,000 deaths each year and accounts for almost half of the nearly 4,000 liver transplantations performed

annually. The viral ribonucleic acid is in blood, saliva, seminal fluid, tears, ascitic fluid, or cerebral spinal fluid (Nelson & Williams, 2007). The most common routes of transmission are injection, drug use, donated blood, blood products, transplanted organs, needle-stick injuries (for those who work in the health care setting), and birth to a HCV-infected mother (CDC, 2009).

Symptoms of HCV infection are indistinguishable from other types of hepatitis (Tilg & Diehl, 2000). Acute HCV infection typically goes unnoticed and can persist for several years either without symptoms or with vague symptoms such as malaise (Tilg & Diehl, 2000). Over time, approximately 2% to 25% of all individuals with HCV will develop liver cirrhosis and/or liver cancer (Heymann, 2004). HCV-infected individuals may be asymptomatic for several years, in some cases more than 20 years, making estimates of infected individuals difficult (Obrador et al., 2006). Although there were only 802 reported cases of HCV infections in the United States in 2006, a much higher number—approximately 19,000 new cases—is estimated after adjusting for those who are asymptomatic (CDC, 2008). As of early 2011, chronic HCV infection affected approximately 3.2 million individuals in the United States (CDC, 2011).

HCV infection reached its peak in the early 1990s, so the infection is currently most prevalent in those born between 1945 and 1965 (CDC, 2011). Although the number of cases of HCV infection has declined in the United States since that peak period, possibly due to increased awareness of the risk factors associated with blood transfusions and drug use (Sy & Jamal, 2006), HCV infection continues to be a major burden of disease throughout the world (Obrador et al., 2006). The CDC has suggested that the

incidence of HepC in the United States has decreased since 1988, but the latency period of HepC, that interval between contraction of the disease and the appearance of symptoms, is lengthy. The World Health Organization (2008) estimated approximately 3% of the worldwide population—over 170 million people—had HCV in 1999.

Hepatocellular carcinoma (HCC) is a primary malignant liver tumor; it is the most common and severe complication of HepC and cirrhosis (Nicolau et al., 2002). According to the NCI (2010), HCC is the fourth most common cancer in the world. Annual age-adjusted incidence rates vary from 2.1 per 100,000 in North America to 80 per 100,000 populations in China (NCI, 2010). Across all racial/ethnic groups, men contract HCC more often than do women; the disease is most prominent among Chinese Americans, in whom the annualized incidence rate of HCC among men is 20.9 per 100,000 and, among women, 8.0 per 100,000 (NCI, 2010).

Alcoholic Liver Disease

The most common toxicant associated with hepatitis is alcohol (Galfione et al., 2007). Alcoholic liver disease, also referred to as alcoholic hepatitis or steatohepatitis, is considered the third leading preventable cause of death in the United States (Lucey, Mathurin, & Morgan, 2009). Mortality typically ensues after decades of alcohol abuse, a mean daily intake of approximately 100 g (i.e., approximately 3.6 oz) of alcohol (Lucey et al., 2009). Signs and symptoms of alcoholic hepatitis include rapid onset of jaundice, fever, enlarged and tender liver, ascites, and possible encephalopathy (Heymann, 2004). Alcoholic hepatitis begins with fatty accumulation within the individual hepatocytes (Angulo, 2002). In its early stages, alcoholic hepatitis is reversible. With progressive

alcoholic abuse, the liver enlarges and, with that change in size, its architecture becomes disrupted and fibrotic (W. M. Lee, 2003).

Once the liver has become fibrotic and nodular, cirrhosis occurs. Alcoholic cirrhosis is an advanced liver disease characterized by diffuse and extensive liver fibrosis and loss of liver function (Nelson & Williams, 2007). Laboratory findings resulting in a diagnosis of cirrhosis include a decreased platelet count, an increased international normalized ratio, and an increased ratio of alanine aminotransferase (ALT) to aspartate aminotransferase (AST); that is, > 2 (Burroughs & Cholongitas, 2007). AST and ALT leak from damaged cells and are indicators of liver injury (Angulo, 2002). Elevated white blood count, neutrophil count, and total serum bilirubin levels are additional indicators of liver damage (Lucey et al., 2009). Although these various laboratory test results are irrefutable, microscopic analysis of a small piece of the liver will determine a definitive diagnosis of alcoholic hepatitis. Microscopic analysis of an alcoholic liver reveals ballooned and swollen individual hepatocytes that often contain eosinophilic inclusion bodies known as Mallory bodies or alcoholic hyaline (Lucey et al., 2009). The presence of large fat globules (i.e., steatosis) is common in alcoholic hepatitis. Over time, the fat globules can turn into liver fibrosis (W. M. Lee, 2003).

An individual with alcoholic hepatitis metabolizes alcohol through an oxidative process from acetaldehyde to acetate (W. M. Lee, 2003). The process promotes lipogenesis, which in turn leads to fat-filled hepatocytes and subsequent remodeling of the liver (Lucey et al., 2009). The increased fat content within the individual hepatocytes reduces the ability of the liver to complete vital processes such as metabolism and

filtration (Tilg & Diehl, 2000). Sonography is helpful in identifying hepatic abscesses, HCC, and accompanying ascites (Nicolau et al., 2002). Sonography-guided paracentesis (i.e., aspiration of ascites) is also routinely performed (Hagen-Ansert, 2006) to confirm the extent of liver damage. As with other acute liver diseases, alcoholic hepatitis may lead to chronic liver failure, fibrosis, cirrhosis, and possibly HCC (Obrador et al., 2006). Alcoholic cirrhosis may lead to life-threatening biliary obstruction, portal hypertension, ascites, and esophageal varices with possible upper gastrointestinal bleeding (Lucey et al., 2009).

Complications of advanced cirrhosis include hepatic encephalopathy (i.e., inflammation of the brain; Nelson & Williams, 2007) and a significant risk of HCC (NCI, 2010). Portal hypertension occurs when nodularity within the cirrhotic liver causes increased intrahepatic pressure (Sharara & Rockey, 2001). Because blood follows the path of least resistance, portal venous flow can reverse and find another pathway back to the inferior vena cava (Hagen-Ansert, 2006). Portal hypertension can lead to the formation of gastric or gastroesophageal varices, which have a high risk of rupture (Castéra et al., 2008). The morbidity and mortality of an individual increases with the presence of esophageal varicies. Endoscopy has been used to determine the size and progression of esophageal varices, along with catheterization techniques used to measure the hepatic venous pressure gradient (HVPG) employed to determine which patients are at greatest risk for rupture (HVPG > 12mmHg; Sharara & Rockey, 2001).

Nonalcoholic Liver Disease

Alcohol abuse is not the only risk factor for liver disease. NAFLD is a catchall term for a condition also known as nonalcoholic steatohepatitis, diabetic hepatitis, fatty-liver hepatitis, and nonalcoholic Laennec's disease (Angulo, 2002). NAFLD is the preferred term because it encompasses a wide range of conditions including mild steatosis advancing to steatohepatitis, liver fibrosis, and finally cirrhosis (Ratziu et al., 2006). The clinical presentation of an individual with NAFLD is similar to that of alcoholic liver disease; however, the pathogenesis is distinctly different (Tilg & Diehl, 2000).

NAFLD is the most common liver disease in the United States (Angulo, 2002). An estimated 70 million adults in the United States have liver disease (Bellentani & Marino, 2009). Multiple risk factors contribute to NAFLD, and the disease affects 10% to 24% of the populations in various countries (Angulo, 2002). Risk factors for NAFLD include obesity (Fan & Farrell, 2008), Type 2 diabetes mellitus (Angulo, 2002), and hyperlipidemia (Fan & Farrell, 2008). Regardless of the degree of obesity, the presence of diabetes mellitus significantly increases the risk and severity of associated NAFLD (J. Y. Lee et al., 2007). People with truncal obesity are at higher risk for NAFLD, even with a normal BMI (Angulo, 2002).

The steadily increasing trend of obesity in the United States (CDC, 2011) and the association between obesity and Type 2 diabetes explains the concurrent increase in the incidence and prevalence of NALFD. Clinical indicators of NAFLD include hepatomegaly, decreased platelet count, and mild to moderately increased serum levels of

AST, ALT, or both (Ratziu et al., 2006). As the degree of fibrosis increases, the AST: ALT ratio increases (Obrador et al., 2006). Other laboratory abnormalities indicative of NAFLD include hypoalbuminemia, a prolonged prothrombin time, and hyperbilirubinemia as the liver disease progresses (Angulo, 2002). Ultrasound findings with NAFLD include increased echogenicity compared to that found in the kidneys, and ranges from mild coarseness to a loss of visualization of the vessels and diaphragm (Hagen-Ansert, 2006).

Sonography has historically been useful in attempting to detect fatty infiltration leading to fibrosis or cirrhosis (Nicolau et al., 2002), but the increase in obesity has caused difficulty in distinguishing between fatty infiltration and fibrosis by imaging alone. Supplementation of sonographic images with Doppler-derived pressure gradients has been posited to increase sensitivity of detection of chronic liver disease (Obrador et al., 2006). A diagnosis of NAFLD includes a combination of unexplained hepatomegaly, elevated AST and ALT, and findings of sonographic or computed tomography suggestive of fatty infiltration of the liver. After NAFLD has been diagnosed, liver biopsy determines the severity of liver disease (Herrine & Friedman, 2005).

Research Gaps

The literature reviewed for this study revealed the current state of knowledge was insufficient to support the value of any alternative measures to liver biopsies as a means of predicting when acute hepatitis or acute liver disease will turn to liver fibrosis, leading to irreversible cirrhosis. A combination of biomarkers and TE provide assistance in detecting liver fibrosis (Castéra et al., 2008), but these methods have not yet replaced

liver biopsy. The driving force behind this study was to determine the level at which the liver is no longer porous, and to enable a better understanding of when fibrosis is causing an increase in venous pressure. Endoscopic pressure gradients can accurately detect HVPGs when liver disease is chronic and extensive (Sharara & Rockey, 2001). The measured pressure gradient used in endoscopy is mmHg. An alternative method of predicting liver fibrosis as a pressure gradient would provide a comparative analysis and possibly aid in earlier detection of chronic liver changes such as fibrosis/cirrhosis.

A meta-analysis conducted by Bonekamp et al. (2009) demonstrated that hepatic fibrosis, unlike cirrhosis, may be reversible. Consequently, the ability to detect early liver fibrosis was of immense clinical utility and potential social benefit. The analysis of 153 studies related to alternative approaches to the prediction of chronic liver disease found elastography (either ultrasound or magnetic resonance imaging [MRI]) to be the most promising (Bonekamp et al., 2009). Other proposed methods included a combination of biomarkers, elastography, and ultrasound techniques. Alternative noninvasive tests will predict chronic liver disease so that clinicians will not rely on liver biopsy alone and the patient can receive beneficial treatment before early liver disease manifests irreversible damage.

The liver is a porous organ that allows for fluid exchange of cellular contents and acts as a highly effective filter. The study assumed that, in the setting of fatty infiltration, the liver remains porous and the vascular network is undisturbed. When the liver becomes fibrotic or cirrhotic, the ability of the vessels to supply blood to and from the liver is disturbed due to the nodular texture of the liver. A review of the literature,

discussed in detail in chapter 2, yielded no prior study having assessed Doppler-derived portal, splenic, and HVPGs hepatic venous pressure gradients (mmHg) in conjunction with sonographic assessment of portal vein diameter and liver echogenicity grading across the spectrum of liver disease. The lack of knowledge about the association between chronic liver disease and intraabdominal venous pressures necessitated further investigation. The rationale for why these variables would predict liver fibrosis/disease was based on the laws of fluid hemodynamics. As the radius of a vessel decreases, the velocity and/or pressure increases. As the liver becomes more nodular, it was hypothesized that the lumen of the veins becomes more narrow, causing a reduction in size and increase in the venous pressure.

High-priority research areas included a method to quantify the Doppler-derived portal vein and splenic vein pressure gradient, the hepatic venous waveform analysis, liver echogenicity, and portal vein diameter. The Doppler-derived pressure gradient model in this study was a quantitative tool designed to determine the presence or absence of chronic liver disease. Stauber and Lackner (2007) recommended defining a diagnostic algorithm for staging hepatic fibrosis. The identified challenge was to develop and validate methods that can be routinely applied and provide clinically meaningful results that add substantially to routine clinical assessment, and potentially reduce the need for liver biopsy, at least in some patients. Validation of such a method was a high-priority research need.

Problem Statement

Chronic liver and gallbladder disease, chronic hepC, and liver cancer collectively account for approximately one quarter of direct health care costs, amounting to $9.1 billion (Kim, Brown, Terrault, & El-Serag, 2002). The problem is high echogenicity of the liver used to be a highly reliable predictor of liver fibrosis (Hagen-Ansert, 2006); however, the increased prevalence of patient obesity has made echogenicity a less reliable indicator (Fan & Farrell, 2008). It is possible to have increased echogenicity secondary to fatty infiltration of the liver due to obesity and not due to liver fibrosis (Hagen-Ansert, 2006). It would prevent needless biopsies and permit early treatment of liver disease if Doppler studies could determine whether the liver has fatty infiltration of the liver due to obesity, or is actually fibrotic due to chronic liver disease (Zwiebel & Pellerito, 2005). The identified problem was that sonographic imaging alone is no longer as effective in detecting liver disease due to the increase in obesity. Additionally, noninvasive tests reduce the amount of complications related to liver biopsies. This study described the relationship between the portal vein diameter, portal, hepatic, and splenic pressure gradient, the hepatic venous waveform, and the echograde; and the prediction of liver disease.

Nature of the Study

Multiple logistic regression models assessed the effect of baseline characteristics on the presence of chronic liver disease. Many studies have proposed noninvasive tests to replace liver biopsy (Barbaro et al., 2000; Liu et al., 2007; Obrador et al., 2006; Sebastiani, 2009). These studies examined either a single biochemical marker or a

combination of biochemical markers and other noninvasive imaging. A primary goal of this study was to identify the relationship between portal, hepatic, and splenic venous pressure; portal vein diameter; and the echogenicity of liver parenchyma and liver disease. A secondary goal of the study was to develop a sonographic screening method that would predict chronic liver disease using Doppler-derived pressure gradients rather than rely on current velocity measurements alone. Increases in portal vein diameter in patients with chronic liver disease was calculated and then applied to a mathematical modifier. This calculation resulted in a modified pressure gradient that correlated with invasive pressure gradients obtained in the endoscopy laboratory. The dependent variable in the study was the presence or absence of chronic liver disease. The independent variables were liver echogenicity, portal vein diameter; splenic, hepatic, portal, modified portal venous pressure gradient; and hepatic venous waveform analysis.

Research Question

The following research question guided the study: Will the hepatic venous pressure gradient (HVPG), the hepatic venous waveform (HVW), the portal vein diameter (PVD), the portal vein pressure gradient (PVPG), the modified portal vein pressure gradient (MPVPG), the splenic vein pressure gradient (SVPG), or the echograde (ECHOGRADE) predict the presence or absence of liver disease after controlling for age, ethnicity, and BMI, and after stratification by gender?

The following were the null and alternative hypotheses:

- Null hypothesis: The hepatic venous pressure gradient (HVPG), the hepatic venous waveform (HVW), the portal vein diameter (PVD), the portal vein

pressure gradient (PVPG), the modified portal vein pressure gradient (MPVPG), the splenic vein pressure gradient (SVPG), or the echograde (ECHOGRADE) will not predict the presence or absence of liver disease after controlling for age, ethnicity, and BMI, and after stratification by gender.

- Alternate hypothesis: One or more of the following, including hepatic venous pressure gradient (HVPG), the hepatic venous waveform (HVW), the portal vein diameter (PVD), the portal vein pressure gradient (PVPG), the modified portal vein pressure gradient (MPVPG), the splenic vein pressure gradient (SVPG) or the echograde (ECHOGRADE) will predict the presence or absence of liver disease after controlling for age, ethnicity, and BMI, and after stratification by gender.

Purpose of the Study

The purpose of the study was to address the gap in related research by linking Doppler-derived pressure gradients with liver fibrosis. This research was the first independent study to assess the value of Doppler-derived portal, splenic, and hepatic venous pressure gradients in conjunction with sonographic assessment of hepatic venous waveform, portal vein diameter, and liver echogenicity for the diagnosis of liver disease. The study provided an important step in the development of a new noninvasive method that should be of great benefit to patients. I used multiple logistic regression and receiver operating characteristics (ROC) curves to test the hypotheses. The study set the stage for future research to evaluate the effectiveness of the Doppler-derived pressure gradients in

determining associations between acute liver diseases before life-threatening, chronic liver changes manifest.

Theoretical Foundation

The mechanism of action in liver fibrosis provided the theoretical foundation for this study. Liver fibrosis is the excessive accumulation of extracellular matrix proteins, including collagen, which manifests with most liver disease (Rosenberg, 2003). Advanced liver fibrosis leads to cirrhosis, liver failure, and portal hypertension that often requires liver transplantation (Rosenberg, 2003). These conditions often occur after initial inflammation of the liver (Herrine & Friedman, 2005), referred to as hepatitis. Doppler is the mechanism used to test intraabdominal venous pressure with the use of an ultrasound machine (Dietrich et al., 1998). The ultrasound transducer produces transmitted sound waves in the body. An image is produced on the screen of the ultrasound machine by the reflection of echo signals *bouncing* off various tissues in the body. The source of the reflected echo signal is moving red blood cells. A Doppler shift determines the difference in frequency between the transmitted frequency and reflected frequency.

The reflected signal indicates both direction and velocity of the red blood cells traveling within the region of interest. On the image display, the *y*-axis represents the velocity and the *x*-axis represents time (Zwiebel & Pellerito, 2005). Within the blood vessels, velocity changes with physiologic variations such as heart rate, respiration, and patient condition such as hypertension or anemia (Bolognesi et al., 2006). Multiple Doppler signals captured from within the patient should allow the observer to compare the velocities of flow in several organs across several Doppler sites. Fluid dynamics will

change in the setting of arterial or venous narrowing (referred to as stenosis) or dilatation (i.e., aneurysm; Hagen-Ansert, 2006). Examination by Doppler can provide a peak velocity or pressure gradient with a great deal of precision by measuring the velocity in the center of the vessel of interest (Zweibel & Pellerito, 2005).

Standardized abdominal Doppler exams currently use only velocity measurements (Hagen-Ansert, 2006). By adapting the abdominal software presets to include cardiac presets, a velocity measurement was changed to a pressure gradient (mmHg). This conversion allowed a fluid comparison between known catheterization venous pressures and sonographic Doppler-derived pressure gradients. This protocol provided a rapid assessment of the intrahepatic, portal, hepatic, and splenic venous pressures using abdominal sonographic techniques. The design of the study sets the stage for future research to evaluate the effectiveness of Doppler-derived pressure gradients in determining associations between acute liver disease before life-threatening, chronic liver changes become manifest.

Definition of Terms

The various terms and phrases used in this study were defined as follows:

Alanine aminotransferase (*ALT*): An enzyme present in tissues that is slightly elevated in patients with acute cirrhosis, hepatic metastasis, and pancreatitis. There is an increase in this level in patients with infectious hepatitis and obstructive jaundice (Hagen-Ansert, 2006).

Alcoholic hepatitis: Also known as alcoholic liver disease, alcoholic hepatitis is a clinical syndrome of jaundice and liver failure that generally occurs after decades of heavy alcohol use (mean intake, approximately 100 g per day; Lucey et al., 2009).

Ascites: Accumulation of serous fluid within the peritoneal cavity (Hagen-Ansert, 2006).

Aspartate aminotransferase (*AST*): An enzyme present in tissues and associated with a high rate of metabolic activity, one of which can be in the liver. Any disease that injures the hepatic cells causes an elevation in AST. Significant elevations are present in hepatitis and cirrhosis (Hagen-Ansert, 2006).

Child-Pugh class: Classification of the severity of cirrhosis based on assessment of the following variables: encephalopathy, ascites, bilirubin levels, and prothrombin time (Sharara & Rockey, 2001).

Chronicity: Characterized by long duration, the state of being chronic (Chronicity, n.d.).

Cirrhosis: An abnormal liver condition characterized by irreversible scarring of the liver. Alcohol and viral hepatitis are among the many causes of cirrhosis (Cirrhosis, n.d.; Heymann, 2004).

Doppler: A change in frequency as red blood cells move from a lower frequency sound source at rest toward a higher frequency sound source. Doppler is measured in cm/second or m/second (Hagen-Ansert, 2006).

Echocardiogram: An ultrasound examination of the heart (Hagen-Ansert, 2006).

Echogenicity: The strength or amplitude of the reflected echo signal reflected using ultrasound. The brighter (whiter) the echo, the greater the echogenicity (Hagen-Ansert, 2006).

Esophageal varices: A tortuous dilatation of an esophageal vein, especially in the distal portion. This situation results from any condition that causes portal hypertension (Venes, 2001).

FibroTest (*FT*)®: The biochemical markers registered by Biopredictive and used to detect liver fibrosis. Tests include total bilirubin, alpha-2 macroglobulin, apolipoprotein A-1, and hemoglobin as well as Biopredictive's ActiTest®, which includes ALT. Values of FT and ActiTest range from 0 to 1.0, with higher values indicating a greater probability of fibrosis (Castéra et al., 2009).

Hepatic encephalopathy: A brain dysfunction present in patients with chronic liver disease and portal hypertension, during which chemicals normally detoxified in the liver are shunted past the liver and left to circulate in the blood (Venes, 2001).

Hepatic vein: The vein that takes blood from the liver to the inferior vena cava (Venes, 2001).

Hepatitis: An inflammation of the liver, typically caused by exposure to an infectious agent, a toxin, or a drug (Venes, 2001).

Hepatocytes: Specialized epithelial cells that are the functional parenchymal cells of the liver (Tilg & Diehl, 2000).

Hepatomegaly: An enlargement of the liver (Hagen-Ansert, 2006).

Hypoalbunemia: The condition of decreased albumin in the blood (Venes, 2001).

Liver fibrosis: The excessive accumulation of extracellular matrix proteins including collagen that manifests with most types of chronic liver diseases. Advanced liver fibrosis results in cirrhosis, liver failure, and portal hypertension, and often requires liver transplantation (Rosenberg, 2003).

Metavir: A liver biopsy scoring system graded on a scale including both the fibrosis score from F0 through F4 and the inflammation activity score from A0 through A3 (Sharara & Rockey, 2001).

Modified Bernoulli equation: An equation used to change a velocity measurement to a pressure gradient ($4V^2$) using sonographic Doppler techniques; a routine measurement used in echocardiography (Lai, Mertens, Cohen, & Geva, 2009).

Nonalcoholic fatty liver disease (*NAFLD*): A wide spectrum of liver damage ranging from simple steatosis to steatohepatitis or advanced liver fibrosis (Angulo, 2002).

Portal hypertension: Increased pressure in the portal vein caused by an obstruction of the flow of blood through the liver. Portal hypertension is found in diseases such as cirrhosis, in which the condition is responsible for ascites, splenomegaly, and the formation of varices (Bolognesi et al., 2006).

Portal vein: A vein formed by the union of veins from the abdominal viscera, which then takes blood to the liver. It is made of the combined superior and inferior mesenteric, splenic, gastric, and cystic veins (Venes, 2001).

Pressure gradient (*mmHg*): The force driving flow through a vessel, measured in mmHg. To change a velocity measurement in meters/second to a pressure gradient, the modified Bernoulli equation ($4V^2$) must be applied (Zagzebski, 1996).

Prothrombin: A plasma protein coagulation factor synthesized by the liver that is converted to thrombin by prothrombinase and thrombokinase in the presence of calcium ions (Venes, 2001).

Sonography: A high-resolution ultrasound imaging technique used to visualize internal organs and vessels in normal and pathological states (Hagen-Ansert, 2006).

Spectral analysis: A sonographic method used to display Doppler-derived velocities using fast Fourier transform. The vertical axis represents the velocity of blood in vessels in either a positive or negative direction, or the horizontal axis measures time (Hagen-Ansert, 2006).

Splenomegaly: An enlargement of the spleen (Venes, 2001).

Splenic vein: The venous drainage from the spleen toward the portal vein (Venes, 2001).

Steatosis: The fatty accumulation within liver cells (Hangen-Ansert, 2006).

Stenosis: Narrowing of a blood vessel caused either by internal blockage (i.e., plaque or thrombus) or external compression (i.e., cirrhosis or tumor; Zweibel & Pellerito, 2005).

Telangectasis: A vascular lesion formed by dilatation of a group of small blood vessels (Venes, 2001).

Transient elastography: A noninvasive method to assess liver fibrosis by measuring liver stiffness in kilopascals (kPa; Castéra et al., 2008).

Operational Definitions of Variables

The following variables were used in this study.

Dependent Variable

Disease (*DISEASE*): The dataset was divided into two classifications of those patients with (1) or without (0) liver disease.

Independent Variables

EchoGrade (*ECHOGRADE*): The echogenecity of liver, as graded on a scale from 0 to 3 (Hagen-Ansert, 2006).

Hepatic venous pressure gradient (*HVPG*): The intravenous pressure in hepatic veins, measured in mmHg. This pressure is measured directly with an intravenous catheter or indirectly through a Doppler-derived pressure gradient on an ultrasound machine. To record a pressure gradient rather than a velocity, the cardiac preset must be applied (i.e., using the Bernoulli equation) to the recorded velocity measurement (Zagzebski, 1996).

Hepatic venous waveform analysis (*HVW*): Hepatic venous waveform, measured by spectral Doppler of the middle hepatic vein. HVW is measured as an ordinal variable from 1 to 3 as monophasic, biphasic, or triphasic (Zweibel & Pellerito, 2005).

Modified portal vein pressure gradient (*MPVPG*): Calculated pressure gradient derived from the measured portal vein diameter divided by the established mean portal vein diameter. This is multiplied by the portal vein pressure gradient and the portal vein radius to the fourth power to follow the hemodynamic principles of the Bernoulli equation (Zweibel & Pellerito, 2005).

Portal vein diameter (*PVD*): Portal vein diameter measured with calipers using the ultrasound machine caliper function (Hagen-Ansert, 2006).

Portal vein pressure gradient (*PVPG*): The intravenous pressure in portal vein, measured in mmHg using the vascular applications of the ultrasound machine (Zweibel & Pellerito, 2005).

Splenic vein pressure gradient (*SVPG*): The intravenous pressure in portal vein, measured in mmHg using the vascular applications of the ultrasound machine (Zweibel & Pellerito, 2005).

Covariates

Age (*AGE*): The age range of the data set was between 18 and 75 years.

Body mass index (*BMI*): The BMI range of this dataset included all patients with a BMI < 35.

Ethnicity (*E*): The ethnicities of the patients were coded as follows: White (non-Hispanic), Black (non-Hispanic), Hispanic, and Other. There was a set of three dummy variables White (*yes* = 1, *no* = 0), Black (*yes* = 1, *no* = 0), and Hispanic (*yes* =1, *no* =0). All others were coded as 0 on all three of these variables.

Assumptions, Limitations, Scope, and Delimitations

Assumptions of the study included the following items:

- HepC was accurately diagnosed.
- Patients' data in this study were representative of a larger population residing in the geographic region.
- Sonography with Doppler can accurately measure pressure gradients. A major hypothesis of this study was that there was an association between increased

portal, hepatic, or splenic venous pressure gradients, as well as portal vein diameter, hepatic venous waveform, or liver echogenecity and liver disease.

- Based on the literature review, liver disease can lead to cirrhosis and an accurate diagnosis of liver disease is essential for timely treatment and a positive prognosis.
- A final assumption was that the literature review, presented in chapter 2, of alternative methods including both ultrasound and magnetic resonance-based elastography, biochemical markers, and Doppler techniques has accurately determined what currently exists and how Doppler-derived pressure gradients might assist in predicting the chronicity of liver disease.

Limitations, scope, and delimitations of the study included the following items:

- The study was restricted to the central California geographic area. Generalization of the results of the study may or may not relate to geographic areas with a similar population base and similar inherent risks for chronic liver disease.
- The study was limited to the variables in the dataset.
- The study excluded those patients with a BMI > 35 with the exception of 57 subjects who were included for comparison.

Significance of the Study

The health care burden of chronic liver disease is substantial (Bugianesi, 2005). This burden includes a financial strain on the health care system, as well as a long debilitating illness for the individual patients. The American Gastroenterological

Association (as cited in Kim et al., 2002) estimated the economic burden of common gastrointestinal and liver disorders including chronic liver disease, chronic HepC, liver cancer, and gallbladder disease as accounting for approximately one quarter ($9.1 billion) of all direct costs for health care. A review of literature yielded little scientific data to support or refute the advantages of alternative screening mechanisms in determining the chronicity of liver disease. It was recognized that liver biopsy is invasive, has considerable risks, and does not always provide an accurate assessment of the degree of liver fibrosis (Castéra et al., 2008) but, due to the lack of other alternatives, liver biopsy remains the gold standard for the diagnosis of liver fibrosis leading to cirrhosis (Herrine & Friedman, 2005).

The significance of the study was that the diagnostic method of Doppler-derived pressure gradients provided a new approach to determine the relative likelihood of someone having liver disease depending on values of the independent variables after controlling for all the other variables in the equation. The advantage of developing this method was that this method will aid referring physicians to more effectively treat patients whose acute liver disease is beginning to progress into chronic liver disease. With earlier aggressive treatment and intervention, severe adverse health outcomes leading to irreversible liver cirrhosis might be reduced. Prevention of liver disease is not always possible, but early intervention and treatment will lead to a decrease in morbidity and mortality related to chronic liver disease. This method will provide positive social change that could possibly improve the human condition of individuals living with liver disease. There was evidence that alternative testing such as the use of fibroelastosis and

biochemical markers are helping to predict liver fibrosis (Pickerell, 2010; Ratziu et al., 2006). This study adds to the current body of knowledge and yielded worthwhile insight into the value of an alternative, noninvasive method to determine the chronicity of liver disease.

Summary

Chronic liver disease caused by hepatitis, alcoholism, or NALFD is a major health problem that results in increased morbidity and greater expenditures of health care dollars (CDC, 2005). Alcoholic hepatitis is the third leading preventable cause of death in the United States (Lucey et al., 2009), and it is estimated that as many as 70 million Americans may suffer from NALFD (Angulo, 2002). There was a need to add to the body of knowledge regarding alternative methods to predict the chronicity of liver disease.

Presented in chapter 2 is a literature review covering the current research and information on diagnostic tests to detect liver disease, alternative noninvasive methods of predicting the chronicity of liver disease, an examination of the ultrasound method chosen for this study, and treatment options for chronic liver disease. There is a description of the research design and approach offered in chapter 3. The secondary data analysis design evaluated the association between increased portal, splenic, and hepatic vein pressure gradients as well as assessing the echogenicity of the liver and portal vein diameter is detailed. The population of study and the instrumentation and materials utilized is described in chapter 3, and the data collection and analysis process is also explained. Chapter 3 also discusses the protection of the patient's rights. Chapter 4

provides the results of the analysis of the dataset, and chapter 5 discusses the impact of the research as well as the future implications related to this study.

Chapter 2: Literature Review

The conceptual framework of the study was based on an understanding of the relationships between liver disease and increased intrahepatic pressures or altered imaging characteristics as assessed by sonographic measurements. The review of related literature presented in this chapter includes recent studies to evaluate both biopsy techniques and alternative methods to predict the chronicity of liver disease, the manner in which sonography was used in the diagnosis and prediction of chronic liver disease, and how assessment of intrahepatic and splenic blood flow might aid in earlier detection. This chapter is organized in sections according to the topics of liver biopsies, biochemical screening tests, ultrasound and magnetic resonance-based elastography, and ultrasound screening with and without Doppler. Literature about other alternative screening methods such as ultrasound-based and magnetic resonance-based elastography and biomarkers such as FT® and FibroScan® determine efficacy as compared to invasive liver biopsy procedures are presented. Most research on assessing the chronicity of liver disease has focused on liver biopsy, which has inherent risks and does not always accurately identify the severity of disease. There is a lack of alternative, noninvasive methods and this gap is of particular clinical interest. This study determined the value of an alternative noninvasive method to predict chronic liver disease. Through the present study, a determination of the value of an alternative noninvasive method to predict chronic liver disease was sought.

Literature Review Strategy

A literature search tapped various Internet databases such as MEDLINE, EBSCOhost, CINAHL, and peer-reviewed journals such as the *Journal of Hepatology* and the *New England Journal of Medicine*, and government websites such as CDC and the World Health Organization. The literature search was performed using keywords related to the research questions including viral hepatitis, liver cirrhosis, hepatic, liver fibrosis, ascites, elastography, liver biopsy, Metavir, Doppler, alcoholic liver disease, nonalcoholic steatohepatitis (NASH), portal vein, splenic vein, hepatic vein, sonography, FibroScan®, and FT®. I evaluated each study carefully to determine article content and type. Studies were included in this literature review if they were conducted after the year 2000, if they were primary studies published in peer-reviewed journals dealing with hepatology, hepatitis, liver biopsy, or sonographic, and/or alternative techniques for assessing the chronicity of liver disease. Meta-analyses of comparative diagnostic capabilities were included to increase the researched sample and overall body of knowledge. Some textbook references were included due to the perceived value and relevance to the topic area of the study. Articles from government agencies and respected organizations were reviewed for statistics and supporting information.

Detection of Liver Disease

Liver Biopsy

The liver biopsy has been the cornerstone of clinical hepatology for many years (Sebastiani, 2009). According to Herrine and Friedman (2005), the purpose of performing this procedure is to determine which patients are in need of antiviral treatment and, based

on the nature and extent of the disease, which patients will likely respond favorably to the intervention. An accurate assessment of the severity of liver fibrosis is essential in determining when antiviral treatment is recommended (Sebastiani, 2009). Liver biopsy remains the gold standard to grading fibrosis; however, it harbors a risk of complications including sampling error and inaccuracy due to interobserver and intraobserver variability of histopathologic interpretation (Bonekamp et al., 2009). According to Castéra et al. (2008), even when an experienced physician performs the biopsy and an expert pathologist interprets the results, error rates of up to 20% can occur due to sampling (i.e., too small or missed pathology) errors and/or intraobserver variability in reporting the fibrosis stage.

Liver biopsies are typically reliable for establishing and determining the particular type of liver disease, but they are less reliable in determining severity (Goodman, 2007). To stage a disease, a determination of the extent of progression toward either organ failure or death is needed. The overall goal of staging is the prediction of patient outcome (Rosenberg, 2003). There are two simple grading and stage scores for chronic viral hepatitis: the Batts-Ludwig and the Metavir (Desmet, Gerber, Hoofnagle, Manns, & Scheuer, 1994).

Disease status is rated from Grade 0 through Grade 4 according to the Batts-Ludwig scoring system and from Status A-1 (or F0) through Status A-3 (or F4) according to the Metavir scoring system. In both scoring systems, 0 = *no fibrosis* and 4 = *cirrhosis*. Both systems are widely used and help to identify disease grade and severity and are used to quantify the degree of fibrosis. The reliability of these scoring systems is

acknowledged as subjective and based largely on the experience of the pathologist (Goodman, 2007). Because liver disease scoring systems are semiquantitative and prone to intraobserver and interobserver variability, these systems pose limitations. Other drawbacks of liver biopsy, in general, are a 20% rate of patient discomfort, 0.1% to 0.3% of cases experiencing significant morbidity, and a 0.02% to 0.24% mortality rate (Liu et al, 2007).

Although a mortality rate of 0.02% to 0.24% was not high compared to that of other invasive diagnostic procedures, the study provided an opportunity to further reduce the risk by exploring alternative, noninvasive methods. Capture of a small liver sample might limit the amount of pathologic tissue and reduce the ability to stage the sample. Intervariability within liver samples taken from the same patient has been observed. Even when an experienced physician performs the biopsy and an expert pathologist interprets the results, there can be to a 20% error rate (Castéra et al., 2008). Because normal transaminase values suggest a lack of significant hepatocellular disease, Ratziu et al. (2006) proposed that it might be unethical to perform routine liver biopsies on patients whose serum transaminase values are in the normal range.

In patients with chronic viral hepatitis, the stage of liver fibrosis is the most reliable parameter to determine the progression of liver injury, but liver biopsies are invasive and present increased risks, especially among those with clotting disorders (Bernatik, Stobel, Hahn, & Becker, 2002). The interpretation of biopsies using fibrosis stage scoring is problematic because these interpretations are based on qualitative descriptors rather than quantitative measure (Rosenberg, 2003). Combination algorithms

of noninvasive methods such as TE, biochemical markers, and Doppler parameters have been proposed to replace invasive and potentially unreliable liver biopsies in predicting the chronicity of liver disease (Herrine & Friedman, 2005).

Alternative Methods

Biochemical markers. An alternative method of predicting liver fibrosis involved the use of biochemical markers such as Fibrotest (FT®). Ratziu et al. (2006) conducted a study to validate the diagnostic utility of FT in patients with NAFLD. The sample consisted of 170 patients with suspected NAFLD who had undergone liver biopsies. All patients had either abnormal serum transaminases, steatosis by sonographic criteria, or one feature of the metabolic syndrome related to chronic liver disease. Two panel markers included (a) FT with total bilirubin, gamma-glutamyl transferase, Alpha-2 macroglobin, apolipoprotein A-1, and haptoglobin, corrected for age and gender, as is designed for a quantitative assessment of fibrosis; and (b) ActiTest®, which includes ALT in addition to the specified markers and is designed for a quantitative assessment of histological activity in chronic viral hepatitis. ActiTest encompasses FT and ALT. Results indicated that FT was comparable to liver biopsy for advanced liver fibrosis (Ratziu et al., 2006). There was 77% sensitivity and 90% negative predictive value for advanced fibrosis (FT score of 0.70). ALT levels did not significantly change with advancing fibrosis, so ALT levels alone were not a predictor of fibrosis.

Many comparison studies have considered the variability of liver biopsies. This variability is of clinical significance because all noninvasive tests are compared to an imperfect gold standard. Burroughs and Cholongitas (2007) provided a comprehensive

comparison of six different noninvasive tests for predicting liver fibrosis including FT, Becton Dickinson Fibrometer™, Quest Diagnostic HepaScore™, Forns index, and the aspartate aminotransferase/platelet ratio index (APRI). The sample consisted of 180 biopsies taken from 180 patients with chronic hepatitis. This comparison also included noninvasive tests such as ultrasound, computed tomography, Fibroscan®, and Doppler. Burroughs and Cholangitas could not confirm the single noninvasive test; however, they found that a combination of at least two scores improved the diagnostic accuracy. The FT and APRI, when considered together, ruled out significant fibrosis with a negative predictive value of 94.1%. The results indicated that an initial liver biopsy might still be needed, but subsequent noninvasive tests might be sufficient to follow up for a confirmation of fibrosis.

Patel et al. (2004) evaluated the diagnostic accuracy of biochemical blood panels in patients with chronic HepC to develop a predictive algorithm that differentiates between no or mild liver fibrosis (i.e., a Metavir score of F0-F1) and moderate or severe liver fibrosis (i.e., a Metavir score of F2-F4). These researchers also sought to validate the findings with external cohorts drawn from other facilities. Patel et al. included 596 patients with chronic hepatitis in their study. Serum samples from healthy volunteers served as controls for the serodiagnostic assays. Seven fibrogenesis markers were subsequently evaluated blindly in stored serum samples from the initial cohort to enable selection the optimal combination of markers to distinguish the various stages of fibrosis. Taking into consideration cost, clinical performance, and time, the following three markers were selected: HA, TIMP-1, and A2M. The three-marker panel test was used and

validated with the external cohort. Including the external cohort, a combined study population consisted of 696 patients. The overall area under-the-curve score, sensitivity, and specificity were 0.823, 76.9%, and 73.2%, respectively. A positive predictive value and accuracy rate of 75% was indicated. The three-marker panel was useful in differentiating between relative broad ranges of fibrosis but unable to separate intermediate ranges of fibrosis. Liver biopsy was still considered more sensitive in predicting liver fibrosis than was biochemical markers, but these markers might still be useful when biopsy is contraindicated.

Transient and Real-Time Ultrasound and MRI Elastography

Ultrasound-based TE has been used to detect liver fibrosis in Europe but has yet to be approved by the U.S. Food and Drug Administration for use in the United States. The one-dimensional technique is used to determine TE—the stiffness of the liver. It is best suited for excluding cirrhosis rather than predicting the condition (Bonecamp et al., 2009). Ultrasound-based TE is helpful in the diagnosis and staging of hepatic fibrosis and chronic liver disease, as well as in the detection of subtle liver tumors. The mechanical vibrations caused by elastography are proportional to the stiffness of the tissues. This technique can differentiate normal or porous liver tissue from tissue that is scarred and/or fibrotic (Pickerell, 2010). TE (i.e., Fibroscan®) is a valuable alternative to liver biopsy because of its low cost and ease of use, but a specific ultrasound unit must be purchased and cannot be used for other sonography procedures. Examination by TE is painless and the results are immediately available. A disadvantage of this technique is that accurate

measurements are difficult to obtain from obese patients and those with small intercostal spaces (Sebastiani, 2009).

Castéra et al. (2008) compared Fibroscan® with standard laboratory tests and noninvasive scores with the objective of assessing the accuracy of TE for the detection of cirrhosis and esophageal varices in patients with chronic HepC, as compared to standard laboratory tests (e.g., amino acid racemization, APRI, and platelet count) and noninvasive scores (i.e., the FT® and Lok index). TE was performed on the same day as liver biopsies on 298 patients and serum fibrosis markers were collected. The diagnostic performance of TE was found to be superior in both positive likelihood ratio and area under the ROC curve (95% CI) for the diagnosis of cirrhosis. At a cutoff of 14.6 kPa, cirrhosis could be predicted with 90% certainty and excluded with 92% certainty. The study by Castéra et al. demonstrated that TE is currently the most accurate noninvasive method for the detection of cirrhosis, but the rates of correctly identifying patients with esophageal varices did not indicate an advantage to using TE as a replacement for endoscopy in screening for esophageal varices. Because NAFLD can lead to liver fibrosis and cirrhosis, is a potential concern with the use of elastography. Many patients with NAFLD are obese, and the failure rate of TE in obese patients ranges between 2.4% and 9.4% (Castéra et al., 2008). This failure rate presents a disadvantage compared to magnetic resonance elastography (MRE).

Real-time sonographic elastography is another method that has been integrated with sonography. Sonographic elastography has been applied to many different biopsy applications including biopsies of breast, thyroid, cardiac tissue, and liver (Pickerell,

2010). An ultrasound transducer probe is mounted on a vibrator. Vibrations are sent into the liver. The vibrations of mild amplitude and low frequency (50 Hz) cause an electric shear wave to propagate into the liver (Castéra et al., 2008). The returning pulse-echo recording measures the shear wave velocity, which is directly related to tissue stiffness, and is represented by the following equation for Young's elastic modulus:

$$(E = 3\ pv^2)$$

where v = shear velocity and p = density of the tissue, which is assumed to be constant. Dedicated machine-based software determines whether each measurement (measured in kPa) is successful (Talwalkar, 2008). TE measures stiffness in a volume that approximates a cylinder 1 cm wide and 4 cm long. Because this volume represents a much larger sample than the liver biopsy, it is a superior method of detecting liver fibrosis when compared to the liver biopsy (Castéra et al., 2008).

Similar to ultrasound-based elastography, MRE is another noninvasive method that can be used to assess the elastic properties of soft tissues, including the liver (Bonekamp et al., 2009). MRE is a relatively new method for staging liver disease and more research is needed to confirm or refute the clinical utility of the method. To date, there is no commercially available MRE wave-generator device; however, MRE can be implemented on standard magnetic resonance systems by using a combination of resistive electromechanical drivers, piezoelectric devices, electromagnetic coils, or pneumatic drivers. Preliminary results have indicated that the shear elastic properties of the liver increased according to the stage of liver fibrosis. Bonekamp et al. (2009) found a statistically significant difference between patients with Metavir scores of F0 through F1

fibrosis versus those with scores of F2 through F3. The elastic maps of the liver became more heterogeneous as the extent of fibrosis increased. Replicability of MRE for elasticity and viscosity was good. Of greatest significance, MRE could clearly distinguish between the intermediate stages of fibrosis. This feat has proven difficult using biochemical testing (e.g., AST: platelet ratio index) in which only advanced fibrosis or minimal fibrosis could be separated.

Yin et al. (2007) studied the clinical utility of MRE for the detection liver fibrosis. MRE was performed on 35 volunteers with healthy livers and 50 patients with biopsy-proven liver disease. Inclusion criteria included liver biopsy within 1 year, age 18 years or older, and/or a diagnosis of compensated liver cirrhosis by histology or combination of clinical and imaging criteria. Exclusion criteria included a history of HCC or other liver tumor, contraindication for MRI such as surgical clips or a pacemaker, history of liver resection or transplantation, and/or decompensating events (e.g., esophageal variceal rupture or hepatic encephalopathy). MRE was performed using a 1.5-T whole-body imager with a full-body coil. Low-amplitude mechanical waves were introduced into the body at 60 Hz. Total acquisition time for the images was 40 seconds. MR elastogram images displayed the overall shear stiffness of the liver. The fat: water ratio was also obtained using the standard MRI liver-imaging protocol. Yin et al. found that liver stiffness correlated very well with fibrosis grades. Analysis of the ROC curve indicated that, with a shear stiffness cutoff value of 2.93 kPa, the predicted sensitivity was 98% and the specificity was 99% for detecting all grades of liver fibrosis. Yin et al. concluded that liver stiffness did not appear to be influenced by the degree of steatosis.

Preliminary results indicated that MRE was a safe and noninvasive method for the detection of liver fibrosis. The study by Yin et al. (2007) revealed several advantages to MRE over other noninvasive methods for detecting liver fibrosis. These included (a) a freely oriented field of view, (b) lack of need for an optimum field of view in contrast to TE, (c) compatibility with other MR coils, (d) operator independence, (e) insensitivity to body habitus, (f) the concurrent addition of conventional MR at the time of the study, and (g) a global view of the entire liver using a multislice method. Additional studies involving larger samples will confirm the sensitivity and specificity, as well as the diagnostic accuracy of this method.

Sonographic Imaging Assessment

Sonography evaluates liver size, shape, and internal characteristics in a noninvasive manner (Hagen-Ansert, 2006). The process uses ultrasound technology to determine the presence of chronic liver disease. In the early stages of liver disease, sonography is of limited value because the liver parenchymal pattern may appear normal; even so, sonography is useful in detecting the late chronic changes associated with cirrhosis and HCC (Obrador et al., 2006). Sonographic findings include increased coarseness of the liver, nodularity, ascites, and liver mass, if a tumor is present (Hagen-Ansert, 2006). Coarse hepatic echotexture and mildly increased echogenicity is common in cirrhosis (Nicolau et al., 2002). With advanced sonographic equipment, it is now possible to detect subtle changes in early liver disease, and the echogenicity can be graded from normal to cirrhosis (Hagen-Ansert, 2006).

Obesity may also cause architectural changes in the liver without underlying liver disease (Obrador et al., 2006). The liver may become infiltrated with fat and have an overall increase in size and echogenicity, confounding the diagnosis of liver fibrosis (Rumack, Wilson, & Charboneau, 2005). Fatty infiltration can be graded sonographically from 1 to 3 (Hagen-Ansert, 2006). At Grade 1, a slight increase in coarseness and echogenicity of the liver parenchymal pattern is typically noted (Hagen-Ansert, 2006), but the diaphragm and intrahepatic vessels can still be seen. At Grade 2, moderate increase in the coarseness and echogenicity of the liver is noted (Hagen-Ansert, 2006). Because of attenuation (i.e., weakening of the sound beam), the sound beam experiences more difficulty in penetrating the liver and there is evidence of decreased visualization of the diaphragm and intrahepatic vessels (Hagen-Ansert, 2006). At Grade 3, a marked increase in coarseness and echogenicity either with poor or absent visualization of the diaphragm and intrahepatic vessels is noted (Hagen-Ansert, 2006).

Fatty infiltration is reversible because the individual hepatocytes are filled with fat (Tilg & Diehl, 2000). Changes in diet or cessation of alcoholic beverages can reduce the fatty content and return the liver to a relatively normal and homogeneous texture. Once the liver has become fibrotic and the parenchyma degenerates, as seen in cirrhosis, the process is irreversible (Hagen-Ansert, 2006). Another sonographic measurement useful for predicting cirrhosis is the caudate: right lobe ratio (Goldberg & McGahan, 2006). When the liver becomes fibrotic, the right and left lobes tends to shrink more than the caudate lobe (Goldberg & McGahan, 2006). This disparity is due to the dual arterial blood supply to the caudate lobe. The ratio compares the transverse diameter of the

caudate to the right lobe in a transverse imaging plane. Goldberg and McGahan (2006) proposed a cutoff ratio of 0.65 after finding the proposed ratio of 0.65 or greater had a sensitivity of 84% and a specificity of 100%.

Portal Vein Diameter

An association exists between an increased portal venous diameter with liver cirrhosis and portal hypertension (Nicolau et al., 2002). The extent to which this association is a predictor of liver fibrosis has not been determined. The portal vein is easily visualized when liver texture is homogeneous, but becomes difficult to see with advanced fatty infiltration of the liver (Rumack et al., 2005). A measurement threshold of 13 mm in diameter is a predictor of portal hypertension in patients with cirrhosis (Hagen-Ansert, 2006). The present study explored the portal venous diameter (PVD) by gender (G) and by liver echogenicity grades (ECHOGRADE), as assessed by real-time sonography.

In a study conducted by Weinreb, Kumari, Phillips, and Pochaczevsky (1982), the right portal vein was measured in an anterior-posterior plane near the porta hepatis where the portal vein enters the liver. Of particular interest was whether the change in diameter would affect the overall pressure gradient. Weinreb et al. determined the normal portal vein diameter measurement on 107 patients, aged 21-40 years, is 11 +/- 2 mm. According to a known hemodynamic law, Poiseuille's law, the radius of the vessel has the largest effect on flow (Celli, 1997). Poiseuille's law states that the volume of fluid passing per unit time through a tube is directly proportional to the pressure gradient multiplied by the fourth power of the radius of the tube (Daugherty & Franzini, 1977). A more exact

method of computing the blood flow through the portal vein could be conducted by calibrating Poiseuille's model:

$$\frac{dV}{dt} = \frac{\pi R^4}{8\eta}\frac{|\Delta P|}{L}$$

where V = the volume of blood (m^3), t = the time (sec), dV/dt = the flow rate of the blood (m^3/sec), R = the radius of the vein (m), η = the dynamic fluid viscosity of the blood (Pascal.sec), ΔP = the pressure gradient (Pascals), and L = the length of the vein (m).

The radius of the vein has such a large effect on flow, and in the setting of cirrhosis, the portal vein is dilated (Hagen-Ansert, 2006). This study suggested applying a mathematical modifier based upon the difference in diameter in patients with cirrhosis or chronic liver disease and compared to the known median diameter of a portal vein in a healthy liver. For example, if the known median diameter of the portal vein in a healthy liver is 1.1 cm and the portal vein diameter of a patient with cirrhosis is 2.2 cm, then the following mathematical modifier may apply:

Measured pressure gradient (PVPG) x Portal vein ratio (PVR)

x (diameter of the portal vein x 0.5)^4.

In the example, assuming the measured pressure gradient was 2 mmHg, then the calculation for the modified pressure gradient would be as follows:

(2 mmHg) (2) (2.2 x 0.5)^4 = 5.4 mmHg

Portal vein ratio (PVR) would equate to the multiple of the mean that was determined from the known normal portal vein diameter. This modified portal vein

pressure gradient (MPVPG) more closely aligns with the pressure gradients found in endoscopy measurements (Sharara & Rockey, 2001).

Doppler Assessment

In addition to real-time imaging of the liver by sonography, complimentary techniques can improve the diagnostic capabilities, including duplex Doppler, color Doppler, power Doppler, ultrasound contrast agents, and harmonic imaging (Nicolau et al., 2002). In the liver, the portal and hepatic veins were evaluated with both color and spectral Doppler. Color Doppler displays color-coded information over the two-dimensional image to determine the presence and direction of the blood flow. The mean velocity of the red blood cells circulating into and from the liver was displayed. Blood flowing toward the transducer is indicated in red and blood flowing away from the transducer is coded as blue (Rumack et al., 2005). Flow travels toward the liver in the portal vein and away from the liver in the hepatic veins (Hagen-Ansert, 2006). Using standardized protocol, color Doppler of the portal vein was indicated in red and hepatic venous flow was indicated in blue.

Although color Doppler is advantageous in determining the presence and direction of blood flow, it is not considered a quantitative process because it lacks the ability to calculate the peak velocity. Spectral Doppler is the accepted method for determining the peak velocity and/or pressure gradient. It allows the sonographer to place a sample volume (gate) at a specific point inside the vessel. The peak velocity was measured over time. This technique produces a waveform including the peak velocity, pressure gradient, and waveform analysis. In this study, the modified portal vein pressure

gradient (MPVPG), portal vein pressure gradient (PVPG), hepatic venous pressure gradient (HVPG), and splenic vein pressure gradient (SPPG) were in the dataset as well as the hepatic venous waveform (HVW) analysis.

With liver fibrosis or cirrhosis, the liver texture becomes hardened and the flow within the vessels responds to the change in texture. The hepatic veins are usually multiphasic from the movement of the tricuspid valve annulus toward the heart apex, atrial overfilling, tricuspid valve opening, and the atrial contraction (Goldberg & McGahan, 2006). When the liver hardens, the hepatic veins can become compressed and show a more continuous flow pattern. Hardening of the liver may also trigger reversed flow in the portal vein, causing blood to take a collateral pathway from the liver to return blood to the inferior vena cava. This condition is portal hypertension (Rumack et al., 2005). Both color Doppler and spectral Doppler is invaluable in determining the intrahepatic blood flow hemodynamics. Velocity measurements alone have never been standardized (Goldberg & McGahan, 2006).

In this study, the method of testing was to translate the data from the acquired data set in pressure gradients instead of velocity measurements. Using Doppler criteria of pressure gradients instead of velocity measurements will help to establish a cutoff point at which the liver is changing from fatty infiltration to liver fibrosis. To change a velocity measurement, the Bernoulli equation was applied. The estimation of pressure differences between two anatomic structures is one of the most common applications in echocardiography (sonography of the heart). The modified Bernoulli equation states that the change in pressure is equal to 4 multiplied by the velocity squared ($4V^2$; Lai et al.,

2009). By applying the cardiac presets (Bernoulli equation) to the abdominal Doppler velocity measurements, these pressure gradients can be determined noninvasively. This method was used when acquiring the data set. The dataset values were retrospectively altered by applying a mathematical modifier, taking into account the increase in portal vein diameter with advancing liver disease.

A few noteworthy studies have focused on the association of early liver fibrosis with Doppler-derived measurements. Doppler ultrasonography is a valuable noninvasive method useful in the study of intrahepatic hemodynamics in liver disease (Bernatik et al., 2002). Bernatik et al. (2002) compared Doppler parameters of the portal vein, hepatic artery, and hepatic vein in patients with different stages of liver fibrosis. Their study included 43 patients with biopsy-proven chronic viral hepatitis without cirrhosis. All patients had elevated ALT and AST levels. Patients with a history of chronic alcoholism were excluded from the study. Both the maximum and mean velocity was measured in the portal vein. The resistive index was measured in the hepatic artery. Results indicated that with severe fibrosis and cirrhosis, there were hemodynamic changes in the hepatic vein (biphasic or monophasic) and increased resistance in the hepatic artery (Bernatik et al., 2002). In early liver fibrosis, the addition of Doppler parameters was not of clinical significance in assessing the stage of liver fibrosis or for differentiating mild fibrosis from severe fibrosis.

In another study involving 565 consecutive patients with chronic liver disease, Liu et al. (2007) used splenic arterial pulsatility index (SAPI) and portal vein mean velocities to evaluate the severity of hepatic fibrosis before liver biopsy. Using

multivariate logistic regression, it was revealed that the SAPI and the mean portal vein velocity were predictive of significant fibrosis and cirrhosis. Specifically, the predicted probability of patients having significant hepatic fibrosis and cirrhosis was a function of increased SAPI and decreased portal vein mean velocities (Liu et al., 2007). The mean velocity of the portal vein was decreased as the level of liver fibrosis increased. A possible explanation for this phenomenon is that, as the liver becomes more nodular, the intrahepatic venous flow may take the path of least resistance. It may be easier for the blood to follow collateral channels rather than course through a nodular liver. As collateral venous flow increases, the amount of flow traversing the liver may was reduced. This change in blood flow through the liver would result in lower portal venous velocity (Liu et al., 2007).

O'Donohue, Ng, Catnach, Farrant, and Williams (2004) investigated the clinical utility and diagnostic value of measuring the splenic size, portal vein velocity, hepatic venous profile, and hepatic arterial resistance in a cohort of 49 controls and 45 patients with biopsy-proven liver disease. Of all of these variables in their study, the only predictive value for liver fibrosis or cirrhosis was increased splenic size (> 15 cm) and an abnormal hepatic venous profile. Doppler parameters of portal vein velocity, portal vein diameter, and hepatic arterial resistive index were no different between the controls and patients or between cirrhotic and noncirrhotic liver disease. A possible limitation to this study was the small sample size of only 45 patients with liver disease and 49 controls.

Dietrich et al. (1998) analyzed Doppler spectral waveforms in 135 patients with chronic HepC. Spectral waveforms were analyzed in the right hepatic vein as well as the

portal vein velocity. Although previous studies (Bernatik et al., 2002; O'Donohue et al., 2004) had suggested that the change in normal triphasic waveform to monophasic was caused by liver fibrosis, the study by Dietrich et al. concluded that intrahepatic fat deposition was associated with this change more than was liver fibrosis or cirrhosis. There did not appear to be a distinct difference in the Doppler waveform of the hepatic vein in the setting of fibrosis and cirrhosis. A pronounced pulsatility in the portal vein was associated with portal inflammation. In the setting of cell death, as seen in cirrhosis, there is an inflammatory reaction. This cell death evokes an inflammatory reaction (portal inflammation) that is morphologically manifested by the appearance of inflammatory cells, together with edema and congestion around the damaged hepatocytes (Dietrich et al., 1998).

Barbaro et al. (2000) researched the correlation of MRI liver volume and Doppler sonographic portal hemodynamics with the histologic liver biopsy findings in patients with chronic HepC. The ratio between portal blood flow and liver volume determined the portal flow index (PFI) of the right and left lobes. The results reported by Barbaro et al. indicated that an elevation in the volume of the left hepatic lobe and a reduction in the left PFI might help to diagnose patients with chronic HepC and that the postprandial left PFI might also help to differentiate the degree of fibrosis. The three lobes of the liver (right, left, and caudate) are functionally different. The right lobe receives blood mainly from the superior mesenteric vein, the left lobe receives more blood from the splenic vein, and the caudate lobe receives blood from both sources (Hagen-Ansert, 2006). This

difference occurs in all individuals, not just those with liver disease. This information provided the rationale for the difference in right and left portal venous indices.

Berzigotti et al. (2005) remarked that propranolol and nadolol decrease hepatic venous pressure in patients with cirrhosis whose esophageal varices were at risk for bleeding. The study included Doppler analysis of the portal vein, superior mesenteric artery, splenic artery, and hepatic artery. Pulsatility index and resistive index measurements were obtained on the arteries and the mean velocity of the portal vein and portal vein diameter was recorded (Berzigotti et al., 2005). These Doppler parameters were compared to endoscopy-recorded HVPG pre- and posttreatment with the beta-blocker nadolol. Results indicated that with proper response, nadolol induces splanchnic (intestinal vessel) vasoconstriction and reduction of HVPG, but in patients with splanchnic vasodilatation in the baseline study, there was a reduced response to treatment with beta-blockers. HVPG repeat measurements were recommended to continually monitor the response of the treatments.

Liu et al. (2007) explored hepatic artery and splenic artery resistance in the setting of advanced liver disease. In a healthy person, the liver and spleen are considered a low-resistance vascular bed. To illustrate this point, both the liver and spleen are organs that require blood throughout the cardiac cycle, both in systole and diastole. As a result, the Doppler waveform in these arteries displays a fair amount of diastolic flow. When the liver becomes fibrotic, the liver function starts to decrease (Guthrie, 2008). In organ failure, the blood flow pattern changes as a reflection of flow demand to a nonfunctioning or poorly functioning organ. The body adapts and only provides flow to perfuse the organ

as a tissue instead of as a viable organ. In this setting, there is little or no flow in diastole and the resistive indices in these arteries increase. This situation is much like the flow to extremities. Arms and legs do not require flow throughout the cardiac cycle because they are not organs. Only in the setting of exercise, when the oxygen demand increases, is there a substantial flow in diastole. Organs should never exhibit flow like that seen in the extremities (Guthrie, 2008). The study by Liu et al. exemplified this point. In the setting of chronic liver disease, specifically liver fibrosis and cirrhosis, diastolic flow increased. This change in diastolic flow raised the SAPI. Liu et al. concluded that the SAPI was accurate in predicting both significant liver fibrosis and cirrhosis, with under-the-curve scores of 0.87 and 0.90, respectively. The change in under-the-curve scores means that the normal SAPI falls below 0.87 for fibrosis and 0.91 for cirrhosis. Additionally, the lower the SAPI, the more flow that goes to the organ through increased diastolic flow.

Liver fibrosis is a known cause of regional hepatic and systemic hemodynamic changes (Bolognesi et al., 2006). Bonekamp et al. (2009) aimed to determine if imaging modalities could diagnose and stage hepatic fibrosis and cirrhosis accurately. A systemic review of 628 studies that compared ultrasonography with elastography was performed. The inclusion criteria were studies that were written in either English or German; used liver biopsy as a reference; reported sensitivity, specificity, and diagnostic accuracy; or described a completely new imaging approach (Bonekamp et al., 2009). Studies were excluded if they did not use liver biopsy as a reference or if they had a very small sample size.

In the analysis reported by Bonekamp et al. (2009), the study by Hirata, Akbar, Horiike, and Onji (as cited in Bonekamp et al., 2009) found a lack of consistency in determining the best ultrasound markers for liver fibrosis or cirrhosis. The hepatic parenchymal pattern and splenic size were helpful in determining cirrhosis, but not necessarily discriminating between fibrosis and cirrhosis (Hirata et al., as cited in Bonekamp et al., 2009). Bonekamp et al. found that the published data on Doppler ultrasound in liver fibrosis was quite limited, showed a lack of reproducibility, and the results were contradictory. A study by Bolognesi et al. (as cited in Bonekamp et al., 2009) suggested that ultrasound and Doppler ultrasound were helpful in determining liver cirrhosis, but not (yet) clinically useful for assessing the stage of liver fibrosis.

Endoscopy Prediction of Variceal Hemorrhage

Cirrhosis is the most common cause of portal hypertension (Bolognesi et al., 2006). Portal hypertension in conjunction with liver fibrosis/cirrhosis increases the chance of morbidity or mortality. Portal hypertension occurs when the intrahepatic venous pressure exceeds systemic pressure, allowing the normal hepatopetal blood flow toward the liver to reverse and take a path of lesser resistance. Varices are portosystemic collaterals formed after preexisting vascular channels are dilated secondary to portal hypertension (Sharara & Rockey, 2001). Although there is a high prevalence of varices in patients with cirrhosis, only about one third of the patients will actually develop varices.

Screening endoscopy determines the presence and size of the varices. Endoscopy predicts variceal hemorrhage by visualization of large varices and endoscopic red signs (e.g., red wale markings) of the variceal wall. Gastroesophageal variceal hemorrhages are

a major complication of portal hypertension associated with a significant increase in morbidity and mortality. Up to 30% of initial ruptures are fatal, and it is estimated that up to 70% have recurrent bleeding (Sharara & Rockey, 2001). Because gastroesophageal rupture is the most severe complication of cirrhosis, it is necessary to determine not only if a patient has varices, but also which patients are at highest risk for rupture.

Performing upper gastrointestinal endoscopy as a screening process on every patient with cirrhosis would result in many unnecessary tests. A noninvasive method would be helpful in identifying patients with varices before endoscopy. A low platelet count is seen in patients with varices. Other prognostic factors for varices include a portal vein diameter greater than 13 mm, advanced Child-Pugh class, hypoalbuminaemia, telangiectasis, low prothrombin activity, and splenomegaly.

To predict the presence or absence of varices, a model was developed using a combination of laboratory results and portal vein diameter. This model included a platelet count of < 100,000/mm, portal vein diameter > 13 mm, and a prothrombin activity of < 70% (de Franchis, 2003). However, when this model was tested, it was found to have poor sensitivity and specificity. Specifically, 42% of the patients in the study who were classified by this model as having varices had none, and 34% who were scored at low risk had varices (de Franchis, 2003). Regarding endoscopy findings, the presence of red wale markings on varices identified using the initial endoscopy was the only true predictor of bleeding. The 2-year bleeding rate was higher on those with small varices on the initial endoscopic exam than on those without varices and that those with an alcoholic

etiology for cirrhosis tended to have a higher risk of developing varices (de Franchis, 2003).

Although the idea of using alternative methods for predicting the presence or severity of varices seems promising, to date it has not proven reliable. Screening endoscopy remains the test of choice for detection and progression of gastroesophageal varices. The addition of catheterization of the right hepatic vein to determine the pressure gradient has increased the sensitivity and specificity of identifying the risk of variceal rupture. The proposed sonographic Doppler-derived pressure method using the Bernoulli equation to obtain a pressure gradient (in mmHg) is hypothesized to be comparable to catheterization of the right hepatic vein in the ability to detect increased right hepatic venous pressure and consequently the risk of variceal rupture.

Statistical Methodology in the Study

I used logistic regression to analyze the data in this study. Logistic regression constructs models by using an iterative procedure known as a maximum likelihood method that cycles through many repetitions to find the best fit to the data. In addition, an odds ratio (OR) was computed for each *X* variable (Hosmer & Lemeshow, 2000). The calculation of the OR permits the likelihood of a specified outcome (e.g., the presence of disease) to be compared between two different groups of patients.

ORs computed using logistic regression are sometimes misinterpreted by medical researchers because the ratios might be confused with relative risks (Dawson & Trapp, 2004). For example, Moss, Wellman, and Corsonsis (2003) reported that 40% of the articles they reviewed in the medical literature did not interpret the results of logistic

regression appropriately. A detailed explanation of the OR is provided here. The OR and the relative risk (sometimes called the risk ratio) both compare the likelihood of an event (e.g., the presence of a disease) between two groups; however, the OR compares the odds, whereas the risk ratio compares the probabilities. Odds and probability are not equivalent. The probability of a patient having a disease is equal to the number patients with the disease divided by the total number of patients in the sample. The odds of a patient having a disease are the number of patients with the disease divided by numbers who do not have the disease.

Odds and probability are closely related using two formulae:

Odds = probability/(1 - probability) and probability = odds/(1 + odds)

The odds ratio for an independent (*X*) variable in a logistic regression equation is the antilogarithm of its regression coefficient. The odds ratio of *X* predicts the likelihood of the outcome changing from one category to another category, in response to a 1-unit change in the value of *X*. If OR = 1.0, then *X* has no effect on the dependent variable. If OR > 1.0, then an increase in *X* elevates the likelihood of a change in the dependent variable. If OR < 1.0, then an increase in *X* elevates the likelihood of a change in the dependent variable (Hulley et al., 2001).

A hypothetical example clarifies the interpretation of the odds ratio. Consider a binary logistic regression model comprising a dependent variable with two categories, coded 0 and 1 (where 0 represents a group of healthy patients without liver disease, and 1 represents a group of patients diagnosed with liver disease); *X* is the PVD (cm) and OR = 3.0. The interpretation of the odds ratio is that if the PVD of a patient expands by 1.0 cm

(e.g., from 1.0 cm to 2.0 cm), then the likelihood of a patient having liver disease will be 3 times greater than the likelihood of a patient not having liver disease. For *n* units of change in *X*, the log odds changes by OR^n. This relationship implies that if the diameter of the portal vein expands by 2.0 cm (e.g., from 1.0 cm to 3.0 cm), then the likelihood of a patient having liver disease is $3.0^2 = 9$ times greater than a patient not having liver disease.

Logistic regression is much less restrictive than linear regression. Unlike linear regression, the variables do not have to be normally distributed, linearity between the dependent and independent variables is not assumed, and the variance in the dependent variable does not have to be equal across all the independent variables (Hosmer & Lemeshow, 2000). Logistic regression does, however, assume that excessive multicollinearity is not present (i.e., the independent variables must not be too highly correlated with each other). If excessive multicollinearity occurs, then the logistic regression coefficients and the odds ratios are biased and the overall model becomes difficult, if not impossible, to interpret. The computed modified portal vein pressure gradient incorporates both the portal vein diameter and the portal vein pressure gradients. This pressure gradient suggests that there may be at least a moderate multicollinearity. If after logistic regression, excessive multicollinearity was suspected, a test of the relationship of these independent variables was performed. The modified portal vein pressure gradient was used in the final model. ROC was used to determine the probability of liver disease based on the independent variables (sonographic measures). ROCs were generated on only the specific independent variables that show a statistically significant

correlation between the independent variable and liver disease. Because each of the independent variables in this study are diagnostic tests, independent of each other, ROCs are an efficient way to display the relationship between sensitivity and specificity for tests that have continuous outcomes (Lang & Secic, 1997). The ROC is a plot of the sensitivity (true positives) relative to the false positive rate (Dawson & Trapp, 2004). The closer the proximity of the ROC to the upper left-hand corner of the graph, the more accurate the ROC is. In this study, the ROC was used to determine the true positives to the false negatives only on the specific independent variables that showed statistical significance by the multiple logistic regression analysis to predict liver disease. The original design was to include another category of independent variables including STATUS of disease. The independent variable shown in Table 1 was considered under the heading of STATUS:

Table 1

Independent Variable Considered Under Original Design

STATUS	Presence of a specified type of liver disease	Nominal	0 = liver disease is absent 1 = gallbladder (GB) disease 2 = nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD) 3 = hepatitis 4 = cirrhosis and ascites

A logistic regression model must be specified with respect to the measurement level of the dependent variable. In a binary logistic regression model, the dependent variable is dichotomous, representing two possible categories, coded in binary form with

0 and 1, where 0 = *a reference category* (e.g., disease is absent) and 1 = *an observed outcome* (e.g., disease is present). Binary logistic regression was therefore appropriate for this study using DISEASE as the dependent variable. The model of STATUS was proposed due to curiosity as well as the opinion that the research would be more meaningful if the independent variables could predict not only disease or no disease, but also the specific type of disease. In a nominal logistic regression model, the dependent variable represents three or more numerically coded qualitative categories (e.g., 0 = *liver disease is absent*; 1 = *gallbladder* (*GB*) *disease*; 2 = *nonalcoholic steatohepatitis* (*NASH*) *and nonalcoholic fatty liver disease* (*NAFLD*); 3 = *hepatitis*; 4 = *cirrhosis and ascites*) but no implicit hierarchy or order is implied by the codes. Nominal logistic regression was therefore appropriate for this study using STATUS as the dependent variable. However, the maximum likelihood or optimization algorithm may be limited when more than one independent variable is included (Hosmer & Lemeshow, 2000). For this reason, it was decided to forego STATUS as a dependent variable. However, after the analysis was performed, STATUS may be reintroduced for future studies. This model used the independent variables that populate a statistically significant correlation in predicting chronic liver disease using the binary logistic regression model of DISEASE.

Summary

The review of related literature presented in this chapter included recent studies to evaluate both biopsy techniques and alternative methods to predict the chronicity of liver disease, the manner in which sonography is used in the diagnosis and prediction of chronic liver disease, and how assessment of intrahepatic and splenic blood flow might

aid in earlier detection. This chapter was organized in sections according to the topics of liver biopsies, biochemical screening tests, ultrasound and magnetic resonance-based elastography, and ultrasound screening with and without Doppler. Literature about other alternative screening methods such as ultrasound-based and magnetic resonance-based elastography and biomarkers such as FT® and FibroScan® were reviewed relative to efficacy as compared to invasive liver biopsy procedures. Ultrasound and Doppler techniques are helpful in determining the presence of fatty infiltration of the liver or cirrhosis, ascites, portal vein diameter, and flow direction in the hepatoportal system (Hagen-Ansert, 2006). Further research was needed to determine if portal, hepatic, or splenic vein pressure gradients could assist in predicting chronic liver disease. The specific research design and methodology related to testing this noninvasive method in detecting liver disease as an extension of research reviewed in this chapter is presented in chapter 3.

Chapter 3: Research Methodology

Chapter 3 presents the research design and approach, sample population and size, screening criteria, and study variables for the study. The research methodology included performing a secondary data analysis of a data set that included 546 patients who received an abdominal sonogram at a medical facility in the western United States between March 2010 and December 2010. As there were 10 patients with missing data, the data set included 536 patients. This data set included the dependent variable (DISEASE) and the independent variables of liver echogenicity, portal vein diameter, and portal, modified portal, splenic, and hepatic venous pressure gradients. All information included in the data set had no patient identifiers. Binary logistic regression compared all independent variables with the dependent variable DISEASE to determine if any or all of the independent variables could noninvasively predict liver disease. The implication for social change was that if a noninvasive sonographic marker can be developed to predict individuals at risk for chronic liver disease, based on the analysis of the data, then interventional procedures such as earlier medical treatment might be performed before portal hypertension leads to irreversible damage to the liver and other organs. Additionally, if liver disease is detected earlier, the health care costs associated with providing care and services to those with chronic liver disease will decrease.

Many studies have proposed noninvasive tests to replace liver biopsy (Barbaro et al., 2000; Bernatik et al., 2002; Liu et al., 2007; Obrador et al., 2006; Sebastiani, 2009). These studies examined either a single biochemical marker or a combination of biochemical markers and other noninvasive imaging. The overarching goal of this study

was to develop a sonographic screening method that will predict chronic liver disease using Doppler-derived pressure gradients.

Research Design and Approach

The study included statistical analysis of an existing data set. The exact method and equipment used in data collection appears in Appendix A. The data set includes the following data: gender; race/ethnicity; portal vein diameter (in cm); liver echogenicity grade; portal vein, hepatic vein, and splenic vein pressure gradient (in mmHg); hepatic vein waveform analysis; and disease status. The cross-sectional study design allows for the use of standardized sonographic protocols in the patient population referred for abdominal sonograms. No additional sonographic information was added to the traditional abdominal sonographic protocol. A cross-sectional design refers to a study that is conducted at a single point in time (Creswell, 2003). The research involved analyzing the data set recorded from the abdominal sonograms.

Sample Selection and Size

The sample in the data set was drawn from residents of Fresno and Madera counties in central California and nonresidents who received their care at a health care center in the western United States. The sample includes individuals who received care from March 2010 to December 2010. The majority of these individuals are residents of the two counties. According to the U.S. Census Bureau (2006), the estimated population in these two counties in 2006 was 1,041,130. This geographic area is an economically depressed region of the United States. For the time period during which the data set was generated, Fresno County reported 13.9% of families living below the poverty level and

17.8% of individuals living below the poverty level; Madera County reported 16.5% of families living below the poverty level and 21.2% of individuals living below the poverty level. These poverty levels are notably higher than the national average of 9.6% and 13.2%, respectively (U.S. Census Bureau, 2006).

The U.S. Census Bureau (2006) reported race/ethnicities for the area as follows: 61.3% Caucasian or European American, 5.1% Black or African American, 48.2% Hispanic or Latino, 8.7% Asian, 1.1% American Indian and Alaska Native, and less than 0.1% Native Hawaiian and Other Pacific Islander. These statistics suggest that some of the Hispanic and Latino population did not mark any race. The dataset represented the same relative ratio of race/ethnicity as reported in this geographic region. The reported median household income was $45,805. The median age of residents in the two counties was 30.1. Of the population in the area under study, 50.4% were men and 49.6% were women (U.S. Census Bureau, 2006). These residents represent the individuals who are included in the data set.

The participants represented in the data set include both men and women between the ages of 18 and 70, as well as all racial and ethnic groups. Exclusionary criteria for analysis were those with known hepatocellular carcinoma, congestive heart failure, blood clotting disorder, or morbid obesity (BMI > 35), as recorded in the data set at the time of the abdominal sonogram. Demidenko (2007) reviewed various methods of analysis suitable for computing the minimum sample size for logistic regression analysis and concluded that there is no consensus on the best method. Consequently, several approaches are applied here to determine the sample size requirements for this study.

According to Long (1997), the absolute minimum sample size for binary logistic regression analysis is 100 cases. According to Hosmer and Lemeshow (2000), binary logistic regression requires a minimum of 10 and preferably 30 or more cases for each independent variable. In this study, there were potentially up to seven independent variables (PVD, PVPG, MPVPG, HVW, SVPG, HVPG, and ECHOGRADE); therefore, the minimum sample size is between 70 and 210. According to Peduzzi, Concato, Kemper, Holford, and Feinstein (1996), the absolute minimum sample size for binary logistic regression is $N = (10k) / p$ where k = the maximum number of independent variables and p = the probability of expected events in the dependent variable. In this study, the maximum number of independent variables = 7 and the expected prevalence of liver disease = .6. Consequently the minimum sample size is (10 x 7) / .6 = 117. Finally, power analysis was performed using G*Power 3.1.2 software (Erdfelder, Faul, & Buchner, 1996). The input parameters for a two-tailed test were expected prevalence of liver disease = .6; expected odds ratio = 1.5, significance level = .05 and power = .8. The computed minimum sample size = 215.

The sample size used in this study, extracted from a database containing 536 cases, reduced to 478 with the removal of those with a BMI greater than 35, was in excess of the minimum required sizes. I also stratified the sample using the variable of gender before using logistic regression analysis to adjust for other confounders. Because the male/female ratio was approximately 1:1, the available sample size remained adequate for the purposes of logistic regression analysis.

Screening Criteria

Screening criteria can either directly or indirectly affect the results of a study. Obesity is a confounder for echogenicity of the liver. As BMI increases, the liver tends to become fat-infiltrated. Patient BMI information was included in the data set. Obese patients (BMI 25-35) were included and morbidly obese (BMI > 35) were excluded from the study. A fat-infiltrated liver appears more echogenic (i.e., whiter than a normal liver) on the image (Hagen-Ansert, 2006). This appearance may mimic that of early liver fibrosis and may be indistinguishable by sonographic imaging alone. Venous pressure is increased in congestive conditions such as congestive heart failure and severe tricuspid regurgitation. Those patients with known congestive heart failure by report were excluded from the study, but it was assumed that not all patients referred for abdominal sonograms were aware of having an underlying cardiac disease.

Study Variables

Dependent variable. There was one dependent variable in this study. The dependent variable, DISEASE, divided the sample of patients into two mutually exclusive groups according to whether or not the patients were diagnosed with liver disease. DISEASE was coded in binary format, where 0 = *disease is absent* and 1 = *disease is present* (see Table 2). The information used to validate the dependent variables was based on the medical records for each patient, including the results of liver function tests (e.g., AST and ALT).

Variables. The dependent and independent variables are listed in Table 1.

Table 2

Dependent and Independent Variables

Variable	Definition	Level	Groups/Units/Codes/ Measures
	Dependent variable		
DISEASE	Presence of liver disease	Nominal	0 = liver disease is absent 1 = liver disease is present
	Independent variables		
PVD	Portal vein diameter	Interval	Cm
MPVPG	Modified portal vein pressure gradient = PVPG x RPVD x PVR4		
HVPG	Doppler-derived hepatic vein pressure gradient		
SVPG	Doppler-derived splenic vein pressure gradient		
PVPG	Doppler-derived portal vein pressure gradient		
HVW	Doppler measures of hepatic vein waveform	Ordinal	1 = monophasic (continuous flow due to increased liver resistance or cardiac overload) 2 = biphasic (some resistance to flow) 3 = triphasic (normal)
ECHO-GRADE	Sonographic measures echogenicity	Ordinal	0 = normal (not echogenic) 1 = grainy liver (vessels and diaphragm seen) 2 = fatty liver (vessels not seen, diaphragm seen) 3 = fatty liver (vessels and diaphragm not seen)

The first group of independent variables included morphometric (changes is size, shape, or characteristics) measures of the hepatic venous system made at the interval level, specifically the portal vein diameter (PVD). The mean PVD should be about 1.1 cm (Wiersema, Chak, Kopecky, & Wiersema, 1995). The second group of independent variables included physiological measurements of the venous system made at the interval level, specifically the Doppler-derived pressure gradients for the hepatic vein (HVPG) and the splenic vein (SVPG) in mmHg. The third group of independent variables included the results of diagnostic tests, specifically the Doppler measures of hepatic vein waveform (HVW), indicated by spectral analysis, measured on an ordinal scale from 1 to 3, and the sonographic measures of echogenicity (ECHOGRADE), measured on an ordinal scale from 0 to 4.

The modified portal vein pressure gradient (MPVPG), when combined the physiological and the morphometric measures into one composite variable, was assumed proportional to the blood flow through the portal vein. Proportionality of these combined measures is important because the portal vein blood flow profile is closely related to liver disease status. MPVPG was based on Poiseuille's law, which states that the volume of fluid passing per unit time through a tube is directly proportional to the pressure gradient multiplied by the fourth power of the radius of the tube (Daugherty & Franzini, 2007). A more exact method of computing the blood flow through the portal vein is derived by calibrating using Poiseuille's model:

$$\frac{dV}{dt} = \frac{\pi R^4}{8\eta}\frac{|\Delta P|}{L}$$

where V = the volume of blood (m^3), t = the time (sec), dV/dt = the flow rate of the blood (m^3/sec), R = the radius of the vein (m), η = the dynamic fluid viscosity of the blood (Pascal.sec), ΔP = the pressure gradient (Pascals), and L = the length of the vein (m). All the parameters needed to calibrate the model were not available for the purposes of this study but are constant within each individual subject.

Covariates. Demographic profiles of the patients were recorded in the data set in terms of their gender and ethnicity. The BMI of each patient was also recorded. Gender could influence the relationship between the dependent and independent variables. The liver is a sexually dimorphic organ, exhibiting major physiological and biochemical differences between men and women (Colby, 1980). The statistical analysis was stratified to take into account possible differences between men and women. The category of gender was represented in the data set by dummy binary variables coded with 1 = *male* and 2 = *female*. Ethnicity was recorded to ensure that the dataset adequately reflected the general population but is a control variable, not an independent variable (see Table 3).

Table 3

Covariates

Variable	Definition	Level	Measurement
AGE	Age of participant	Nominal	Only those 18-75 were included in dataset
BMI	Body mass index	Nominal	Only those with BMI < 35 were included in dataset
HISPANIC	Caucasian or non-Caucasian Hispanic ethnicity	Nominal	0 = not Hispanic 1 = Hispanic
BLACK	African American ethnicity	Nominal	0 = not African American 1 = African American
WHITE	Caucasian ethnicity	Nominal	0 = not Caucasian 1 = Caucasian

Analysis

This study compared the sensitivity and specificity of the independent variables with respect to predicting the dependent variable. Specifically, the portal, hepatic, and splenic vein pressure gradients, HVW analysis, liver echogenicity, and portal vein diameter from the data set were analyzed. The exact method of data collection appears in Appendix A.

Logistic Regression

Logistic regression analysis conducted with SPSS Version 17 was used to construct predictive models defined by the following generalized equation:

$$log\ p/\ (1\text{-}p) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + ... + \beta_k X_k$$

where $\log \pi/(1-\pi)$ is the logit (log odds) of an outcome defined by the coding of the dependent variable, p = the probability of an outcome defined by the coding of the dependent variable, β_0 is a constant or baseline value, and $\beta_1, \beta_2 \ldots \beta_k$ are the logistic regression (β) coefficients for k independent or predictor (X) variables (Hosmer &

Lemeshow, 2000). A logistic regression model is specified properly according to the measurement level of the dependent variables. In a binary logistic regression model, the dependent variable is dichotomous, representing two possible categories, coded in binary form with 0 and 1, where 0 = *a reference category* (e.g., disease is absent) and 1 = *an observed outcome* (e.g., disease is present). Binary logistic regression was appropriate for the study using DISEASE (see Table 2) as the dependent variable.

Statistical Assumptions

Logistic regression is much less restrictive than linear regression. Unlike linear regression, the variables do not have to be normally distributed, linearity between the dependent and independent variables is not assumed, and the variance in the dependent variable does not have to be equal across all the independent variables (Hosmer & Lemeshow, 2000). Logistic regression does, however, assume that excessive multicollinearity is not present (i.e., the independent variables must not be too highly correlated with each other). If excessive multicollinearity occurs, then the logistic regression coefficients and the odds ratios are biased and the overall model becomes difficult, if not impossible, to interpret. The computed modified portal vein pressure gradient incorporated both the portal vein diameter and the portal vein pressure gradients. This combination suggested that there may be at least a moderate degree of multicollinearity. For this reason, I used only the modified portal vein pressure gradient in the final model. In this study, logistic regression determined whether chronic liver disease can or cannot be determined, noninvasively, by any or all of the independent variables including the PVD, HVPG, PVPG, MPVPG, SVPG, HVW, or ECHOGRADE.

To determine the probability of liver disease based on the independent variables (sonographic measures), ROCs was employed. ROCs were generated on only the specific independent variables that showed a statistically significant correlation between the independent variable and liver disease. ROCs are an efficient way to display the relationship between sensitivity and specificity for tests that have continuous outcomes. The ROC is a plot of the sensitivity (true positives) relative to the false positive rate (Dawson & Trapp, 2004). The closer the proximity of the ROC to the upper left-hand corner of the graph, the more accurate the ROC is. In this study, the ROC was be used to determine the true positives to the false negatives only on the specific independent variables that showed statistical significance by the multiple regression analysis to predict liver disease.

Overall, data analysis sought to answer the following research question:
Will the hepatic venous pressure gradient (HVPG), the hepatic venous waveform (HVW), portal vein diameter (PVD),the portal vein pressure gradient (PVPG), the modified portal vein pressure gradient (MPVPG), the splenic vein pressure gradient (SVPG), and the echograde (ECHOGRADE) predict the presence or absence of liver disease after controlling for age, ethnicity, and BMI, and after stratification by gender?

- Null hypothesis: The hepatic venous pressure gradient (HVPG), the hepatic venous waveform (HVW), portal vein diameter (PVD), the portal vein pressure gradient (PVPG), the modified portal vein pressure gradient (MPVPG), the splenic vein pressure gradient (SVPG), or the echograde

(ECHOGRADE) will not predict the presence or absence of liver disease after controlling for age, ethnicity, and BMI, and after stratification by gender.

- Alternate hypothesis: One or more of the following, including hepatic venous pressure gradient (HVPG), the hepatic venous waveform (HVW), portal vein diameter (PVD), the portal vein pressure gradient (PVPG), the modified portal vein pressure gradient (MPVPG), the splenic vein pressure gradient (SVPG), or the echograde (ECHOGRADE) will predict the presence or absence of liver disease after controlling for age, ethnicity, and BMI, and after stratification by gender.

One aspect of the study that ensured internal validity was the characterization of the dependent and independent variables. Those patients with known hepatitis, liver fibrosis, cirrhosis, or esophageal varices had their diagnosis validated by laboratory results contained in the patients' electronic medical records to ensure the patients belonged in the respective group. This information was assumed to be accurate in the data set.

Protection of Patient's Rights

Informed consent was not required for this study because the study involved a retrospective secondary data analysis of a data set with no patient identifiers. In the original data collection, a description of the protection of participants' rights was made available to all patients at the time of registration for their abdominal sonogram appointment. This protocol adhered to the mandates of the Health Insurance Portability and Accountability Act of 1996. This act protects the privacy of health information that

could identify the respective patient and is strictly followed by hospitals to protect patient rights (U.S. Department of Health and Human Services, n.d.). The participants in the data set included patients referred for abdominal sonograms. Hospital internal review board approval was properly obtained for the original data collection. The data set did not include any identifying patient information such as the medical record number. All data was recorded in numerical order only (i.e., 0001, 0002, 0003). Paper copies of the recorded data will be maintained by me in a secure file until 5 years after study completion. The database will be maintained on an external hard drive purchased exclusively for the study and maintained solely by the researcher. The database is password-protected to prevent unauthorized access. I obtained Walden institutional review board approval to conduct the research. The approval number was 08-08-11-0075423.

Summary

The ability to noninvasively detect liver disease is of great importance in selection of treatment strategies, as well as in the prediction of overall prognosis. The gold standard for assessing liver disease, the liver biopsy, is an invasive procedure that carries risks. Despite the limitations of liver biopsy and in the absence of better alternatives, it remains the gold standard for assessing the severity of liver inflammation and fibrosis. Noninvasive tests will predict the chronicity of liver disease and eliminate reliance on liver biopsy alone to allow patients to receive more timely diagnosis and treatment before irreversible damage occurs. This research sought to predict, through a novel noninvasive Doppler method, the presence or absence of chronic liver disease. The chosen statistical

analysis included both multiple logistic regression and ROC curves to analyze the data in the preexisting dataset. Chapter 4 describes the results of the statistical analysis and clinical significance of the findings.

Chapter 4: Results

This chapter presents the results of the analysis of the relationship between the pressure gradient in the portal vein, splenic vein, or hepatic vein, and increased liver echogenicity, hepatic venous waveform, or portal vein diameter and diagnosis of liver disease after controlling for gender, ethnicity, and BMI. The demographics of the patients, and their morphometric, physiological, and diagnostic measures are statistically described, based on a preexisting data set. I used binary logistic regression to determine whether an increase in the portal vein diameter (PVD) associated with an elevated modified pressure gradient in the portal vein (MPVPG), together with changes in the pressure gradients in the splenic vein (SVPG) and hepatic vein (HVPG), higher echogenicity (ECHOGRADE), and changes in the hepatic venous waveform (HVW) phases were statistically significant predictors of the likelihood of liver disease. I computed sensitivities, specificities, and ROC curves to compare the probabilities at which MPVPG, ECHOGRADE, and HVW correctly identified the presence of liver disease in male patients and female patients. This chapter presents the findings in five sections, including screening, descriptive statistics, collinearity, binary logistic regression analysis, and sensitivity and specificity.

Screening

I screened the variables for 545 cases recorded between March 2010 and December 2010 in a database at one medical center in the western United States. I identified numerous missing values, originally entered as a blank or a zero (see Table 4). After exclusion of cases with missing values, the total number of cases was 522. The

database included a capacity to classify three mutually exclusive categories of Hispanic patients (i.e., Hispanic White, Hispanic Black, and Hispanic American Indian); however, no patients were recorded in these categories. All Hispanic patients were therefore grouped into one category.

Table 4

Variables and Missing Values

Variable	Definition	Measures	Missing
GENDER	Gender	0 = female 1 = male	0
BMI	Body mass index	kg/m^2	4
WHITE	White race (not Hispanic)	0 = no 1 = yes	0
BLACK	Black race (not Hispanic)	0 = no 1 = yes	0
HISPANIC	Hispanic race	0 = no 1 = yes	0
OTHER	Asian or American Indian	0 = no 1 = yes	0
DISEASE	Presence of liver disease	0 = liver disease absent 1 = liver disease present	0
PVD	Portal vein diameter	mm	5
PVPG	Portal vein pressure gradient	mmHg	14
MPVPG	Modified portal vein pressure gradient	mmHg mm^4	19
HVPG	Doppler-derived hepatic vein pressure gradient	mmHg	3
SVPG	Doppler-derived splenic vein pressure gradient	mmHg	27
HVW	Doppler measures of hepatic vein waveform	1 = monophasic (continuous flow due to increased liver resistance or cardiac overload) 2 = biphasic (some resistance to flow) 3 = triphasic (normal)	4
ECHO-GRADE	Sonographic measures of echogenicity	0 = normal (not echogenic) 1 = grainy liver (vessels and diaphragm seen) 2 = fatty liver (vessels not seen, diaphragm seen) 3 = fatty liver (vessels and diaphragm not seen)	4

Descriptive Statistics

Demographics

The demographic profiles of the patients are summarized in Table 5 and Table 6. Ethnicity defines a group of people who share a common heritage, language, culture, religion, and/or ideology; however, the database did not classify patients according to ethnicity, as assumed by the null hypothesis. The categories included in the variable RACE were WHITE (not Hispanic); BLACK (not Hispanic); HISPANIC, or OTHER (Asian or North American Indian; see Table 5).

Table 5

Frequency Distributions of GENDER, BMI, RACE, DISEASE, HVW, and ECHOGRADE

		Female		Male			
Variable	Value/code	*f*	%	*f*	%	*N*	%
GENDER		251	48.1%	271	51.9%	522	100.0%
BMI	< 25 kg/m^2	89	17.0%	72	13.8%	161	30.8%
	25-35 kg/m^2	140	26.8%	164	31.4%	304	58.2%
	> 35 kg/m^2	22	4.2%	35	6.7%	57	10.9%
RACE	WHITE (not Hispanic)	68	13.0%	84	16.1%	152	29.1%
	BLACK (not Hispanic)	34	6.5%	36	6.9%	70	13.4%
	HISPANIC	104	19.9%	112	21.5%	216	41.4%
	OTHER	45	8.6%	39	7.5%	84	16.1%
DISEASE	Absent	96	18.4%	100	19.2%	196	37.5%
	Present	155	29.7%	171	32.8%	326	62.5%
HVW	1 = monophasic	35	6.7%	42	8.3%	78	15.0%
	2 = biphasic	77	14.8%	87	16.8%	164	31.6%
	3 = triphasic (normal)	137	26.4%	140	27.0%	277	53.4%
ECHO GRADE	0 = normal	21	4.0%	17	3.3%	38	7.3%
	1 = grainy liver	80	15.4%	66	12.7%	146	28.0%
	2 = fatty liver	101	19.4%	125	24.0%	226	43.4%
	3 = fatty liver	49	9.4%	62	11.9%	111	21.3%

The sample consisted of 522 patients, with an approximately equal number of male patients (n = 251, 48.1%) and female patients (n = 271, 51.9%). The dominant race was Hispanic (n = 216, 41.4%), followed in order of percentages by White (n = 152, 29.1%), other races (n = 84, 16.1%), and Black (n = 70, 13.4%). Men and women were relatively equally represented within each racial group (see Table 6).

Table 6

Cross-Tabulation of BMI and GENDER

BMI (kg/m^2)	Measure	GENDER Female	GENDER Male	Total
< 25	*f*	89	72	161
	% within GENDER	35.5%	26.6%	30.8%
	% of Total	17.0%	13.8%	30.8%
25-35	*f*	140	164	304
	% within GENDER	55.8%	60.5%	58.2%
	% of Total	26.8%	31.4%	58.2%
> 35	*f*	22	35	57
	% within GENDER	8.8%	12.9%	10.9%
	% of Total	4.2%	6.7%	10.9%

Over half (n = 304, 58.2%) of the patients were classified as overweight to obese (BMI = 25-35 kg/m^2). Over one tenth (n = 57, 10.9%) of the patients were excessively overweight (BMI > 35 kg/m^2). The cross-tabulation (see Table 6) indicated that relatively similar proportions of male patients and female patients were within each BMI group.

Prevalence of Liver Disease

Among the 326 patients identified with liver disease, 97 (29.8%) were diagnosed with hepatitis, 94 (28.8%) with gallbladder disease, 68 (20.9%) with cirrhosis or ascites, and 67 (20.6%) with nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD). The prevalence of liver disease in the sample was relatively equally distributed between female patients (n = 155, 29.7%) and male patients (n = 171, 32.8%). Liver disease was prevalent among all the racial groups in the sample. Cross-tabulations revealed the greatest prevalence of liver disease among the Hispanic female patients. Of 104 Hispanic female patients, 72 (46.5%) had liver disease. Among 112 Hispanic male patients, 72 (42.1%) had liver disease (see Table 7).

Table 7

Prevalence of Liver Disease, Stratified by GENDER and RACE

			DISEASE		
GENDER	RACE	Measure	Disease absent	Disease present	*N*
Female	White	*f*	30	38	68
		% within DISEASE	31.3%	24.5%	27.1%
		% of total	12.0%	15.1%	27.1%
	Black	*f*	13	21	34
		% within DISEASE	13.5%	13.5%	13.5%
		% of total	5.2%	8.4%	13.5%
	Hispanic	*f*	32	72	104
		% within DISEASE	33.3%	46.5%	41.4%
		% of total	12.7%	28.7%	41.4%
	Other	*f*	21	24	45
		% within DISEASE	21.9%	15.5%	17.9%
		% of total	8.4%	9.6%	17.9%
Male	White	*f*	34	50	84
		% within DISEASE	34.0%	29.2%	31.0%
		% of total	12.5%	18.5%	31.0%
	Black	*f*	13	23	
		% within DISEASE	13.0%	13.5%	13.3%
		% of total	4.8%	8.5%	13.3%
	Hispanic	*f*	40	72	112
		% within DISEASE	40.0%	42.1%	41.3%
		% of total	14.8%	26.6%	41.3%
	Other	*f*	13	26	39
		% within DISEASE	13.0%	15.2%	14.4%
		% of total	4.8%	9.6%	14.4%

The true prevalence of a disease is defined as "the total number of existing cases of a given disease at a given time, divided by the population at that time" (Kuzma & Bohnenblust, 2005, p. 292). The minimum sample size (*N*) required to evaluate the true prevalence of a given disease in a population, with a margin of error of 5%, is computed using the formula

$$N = Z^2 [\hat{P} (1- \hat{P})] / e^2$$

where $Z = 1.96$; $\hat{P}$ is a point estimate or a best guess of the prevalence, based on a random sample, and $e = .05$. The point estimate based on my study sample (i.e., the patients treated at a medical center in the western United States from March 2010 to December 2010) was 326 / 522 = .625 or 62.5%. Substituting $\hat{P} = .625$ into the formula indicates that the minimum sample size to evaluate the true prevalence of liver disease in the population is $N = 360$, assuming a 5% margin of error. Consequently, a sample size of $N = 522$ appears to be sufficiently large to measure the true prevalence of liver disease among the population of all patients treated at the medical center; however, because my study sample was not collected at random, the point estimate is biased and the true prevalence of liver disease in the population might not be accurately evaluated.

Morphometric and Physiological Measures

The PVD measurements were normally distributed, reflected by bell-shaped frequency distributions, whereas the frequency distributions for the MPVPGs were skewed (see Figure 1).

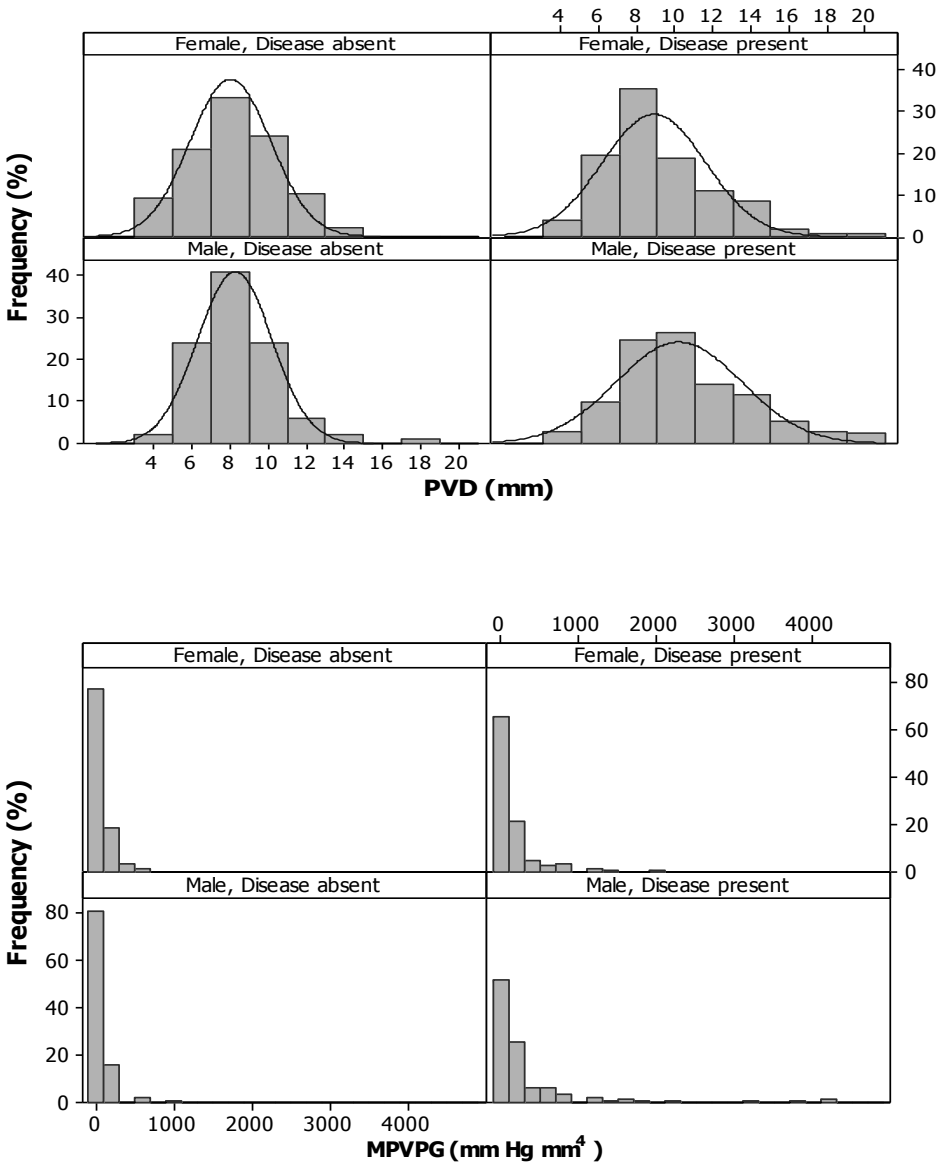

Figure 1. Frequency distributions of PVD and MPVPG.

Figure 2 illustrates the differences between the mean PVD measurements of male and female patients in the presence and absence of liver disease.

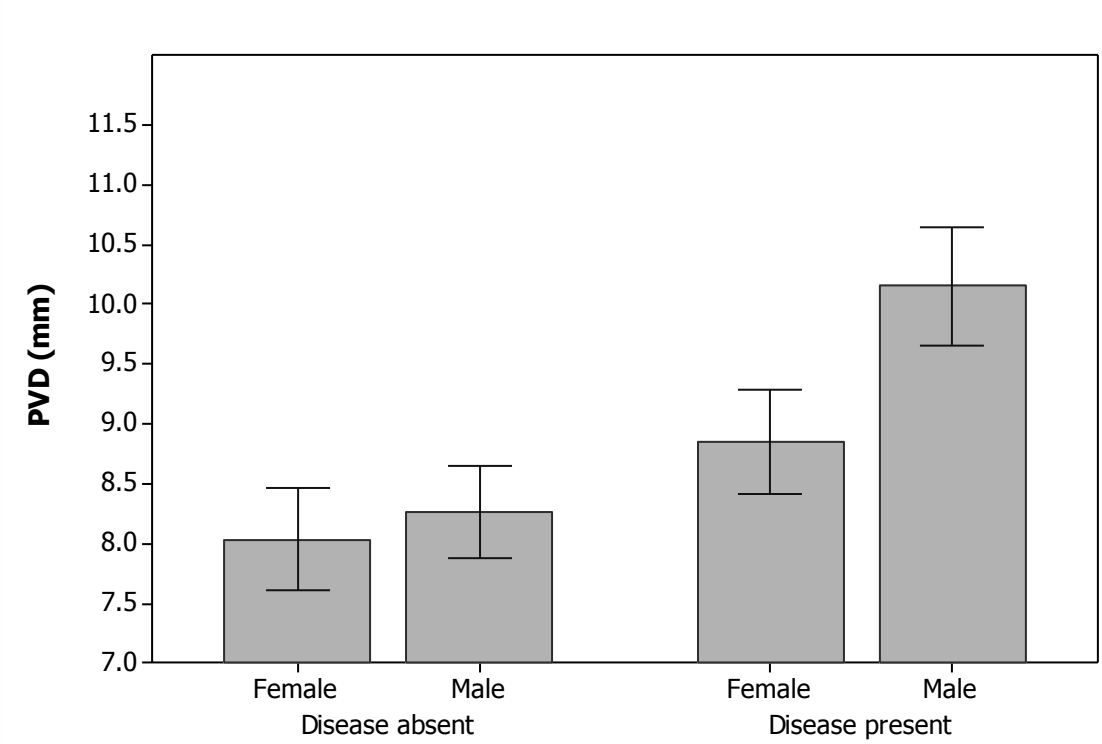

Figure 2. Mean PVDs, ± 95% CI.

When liver disease was absent, the mean PVD (mm) in male patients (M = 8.27, SD = 1.95) was .24 mm wider than in female patients (M = 8.03, SD = 2.11). However, an independent samples t test indicated that this difference was not significant at $\alpha = .05$ (t (194) = .812, p = .418). When liver disease was present, I observed sexual dimorphism of the portal vein diameter. The mean PVD in male patients (M = 10.15, SD = 3.30) was 1.3 mm wider than in female patients (M = 8.85, SD = 2.72). An independent samples t test assuming equal variances indicated that the difference between the mean PVD in male patients and female patients with liver disease was statistically significant at $\alpha = .05$

(t (324) = 3.911, p < .001). Sexual dimorphism of the portal vein had implications for the computation of the ratio of the observed PVD to the mean PVD in the absence of liver disease (RPVD). The RPVD (PVD/M) was calculated assuming M = 8.27 mm for male patients and M = 8.03 mm for female patients.

Theoretically, it is not essential that the variables in a binary logistic regression analysis be normally distributed; however, highly skewed predictor variables might cause instability including inaccurate odds ratios and 95% confidence intervals (Hosmer & Lemeshow, 2000). A $\log_{10}$ (logt) transformation was therefore used to normalize the MPVPG measurements. Normality was indicated by approximately bell-shaped frequency distributions (see Figure 3).

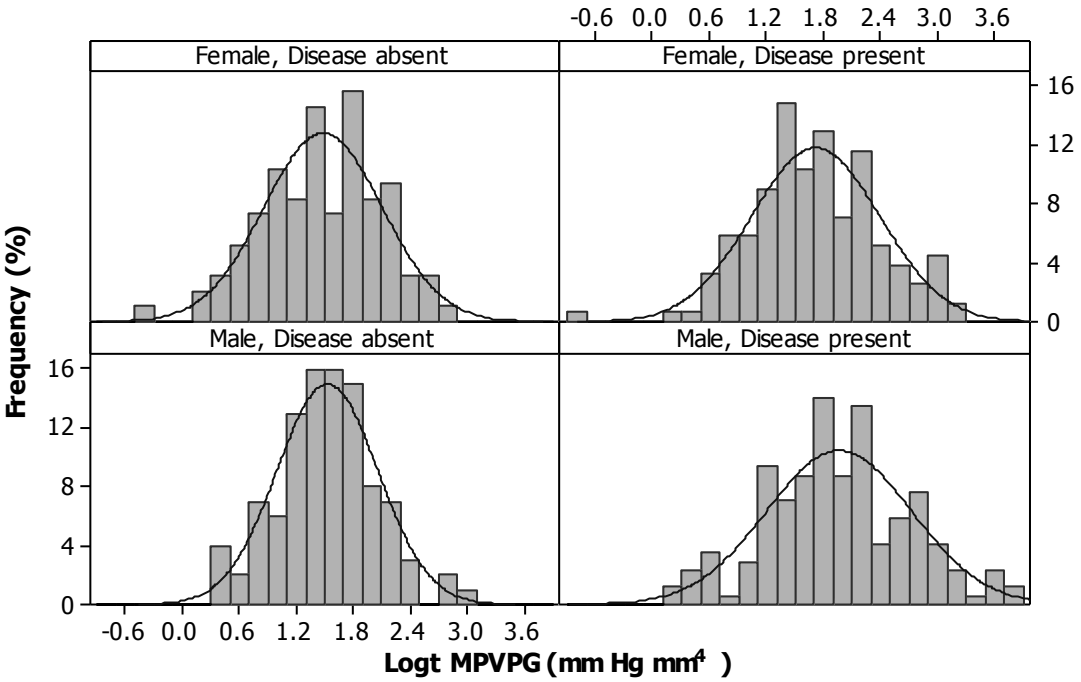

Figure 3. Frequency distribution of logt MPVPG.

The mean logt MPVPGs ± 95% confidence intervals in male and female patients with and without liver disease are compared in Figure 4. When liver disease was absent, the MPVPG in male patients (logt M = 1.527, SD =.532; antilog M = 33.65) was similar to that in female patients (logt M = 1.482, SD = .622; antilog M = 30.33). An independent samples t test assuming equal variances indicated that the difference in mean MPVPG with respect to gender was not statistically significant at α = .05 (t (194) = .511, p = .582). When liver disease was present, the MPVPG in men (logt M = 1.958, SD = .763; antilog M = 90.78) was higher than that in women (logt M = 1.711, SD = .675; antilog M = 51.40). An independent samples t test assuming equal variances indicated that the difference between the logt mean MPVPG in male patients and female patients with liver disease was statistically significant at α = .05 (t (324) = 3.079, p = .002).

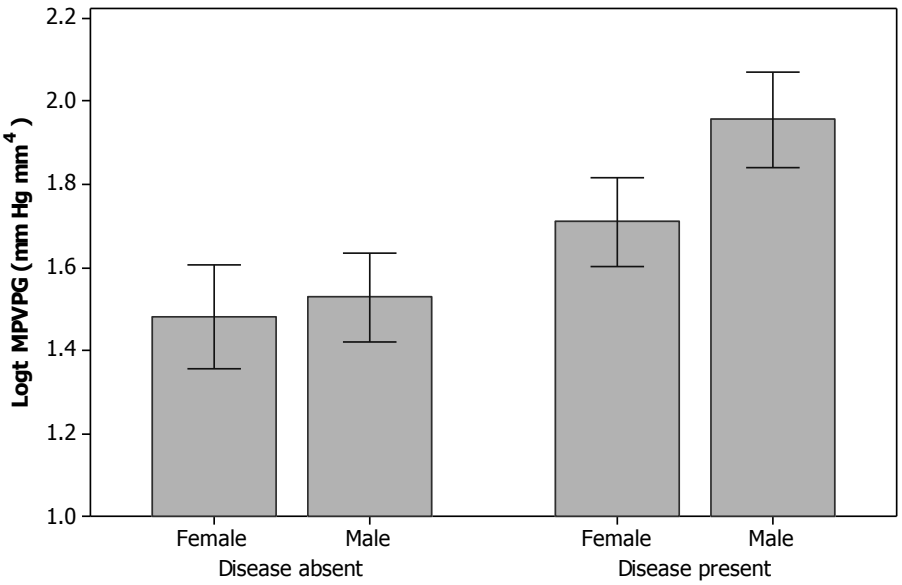

Figure 4. Mean logt MPVPGs ± 95% CIs with respect to DISEASE and GENDER.

The skewed HVPG and SVPG measurements were normalized by logarithmic transformations. For a graphic representation to compare the logarithmically transformed measurements ± 95% confidence intervals (see Figure 5.)

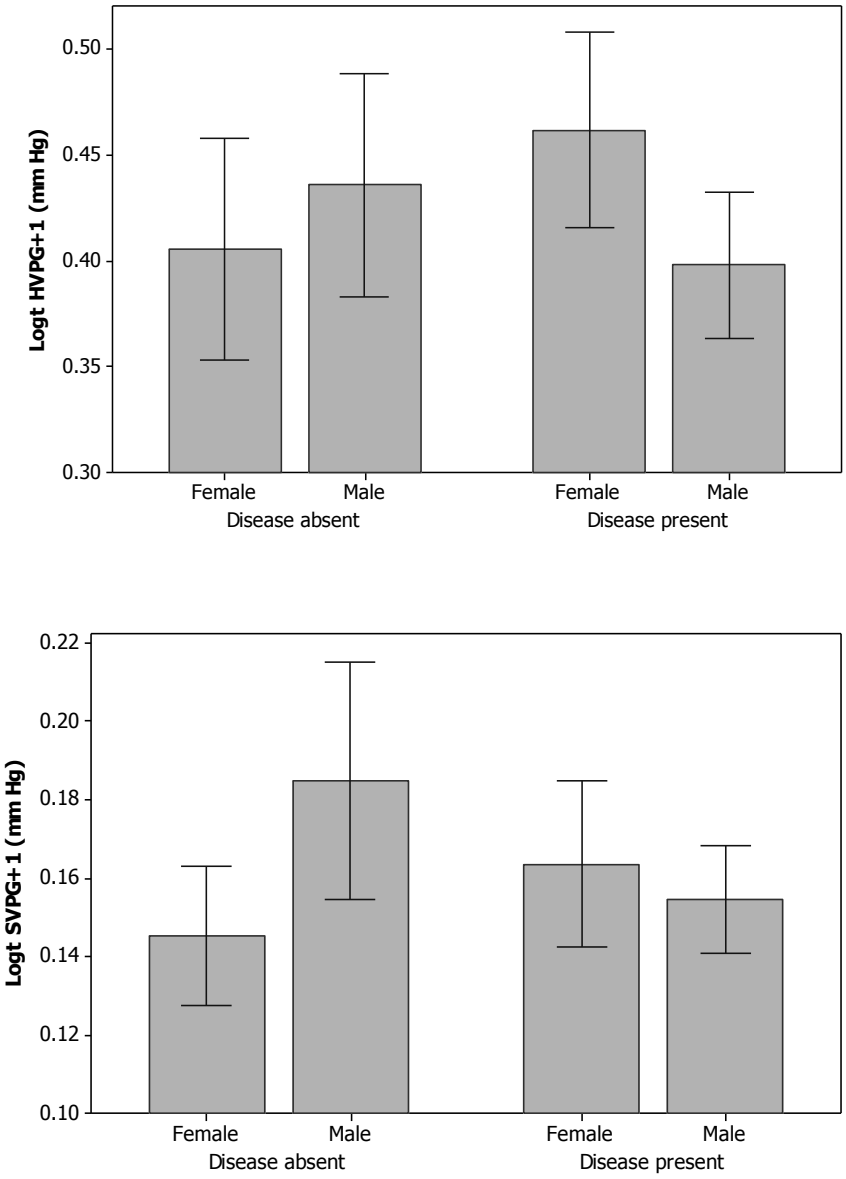

Figure 5. Mean HVPGs and SVPGs ± CIs with respect to DISEASE and GENDER.

Independent samples *t* tests assuming equal variances revealed no statistically significant differences at α = .05 between the mean logt HVPG in male patients and female patients when liver disease was absent (*t* (189) = .719, *p* = .473) and when liver disease was present (*t* (314) = 1.797, *p* = .073). I found a statistically significant difference in the mean logt SVPG between male patients and female patients when liver disease was absent (*t* (165) = 2.168, *p* = .032) but not when liver disease was present *(t* (293) = .859, *p* = .859).

Hepatic Vein Waveform

Cross-tabulation revealed that among 325 patients diagnosed with liver disease, the abnormal monophasic and biphasic waveforms (HVW 1 and HVW 2) were observed among 175 (53.8%), compared to 67 (34.5%) of the 194 patients who were not diagnosed with liver disease (see Table 8).

Table 8

Cross-Tabulation of Prevalence of Liver Disease and HVW Phase

		DISEASE		
HWV phase	Measure	Disease absent	Disease present	*N*
1 (monophasic)	*f*	13	65	78
	%	2.5%	12.5%	15.0%
2 (biphasic)	*f*	54	110	164
	%	10.4%	21.2%	31.6%
3 (triphasic)	*f*	127	150	277
	%	24.5%	28.9%	53.4%
Total		194	325	519
%		37.4%	62.6%	100.0%

Echogenicity

I found positive echogenic evidence for fatty liver (ECHOGRADE > 1) in over three quarters (n = 250, 76.9%) of the 325 patients who were diagnosed with liver disease, and in less than half (n = 87, 44.4%) of the 196 patients who did not have liver disease (see Table 9).

Table 9

Cross-Tabulation of Prevalence of Liver Disease and ECHOGRADE Score

		DISEASE		
ECHOGRADE	Measure	Disease absent	Disease present	*N*
0 (normal)	*f*	29	9	38
	%	5.6%	1.7%	7.3%
1 (grainy liver; vessels and diaphragm seen)	*f*	80	66	146
	%	15.4%	12.7%	28.0%
2 (fatty liver; vessels not seen; diaphragm seen)	*f*	62	164	226
	%	11.9%	31.5%	43.4%
3 (fatty liver; vessels and diaphragm not seen)	*f*	25	86	111
	%	4.8%	16.50%	21.30%
Total		196	325	521
%		37.6%	62.4%	100.0%

Collinearity

Collinearity inflates the variances, resulting in lack of statistical significance for the predictor variables, and the wrong signs and magnitudes for the regression coefficients (Homer & Lemeshow, 2000). Consequently, I explored the intercorrelations using a matrix of Cramer's V coefficients between the nominal and/or ordinal level

variables (see Table 10) and Spearman's rank correlation coefficients between the ordinal and/or interval level variables (see Table 11).

Table 10

Correlations (Cramer's V Coefficients) Between DISEASE, BMI, RACE, HVW, and ECHOGRADE

Gender	Variable	DISEASE	BMI	RACE	HVW
Female	BMI	.128			
	RACE	.138	.211*		
	HVW	.155*	.159*	.103	
	ECHOGRADE	.371*	.126	.082	.107
Male	BMI	.100			
	RACE	.053	.046		
	HVW	.271*	.073	.115	
	ECHOGRADE	.333*	.069	.106	.156*

Note. * Significant correlation at $p < .05$.

Table 11

Correlations (Spearman's Rank Coefficients) Between BMI, MPVPG, SVPG, HVPG, ECHOGRADE, HVW, and PVD

GENDER	VARIABLE	BMI	MPVPG	SVPG	HVPG	ECHOGRADE	HVW
Female	MPVPG	.085					
	SVPG	-.069	.163*				
	HVPG	.115	.051	-.057			
	ECHOGRADE	.070	-.076	-.036	-.034		
	HVW	.200*	-.152*	-.121	.038	-.111	
	PVD	.083	.945*	.092	.040	-.057	-.161*
Male	MPVPG	-.208*					
	SVPG	-.053	.179*				
	HVPG	-.023	.052	.041			
	ECHOGRADE	.014	.018	-.042	-.033		
	HVW	.070	.132*	-.127*	-.029	-.158*	
	PVD	-.213*	.952*	.141*	.051	.061	-.142*

Note. * Significant correlation at $p < .05$.

The dependent variable DISEASE was positively correlated with HVW and ECHOGRADE at $p < .05$ in both male patients and female patients, reflecting the significance of Doppler measures of HVW and sonographic measures of echogenicity for the diagnosis of liver disease (see Table 11). I found some statistically significant coefficients (Cramer's $V = .159$ to $.211$) between BMI and RACE (see Table 11) and between the MPVPG, SVGP, ECHOGRADE, and HVW (Spearman's $\rho = .132$ to $.163$), reflecting weak correlations between the predictor variables (see Table 12). The MPVPG is a mathematical function of the PVD; consequently, the MPVPG and the PVD were strongly correlated (Spearman's $\rho = .945$, $p < .001$ for women and Spearman's $\rho = .952$, $p < .001$ for men).

Table 12

Logistic Regression Model I to Predict the Presence of Liver Disease Among Female Patients (N = 251, Including BMI > 35)

								95% CI for OR	
Gender	Predictor	*B*	*SE*	Wald	*df*	*p*	*OR*	Lower	Upper
Female	WHITE	.091	.517	.031	1	.860	1.095	.398	3.017
	BLACK	.145	.584	.062	1	.803	1.156	.368	3.629
	HISPANIC	.972	.497	3.830	1	.050*	2.643	.999	6.998
	LogtMPVPG	.751	.282	7.111	1	.008*	2.118	1.220	3.678
	LogtSVPG	.605	.890	.462	1	.497	1.831	.320	10.488
	LogtHVPG	.697	.624	1.245	1	.264	2.007	.590	6.821
	ECHOGRADE			35.372	3	< .001*			
	ECHOGRADE(1)	.759	.571	1.766	1	.184	2.137	.697	6.550
	ECHOGRADE(2)	2.496	.596	17.533	1	< .001*	12.131	3.772	39.016
	ECHOGRADE(3)	3.158	.740	18.219	1	< .001*	23.535	5.519	100.366
	HVW			5.975	2	.051			
	HVW(1)	1.190	.636	3.502	1	.061	3.287	.945	11.430
	HVW(2)	.738	.391	3.567	1	.059	2.091	.973	4.495
	Constant	-2.264	1.178	3.696	1	.055	.104		

Note. B = regression coefficient. *SE* = standard error. Wald = Wald's χ^2. OR = odds ratio. CI = confidence interval. * Significant at $p < .05$.

Binary Logistic Regression Models

Although I identified statistically significant correlations between MPVPG, HVPG, ECHOGRADE, SVPG, and HVW (see Table 12), I found no evidence for strong collinearity, indicated by correlation coefficients > .8. Consequently, it was justified to include these five measures as predictors of liver disease in the logistic regression. Because the collinearity between the PVD and the MPVPG could bias the statistical inferences, the PVD was not included as an independent variable alongside the MPVPG. It is a common practice to combine the variables responsible for collinearity into a single variable (Homer & Lemeshow, 2000).

I constructed four binary logistic regression models using SPSS to predict the log odds of liver disease (1 = *disease present* or 0 = *disease absent*) in 522 patients, stratified by gender (n = 251 female patients and n = 271 male patients). MODEL I was constructed for all female patients and MODEL II for all male patients. Model III excluded 22 obese female patients with BMI > 35. Model IV excluded 35 obese male patients with BMI > 35.

I interpreted the odds ratios (ORs) and their 95% confidence intervals (CIs) for each predictor variable. The ORs were computed for each category of RACE, ECHOGRADE, and HVW, relative to their reference categories. I stipulated 0 (*no*) as the reference category for RACE, represented by the dummy variables, WHITE, BLACK, and HISPANIC, where 1 = *yes* or 0 = *no*. I entered ECHOGRADE as one ordinal variable, containing four levels (0, 1, 2, and 3) where 0 (normal) was the stipulated

reference category. I entered HVW as one ordinal variable, containing three levels (1, 2, and 3) where 3 (triphasic or normal waveform) was the stipulated last reference category.

MODEL I. Females, Including BMI > 35

I constructed the first binary logistic regression model to predict the likelihood of the presence of liver disease among 251 female patients, including those with BMI > 35 (see Table 13.) The omnibus tests of the model coefficients indicated that the model was statistically significant (χ^2 ,11 = 61.704, $p < .001$). The Nagelkerke *R* square was .343. The null hypothesis was rejected. I found that RACE (HISPANIC), MPVPG, and ECHOGRADE were statistically significant predictors of the likelihood of liver disease. The edited SPSS output is presented in Table 13 (where *B* is the regression coefficient, *SE* is the standard error, Wald is the Wald's χ^2 statistic, OR is the odds ratio, and CI is the confidence interval).

The race variables of BLACK and WHITE, together with the physiological measurements of HVPG, SVPG, and HVW, were not significant predictors of liver disease in the female patients, indicated by $p \geq .05$ for Wald's χ^2. The race variable of HISPANIC was, however, a marginally significant predictor (χ^2, 1 = 3.830, $p = .05$). The OR indicated that the likelihood of a Hispanic woman having liver disease would be, on average, 2.643 times greater than that of a non-Hispanic woman. The 95% CI indicated that the mean OR in the population was .999 to 6.998 in 95% of cases. This CI is consistent with the cross-tabulation revealing the highest prevalence of liver disease among Hispanic female patients (see Table 6). Logt MPVPG was a significant predictor of liver disease (χ^2, 1 = 7.111, $p = .008$). The likelihood of liver disease was predicted to

be 2.118 times greater for every logarithmic ($\log_{10}$) unit increase in MPVPG (95% CI = 1.220, 3.678). ECHOGRADE was a significant predictor of liver disease ($\chi 2,3 = 35.372$, $p < .001$) in female patients. If ECHOGRADE = 1, then the likelihood of a female having liver disease was the same as that of a patient whose ECHOGRADE = 0 (i.e., normal) because the OR was not significantly different from 1.0. If ECHOGRADE = 2, then the likelihood of a woman having liver disease would be approximately 12 times greater than that of a patient whose ECHOGRADE was 0 (95% CI = 3.772, 39.016). If ECHOGRADE = 3, then the likelihood of a female patient having liver disease would be more than 23 times greater (95% CI = 5.519, 100.366). Sonographic measures of echogenicity (ECHOGRADE = 2 and 3) provided the highest ORs (12.131 and 25.535, respectively) with respect to diagnosing the presence of liver disease in women. HVW was not a significant predictor of liver disease at $\alpha = .05$.

Model II. Males, Including BMI > 35

I constructed the second binary logistic regression model to predict the likelihood of the presence of liver disease among 271 male patients including those with BMI > 35. The edited SPSS output is presented in Table 13. The omnibus tests of the model coefficients indicated that the model was statistically significant ($\chi^2 ,11 = 64.161$, $p < .001$). The Nagelkerke *R* square was .329. The null hypothesis was rejected. I found that MPVPG, SVPG, ECHOGRADE, and HVW were statistically significant predictors of the likelihood of liver disease.

Table 13

Logistic Regression Model II to Predict the Presence of Liver Disease Among Male Patients (N = 271, Including BMI > 35)

								95% CI for OR	
Gender	Predictor	*B*	*SE*	Wald	*df*	*p*	*OR*	Lower	Upper
Male	WHITE	.257	.498	.266	1	.606	1.293	.487	3.432
	BLACK	.198	.581	.116	1	.733	1.219	.391	3.803
	HISPANIC	.338	.474	.510	1	.475	1.403	.554	3.551
	LogtMPVPG	1.119	.265	17.869	1	< .001*	3.063	1.823	5.146
	LogtSVPG	-1.999	.767	6.787	1	.009*	.135	.030	.610
	LogtHVPG	-.877	.635	1.909	1	.167	.416	.120	1.444
	ECHOGRADE			16.972	3	< .001*			
	ECHOGRADE(1)	1.886	.778	5.885	1	.015*	6.594	1.437	30.268
	ECHOGRADE(2)	2.779	.754	13.581	1	< .001*	16.105	3.673	70.610
	ECHOGRADE(3)	2.709	.806	11.288	1	.001*	15.020	3.092	72.961
	HVW			12.064	2	.002*			
	HVW(1)	1.659	.559	8.810	1	.003*	5.257	1.757	15.726
	HVW(2)	.849	.360	5.552	1	.018*	2.338	1.154	4.740
	Constant	-6.506	1.295	25.247	1	.000*	.001		

Note. B = regression coefficient. *SE* = standard error. Wald = Wald's χ^2. OR = odds ratio. CI = confidence interval. * Significant at $p < .05$.

Among the male patients , the race variables of BLACK, WHITE, and HISPANIC and the measurement of HVPG were not statistically significant predictors of liver disease, indicated by $p > .05$ for the Wald's χ^2statistics. Logt MPVPG was, however, a significant predictor of liver disease (χ^2, 1 = 17.869, $p < .001$). The likelihood of liver disease would be, on average, about 3 times greater for every one $\log_{10}$ increase in MPVPG (95% CI = 1.823, 5.146). In contrast, the odds changed by .135 (95% CI = .030, .160) for every 1 unit change in logt SVPG. The OR of less than 1 implied that the likelihood of liver disease was less when the SVPG increased, consistent with the results presented earlier in this chapter (see Figure 5), indicating that the mean SVGP was highest in male patients without liver disease.

For the male patients, including those with BMI > 35, ECHOGRADE was a highly significant predictor of liver disease (χ^2, 3 = 972, $p < .001$). If ECHOGRADE = 1, then the likelihood of a male patient having liver disease was about 6.6 times greater (95% CI = 1.437, 30.268) than a patient whose ECHOGRADE was 0 (i.e., normal). If ECHOGRADE = 2, then the likelihood of the presence of liver disease would be, on average, approximately 16 times greater than that of a patient whose ECHOGRADE was 0 (95% CI = 3.673, 70.610). If ECHOGRADE = 3, then the likelihood of a male patient having liver disease would be, on average, approximately 15 times greater (95% CI = 3.092, 72.961).

The HVW was a significant predictor of liver disease in male patients, including those with BMI < 35 (χ^2, 2 = 12.064, $p = .002$). If HVW = 1 (i.e., monophasic), then the likelihood of liver disease was about 5.3 times greater (95% CI = 1.757, 15.726) than a

patient whose HVW = 3 (i.e., triphasic or normal). If HVW = 2 (i.e., biphasic), then the likelihood of a man having liver disease would be, on average, approximately 2.3 times greater (95% CI = 1.154, 4.470) than that of a patient whose HVW was triphasic.

Sonographic measures of echogenicity (ECHOGRADE = 1, 2, and 3) provided the highest ORs (6.954, 16.105, and 15.020, respectively) to predict the presence of liver disease in men. The OR estimates for HVW (1 and 2) were less than those for ECHOGRADE (OR = 5.257 and 2.338, respectively). The logt MPVG, based on a different scale of measurement to ECHOGRADE and HVW, provided the lowest likelihood for predicting liver disease in men (OR = 3.063).

Model III. Females, Excluding BMI > 35

I constructed the third binary logistic regression model to predict the likelihood of the presence of liver disease among 195 female patients who had a BMI of less than 35. The edited SPSS output is presented in Table 14. The omnibus tests of the model coefficients indicated that the model was statistically significant (χ^2 ,11 = 69.433, $p <$ .001). The Nagelkerke *R* square was .413. The null hypothesis was rejected. I found that RACE (HISPANIC), MPVPG, HVW, and ECHOGRADE were statistically significant predictors of the likelihood of liver disease. Among the female patients with BMI < 35, the race variables of BLACK and WHITE and the physiological measurements of HVPG and SVPG were not significant predictors of liver disease, indicated by $p > .05$ for Wald's χ^2. The race variable of HISPANIC was, however, a significant predictor (χ^2, 1 = 4.161, $p = .041$). The OR indicated that the likelihood of a Hispanic woman having liver

disease would be, on average, almost three times greater than that of a female patient who was not Hispanic (95% CI = 1.044, 8.530).

Table 14

Logistic Regression Model III to Predict the Presence of Liver Disease Among Female Patients (N = 195, with BMI < 35)

								95% CI for OR	
Gender	Predictor	*B*	*SE*	Wald	*df*	*p*	*OR*	Lower	Upper
Female	WHITE	.328	.559	.345	1	.557	1.389	.464	4.155
	BLACK	.448	.654	.468	1	.494	1.565	.434	5.639
	HISPANIC	1.093	.536	4.161	1	.041*	2.984	1.044	8.530
	Logt MPVPG	.822	.311	6.973	1	.008*	2.274	1.236	4.185
	Logt SVPG	.467	.949	.242	1	.623	1.595	.248	10.237
	Logt HVPG	.969	.682	2.020	1	.155	2.635	.693	10.024
	ECHOGRADE			40.236	3	.000*			
	ECHOGRADE(1)	.548	.577	.903	1	.342	1.730	.558	5.359
	ECHOGRADE(2)	2.847	.626	20.699	1	.000*	17.240	5.056	58.781
	ECHOGRADE(3)	3.558	.850	17.534	1	.000*	35.091	6.637	185.543
	HVW			5.860	2	.053			
	HVW(1)	1.106	.687	2.595	1	.107	3.022	.787	11.606
	HVW(2)	.912	.436	4.374	1	.046*	2.489	1.059	5.851
	Constant	-2.549	1.264	4.065	1	.044*	.078		

Note. B = regression coefficient. *SE* = standard error. Wald = Wald's χ^2. OR = odds ratio. CI = confidence interval. * Significant at $p < .05$.

I found that MPVPG was a significant predictor of liver disease in female patients with a BMI < 35 (χ^2, 1 = 6.973, p = .008). The likelihood of liver disease would be about 2.3 times greater for every 1-unit increase in logt MPVPG (95% CI = 1.236, 4.185).

ECHOGRADE was also a highly significant predictor of liver disease (χ^2, 3 = 40.236, p < .001). If ECHOGRADE = 1, then the likelihood of a female patient having liver disease was the same as that of a patient whose ECHOGRADE = 0 (i.e., normal) because the OR was not significantly different from 1.0. If ECHOGRADE = 2, then the likelihood of a woman having liver disease would be, on average, approximately 17.2 times greater than that of a patient whose ECHOGRADE was 0 (95% CI = 5.056, 58.781). If ECHOGRADE = 3, then the likelihood of a female patient having liver disease would be, on average, approximately 35 times greater (95% CI = 6.637, 185.453).

The HVW was a marginally significant predictor of liver disease in women with a BMI < 35 (χ^2, 2 = 5.860, p =.053). If HVW = 2, then the likelihood of liver disease was about 2.5 times greater (95% CI = 1.059, 5.851) than if HVW = 3 (*normal*).

Model IV. Males, Excluding BMI > 35

I constructed the fourth binary logistic regression model to predict the likelihood of the presence of liver disease among 202 male patients who had a BMI < 35. The edited SPSS output is presented in Table 15. The omnibus tests of the model coefficients indicated that the model was statistically significant (χ^2 ,11 = 56.478, p < .001). The Nagelkerke R square was .337. The null hypothesis was rejected. I found that MPVPG, SVPG, ECHOGRADE, and HVW were statistically significant predictors of the likelihood of liver disease.

Table 15

Logistic Regression Model IV to Predict the Presence of Liver Disease Among Male Patients (N = 202, with BMI < 35)

							95% CI for OR	
Gender	Predictor	*B*	SE	Wald	*df*	*p*	*OR*	Lower	Upper
Male	WHITE	.099	.564	.031	1	.861	1.104	.366	3.331
	BLACK	-.437	.639	.468	1	.494	.646	.184	2.261
	HISPANIC	-.214	.529	.163	1	.686	.808	.287	2.276
	LogtMPVPG	1.094	.287	14.518	1	< .001*	2.985	1.701	5.239
	LogtSVPG	-2.332	.830	7.887	1	.005*	.097	.019	.494
	LogtHVPG	-.767	.684	1.260	1	.262	.464	.122	1.773
	ECHOGRADE			11.418	3	.010*			
	ECHOGRADE(1)	1.762	.818	4.636	1	.031*	5.826	1.171	28.978
	ECHOGRADE(2)	2.448	.791	9.577	1	.002*	11.560	2.453	54.468
	ECHOGRADE(3)	2.510	.850	8.713	1	.003*	12.306	2.324	65.153
	HVW			12.096	2	.002*			
	HVW(1)	1.866	.619	9.087	1	.003*	6.462	1.921	21.739
	HVW(2)	.901	.396	5.172	1	.023*	2.463	1.133	5.356
	Constant	-6.090	1.380	19.463	1	< .001*	.002		

Note. B = regression coefficient. *SE* = standard error. Wald = Wald's χ^2. OR = odds ratio. CI = confidence interval. * Significant at $p < .05$.

Among the male patients (see Table 15) with BMI < 35, the race variables of BLACK, WHITE, and HISPANIC and the variable HVPG were not significant predictors of liver disease, indicated by $p > .05$ for Wald's χ^2. Logt MPVPG was, however, a significant predictor of liver disease (χ^2, 1 = 14.518, $p < .001$). The OR indicated that the likelihood of liver disease would be, on average, nearly 3 times greater for every logarithmic unit increase in MPVPG (95% CI = 1.701, 5.239). In contrast, the odds changed by only .097 (95% CI = .019, .494) for every 1-unit increase in logt SVPG. ECHOGRADE was a significant predictor of liver disease (χ^2, 3 = 11.418, $p = .010$) in male patients with a BMI < 35. If ECHOGRADE = 1, then the likelihood of a male patient having liver disease would be about 5.8 times greater than a patient wiwth ECHOGRADE = 0 (95% CI = 1.171, 28.978). If ECHOGRADE = 2, then the likelihood of a man having liver disease would be, on average, approximately 11.6 times greater (95% CI = 2.453, 54.468). If ECHOGRADE = 3, then the likelihood of a male patient having liver disease would be, on average, approximately 12.3 times greater (95% CI = 2.324, 65.153). HVW was also a significant predictor of liver disease in male patients (χ^2, 2 = 12.096, $p = .002$). If HVW = 1 (i.e., monophasic), then the likelihood of a male patient having liver disease was about 6.5 times greater (95% CI = 1.921, 21.739) than a patient whose HVW = 3 (i.e., triphasic). If HVW = 2 (i.e., biphasic), then the likelihood of a man having liver disease would be, on average, approximately 2.5 times greater (95% CI = 1.133, 5.356) than if the HVW was triphasic.

Sonographic measures of echogenicity (ECHOGRADE = 1, 2, and 3) provided the highest ORs (OR = 5.826, 11,560, and 12.306, respectively) to predict the presence of liver disease in men with a BMI < 35. The HVW (1 and 2) also provided relatively high ORs for predicting liver disease in men (OR = 6.462 and 2.463, respectively) relative to those with a triphasic waveform. Logt MPVG, using a different scale of measurement to ECHOGRADE and HVW, provided a relatively low OR (2.985) for predicting the presence of liver disease.

Sensitivity and Specificity

Sensitivity is the conditional probability that the test will be positive if the disease is present. Specificity is the conditional probability that the test will be negative if the disease is absent. Sensitivity and specificity cannot exceed 100%, and neither can their CIs. The lower and upper limits of the 95% CIs in this study were calculated using the efficient-score method, corrected for continuity, as described by Newcombe (1998). I used an online calculator to compute the sensitivity and specificity values (Lowry, n.d.).

I estimated and compared the sensitivities and specificities with respect to (a) MPVPG; (b) ECHOGRADE; (c) HVW; and (d) a combination of MPVGP, ECHOGRADE, and HVW using the predictions made by the four logistic regression models. The predictions of DISEASE were obtained using the save predicted group membership option in SPSS, where 0 = *disease absent* and 1 = *disease present*.

I cross-classified the frequencies of 251 female patients (see Table 16) and 271 male patients (see Table 17) according to whether liver disease was present or absent as declared by Fibrotest (FT)® and/or Alanine aminotransferase (ALT) markers (in the

columns) and according to whether MPVPG liver disease was present or absent at eight specified MPVPG cutoff levels (in the rows). The midpoint sensitivities, specificities, and 95% CIs were calculated using the methods described by Kuzma and Bohnenblust (2005). The specificity varied between male patients and female patients. In female patients, the specificity was 100% at MPVPG ≥ 1000, declining to 93.8% at MPVPG ≥ 250, 77.0% at MPVPG ≥ 100, and 21.8% at MPVPG ≥ 10 (see Table 15). In male patients, the specificity declined from 99.0% at MPVPG ≥ 1000 to 81% at MPVPG ≥ 250, 81.0% at MPVPG ≥ 100, and 15.0% at MPVPG ≥ 10 (see Table 16).

Table 16

Sensitivity and Specificity at Eight Cutoff Levels of MPVPG Among Female Patients (N = 251)

	DISEASE				95% CI	
MPVPG cutoff level	Disease absent	Disease present	Conditional probability	Mid-point	Lower	Upper
≥10	75	134	Sensitivity	.864	.798	.912
< 10	21	21	Specificity	.218	.143	.317
≥25	56	105	Sensitivity	.677	.596	.749
< 25	40	50	Specificity	.417	.318	.522
≥ 50	39	76	Sensitivity	.490	.409	.571
< 50	57	79	Specificity	.593	.488	.691
≥ 75	30	62	Sensitivity	.400	.323	.481
< 75	66	93	Specificity	.687	.583	.776
≥ 100	22	53	Sensitivity	.341	.268	.422
< 100	74	102	Specificity	.770	.671	.847
≥ 250	6	26	Sensitivity	.167	.114	.238
< 250	91	129	Specificity	.938	.864	.974
≥ 500	1	13	Sensitivity	.084	.047	.142
< 500	95	142	Specificity	.989	.935	.999
≥ 1000	0	4	Sensitivity	.025	.008	.069
< 1000	96	151	Specificity	1.000	.952	1.000

Table 17

Sensitivity and Specificity at Eight Cutoff Levels of MPVPG Among Male Patients (N = 271)

	DISEASE				95% CI	
MPVPG cutoff level	Disease absent	Disease present	Conditional probability	Mid-point	Lower	Upper
≥ 10	85	156	Sensitivity	.912	.856	.948
< 10	15	15	Specificity	.150	.089	.238
≥ 25	58	130	Sensitivity	.760	.687	.821
< 25	42	41	Specificity	.420	.323	.523
≥ 50	36	110	Sensitivity	.880	.806	.929
< 50	64	61	Specificity	.294	.179	.440
≥ 75	30	124	Sensitivity	.617	.611	.720
< 75	70	77	Specificity	.700	.598	.785
≥ 100	19	84	Sensitivity	.491	.414	.568
< 100	81	87	Specificity	.810	.717	.878
≥ 250	4	46	Sensitivity	.269	.206	.343
< 250	96	125	Specificity	.960	.894	.987
≥ 500	3	31	Sensitivity	.181	.128	.249
< 500	97	140	Specificity	.970	.908	.992
≥ 1000	1	14	Sensitivity	.082	.047	.136
< 1000	99	157	Specificity	.990	.938	.999

A ROC curve (see Figure 6) is a visual representation of the relationship between the sensitivity (percentage of true-positive tests) and 1 - specificity (percentage of false-positive tests) based on the eight cutoff points of MPVPG used in Table 16 and Table 17.

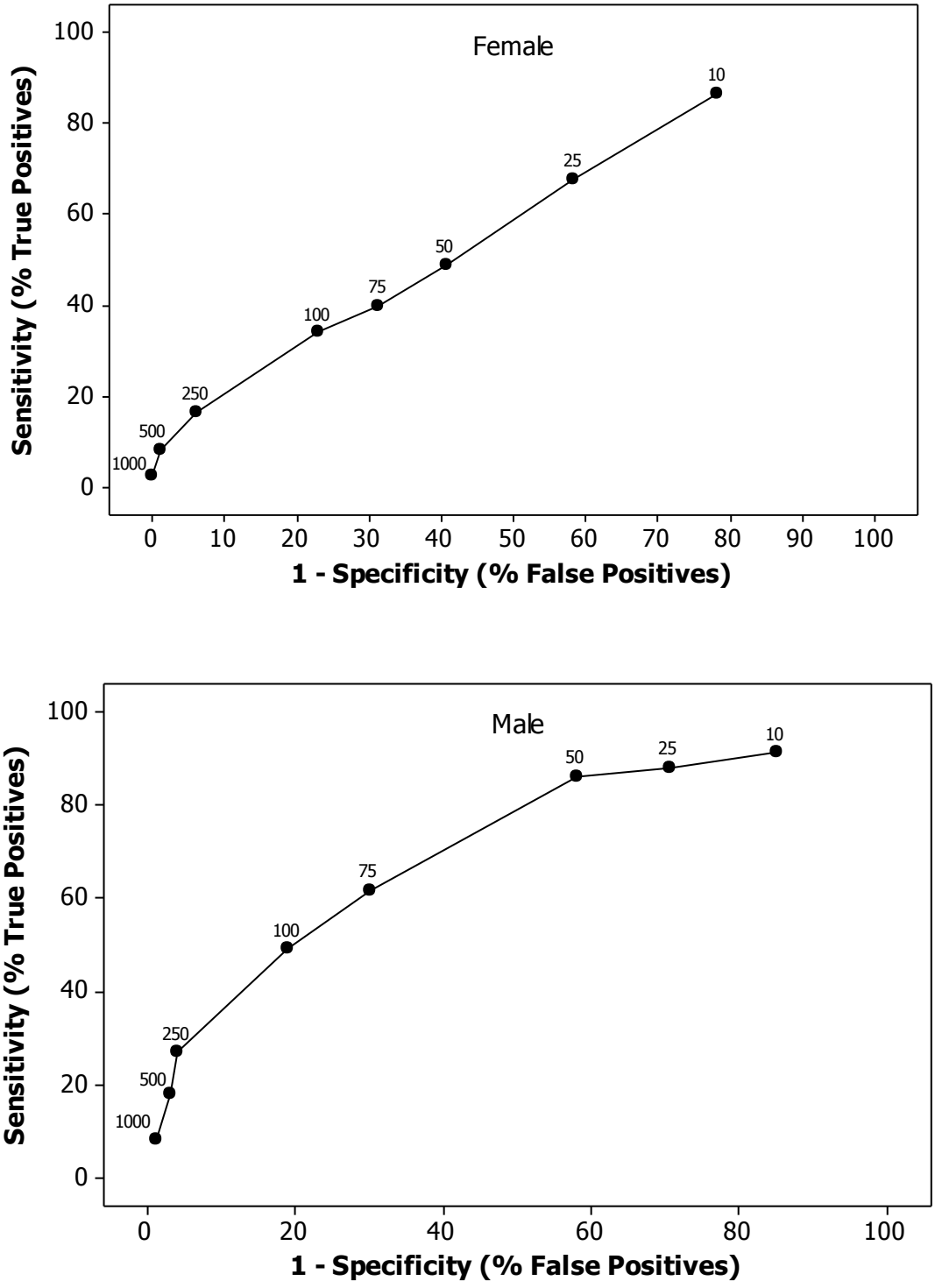

Figure 6. ROC curves for eight cutoff levels of MPVPG in male and female patients.

The two ROC curves (see Figure 6) revealed that the sensitivity for each cutoff level of MPVPG was generally greater among male patients than among female patients. Each graph was not a typical rectilinear ROC curve with a distinct inflexion point at the top left-hand corner, representing a high proportion of true positives corresponding to a low proportion of false positives. The shallow slopes of the ROC curves without distinct inflexion points indicated that if any given level of MPVPG assumed to represent a positive test for liver disease is lowered, then the sensitivity is increased, and the false-positive rate is also increased. Consequently, it is difficult to choose an appropriate level of MPVPG to represent a true-positive test result. Nevertheless, based on the logarithmically transformed MPVPGs in male patients (antilog $M = 90.78$) and female patients (antilog $M = 51.40$) diagnosed with liver disease, I suggest tentatively that positive test results with reasonable sensitivity could be declared if the MPVG is ≥ 50 mmHg mm^4.

The sensitivities for the sonographic measures of echogenicity in male patients and female patients, for comparison with those computed for the MPVPGs, are presented in Table 18 and Table 19, respectively. The sensitivities remained relatively high (85.3% to 96.8%) and the specificities remained relatively low (25.0% to 62.5%) across all three levels of ECHOGRADE (1, 2, and 3) relative to ECHOGRADE 0 (normal). For the male patients, the sensitivities were consistently higher and the specificities were consistently lower than for the female patients. Because there were only three points, I considered it inappropriate to construct ROC curves for the ECHOGRADE scores.

Table 18

Sensitivity and Specificity for Two Cutoff Levels of ECHOGRADE in Female Patients

	DISEASE				95% CI	
ECHOGRADE cut-off level	Disease absent	Disease present	Conditional probability	Mid-point	Lower	Upper
1 (positive)	45	35	Sensitivity	.853	.701	.939
0 (negative)	15	6	Specificity	.250	.151	.381
2 (positive)	27	74	Sensitivity	.925	.838	.969
0 (negative)	15	6	Specificity	.357	.219	.520
3 (positive)	9	40	Sensitivity	.869	.730	.945
0 (negative)	15	6	Specificity	.625	.407	.804

Table 19

Sensitivity and Specificity for Two Cutoff Levels of ECHOGRADE in Male Patients

	DISEASE				95% CI	
ECHOGRADE cut-off level	Disease absent	Disease present	Conditional probability	Mid-point	Lower	Upper
1 (positive)	35	31	Sensitivity	.911	.752	.977
0 (negative)	14	3	Specificity	.286	.170	.435
2 (positive)	35	90	Sensitivity	.968	.902	.991
0 (negative)	14	3	Specificity	.286	.170	.435
3 (positive)	16	46	Sensitivity	.938	.821	.984
0 (negative)	14	3	Specificity	.467	.288	.653

I found that the estimated sensitivities for the two phases of HVW in male patients and female patients were lower than those estimated for the ECHOGRADE scores (see Table 20 and Table 21, respectively). The sensitivities for the monophasic and biphasic waveforms, relative to the triphasic (normal) waveform, were consistently higher (34.2% and 44.7%) in male patients than in female patients (25.9% and 29.8%). The specificities for the monophasic and biphasic waveforms in male patients (93.0% and 70.5%) were also consistently higher than in female patients (88.2% and 69.8%). Because

there were only two points, I considered it inappropriate to construct ROC curves for the HVW phases.

Table 20

Sensitivity and Specificity for Two Cutoff Levels of HVW in Male Patients

HVW cutoff level	DISEASE: Disease absent	DISEASE: Disease present	Conditional probability	Mid-point	95% CI: Lower	95% CI: Upper
1 (monophasic)	5	38	Sensitivity	.342	.256	.439
3 (triphasic)	67	73	Specificity	.930	.838	.974
2 (biphasic)	28	59	Sensitivity	.447	.361	.535
3 (triphasic)	67	73	Specificity	.705	.601	.792

Table 21

Sensitivity and Specificity for Two Cutoff Levels of HVW in Female Patients

HVW cutoff level	DISEASE: Disease absent	DISEASE: Disease present	Conditional probability	Mid-point	95% CI: Lower	95% CI: Upper
1 (monophasic)	8	27	Sensitivity	.259	.180	.356
3 (triphasic)	60	77	Specificity	.882	.775	.944
2 (biphasic)	26	51	Sensitivity	.398	.314	.489
3 (triphasic)	60	77	Specificity	.698	.588	.789

I found that the estimated sensitivities based on the group memberships (0 = *disease absent* or 1 = *disease present*) predicted by the four logistic regression models (see Table 22) were consistently lower than those estimated for the ECHOGRADE scores (see Table 18 and Table 19) but consistently higher than those estimated for the HVW

scores (see Table 20 and Table 21). The midpoint sensitivities for the female patients using Models I and III (74.3% and 82.0%) were similar to the sensitivities for the male patients using Models II and IV (73.5% and 76.6%). The sensitivities appeared to be consistently higher within each gender when obese patients with BMI > 35 were excluded; however, because the 95% confidence intervals were wide and overlapped, no significant differences between the sensitivities at the .05 level could be inferred.

Table 22

Sensitivity and Specificity Using the Predictions of the Logistic Regression Models

		DISEASE				95% CI	
Model	Predicted group Membership	Disease absent	Disease present	Conditional probability	Mid-point	Lower	Upper
I	1	27	110	Sensitivity	.743	.663	.809
	0	39	38	Specificity	.590	.463	.708
II	1	22	128	Sensitivity	.735	.662	.798
	0	38	46	Specificity	.633	.498	.751
III	1	22	105	Sensitivity	.820	.740	.880
	0	45	23	Specificity	.671	.545	.778
IV	1	18	115	Sensitivity	.766	.689	.831
	0	34	35	Specificity	.653	.508	.777

I found that the estimated specificities based on the group memberships predicted by the four logistic regression models (see Table 22) were consistently higher than those estimated for the ECHOGRADE scores (see Table 18 and Table 19) but consistently lower than those estimated for the HVW scores (see Table 20 and Table 21). The midpoint specificities for the female patients using Models I and III (59.0% and 67.1%)

were relatively similar to the specificities for the male patients using Models II and IV (63.3% and 65.3%). Because the 95% confidence intervals were wide, and overlapped, no significant differences between the specificities at the .05 level with respect to the BMI of the patients could be inferred.

Conclusions

The findings are summarized with bar charts to facilitate visual interpretation of the data.

Demographics

The sample of 522 patients included an approximate 1:1 ratio of male patients to female patients. The dominant racial group was Hispanic, followed by White, Other races, and Black. Male patients and female patients were relatively equally represented within each racial group. Over half of the patients were classified as overweight to obese (BMI = 25-35 kg/m^2), with more than one tenth of patients classified as excessively obese (BMI > 35 kg/m^2). Liver disease was diagnosed as present in the majority (n = 326, 62.5%) of patients. The point estimates of the prevalence of liver disease were relatively equally distributed between genders, and most prevalent among the Hispanic female patients.

Testing of Null Hypothesis

I analyzed morphometric and physiological data for 522 patients, constructed four binary logistic regression models, and estimated sensitivities and specificities to test the hypothesis that the pressure gradient in the portal vein, splenic vein, or hepatic vein; and increased liver echogenicity, hepatic venous waveform, or portal vein diameter are

associated with the diagnosis of liver disease after controlling for gender, ethnicity, and BMI. I obtained the following evidence to support the rejection of the null hypothesis:

RACE. The ORs indicated that the likelihood of Hispanic female patients having liver disease was about 2 to 3 times greater than for female patients who were not Hispanic. The ORs for White and Black patients relative to other races were not significantly different from 1, indicating that the likelihoods of liver disease in Black and White patients were not greater than for the other races.

PVD. The mean PVD was highest in patients with liver disease. I observed significant differences between the mean PVD measurements of male patients and female patients in the presence and absence of liver disease. Sexual dimorphism of the portal vein had implications for the computation of the MPVPG in the absence of liver disease.

MPVPG. When liver disease was absent, the MPVPG in male patients was similar to that in female patients. When liver disease was present, the MPVPG was elevated, and significantly higher in male patients than in female patients . The responses of men and women to the measures of MPVPG are summarized in Figure 7. The ORs were consistently higher in male patients than in female patients, implying that an elevated MPVPG indicated a greater likelihood of liver disease in men than in women. Within each gender, the ORs with respect to MPVPG were similar when patients with a BMI > 35 were included, compared to the ORs when patients with a BMI > 35 were excluded.

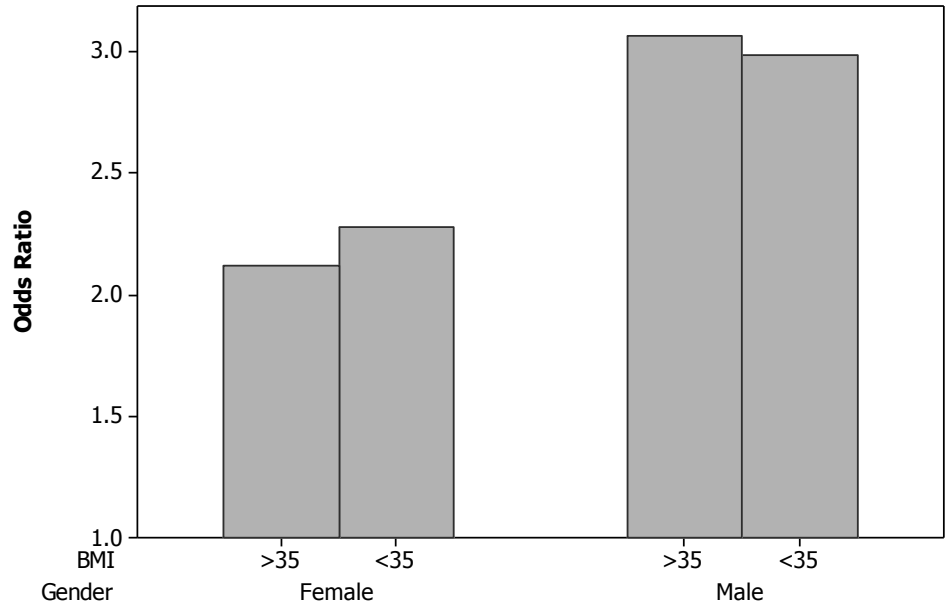

Figure 7. Responses of male patients and female patients to measures of MPVPG.

SVPG. I found a significant difference in the SVPG between genders. The responses of men and women to the measures of SVPG are summarized in Figure 8. The ORs were not significantly different from 1 in female patients, but significantly less than 1 in male patients. This finding implied that when the SVPG was elevated, the likelihood of liver disease was less in men, but not so in women. Within each gender, the ORs for SVPG were similar in patients in the two groups stratified according to their BMI.

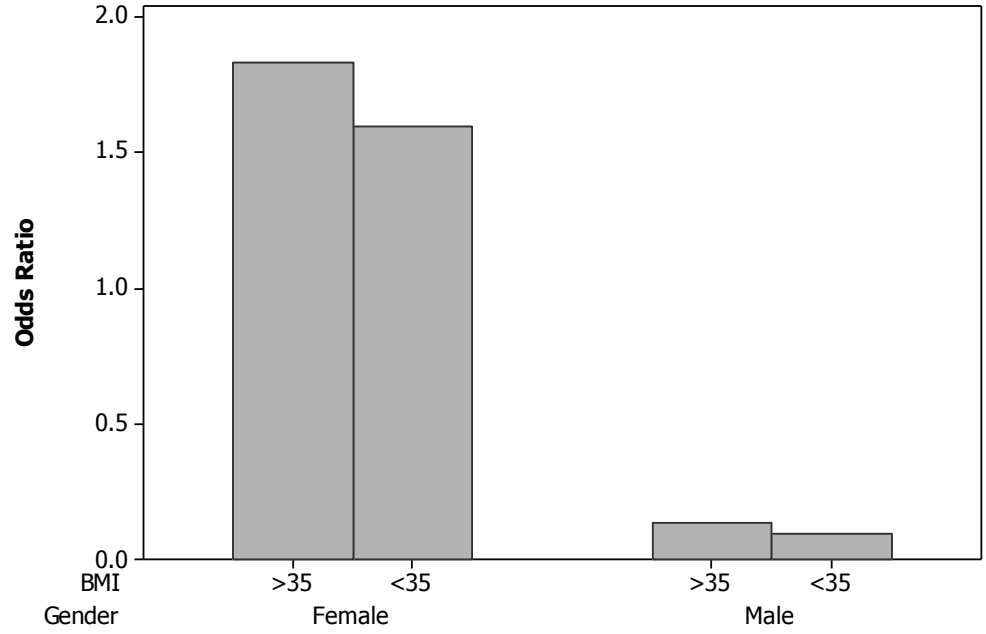

Figure 8. Responses of male and female patients to measures of SVPG.

HVPG. The mean measures of the HVPG were not significantly different with respect to gender. The responses of men and women to the measures of HVPG are compared in Figure 9. The pattern of the ORs with respect to gender was similar to that observed for the SVPGs (see Figure 8); however, because the ORs in both male patients and female patients were not significantly different from 1, associated with the wide 95% CIs, there was no statistical evidence to indicate that the HVPG could be used as a predictor of liver disease. The ORs for HVPG did not differ with respect to BMI.

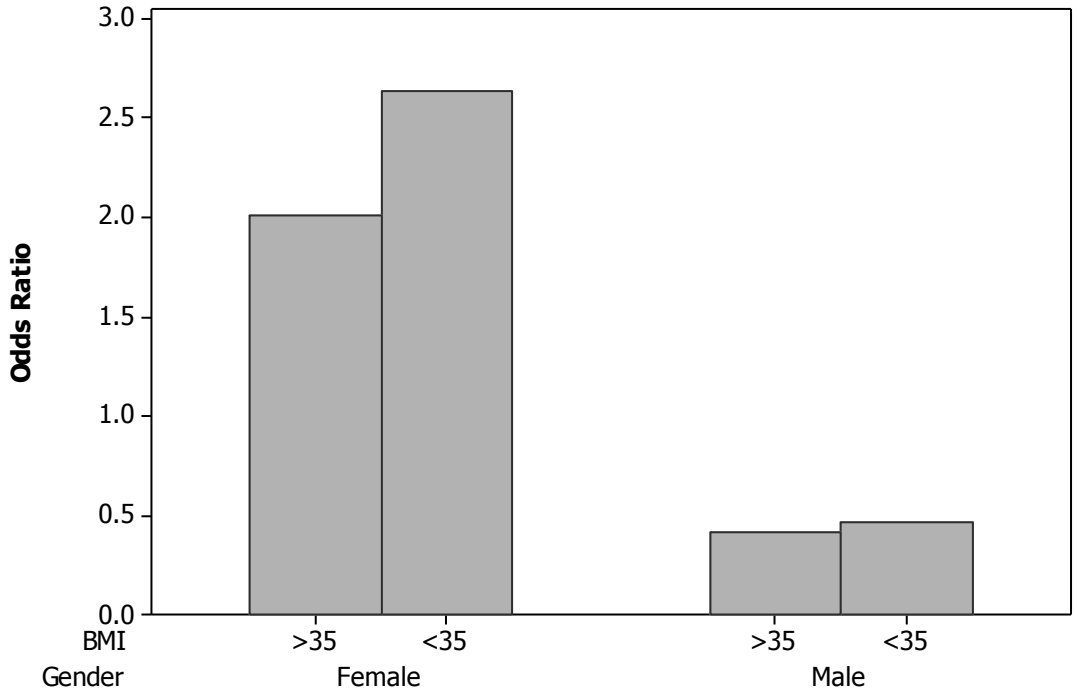

Figure 9. Responses of male and female patients to measures of HVPG.

ECHOGRADE. The ORs for the sonographic measures of echogenicity were higher than those for the Doppler-derived pressure gradients; however, the ORs were not comparable, because the scales of measurement were different (logarithms for the pressure gradients and ordinal categories for ECHOGRADE). The differences between the responses of men and women are illustrated in Figure 10.

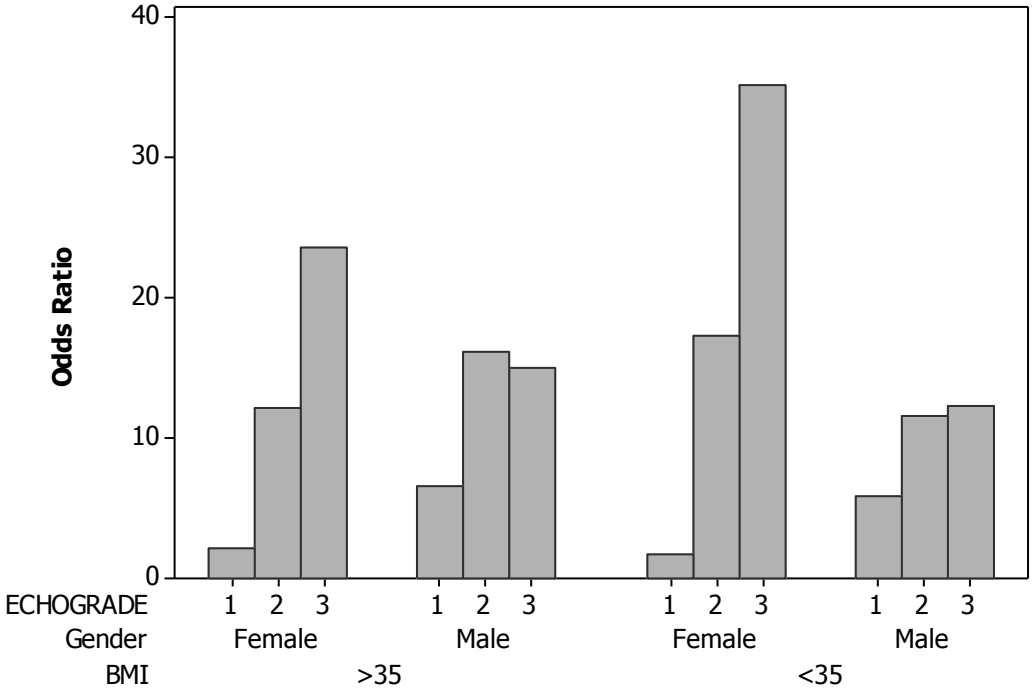

Figure 10. Responses of male and female patients to sonographic measures of echogenicity.

A systematic stepwise increase in the OR with respect to a unit increase in ECHOGRADE was observed in female patients. In male patients, however, there was little change in the OR between ECHOGRADE 2 and 3. The ORs were consistently lower when female patients with a BMI > 35 were included compared to the ORs when female patients with a BMI > 35 were excluded. In contrast, the ORs were consistently higher in the male patients group, which included those with BMIs > 35.

HVW. The differences between the responses of men and women to the HVW phases are summarized in Figure 11. The ORs were less than for ECHOGRADE. In male patients, there was a systematic reduction in the OR with respect to an increase in HVW from 1 (monophasic) to 2 (biphasic) relative to triphasic (normal). The biphasic

waveform was only a marginally significant predictor of liver disease in women with a BMI < 35. When women with a BMI > 35 were included in the analysis, the ORs for both the monophasic and biphasic waveforms were not significantly different from 1.

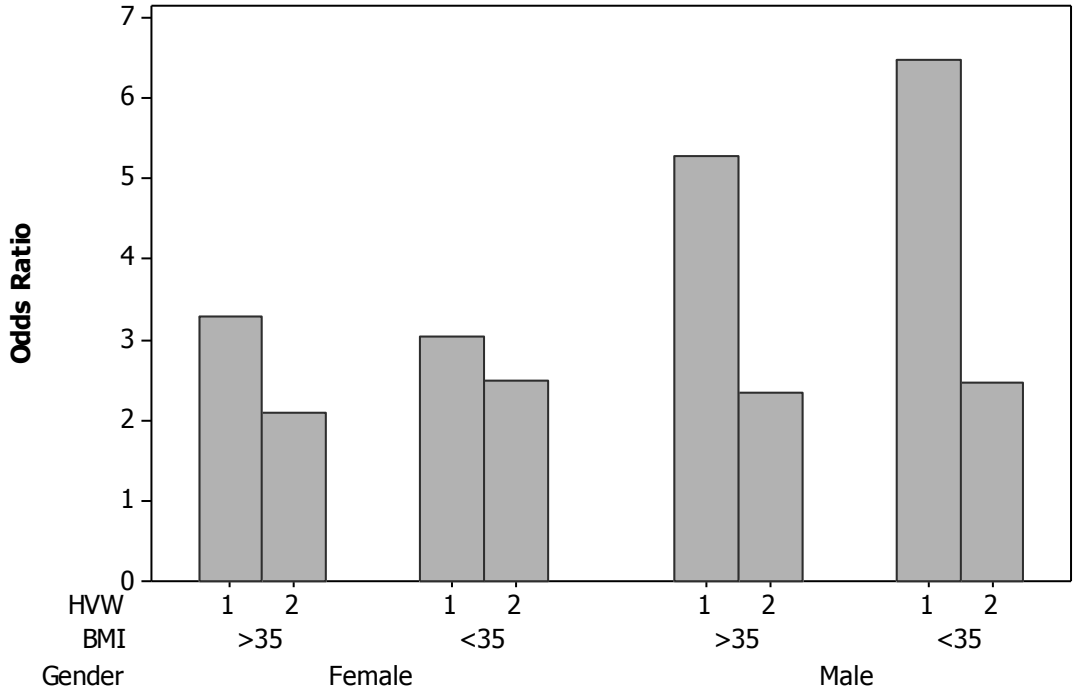

Figure 11. Responses to male patients and female patients to the HVW phases.

ROC Curves

The inferences that I drew from the ROC curves were that (a) the sensitivity for each given cutoff level of MPVPG was generally higher among male patients than among female patients; and (b) when any given level of MPVPG assumed to represent a positive test for liver disease was lowered, both the sensitivity and the false-positive rate tended to increase. The curves were not rectilinear, with a clear inflexion point, which could be

used as a criterion for choosing a level of MPVPG to represent positive test results. I tentatively suggest a possible cutoff to diagnose liver disease of about 50 mmHg mm^4.

Sensitivity and Specificity

For a visual comparison of the sensitivities of ECHOGRADE (1, 2, and 3 relative to 0), MPVPG ($\geq$ 50 relative to < 50 mmHg mm^4), and HVW (1 and 2 relative to 3) with respect to male patients and female patients (see Figure 12).

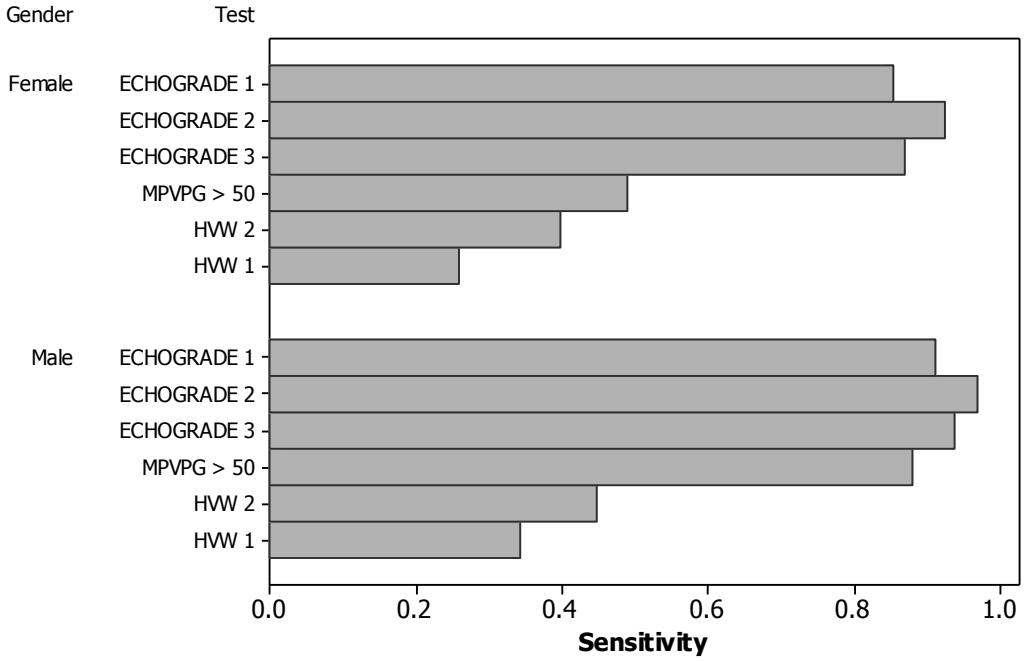

Figure 12. Comparison of sensitivities of ECHOGRADE, MPVPG, and HVW.

The conditional probabilities that the tests will be positive if liver disease is present were consistently higher for the three levels of ECHOGRADE than for the MPVPG and the HVW. The sensitivity for MPVPG using a cutoff point of 50 mmHg mm^4 was higher in male patients than in female patients. The sensitivities for both the

biphasic and monophasic waveforms were consistently higher in male patients than in female patients. Evidence is provided to indicate that the probabilities of true-positive responses to the three diagnostic tests for liver disease varied with respect to gender.

For a comparison of the specificities of ECHOGRADE (1, 2, and 3 relative to 0) MPVPG ($\geq$ 50 relative to < 50 mmHg mm^4), and HVW (1 and 2 relative to 3) with respect to male patients and female patients (see Figure 13).

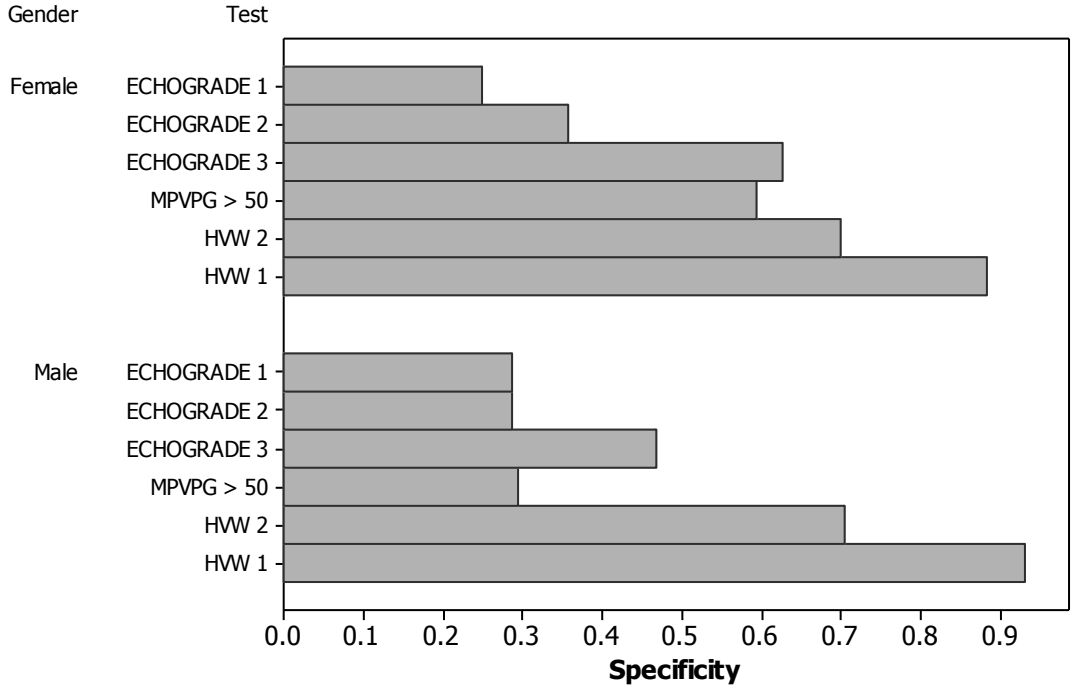

Figure 13. Comparison of specificities of ECHOGRADE, MPVPG, and HVW.

The conditional probabilities that the tests will be negative if liver disease is absent were consistently lower for the three levels of ECHOGRADE than for the monophasic and triphasic measures of HVW. Both the ECHOGRADE scores and the HVW levels provided higher specificities than the MPVPG. The specificities for

ECHOGRADE were consistently lower in male patients than in female patients, whereas the specificities for HVW in male patients and female patients were similar. The specificity for the MPVPG using my suggested cutoff level of 50 mmHg mm^4 was higher in male patients than in female patients. It is evident that the probabilities of true-negative responses to the three diagnostic tests for liver disease varied with respect to gender.

I found no consistent improvements in sensitivity or specificity when the estimates were based on the predicted presence or absence of liver disease using the logistic regression models containing multiple variables including MPVPG, ECHOGRADE, and HVW.

Chapter 5: Discussion

Overview

In this study, I tested the hypothesis that the Doppler-derived pressure gradient in the portal vein (MPVPG), splenic vein (SVPG), or hepatic vein (HVPG), and increased liver echogenicity (ECHOGRADE score), hepatic venous waveform (HVW level), or portal vein diameter (PVD) is associated with the diagnosis of liver disease after controlling for gender, ethnicity, and BMI. The statistical evidence that I obtained to reject the null hypothesis is discussed in this chapter. The rationale for my study was that chronic liver disease is a significant burden accounting for approximately $9 billion per year in health care expenditures. Currently, the gold standard for diagnosing liver disease is biopsy; however, liver biopsy is invasive and harbors significant risks to patients with chronic liver disease, including bleeding and infection. The purpose of this study was to determine the extent to which Doppler-derived pressure gradients of the portal, hepatic, and splenic vein, ECHOGRADE, and HVW could accurately detect liver disease, and thereby reduce the need for invasive biopsies. Sonographic imaging is one potential alternative (Nicolau et al., 2002); however, with the substantial increase in rates of obesity, the ability to determine fatty infiltration from fibrosis by imaging alone has become more difficult. Consequently, sonographic imaging may be less effective for the detection of liver disease in patients who are excessively obese (defined a BMI > 35 kg/m^2). Obrador et al. (2006) proposed that Doppler-derived pressure gradients in addition to sonographic images may increase the sensitivity for the detection of chronic liver disease. Consequently, I evaluated Doppler-derived pressure gradients and HVWs

for their applicability as possible alternatives for the noninvasive diagnosis of liver disease. Abnormal changes in the hepatic circulation may potentially provide diagnostic tests with higher sensitivity and lower specificity for the detection of hepatocellular disease than sonographic measures of echogenicity.

I analyzed a preexisting data set based on a convenience sample of 522 patients treated at a medical center in the western United States from March 2010 to December 2010. The data set was de-identified with no patient identifiers at the time of the analysis. The data analysis involved descriptive statistics, binary logistic regression, and estimates of sensitivity and specificity, including ROC curves, as follows.

Descriptive Statistics

Liver disease was prevalent among all races (White, Black, Hispanic, Asian, and North American Indian), with the highest prevalence among Hispanic female patients (46.5%). The PVD measurements (mm) for the 522 patients were normally distributed. When liver disease was absent, the mean PVD (mm) in male patients was not significantly different from that of female patients; however, when liver disease was present, indicated by enzyme levels, I observed sexual dimorphism of the portal vein. The mean PVD was significantly wider in male patients than in female patients.

I found that the Doppler-derived pressure gradients were not normally distributed but could be normalized by logarithmic transformation. When liver disease was absent, the modified portal vein pressure gradient (MPVPG), computed as a function of the PVPG and the PVD, was similar in both male patients and female patients. When liver disease was present, the MPVPG was elevated and significantly higher in male patients

than in female patients. I also found significant differences between the SVGP but not the HVGP with respect to gender and the presence or absence of liver disease.

Binary Logistic Regression

I used binary logistic regression to construct four models to predict the likelihood of the dependent variable DISEASE, represented by 1 = *liver disease is present* (diagnosed by enzyme tests) and 0 = *absent*. The independent variables were MPVPG, HVPG, SVGP, ECHOGRADE, and HVW. I stratified the results by gender and BMI (including excessively obese patients with BMI > 35 or excluding patients with BMI > 35). Even though there were only 57 subjects with a BMI > 35, I believed it was of value to determine if excessive obesity influenced the results. I controlled for RACE (White, Black, Hispanic, or Other) as a categorical covariate.

Sensitivity and Specificity

The ROC curves for male patients and female patients based on the MPVPG measures were not rectilinear with obvious inflexion points, which could be used as criteria for choosing a level of MPVPG to represent positive test results (Dawson & Trapp, 2004). When any given level of MPVPG assumed to represent a positive test for liver disease was lowered, then both the sensitivity and the false-positive rate tended to increase. I tentatively suggest a possible cutoff level to diagnose liver disease at an MPVPG of about 50 mmHg mm^4.

The specificities were consistently higher for the three levels of ECHOGRADE than for the MPVPG and the HVW. The sensitivity for MPVPG using my proposed cutoff point of 50 mmHg mm^4 was higher in male patients than in female patients. The

sensitivities for both the biphasic and monophasic waveforms were consistently higher in male patients than in female patients. The specificities were consistently lower for the three levels of ECHOGRADE than for the monophasic and triphasic measures of HVW. Both the ECHOGRADE scores and the HVW levels provided higher specificities than the MPVPG. The specificities for ECHOGRADE were consistently lower in male patients than in female patients, whereas the specificities for HVW in male patients and female patients were similar.

Limitations of Study

There were few limitations to the study. The sample size was not small, with a near-equal distribution of male patients (n = 251, 48.1%) and female patients (n = 271, 51.9%). An a priori power analysis indicated that the sample sizes were above the minimum required to correctly reject the null hypothesis at $\alpha = .05$ with a statistical power of .80 using binary logistic regression. A post-hoc power analysis indicated that the sample sizes of 271, 251, 229, and 236 used in the four binary logistic regression models provided powers of .992, .987, .979, and .982, respectively.

This study was based on a convenience sample because the variables used in the statistical analysis were not collected at random, but extracted from a database at one medical center in the western United States. No attempt was made to ensure that the variables accurately and completely represented the population. Nevertheless, the sample population matched the overall mix of races represented by the geographic region, and the ratio of male patients to female patients was approximately equal. Because the sample of patients in this investigation was not necessarily representative of every patient with

liver disease in the United States, the results cannot necessarily be generalized so that they apply to that population. The convenience sample used in this investigation might represent a threat to the external validity of the results; nevertheless, medical researchers frequently employ convenience samples for practical reasons (Kuzma & Bohnenblust, 2005).

A potential limitation to the study was the generalization of several groups of diseases into one dependent variable of liver disease. Based on the different hepatocellular and physiological changes that develop different types of liver diseases (e.g., cirrhosis versus gallbladder disease), it is possible that the Doppler-derived pressure gradients might have yielded greater prognostic value if the dependent variable had been classified into multiple diseases.

Interpretation of Findings

RACE

The odds ratios (ORs) indicated that the likelihood of Hispanic female patients having liver disease was about 2 to 3 times greater than female patients who were not Hispanic; however, the likelihood of liver disease in Black and White patients were not greater those in other races. The data collected in the Fourth National Health and Nutrition Examination Survey also indicated that the prevalence of risk factors for liver disease varied by race. According to that survey, Hispanics and Blacks have a greater risk of developing liver disease than their White counterparts (Flores et al., 2008).

PVD

The increase that I observed in the diameter of the portal vein in patients with liver disease, including sexual dimorphism, reflects the potential clinical significance of this morphometric measure as an alternative diagnostic test. My results, however, have not been confirmed by other researchers. In comparison, Weinreb et al. (1982), working in the United States, reported that the mean PVD (mm) in 107 healthy adult patients, aged 21 to 40 years, based on sonographic measures (M = 11.0, SD = 2.0), was higher than in my study (with no difference between male patients and female patients). Solhjoo, Mansour-Ghanaei, and Moulaei-Langorudi (2011), working in Iran, similarly reported larger mean portal vein diameters (mm) than those reported in my study. They found no significant difference between 31 patients with nonalcoholic liver disease (M = 10.77, SD = 1.51 mm) and 31 controls (M = 10.35, SD = 1.57 mm). The differences between the results of my study and others could be due to sampling bias and/or due to the use of different instrumentation to estimate the PVD.

HVW

I found that the hepatic vein waveform proved to be a useful noninvasive measure to predict the presence of liver disease. The HVW was a marginally significant predictor of liver disease in women with a BMI < 35. If HVW = 2, then the likelihood of liver disease was about 2.5 times greater than if HVW = 3 (normal). HVW was also a significant predictor of liver disease in male patients, including those with BMI > 35. If HVW = 1 (i.e., monophasic), then the likelihood of a male patient having liver disease was about 6.5 times greater than a patient whose HVW = 3 (i.e., triphasic). If HVW = 2

(i.e., biphasic), then the likelihood of a man having liver disease would be, on average, approximately 2.5 times greater than if the HVW was triphasic. The reason for this outcome was that increased intrahepatic blood pressure may generate abnormal continuous monophasic or biphasic waveforms in the hepatic vein. In healthy patients, the HVW is usually triphasic because of the movement of the tricuspid valve annulus toward the heart apex, atrial overfilling, tricuspid valve opening, and the atrial contraction (Goldberg & McGahan, 2006). When the liver hardens due to disease, the hepatic veins can become compressed and show a more continuous flow pattern. The results of my study validated the observations of Goldberg and McGahan (2006) and Solhjoo et al. (2011) by identifying a statistically significant relationship between the HVW and liver disease.

ECHOGENICITY

I found that measures of echogenicity generally provided the highest ORs to predict the presence of liver disease, rather than the hepatic vein waveform or the pressure gradients. ECHOGENICITY also provided consistently higher sensitivities and lower specificities.Elevated measures of echogenicity appeared to indicate a greater likelihood of liver disease in women than in men, and there was evidence that a high BMI influenced these measures. The data support my suggestion that sonographic imaging may be less effective to detect liver disease if the sample includes excessively obese patients.

My results are consistent with those reported by Obrador et al. (2006), who found that obesity may causes architectural and hence echogenic changes in the liver in the

absence of underlying liver disease. Rumack et al.(2005) also concluded that a fat-infiltrated liver with increased size and echogenicity confounds the diagnosis of liver fibrosis. Although obesity was presumed to hinder the ability of sonography to distinguish fatty infiltration from liver fibrosis leading to cirrhosis, the results of my study indicated that ECHOGRADE remains a more consistent indicator of liver disease than does the HVW.

Pressure Gradients

The data I collected to describe the variability in the MPVG appear to reflect the potential clinical significance of Doppler-derived hemodynamic measures as an alternative diagnostic test for liver disease. A comprehensive and exhaustive search of journals and electronic databases yielded no published studies against which to compare the results of my analysis of the portal vein pressure gradients, taking into account the variability of the portal vein diameter, in order to predict the presence of liver disease. My results confirmed other observations that acute or chronic liver disease may block the blood flow throughout the liver, causing blood to back up into the hepatic portal circulation, resulting in portal vein hypertension and expansion (Hagen-Ansert, 2006).

The ORs for the MPVPG were less than those for ECHOGRADE; however, the ORs were not directly comparable because of the different scales of measurement used. The ORs measured between the successive ordinal increments of ECHOGRADE, from 1 to 2 to 3, relative to ECHOGRADE 0, corresponded to substantial differences in liver disease status (i.e., 1 = *grainy liver* (vessels and diaphragm seen); 2 = *fatty liver* (vessels not seen, diaphragm seen); and 3 = *fatty liver* (vessels and diaphragm not seen) relative to

0 = *normal* (not echogenic). In contrast, the ORs measured between successive logarithmic increments in MPVPG measured in mmHg mm^4, did not indicate comparable differences in liver disease status to those indicated by the ordinal categories of ECHOGRADE. For example, the likelihood of liver disease would be about twice as high in a patient with a logt MVPG of 2 (equivalent to a measured MPVG of 100 mmHg mm^4) than in a patient with a logt MPVPG of 1 (equivalent to a measured MPVPG of 10 mmHg mm^4). The likelihood of liver disease would be about twice as high in a patient with a logt MVPG of 3 (equivalent to a measured MPVG of 1000 mmHg mm^4) than in a patient with a logt MPVPG of 2 (equivalent to a measured MPVPG of 10 mmHg mm^4).

The main problem limiting the use of the MPVPG to detect liver disease is its relatively low sensitivity and relatively high specificity compared to measures of echogenicity. I found that the ROC curve had a shallow slope and did not include an obvious inflexion that could be used to accurately predict the presence of liver disease. Gender differences also confounded the results.The specificity for the MPVPG using my suggested cut-off level of 50 mmHg mm^4 was higher in male patients than in female patients. I found no consistent improvements in sensitivity or specificity when the estimates were based on the predicted presence or absence of liver disease using the logistic regression models containing multiple variables, including MPVPG, ECHOGRADE, and HVW.

My results were consistent with those reported by Bernatik et al. (2002), who noted that where severe fibrosis and cirrhosis were identified, there were hemodynamic changes in the hepatic vein (biphasic or monophasic). The addition of Doppler-derived

pressure gradients was not, however, of clinical significance in assessing the stage of liver fibrosis or for differentiating mild fibrosis from severe fibrosis. In conclusion, I was not able to confirm my suggestion that abnormal changes in the hepatic circulation may provide tests with higher sensitivity and lower specificity for the diagnosis of hepatocellular disease than sonographic measures of echogenicity.

Implications for Social Change

Chronic liver disease, whether caused by hepatitis, alcoholism, or NALFD, is a major health problem that results in increased morbidity and greater expenditures of health care dollars (CDC, 2005). Alcoholic hepatitis is the third leading preventable cause of death in the United States (Lucey et al., 2009), and it is estimated that as many as 70 million Americans may be diagnosed with NALFD (Angulo, 2002). The health care burden of chronic liver disease is substantial (Bugianesi, 2005). This burden includes a financial strain on the health care system, as well as a long, debilitating illness for the individual patients. The American Gastroenterological Association (as cited in Kim et al., 2002) estimated the economic burden of common gastrointestinal and liver disorders, including chronic liver disease, chronic HepC, liver cancer, and gallbladder disease as accounting for approximately one quarter ($9.1 billion) of all direct costs for health care.

The results of this study have confirmed that alternative, noninvasive methods (echogenicity, hepatic waveform, and possibly the MPVPG) have clinical significance to detect liver disease. This noninvasive approach can aid referring physicians to more effectively treat patients whose acute liver disease is starting to progress into chronic liver disease. With earlier aggressive treatment and intervention, severe adverse health

outcomes leading to irreversible liver cirrhosis might be avoided. Prevention of liver disease is not always possible, but early intervention and treatment might lead to a decrease in morbidity and mortality related to chronic liver disease. The results of this study may lead to social change that could possibly improve the human condition of individuals living with liver disease. There is evidence that alternative testing such as the use of fibroelastosis and biochemical markers are helping to predict liver fibrosis (Pickerell, 2010; Ratziu et al., 2006). This study adds to the current body of knowledge and yielded worthwhile insight into the value of providing alternative, noninvasive methods to predict liver disease and encourage less reliance on liver biopsy alone.

Recommendations for Action

The results of this study showed that an ECHOGRADE of 2 or 3 predicts liver disease in both men and women. An HVW of 1 predicts liver disease in men and an HVW of 2 may predict liver disease in women. Not all imaging facilities grade liver echogenicity, instead recording only "fatty infiltration of the liver." Based on the results of this study, I recommend both grading of ECHOGRADE and adding HVWs to the abdominal sonographic protocols to help in the early detection of liver disease. This study included two novel applications. First, applying cardiac presets (from the Bernoulli equation) allowed velocity measurements in the hepatic, portal, and splenic veins to be displayed in pressure gradients. Hepatologists who are accustomed to working with pressure gradients rather than velocity measurements should consider using this alternative measurement if sonographic software is available. Second, the portal vein diameter increases with liver disease. The modified pressure gradient (taking into account

this increase in diameter) did not prove statistically significant in female patients but did in male patients when using all types of liver disease as the dependent variable. Recommendations regarding the modified pressure gradient warrant a separate discussion, which follows in the next section.

Recommendations for Further Study

The results of this study indicate that ECHOGRADE and HVW are statistically significant predictors of liver disease, and Doppler-derived pressure gradients may also have the potential to predict liver disease, but are not as sensitive as ECHOGRADE and HVW. Based on these results, I recommend that future researchers not conduct further investigations on the HVPG or SVPG. Instead, I recommend future researchers to determine if the MPVPG will predict different types of liver disease status. Due to the large number of independent variables in the present study, as well as the restricted sample size, it was unfeasible to break down the dependent variable into separate groups. My clinical justification for predicting the variable STATUS (see Table 23) using MPVPG as an independent variable is that my preliminary analysis (not included in chapter 4) indicated that the mean logt MPVPG measurements increased systematically with respect to a change in liver disease status (see Figure 14).

Table 23

Suggested Independent Variable

Variable	Definition	Level	Groups
STATUS	Presence of a specified type of liver disease	Nominal	0 = liver disease is absent 1 = gallbladder (GB) disease 2 = hepatitis 3 = NASH and NAFLD 4 = cirrhosis and ascites

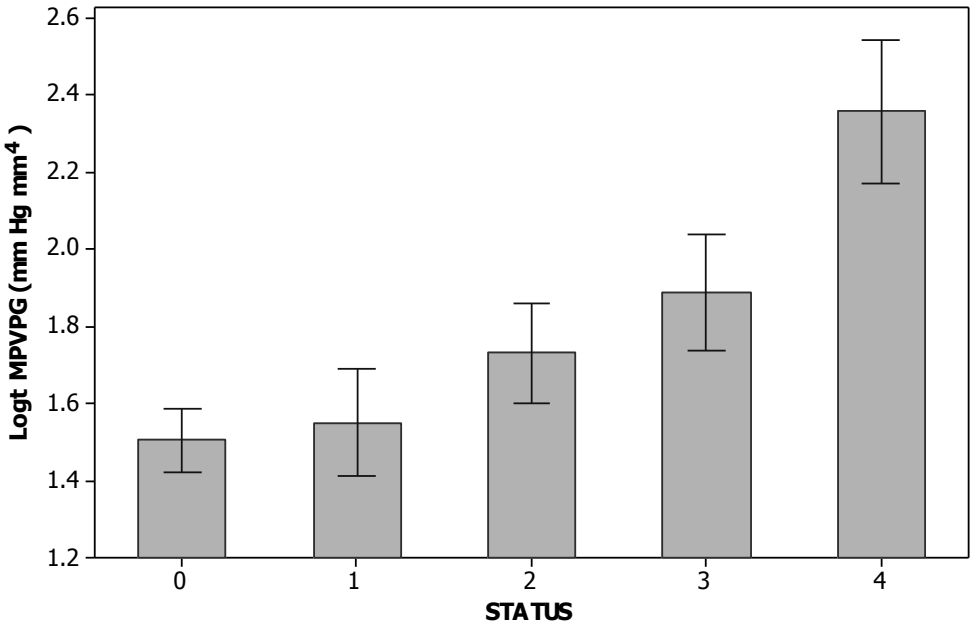

Figure 14. Relationship between liver disease status and mean logt MPVPGs ± 95% CIs.

I recommend future researchers utilize STATUS to make the research more meaningful, because the independent variables could predict not only disease or no disease, but also the specific type of disease. In a multinominal logistic regression model, the dependent variable represents three or more numerically coded qualitative categories (e.g., 0 = *liver disease is absent*; 1 = *gallbladder* (*GB*) *disease*; 2 = *hepatitis*; 3 = NASH and NAFLD; 4 = *cirrhosis and ascites*) but no implicit hierarchy or order is implied by the codes. Since the maximum likelihood or optimization algorithm might be limited when more than one independent variable is included (Hosmer & Lemeshow, 2000), I decided to forego using STATUS as a dependent variable in this study. However, now that the analysis has been performed using several other independent variables that proved to be of limited statistical significance, STATUS might be reintroduced in future studies. Such a model could use the independent variables that populate a statistically significant correlation in predicting liver disease (ECHOGRADE, HVW, and MPVPG only) using the binary logistic regression model to predict each disease status. Future researchers might want to consider conducting additional studies with laboratory liver panels (i.e., MELD scores) with ECHOGRADE and HVW to try and increase the diagnostic accuracy of multiple noninvasive tests. MRE shows promise as a noninvasive measure and should be monitored for advancements in this technology to noninvasively predict liver disease.

Studies similar to this study need to be conducted to evaluate regional differences in predicting liver disease using these sonographic measures. In this study, I applied the Bernoulli equation to change velocity to pressure gradients. This application was a novel

approach to abdominal sonography and should be tested in other regional facilities to determine the utility and efficacy for referring physicians. Application of the MPVPG and HVW in all abdominal sonograms will help to validate this method and provide an additional method of screening for liver disease across the nation and abroad.

Dissemination of Results

Key stakeholders in the study included hepatologists, internal medicine physicians, radiologists, sonographers, sonography professional organizations, and epidemiologists. Findings resulting from the study will be disseminated through presentations at scholarly sonography and hepatology conventions commonly attended by medical and/or epidemiology professionals. Results of the study will be provided to those physicians who routinely refer patient to the participating hospital for abdominal sonographic examinations.

Conclusions

The results from this study showed significant associations between ECHOGRADE, HVW, and liver disease using this noninvasive sonographic methodology. This study will add to the current body of knowledge in sonographic methodology to help predict disease before irreversible liver damage occurs. In both male patients and female patients, as the ECHOGRADE of the liver increased, so did the risk of liver disease. The HVW had an inverse relationship with liver disease. As the HVW decreased from triphasic to monophasic, the OR increased for liver disease. In this study, Doppler-derived pressure gradients of the hepatic, portal, and splenic vein were not so sensitive measure of liver disease. Future researchers should consider separating the

dependent variable into multiple liver disease states. The-Doppler-derived pressure gradients used in this study might predict certain types of liver disease but may be nonspecific when all types of liver disease are combined.

This study introduced two novel methods. One method involved applying the cardiac presets to the abdominal sonogram to change velocity measurements to pressure gradients. This method might help referring hepatologists who work with pressure gradients rather than velocity measurements in their clinical practice to correlate clinical findings with the recorded venous pressure gradients. A new mathematical modifier was used, which took into account the known dilatation of the portal vein with increasing liver fibrosis and multiplied it by the portal vein pressure gradient. This mathematical modifier might provide a pathway for additional research following the hemodynamic principles laid down by pioneers in vascular pathophysiology where the largest contributing factor in flow is a reduction or increase in radius.

The literature review conducted for this study demonstrated that liver disease remains a major health care burden, both in terms of human suffering and fiscal impact. The current gold standard in detecting liver disease is liver biopsies, but these tests are invasive and harbor significant risks. Results of this study offer a positive social change in the form of an alternate noninvasive sonographic method to predict liver disease. Use of this method could result in earlier clinical interventions before irreversible liver damage occurs as well as reduce the number of invasive liver biopsies, which could lead to improvements in overall health status and reductions in overall health costs.

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Appendix A: Instrumentation Used in Creating the Data Set

Ultrasound

The ultrasound equipment used in performing the sonograms was a high-resolution general imaging ultrasound system. The ultrasound transducers used for obtaining the measurements in the data set included both the 4-MHz vector array transducer and 6-MHz curved array transducer, depending on the patient body habitus. Both of these transducers had vascular applications to perform both color and spectral Doppler examinations. Six ultrasound units of like kind were used to obtain the required data. Each machine had yearly preventive maintenance checks and the machines were calibrated to the manufacturer specifications. All machines had the same software platforms to ensure as little variability as possible between machines.

Sonographic Protocol

For all participants, I consistently followed the sonographic protocol used in creating the data set. All participants received a complete abdominal sonographic examination using the standard imaging protocol followed at the health care center. All sonographic procedures adhered to the "as low as reasonably achievable" principle of exposure. Although no adverse bioeffects have been confirmed as attributable to the use of ultrasound for diagnostic purposes, following the principle of minimizing exposure ensured that the exam was done only when medically indicated and in a timely fashion. Following is the abdominal sonogram protocol I used to collect the data that was analyzed as part of the study.

1. I introduced myself (the sonographer) to the patient.

2. I explained the examination to the patient.
3. I obtained a complete patient history related to the current visit. This history included reviewing any relevant laboratory or ancillary imaging reports.
4. I placed the patient in a supine position and placed towels below the patient's shirt and above the pants to protect the patient's clothing from the acoustic gel.
5. I applied warm gel to the patient's abdomen.
6. I chose an appropriate transducer, based on the patient's body habitus, with which to conduct the examination. I used a 4-MHz vector array (4V2) transducer on large patients or to obtain images between the ribs. A 6-MHz curved linear array (6C3) was optimum if the images could be obtained subcostally and the frequency of the transducer could penetrate the region of interest.
7. I obtained longitudinal and transverse images of the following organs: liver, pancreas, gallbladder, kidneys, and spleen. I obtained additional oblique images of the gallbladder in the left lateral decubitus position. I also took longitudinal and transverse measurements of each organ, as well as measurements of the common bile duct, and gallbladder wall, and the anterior-posterior measurement of the portal vein.
8. I took color and spectral Doppler measurements of the following vessels: right portal vein, middle and right hepatic vein, and splenic vein. I took all of the Doppler measurements with an imaging angle of between 0 and 20 degrees to

ensure an accurate Doppler measurement. The color region of interest box was narrowed to improve the temporal resolution and increase the frame rate (fewer color lines over time). The sample volume (gate) was set at 1-2 mm to only detect flow in the center of the vessel. The pulse repetition frequency (scale) was set such that the waveform would take up approximately 50% of the Doppler scale. To obtain a pressure gradient from a velocity measurement, I changed the imaging presets to a cardiac setting. This routine step was adopted for all abdominal sonograms and was not specific to the participants in this study. This change involved me taking the following steps on the ultrasound machine:

a. going to setup;
b. selecting the Settings/Measurements/Calipers option;
c. on the dropdown list, switching protocol from Abdominal to Cardiac Doppler presets; and
d. returning to the main menu to continue imaging.

9. I had the patient reposition to a position in which both the middle and right hepatic vein could be imaged at a 0- to 20-degree angle.
10. I obtained the color Doppler signal. Under normal conditions, the hepatic veins traveling away from the transducer are displayed in blue. The color Doppler signal is useful (and I used it) to confirm the presence of flow as well as the direction of flow in the intrahepatic vessels.

11. I obtained the spectral Doppler component, placed the sample volume (gate) within the hepatic vein and then recorded the waveform.
12. I froze the image on the display screen and measured the peak systolic velocity of the respective hepatic vein.
13. I placed the second caliper over the velocity measurement to obtain the pressure gradient.
14. I recorded the pressure gradient of both the middle and right hepatic veins on the worksheet. Using the same technique and Doppler angle, I obtained the venous waveform in the right portal vein and splenic vein.
15. I took additional images if pathology was detected.
16. I wiped off the patient's abdomen and escorted the patient out of the room.
17. I filled out the technical worksheet and scanned it into the system for review by the radiologist.
18. I sent the final report to the referring physician.

Sonographic Data

I graded the liver texture in the sonographic analysis and recorded the grade in the data set. A grade of 0 reflected normal texture. A grade of 1 equated to a mildly coarse texture and increased echogenicity; the diaphragm and intrahepatic vessels were well visualized. A grade of 2 referred to a moderately diffuse coarseness of the liver texture and increased echogenicity; the diaphragm and intrahepatic vessels were difficult to visualize. A grade of 3 reflected a marked diffuse coarseness of the liver texture with or without liver lobulation; the diaphragm and intrahepatic vessels were poorly or not

visualized. In addition to grading the liver texture, I noted the liver contour as either smooth or lobulated.

With cirrhosis, liver echogenicity decreases and the liver itself becomes nodular and shrinks in size (Hagen-Ansert, 2006). I noted the presence or absence of splenomegaly and ascites. I obtained the diameter of the right portal vein at a 90-degree angle (normal incidence) to the vessel wall. I obtained an anterior-posterior dimension from the inner wall to inner wall of the vessel lumen. As reported by Hagen-Ansert (2006), an anterior-posterior dimension of greater than 1.3 cm has been found in patients with cirrhosis and portal hypertension.

Hepatic venous waveform analysis. The hepatic venous waveform in a healthy liver is triphasic. This waveform is a reflection of the tricuspid annulus moving toward the apex, the tricuspid valve opening, and the atrial contraction of the heart. With increased intrahepatic pressure due to obstruction such as that caused by fibrosis or cirrhosis, or congestion such as that caused by tricuspid valve regurgitation, the triphasic waveform can be lost. The pattern will first become biphasic with loss of the atrial contraction wave and eventually become monophasic with a constant antegrade signal due to venous obstruction (Goldberg & McGahan, 2006). I graded the hepatic venous signal at the time of the abdominal sonogram in the following manner: 3 = triphasic, 2 = biphasic, 1 = monophasic.

Hepatic, portal, and splenic venous pressure gradient. The hepatic venous pressure in a healthy liver is less than 5mmHg, as measured by the technique described in Sonographic Protocol. The right portal venous signal should reflect a continuous pattern

and flow toward the transducer. Pulsation in the flow is suggestive of right heart failure such as severe tricuspid regurgitation (Zwiebel & Pellerito, 2005). The splenic vein should display flow away from the transducer in a continuous pattern. I imaged the splenic hilum (i.e., where the vessels connect with the spleen) to identify the presence of splenic varices in the setting of an enlarged spleen and cirrhotic liver. Splenic varices are dilated veins that enlarge in the setting of portal hypertension (Hagen-Ansert, 2006). I noted the presence of varices, as well as both color and spectral Doppler within the varices. I recorded the recorded pressure gradient of the portal vein, splenic vein, and right hepatic vein in the data set for further statistical analysis. I also recorded the presence or absence of varices in the data set.

Determination of Disease Status

I used patient referral for an abdominal sonogram and self-reported health symptoms as well as the respective patient medical records to determine the disease status. Disease status included history of alcohol abuse, NAFLD, HepC, or other known liver diseases such as hepatocellular carcinoma. I checked laboratory values to determine a history of hepatocellular disease, including ALT and AST. If the patient had increased ALT levels, the laboratory results also included a second-generation enzyme-linked immunosorbent assay antibody to HepC (anti-HCV) to determine the presence or absence of HepC. I checked liver biopsy results at the time of the abdominal sonogram to determine those patients with liver fibrosis or cirrhosis. I checked endoscopy results to determine the presence or absence of esophageal varices.

Appendix B: Sample of Data Set

Gender[a]	Disease[b]	Disease status[c]	PV diam.[d]	PVPG[e]	HVPG[f]	HVW[g]	SVPG[h]	EG[i]	Ht[j]	Wt[k]	ALT[l]	AST[m]	Ethnicity[n]
1	0	0	0.5	0.1	0.2	2	0.1	1	67	134	0	0	4
2	0	0	0.7	0.2	0.3	2	x remove	2	65	185	1	1	4
1	1	3	1.8	0.3	0.2	1	0.2	3	69	190	1	1	1
2	1	1	0.9	0.1	0.2	3	0.1	3	60	159	0	0	4
2	1	1	1	0.2	0.5	3	0.1	2	62	180	1	1	4
1	0	0	0.6	0.1	0.3	3	0.6	3	64	195	0	0	1
2	0	0	0.5	0.1	0.3	3	0.1	2	67	170	0	0	2
1	1	2	0.8	0.1	0.7	3	0.2	3	65	155	1	1	3
1	0	0	0.8	0.1	0.4	3	0.1	2	63	175	1	1	4
2	1	3	0.8	0.2	0.8	1	0.1	2	64	162	1	1	4
1	0	0	0.65	0.1	0.7	3	0.1	3	63	150	0	0	4
1	0	0	0.7	0.1	0.4	2	0.1	3	64	185	1	1	4
1	0	0	0.7	0.2	0.5	3	0.1	3	56	205	1	1	3
1	1	1	0.7	0.1	0.2	2	0.2	3	64	185	1	1	3
1	1	4	1.5	0.1	0.3	1		2			1	1	4

Note. [a]Gender: 1 = male, 2 = female. [b]Disease: 1 = yes, 2 = no. [c]Disease status: 0 = no, 1 = GB disease, 2 = hepatitis, 3 = NASH, fatty liver, 4 = cirrhosis/ascites. [d] PV diam. = portal vein diameter. [e]PVPG = Portal vein pressure gradient measured in mmHg. [f]HVPG = hepatic vein pressure gradient measured in mmHg. [g]HVW = hepatic vein waveform, 1 = monophasic, 2 = biphasic, 3 = triphasic. [h]SVPG = splenic vein pressure gradient measured in mmHg. [i]0 = normal, 1 = coarse, 2 = echogenic liver, vessels seen, nonvisualized diaphragm, 3 = echogenic, nonvisualized vessels or diaphragm. [j]Ht = height in inches. [k]Wt = weight in pounds. [l]ALT = elevated ALT liver function test: 1 = yes, 2 = no. [m]AST = elevated AST liver function test: 1 = yes, 2 = no.

Curriculum Vitae

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EDUCATION

Ph.D., Public Health /Epidemiology, Walden University / December 2011

Doctor of Health Science / 2006
Nova Southeastern University, Fort Lauderdale-Davie, FL

Master of Science, Health Services Administration/2004
University of St. Francis, Joliet, IL

Bachelor of Science, Ultrasound–Vascular Option /2002
Oregon Institute of Technology, Klamath Falls, OR

TRAININGS AND CERTIFICATIONS

RDMS-Registered Diagnostic Medical Sonographer
Specialties: Abdomen, Ob/Gyn, Breast, Neurosonography, Ophthalmology

RDCS-Registered Diagnostic Cardiac Sonographer
Specialties: Adult, Pediatric, and Fetal Echocardiography

RVT-Registered Vascular Technologist

ROUB-Registered Ophthalmic Ultrasound Biometrist

CRT-Certified Radiology Technologist (Radiology, Mammography, Fluoroscopy)

ARRT-American Registry of Radiology Technologists (Radiology, Mammography)

CCI-Registered Vascular Specialist (RVS) and Registered Cardiac Sonographer (RCS)

EMPLOYMENT

January 2009-Present: Technical Director/ Ultrasound Supervisor, Community Regional Medical Center, Fresno, CA
Program Director, CRMC Diagnostic Medical Sonography Program—General and Cardiac Tracks

September 2010-Current: Adjunct Faculty: Fetal Echocardiography
George Washington University, Washington, DC.

June 2001-December 2010: Director, Merced College Sonography Program—General and Cardiac Tracks

February 2000-February 2005: Per diem Vascular Sonographer, Stanford Medical Center, Palo Alto, CA

May 1998-December 2008: Lead Sonographer, Children's Hospital Central CA Madera, CA (Radiology/Cardiology)

May 1994-April 1998: Sonographer, Mercy Hospital and Health Services, Merced, CA

January 1990-April 1994: Sonographer, Los Banos Diagnostics, Los Banos, CA

January 1989-December 1989: Radiology Intern, Mercy Hospital and Health Services

June 1985-December 1989: Sonographer Trainee, Merced Diagnostic Services

PROFESSIONAL ORGANIZATIONS, AWARDS, AND HONORS

September 2011-Current: President, Society of Diagnostic Medical Sonography

October 2007-September 2011: Board Member, Society of Diagnostic Medical Sonography

May 2008-Current: Member, American Society of Echocardiography

June 2010-Current: Member, American Institute of Ultrasound in Medicine

October 2010: Distinguished Educator Award: Society of Diagnostic Medical Sonography

October 2010: Fellow Award, Society of Diagnostic Medical Sonography

September 2003, 2004, 2005: *Who's Who Among America's Teachers* Award

March 2001: Member, People to People Ambassador- Ultrasound Delegation to Australia

PUBLICATIONS

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