Elastography of the Spleen as an Acute Measure of Portal Hypertension in Patients with Transjugular Intrahepatic Portosystemic Shunt (TIPS): A Systematic Review of the Literature and Future Directions

Samantha King
BA, Purdue University, 2011

Submitted to the graduate degree program in Clinical Research and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Master of Science.

Chair: Won Choi, PhD, MPH

Jill Jones, MD

Jacqueline Hill, PhD, MPH

Jonathan Mahnken, PhD

Date Defended: 11 April 2017

The thesis committee for Samantha King certifies that this is the approved version for the following thesis:

Elastography of the Spleen as an Acute Measure of Portal Hypertension in Patients with Transjugular Intrahepatic Portosystemic Shunt (TIPS): A Systematic Review of the Literature and Future Directions

____

Chair: Won Choi, PhD, MPH

Date Approved: 12 May 2017

Abstract

Background: Although Transjugular Intrahepatic Portosystemic Shunts (TIPS) are effective procedures to alleviate portal hypertension [1], these artificial shunts are inherently prone to stenosis over time and therefore require monitoring [2]. Because direct portal pressure measurement is invasive and impractical for clinical follow-up, noninvasive monitoring measures have been attempted. Due to its anatomic relationship with the portal vein, spleen stiffness (SS), quantified via elastography, has been proposed as a noninvasive measure of TIPS function. Therefore, the objectives of this study were to: (a) review literature on SS as an acute measure of portal hypertension and shunt function in patients with TIPS, and (b) characterize the cohort of patients undergoing TIPS insertion at the University of Kansas Medical Center (KUMC) in anticipation of a prospective study at this institution.

Methods: Through a systematic search of PubMed, five studies measuring SS before and after TIPS placement were identified and compared [3-7]. Data extracted from each study included: geographic location, number of subjects, subject characteristics, timing of elastography measurements, elastography exam technique, and findings. Additionally, the HERON (Healthcare Enterprise Repository for Ontological Narration) institutional database was used to generate a potential cohort of study subjects that included all adults who underwent TIPS insertion at KUMC from January 1, 2010 through September 27, 2016. CPT, ICD-9 and ICD-10 diagnosis codes, vital status, and death date were selected using the HERON query tool. TIPS outcomes, including TIPS revision, liver transplantation, and mortality, were measured at six months, one year, two years, and beyond two years.

Results: Four of the five studies found that splenic stiffness decreased after TIPS placement [3, 4, 6, 7], while the fifth documented mixed results [5]. Timing of measurements, imaging modalities, and embolization of collateral veins during TIPS placement differed among studies. The HERON search resulted in 298 patients for our cohort analysis – 59.1% were male, 85.2% were white, with an average of 56.3 years (SD±12.5). Within the follow-up period (range zero months to over five years), 30% (n=90) of patients underwent at least one TIPS revision, 16% (n=47) underwent liver transplantation, and 15% (n=46) died after TIPS placement.

Conclusions: Reports of the utility of splenic elastography as an acute measure of portal hypertension in TIPS patients are promising, although somewhat conflicting. Discrepancies in study findings may be attributed to differences in patient characteristics, elastography technique and timing, or embolization of collateral veins. A larger, prospective study is warranted, as elastography has the potential to be a safe, noninvasive, cost-effective measure of TIPS function. Because KUMC performs a substantial number of TIPS procedures in a diverse patient population, it is an ideal site for such a future study.

Acknowledgements

First, I would like to thank my Thesis Committee. I would like to thank Won Choi for serving as the Chair of my Committee, providing valuable guidance on writing a systematic review, and editing multiple drafts of this document. I would like to thank Jill Jones for serving as my project mentor, conceptualizing this project, providing content expertise throughout the process, regularly communicating with all individuals involved, and editing this paper. I would like to thank Jacqueline Hill for her expertise in implementation of clinical research, including her help with IRB submission and revisions, form design, database construction, and billing. I would also like to thank Jacqueline for editing multiple revisions of this document, including table design and presentation of data. I would like to thank Jonanthan Mahnken for statistical guidance with this project, particularly with regards to understanding the statistical analyses performed by each study in the literature review.

Additionally, I would like to thank Philip Johnson and the Department of Radiology for granting us funding for the pilot portion of our planned prospective study. I would like to thank Carissa Walter from Radiology Research for her efforts, along with Jacqueline, in IRB submission and revisions, form design, database construction, and billing.

Lastly, I would like to thank Russ Waitman, Tamara McMahon, and Maren Wennberg from Enterprise Analytics for all of their guidance with the informatics portion of this project. Specifically, I would like to thank Russ for his initial guidance through HERON and SQLite. I would like to thank Tamara and Maren for their mentorship in coding and "big data" analysis, and I would like to thank Maren for working with me to revise my data query. This project would not have been possible without all of the aforementioned individuals.

Table of Contents

Chapter I: Introduction

The Transjugular Intrahepatic Portosystemic Shunt (TIPS) is an effective procedure to alleviate portal hypertension [1]. By creating an artificial pathway from the portal to the hepatic vein, TIPS allows blood from the congested portal circulation to bypass the fibrotic liver and directly enter the systemic circulation [1]. Unfortunately, TIPS are inherently prone to stenosis or complete occlusion over time, and thus require frequent monitoring [2]. Direct measurement of the Hepatic Venous Pressure Gradient (HVPG) is the gold standard for quantifying portal hypertension and shunt patency. However, HVPG is an invasive test requiring central venous access and iodinated contrast material, making it an impractical method for frequent clinical follow-up [8]. For this reason, noninvasive measures of portal hypertension in patients with TIPS have been attempted. One noninvasive measure, elastography, is an imaging modality that quantifies tissue stiffness. Due to its anatomic relationship with the portal vein, splenic stiffness (SS), measured via elastography, has been proposed as noninvasive measure of TIPS function.

Current clinical follow-up for TIPS patients uses periodic Doppler ultrasound studies to monitor for early hemodynamic changes [9]. However, Doppler exams for TIPS are operator-dependent, and their use is inconsistent in clinical practice [9]. Additionally, the accuracy of Doppler measurements for TIPS can be greatly affected by patient respiration during the exam [10]. Measurements of flow velocities are also limited by depth of the vessel of interest from the body surface, which can be greatly increased by large patient body habitus and presence of ascites [9]. Moreover, Doppler parameters were established in the 1990s [11] and have not been updated since the transition from the use of bare metal to covered stents in TIPS procedures [2]. Furthermore, venous hemodynamics in patients with TIPS are complex, as collateral circulation may develop uniquely in each patient [12, 13]. Thus, portal circulation velocities may not accurately approximate TIPS function. Reports of the sensitivity of Doppler parameters in detecting TIPS dysfunction range from 33-93% [9].

A potential complement to Doppler exams is elastography measurement of SS. Elastography is a medical imaging modality that can map and/or quantify tissue stiffness [14]. There are several forms of elastography, including Acoustic Radiation Force Impulse imaging (ARFI, also commonly referred to as shear wave elastography) and Magnetic Resonance Elastography (MRE). ARFI is a form of ultrasound elastography that sends acoustic waves into the body and measures the velocity of the resulting shear wave to determine the stiffness of the tissue sampled [14]. Similarly, MRE uses magnetic resonance imaging to measure the propagation of shear waves generated after a mechanical impulse is delivered to the area of interest [14].

Several studies have shown that SS, measured via elastography, is directly correlated to HVPG [15, 16]. Since the splenic vein drains into the portal vein, increased portal pressure results in splenic congestion, which is reflected by increased SS [15, 16]. However, these studies measured SS and HVPG at one point in time [15, 16]. What is not known is whether an acute change in portal pressure, such as after TIPS placement, is reflected by a corresponding change in SS. Therefore, the primary purpose of this study is to review the current literature on how SS changes after portal pressure is reduced during TIPS placement. If there is a measureable decrease in SS after TIPS placement, elastography of the spleen may be an accurate acute measure of portal hypertension, and therefore, a non-invasive measure of shunt function in the clinical follow-up of TIPS patients. Accurately diagnosing shunt malfunction would increase the opportunity for early intervention before symptomatic shunt failure. The secondary purpose of this study is to characterize the cohort of patients undergoing TIPS placement at the University of Kansas Medical Center (KUMC), a regional liver transplant center, in support of conducting a prospective study at this institution.

Chapter II: Methods

Review of the Literature

We conducted a search in the electronic database PubMed on February 23, 2017 using key words indexed by Medical Subject Headings (MeSH). We used MeSH to generate the following search: “(("Elasticity Imaging Techniques"[Mesh] OR elastography OR shear wave elastography OR transient elastography)) AND (("Spleen"[Mesh]) AND (("Hypertension, Portal"[Mesh]) OR "Portosystemic Shunt, Transjugular Intrahepatic"[Mesh])).” We searched only for studies published since 2010 because the first commercially available machines capable of performing imaging-based elastography became available in the late 2000s [14]. Prior to that time, imaging-based elastography was available at limited institutions for research purposes only [14]. After limiting our search results to publications in the English language, 62 potential studies were reviewed. Upon discovering that many of the studies in our search results were not specific to TIPS patients, we narrowed our search to “elastography AND spleen AND transjugular intrahepatic portosystemic shunt,” which yielded six papers. Studies were selected for inclusion if they obtained elastography measurements of SS before and after the TIPS procedure. A total of five studies were included in the final literature review. A diagram of literature searches and study inclusion is depicted in Figure 1.

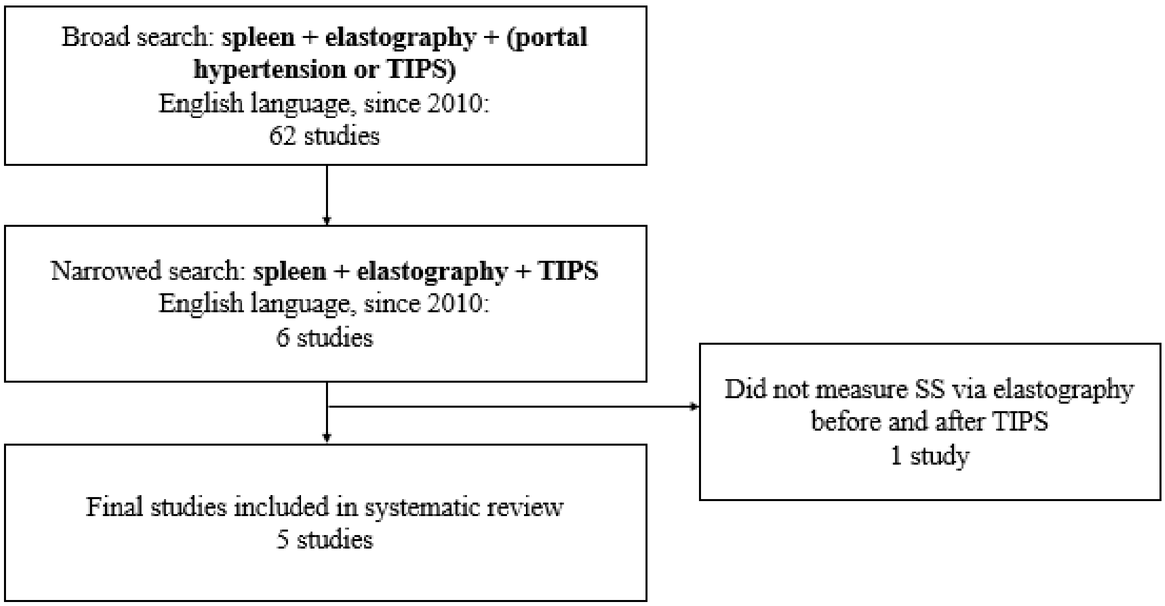

Figure 1: Literature Search Flow Diagram

A template was created for data extraction from each study. Data items included: study geographic location; number of subjects; subject characteristics, such as gender, age, etiology of cirrhosis, and indication for TIPS placement; timing of elastography measurements in relation to TIPS placement; elastography exam technique; and elastography exam results.

Characterization of the TIPS Patient Population at KUMC

We used the HERON (Healthcare Enterprise Repository for Ontological Narration) institutional database to generate a cohort of potential study patients at KUMC by using the i2b2 (Informatics for Integrating Biology and the Bedside) query tool with specific diagnosis and procedural codes. HERON is an integrated data repository that utilizes electronic medical records, billing systems, and cancer registries at KUMC [17]. All adult patients who underwent TIPS placement at KUMC between January 1, 2010 and September 27, 2016 were initially included in the search. We selected January 2010 as our start date because that is when KUMC transitioned to electronic medical records. Current Procedural Terminology (CPT) codes for

TIPS placement and revision, as well as liver transplantation, were selected in the i2b2 system. Additionally, select International Classification of Diseases (ICD-9 and ICD-10) diagnosis codes were pulled to estimate the etiology of each patient's liver disease. Vital status and date of death, if available, were also selected.

De-identified records were collected and managed using REDCap electronic data capture tools hosted at KUMC [18]. SQLite and SAS 9.4 were used to analyze the data. Date of initial TIPS placement was used at the baseline time point for all temporal analyses. Patients were excluded if they were denoted as deceased with an unknown death date (n=11), underwent liver transplantation before TIPS placement (n=11), or underwent TIPS revision before initial placement (n=2). After exclusion, our final analysis included 298 patients. A study flow diagram is depicted in Figure 2.

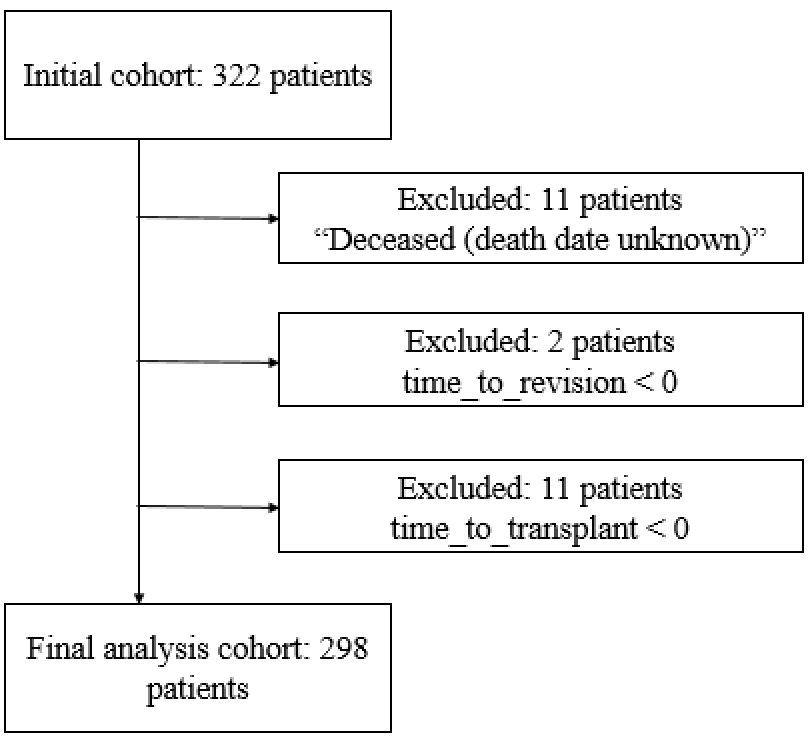

Figure 2: HERON Study Flow Diagram

Etiology of patients' liver disease was attributed to select diagnoses that were recorded before, or within 30 days after, initial TIPS placement. For the purpose of comparing outcomes based on etiology of liver disease, patients were divided into two etiologic groups: Alcohol and Other. Patients were considered to have cirrhosis due to alcohol if they had an ICD-9 or ICD-10 code denoting alcoholic liver disease (diagnostic group "Alcohol"). All patients without a relevant diagnosis code indicating alcoholic cirrhosis were considered to have cirrhosis due to another cause (diagnostic group "Other"). The diagnostic group "Other" included both patients with a diagnosis code for an etiology of liver disease other than alcoholic cirrhosis, and patients without any of the diagnostic codes selected.

Chapter III: Results

Review of the Literature

A total of five studies measuring SS before and after TIPS placement met inclusion criteria. A summary of each study is included in Table 1. Four studies utilized ARFI [3-6] while one used MRE [7]. Four studies found that SS decreased after TIPS placement [3, 4, 6, 7]. The fifth study found that splenic stiffness decreased in 58% (11 of 19) participants, but increased in 42% (8 of 19) following TIPS placement [5].

Three studies were conducted by the same research group in Chongqing, China (Gao and Ran et al.) in patients who had a history of cirrhosis secondary to Hepatitis B virus (HBV) infection and a history of bleeding gastroesophageal varices [3, 4, 6]. In those three studies, ARFI measurements of SS were taken one day before and 3-10 days after TIPS placement in fasting patients[3, 4, 6]. All three studies found a significant decrease in SS after TIPS placement. The 2012 study of 10 TIPS patients found that SS decreased from 3.65 (SD±0.32) pre-TIPS to 3.27 (SD±0.30) post-TIPS placement ($p<0.001$). The 2013 study of 12 TIPS patients found that SS decreased from 3.50 (SD±0.46) pre-TIPS to 3.15 (SD±0.39) post-TIPS placement ($p=0.00015$). Finally, the 2016 study found that SS decreased from 3.64 (SD±0.23) pre-TIPS to 3.18 (SD±0.21) post-TIPS placement ($p=0.0002$).

Similarly, Guo et al. conducted a study of 10 TIPS patients in Berlin, Germany using MRE to measure SS one day before and 2-3 days after TIPS placement [7]. The study does not mention the etiology of liver disease in the subjects, nor does it comment on patient fasting status. In congruency with the results of the three previously mentioned studies conducted by Gao and Ran [3, 4, 6], Guo et al. observed a significant decrease in SS after TIPS (pre-TIPS SS: 8.44 ± 1.36 kPa, post-TIPS SS: 7.06 ± 1.32 kPa, $p=0.01$).

Finally, a fifth study at the University of Michigan by Novelli et al. utilized ARFI to measure SS in 19 TIPS patients within one hour before, and immediately after, the TIPS procedure [5]. They also measured SS on post-operative day one in all patients, and on each subsequent day that the patient remained hospitalized after the TIPS procedure, up to day three. Though not explicitly stated, it can be inferred that patients were fasting for elastography measurements of SS obtained immediately before and after TIPS placement, as patients are required to fast for this surgical procedure [1]. However, the study authors do mention that exams on subsequent days of hospitalization (days 1-3) were obtained in a non-fasting state. In contrast to the studies by Gao and Ran et al. in which all patients had cirrhosis secondary to HBV [3, 4, 6], patients in this study had varying etiologies of cirrhosis. Causes of liver disease reported include alcohol, Hepatitis C virus (HCV), nonalcoholic steatohepatitis (NASH), cryptogenic, and other. In contrast to all previously discussed studies, this study did not report a significant decrease in SS after TIPS placement. While SS decreased in 58% (11/19) of patients, SS increased in 42% (8/19) of patients. Novelli et al. mention that patients with portosystemic collateral veins embolized during the TIPS procedure were more likely to demonstrate increased splenic stiffness after TIPS placement than those who did not undergo collateral embolization [5]. None of the other four studies mention collateral embolization.

Table 1: Study Characteristics

	Gao et al.	Ran et al.	Guo et al.	Novelli et al.	Gao et al.
Publication year	2012	2013	2015	2015	2016
Journal	Clinical Imaging	J Ultrasound Med	Invest Radiol	J Ultrasound Med	J Ultrasound Med
Location	Chongqing, China	Chongqing, China	Berlin, Germany	Ann Arbor, MI, USA	Chongqing, China
Subjects	10 TIPS patients	12 TIPS patients	10 TIPS patients	19 TIPS patients	33 TIPS patients
Patient age (mean ± SD, or mean (range))	38.6 ± 6.4	42.6 ± 11.0	60.5 ± 9.8	54 (22-79)	45 (28-75)
Etiology of liver disease	HBV	HBV	Not specified	Varied (EtOH, HCV, NASH, cryptogenic)	HBV
Patients fasting for all exams?	Yes	Yes	Not specified	No	Yes
Imaging modality	ARFI	ARFI	MRE	ARFI	ARFI
Timing of measurements relative to TIPS placement	One day before, 3-9 days after	One day before, 3-9 days after	One day before, 48-72 hours after	Within 1 hour before, immediately after, and on each subsequent day of hospitalization	One day before, 3-9 days after AND up to 12 months follow-up
Statistical analysis	Paired t-test	Paired t-test	Wilcoxon Signed-Rank Test	Nonparametric Mann-Whitney U Test	Paired t-test
Significant decrease in splenic stiffness after TIPS?	Yes	Yes	Yes	No Decreased in 58% (11/19), increased in 42% (8/19)	Yes
Mean SS pre-TIPS	3.65 ± 0.32 m/s	3.50 ± 0.46 m/s	8.44 ± 1.36 kPa	Not reported*	3.64 ± 0.23 m/s
Mean SS post- TIPS	3.27 ± 0.30 m/s	3.15 ± 0.39 m/s	7.06 ± 1.32 kPa	Not reported*	3.18 ± 0.21 m/s
p-value	<0.001	0.00015	0.01	Not reported*	0.0002

*Novelli et al. do not report values for mean spleen stiffness before and after TIPS, nor do they compare post-TIPS SS to pre-TIPS SS. Rather, they report mean changes in spleen stiffness. In 42% (8/19) of patients, SS increased, with a mean increase in Young modulus ± SD of 6.54 ± 6.29 kPa after TIPS. In 58% (11/19) of patients, the spleen became softer after TIPS (Young modulus decreased by an average ± SD of 9.57 ± 8.82 kPa). They used the Mann-Whitney U Test to compare the change in the spleen modulus after TIPS placement between the group with embolized or spontaneously thrombosed competitive shunts and those without shunts, and found a difference in change in SS between the groups (p<0.04).

Characterization of the TIPS Patient Population at KUMC

A total of 298 patients were included in this analysis. The cohort was 59.1% male, 85.2% white, and had a mean (SD) age at TIPS insertion of 56.3 (12.5) years. Patient characteristics are displayed in Table 2.

Table 2: Patient Demographics

Characteristic	Value
Mean age, years (SD)	56.3 (12.5)
Gender, n (%)	
Male	176 (59.1%)
Female	121 (40.6%)
Unknown	1 (0.3%)
Race, n (%)	
White	254 (85.2%)
African-American	6 (2.0%)
Asian	2 (0.7%)
Other/unknown	36 (12.1%)
Language, n (%)	
English	285 (95.6%)
Spanish	9 (3.0%)
Other/unknown	4 (1.3%)
Diagnosis, n (%)[a]	
Alcoholic cirrhosis	151 (50.7%)
AIH	17 (5.7%)
HBV	8 (2.7%)
HCV	99 (33.2%)
NAFLD/NASH	43 (14.4%)
PBC	23 (7.7%)
PSC	3 (1.0%)
Number of diagnoses, n (%)[b]	
0	63 (21.1%)
1	142 (47.7%)
2	78 (26.2%)
3	14 (4.7%)
4	1 (0.3%)

[a] Percentages for diagnoses do not add up to 100% as some patients had none or multiple of the diagnoses listed. AIH = Autoimmune hepatitis; HBV = Hepatitis B Virus; HCV = Hepatitis C Virus; NAFLD = Nonalcoholic Fatty Liver Disease, NASH = Nonalcoholic Steatohepatitis; PBC = Primary Biliary Cirrhosis; PSC = Primary Sclerosing Cholangitis
[b] Indicates the number of selected diagnoses a given patient had in his or her medical record.

Patient outcomes are displayed in Table 3. Thirty percent (n=90) of patients underwent at least one TIPS revision procedure. Seventeen percent (n=51) underwent revision within six months post-TIPS placement, 22% (n=66) within one year, and 27% (n=79) within two years. Sixteen percent (n=47) of patients underwent liver transplantation after TIPS insertion, with 7% (n=21) receiving a transplant six months post-TIPS, 10% (n=30) within one year, and 14% (n=42) within two years. Twenty-eight percent (n=82) of patients died after TIPS placement, with 15% (n=46) of patients dying within six months post-TIPS, 21% (n=62) within one year and 24% (n=72) within two years.

Table 3: Outcomes for TIPS patients at KUMC

	TIPS Revision (n=90)	**Transplant** (n=47)	**Death** (n=82)
By 6 months	51 (56.7%)	21 (44.7%)	46 (56.1%)
By 1 year	66 (73.3%)	30 (63.8%)	62 (75.6%)
By 2 years	79 (87.8%)	42 (89.4%)	72 (87.8%)
Beyond 2 years	90 (100%)	47 (100%)	82 (100%)

Note: numbers above are cumulative. For example, the number of patients having undergone a TIPS revision by 1 year includes those patients who underwent a revision by six months. Percentages reflect the proportion of total patients who experienced the given outcome by the specified time point.

We compared the incidence of the above outcomes (TIPS revision, liver transplant, death) in patients with and without a diagnosis of alcoholic liver disease. Patients with alcoholic liver disease were not significantly more or less likely to undergo TIPS revision [OR=1.23; 95% CI (0.77, 2.07);], receive a liver transplant [OR=0.72, 95% CI (0.39, 1.36)], or die [OR=0.97, 95% CI (0.58, 1.61)] during the follow-up period than patients with cirrhosis due to a cause other than alcoholic liver disease. These results are displayed in Table 4.

Table 4: Outcomes by Diagnosis: Alcohol vs. Other

	Odds Ratio	95% Confidence Interval
Revision	1.3	(0.8, 2.1)
Transplant	0.72	(0.4, 1.4)
Mortality	1.0	(0.6, 1.6)

Chapter IV: Discussion

Review of the Literature

In this systematic literature review, we found five published studies measuring SS via elastography before and after TIPS placement. Three studies were conducted by the same research group in China [3, 4, 6], while another was conducted in Germany [7], and one in the United States [5]. Four studies utilized ARFI [3-6], while one used MRE [7], to measure SS. Four of the five studies found a significant decrease in SS after TIPS placement [3, 4, 6, 7], while a fifth study found inconclusive results [5]. Differences in study findings could be attributed to timing of measurements with respect to the TIPS procedure, elastography imaging modality and techniques, patient baseline characteristics, and/or embolization of collateral veins.

One possible explanation for the discrepancy in study findings is the timing of elastography measurements. All four studies that found a significant decrease in SS after TIPS took post-TIPS SS measurements between three and twelve days after the procedure [3, 4, 6]. The study by Novelli et al., which found that SS increased in 42% (8/19) of patients, took post-TIPS SS measurements immediately following the procedure [5]. It may be that the correlation between HVPG and SS [16] is simply a reflection of congestion of the spleen with venous blood. However, it is also possible that increased SS in the setting of portal hypertension is additionally attributable to some degree of fibrosis in response to venous congestion [19, 20]. If increased SS in the setting of increased HVPG is solely due to venous congestion, then a change in SS should be immediately detectable following the relief of venous congestion associated with TIPS placement. On the other hand, fibrotic changes would take longer to correct. It is possible that Novelli et al.'s mixed findings could be attributable to the fact that their measurements were obtained immediately after the procedure, when changes due to vascular congestion should be detectable, but fibrotic and architectural changes may not.

Another possible explanation for the discrepancy in study findings may be differences in imaging modalities. While four of the five studies used ARFI [3-6], one used MRE [7]. To our knowledge, no studies have been done comparing MRE and ARFI in the spleen, as elastography of the spleen is not widely performed. However, elastography is commonly used in measurement of hepatic fibrosis and staging of cirrhosis [21]. Yoon et al. conducted a study comparing MRE and ARFI measurements of liver stiffness in 75 patients [22]. Authors found no difference in technical success rates between the two elastography modalities in the liver, but did find that ultrasound-based shear wave elastography resulted in less reliable measurements [22]. Additionally, this study observed a moderate correlation between MRE and ARFI measurements ($r=0.724$, $p<0.001$). Though not directly applicable to the spleen, this study by Yoon et al. demonstrates that there is moderate correlation between MRE and ARFI measurements of tissue stiffness in the liver, and MRE exams may be more reliable than elastography measurements obtained via ultrasound.

In addition to imaging modality used to obtain elastography measurements, exam technique may have contributed to the variability in findings across studies. Elastography exams are most accurately performed during patient breath-hold [16]. In the studies by Gao and Ran et al. [3, 4, 6] authors deferred post-TIPS SS measurements to several days after the procedure as “patients could not tolerate the exam” immediately post-operation. However, it is uncertain exactly why patients could not tolerate the exam, as the authors do not elaborate further. We postulate that the patients’ difficulty tolerating the exams could be attributable to post-operative pain, or the type of sedation used during the procedure. On the other hand, Novelli et al. performed post-TIPS SS exams “immediately following the procedure.” Authors did not mention the patient’s ability to hold his or her breath or to tolerate the exam. However, it is possible that patients in this study by Novelli et al. were not able to perform optimal breath-hold during the examination, which could have affected measurements of SS.

An additional factor that may affect the accuracy of elastography measurements is patients’ fasting status. After a meal, blood flow to the portal circulation is increased, which could falsely inflate SS measurements. Although Gao and Ran et al. state that patients were fasting for all elastography exams [3, 4, 6], the study by Guo et al. does not comment on patient fasting status [7]. Though not explicitly stated, patients in the study by Novelli et al. can be presumed to have been fasting for measurements immediately before and after TIPS placement, as patients are required to fast in preparation for this surgical procedure. However, Novelli et al. do explicitly state that patients were not fasting for exams on subsequent days of hospitalizations. Therefore, it is possible that Novelli et al. performed post-TIPS SS measurements too soon after TIPS placement to detect a meaningful decrease in SS. It is possible that this study may have detected a decrease in SS by post-operative days one through three had patients been fasting for these exams.

Another potential factor that could explain the differences in study findings is patient baseline characteristics, such as etiology of liver disease. In all three studies performed in China, all patients included had cirrhosis induced by HBV [3, 4, 6]. In contrast, patients in the US study had varying etiologies of liver disease, including alcohol, NASH, and HCV [5]. Guo et al. do not comment on the etiology of liver disease in their patients [7]. Due to differences in patient baseline characteristics, these studies may not be directly comparable. It is not known how various causes of cirrhosis may affect portal circulation, and therefore SS. However, it is possible that the cause of a patient's liver disease could affect these measurements.

Yet another potential explanation for the discrepancy in findings between studies is the embolization of collateral veins during the TIPS procedure. Because collateral circulation may develop in patients with cirrhosis [12, 13], physicians performing TIPS procedures may look for collateral veins that have developed to facilitate blood bypassing the fibrotic liver and created "competitive shunts." Some physicians embolize these collateral veins so they are not competing with the newly-formed TIPS for blood flow. Novelli et al. note that patients who underwent embolization of collateral veins during TIPS placement were significantly more likely to show an increase in SS after TIPS. However, not all 8 of the 19 patients in this study with increased SS after TIPS underwent collateral vein embolization, so this factor alone cannot fully explain the surprising finding of increased SS in some patients after TIPS placement. Interestingly, though Novelli et al. comment heavily on embolization of collateral veins during the TIPS procedure, this strategy is not mentioned by any other studies in this review. Therefore, it is unknown if this procedure took place in, or contributed to the results of, the other studies.

A limitation of this systematic review is that there is potential for bias across studies, particularly since the same group of investigators published three of the five studies [3, 4, 6]. Initially this evoked a concern for patient overlap between these three studies. However, each study lists the date ranges in which patients were recruited, and they do not overlap between the three studies by Gao and Ran et al., reducing the concern for patient overlap. There is also a potential for publication bias. It is possible that more studies assessing elastography of the spleen before and after TIPS have been performed but not published, particularly if they found no significant decrease in SS after TIPS placement.

Characterization of the TIPS Patient Population at KUMC

Utilizing the HERON institutional database, we characterized the cohort of patients who underwent TIPS placement at our institution over a six and a half year period. We found that our TIPS patient population is diverse with respect to age, gender, and etiology of liver disease. We also found that 30% of our TIPS patients undergo at least one TIPS revision, and about 16% receive a liver transplant after having a TIPS. This supports the need for a more accurate tool to support clinical follow-up of TIPS function.

A potential limitation of this cohort analysis is that HERON is an institution-specific database, meaning that follow-up data is only present when patients receive follow-up care at our institution. One advantage to studying this specific population at KUMC is that we are a regional liver transplant center, and one could argue that patients with liver disease are more likely to continue follow-up here than elsewhere in the area. Another possible limitation of this analysis is the length of opportunity for follow-up. Patients undergoing TIPS near the end of the specified date range in the query (say, September 2016) would have less opportunity for follow-up than patients undergoing TIPS placement early in the specified date range (January 2010), which could skew outcomes results.

Conclusion

Elastography of the spleen has the potential to be an accurate acute measure of portal hypertension in patients with TIPS. Based on the results of our systematic review of the literature, the data supporting its potential are promising, yet somewhat conflicting. Additionally, all studies performed on this application of elastography have been small, ranging from just 10-33 patients. Furthermore, most studies on this topic have been performed in Asia and Europe, with only one study in the United States. Therefore, a larger, prospective study is warranted, particularly one applicable to the US population of patients with cirrhosis.

KUMC is a regional liver transplant center, performing a high volume of TIPS procedures. The population of patients undergoing TIPS placement at KUMC is diverse with respect to age, gender, and etiology of liver disease, making KUMC an ideal site for a future study. This future study would contribute valuable data to support or refute the use of SS to measure TIPS function. More accurate monitoring of TIPS patients could significantly reduce morbidity and mortality from shunt failure.

References

1. Rossle, M., et al., *The transjugular intrahepatic portosystemic stent-shunt procedure for variceal bleeding.* N Engl J Med, 1994. **330**(3): p. 165-71.
2. Perarnau, J.M., et al., *Covered vs. uncovered stents for transjugular intrahepatic portosystemic shunt: a randomized controlled trial.* J Hepatol, 2014. **60**(5): p. 962-8.
3. Gao, J., et al., *The stiffness of the liver and spleen on ARFI Imaging pre and post TIPS placement: a preliminary observation.* Clin Imaging, 2012. **36**(2): p. 135-41.
4. Gao, J., et al., *Shear Wave Elastography of the Spleen for Monitoring Transjugular Intrahepatic Portosystemic Shunt Function: A Pilot Study.* J Ultrasound Med, 2016. **35**(5): p. 951-8.
5. Novelli, P.M., K. Cho, and J.M. Rubin, *Sonographic assessment of spleen stiffness before and after transjugular intrahepatic portosystemic shunt placement with or without concurrent embolization of portal systemic collateral veins in patients with cirrhosis and portal hypertension: a feasibility study.* J Ultrasound Med, 2015. **34**(3): p. 443-9.
6. Ran, H.T., et al., *Spleen stiffness and splenoportal venous flow: assessment before and after transjugular intrahepatic portosystemic shunt placement.* J Ultrasound Med, 2013. **32**(2): p. 221-8.
7. Guo, J., et al., *In vivo abdominal magnetic resonance elastography for the assessment of portal hypertension before and after transjugular intrahepatic portosystemic shunt implantation.* Invest Radiol, 2015. **50**(5): p. 347-51.
8. Castera, L., M. Pinzani, and J. Bosch, *Non invasive evaluation of portal hypertension using transient elastography.* J Hepatol, 2012. **56**(3): p. 696-703.

9. Benito, A., et al., *Doppler ultrasound for TIPS: does it work?* Abdom Imaging, 2004. **29**(1): p. 45-52.

10. Kliewer, M.A., et al., *Transjugular intrahepatic portosystemic shunts (TIPS): effects of respiratory state and patient position on the measurement of Doppler velocities.* AJR Am J Roentgenol, 2000. **175**(1): p. 149-52.

11. Kanterman, R.Y., et al., *Doppler sonography findings associated with transjugular intrahepatic portosystemic shunt malfunction.* AJR Am J Roentgenol, 1997. **168**(2): p. 467-72.

12. Wind, P., et al., *Anatomy of spontaneous splenorenal and gastrorenal venous anastomoses. Review of the literature.* Surg Radiol Anat, 1998. **20**(2): p. 129-34.

13. Kondo, T., et al., *Influence of paraumbilical vein patency on the portal hemodynamics of patients with cirrhosis.* J Clin Gastroenterol, 2014. **48**(2): p. 178-83.

14. Sarvazyan, A., et al., *An Overview of Elastography - an Emerging Branch of Medical Imaging.* Curr Med Imaging Rev, 2011. **7**(4): p. 255-282.

15. Colecchia, A., et al., *Liver and spleen stiffness and other noninvasive methods to assess portal hypertension in cirrhotic patients: a review of the literature.* Eur J Gastroenterol Hepatol, 2015. **27**(9): p. 992-1001.

16. Takuma, Y., et al., *Portal Hypertension in Patients with Liver Cirrhosis: Diagnostic Accuracy of Spleen Stiffness.* Radiology, 2016. **279**(2): p. 609-19.

17. Waitman, L.R., et al., *Expressing observations from electronic medical record flowsheets in an i2b2 based clinical data repository to support research and quality improvement.* AMIA Annu Symp Proc, 2011. **2011**: p. 1454-63.

18. Harris, P.A., et al., *Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support.* J Biomed Inform, 2009. **42**(2): p. 377-81.

19. Manenti, A., et al., *Experimental congestive splenomegaly: histological observations in the rat.* Pathologica, 1993. **85**(1100): p. 721-4.

20. Terayama, N., et al., *Pathology of the spleen in primary biliary cirrhosis: an autopsy study.* Pathol Int, 1994. **44**(10-11): p. 753-8.

21. Barr, R.G., et al., *Elastography Assessment of Liver Fibrosis: Society of Radiologists in Ultrasound Consensus Conference Statement.* Radiology, 2015. **276**(3): p. 845-61.

22. Yoon, J.H., et al., *Hepatic fibrosis: prospective comparison of MR elastography and US shear-wave elastography for evaluation.* Radiology, 2014. **273**(3): p. 772-82.