QUALITY OF CARE IN PATIENTS WITH CIRRHOSIS AND ASCITES, HEPATIC ENCEPHALOPATHY OR SPONTANEOUS BACTERIAL PERITONITIS

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By
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QUALITY OF CARE IN PATIENTS WITH CIRRHOSIS AND ASCITES, HEPATIC ENCEPHALOPATHY OR SPONTANEOUS BACTERIAL PERITONITIS

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Objective: To analyze concordance with evidence-based clinical care guidelines in real world clinical practice in patients with cirrhosis and ascites, hepatic encephalopathy (HE), or spontaneous bacterial peritonitis (SBP).

Methods: A retrospective cohort analysis of the UPMC EMR database (2009-2014) with access to full outpatient and limited inpatient data was conducted to identify patients with cirrhosis and ascites, HE or SBP. Data regarding patient demographics, clinical characteristics, laboratory values and medication utilization were extracted. Analyses included examination of patient demographic and clinical characteristics, change in disease severity (via MELDNa scoring) from cirrhosis to complication development and outpatient/inpatient healthcare utilization patterns. Additionally, concordance with investigator-designed quality care indicators adapted from
AASLD guidelines and other sources were assessed to understand real world clinical care. Patient- and physician- factors predicting concordance with pharmacotherapy recommendations were assessed via the use of logistic regression models.

**Results:** The inclusion/exclusion criteria yielded 4,116 patients with liver cirrhosis and 986, 665 and 148 patients with ascites, HE, and SBP respectively. Concordance with quality indicators ranged from 49.83\% (recommended medication for HE) to 99.32\% (MELD at SBP index). Body mass index and physician type were the only predictors that predicted concordance within the regression models for the selected indicators (prescription for recommended ascites and HE medications). A significant increase in MELDNa was observed from cirrhosis to complication index. No differences in healthcare utilization patterns were observed across complications.

**Conclusions:** Several opportunities for improvement in quality of care were noted. However, factors assessed in this study revealed limited information regarding opportunities to improve concordance to clinical guidance.
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LIST OF ABBREVIATIONS

AASLD: American Association for the Study of Liver Diseases
ACEI: Angiotensin converting enzyme inhibitor
ALP: Alkaline phosphatase
ALT: Alanine aminotransferase
AMI: Acute myocardial infarction
ANOVA: Analysis of variance
ARB: Angiotensin II receptor blockers
AST: Aspartate aminotransferase
BB: Beta-blockers
BMI: Body mass index
BUN: Blood urea nitrogen
CITI: Collaborative Institutional Training Initiative
CKD: Chronic kidney disease
COPD: Chronic obstructive pulmonary disease
CT: Computerized tomography
EMPI: Enterprise master person index
EMR: Electronic medical records
ESPEN: European Society for Clinical Nutrition and Metabolism
GGT: Gamma-glutamyl transferase
GI: Gastrointestinal
HCC: Hepatocellular carcinoma
HE: Hepatic encephalopathy
HIPAA: Health Insurance Portability and Accountability Act
HRQoL: Health-related quality of life
HRS: Hepatorenal syndrome
HVPG: Hepatic venous pressure gradient
ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification
IV: Intravenous
LVP: Large volume paracentesis
MELD: Model for End-stage Liver Disease
MELDNa: Model for End-stage Liver Disease with Sodium
MRI: Magnetic resonance imaging
NHANES: National Health and Nutrition Examination Survey
NSAID: Nonsteroidal anti-inflammatory drugs
PAD: Peripheral artery disease
PH: Portal hypertension
PMN: Polymorphonuclear leukocytes
PPI: Proton pump inhibitors
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS: Portosystemic shunt
SAS: Statistical Analysis System
SBP: Spontaneous bacterial peritonitis
SQL: Structured query language
UPMC: University of Pittsburgh Medical Center
US: United States
VA: Veterans Affairs
CHAPTER 1: INTRODUCTION

Liver cirrhosis

Background

Cirrhosis is a chronic condition of the liver characterized by the development of scarred tissue and subsequent reduced capacity of liver function.\textsuperscript{1} The liver is involved in multiple tasks such as processing of nutrients and their distribution, protein production and regulation, drug metabolism, removal of toxic waste, and bile production, which are affected by cirrhosis.\textsuperscript{1,2} Common etiologies of cirrhosis include chronic alcohol abuse, viral infections like chronic hepatitis B, C or D, nonalcoholic fatty liver disease, bile duct disease caused by backing up of bile into the liver, autoimmune hepatitis and genetic diseases like hemochromatosis, Wilson’s disease or glycogen storage disease.\textsuperscript{1,2} The progressive nature of the disease eventually leads to downstream complications such as portal hypertension (PH), esophageal varices, ascites, spontaneous bacterial peritonitis (SBP), gastrointestinal bleeding, hepatic encephalopathy (HE), renal failure and hepatocellular carcinoma (HCC); all of these complications are associated with increased morbidity and mortality.\textsuperscript{3} The associated 1-year mortality is 1%, 3.4%, 20%, 57%, and 67% for compensated cirrhosis with no esophageal varices, compensated cirrhosis with varices, decompensated cirrhosis with ascites, decompensated cirrhosis with gastrointestinal bleeding, and infections and renal failure, respectively.\textsuperscript{3} Cirrhosis and its complications also impair health-related quality of life (HRQoL). Factors such as insomnia, anemia, pruritus, muscle spasms, clinically overt fatigue, depression and anxiety, and the presence of complications such as ascites and HE are known to affect HRQoL negatively.\textsuperscript{4-6}
**Pathophysiology**

Damage and destruction of liver tissue resulting from the aforementioned etiologies initiates a healing process where healthy liver tissue is counterintuitively replaced by fibrous tissue.\(^7\) This process, called fibrogenesis, leads to liver fibrosis, which can progress to cirrhosis depending on the underlying etiology, host factors and environmental factors.\(^7\) Cirrhosis is accompanied by the distortion of the hepatic vasculature, which involves angiogenesis, or the formation of new blood vessels. Cirrhosis can lead to major consequences such as impaired hepatocytes, increased intrahepatic resistance and development of HCC.\(^7\) The hepatic vascular alterations are accompanied by other circulatory abnormalities such as splanchnic vasodilation, hypoperfusion of kidneys, water and salt retention, and increased cardiac output.\(^7\) All these processes result in PH, which further develops into serious complications such as ascites, SBP, HE which are associated with higher mortality as discussed previously.\(^3,7\) Hepatocytes are responsible for carrying out major functions of the body such as protein synthesis and storage, carbohydrate metabolism, lipid metabolism, detoxification of endogenous and exogenous substances; therefore, hepatocyte impairment affects these processes adversely.\(^7,8\) Particularly, low albumin levels lead to decrease in oncotic pressure allowing leakage of fluid from the interstitial spaces into the peritoneal cavity. The combination of low oncotic pressure with PH contributes towards the development of ascites.\(^9\) As mentioned earlier, hepatocyte dysfunction affects protein production which has an effect on creatinine levels (a marker of kidney function) and clotting factors (increasing bleeding risk) indicating liver damage. Also, the affected detoxification process may lead to increased ammonia levels, which is a contributing factor for HE.
Signs, symptoms, diagnosis

Early stage cirrhosis is typically difficult to diagnose until decompensation occurs as the symptoms are not profound. Initial symptoms experienced by patients are generally non-specific such as fatigue, weakness, decreased appetite, weight loss, and nausea. More specific symptoms include nevus araneus (spider angioma, i.e. spider-like blood vessels), severe itching (due to elevated bilirubin), abdominal distention due to fluid accumulation (ascites), edema in the feet, ankles or legs, and jaundice. These signs/symptoms can be further used as a basis to conduct diagnostic testing for confirmation.

Diagnostic techniques for cirrhosis are multimodal. A medical/family history provides information on potential past exposure to hepatitis viruses (most commonly B or C), as well as personal history of alcoholism or genetic and other prognostic factors that may have contributed to the disease development. Laboratory blood work assessing liver enzyme levels for aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT) are generally conducted. Elevated levels of AST and ALT are markers of acute liver death. However, as cirrhosis progresses, these levels might not always be elevated due to fewer healthy hepatocytes releasing these markers when injury occurs. Elevated ALP levels suggest blockage of the bile ducts, and elevated GGT levels indicate use of alcohol or bile duct diseases. Similarly, blood protein levels can also be informative, including serum bilirubin (SBili), serum creatinine (SCr), international normalized ratio (INR), and albumin. SBili tests the bilirubin level in blood and elevated levels indicate potential liver disease. SCr is a measure of kidney function and elevated levels indicate abnormal kidney function, though this may be misleadingly low in patients with severe cirrhosis due to lack of creatinine production by the liver. INR is a measure of blood clotting ability with elevated levels suggesting longer time for blood clotting, resulting from a lack of production of clotting
Reduced levels of albumin is an indication of liver disease and can lead to ascites and abnormal fluid retention in extremities due to a decreased oncotic pressure within the circulatory system.\textsuperscript{1,10} Sbili, SCr and INR have continued importance to cirrhosis as they are useful indicators to calculate the Model for End-Stage Liver Disease (MELD) score.\textsuperscript{1} The MELD score, developed by Kamath \textit{et al}.\textsuperscript{11} is a measure of the disease severity and is used as a predictor of 3-month survival to prioritize patients for liver transplantation. The MELD score is calculated as follows:

\[
\text{MELD score} = (0.957\times \log_{e} (\text{SCr}) + 0.378\times \log_{e} (\text{SBili}) + 1.120\times \log_{e} (\text{INR}) + (0.643)) \times 10
\]

The Organ Procurement and Transplantation Network recently updated the MELD score in January 2016, including serum sodium (SNa) in the equation. The MELDNa (updated score) is calculated as follows:\textsuperscript{12}

1. Calculation of the MELD:
\[
\text{MELD} = (0.957\times \log_{e} (\text{SCr}) + 0.378\times \log_{e} (\text{SBili}) + 1.120\times \log_{e} (\text{INR}) + (0.643)) \times 10
\]

2. Calculation of corrected SNa for patients with a serum glucose > 120 mg/dl:\textsuperscript{13}
\[
\text{Corrected serum sodium (CSNa)} = \text{SNa} + \{0.024*(\text{serum glucose} – 100)\}
\]

3. Calculation of the MELDNa using the following formula:\textsuperscript{14}
\[
\text{MELDNa} = \text{MELD} + 1.32\times(137 – \text{SNa/cSNa}) – [0.033\times\text{MELD}* (137 – \text{SNa/cSNa})]
\]

For both the scores, patients who have undergone dialysis twice in a week and have SCr > 4, their SCr value is set at 4.\textsuperscript{15,16} Any laboratory value < 1 for SCr, Sbili and INR is set at 1.\textsuperscript{15,16} Limits for SNa or CSNa values are set between 125 Mmol/L and 137 Mmol/L, with extreme values outside of this range adjusted accordingly.\textsuperscript{17} A higher score corresponds with increased severity of disease and mortality. \textbf{Table 1} provides information on MELD/MELDNa score and associated mortality.
Table 1. MELD/MELDNa score and associated 3-month mortality

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<tr>
<td>≤ 9</td>
<td>1.9%</td>
</tr>
<tr>
<td>10-19</td>
<td>6.0%</td>
</tr>
<tr>
<td>20-29</td>
<td>19.6%</td>
</tr>
<tr>
<td>30-39</td>
<td>52.6%</td>
</tr>
<tr>
<td>≥ 40</td>
<td>71.3%</td>
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*MELD = Model for End-Stage Liver Disease; MELDNa = Model for End-Stage Liver Disease with Sodium*
Finally, imaging tests like ultrasound, computerized tomography (CT) scans, and magnetic resonance imaging (MRI) are used to study the liver surface, and to determine the presence of gastric varices and splenomegaly. Liver biopsy may be utilized to evaluate tissue for diagnosing the presence of damage or disease.

Epidemiology and economic burden

According to 1999-2010 National Health and Nutrition Examination Survey (NHANES) data, the prevalence of liver cirrhosis in the United States (US) is estimated at 633,323 adults (0.27%).\textsuperscript{18} The prevalence by age is bimodal in nature, peaking in the 4\textsuperscript{th}/5\textsuperscript{th} decade of life and again after 75 years of age.\textsuperscript{18} Cirrhosis prevalence is higher in males and in non-Hispanic African-Americans, and Mexican-Americans.\textsuperscript{18} The 2014 National Vital Statistics Reports ranks chronic liver disease and cirrhosis as the 12\textsuperscript{th} leading cause of death accounting for 38,170 deaths (1.5% of all deaths due to all causes) with an age-adjusted death rate of 10.4 per 100,000.\textsuperscript{19} The 2010 National Center for Health Statistics reported an estimated 101,000 short hospital stays associated with chronic liver disease and cirrhosis,\textsuperscript{20} and an estimated 635,000 ambulatory visits in patients with cirrhosis in 2009.\textsuperscript{12}

The economic burden of chronic liver disease and cirrhosis (ICD-9-CM 571.xx) based on national hospital inpatient data in 2014 is estimated at approximately $1.5 billion with alcoholic cirrhosis of liver (approximately $717 million), cirrhosis of liver without mention of alcohol (approximately $457 million), and acute alcoholic hepatitis (approximately $190 million) contributing to the majority inpatient costs.\textsuperscript{21} Chronic liver disease and cirrhosis accounted for an estimated $2.5 billion in direct costs (drug costs and hospitalizations) and $10.6 billion in indirect costs (loss of work productivity) in 2004.\textsuperscript{22}
Treatment and guidelines

Liver cirrhosis does not have a definitive medical cure outside of transplantation, however treatments are available to delay disease progression, reduce liver damage and decrease or manage complications.\textsuperscript{2} The American Association for the Study of Liver Diseases (AASLD), an organization of scientists and health care professionals with expertise in liver diseases, provides evidence-based guidelines with recommendations on preferred approaches for diagnostic, therapeutic and preventive aspects of liver disease care with the goal of preventing, curing, and managing symptoms of liver disease.\textsuperscript{23,24} Based on the target liver condition, the committee provides specific recommendations to be followed by practitioners in their daily practice. The following sections describe selected complications and published AASLD management guidelines.

Complications

As discussed previously, as cirrhosis progresses it can lead to several downstream complications, such as esophageal varices, ascites, SBP, gastrointestinal bleeding, HE, renal failure and HCC which are associated with 1-year mortality as low as 1\% to as high as 67\%.\textsuperscript{2,3} The development of complication stems from the restricted blood flow from the portal vein through the liver which develops into PH, indicated by a hepatic-vein pressure gradient (HVPG) of greater than 5 mmHg.\textsuperscript{3} If left uncontrolled, it develops into clinically significant PH (HVPG > 10 mmHg).\textsuperscript{3} This commonly results in gastroesophageal varices, (characterized by dilation of vessels in the esophagus) and increased incidence of HCC.\textsuperscript{3} In particular, a HVPG $\geq 12$ mmHg is associated with an increased risk of variceal bleeding which can be fatal if not treated urgently.\textsuperscript{3} PH, sodium retention, changes in circulatory oncotic pressure, and splanchnic vasodilation (due to increased nitric oxide production) are major contributors to the development of ascites, which is characterized by excess fluid in
peritoneal cavity.² Bacterial infection of this excess peritoneal fluid is called SBP.³ The
destruction of liver tissue limits the removal of toxic nitrogenous substances from the body
leading to HE (characterized by altered mental status, confusion, and potentially a coma).²⁵

**Figure 1** presents a simplified outline of the progression of cirrhosis. The focus of present
study will be on ascites, SBP, and HE and the following sections will provide details of these
selected complications.
Figure 1. Basic schematic presentation of cirrhosis progression

Early liver cirrhosis

Portal hypertension (HVPG > 5 mmHg)

Gastroesophageal varices (HVPG > 10 mmHg; characterized by dilation of vessels in the esophagus)

Reduced effective blood volume, increased cardiac output and water and sodium retention

Ascites (retention of excess peritoneal fluid)

Spontaneous bacterial peritonitis (bacterial infection of peritoneal fluid)

Portal-systemic shunting resulting from variceal bleeding (HVPG ≥ 12 mmHg)

Increased levels of nitrogenous products in the blood

Hepatic encephalopathy (altered mental condition)

HVPG: Hepatic-vein pressure gradient
Ascites

Ascites is the most common complication of cirrhosis, and develops as a result of fluid accumulation in the peritoneal cavity due to increased portal pressure and changes in circulatory oncotic pressure.\textsuperscript{3,26} As cirrhosis progresses, homeostatic activation of vasoconstrictor and anti-natriuretic factors occurs to maintain the effective blood volume.\textsuperscript{3} This leads to water and salt retention and eventual fluid accumulation in the peritoneal cavity due to increased portal pressure.\textsuperscript{3} Approximately 50\% of patients with cirrhosis who do not have HE or variceal hemorrhage (two of the most common other complications) develop ascites over a period of 10 years.\textsuperscript{27} The 1-year and 5-year mortality rates associated with ascites is 15\% and 44\%, respectively, and it is the most common reason for complication-related hospital admissions among cirrhotic patients.\textsuperscript{27} Based on severity, ascites can be classified as mild (not clinically evident, but diagnosable by ultrasound), moderate (symmetrical distension of stomach) or severe (noticeable tense distension of stomach).\textsuperscript{28} Diagnosis is ascertained by several components. Physical examination focuses on checking for bulging abdominal flanks due to accumulation of fluid and may include an ultrasound to visualize the fluid.\textsuperscript{27} Finally, an abdominal paracentesis is utilized to extract abdominal ascitic fluid to test for ascitic cell count, levels of albumin and total protein, and for the presence of bacteria.\textsuperscript{27} Patient medical history may also be reviewed for additional cause of ascites such as cancer, heart failure, severe renal disease, thyroid disease, and tuberculosis.\textsuperscript{27} The goals of ascites management within the AASLD guidelines are to (1) control ascites, (2) prevent or relieve ascites symptoms such as dyspnea or abdominal pain and distension, and (3) prevent development of SBP and hepatorenal syndrome (HRS).\textsuperscript{28} AASLD-recommended pharmacological therapies include:\textsuperscript{27}

1) Baclofen: For patients with alcohol dependence to reduce cravings. Administered orally at 5 mg three times daily (tid) for 3 days and then titrated to 10 mg tid.
2) **Diuretics**: To aid in removal of volume overload (primarily ascites) and sodium. First-line initial combination of oral spironolactone (100 mg) and oral furosemide (40 mg) administered in the morning is recommended to achieve rapid natriuresis and to maintain normokalemia. Oral spironolactone as single therapy can be used in patients with minimal fluid overload. Second-line diuretics include amiloride, triamterene, metolazone, and hydrochlorothiazide.

In patients with ascites, the vasodilatory effect (reduced blood pressure) of nitric oxide is mediated by endogenous vasoconstrictors such as vasopressin, angiotensin, and aldosterone. Therefore, AASLD recommends caution/avoidance in the use of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) in patients with ascites, unless there is compelling indication, as these agents counteract diuretics. In patients with refractory ascites (ascites that does not recede post use of therapeutic paracentesis, sodium restriction and diuretics), the risks of beta blockers (BB) should also be carefully considered due to their effects on blood pressure and potential for paracentesis-induced circulatory dysfunction, though these medications are recommended in PH. Lastly, nonsteroidal anti-inflammatory drugs (NSAID) should be avoided in ascites as they reduce urinary sodium excretion and can induce azotemia. Lastly, AASLD states that proton pump inhibitors (PPI) use has an increased association with SBP (due to changes in bacterial growth in the GI tract) and its use should be restricted to indications where necessary.

Non-pharmacological strategies for ascites management include restriction of dietary sodium to 2000 mg/day in conjunction with diuretics, monitoring urine sodium and fluid restriction in patients with hyponatremia. In patients with significant edema, weight loss (due to fluid loss using diuretics) is recommended. On resolution of edema, weight loss (due to fluid loss) of 0.5 kg/day is considered reasonable. Use of large volume paracentesis is recommended for patients with refractory ascites.
Spontaneous bacterial peritonitis

SBP results from bacterial infection of the ascitic fluid caused by translocation of bacteria-infected GI tract fluid. In patients with cirrhosis and ascites, there is an increased intestinal mucosal permeability, as a result of which bacteria migrate from lymph nodes to blood and eventually ascitic fluid. Prolonged bacteremia, compromised host defenses, intrahepatic shunting of colonized blood and defective bactericidal activity within the ascitic fluid are additional factors that may lead to SBP. The estimated incidence rate of at least one episode of SBP is 10-15% over 1-year in patients with ascites. SBP is associated with 20% of in-hospital mortality among cirrhotic patients. In patients surviving SBP hospitalization, the 1-year and 5-year mortality is approximately 70% and 80%, respectively. The recurrence rate of SBP is approximately 40-70% within the first year of successfully clearing an episode of SBP using antibiotic therapy.

SBP is diagnosed by the presence of elevated absolute polymorphonuclear leukocyte (PMN) count of ≥ 250 cells/mm³ in the ascitic fluid without an evident intra-abdominal surgically treatable source of infection. Prevention is initiated with the use of primary (before the first episode) and secondary (after the first episode) prophylaxis agents. The goal of prophylaxis is to prevent the development of SBP in patients who potentially are at risk, including those with ascitic fluid having a total protein < 1.5 g/dl along with impaired renal function (SCR ≥ 1.2 mg/dl, blood urea nitrogen (BUN) ≥ 25 mg/dl, or SNa ≤ 130 mEq/L) or liver failure. It is also recommended to provide prophylaxis for 7-10 days immediately post variceal hemorrhage. Secondary prophylaxis is always recommended after a prior episode of SBP. AASLD recommends the following pharmacological therapies for prophylaxis of SBP:

1) Primary prophylaxis:
   a. Norfloxacin 400 mg daily or trimethoprim/sulfamethoxazole double-strength (800/160 mg) once daily, or
b. Ceftriaxone 1 gram daily intravenously for 7 days or norfloxacin 400 mg
twice daily dose for 7 days in patients with cirrhosis and GI hemorrhage.27

2) Secondary prophylaxis:
   a. Norfloxacin 400 mg daily or trimethoprim/sulfamethoxazole double-strength
      (800/160 mg) once daily,27 or
   b. Ciprofloxacin 500 mg daily may be utilized as an alternative in combination
      with trimethoprim/sulfamethoxazole double strength.27,30

In patients who develop SBP, AASLD recommends initiation of empiric treatment in patients
with PMN ≥ 250 cells/mm³ in ascitic fluid in a community-acquired setting who have not
recently received beta-lactam antibiotics.27 These patients should receive a third-generation
cephalosporin, preferably IV cefotaxime (2 grams every 8 hours).27 Patients with PMN ≥ 250
cells/mm³ in ascitic fluid in a nosocomial setting and/or who have recently received beta-
lactam antibiotics should receive antibiotic therapy according to local susceptibility
patterns.27 Finally, patients with PMN ≤ 250 cells/mm³ in ascitic fluid and signs/symptoms of
infection (temperature > 100° F or abdominal pain or tenderness) should receive IV
cefotaxime 2 grams every 8 hours (or a similar cephalosporin) while awaiting results of
culture for SBP confirmation.27

Oral fluoroquinolones such as ciprofloxacin, levofloxacin, moxifloxacin may be used as an
effective alternative to cefotaxime in patients without vomiting, shock grade II or higher HE,
or SCr > 3 mg/dl.27 Patients with SCr > 1 mg/dl, BUN > 30 mg/dl or Sbili > 4 mg/dl, should
also receive albumin 1.5 g/kg of body weight within 6 hours of detection and 1 g/kg on day 3,
though some clinicians recommend this therapy in all patients being treated for SBP.27
Hepatic encephalopathy

HE is a form of cognitive dysfunction caused by liver insufficiency and/or portosystemic shunting (PSS), which eventually manifests into multiple neurological or psychiatric abnormalities. Scarred liver tissue in cirrhosis is unable to effectively remove ammonia and other nitrogenous waste from the body. These waste products build up in the body and are transported through the blood to the brain adversely affecting neuronal conduction. HE is associated with a 1-year mortality rate of 64%.

HE is described in two forms: overt HE (OHE) and covert HE (CHE). Minimal HE (MHE) is a type of CHE, with no clinical sign or cognitive changes that might indicate HE which might be seen in Grade I HE (another type of MHE) or OHE. OHE is characterized by varied neurological and psychiatric abnormalities such as lethargy, disorientation, obvious personality change, inappropriate behavior, dyspraxia, asterixis, somnolence, confusion, bizarre behavior and coma. MHE is characterized by normal mental and neurological status but may present with a slight delay in coordination. Prevalence of OHE is 10-14% at time of cirrhosis diagnosis, 16-21% in those with decompensated cirrhosis and 10-50% in patients with a transjugular intrahepatic portosystemic shunt. Overall, 30-40% of patients with cirrhosis develop OHE at some point during their clinical course. MHE develops in 20-80% of patients with cirrhosis. The annual economic burden of HE-attributable hospitalization is estimated to range from $1 billion to $7 billion.

Diagnostic techniques used for HE in patients with the aforementioned symptoms include clinical evaluation for signs suggestive of liver insufficiency and/or PSS in patients with no other obvious cause of brain damage. Clinical scales (to analyze severity) such as the West Haven criteria, as well as neuropsychological or neurophysiological tests (diagnose cognitive dysfunction) are also used. Use of psychometric or neurophysiological tests such as portosystemic encephalopathy syndrome test, critical flicker frequency test, continuous
reaction time test, inhibitory control test, Stroop test, SCAN test, electroencephalography may provide additional information. MRI and CT scans are used in general for first-time HE and in case of clinical suspicion of other pathology for brain disease. Finally, laboratory testing to assess levels of ammonia in the blood is commonly performed. However, this testing alone does not add any diagnostic, staging or prognostic value. Diagnosis is made purely by a combination of symptoms, laboratory values and lack of other possible causes. The AASLD provides guidelines for treatment of OHE, however MHE does not have any specific guidelines, as its presence is not completely obvious to detection through routine clinical examination. The recommendations are as follows:

1) **Nonabsorbable disaccharides**: Lactulose 25 mL every 1-2 hours is recommended until at least two soft or loose stools per day are produced and titrated further to maintain two or three bowel movements per day. Lactulose works by preventing absorption of ammonia within the gut. It is utilized as treatment for OHE, but also for prevention of recurrent episodes of HE after the first episode.

2) **Rifaximin**: Used as an add-on therapy or alternative therapy to lactulose to prevent OHE recurrence in patients who have experienced one or more bouts of OHE while on lactulose therapy.

3) **Neomycin**: Used as an alternative therapy (last line) as it inhibits glutaminase which is responsible for ammonia generation.

Non-pharmacological treatments for HE include maintaining a daily energy intake of 35-40 kcal/kg of body weight and daily protein intake of 1.2-1.5 g/kg of body weight/day.

**Problem statement**

Medical care for chronic disease generally involves the use of multiple diagnostic, therapeutic and preventive measures. When available, evidence-based guidelines provide a
strong framework for practitioners to implement recommendations, which improves the quality of care and establishes a strong evidence-based practice. However, it is not uncommon to see deviations from these evidence-based guidelines in the real-world practice, which adversely impacts clinical care resulting in increased morbidity and mortality. AASLD provides evidence-based guidelines for management of ascites, SBP and HE. Use of these guidelines by healthcare professionals can provide guidance to quality care, reduce disease burden, and decrease associated high mortality rates of the condition. However, there is a need to evaluate how well these guidelines are utilized in practice, and what patient- and physician-related factors may predict quality of care against clinical guidance. Identifying these opportunities for clinical improvement aims to advance disease management and patient experience of cirrhosis care.

**Hypothesis**

The overall hypothesis of this study is that there is no deviance from AASLD guidelines for the selected therapies and quality indicators for quality care in patients with cirrhosis who develop ascites, SBP and HE.

**Research questions**

1. To describe the demographic and clinical characteristics of patients with liver cirrhosis
2. To evaluate the change in severity (MELDNa) from cirrhosis to development of ascites, SBP and HE
3. To assess the healthcare utilization patterns of patients with documented ascites, HE and SBP
4. To assess concordance with selected AASLD guidelines, and quality indicators and determine the relationship between patient- and physician-related factors that influence concordance
CHAPTER 2: LITERATURE REVIEW

The aim of the literature review was to identify studies assessing concordance of clinical care to established/recommended care guidelines/quality indicators and quality of care in patients with liver cirrhosis and/or ascites, SBP and HE.

Search strategy

A systematic literature search was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which were modified as PubMed was the only database used.35 Peer-reviewed publications were searched using PubMed. The search strategy included the keywords and/or combinations extracted from PubMed MeSH terms (Refer Table 2). Broader terms used to extract MeSH terms were cirrhosis, alcoholic cirrhosis, ascites, peritonitis, hepatic encephalopathy, guideline adherence, benchmarking, quality of healthcare, quality assurance, health care, quality indicators, health care and standard of care. In addition to extracted keywords, quality of care was also used.

Inclusion/exclusion criteria

The inclusion criteria were as follows:

1. Studies published between January 2000 – July 2016,
2. Studies in English language,

The exclusion criteria were as follows:

1. Literature reviews, randomized clinical trials, dissertations, commentaries, editorials, summary reports and conference abstracts,
2. Not focused on quality of care/guideline compliance in cirrhosis ascites, SBP and HE.
The PRISMA chart showing search strategy is shown in **Figure 2**.
Table 2. MeSH terms extracted from PubMed for literature search

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>Complications</th>
<th>Quality of care/ Guideline adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cirrhosis</strong></td>
<td><strong>Complications</strong></td>
<td><strong>Guideline adherence</strong></td>
</tr>
<tr>
<td>• Liver cirrhosis(es)</td>
<td>• Ascites</td>
<td>• Policy compliance</td>
</tr>
<tr>
<td>• Hepatic cirrhosis(es)</td>
<td>• Ascites</td>
<td>• Protocol compliance</td>
</tr>
<tr>
<td>• Liver fibrosis(es)</td>
<td>• <em>SBP</em> Peritonitis</td>
<td>• Institutional adherence</td>
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<tr>
<td><strong>Alcoholic cirrhosis</strong></td>
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<tr>
<td>• Alcoholic liver cirrhosis</td>
<td>• HE Hepatic encephalopathy(ies)</td>
<td><strong>Quality of healthcare</strong></td>
</tr>
<tr>
<td>• Alcoholic cirrhosis</td>
<td>• Portosystemic encephalopathy(ies)</td>
<td>• Quality improvement(s)</td>
</tr>
<tr>
<td>• Alcoholic hepatic cirrhosis</td>
<td>• Portal systemic encephalopathy(ies)</td>
<td></td>
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<tr>
<td><strong>Miscellaneous</strong></td>
<td>• Hepatocerebral encephalopathy(ies)</td>
<td><strong>Quality assurance, health care</strong></td>
</tr>
<tr>
<td>• Cirrhosis(es)</td>
<td>• Hepatic coma(s)</td>
<td>• Healthcare quality assurance(s)</td>
</tr>
<tr>
<td>• Cirrhotic</td>
<td>• Hepatic stupor(s)</td>
<td>• Health care quality assurance(s)</td>
</tr>
<tr>
<td></td>
<td>• Fulminant hepatic failure with cerebral edema</td>
<td>• Healthcare quality assessment(s)</td>
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<td></td>
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<td>• Health care quality assessment(s)</td>
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<tr>
<td><strong>HE</strong>: hepatic encephalopathy; <strong>SBP</strong>: spontaneous bacterial peritonitis</td>
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<td><strong>Quality indicators, health care</strong></td>
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<td></td>
<td></td>
<td>• Healthcare quality indicator(s)</td>
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<tr>
<td></td>
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<td>• Healthcare global trigger tool</td>
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<td><strong>Benchmarking</strong></td>
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<td>• Best practice analysis</td>
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<td>• Benchmark</td>
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<td>• Health care benchmarking</td>
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<td><strong>Standard of Care</strong></td>
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<td>• Standard of care</td>
<td></td>
<td><strong>Miscellaneous</strong></td>
</tr>
<tr>
<td>• Care standard(s)</td>
<td></td>
<td>• Quality of care</td>
</tr>
</tbody>
</table>

HE: hepatic encephalopathy; SBP: spontaneous bacterial peritonitis
Figure 2. Modified PRISMA diagram for literature review

Records identified through searching PubMed using combination of extracted MeSH terms (n=1,329)

Records screened (n=1,329)

Records excluded (n=1,303)

Full-text articles assessed for eligibility (n=26)

Full-text articles excluded (n=14)
- 5 research letters and commentaries
- 2 reviews
- 1 abstract
- 3 on cirrhosis but with specific focus on hepatocellular carcinoma, hemorrhage, gastrointestinal bleeding
- 1 on validity of quality indicators
- 1 on development of quality indicators
- 1 article in French

Studies included in qualitative synthesis (n=12)

Studies included in qualitative synthesis (n=12)

MeSH: medical subject headings
Table 3. Studies evaluating quality of care, guideline/quality indicator concordance

<table>
<thead>
<tr>
<th>Study (year) Country</th>
<th>Aim</th>
<th>Cirrhosis/Complication</th>
<th>Setting</th>
<th>Study Sample</th>
<th>Benchmark/Quality improvement/Quality of care</th>
<th>Study findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>US-based</td>
<td></td>
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</tbody>
</table>
| Sclair SN<sup>36</sup> (2016) US | To study the adherence to cirrhosis-specific QI | Cirrhosis | Retrospective cohort study of patients seen at 3 healthcare facilities (Faculty practice: University of Miami Health System; Safety-net: Jackson Memorial Hospital and VA; Miami VA Medical Center) between Oct 1 2010 - Mar 31 2011 | ≥18 years; ICD-9-CM diagnosis cirrhosis (571.2, and 571.5) n=242 total with n=85 Faculty Practice; n=81 Safety Net; n=76 VA | Adherence to 6/41 QI developed by Kanwal F et al (2010)<sup>37</sup> for cirrhosis | Adherence ranges for QI:  
  • Faculty practice: 30-66%  
  • Safety-net: 25-73%  
  • VA: 30-63% |
| Tapper EB<sup>38</sup> (2016) US | To study the effects of QI protocol on 30-day readmission of patients with liver cirrhosis | HE, SBP | Prospective study at the inpatient facility of Beth Israel Deaconess Medical Center between 2010 - 2013 | All patients admitted to liver unit n=824 total | Two phase QI protocol (hand-held checklist and electronic phase vs usual care) targeted at: Use of rifaximin for all patients with HE; Adjusting lactulose dose to mental status using the Richmond Agitation and Sedation Scale; Timely administration of correct dose of antibiotics and albumin; Maximizing patients who received primary and secondary prophylaxis for SBP | 67.7% of admitted overt HE patients had documentation of use of rifaximin  
  • 42% of patients with history or index admission of SBP received secondary antibiotic prophylaxis  
  • Checklist and electronic phases received 8738 and 8858 20 mL of lactulose doses respectively (vs 6209 doses in usual care) |
| Lim N<sup>39</sup> (2015) US | To study the relationship between physician specialty and | HE, RA, SBP | Retrospective study of electronic medical records at inpatient visits at University of Vermont | ≥18 years; inpatient discharge diagnosis of ICD-9-CM 571.2, 571.5 and 571.6 | 3 practice-based QM each for RA and SBP from AASLD 2009/2012 guidelines. 3 practice- | Quality of care criteria met:  
  • RA: 20/39 admissions  
  • HE: 56/83 admissions  
  • SBP: 11/33 admissions |
<table>
<thead>
<tr>
<th>Study</th>
<th>Topic</th>
<th>Scope</th>
<th>Methodology</th>
<th>Sample Size</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghaoui R(^{40}) (2015) US</td>
<td>Inpatient quality of care i.e. adherence to evidence-based specialty society practice guidelines</td>
<td>Medical Center between Jun 2009 - Jul 2013</td>
<td>n=247 total</td>
<td>8 and 2 inpatient QI for ascites and HE respectively developed by Kanwal F et al (2010)(^{17})</td>
<td>• Intensivists-managed patients received significantly better quality of care • Gastroenterology consultation was associated with a significantly higher adherence to quality indicators for HE but not for other complications</td>
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<td></td>
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<td>To study the impact of implementing mandatory gastroenterologist consultation (MC) on adherence to QI and outcomes compared to usual care (UC)</td>
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<td></td>
<td></td>
<td>Ascites, HE</td>
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<td>Comparison of prospective cohort with MC intervention to retrospective review of UC managed patients at Baystate Medical Center.</td>
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<td></td>
<td>≥18 years; patients with suspected/established ascites, HE</td>
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<td>n=303 total with UC n=149; MC n=154</td>
</tr>
<tr>
<td>Johnson KB(^{41}) (2015) US</td>
<td>To study the adherence to guidelines for reducing the albumin dose at large-volume paracentesis (LVP)</td>
<td>Ascites</td>
<td>Retrospective cohort study of patients with LVPs at Department of Radiology, Massachusetts General Hospital between Jul 1, 2009 - Jan 31, 2014</td>
<td>n=935 total with pre-guideline (PrG) (July 1, 2009 - Jun 30, 2011): n=288; 4-point LVP guidelines established by interdisciplinary group of radiologists, hepatologists and transfusion medicine specialist</td>
<td>PoG group: 36.3% of LVPs performed in accordance to guidelines</td>
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<td>Adherent vs non-adherent:</td>
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<td>• Volume of ascites removed was statistically higher (5.6 vs 5.2; p&lt;0.001)</td>
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<td></td>
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<td></td>
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<td>• Albumin dose administered (g/L of ascites) and cost per LVP was significantly lower</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Study Objective</td>
<td>Methodology</td>
<td>Sample Characteristics</td>
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<tr>
<td>Ghaoui R</td>
<td>2014</td>
<td>US</td>
<td>To study adherence to QI in patients admitted with decompensated cirrhosis</td>
<td>Retrospective cohort study of patients admitted to Baystate Medical Center between Jan 1, 2009 - Dec 31, 2009</td>
<td>≥18 years; ICD-9-CM diagnosis of 571.0-571.9, 572-572.4 and 576.0 n=149 total</td>
</tr>
<tr>
<td>Desai AP</td>
<td>2014</td>
<td>US</td>
<td>To study the effect of co-management between hospitalists and hepatologists on quality of care and adherence to management guidelines for Chronic Liver Disease and SBP</td>
<td>Retrospective chart review of patients admitted with CLD and SBP at University of Chicago Medical Center between July 1, 2004 - June 30, 2010</td>
<td>≥18 years; Patients with ICD-9-CM for peritonitis (567.23, 567.0, 567.21, 567.29, 567.89, and 567.9) and Current Procedural Terminology code for paracentesis (49080) n=56 total with Conventional Model group (CM) (July 1, 2004 - June 30, 2006): n=26; Co-management group (CoM) (July 1, 2006 - June 30, 2010): n=30</td>
</tr>
<tr>
<td>Kanwal F</td>
<td>2012</td>
<td>US</td>
<td>To study quality of ascites care provided to Veterans using established QI</td>
<td>Retrospective cohort study using records from administrative and clinical database followed by a structured implicit review of patient medical charts using data from Veteran electronic</td>
<td>Patients with ICD-9-CM for cirrhosis (571.2, 571.5, 571.6) or related complications (456.0, 456.1, 456.20, 456.21, 572.2, 572.3, 572.4, 572.8, 789.5) in inpatient or</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>Study Population</td>
<td>Outcomes</td>
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<tr>
<td>Le S et al. (2016)</td>
<td>Australia</td>
<td>Retrospective cohort study</td>
<td>Outpatients seen at Monash Hospital between Jan 2000 - Oct 2012</td>
<td>Adherence to QI developed by Kanwal F et al. (2010) for ascites. Adherence ranged from 70-92%. 2 QI were significantly associated with lower relative risk of 30-day readmission. 1 QI each was significantly associated with lower and higher relative risk of 90-day mortality.</td>
<td></td>
</tr>
<tr>
<td>Thevenot T et al. (2013)</td>
<td>France</td>
<td>Prospective national survey</td>
<td>Hepatogastroenterologist practitioners in general hospitals (GH) and university hospitals (UH) between Nov 2011 - Mar 2012</td>
<td>EASL, AASLD - 94.8% practitioners prescribed secondary prophylaxis for SBP (93.5% of GH vs 98.1% of UH practitioners) - 72.3% practitioners used antibiotics for primary prophylaxis of SBP (70.7% of GH vs 76.4% of UH)</td>
<td></td>
</tr>
<tr>
<td>Morando F et al. (2013)</td>
<td>Italy</td>
<td>Prospective cohort study</td>
<td>Outpatients discharged from the General Hospital of Padova between Jan 1, 2011 - Jun 30, 2011</td>
<td>Team of consultant hepatologists, nurses and clinicians involved in providing improved care through implementing various quality improvement initiative. Group 1 vs Group 2: Reduction of mortality rate in patients with responsive ascites (24.2%, p&lt;0.05) and those with refractory ascites (20.1%, p=NS). Significantly lower percentage of 30-day emergent readmission to the hospital (15.4 vs 15.4%; p=0.01). Significantly lower percentage of emergency hospitalization.</td>
<td></td>
</tr>
<tr>
<td>Gundling F\textsuperscript{48} (2009) Germany</td>
<td>To study adherence to nutrition specific recommendations by gastroenterologists</td>
<td>Cirrhosis</td>
<td>Prospective survey of gastroenterologists at Bavarian Society of Gastroenterology between Jul 1, 2007 - Sep 1, 2007</td>
<td>Gastroenterologists n = 239 total</td>
<td>Questionnaire (in addition to 9 nutrition specific questions) seeking information on knowledge of recent guidelines on enteral nutrition (EN) and estimated relevance of such guidelines, if such guidelines can be realizable in daily practice and whether careful advising by professional dieticians is meant to be important for patients with liver cirrhosis</td>
</tr>
</tbody>
</table>

- 56% familiar with guidelines on EN in patients with chronic liver disease
- 92% believed that evidence-based guidelines are both important and relevant for everyday practice
- 84% considered such recommendations as realizable in daily practice

\textsuperscript{AASLD: American Association for Study of Liver Diseases; EASL: European Association for Study of the Liver HE: hepatic encephalopathy; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; PPCACP: Practice Parameters Committee of the American College of Gastroenterology; RA: refractory ascites; SBP: spontaneous bacterial peritonitis; QI: quality indicator; QIm: quality improvement; QM: quality measures; VA: Veterans Affairs}
Results

Table 3 provides a summary of the studies regarding complications, setting, study sample, benchmark/quality improvement/quality of care criteria and study findings. A total of 12 articles were identified based on the inclusion/exclusion criteria out of which 8 were conducted in the US\textsuperscript{36,38-44} and 4 were international studies\textsuperscript{45-48} (1 each in Germany, Italy, France and Australia). Ten studies looked at concordance to quality indicators (QI)/guidelines whereas two studies focused on quality improvement. Ascites was the most common complication studied (7/12 studies, 58.3%), followed by SBP (5/12 studies, 41.7%) and HE (4/12 studies, 33.3%). For the purpose of the review the study findings are categorized into two categories: Concordance with QI/guidelines and Quality improvement.

Concordance with QI/guidelines

Five of the 10 studies on concordance with QI/guidelines (4 US and 1 in Australia) used QI established by Kanwal F \textit{et al}\textsuperscript{37} Sclair SN \textit{et al}\textsuperscript{36} retrospectively compared the concordance to six QI in three hepatology clinics [University of Miami Health System (faculty practice), Jackson Memorial Hospital (safety-net hospital), and Miami VA Medical Center VA)] in the Miami Health District, USA) for patients with cirrhosis receiving care from faculty at the University of Miami. The percentage concordance to QI ranged from 30-66% (safety-net hospital), 25-73% (faculty practice) and 39-63% (VA). Patients at the safety-net hospital and VA received statistically higher Hepatitis A/B vaccination and hepatocellular carcinoma surveillance in comparison to faculty practice patients. However, receipt of screening endoscopy and discussions on liver transplant were statistically higher in faculty practice as compared to the other two. Multivariate analysis results showed that patients with >10 hepatologist visits had statistically higher odds of receiving Hepatitis B vaccination and liver transplant discussion (OR: 3.31, 95% CI 1.21-9.02; p<0.05 and OR 2.98, 95% CI 1.08-8.17;
p<0.05 respectively vs 1-3 hepatologist visits). Females were more likely to receive a Hepatitis B vaccination (OR: 2.62, 95% CI 1.17-5.91; p<0.01), and African-American patients were less likely to receive liver transplant discussion (OR: 0.36, 95% CI 0.13-1.0; p<0.05).

Ghaoui R et al\(^40\) compared concordance to eight QI (for ascites) and two QI (for HE) between patients managed by gastroenterologist (prospective) and patients managed by usual care (retrospective). In the prospective phase, concordance with QI for ascites ranged from 60-97.6% and for HE was 85.8-94.7%. For the gastroenterology group in comparison to usual care, following QI were better met: (1) ascites: receipt of diagnostic paracentesis for ascites-related admission (82.2 vs 39.9%; p<0.001), checking for ascites cell count for those receiving paracentesis with a known portal hypertension-related ascites admission (75.8 vs 14.14%; p<0.001), use of sodium restriction and diuretics combination (66.4 vs 30.6%; p<0.001) and (2) HE: empirical treatment (95.3 vs 94.7%), and better documentation of search for underlying etiologies (85.8% vs 53.6%; p<0.001). In an earlier retrospective study, Ghaoui R et al\(^42\) looked at concordance with 7 and 2 inpatient QI for ascites and HE, respectively. The concordance with ascites QI ranged from 14.4-76.9% and for HE 53.6-95.4%. Kanwal F et al\(^44\) retrospectively identified concordance with QI at the VA for patients with ascites and SBP using 8 QI. The concordance with QI ranged from 22.2-82.8%.

Multivariate regression results showed that patients with higher serum sodium (125-135 mEq/ml and >135 mEq/ml) had lower odds of receiving recommended care (OR: 0.72, 95% CI 0.52-0.99 and 0.58, 95% CI 0.35-0.74 respectively vs serum sodium < 125 mEq/ml); patients with albumin ≥ 3 mg/dl had lower odds of receiving recommended care (OR: 0.51, 95% CI 0.35-0.74) vs albumin ≤ 2.2 mg/dl); patients without comorbidities received recommended care compared to patients with comorbidities (Deyo index 0 vs > 3; OR: 2.21, 95% CI 1.43-3.43); patients who saw a specialist received higher quality of ascites care than
those who did not (OR: 1.33, 95% CI 1.01-1.74); the VA facility with academic affiliation provided better care compared to those without such affiliation (OR: 1.73, 95% CI 1.29-2.35). Le S et al\textsuperscript{45} studied the effect of concordance with QI on 30-day readmission and 90-day mortality of patients with ascites. Concordance with eight of the selected QI ranged from 70-92%. Patients who received an abdominal paracentesis within 30-days of ascites diagnosis and those receiving abdominal paracentesis during index ascites admission had lower odds of 30-day readmission (OR: 0.41, 95% CI 0.22-0.41; p=0.004 and OR: 0.57, 95% CI 0.38-0.57; p=0.006, respectively). Patients with normal renal function receiving diuretics within 30-days of ascites diagnosis had lower odds of 90-day mortality (OR: 0.28, 95% CI 0.10-0.77; p=0.01). Interestingly, patients receiving primary prophylaxis (with ascitic fluid protein < 1 g/dl and serum bilirubin > 2.5 mg/dl) within 3 to 30-days of the test result had higher odds of 90-day mortality (OR: 2.30, 95% CI 1.05-5.05; p=0.04).

Lim N et al\textsuperscript{39} studied the relationship between physician and inpatient quality of care, as measured by concordance with evidence-based guidelines (AASLD and Practice Parameters Committee of the American College of Gastroenterology) for refractory ascites, SBP and HE. Quality of care criteria was met in 20/39 inpatient admissions for refractory ascites; 56/83 admissions for HE and 11/33 admissions for SBP. A significantly higher proportion of intensivist-managed admissions, compared with those managed by hospitalists, met criteria for concordance with quality care indicators for HE (100 vs 63%; p=0.03), but not for refractory ascites or SBP. Gastroenterology consultation was obtained in a significantly higher proportion of admissions that met quality care criteria (68.7% vs 54.0%; p=0.023). Among hospitalist-managed admissions, gastroenterology consultation was associated with a significantly higher concordance with quality indicators for HE (86.9% vs 52%, p=0.004) only.

Specifically for SBP, not having a timely diagnostic paracentesis was associated with
significantly increased median length of hospital stay (5 days vs 13 days; p=0.02).

Johnson KB et al\(^4\) assessed the effect of concordance with 4-point guideline for reducing albumin dose at large-volume paracentesis (LVP). Of the total 647 LVPs performed, only 235 were in concordance with the guidelines. In comparison to the non-concordant LVPs, concordant LVPs had a significantly higher volume of ascites removed (5.6 vs 5.2 L; p<0.0001); significantly lower amount of albumin dose delivered (7.4 vs 11.9 g/L; p<0.0001) and lower cost per LVP ($1,824.20 vs $2,107.63; p<0.0001).

Desai AP et al\(^4\) compared the concordance with 12 evidence-based indicators for SBP patients treated by co-management model team (hospitalist team and liver consult team) versus conventional model team (house staff team and liver consult team). The concordance ranged from 17-100% for the co-management model team and 22-100% for the conventional model team. The co-management model team provided overall better care and significantly better care for 5/12 measures. Co-management group had non-significant longer length of stay (11 vs 6 days) and cost of hospital stay ($82,888 vs $41,518). Percentage of readmission at 30-days was non-significantly higher for co-managed group (31 vs 17%). However, percentage of in-hospital mortality and mortality rate at 30-days was non-significantly lower (13 vs 27% and 0 vs 5% respectively).

Thevenot T et al\(^4\) prospectively studied French national prescribing patterns of practitioners treating SBP. Results showed that 72.3% prescribed primary prophylaxis for SBP (76.4% university hospital based and 70.7% primary hospital based) and 94.8% prescribed secondary prophylaxis for SBP (98.1% university hospital based and 93.5% primary hospital based). Second-generation quinolones were prescribed majorly for primary and secondary prophylaxis. High frequency use (> 75%) of primary prophylaxis was significantly associated with high frequency use of secondary prophylaxis (OR: 3.57, 95% CI 1.41-9.09; p=0.007). High frequency use of secondary prophylaxis was significantly associated with high
frequency use of primary prophylaxis (OR: 2.86, 95% CI 1.16-7.19; p=0.022). Overall, there
was high concordance with guidelines by the practitioners.

Gundling F et al48 studied concordance with European Society for Parenteral and Enteral
Nutrition (ESPEN) guidelines by gastroenterologists for patients with cirrhosis. Of the 239
responses, 56% responded that they were familiar with guidelines on enteral nutrition. 92%
believed that evidence-based guidelines are both important and relevant for everyday practice
and 84% considered such recommendations as realizable in daily practice. 85% answered that
careful dietary counseling by professional dieticians would be important for treatment. 42%
recommended their patients a protein-rich diet containing 1.2-1.5 g/kg body weight/day,
whereas 15% advised a low-protein diet containing less than 40 g of protein/day or just the
same amount of protein as recommended in patients without cirrhosis. 45% were aware of the
optimal daily energy intake of whereas 43% underestimated the amount of required daily
energy while 11% advised higher energy intake.

Quality Improvement (QIm)

Tapper EB et al38 performed a prospective study to assess the effect of a QIm protocol on 30-
day readmission for HE. A two-phase (hand-held checklist and electronic) QIm initiative
targeted at: (1) use of rifaximin for all patients with HE, (2) adjusting lactulose dose to
mental status using the Richmond Agitation and Sedation Scale (3) timely administration of
correct dose of antibiotics and albumin, and (4) maximizing patients who received primary
and secondary prophylaxis for SBP was implemented compared against usual care. Results
showed that 67.7% of patients admitted with overt HE had documentation of use of
rifaximin; 42% with history or index admission of SBP received secondary antibiotic
prophylaxis; checklist and electronic phases received 8,738 and 8,858 20 mL of lactulose
doses respectively (vs 6,209 doses in usual care). Among patients initially admitted with
OHE, the proportion readmitted within 30-days was significantly lower in the electronic phase (26.0%) compared with the checklist (44.7%; p<0.001) and control phases (48.9%; p=0.002) respectively. The use of rifaximin for patients admitted for overt HE was associated with lower odds of 30-day readmission (OR: 0.39, 95% CI 0.16-0.87; p=0.02). Patients with SBP who received secondary prophylaxis had lower odds of 30-day readmission (OR: 0.40, 95% CI 0.21-0.75; p=0.004). There was no significant association for 90-day mortality. Patients with OHE who received 6 cups or more of lactulose had lower odds of 30-day readmission (OR: 0.39, 95% CI 0.16-0.87; p=0.02).

Morando F et al\textsuperscript{47} studied the efficacy and financial sustainability of care management group (CM) comprising of consultant hepatologists, nurses and clinicians versus standard care (SC) for outpatients with ascites. Patients with responsive ascites and refractory ascites in CM group had reduced 12-month mortality rate (24.2%; p<0.05 and 20.1%, p=NS. respectively) as compared to SC. Patients in CM group had significantly lower percentage of 30-day emergent readmission to the hospital (15.4 vs 42.4%; p<0.01) and lower percentage of emergency hospitalization during 12-month follow-up (46.2 vs 71.2%; p<0.025) as compared to SC. Global costs for CM was significantly lower for as compared to SC ($1,479.19 vs $2,816.13; p=0.05).

Gaps in the literature

Studies focused on assessing concordance with guidelines/QI showed that concordance varied and there was no specific trend observed due to the different guidelines/QI being assessed.\textsuperscript{36,39-46,48} Results showed that specialists (hepatologists, gastroenterologists, collaborative groups) provided better quality of care and were more concordant with guidelines.\textsuperscript{39,40,43,44,47,48} Better concordance/implementation of QI\textsubscript{m} was generally associated with lower odds of 30-day readmission.\textsuperscript{38,45,47} However, Desai AP et al\textsuperscript{43} found higher odds
of re-admission associated with quality care. For the outcome of mortality, better concordance/implementation of QIm was associated with lower odds of 30-day mortality (Desai AP et al\textsuperscript{13}) and of 12-month mortality (Morando F et al\textsuperscript{47}). However, Le S et al\textsuperscript{45} found higher odds of 90-mortality. Overall, there was no consistency in the guidelines/QI used for assessment, though QI by Kanwal F et al\textsuperscript{37} were used the most. For US-based studies, concordance with evidence-based guidelines such as AASLD was assessed in only one study.\textsuperscript{39} Majority of the studies did not discuss patient-related factors associated with guidelines/QI concordance, while physician factors were discussed in few. The results of this literature analysis provide sufficient justification for the aims of the present analysis to assess the patient- and physician-related factors associated with concordance/deviance to AASLD guidelines and selected quality indicators using retrospective EMR data.
CHAPTER 3: METHODOLOGY

The main goal was to assess concordance with evidence-based care in real world practice and thus EMR was used as the data source, as they provide an in-depth understanding of current clinical care.

Data source

The study design is a retrospective cohort analysis using electronic medical records (EMR) from a large academic-based healthcare organization, the University of Pittsburgh Medical Center (UPMC). The organization includes more than 20 hospitals and 500 outpatient offices providing healthcare across southwestern Pennsylvania. The UPMC network additionally has an insurance division, which covers nearly 3 million members.\textsuperscript{49}

UPMC EMR database

A data extraction was requested from the UPMC Center for Assistance in Research using eRecord (CARe), which provides access requests for healthcare data within the UPMC network.\textsuperscript{50} CARe works with researchers to review research protocols, provide programming support and access to other resources. The UPMC EMR data held through CARe contains both inpatient and outpatient data on patient demographics and clinical characteristics, clinical diagnoses, healthcare utilization, laboratory tests and associated results and prescribed medications, among other data. In coordination with a UPMC clinician (Dr Nemecek, thesis committee member), a data request was created for both Epic (outpatient data) and Cerner (inpatient) systems.
Data protection

Data extracted from the UPMC network was based upon an Enterprise Master Person Index (EMPI) identification for the organization. This was subsequently converted to a dummy patient ID (Code) for the purposes of data manipulation. No patient identifiers were present in the data to maintain patient confidentiality. The researchers involved in the study were certified by the Collaborative Institutional Training Initiative (CITI). The study was carried in compliance with The Health Insurance Portability and Accountability Act of 1996 (HIPAA). The study was approved by institutional review boards at both Duquesne University and UPMC.

Database structure

The EMR database extracted by UPMC CARe and provided to the study investigators was organized into a relational database structure. Relational databases have different tables, which contain multiple rows and columns. Columns represent specific data attributes that are stored in the table. For example, the DEMOGRAPHICS table includes columns such as year of birth, sex, race etc. Rows represent data that is specific to each observation. For example, each row in DEMOGRAPHICS table represents associated information for each patient. A primary key, or unique identifier, relates all the tables in the database to each other. The EMR database organized from the data extract contained five related tables, with a dummy patient ID (Code) serving as the primary key. The five tables in the database are as follows: DEMOGRAPHICS, OFFICE VISITS, HOSPITAL VISITS, LABORATORY TESTS, and MEDICATIONS. Figure 3 depicts the database structure.
Figure 3. Extracted UPMC EMR database structure

- **DEMOGRAPHICS**
  - Year of birth
  - Sex
  - Race
  - Ethnicity

- **OFFICE VISITS**
  - Office visit date
  - Height
  - Weight
  - Provider specialty
  - Primary diagnosis (ICD-9-CM)
  - Other diagnoses (ICD-9-CM)

- **LABORATORY TESTS**
  - Test name
  - Result date
  - Test value

- **HOSPITAL VISITS**
  - Hospital visit date
  - Type of visit (OP, IP, ER)
  - Provider specialty
  - Diagnosis code (ICD-9-CM)
  - Diagnoses description

- **MEDICATIONS**
  - Name
  - Ordering date
  - Dose
  - Dose unit
  - Route
  - Frequency
  - Directions of use

*ER: emergency room; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; IP: inpatient visit; OP: outpatient*
**Study sample**

Identification of study sample involved a two-step process:

*Step 1*

Creation of the study sample began with a data extraction by programmers from UPMC CARe. This step-involved isolation of patients from the UPMC database based on following inclusion criteria:

1. At least 18 years of age
2. At least two International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) outpatient visit coding for cirrhosis (571.2, 571.5, 571.6) or ascites (789.59), spontaneous bacterial peritonitis (SBP) (567.23) or hepatic encephalopathy (HE) (572.2)
3. Outpatient visits between January 1, 2009 and December 31, 2014
4. At least 365 days of total EMR activity

This step yielded an initial cohort size of n=7,824. Detailed data from outpatient and limited data from inpatient files were extracted for patients within this cohort and delivered to the study investigators.

*Step 2*

To suit the specific study goals, a secondary step of data refinement was conducted by the investigators and comprised of the following inclusion criteria:

1. Age between 18 and 90 years
2. At least one ICD-9-CM coding for alcoholic cirrhosis (571.2) or non-alcoholic cirrhosis (571.5) as a primary or secondary diagnostic code at an outpatient visit
This step yielded a study sample of n= 4,116, which was further stratified into three groups based on the type of cirrhosis coding recorded during patient office visits. As each patient had multiple office visits, they were stratified into:

1. Alcoholic cirrhosis (Alc): ICD-9-CM 571.2 only
2. Non-alcoholic cirrhosis (N-Alc): ICD-9-CM 571.5 only
3. Undetermined (Und): ICD-9-CM: 571.2 and 571.5 both

Complications observed after the first diagnoses of cirrhosis i.e. cirrhosis index (explained shortly) were used as a part of the analysis. A total of 986, 665, and 148 patients with ascites, HE, and SBP were identified, respectively.

Sample selection is represented in Figure 4.
Figure 4. Patient selection criteria for study cohort

Step 1

Patient sample extracted by CARe using initial inclusion criteria (n=7,824)

Step 2

Outpatient visits between January 1, 2009 and December 31, 2014 (n=7,619)

Patients with at least one ICD-9-CM coding for alcoholic (571.2) or non-alcoholic (571.5) cirrhosis as a primary/secondary outpatient visit code (n=5,594)

Patients with < 365 days of data (n=1,475)

Patients with data > 365 days of data (n=4,119)

Patients < 18 years and > 90 years (n=3)

Final cohort meeting inclusion/exclusion criteria (n=4,116)

Alcoholic cirrhosis (ICD-9-CM: 571.2) (n=404)

Nonalcoholic cirrhosis (ICD-9-CM: 571.5) (n=3,284)

Undetermined (ICD-9-CM: 571.2/571.5) (n=428)

Patients with no outpatient visits (n=205)

Patients with no primary/secondary cirrhosis coding (n=2,025)

Patients with data = 365 days of data (n=4,119)

Ascites (n=986)

HE (n=665)

SBP (n=148)
Description of study variables

Index dates (cirrhosis, complications)

The cirrhosis index date was defined as the first appearance of a cirrhosis diagnosis ICD-9-CM of 571.2 or 571.5 as a primary or a secondary diagnosis at an outpatient visit during the study timeframe. Similarly, complication index dates were defined as the first appearance of an ascites (789.59) or HE (572.2) diagnosis recorded up to 10 diagnoses codes (including primary diagnoses) at an outpatient visit during the study timeframe. For SBP (567.23) diagnoses recorded up to ten diagnoses codes including primary diagnoses at an inpatient visit was used to define index date as this complication is most commonly diagnosed in the inpatient setting. Complications with a complication index on or after cirrhosis index were used as part of the analysis for this study. Each of these variables is noted in this text as cirrhosis index date, ascites index date, HE index date or SBP index date.

Patient demographic variables

Patient related variables include age, sex, race, and ethnicity. The information was obtained from the DEMOGRAPHICS table and obtained from data reported in outpatient records, although not directly derived from the OFFICE VISITS table.

Age at cirrhosis/complication index date

Age at the cirrhosis index date was calculated as the difference between index date and year of birth. The variable year of birth was originally available in the DEMOGRAPHICS table. Age at cirrhosis index was reported in years and categorized as: 18-40 years, 41-60 years and ≥ 61 years. Age at the complication index date was calculated as the difference between index date and year of birth. The variable year of birth was originally available in the
DEMOGRAPHICS table. Age at complication index was reported in years and categorized as: 18-40 years, 41-60 years and ≥ 61 years.

Sex
The variable sex was used as an indicator of sex of the patient.

Race
The variable was categorized as: Caucasian, African-American, Other (American Indian, Chinese, Filipino, Indian, Korean, Other Asian, Other Pacific Islander), and Undetermined (not reported).

Ethnicity
The variable was categorized as: non-Hispanic, Hispanic and Undetermined (not reported).

Patient clinical variables
Clinical variables included body mass index (BMI) at index date, common co-morbidities, Model for End-Stage Liver Disease score/-Na (MELD and MELDNa) score, and Cirrhosis-specific Comorbidity index (CirCom) score. BMI, common comorbidities, CirCom was derived from information available in the OFFICE VISITS table. MELD was derived from the LABORATORY TESTS table.

BMI at cirrhosis/complication index date
BMI at the cirrhosis index date was calculated based on the height and weight reported at the cirrhosis index date in the OFFICE VISITS table. Height reported in feet and inches was converted to meters and weight reported in pounds was converted to kilograms. BMI was
reported as kilograms/meters\(^2\) (kg/m\(^2\)) in the following established categories:\(^5\) 0-18.5 kg/m\(^2\) (underweight), 18.5-24.9 kg/m\(^2\) (normal), 25-29.9 kg/m\(^2\) (overweight), \(\geq 30\) kg/m\(^2\) (obese) and Undetermined (where BMI could not be determined due to missing height, weight or both). Cases where height was not available at the index date, the height recorded at previous or following outpatient visit was considered for the calculation. Similarly, BMI at complication index date was calculated and reported in following categories: 0-24.9 kg/m\(^2\) (Underweight/Normal), 25-29.9 kg/m\(^2\) (overweight), \(\geq 30\) kg/m\(^2\) (obese) and Undetermined (where BMI could not be determined due to missing height, weight or both). BMI categories at complication index were collapsed due to the smaller sample size of patients within the full stratification.

**Common co-morbidities**

Presence of comorbidities was based on ICD-9-CM coding from the first visit for the patient in the database through three months’ post-cirrhosis index date. Up to ten diagnoses codes (ICD-9-CM) including primary diagnoses code were looked up to determine presence of the comorbidity. The comorbidities included in this study were based on investigator selection of interest and the comorbidities considered by Jepsen et al\(^5\) for developing the CirCom score. The type of co-morbidities included and associated ICD-9-CM is reported in Table 4.
Table 4. Common co-morbidities and their associated ICD-9-CM code

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>ICD 9-CM codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>490.xx – 492.xx</td>
</tr>
<tr>
<td></td>
<td>494.xx</td>
</tr>
<tr>
<td></td>
<td>496.xx</td>
</tr>
<tr>
<td>AMI</td>
<td>410.xx</td>
</tr>
<tr>
<td>PAD</td>
<td>443.9</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>345.xx</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>305.0x</td>
</tr>
<tr>
<td>Substance use other than alcohol</td>
<td>304.xx – 305.1x – 305.9x</td>
</tr>
<tr>
<td>Heart failure</td>
<td>428.xx</td>
</tr>
<tr>
<td>Diabetes</td>
<td>250.xx</td>
</tr>
<tr>
<td>Depression</td>
<td>296.2x – 296.3x</td>
</tr>
<tr>
<td></td>
<td>311.x</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>070.xx</td>
</tr>
<tr>
<td>Bipolar</td>
<td>296.0x – 296.4x – 296.8x</td>
</tr>
<tr>
<td>CKD</td>
<td>585.xx</td>
</tr>
<tr>
<td>Non-metastatic and non-hematological cancer</td>
<td>140.xx – 195.xx</td>
</tr>
<tr>
<td></td>
<td>199.xx</td>
</tr>
<tr>
<td></td>
<td>209.xx</td>
</tr>
<tr>
<td></td>
<td>230.xx – 239.xx</td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td>196.xx</td>
</tr>
<tr>
<td></td>
<td>197.xx</td>
</tr>
<tr>
<td></td>
<td>198.xx</td>
</tr>
<tr>
<td>Hematological cancer</td>
<td>200.xx – 208.xx</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; PAD = peripheral artery disease
Cirrhosis-specific Comorbidity index

The CirCom score is a newly developed cirrhosis-specific scoring system, which measures the burden and effect of comorbidities on mortality. The CirCom score was developed and validated by Jepsen et al\textsuperscript{52} in three different Danish population-based cohorts. The CirCom was replicated in this study and was modified based data availability. Table 5 provides a comparison between the method used by Jepsen et al\textsuperscript{52} and the current study. The CirCom score calculation schematic is given in Figure 5. The CirCom score was calculated at the cirrhosis index date and was reported in the following established categories: 0, 1+0, 1+1, 3+0, 3+1, 5+0, 5+1, in line with the original publication.
### Table 5. Comparison of current study with Jepsen et al\(^5\) for CirCom scoring

<table>
<thead>
<tr>
<th></th>
<th>Jepsen, et al</th>
<th>Current study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country</strong></td>
<td>Denmark</td>
<td>USA</td>
</tr>
<tr>
<td><strong>Aim</strong></td>
<td>Develop and validate CirCom score</td>
<td>Replicate use of CirCom score in US population</td>
</tr>
<tr>
<td><strong>Study cohorts and sample size</strong></td>
<td>3 cohorts:</td>
<td>1 cohort:</td>
</tr>
<tr>
<td></td>
<td>Developmental: Danish patient registry cohort (nationwide alcoholic or unspecified cirrhosis): n= 12,976</td>
<td>UPMC cohort (hospital-based alcoholic and non-alcoholic cirrhosis): n= 4,116</td>
</tr>
<tr>
<td></td>
<td>Validation cohort 1: Aarhus (hospital-based alcoholic cirrhosis): n= 419</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Validation cohort 2: DANVIR (nationwide chronic hepatitis C): n= 4,656</td>
<td></td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td>Chronic obstructive pulmonary disease; acute myocardial infarction; peripheral artery disease; epilepsy; substance abuse other than alcoholism; heart failure; non-metastatic or hematological cancer; metastatic cancer; chronic kidney disease</td>
<td>Chronic obstructive pulmonary disease; acute myocardial infarction; peripheral artery disease; epilepsy; substance abuse other than alcoholism; heart failure; non-metastatic or hematological cancer; metastatic cancer; chronic kidney disease</td>
</tr>
<tr>
<td><strong>Diagnoses codes</strong></td>
<td>ICD-10-CM</td>
<td>ICD-9-CM</td>
</tr>
<tr>
<td><strong>Healthcare visit type</strong></td>
<td>Outpatient and inpatient visits</td>
<td>Outpatient visits</td>
</tr>
<tr>
<td><strong>Comorbidity data available for score calculation</strong></td>
<td>5 years of comorbidity data before cirrhosis diagnosis</td>
<td>Variable timelines for comorbidity data before cirrhosis index date for study years 2009-2014</td>
</tr>
<tr>
<td><strong>Timeline for inclusion of comorbidity for scoring</strong></td>
<td>5 years prior to cirrhosis diagnosis</td>
<td>Any time prior to cirrhosis index date and up to 3 months post-cirrhosis index date</td>
</tr>
<tr>
<td><strong>Definition of ‘active’ Status for comorbidity</strong></td>
<td>Within 7 days prior to cirrhosis diagnosis</td>
<td>Within 7 days prior to cirrhosis index date and up to 3 months post-cirrhosis index date</td>
</tr>
</tbody>
</table>

*CirCom = Cirrhosis-specific Comorbidity index; DANVIR = Danish HCV cohort; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; UPMC = University of Pittsburgh Medical Center; US = United States*
Figure 5. CirCom scoring algorithm adapted from Jepsen et al.\textsuperscript{52}

COPD or AMI or PAD or Epilepsy or Substance abuse except alcoholism or Heart failure or Cancer or CKD

YES

Patient has ‘active’ metastatic cancer

NO

CirCom Score 0

YES

Patient has at least one of the listed comorbidities

NO

CirCom Score 5+0

YES

Patient has ‘active’ AMI and/or ‘Active’ non-metastatic or hematological cancer and/or ‘Inactive’ metastatic cancer and/or CKD

NO

CirCom Score 1+0

YES

Patient has more than one of the listed comorbidities

NO

CirCom Score 1+1

AMI: acute myocardial infarction; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; PAD: peripheral artery disease
Incident/prevalent cases

Patients who had an index cirrhosis diagnosis within 180 days from first visit recorded in the database were classified as prevalent cases whereas patients who had their cirrhosis index visit after 180 days from first visit were classified as incident cases.

Model for End-Stage Liver Disease (MELD)

As mentioned earlier, the MELD score is calculated based on laboratory values from serum SCr in mg/dl, Sbili in mg/dl and INR. The formula for calculating MELD is as follows:

\[
\text{MELD score} = (0.957 \times \log_e (\text{SCr}) + 0.378 \times \log_e (\text{Sbili}) + 1.120 \times \log_e (\text{INR}) + (0.643) \times 10
\]

As mentioned earlier, for patients with SCr > 4, the SCr value was set at 4.0; any laboratory value < 1 for SCr, Sbili, and INR was set at 1. Patients who had a diagnosis coding (within the first 10 diagnosis codings at an outpatient visit) of ICD-9-CM of V45.11 (renal dialysis status) or 585.6 (end-stage renal disease) up to three months prior to and post-cirrhosis index date, and complication index date were assumed to have an active dialysis status and their SCr value was set at 4. The MELD score was calculated based on laboratory values available three months prior, post the cirrhosis index date, and complication index date. To account for varied possible values in the wide/broad window period, the numerical mean of the laboratory values within the time frame was calculated for each test. The score was reported in the following established categories: $11, 15 \leq 9, 10-19, 20-29, 30-39$ and $\geq 40$ and two additional categories of Undetermined (score not calculated due to missing values) and Missing (scores not calculated due to absence of test).
Model for End-Stage Liver Disease with Sodium (MELDNa)

As discussed earlier, The Organ Procurement and Transplantation Network recently updated the MELD score in January 2016, and now includes SNa. The MELDNa (updated score) is calculated as follows:\textsuperscript{12}

1. Calculation of the MELD:
   \[ \text{MELD} = (0.957\log_e (\text{SCr}) + 0.378\log_e (\text{SBili}) + 1.120\log_e (\text{INR}) + (0.643)\times 10 \]

2. Calculation of corrected SNa for patients with a serum glucose > 120 mg/dl:\textsuperscript{13}
   \[ \text{Corrected serum sodium (CSNa)} = \text{SNa} + 0.024*(\text{serum glucose} – 100) \]

3. Calculation of the MELDNa using the following formula:\textsuperscript{14}
   \[ \text{MELDNa} = \text{MELD} + 1.32*(137 - \text{SNa/cSNa}) - [0.033\times \text{O-MELD}*(137 - \text{SNa/cSNa})] \]

Similarly, to MELD, for patients with SCr > 4, the SCr value was set at 4.0; any laboratory value < 1 for SCr, Sbili, and INR was set at 1. Limits for SNa or CSNa values are set between 125 Mmol/L and 137 Mmol/L, with extreme values outside of this range adjusted accordingly.\textsuperscript{17}

Patients who had a diagnosis (within the first 10 diagnosis codings at an outpatient visit) of ICD-9-CM of V45.11 (renal dialysis status) or 585.6 (end-stage renal disease) up to three months prior, and post the cirrhosis index date, and complication index date were assumed to have an active dialysis status and their SCr value was set at 4. The MELDNa score was calculated based on laboratory values available three months prior, and post the cirrhosis index date, and complication index date. To account for varied possible values in the wide/broad window period, the numerical mean of the laboratory values within the time frame was calculated for each test. The score was reported in the following established categories:\textsuperscript{11,15} \leq 9, 10-19, 20-29, 30-39 and \geq 40 and two additional categories of Undetermined (score not calculated due to missing values) and Missing (scores not calculated due to absence of test).
Healthcare utilization variables

Healthcare utilization was quantified for ascites, SBP and HE using the OFFICE VISITS table for office-based visits and HOSPITAL VISITS table for hospital observation, inpatient and emergency room hospital visits. Utilization was quantified in two ways: (1) following a 1-year period from the complication index date, and (2) overall utilization across entire EMR record from the complication index date. Patients had to have at least one year of data to be included in the utilization metric analyses. Healthcare utilization for each type of service was reported as the total number of visits for each complication, mean (± SD) and median (range) visits.

Medication utilization variables

Medication utilization was described for ascites, SBP and HE. Medication-related data was extracted from the MEDICATIONS table. The AASLD guidelines recommend outpatient/inpatient medications to be prescribed for ascites, SBP and HE.27,31 Data on outpatient prescriptions within 30-days post index-date of each complication were analyzed to identify following recommended therapies:

- **Ascites**: 100 mg daily of spironolactone alone or 100/40 mg daily of spironolactone and furosemide in combination.27 The number of patients receiving a prescription, mean (± SD) and median (range) dose was reported.

- **SBP**: Ciprofloxacin 500 mg daily or combination of ciprofloxacin and double strength sulfamethoxazole/trimethoprim (800/160 mg) once daily or sulfamethoxazole/trimethoprim (800/160 mg) alone once daily.27 The number of patients receiving a prescription was reported. Records were also screened for prescription for levofloxacin and moxifloxacin and number of patients receiving each was reported.
- **HE**: Lactulose or lactulose and rifaximin combination.\(^{31}\) The number of patients receiving a prescription, mean (± SD) and median (range) dose was reported.

Medication dose strength per unit of time was calculated based on prescribed dose and frequency. For example, total daily doses of 100 mg (dose strength/unit of time) were calculated as a function of prescribed dose (e.g. 50 mg) and frequency (e.g. twice daily) when appropriate. In case of multiple prescriptions in the 30-days post-index period, the prescription closest to the index date was reported.

In addition to recommended medications, records were also analyzed for the following non-recommended and/or cautioned medication classes and the number of patients receiving that class was reported:

- **Ascites**: NSAID, ACEI, ARB and BB. PPI as a preventive measure.\(^{27}\)
- **HE**: Hypnotics (HYP), opioids (OP), benzodiazepines (BZ) and sedating anti-depressants (AD).\(^{53}\)

**Concordance with quality care indicators**

Concordance with a set of investigator-designed (adapted from AASLD\(^ {27}\) and Kanwal \textit{et al}\(^ {37}\)) quality indicators (Table 6) was also assessed, based on a review of the guidelines and the quality indicators found in the literature review. Quality indicators 1, and 4 to 9 were adapted from AASLD and Kanwal \textit{et al}, and 2 and 3 were investigator-designed as measure of good clinical practice. Concordance with each indicator was reported as number and percentage of eligible patients, to evaluate the proportion of patients receiving established components of quality care.
<table>
<thead>
<tr>
<th>#</th>
<th>Quality indicator</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MELD/MELDNa score available at complication index date</td>
<td>MELD score indicates the severity of the disease and prioritization for liver transplant</td>
</tr>
<tr>
<td>2</td>
<td>MELDNa score available at complication index date</td>
<td>MELDNa is recently updated MELD score which indicates the severity of the disease and prioritization for liver transplant</td>
</tr>
<tr>
<td>3</td>
<td>Weight recorded at each cirrhosis visit</td>
<td>Weight loss may occur as the disease progresses, and weight gain is utilized as a surrogate measure of ascites which requires monitoring</td>
</tr>
<tr>
<td>4</td>
<td>Seen by gastroenterologist at any follow-up visit post index cirrhosis visit</td>
<td>As complex disease process, specialist care is good clinical practice to ensure appropriate treatment</td>
</tr>
<tr>
<td>5</td>
<td>Primary antibiotic prophylaxis for SBP used in qualified patients</td>
<td>AASLD recommends use for patients with cirrhosis/ascites who have ascitic fluid protein &lt; 1.5 g/dL along with impaired renal function (creatinine ≥ 1.2, BUN ≥ 25 or serum Na ≤ 130) or liver failure (Child score ≥ 9 and bilirubin ≥ 3)</td>
</tr>
<tr>
<td>6</td>
<td>Diuretic therapy within 30-days post-ascites diagnosis</td>
<td>AASLD recommends use of spironolactone alone or in combination with furosemide for management of ascites</td>
</tr>
<tr>
<td>7</td>
<td>Secondary antibiotic prophylaxis within 30-days post-SBP hospital admission</td>
<td>AASLD recommends antibiotic treatment for patients surviving an initial episode of SBP</td>
</tr>
<tr>
<td>8</td>
<td>Treatment within 30-days post-HE diagnosis</td>
<td>AASLD recommends use of lactulose alone or in combination with rifaximin for symptomatic HE</td>
</tr>
<tr>
<td>9</td>
<td>Not on any non-recommended therapies Ascites (NSAID/ACEI/ARB/BB)</td>
<td>Classes of medications which either have contraindications or precautions for use in patients with cirrhosis due to potential for worsening or complication of the disease process. Use of PPI in ascites due to an observed association with risk for SBP</td>
</tr>
<tr>
<td></td>
<td>HE (HYP/BZ/AD/OP)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not prescribed PPI in ascites</td>
<td></td>
</tr>
</tbody>
</table>

# = Number; AASLD = American Association for the Study of Liver Diseases; ACEI = angiotensin converting enzyme inhibitor; AD = antidepressant; ARB = angiotensin receptor blocker; BB = beta blocker; BUN = blood urea nitrogen; BZ = benzodiazepine; HE = hepatic encephalopathy; ICD-9-CM = International Classification of Diseases, Ninth Edition, Clinical Modification; HYP = hypnotic; MELD = Model of End-Stage Liver Disease; MELDNa = Model of End-Stage Liver Disease with sodium; Na = sodium; NSAID = nonsteroidal anti-inflammatory; OP = opioid; PPI = proton pump inhibitor; SBP = spontaneous bacterial peritonitis
Data management and statistical analysis

Data management and analysis was performed using Statistical Analysis System 9.4 software (SAS Institute; Cary, NC) and Microsoft SQL Server 2012/2014 (Microsoft; Redmond, WA).

Research questions

Research question 1: To describe the demographic and clinical characteristics of patients with liver cirrhosis

Distribution of patient demographic and clinical characteristics at the cirrhosis index date was evaluated and their difference was assessed using two-way contingency tables across the three extracted cirrhosis etiology categories: alcoholic (Alc), non-alcoholic (N-Alc), and undetermined (Und). Frequencies and column percentages were reported for categorical variables. A post-hoc Bonferroni correction was used to analyze between-group differences for patient characteristics; accordingly, the two-tailed p-value of 0.05 was adjusted to 0.0166 (p-value/number of comparison groups = 0.05/3). Demographic characteristics included age at cirrhosis index date, sex, race and ethnicity. Clinical characteristics included BMI, additional diagnoses of biliary cirrhosis, other cirrhosis related etiology, incident or prevalent case type, common comorbidities, CirCom score, MELD, and MELDNa. One-way analysis of variance (ANOVA) was used to compare across continuous variables.

Research question 2: To evaluate the change in severity (MELDNa) from cirrhosis to development of ascites, SBP and HE

The index dates for cirrhosis and each complication were ascertained. One-way ANOVA with a post-hoc Tukey’s test was used to describe the difference between the MELDNa scores across the three cirrhosis groups for each complication. The change in MELDNa score
for complete cases was assessed using paired t-test, supplemented by the non-parametric equivalent sign test. A time window of 6 months between cirrhosis index date and complication index date (observed any time after 6 months) was used to assess the change to avoid any overlap of MELDNa scores.

Research question 3: To assess the healthcare utilization patterns for ascites, SBP, and HE
Healthcare utilization was quantified for office-based, hospital observation, inpatient, emergency room visits for patients with ascites, HE and SBP. Patients with ≥ 365 days of data post-complication index date and more than 1 visit post-complication index were included in the analysis. Utilization for each type of service was reported as the total number of visits by type of service for each complication and, mean (SD) and median (range) of visits. Utilization was quantified in two ways: visits in the first 365 days’ post-complication index and total visits, adjusted by follow-up time frame. Follow-up was reported as the mean (SD) and median (range) of duration in days. One-way ANOVA with a post-hoc Tukey test was used to assess difference in distribution across Alc, N-Alc, and Und. A non-parametric Kruskal Wallis test was used to supplement the ANOVA. Independent samples t-test was used to assess difference in utilization for office-based, hospital observation, inpatient, emergency room visits between ascites and HE.

Research question 4: To assess concordance with selected AASLD guidelines, and quality indicators and determine the relationship between patient- and physician-related factors that influence concordance
Concordance with each quality care indicator was reported as number and percentage of eligible patients meeting the indicator criteria. Medications prescribed for ascites, HE and SBP 30-days post index visit were extracted and the percentage of patients receiving
recommended medication, mean (SD), median (range) dose was reported. In addition, non-recommended medications were also extracted. A multivariable logistic regression was used to evaluate the association of demographic and clinical characteristics with the receipt of following quality care indicators:

1. Receipt of diuretic therapy within 30-days post ascites index date \((y/n) = \beta_0 + \beta \text{Age}_{\text{ascites\_index}} + \beta \text{Gender} + \beta \text{Race} + \beta \text{BMI}_{\text{ascites\_index}} + \beta \text{MELDNa}_{\text{ascites\_index}} + \beta \text{Physician Type} + \beta \text{No. of comorbidities\_based\_on\_CirCom} + \beta \text{Cirrhosis type}\)

2. Receipt of treatment within 30-days post-HE index date \((y/n) = \beta_0 + \beta \text{Age}_{\text{HE\_index}} + \beta \text{Gender} + \beta \text{Race} + \beta \text{BMI}_{\text{HE\_index}} + \beta \text{MELDNa}_{\text{HE\_index}} + \beta \text{Physician Type} + \beta \text{No. of comorbidities\_based\_on\_CirCom} + \beta \text{Cirrhosis type}\)
CHAPTER 4: RESULTS

A total of n = 4,116 patients were included in the final analysis. Depending on the research question being addressed, sub-samples were utilized and are reported accordingly.

Research question 1: To describe the demographic and clinical characteristics of patients with liver cirrhosis

Sample size
The total sample size extracted based on the inclusion/exclusion criteria was n = 4,116. The demographic and clinical characteristics are listed in Table 7.

Patient demographic variables
A total of 404 (9.82%) patients had a recorded diagnosis for alcoholic cirrhosis, 3,284 (79.79%) had a diagnosis for non-alcoholic, and 428 (10.40%) were deemed undetermined. The mean age for the sample was 58.33 years (standard deviation [SD]: 10.97 years). A total of 40.69% of patients were above 60 years of age whereas patients aged 18-40 years old accounted for only 5.03% of the sample. The sample had a slight majority of males (55.68%) as compared to females (44.32%). Race was reported for 98.66% of the sample and Caucasians (90.33%) formed the majority. Similarly, ethnicity was reported for 97.69% of the sample, with non-Hispanics (97.27%) being the most commonly reported ethnicity.
Table 7. Distribution of demographic and clinical variables (n=4,116)

<table>
<thead>
<tr>
<th>Individual characteristics</th>
<th>Alc, n (%) (n=404)</th>
<th>N-Alc, n (%) (n=3,284)</th>
<th>Und, n (%) (n=428)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (at index)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-40</td>
<td>26 (6.44)</td>
<td>157 (4.78)</td>
<td>24 (5.61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>41-60</td>
<td>282 (69.80)</td>
<td>1,663 (50.64)</td>
<td>289 (67.52)</td>
<td></td>
</tr>
<tr>
<td>&gt; 60</td>
<td>96 (23.76)</td>
<td>1,464 (44.58)</td>
<td>115 (26.87)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>54.3 (10.06)</td>
<td>59.3 (11.09)</td>
<td>54.71 (9.16)</td>
<td>&lt;0.0001 §</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>271 (67.08)</td>
<td>1,724 (52.50)</td>
<td>297 (69.39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>133 (32.92)</td>
<td>1,560 (47.50)</td>
<td>131 (30.61)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>386 (95.54)</td>
<td>2,937 (89.43)</td>
<td>395 (92.29)</td>
<td>0.0062</td>
</tr>
<tr>
<td>African-American</td>
<td>15 (3.71)</td>
<td>285 (8.68)</td>
<td>28 (6.54)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>14 (0.43)</td>
<td>1 (0.23)</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>3 (0.74)</td>
<td>48 (1.46)</td>
<td>4 (0.93)</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>17 (0.52)</td>
<td>0</td>
<td>0.493</td>
</tr>
<tr>
<td>non-Hispanic</td>
<td>395 (97.77)</td>
<td>3,190 (97.14)</td>
<td>419 (97.90)</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>9 (2.23)</td>
<td>77 (2.34)</td>
<td>9 (2.10)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI (at index)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>8 (1.98)</td>
<td>39 ((1.19)</td>
<td>14 (3.27)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>106 (26.24)</td>
<td>596 (18.15)</td>
<td>130 (30.37)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>135 (33.42)</td>
<td>906 (27.59)</td>
<td>142 (33.18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Obese</td>
<td>138 (34.16)</td>
<td>1,587 (48.33)</td>
<td>126 (29.44)</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>17 (4.21)</td>
<td>156 (4.75)</td>
<td>16 (3.74)</td>
<td></td>
</tr>
<tr>
<td><strong>Incident case</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>273 (67.57)</td>
<td>1,768 (53.84)</td>
<td>307 (71.73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No</td>
<td>131 (32.43)</td>
<td>1,516 (46.16)</td>
<td>121 (28.27)</td>
<td></td>
</tr>
<tr>
<td><strong>Other etiology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>62 (15.35)</td>
<td>991 (30.18)</td>
<td>82 (19.16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>12 (2.97)</td>
<td>47 (1.43)</td>
<td>20 (4.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Biliary involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (0.25)</td>
<td>77 (2.34)</td>
<td>2 (0.47)</td>
<td>0.0010</td>
</tr>
<tr>
<td>No</td>
<td>403 (99.75)</td>
<td>3,207 (97.66)</td>
<td>426 (99.53)</td>
<td></td>
</tr>
<tr>
<td><strong>Common comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>34 (8.42)</td>
<td>624 (19.00)</td>
<td>34 (7.94)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SA w/o alcohol</td>
<td>70 (17.33)</td>
<td>342 (10.41)</td>
<td>65 (15.19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COPD</td>
<td>21 (5.20)</td>
<td>210 (6.39)</td>
<td>13 (3.04)</td>
<td>0.017</td>
</tr>
<tr>
<td>Depression</td>
<td>44 (10.89)</td>
<td>311 (9.47)</td>
<td>32 (7.48)</td>
<td>0.23</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>18 (4.46)</td>
<td>159 (4.84)</td>
<td>13 (3.04)</td>
<td>0.243</td>
</tr>
<tr>
<td>Non-met/non-hem cancer</td>
<td>15 (3.71)</td>
<td>148 (4.51)</td>
<td>10 (2.34)</td>
<td>0.095</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4 (0.99)</td>
<td>113 (3.44)</td>
<td>3 (0.70)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>9 (2.33)</td>
<td>43 (1.31)</td>
<td>6 (1.40)</td>
<td>0.335</td>
</tr>
<tr>
<td>PAD</td>
<td>2 (0.50)</td>
<td>39 (1.19)</td>
<td>2 (0.47)</td>
<td>0.271 †</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>4 (0.99)</td>
<td>18 (0.55)</td>
<td>3 (0.70)</td>
<td>0.387 †</td>
</tr>
<tr>
<td>Hematologic cancer</td>
<td>0</td>
<td>21 (0.64)</td>
<td>1 (0.23)</td>
<td>0.208 †</td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td>0</td>
<td>17 (0.52)</td>
<td>1 (0.23)</td>
<td>0.414 †</td>
</tr>
<tr>
<td>AMI</td>
<td>0</td>
<td>6 (0.18)</td>
<td>0</td>
<td>1.000 †</td>
</tr>
</tbody>
</table>

Alc = alcoholic cirrhosis; AMI = acute myocardial infarction; COPD = chronic obstructive pulmonary disease; N-Alc = non-alcoholic cirrhosis, PAD = peripheral artery disease; SA = substance abuse; Und = undetermined. † Fisher’s exact test used; § ANOVA used
Age at cirrhosis index, sex and race significantly varied across the three groups. Patients classified with non-alcoholic cirrhosis were older (59.3 [SD: 11.09] years) as compared to patients who had alcoholic cirrhosis (54.3 [10.06] years) or undetermined cirrhosis (54.71 [9.16] years) (p<0.0001). Patients with alcoholic or undetermined cirrhosis had a higher proportion of Caucasian and male patients, compared to those with non-alcoholic, which had increased proportions of female and African-American patients.

*Patient clinical variables*

BMI at index, incident/prevalent case type, biliary involvement, and presence of comorbidities such as COPD, substance abuse other than alcohol, heart failure and diabetes significantly varied across the cirrhosis categories. Presence of other cirrhosis etiologies such as viral hepatitis and alcohol abuse also showed significant variation of distribution. CirCom, MELD and MELDNa distributions could not be compared across the groups due to low frequencies (n<5) within the categories present.

BMI at index date was calculated for 95.41% of the sample based on the availability of height and weight variables. From the total sample, 44.97% of the patients were obese (≥30 kg/m²), 28.74% were overweight (25-29.9 kg/m²), 20.21% had normal BMI (18.5-24.9 kg/m²) and 1.48% were underweight (0-18.5 kg/m²). While alcoholic and non-alcoholic cirrhosis patients had a larger proportion of obese patients, patients classified with undetermined cirrhosis were most commonly overweight. A total of 57.05% of the cirrhosis cases were incident cases, with alcoholic and undetermined cirrhosis contributing higher proportions than non-alcoholic. Biliary involvement was very low with only 1.94% of the sample having a diagnosis for the same; however, this was significantly more common among those with non-alcoholic cirrhosis. Etiologies of viral hepatitis and alcohol abuse were observed in 27.97% and 1.91% of the total sample, respectively. Diabetes (16.81%) was the most commonly
observed comorbidity, which was most commonly seen in non-alcoholic cirrhosis. Substance abuse other than alcohol was most common among patients classified with alcoholic and undetermined cirrhosis.
Table 7 (cont). Distribution of demographic and clinical variables (n=4,116)

<table>
<thead>
<tr>
<th>Individual characteristics</th>
<th>Alc, n (%) (n=404)</th>
<th>N-Alc, n (%) (n=3,284)</th>
<th>Und, n (%) (n=428)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CirCom</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>299 (74.01)</td>
<td>2,491 (75.85)</td>
<td>335 (78.27)</td>
</tr>
<tr>
<td>1+0</td>
<td>67 (16.58)</td>
<td>425 (12.94)</td>
<td>62 (14.49)</td>
</tr>
<tr>
<td>1+1</td>
<td>13 (3.22)</td>
<td>122 (3.71)</td>
<td>11 (2.57)</td>
</tr>
<tr>
<td>3+0</td>
<td>25 (6.19)</td>
<td>230 (7.00)</td>
<td>19 (4.44)</td>
</tr>
<tr>
<td>3+1</td>
<td>0</td>
<td>7 (0.21)</td>
<td>0</td>
</tr>
<tr>
<td>5+0</td>
<td>0</td>
<td>6 (0.18)</td>
<td>0</td>
</tr>
<tr>
<td>5+1</td>
<td>0</td>
<td>3 (0.09)</td>
<td>1 (0.23)</td>
</tr>
<tr>
<td><strong>MELD (at index)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 9</td>
<td>90 (22.28)</td>
<td>1,081 (32.92)</td>
<td>81 (18.93)</td>
</tr>
<tr>
<td>10-19</td>
<td>166 (41.09)</td>
<td>1,257 (38.28)</td>
<td>240 (56.07)</td>
</tr>
<tr>
<td>20-29</td>
<td>50 (12.38)</td>
<td>244 (7.43)</td>
<td>47 (10.98)</td>
</tr>
<tr>
<td>30-39</td>
<td>7 (1.73)</td>
<td>15 (0.46)</td>
<td>10 (2.34)</td>
</tr>
<tr>
<td>≥ 40</td>
<td>0</td>
<td>1 (0.03)</td>
<td>0</td>
</tr>
<tr>
<td>Undetermined</td>
<td>66 (16.34)</td>
<td>539 (16.41)</td>
<td>35 (8.18)</td>
</tr>
<tr>
<td>Missing</td>
<td>25 (6.19)</td>
<td>147 (4.48)</td>
<td>15 (3.50)</td>
</tr>
<tr>
<td><strong>MELDNa (at index)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 9</td>
<td>56 (13.86)</td>
<td>770 (23.45)</td>
<td>51 (11.92)</td>
</tr>
<tr>
<td>10-19</td>
<td>131 (32.43)</td>
<td>1,096 (33.37)</td>
<td>196 (45.79)</td>
</tr>
<tr>
<td>20-29</td>
<td>62 (15.35)</td>
<td>309 (9.41)</td>
<td>64 (14.95)</td>
</tr>
<tr>
<td>30-39</td>
<td>11 (2.72)</td>
<td>21 (0.64)</td>
<td>12 (2.80)</td>
</tr>
<tr>
<td>≥ 40</td>
<td>0</td>
<td>1 (0.03)</td>
<td>0</td>
</tr>
<tr>
<td>Undetermined</td>
<td>119 (29.46)</td>
<td>940 (28.62)</td>
<td>90 (21.03)</td>
</tr>
<tr>
<td>Missing</td>
<td>25 (6.19)</td>
<td>147 (4.48)</td>
<td>15 (3.50)</td>
</tr>
</tbody>
</table>

*MELD = Model for End-Stage Liver disease; MELDNa = Model for End-Stage Liver disease with Sodium; Missing = score not calculated due to absence of test; Undetermined = score not calculated due to missing values*
CirCom score based on comorbidities recorded from first visit in the database to three months’ post cirrhosis index was calculated for the extracted sample. Seventy-six percent of the patients had a CirCom score of 0 and 13.45% had a score of 1+0, reflecting that 89.37% of the sample had a lower comorbidity burden and associated mortality. Despite an inclusion period of 3 months pre- and post-index date, MELDNa could not be calculated for 32.45% (27.91% undetermined due to missing values for test; 4.54% missing due to absence of test) of the sample. For those with available laboratory results, 34.46 % of the patients had a MELDNa score between 10-19, and the mean MELDNa score for the entire sample was 13.59 (SD: 5.84). Similarly, for MELD, 20.10% (15.56% undetermined due to missing values for test; 4.54% missing due to absence of test) of the sample did not have a score, 40.40% of the sample had score between 10 and 19 and the mean MELD score for the sample was 12.47 (5.27).

Patients with alcoholic and undetermined cirrhosis had a higher proportion of patients in MELDNa categories of 20-29 and 30-39 compared to those with non-alcoholic cirrhosis, which had increased proportions of patients with MELDNa ≤ 9. Patients with undetermined cirrhosis had a higher proportion of patients with MELDNa of 10-19 compared to both alcoholic and non-alcoholic cirrhosis. No variation was observed for the CirCom score.

**Research question 2: To evaluate the change in severity (MELDNa) from cirrhosis to development of ascites, SBP and HE**

**Sample size**

Ascites, HE and SBP were observed in a total of 986 (23.96%), 665 (16.16%) and 148 (3.60%) patients in the sample, respectively.
Distribution and changes in MELDNa

Of the total patients for ascites, HE and SBP, MELDNa scores were available for 805 (81.64%), 538 (80.90%), and 145 (97.97%) patients, respectively (Table 8). For patients with ascites, the mean MELDNa score was significantly higher for undetermined cirrhosis as compared to non-alcoholic cirrhosis (p=0.0003), but not for patients classified with alcoholic cirrhosis. Similarly, for patients with HE, the mean MELDNa score was significantly higher for undetermined cirrhosis and alcoholic cirrhosis compared to patients classified with non-alcoholic cirrhosis (p<0.0001). For SBP patients, mean MELDNa was significantly higher for patients classified with alcoholic cirrhosis as compared to non-alcoholic and undetermined cirrhosis (p=0.0146).
**Table 8. Distribution of complications and mean MELDNa score**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Alc (n=404)</th>
<th>N-Alc (n=3,284)</th>
<th>Und (n=428)</th>
<th>p-value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites (n=805)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>95 (23.51)</td>
<td>542 (16.50)</td>
<td>168 (39.25)</td>
<td>0.0003*</td>
</tr>
<tr>
<td>Mean MELDNa (SD)</td>
<td>17.90 (6.46)</td>
<td>16.15 (5.79)</td>
<td>18.04 (6.38)</td>
<td></td>
</tr>
<tr>
<td>HE (n=538)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>55 (13.61)</td>
<td>377 (11.47)</td>
<td>106 (24.76)</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Mean MELDNa (SD)</td>
<td>18.40 (6.34)</td>
<td>15.91 (5.89)</td>
<td>18.63 (6.61)</td>
<td></td>
</tr>
<tr>
<td>SBP (n=145)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>16 (3.96)</td>
<td>96 (2.51)</td>
<td>33 (7.71)</td>
<td>0.0146*</td>
</tr>
<tr>
<td>Mean MELDNa (SD)</td>
<td>25.88 (6.99)</td>
<td>21.45 (5.71)</td>
<td>20.72 (6.30)</td>
<td></td>
</tr>
</tbody>
</table>

*Alc = alcoholic cirrhosis; ANOVA = Analysis of Variance; HE = hepatic encephalopathy; MELDNa = Model for End-stage Liver Disease with Sodium; N-Alc = non-alcoholic cirrhosis; SBP = spontaneous bacterial peritonitis; SD = standard deviation; Und = undetermined cirrhosis*
When assessing changes in mean MELDNa from cirrhosis index date to complication index date for complete cases, there was a statistically significant increase in the mean MELDNa from cirrhosis index date to each complication index date observed any time after 6 months post cirrhosis index (Table 9). The mean change for MELDNa was highest for SBP patients, followed by ascites and HE.
Table 9. Changes in mean MELDNa from cirrhosis index to ascites, HE, and SBP index

<table>
<thead>
<tr>
<th>Index</th>
<th>Sample size</th>
<th>Mean MELDNa at index (SD)</th>
<th>Mean difference (SD)</th>
<th>t statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>220</td>
<td>13.59 (4.54)</td>
<td>3.455 (5.808)</td>
<td>-8.823</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Ascites</td>
<td>17.04 (6.36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>211</td>
<td>14.23 (5.22)</td>
<td>2.213 (5.880)</td>
<td>-5.467</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>HE</td>
<td>16.44 (6.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>69</td>
<td>15.81 (6.12)</td>
<td>5.783 (7.040)</td>
<td>-6.823</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>SBP</td>
<td>21.59 (5.80)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HE = hepatic encephalopathy; MELDNa = Model for End-stage Liver Disease with Sodium; SBP = spontaneous bacterial peritonitis; SD = standard deviation
Similar results were found when assessing median MELDNa from cirrhosis index date to each complication index date observed any time after 6 months’ post cirrhosis index (Table 10). Patients with SBP had the highest median MELDNa at 21 (compared to 15 at cirrhosis index), while patients with ascites and HE had median MELDNa of 16 (compared to 13 at cirrhosis index) (all changes p<0.0001).
Table 10. Changes in median MELDNa from cirrhosis index to ascites, HE, and SBP index

<table>
<thead>
<tr>
<th>Index</th>
<th>Sample size</th>
<th>Median MELDNa at index (range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>220</td>
<td>13 (6-33)</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Ascites</td>
<td></td>
<td>16 (7-36)</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>211</td>
<td>13 (6-34)</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>HE</td>
<td></td>
<td>16 (6-36)</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>69</td>
<td>15 (7-32)</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td>21 (9-36)</td>
<td></td>
</tr>
</tbody>
</table>

*HE = hepatic encephalopathy; MELDNa = Model for End-stage Liver Disease with Sodium; SBP = spontaneous bacterial peritonitis*
Research question 3: To assess the healthcare utilization patterns for ascites, SBP and HE

Sample size

Ascites, HE and SBP were observed in a total of 986 (23.96%), 665 (16.16%) and 148 (3.60%) patients respectively.

Office-based utilization – 1-year follow-up

A total of 347 (35.91%) patients with ascites had utilization data available for 1-year follow-up from index for office-based visits (Table 11). Overall, patients with ascites had 1,161 visits with mean utilization of 3.34 (SD: 3.10) visits in the 1-year follow-up. The non-alcoholic cirrhosis group had highest numerical utilization, but there were no significant differences seen among cirrhosis groups, via either the ANOVA or Kruskal-Wallis tests for means and medians, respectively. A total of 205 (30.82%) patients with HE had utilization data available for 1-year follow-up for office-based visits. Overall, patients with HE had 615 visits with mean utilization of 3.00 (1.41) visits in the 1-year follow-up. The undetermined cirrhosis group had the highest utilization, but ultimately no significant difference was observed among the cirrhosis groups. A total of 5 (3.55%) SBP patients had visits in a 1-year period from their index hospitalization. They had overall 13 visits with mean utilization of 2.60 (0.54) with median (range) of 3 (2-3). An independent samples t-test comparing overall utilization for ascites and HE showed that there was no significant difference in utilization between the two complications (p=0.074).
Table 11. Office-based visit utilization during 1-year post-ascites, HE, and SBP index

<table>
<thead>
<tr>
<th>Complication</th>
<th>Stratification</th>
<th>Visits, n</th>
<th>Mean (SD)</th>
<th>p-value, ANOVA KW</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>Overall (n=347)</td>
<td>1,161</td>
<td>3.34 (3.10)</td>
<td>-</td>
<td>3 (2-54)</td>
</tr>
<tr>
<td></td>
<td>Alc (n=51)</td>
<td>164</td>
<td>3.21 (1.28)</td>
<td>0.9207 0.8078</td>
<td>3 (2-7)</td>
</tr>
<tr>
<td></td>
<td>Non-Alc (n=212)</td>
<td>720</td>
<td>3.39 (3.78)</td>
<td></td>
<td>3 (2-54)</td>
</tr>
<tr>
<td></td>
<td>Und (n=84)</td>
<td>277</td>
<td>3.29 (1.61)</td>
<td></td>
<td>3 (2-9)</td>
</tr>
<tr>
<td>HE</td>
<td>Overall (n=205)</td>
<td>615</td>
<td>3.00 (1.41)</td>
<td>-</td>
<td>3 (2-14)</td>
</tr>
<tr>
<td></td>
<td>Alco (n=19)</td>
<td>58</td>
<td>3.05 (1.12)</td>
<td>0.6605 0.3424</td>
<td>3 (2-6)</td>
</tr>
<tr>
<td></td>
<td>Non-Alc (n=144)</td>
<td>424</td>
<td>2.94 (1.46)</td>
<td></td>
<td>2 (2-14)</td>
</tr>
<tr>
<td></td>
<td>Und (n=42)</td>
<td>133</td>
<td>3.16 (1.35)</td>
<td></td>
<td>3 (2-8)</td>
</tr>
<tr>
<td>SBP</td>
<td>Overall (n=5)</td>
<td>13</td>
<td>2.60 (0.54)</td>
<td>-</td>
<td>3 (2-3)</td>
</tr>
</tbody>
</table>

ANOVA = Analysis of Variance; Alc = alcoholic cirrhosis; HE = hepatic encephalopathy; SBP = spontaneous bacterial peritonitis; KW = Kruskal Wallis; Non-Alc = non-alcoholic cirrhosis; Und = undetermined cirrhosis
Office-based utilization – overall follow-up

A total of 437 (44.32%) patients with ascites had utilization data available for overall follow-up from index for office-based visits (Table 12). Overall, patients with ascites had 2,163 visits with mean utilization of 4.94 (4.32) visits across 1,085 days of follow-up, corresponding to 1.66 visits/year. The undetermined cirrhosis group had highest utilization, but no significant difference in utilization was seen between the three cirrhosis groups. A total of 277 (41.65%) patients with HE had utilization data available for overall follow-up from index for office-based visits. Overall, patients with HE had 1,257 visits with mean utilization was 4.53 (2.81) visits over 1,049 days of follow-up, corresponding to 1.58 visits/year. The undetermined cirrhosis group had most utilization, but no significant differences were seen in comparison to other cirrhosis groups. A total of 10 (6.71%) SBP patients had data available for overall follow-up from their index hospitalization with a total of 35 visits and a mean of 3.50 (1.17) visits over 1,070 days of follow-up, at 1.19 visits/year. An independent samples t-test comparing overall utilization for ascites and HE showed that there was no significant difference in utilization between the two complications (p=0.1237).
### Table 12. Office-based visit utilization overall post-ascites, HE, and SBP index

<table>
<thead>
<tr>
<th>Complication</th>
<th>Stratification</th>
<th>Visits, n</th>
<th>Mean (SD), Mean/year</th>
<th>p-value, ANOVA KW</th>
<th>Median (range), Median/year</th>
<th>Follow-up in days, mean (SD) Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>Overall (n=437)</td>
<td>2,163</td>
<td>4.97 (4.32) 1.66</td>
<td>-</td>
<td>4 (2-57) 1.5</td>
<td>1,084.75 (531.97) 974</td>
</tr>
<tr>
<td></td>
<td>Alc (n=63)</td>
<td>300</td>
<td>4.76 (2.95) 1.5</td>
<td>0.657 0.223</td>
<td>4 (2-15) 1.38</td>
<td>1,157.68 (565.35) 1,054</td>
</tr>
<tr>
<td></td>
<td>Non-Alc (n=269)</td>
<td>1,308</td>
<td>4.86 (4.76) 1.68</td>
<td>0.223</td>
<td>4 (2-57) 1.56</td>
<td>1,058.16 (534.24) 933</td>
</tr>
<tr>
<td></td>
<td>Und (n=105)</td>
<td>555</td>
<td>5.28 (3.79) 1.74</td>
<td></td>
<td>4 (2-22) 1.39</td>
<td>1,109 (504.69) 1,049</td>
</tr>
<tr>
<td>HE</td>
<td>Overall (n=277)</td>
<td>1,257</td>
<td>4.53 (2.81) 1.58</td>
<td>-</td>
<td>4 (2-17) 1.55</td>
<td>1,049.14 (510.52) 943</td>
</tr>
<tr>
<td></td>
<td>Alc (n=26)</td>
<td>115</td>
<td>4.42 (2.19) 1.40</td>
<td>0.200 0.099</td>
<td>4 (2-10) 1.33</td>
<td>1,151.62 (543.07) 1,098</td>
</tr>
<tr>
<td></td>
<td>Non-Alc (n=200)</td>
<td>878</td>
<td>4.43 (2.80) 1.60</td>
<td></td>
<td>4 (2-17) 1.62</td>
<td>1,010.63 (499.66) 898</td>
</tr>
<tr>
<td></td>
<td>Und (n=51)</td>
<td>264</td>
<td>5.17 (3.07) 1.64</td>
<td></td>
<td>5 (2-16) 1.69</td>
<td>1,147.94 (525.55) 1,081</td>
</tr>
<tr>
<td>SBP</td>
<td>Overall (n=10)</td>
<td>35</td>
<td>3.50 (1.17) 1.19</td>
<td>-</td>
<td>3 (2-5) 1.12</td>
<td>1,070 (570.52) 975</td>
</tr>
</tbody>
</table>

ANOVA = Analysis of Variance; Alc = alcoholic cirrhosis; HE = hepatic encephalopathy; SBP = spontaneous bacterial peritonitis; KW = Kruskal Wallis; Non-Alc = Non-alcoholic cirrhosis; Und = Undetermined cirrhosis
Hospital Observation/emergency utilization – 1-year follow-up

A total of 26 (2.63%) patients with ascites had utilization data available for 1-year follow-up from index for hospital observation visits with a total of 73 visits and overall mean utilization of 2.80 (SD: 1.09) visits (Table 13). A total of 5 (0.75%) patients with HE had utilization data available for 1-year follow-up for hospital observation visits with a total of 15 visits and overall mean utilization of 3.00 (1.73) visits. A total of 16 (1.62%) patients with ascites had utilization data available for 1-year follow-up from index for emergency visits. Overall utilization was 62 visits with mean of 3.87 (3.18) visits. For HE, 5 (0.75%) patients had utilization data available with a total of 12 visits and mean utilization of 2.40 (0.89) visits. ANOVA and Kruskal-Wallis tests were not conducted on hospital observation or emergency visits due to the small sample size, and no data for either utilization type was observed for SBP patients.
Table 13. Hospital observation/emergency visit utilization during 1-year post-ascites and HE index

<table>
<thead>
<tr>
<th>Health service type, Complication</th>
<th>Visits, n</th>
<th>Mean (SD)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital observation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascites (n=26)</td>
<td>73</td>
<td>2.80 (1.09)</td>
<td>2.5 (2-6)</td>
</tr>
<tr>
<td>HE (n=5)</td>
<td>15</td>
<td>3.00 (1.73)</td>
<td>2 (2-6)</td>
</tr>
<tr>
<td><strong>Emergency visits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascites (n=16)</td>
<td>62</td>
<td>3.87 (3.18)</td>
<td>2 (2-13)</td>
</tr>
<tr>
<td>HE (n=5)</td>
<td>12</td>
<td>2.40 (0.89)</td>
<td>2 (2-4)</td>
</tr>
</tbody>
</table>

*HE = hepatic encephalopathy; SD = standard deviation*
Hospital observation/emergency utilization – overall follow-up

A total of 44 (4.46%) patients with ascites had utilization data available for overall follow-up from index for hospital observation visits (Table 14). Overall utilization was 146 visits with mean utilization of 3.31 (3.26) visits over 1,164 days follow-up, corresponding to 1.04 visits/year. For 10 (1.50%) patients with HE with available data, total utilization was 46 visits with mean utilization of 4.60 (5.56) visits over 1,220 days, at 1.38 visits/year. A total of 24 (3.60%) patients with ascites had utilization data available for overall follow-up from index for emergency visits, with total utilization of 99 and mean utilization of 4.12 (4.22) over 845 days, at 1.78 visits/year. A total of 6 (0.90%) patients with HE had available data, with overall utilization of 22 visits and mean utilization of 3.66 (2.25) over 938 days follow-up, corresponding to 1.42 visits/year. ANOVA and Kruskal-Wallis tests were not conducted on hospital observation or emergency visits due to the small sample size. No hospital observation visits were observed for SBP patients, while 2 (1.34%) patients had emergency visits for overall follow-up.
Table 14. Hospital observation/emergency visit utilization overall post-ascites and HE index

<table>
<thead>
<tr>
<th>Health service type, Complication</th>
<th>Visits, n</th>
<th>Mean (SD), Mean/year</th>
<th>Median (range), Median/year</th>
<th>Follow-up in days Mean (SD) Median</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital observation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascites (n=44)</td>
<td>146</td>
<td>3.31 (3.26) 1.03</td>
<td>2 (2-22) 0.61</td>
<td>1,163.73 (541.53) 1,178</td>
</tr>
<tr>
<td>HE (n=10)</td>
<td>46</td>
<td>4.60 (5.56) 1.38</td>
<td>2.5 (2-20) 0.76</td>
<td>1,219.90 (592.77) 1,208</td>
</tr>
<tr>
<td><strong>Emergency visits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascites (n=24)</td>
<td>99</td>
<td>4.12 (4.22) 1.78</td>
<td>2 (2-20) 1.14</td>
<td>844.79 (479.56) 645</td>
</tr>
<tr>
<td>HE (n=6)</td>
<td>22</td>
<td>3.66 (2.25) 1.42</td>
<td>2.5 (2-7) 1.14</td>
<td>937.50 (532.84) 798.50</td>
</tr>
</tbody>
</table>

HE = hepatic encephalopathy; SD = standard deviation
**Inpatient utilization – 1-year follow-up**

A total of 131 (13.28%) patients with ascites had utilization data available for 1-year follow-up from index for inpatient visits with a total of 575 visits at a mean (SD) of 4.39 (3.34) visits ([Table 15](#)). The alcoholic cirrhosis group (n=14) had highest numerical utilization, but results for ANOVA and Kruskal-Wallis showed that there was no significant difference in utilization between the three groups. A total of 67 (10.07%) patients with HE had utilization data available with overall 235 visits and mean of 3.50 (2.02) visits. The undetermined cirrhosis group (n=16) group had most utilization, with the Kruskal-Wallis demonstrating a significant difference in utilization. Independent samples t-test comparison between inpatient visits for ascites and HE showed that ascites patients had a significantly higher number of inpatient visits as compared to HE patients (p=0.0213). A total of 35 (23.48%) SBP patients had inpatient visits in a 1-year period from their index hospitalization with total 77 visits and mean of 2.20 (0.47) visits.
Table 15. Inpatient visit utilization during 1-year post-ascites, HE, and SBP index

<table>
<thead>
<tr>
<th>Complication</th>
<th>Stratification</th>
<th>Visits, n</th>
<th>Mean (SD)</th>
<th>Median (range)</th>
<th>p-value, ANOVA KW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>Overall (n=131)</td>
<td>575</td>
<td>4.39 (3.34)</td>
<td>3 (2-21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alcoholic (n=14)</td>
<td>69</td>
<td>4.92 (4.95)</td>
<td>3 (2-21)</td>
<td>0.5710</td>
</tr>
<tr>
<td></td>
<td>Non-Alc (n=84)</td>
<td>349</td>
<td>4.16 (2.76)</td>
<td>3 (2-15)</td>
<td>0.8648</td>
</tr>
<tr>
<td></td>
<td>Und (n=33)</td>
<td>157</td>
<td>4.75 (3.91)</td>
<td>4 (2-21)</td>
<td></td>
</tr>
<tr>
<td>HE</td>
<td>Overall (n=67)</td>
<td>235</td>
<td>3.50 (2.02)</td>
<td>3 (2-12)</td>
<td>0.1072</td>
</tr>
<tr>
<td></td>
<td>Alcoholic (n=13)</td>
<td>41</td>
<td>3.15 (2.79)</td>
<td>2 (2-12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-Alc (n=38)</td>
<td>123</td>
<td>3.23 (1.60)</td>
<td>3 (2-9)</td>
<td>0.0139*</td>
</tr>
<tr>
<td></td>
<td>Und (n=16)</td>
<td>71</td>
<td>4.43 (2.06)</td>
<td>4 (2-9)</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>Overall (n=35)</td>
<td>77</td>
<td>2.20 (0.47)</td>
<td>2 (2-4)</td>
<td>-</td>
</tr>
</tbody>
</table>

*Alc = alcoholic cirrhosis; ANOVA = Analysis of Variance; HE = hepatic encephalopathy; KW = Kruskal Wallis; Non-Alc = non-alcoholic cirrhosis; SBP = spontaneous bacterial Peritonitis; Und = undetermined cirrhosis
Inpatient utilization – overall follow-up

A total of 160 (16.22%) patients with ascites had utilization data available for overall follow-up from index for inpatient visits with overall 926 visits and mean (SD) of 5.78 (4.72) over 1,006 days follow-up, corresponding to 2.1 visits/year (Table 16). The undetermined cirrhosis group (n=38) group had most utilization, but no significant difference was detected. A total of 87 (13.08%) patients with HE had utilization data available for overall follow-up with total 414 visits at mean of 4.75 (4.09) visits over 913 days, at 1.90 visits/year. The undetermined cirrhosis group (n=20) had the highest, albeit not significantly different, utilization among groups. A total of 47 (31.54%) SBP patients had data available for overall follow-up from their index hospitalization for inpatient visits with a total of 131 visits at 2.78 (1.45) visits over 1,072 days, for a total of 0.95 visits/year.
Table 16. Inpatient visit utilization overall post-ascites, HE, and SBP index

<table>
<thead>
<tr>
<th>Complication</th>
<th>Stratification</th>
<th>Visits, n</th>
<th>Mean (SD), Mean/year</th>
<th>Median (range), Median/year</th>
<th>p-value, ANOVA KW</th>
<th>Follow-up in days, Mean (SD)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>Overall (n=160)</td>
<td>926</td>
<td>5.78 (4.72) 2.1</td>
<td>4 (2-33) 1.61</td>
<td>-</td>
<td>1,005.95 (487.96) 907</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alcoholic (n=18)</td>
<td>104</td>
<td>5.77 (5.42) 2.04</td>
<td>4 (2-24) 1.65</td>
<td>0.4412</td>
<td>1,031.67 (540.74) 885.50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-Alc (n=104)</td>
<td>570</td>
<td>5.48 (4.18) 1.92</td>
<td>4 (2-25) 1.46</td>
<td>0.2660</td>
<td>1,039 (501.81) 1,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Und (n=38)</td>
<td>252</td>
<td>6.63 (5.71) 2.68</td>
<td>4 (2-33) 1.62</td>
<td></td>
<td>903.31 (416.72) 799.50</td>
<td></td>
</tr>
<tr>
<td>HE</td>
<td>Overall (n=87)</td>
<td>414</td>
<td>4.75 (4.09) 1.90</td>
<td>3 (2-27) 1.46</td>
<td>-</td>
<td>913.48 (467.58) 750</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alcoholic (n=13)</td>
<td>62</td>
<td>4.76 (5.38) 1.45</td>
<td>2 (2-19) 0.63</td>
<td>0.2057</td>
<td>1,201.62 (572.47) 1,155</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-Alc (n=54)</td>
<td>229</td>
<td>4.24 (2.84) 1.73</td>
<td>3 (2-15) 1.41</td>
<td>0.1261</td>
<td>895.33 (429.80) 777.50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Und (n=20)</td>
<td>123</td>
<td>6.15 (5.65) 2.9</td>
<td>4 (2-27) 2.41</td>
<td></td>
<td>775.20 (435.28) 605.50</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>Overall (n=47)</td>
<td>131</td>
<td>2.78 (1.45) 0.95</td>
<td>2 (2-7) 0.74</td>
<td>-</td>
<td>1,072.36 (501.18) 988</td>
<td></td>
</tr>
</tbody>
</table>

Alc = alcoholic cirrhosis; ANOVA = Analysis of Variance; HE = hepatic encephalopathy; KW = Kruskal Wallis; Non-Alc = non-alcoholic cirrhosis; SBP = spontaneous bacterial peritonitis; Und = undetermined cirrhosis
Research question 4: To assess concordance with selected AASLD guidelines, and quality indicators and determine the relationship between patient- and physician-related factors that influence concordance

Sample size

Ascites, HE and SBP were observed in a total of 986 (23.96%), 665 (16.16%) and 148 (3.60%) patients, respectively.

Concordance with clinical care guidelines – ascites

Medication data was available for 892 (90.46%) patients with ascites. Of these, 514 (57.62%) received recommended therapy of spironolactone alone or in combination with furosemide within 30-days of index visit. Out of the 514 on recommended therapy, 118 (22.96%) received spironolactone alone with a mean dose (SD) of 85.27 mg (50.49 mg). The remaining 396 (77.04%) received combination therapy with spironolactone/furosemide at a mean dosing ratio of spironolactone to furosemide of 90.75 mg: 43.91 mg. A total of 284 (31.83%) of the 892 patients were receiving medications that would potentially require caution in prescribing in this population, most commonly via the use of BB. Two-hundred and thirty-four patients (26.23%) had a prescription for PPI. Table 17 describes the prescription pattern for ascites.
Table 17. Medication prescription patterns for patients with ascites

<table>
<thead>
<tr>
<th>Medication</th>
<th>Metric</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prescribed therapies (n=514)</strong></td>
<td></td>
</tr>
<tr>
<td>Spironolactone/furosemide</td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>396 (77.04)</td>
</tr>
<tr>
<td>Mean dosing ratio (SD), mg</td>
<td>90.75 (48.49) / 43.91 (30.59)</td>
</tr>
<tr>
<td>Median dosing ratio (range), mg</td>
<td>100 (25-300) / 40 (10-240)</td>
</tr>
<tr>
<td>Spironolactone alone</td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>118 (22.96)</td>
</tr>
<tr>
<td>Mean (SD) dose/day, mg</td>
<td>85.27 (50.49)</td>
</tr>
<tr>
<td>Median dose/day, mg</td>
<td>100 (12.5-300)</td>
</tr>
<tr>
<td><strong>Non-recommended/cautioned therapies (n=892)</strong></td>
<td></td>
</tr>
<tr>
<td>NSAIDS*</td>
<td>65 (7.29)</td>
</tr>
<tr>
<td>Beta-blockers**</td>
<td>230 (25.78)</td>
</tr>
<tr>
<td>ACEI***</td>
<td>26 (2.91)</td>
</tr>
<tr>
<td>ARB*****</td>
<td>18 (2.02)</td>
</tr>
<tr>
<td><strong>Preventive for SBP (n=892)</strong></td>
<td></td>
</tr>
<tr>
<td>PPI*****</td>
<td>234 (26.23%)</td>
</tr>
</tbody>
</table>

* includes aspirin, ibuprofen, naproxen, diclofenac, etodolac, meloxicam;
** includes propranolol, nadolol, carvedilol, labetalol, atenolol, bisoprolol-hydrochlorothiazide, metoprolol succinate-hydrochlorothiazide, metoprolol succinate, metoprolol tartrate;
*** includes benazepril, enalapril maleate, lisinopril, lisinopril-hydrochlorothiazide, quinapril, quinapril-hydrochlorothiazide, ramipril;
**** includes valsartan, azilsartan, medoxomil-chlorthalidone, irbesartan, olmesartan, olmesartan-hydrochlorothiazide;
***** includes omeprazole, esomeprazole, dexlansoprazole, lansoprazole, rabeprazole, pantoprazole
Medication data was available for 606 (91.12%) patients with HE. Of these, 302 (49.83%) received recommended therapy of lactulose alone or in combination with rifaximin within 30-days of index visit. A total of 199 (65.90%) received lactulose alone with a mean dose (SD) of 73.08 ml (46.48 ml). The remaining 103 (34.10%) received combination of lactulose and rifaximin within 30-days of index visit. A total of 173 (28.55%) patients received non-recommended medications such as HYP, BZ, AD, OP. Table 18 describes the prescription pattern for HE.
### Table 18. Medication prescription patterns for patients with HE

<table>
<thead>
<tr>
<th>Medication</th>
<th>Metric</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prescribed therapies (n=302)</strong></td>
<td></td>
</tr>
<tr>
<td>Lactulose</td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>199 (65.90)</td>
</tr>
<tr>
<td>Mean (SD) dose, mL</td>
<td>73.08 (46.48)</td>
</tr>
<tr>
<td>Median (range) dose, mL</td>
<td>60 (10-240)</td>
</tr>
<tr>
<td>Lactulose/rifaximin</td>
<td>103 (34.10)</td>
</tr>
<tr>
<td><strong>Non-recommended/cautioned therapies (n=606)</strong></td>
<td></td>
</tr>
<tr>
<td>Opioids*</td>
<td>124 (20.46)</td>
</tr>
<tr>
<td>Hypnotics**</td>
<td>12 (1.98)</td>
</tr>
<tr>
<td>Benzodiazepines***</td>
<td>45 (7.43)</td>
</tr>
<tr>
<td>Antidepressants ****</td>
<td>32 (5.28)</td>
</tr>
</tbody>
</table>

* includes morphine, codeine, tramadol, hydrocodone, oxycodone, oxymorphone, hydromorphone, fentanyl, methadone;
** includes zolpidem;
*** includes diazepam, lorazepam, temazepam, elonazepam, alprazolam;
**** includes trazodone, amitriptyline, doxepin, nortriptiline, mirtazapine
Concordance with clinical care guidelines – spontaneous bacterial peritonitis

Medication data was available for 105 (70.94%) patients with SBP. Of these, 57 (54.29%) received recommended secondary antibiotic prophylaxis of ciprofloxacin, sulfamethoxazole/trimethoprim, moxifloxacin, norfloxacin or combination of ciprofloxacin and sulfamethoxazole/trimethoprim within 30-days of index hospitalization. A total of 33 (57.89%) patients received some dosage of ciprofloxacin, while 20 (35.08%) received dose combinations of sulfamethoxazole/trimethoprim. **Table 19** describes the prescription pattern for ascites.
### Table 19. Medication prescription patterns for patients with SBP

<table>
<thead>
<tr>
<th>Medication</th>
<th>Metric</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prescribed therapies (n=57)</strong></td>
<td></td>
</tr>
<tr>
<td>Norfloxacin 400 mg daily</td>
<td>1 (1.75)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td>500 mg weekly</td>
<td>1 (1.75)</td>
</tr>
<tr>
<td>500 mg daily</td>
<td>6 (10.52)</td>
</tr>
<tr>
<td>750 mg weekly</td>
<td>19 (33.33)</td>
</tr>
<tr>
<td>750 mg three times weekly</td>
<td>1 (1.75)</td>
</tr>
<tr>
<td>1000 mg daily</td>
<td>4 (7.01)</td>
</tr>
<tr>
<td>1500 mg daily</td>
<td>2 (3.50)</td>
</tr>
<tr>
<td>Moxifloxacin 400 mg daily</td>
<td>1 (1.75)</td>
</tr>
<tr>
<td>Sulfamethoxazole/trimethoprim</td>
<td></td>
</tr>
<tr>
<td>400/80 mg daily</td>
<td>3 (5.26)</td>
</tr>
<tr>
<td>400/80 mg three times weekly</td>
<td>7 (12.28)</td>
</tr>
<tr>
<td>800/160 mg daily</td>
<td>10 (17.54)</td>
</tr>
<tr>
<td>Ciprofloxacin and sulfamethoxazole/trimethoprim</td>
<td></td>
</tr>
<tr>
<td>750 mg weekly + 800/160 mg daily</td>
<td>1 (1.75)</td>
</tr>
<tr>
<td>750 mg weekly + 400/80 mg three times weekly</td>
<td>1 (1.75)</td>
</tr>
</tbody>
</table>
Concordance with clinical quality care parameters

Varied concordance rates were observed across each investigator-assigned quality care parameter (Table 20). Concordance ranged from 49.83% for indicator 8 (recommended HE therapy) to 99.32% for indicator 1 (MELD for SBP). MELD/MELDNa scores were available for almost all SBP patients at index (MELD: 99.32%; MELDNa: 97.97%), followed by ascites (MELD: 89.45%; MELDNa: 81.64%) and HE (MELD: 88.87%; MELDNa: 80.90%). Concordance with recommended therapy was highest for patients with ascites (57.62%), followed by SBP (54.29%) and finally lowest for HE (49.83%). Non-recommended medications were not prescribed to 71.45% and 68.16% of HE and ascites patients, respectively. PPI was not prescribed to 73.77% of the eligible patients with ascites.
Table 20. Concordance with quality indicators

<table>
<thead>
<tr>
<th>Number</th>
<th>Indicator (Eligible n)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MELD score available at complication index date</td>
<td>882 (89.45)</td>
</tr>
<tr>
<td></td>
<td>Ascites (n=986)</td>
<td>147 (99.32)</td>
</tr>
<tr>
<td></td>
<td>SBP (n=148)</td>
<td>591 (88.87)</td>
</tr>
<tr>
<td>2</td>
<td>MELDNa score available at complication index date</td>
<td>805 (81.64)</td>
</tr>
<tr>
<td></td>
<td>Ascites (n=986)</td>
<td>145 (97.97)</td>
</tr>
<tr>
<td></td>
<td>SBP (n=148)</td>
<td>538 (80.90)</td>
</tr>
<tr>
<td>3</td>
<td>Weight recorded at each visit for cirrhosis (n=4,116)</td>
<td>3,280 (79.69)</td>
</tr>
<tr>
<td>4</td>
<td>Seen by gastroenterologist at least once for all follow-up visit post index cirrhosis visit (n=3,444)</td>
<td>2,870 (83.33)</td>
</tr>
<tr>
<td>5</td>
<td>Primary prophylaxis for SBP used in qualified patients (n=33)</td>
<td>20 (60.61)</td>
</tr>
<tr>
<td>6</td>
<td>Diuretic therapy within 30-days post-ascites diagnosis (n=892)</td>
<td>514 (57.62)</td>
</tr>
<tr>
<td>7</td>
<td>Secondary antibiotic prophylaxis within 30-days post-SBP hospital discharge (n=105)</td>
<td>57 (54.29)</td>
</tr>
<tr>
<td>8</td>
<td>Treatment within 30-days post-HE diagnosis (n=606)</td>
<td>302 (49.83)</td>
</tr>
<tr>
<td>9</td>
<td>Not on any contraindicated/non-recommended therapies</td>
<td>608 (68.16)</td>
</tr>
<tr>
<td></td>
<td>Ascites (n=892)</td>
<td>433 (71.45)</td>
</tr>
<tr>
<td></td>
<td>HE (n=606)</td>
<td>658 (73.77)</td>
</tr>
</tbody>
</table>

HE = hepatic encephalopathy; MELD = Model for End-Stage Liver Disease; MELDNa = Model for End-Stage Liver Disease with Sodium; SBP = spontaneous bacterial peritonitis
Patient- and physician-related factors influencing concordance – recommended diuretics
within 30-days of ascites index date

The results of standard multivariable logistic regression are shown in Table 21, with a total of 712 patients included in the logistic regression model. No issues of multicollinearity were identified, with all variance inflation factors < 5. Overweight patients had significantly lower odds (OR: 0.559; 95% CI: 0.375-0.833) of receiving recommended diuretic therapy as compared to patients who were underweight or had normal BMI. Non-gastroenterologist or non-primary care physicians had significantly lower odds of prescribing the recommended diuretic therapy as compared to primary care physicians (OR: 0.283; 95% CI: 0.134-0.598). MELDNa categories were collapsed to ≤ 9, 10-19 and ≥ 20 owing to the sample size and distribution of scores.
Table 21. Predictors of recommended diuretics within 30-days of ascites index date

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference</th>
<th>B</th>
<th>SE</th>
<th>Wald Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td></td>
<td>0.8089</td>
<td>0.5303</td>
<td>2.3264</td>
<td>0.1272</td>
<td></td>
</tr>
<tr>
<td>Age at ascites index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-60</td>
<td></td>
<td>-0.3339</td>
<td>0.3775</td>
<td>0.7824</td>
<td>0.3764</td>
<td>0.716 (0.342 - 1.501)</td>
</tr>
<tr>
<td>≥ 61</td>
<td></td>
<td>-0.5996</td>
<td>0.3872</td>
<td>2.3984</td>
<td>0.1215</td>
<td>0.549 (0.257 - 1.173)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.00227</td>
<td>0.1620</td>
<td>0.0002</td>
<td>0.9888</td>
<td>1.002 (0.730 - 1.37)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td></td>
<td>-0.1509</td>
<td>0.3056</td>
<td>0.2439</td>
<td>0.6214</td>
<td>0.860 (0.472 - 1.565)</td>
</tr>
<tr>
<td>BMI at ascites index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight/Obese</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight/Normal</td>
<td></td>
<td>-0.5813</td>
<td>0.2036</td>
<td>8.1509</td>
<td>0.0043*</td>
<td>0.559 (0.375 - 0.833)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.0997</td>
<td>0.1994</td>
<td>0.2501</td>
<td>0.6170</td>
<td></td>
</tr>
<tr>
<td>MELDNa at ascites index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 9</td>
<td></td>
<td>0.0769</td>
<td>0.2605</td>
<td>0.0871</td>
<td>0.7679</td>
<td>1.080 (0.548 - 1.800)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.1055</td>
<td>0.2836</td>
<td>0.1383</td>
<td>0.7099</td>
<td>0.900 (0.516 - 1.569)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.00692</td>
<td>0.2034</td>
<td>0.0012</td>
<td>0.9729</td>
<td>0.993 (0.667 - 1.480)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1.2625</td>
<td>0.3817</td>
<td>10.9399</td>
<td>0.0009*</td>
<td>0.283 (0.134 - 0.598)</td>
</tr>
<tr>
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<tr>
<td>No. of comorbidities</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>1</td>
<td></td>
<td>-0.0665</td>
<td>0.1930</td>
<td>0.1188</td>
<td>0.7303</td>
<td>0.936 (0.641 - 1.366)</td>
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<td></td>
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<td>-0.0611</td>
<td>0.3356</td>
<td>0.0331</td>
<td>0.8556</td>
<td>0.941 (0.487 - 1.816)</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td>Type of cirrhosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Alcoholic</td>
<td></td>
<td>0.3193</td>
<td>0.2498</td>
<td>1.6337</td>
<td>0.2012</td>
<td>1.376 (0.843 - 2.246)</td>
</tr>
<tr>
<td>Undetermined</td>
<td></td>
<td>0.2940</td>
<td>0.2824</td>
<td>1.0838</td>
<td>0.2979</td>
<td>1.342 (0.771 - 2.334)</td>
</tr>
</tbody>
</table>

Logistic regression modelled for predictors of concordance with ascites therapy 30-day post index (n = 712)
Global null hypothesis for model, Likelihood Ratio test X^2 = 28.9577; Pr > ChiSq = 0.0106
B = parameter estimate, BMI = body mass index; CI = confidence interval; MELDNa = Model for End-Stage Liver Disease with Sodium; OR = odds ratio; PCP = primary care physician; SE = standard error
* Race Other = African-Americans + Others
Number of comorbidities were calculated based on the presence of conditions specified by CirCom
Patient- and physician-related factors influencing concordance – recommended HE therapy within 30-days of HE index

The results of standard multivariable logistic regression are shown in Table 22. A total of 472 patients were analyzed by the model. No issues of multicollinearity were identified, with all variance inflation factors < 5. The model indicated that obese patients had significantly lower odds (OR: 0.431; 95% CI: 0.261-0.714) of receiving recommended HE therapy as compared to patients with underweight or normal BMI. Non-gastroenterologist or non-primary care physicians had significantly lower odds of prescribing the recommended HE therapy as compared to primary care physicians (OR: 0.266; 95% CI: 0.087-0.813). MELDNa categories were collapsed to ≤ 9, 10-19 and ≥ 20 owing to the sample size and distribution of scores.
Table 22. Predictors of recommended therapy within 30-days of HE index date

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference</th>
<th>B</th>
<th>SE</th>
<th>Wald Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td></td>
<td>0.0317</td>
<td>0.6476</td>
<td>0.0024</td>
<td>0.9610</td>
<td></td>
</tr>
<tr>
<td>Age at HE index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41-60</td>
<td></td>
<td>0.5491</td>
<td>0.6190</td>
<td>1.4479</td>
<td>0.2289</td>
<td>1.732 (0.708 - 4.236)</td>
</tr>
<tr>
<td>≥ 61</td>
<td></td>
<td>0.4564</td>
<td>0.4631</td>
<td>1.7862</td>
<td>0.1814</td>
<td>1.857 (0.749 - 4.603)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.1412</td>
<td>0.1973</td>
<td>0.5121</td>
<td>0.4742</td>
<td>1.152 (0.782 - 1.695)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>0.1973</td>
<td>0.1412</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td></td>
<td>-0.3357</td>
<td>0.4167</td>
<td>0.6489</td>
<td>0.4205</td>
<td>0.715 (0.316 - 1.618)</td>
</tr>
<tr>
<td>Caucasian</td>
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<td>0.3357</td>
<td>0.4167</td>
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</tr>
<tr>
<td>Gender</td>
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<tr>
<td>Male</td>
<td></td>
<td>-0.1761</td>
<td>0.2603</td>
<td>0.4578</td>
<td>0.4987</td>
<td>0.839 (0.503 - 1.397)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>-0.8406</td>
<td>0.2571</td>
<td>10.6923</td>
<td>0.0011 *</td>
<td>0.431 (0.261 - 0.714)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td></td>
<td>-0.1804</td>
<td>0.2603</td>
<td>0.4578</td>
<td>0.4987</td>
<td>0.839 (0.503 - 1.397)</td>
</tr>
<tr>
<td>Caucasian</td>
<td></td>
<td>-0.3371</td>
<td>0.2571</td>
<td>10.6923</td>
<td>0.0011 *</td>
<td>0.431 (0.261 - 0.714)</td>
</tr>
<tr>
<td>BMI at HE index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight/Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td></td>
<td>-0.1761</td>
<td>0.2603</td>
<td>0.4578</td>
<td>0.4987</td>
<td>0.839 (0.503 - 1.397)</td>
</tr>
<tr>
<td>Underweight/Normal</td>
<td></td>
<td>-0.8406</td>
<td>0.2571</td>
<td>10.6923</td>
<td>0.0011 *</td>
<td>0.431 (0.261 - 0.714)</td>
</tr>
<tr>
<td>MELDNa at HE index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-19</td>
<td></td>
<td>-0.1804</td>
<td>0.3173</td>
<td>0.3232</td>
<td>0.5697</td>
<td>0.835 (0.448 - 1.555)</td>
</tr>
<tr>
<td>≥ 20</td>
<td></td>
<td>-0.3371</td>
<td>0.3502</td>
<td>0.9265</td>
<td>0.3358</td>
<td>0.714 (0.359 - 1.418)</td>
</tr>
<tr>
<td>No. of comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>-0.1906</td>
<td>0.2323</td>
<td>0.6727</td>
<td>0.4121</td>
<td>0.826 (0.524 - 1.303)</td>
</tr>
<tr>
<td>&gt; 2</td>
<td></td>
<td>-0.2082</td>
<td>0.3716</td>
<td>0.3139</td>
<td>0.5753</td>
<td>0.812 (0.392 - 1.682)</td>
</tr>
<tr>
<td>Type of cirrhosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-alcoholic</td>
<td></td>
<td>0.4395</td>
<td>0.3290</td>
<td>1.7845</td>
<td>0.1816</td>
<td>1.552 (0.814 - 2.957)</td>
</tr>
<tr>
<td>Undetermined</td>
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<td>-0.1279</td>
<td>0.3746</td>
<td>0.1166</td>
<td>0.7327</td>
<td>0.880 (0.422 - 1.834)</td>
</tr>
</tbody>
</table>

Logistic regression modelled for predictors of concordance with HE therapy 30-day post index (n = 472)
Global null hypothesis for model, Likelihood Ratio test $X^2 = 27.4656; Pr > ChiSq = 0.0167$
B = parameter estimate, BMI = body mass index; CI = confidence interval; HE = hepatic encephalopathy; MELDNa = Model for End-Stage Liver Disease with Sodium; OR = odds ratio; PCP = primary care physician, SE = standard error
Number of comorbidities were calculated based on the presence of conditions specified by CirCom
CHAPTER 5: DISCUSSION

This chapter includes discussion of the study results, limitations of the analysis, and finally, implications and opportunities for future research.

Liver cirrhosis and its complications are known to be associated with considerable mortality and morbidity,\(^3\) and the prevalence of cirrhosis remains underestimated.\(^{18}\) Though no cure exists, cirrhosis can be pharmacologically managed to delay the development of further complications. The AASLD guidelines provide evidence-based practice recommendations for diagnostic, therapeutic and preventive aspects of care for liver diseases. Derived from these guidelines, clinicians and researchers have established indicators to measure achievement of evidence-based delivery of quality care, such as those established by Kanwal et al\(^{37}\) A number of subsequent studies have assessed concordance with quality care indicators for ascites, HE and SBP as well as the impact of concordance on clinical outcomes.\(^{39,40,42-46,48}\) Patient- and/or physician-related factors predicting concordance with quality indicators were assessed in only one study, which focused on ascites only.\(^{44}\) Thus, this study was conducted to assess concordance with quality care using selected AASLD recommendations, quality indicators by Kanwal et al\(^{37}\) and investigator developed quality indicators for ascites, HE and SBP and assess patient- and physician-related factors predicting concordance with quality care. The primary goal was to assess the concordance with established evidence-based quality care parameters and/or guidelines and to further assess patient- and physician- factors that influence concordance. Additionally, the study also described other preliminary analyses to give a more complete picture of the care of patients with cirrhosis. The first research question was to describe the sample characteristics that might potentially affect concordance with and receipt of quality care, eventually influencing generalizability of
the results. Describing the demographic and clinical factors provided a survey of the patient sample being analyzed and the potential applicability to other populations. The second research question was to assess the change in disease severity via MELDNa across development of different complications. Understanding the progression of cirrhosis with clinical complications may provide a better idea of how to effectively manage patients. The third research question focused on measuring office-based, inpatient, hospital observation and emergency utilization for each complication. Receipt of poor quality of care can lead to higher healthcare utilization and an overall increased burden on the patient. Healthcare utilization patterns are thus an outcome of quality of care. This study however did not assess utilization patterns as an outcome or predictor of quality care, but rather to understand the burden of utilization for these complications. Finally, the final research questions focus specifically on quality of care achievement and patient- and physician-related predictors.

The first objective of this study was to describe the overall sample based on the patient demographic and clinical characteristics. Surprisingly, in this study 80% of the sample had a diagnosis of non-alcoholic cirrhosis (cirrhosis without the mention of alcohol), whereas only 10% of the sample was diagnosed with alcoholic cirrhosis. Chronic alcoholism is the leading cause of cirrhosis in the US and higher prevalence of alcoholic cirrhosis would be expected in this sample. The National Institute of Alcohol Abuse and Alcoholism reports that of all cirrhosis deaths (for 2013), 47.9% were attributable to alcohol. The Allegheny County Health Survey reports 35% of the surveyed Allegheny County adults (≥ 18 years) self-reported binge drinking (defined as 5 or more drinks for males and 4 or more drinks for females in the past 30-days) for the year 2015-2016, a statistic which fairly remains unchanged when compared to year 2002 (34%) and years 2009-2010 (33%). Similarly, the Substance Abuse and Mental Health Services Administration report on National Survey on Drug Use and Health revealed that 25.6% of the surveyed adults (≥ 12 years) in the
Pittsburgh Metropolitan Statistical Area self-reported binge drinking, as compared to the national statistic of 23.2% (2005-2010). Though binge drinking does not necessarily indicate alcoholism and further development of alcoholic cirrhosis, based on these statistics it would be safe to assume that our sample had significantly low number of alcoholic cirrhosis patients than expected. Ten percent of the patients were classified as having ‘Undetermined cirrhosis’ (ICD-9-CM diagnosis for both alcoholic and non-alcoholic cirrhosis). Alcoholic cirrhosis and non-alcoholic cirrhosis are two distinct exclusive classifications for identifying the type of cirrhosis. It is surprising that 10% of the sample had a primary/secondary diagnosis for both. This finding highlights the need for careful use of diagnosis codes to classify patients based on underlying etiology as it may influence the nature of management of such misclassified patients.

The estimates of age (mean age of 58.33 years), predominance of male gender (55.68%), high BMI (30.5) and high prevalence of comorbid diabetes (16.81%) found in our study, though not similar to the US national estimates for cirrhosis provided by Scaglione et al using NHANES, were seen in a higher proportion for the mentioned characteristics. Scaglione et al indicated a higher prevalence in non-Hispanic African-Americans (29.3%) and Mexican-Americans (34.3%). Our study was composed with a majority Caucasian population (90.33%), which can be attributable to the demographics of the region of Pittsburgh (64.8% non-Hispanic white, 2010 Census Bureau) served by the UPMC network. Based on age distribution, male majority, number of patients with history of alcohol abuse and substance abuse other than alcohol, it can be hypothesized that patients classified with undetermined cirrhosis in this study might have alcoholic cirrhosis, but might have been misclassified as those with non-alcoholic cirrhosis. This can be speculated based on the similarity of the aforementioned patient characteristics. This study also utilized the CirCom score as an indicator of cirrhosis-specific comorbidity burden, as compared to the more generic Charlson
Comorbidity Index. Jepsen et al\textsuperscript{52} identified the comorbidities that impact survival in patients with liver cirrhosis. Using a comorbidity score specific to cirrhosis would help understand the burden in these patients much better than using a generic comorbidity index. Thus, the current study tried to replicate this score in the study population being assessed to understand their comorbidity burden. The original study developing the CirCom looked back 5 years from first cirrhosis diagnosis to identify comorbidities, whereas our study had a variable period before the index diagnosis as a result of EMR health system entry. Also, this study used ICD-9-CM codes as compared to ICD-10 codes that were used in the original study, and the definition of ‘active’ comorbidity as described in the present methods differed from that of the original study. Though there were methodological variations, the distribution of CirCom score observed was found to be similar to the original study.\textsuperscript{52} Approximately 76% of the present sample was classified with CirCom score 0 (indicating no comorbidities), and only 0.09% classified with CirCom score 5+1 (indicating high comorbidity burden). Current study found a similar distribution trend as observed in the original study; as the score increased from 0 to 5+1, the percentage of sample classified under each score decreased with increasing severity. Based on the methodology used for the CirCom distribution it can be said that this sample had a relatively low comorbidity burden, however an unequal time inclusion period for comorbidities for each patient may have introduced some variation into the distribution, namely a lower rate of comorbidity than the actual prevalence.

The MELD/MELDNa score is an indicator of disease severity and is used to prioritize patients for liver transplant. It is calculated based on the laboratory testing for serum creatinine, bilirubin, INR and sodium (for MELDNa only) which are not more than 48 hours old.\textsuperscript{17} In this study, a wider time frame was utilized, ranging from 3 months prior to 3 months post the cirrhosis/complication index date. This time frame was used to cast a wider net to capture the severity of the patient using the retrospective design, as well as potential delays in
laboratory tests in the outpatient setting. Though such a wide time frame was used, MELD/MELDNa score could not be calculated for all the patients, with 20.10% and 32.46% having data thereby making it difficult to calculate MELD and MELDNa respectively. This could be potentially explained by several factors: (i) non-entry of values in the EMR, (ii) lab test not ordered/performed, and (iii) the retrospective nature of study with no access to paper medical charts.

Non-entry of lab values in the EMR for either or all the tests makes it impossible to calculate the score as it is dependent on complete values. Though the records were identified based on primary and secondary diagnosis for cirrhosis, there might have been an error in ordering lab tests to calculate MELD/MELDNa. However, the error rate associated can be expected to be low as a primary care physician or specialist would order these tests based on clinical experience. Still, there is a chance that the necessary lab values were not ordered as a deficit in good clinical care. It should be noted that the use of MELDNa was approved in January 2016, and thus not all physicians would have specifically recommended a test for serum sodium as the study used EMR data from 2009-2014, leading to a MELDNa that could not be calculated. However, as serum sodium is part of a basic metabolic panel commonly ordered as a part of general clinical care, this cause would be less likely. Finally, records were identified retrospectively using EMR, there is a possibility that the lab values obtained were entered in paper medical charts for the patients but not in the EMR. The use of EMR within the UPMC network is standard, but the degree to which supplemental paper is used in individual offices is unknown.

The second study objective was to assess the change in disease severity via the MELDNa from index date of the cirrhosis to the index date of each complication. In cirrhosis, liver function is progressively affected due to disease pathophysiology. This affects the normal functioning leading to elevated levels of creatinine, bilirubin, sodium and delayed clotting
time, all of which are assessed with the MELDNa. A change in MELDNa score from cirrhosis to complication index date was assessed to understand the change in severity and extent of worsening of the disease over time. As a 3-month pre/post window from index date of cirrhosis and complication was used, only those complications with an index date any time 6 months after the cirrhosis index were used to measure the change. The analysis showed that there was a statistically significant increase in the severity from cirrhosis index to each of the complication. The significant increase in severity indicates that severity can increase even over a short period (6 months). As more complications develop, the increase in severity, suggests that patients with cirrhosis are at an increased risk of mortality, as a higher severity score corresponds with higher 3-month mortality and need for liver transplant. An increase in MELDNa score as complications develop was seen, helping to verify the use of this scoring system as a marker of disease severity.

The third study objective was to measure office-based, hospital observation, inpatient and emergency utilization for the complications. Patients who had at least 365 days of data available post-index and more than one visit were included and visits in a 1-year period from index of complication as well as visits irrespective of follow-up period post-index was measured. Office-based visits could be enumerated for ascites and HE only. Office visits for patients with SBP could not be enumerated as these patients are generally seen in an inpatient facility, as they are primarily diagnosed, managed and treated in such setting. For both patients with ascites and HE, there was no significant difference in office-based utilization between the three groups (alcoholic, non-alcoholic, undetermined) for both follow-up periods. Based on the results, the underlying diagnosis may not necessarily impact the severity of complication and eventually office-based utilization. Ascites patients had more number of visits as compared to HE patients. This may have been observed as patients with ascites might need paracentesis and more chronic care. However, mean office-based
utilization between patients with ascites and HE did not significantly vary when compared over 1-year as well as overall follow-up. Both the conditions require medical intervention due to their complexity. Based on the results, it can be said that the burden of office-based visits is not significantly different between patients with ascites and HE. Hospital observation and emergency visits was observed in <5% of both ascites and HE patients for both the follow-up period. Though, a small number of patients were analyzed, ascites patients had higher mean emergency visits as compared to HE patients. Ascites patients may experience dyspnea and abdominal pain due to the distension around the abdominal area and might require emergent care for these conditions. HE patients had slightly more hospital observations as compared to ascites. HE is episodic in nature and may require visits to the hospital so that the episodes are managed effectively. Similarly, inpatient visits did not significantly differ amongst the diagnosis groups in patients with ascites for both 1-year and overall follow-up period.

However, in patients with HE, a significant difference was observed on the Kruskal-Wallis test (median/mean-rank) but not the ANOVA (mean visits) when comparing visits in 1-year follow-up. Kruskal-Wallis test requires the distribution of dependent variable across independent groups to have a similar shape to compare medians. The underlying distribution of inpatient visits was not similar across the three groups; thus, it can be said that the mean rank visit score differed but not the median visits. When comparing inpatient visits in HE irrespective of follow-up, no significant difference was observed. For a 1-year follow-up, ascites patients had significantly more inpatient visits than HE patients. This can be expected as ascites patients may need inpatient services for the management of co-existing complications such as SBP. No significant difference was observed in inpatient visits when follow-up irrespective of time was considered. For SBP, 23.48% and 31.5% of patients had inpatient visits in 1-year and overall follow-up, respectively. Differences across diagnosis groups was not assessed due to the relatively small sample size and none to negligent office-
based, hospital observation and emergency visits were observed. In general, comorbidity burden may affect utilization patterns. However, 80% of our sample had low comorbidity based on the CirCom score and thus the observed utilization patterns might not have been influenced by the comorbid conditions.

The fourth and main objective of the study was to measure concordance with quality care parameters and to assess patient- and physician- factors that influence concordance with these quality care parameters. This question was divided into three parts: (i) concordance with prescribing recommended medications for ascites, HE and SBP; (ii) concordance with selected quality care parameters discussed in Table 6; and (iii) assessment of patient- and physician-related factors that influence concordance with prescription of recommended medications for ascites and HE. The timeline for assessing concordance to guideline varied based on the QI. For QI 1 and 2, the concordance was based on MELD and MELDNa score that could be reported at the complication index based on the 3-month pre/post inclusion criteria for the contributing test values. QI 3 which assessed reporting of weight, the concordance was based on the date of cirrhosis visit. QI 4 looked at follow-up visit with gastroenterologist, and visits following cirrhosis index were assessed. QI 5 to 9 which focused on prescriptions used a 30-day window from complication index as was used by Kanwal et al.

For ascites management, outpatient prescribing of a combination of spironolactone and furosemide or spironolactone alone is recommended as a first line therapy by AASLD, with a recommended starting dose of 100 mg and 40 mg daily of spironolactone and furosemide combination respectively, or 100 mg daily of spironolactone alone.27 The study results revealed that only 58% of patients received either of the recommended diuretic therapies within 30-days of outpatient visit. Of these patients 23% received spironolactone alone with a mean (SD) daily dose of 85.27 mg (50.49) and 77% received combination therapy with a
mean (SD) dosing ratio for spironolactone: furosemide of 90.75 (48.49) mg to 43.91 (30.59) mg. Forty-two percent of patients did not receive or have any record of receiving any of the assessed diuretic therapies within 30-days of outpatient visit.

The mean dose and mean dosing ratio for spironolactone and spironolactone: furosemide combination respectively deviated slightly from the recommended doses. This may be explained by the clinical judgment of the physician, who might have preferred a lower or higher dose than recommended to be prescribed based on patient clinical factors such as blood pressure, renal function or potassium abnormalities. It also may reflect a lower starting dose and lack of upward titration over time. Additionally, as patients were identified with ascites between 2009-2014 based on availability of the data, it is possible that the patients might have had ascites before 2009 which is not captured and physician would have prescribed (or adjusted) a lower or higher dose based on the prior knowledge of the response and need of the patient for the dose of therapy.

Overall, the concordance with prescribing outpatient diuretic medications was lower compared to earlier studies. Studies by Kanwal et al and Le et al assessing quality of care in VA (n=774) and tertiary care hospital (n=302) population showed that concordance with diuretic therapy was 82.8% and 86% respectively, broadly higher as compared to our study. In our study, it is possible that the patients may have received the recommended therapy more than 30-days after outpatient visit. In addition, it is possible that the prescription details were not recorded in the EMR. Lack of appropriate diuretic therapy can have severe clinical implications as they help in reducing the volume of ascitic fluid. Ascites itself is associated with 1- and 5-year mortality of 15% and 44%, respectively; and SBP is further associated with in-hospital 20% mortality. ARB, ACEI, NSAID and BB were prescribed to 2.02%, 2.91%, 7.29% and 25.78% of the patients with ascites in the study. These medications are to be used with caution in patients.
with ascites, utilizing clinical judgment and consideration of comorbid conditions which may warrant prescription. PH is a common cause leading to ascites and is managed by BB, thus about a quarter of patients might have had a prescription for managing their PH.\textsuperscript{58-60} NSAID, ARB, and ACEI interfere with renal perfusion and lead to reduce sodium excretion (due to NSAID) and development of rapid renal failure (NSAID, ARB, and ACEI).\textsuperscript{27} Poor kidney function will eventually lead to salt and water accumulation worsening the ascites and/or progress to HRS which is associated with median survival time of 2 weeks and 6 months for HRS type 1 and HRS type 2 respectively.\textsuperscript{61} This analysis is unable to state whether use of these medications was completely clinically appropriate.

The AASLD mentions that use of PPI is associated with increased risk in patients with cirrhosis and ascites. Though, there is no guideline around it, we assessed patients with ascites with a prescription for PPI. Of the eligible 892 patients, 234 (26.23\%) of the patients had a PPI prescription. Though AASLD specifies restricting the use of PPI (citing only one study) to only those conditions where needed, controversy exists around the association between PPI use and risk of SBP.\textsuperscript{27,62} Multiple studies using retrospective, prospective designs, systematic reviews and meta-analyses have shown conflicting results (positive as well as negative association) and there is no conclusive evidence or consensus confirming a causality to support a guideline on using caution while prescribing ascites patients with PPI to reduce SBP risk.\textsuperscript{62-81} Though our study found over a quarter patients with ascites having a prescription for PPI, it cannot be strongly said that deviation from quality care was observed, due to the conflicting evidence. PPI may have been prescribed to these patients for other existing conditions which were not analyzed as a part of this study.

Recommended therapies for HE were prescribed to 50\% of patients, which was similarly poor to prescribing for ascites. A total of 66\% of those receiving recommended therapy were prescribed lactulose; whereas the remaining 34\% were prescribed lactulose and rifaximin in
combination. Lactulose and lactulose with rifaximin as an add-on has been recommended by the AASLD guidelines for HE management based on meta-analysis and clinical trial data.\textsuperscript{31,82-86} HE is characterized by cognitive and motor dysfunctionality and considering that AASLD recommends the aforementioned medications, the observed poor concordance is of concern, particularly as the associated 1-year mortality rate is up to 64\%.\textsuperscript{3} It is to be noted that AASLD guidelines are mostly focused on management of OHE, and not CHE or MHE. The guidelines recommend CHE/MHE treatment on a case-by-case basis, using the same treatments as for OHE. We could not ascertain if the patient had OHE or CHE/MHE which might have contributed to the observed concordance, as patients with MHE/CHE might not have received the treatment. In addition, hypnotics, antidepressants, benzodiazepines and opioids were prescribed to 1.98\%, 5.28\%, 7.43\% and 20.46\% of the eligible patients for HE quality care parameter. Though not specifically mentioned in the AASLD guidelines, literature supports avoidance of these medications in HE as they can cause cognitive dysfunction or even worsen the condition and thus good clinical judgment would suggest that these medications should be prescribed with care.\textsuperscript{53}

Long-term outpatient antibiotics within 30-days of hospital discharge post-SBP is a recommended secondary prophylactic strategy by Kanwal \textit{et al}\textsuperscript{37} and AASLD (with no specific mention of 30-day window). Secondary prophylaxis was prescribed to 54\% of patients, which was overall less than optimal, but lies between HE (lower) and ascites (higher) concordance. Majority of patients (57.89\%) were prescribed varied doses of ciprofloxacin (with 57.57\% receiving a 750 mg/weekly dose); followed by varied doses of sulfamethoxazole/trimethoprim (35.08\%). Thevenot \textit{et al}\textsuperscript{46} in their study assessing prescribing for GI bleeding and SBP, found that 94.8\% of the practitioners prescribed secondary prophylaxis over life (defined as resolution of ascites or until transplantation), a significantly higher concordance as compared to our study. Le \textit{et al}\textsuperscript{45} assessing quality care
and its association with outcomes in hospitalized patients found 70% concordance rate for the patients eligible for secondary prophylaxis. Kanwal et al.\textsuperscript{44} in their study assessing quality of care for ascites in VA population found that of the 30 eligible patients only 30% received secondary prophylaxis. Overall, this study found less than desirable concordance to the quality care parameter, lower than studies by Thevenot \textit{et al.}\textsuperscript{46}, and Le \textit{et al.}\textsuperscript{45}, but comparatively better than Kanwal \textit{et al.}\textsuperscript{44} Recurrence rate of SBP is approximately 40-70% within the first year of successfully clearing an episode of SBP using antibiotic therapy.\textsuperscript{29} The less than desirable concordance observed is a cause of concern as patients surviving SBP hospitalization have an associated 1-year and 5-year mortality of approximately 70% and 80%.\textsuperscript{29}

When identifying patients eligible for this SBP indicator, up to ten ICD-9-CM codes including primary diagnoses for that hospitalization were used to identify SBP patients. There is a possibility that patients who did not present with SBP as a primary condition for hospitalization did not receive the recommended antibiotic prophylaxis. Due to retrospective nature of this study it is difficult to assess if the non-prescribing is attributable to SBP not being the primary condition for hospitalization. Irrespective of SBP being primary or non-primary reason for hospitalization it would be expected that patients receive outpatient antibiotic prophylaxis post discharge to avoid recurrence of the condition. In general, concordance with outpatient prescription was observed to be less than desirable which can eventually influence healthcare utilization patterns, clinical outcomes, and mortality. Though, association between concordance to medication and utilization patterns was not assessed, the observed concordance might affect utilization in a general sense.

MELD/MELDNa scores could be comparatively better calculated at complication index as compared to cirrhosis index. Amongst the three complications, MELD/MELDNa score at complication index was calculated for nearly all the patients with SBP. HE had the least
number of patients for whom the score could be calculated. A window of 3-month pre/post complication index was used to identify test values used to calculate MELD/MELDNa scores. Though such a broad window was used, the severity scores could only be calculated for ≤ 90% for the complication samples (except SBP). This is less than desirable as MELD/MELDNa are used as a severity measure to prioritize transplant patients. The absence of lab values used to calculate MELD/MELDNa at complication index can be explained by similar reasons discussed earlier for MELD/MELDNa scores at cirrhosis index. The observed concordance to MELD/MELDNa was significantly better than the prescription patterns. Higher concordance to MELD/MELDNa might have been observed as severity documentation gives an idea to the physician about the clinical condition/progression of a patient and is more information-gathering than interventional; whereas, the treatment modality used might vary based on the patient and the physician judgement. This study analyzed outpatient prescribing patterns, thus we might have observed lower rates of concordance as compared to MELD/MELDNa documentation (where a broad inclusion window was used for the score calculation).

Measures for weight and appointments with gastroenterology were included as measures of quality care based on good clinical practice, as opposed to specific guideline recommendations. Weight loss can be due to multiple reasons, and is common symptom of cirrhosis progression. In addition, weight gain (due to fluid accumulation) can be used as a surrogate measure for monitoring the status of ascites. Of all the cirrhosis-specific office-based outpatient visits, weight was recorded in 79.69% of total visits. Gastroenterologists are specialists in cirrhosis-related care and thus it is important that patients are seen by such specialists to receive best care for management of the condition. Eighty-three percent of patients with cirrhosis were seen by a gastroenterologist for at least one of the follow-up office-based outpatient visit recorded in the EMR. For the remaining 17% who did not have a
record of follow-up visit with gastroenterologist, reasons for no follow-up could not be assessed due to the nature of the study. Also, depending on the severity of the patient, the patient might have been referred to an inpatient setting, this again was not confirmed as a part of the analysis.

In patients with ascites with low ascitic fluid protein, along with impaired renal function or liver failure, AASLD\textsuperscript{27} and Kanwal \textit{et al}\textsuperscript{37} recommend long-term use of norfloxacin or trimethoprim/sulfamethoxazole as a primary prophylactic measure to reduce bacterial infection and mortality. In this study, 33 patients were identified as eligible for this therapy, of these only 22 (60.61\%) received it within 30-days of outpatient visit. Eligible patients were identified based on diagnosis of ascites at index and the necessary lab values. However, Child-Pugh score could not be included in the decision process as there was no information available in the EMR for grade of hepatic encephalopathy, which is necessary to calculate the score. This study found comparatively better rates of concordance with this quality parameter as compared to those by Kanwal \textit{et al}\textsuperscript{44} (22.2\%) and Ghaoui \textit{et al}\textsuperscript{40,42} (33.3\%) but lower than those by Thevenot \textit{et al}\textsuperscript{46} (72.3\%) and Le \textit{et al}\textsuperscript{45} Primary prophylaxis is recommended by AASLD as a measure to reduce risk of SBP and mortality.\textsuperscript{27}

Logistic regression models assessing factors associated with concordance with guidelines had limited predictability. BMI and physician type, for both ascites and HE model were the only variables that were associated with concordance with recommended therapy for ascites and HE. Among the different studies that assessed quality of care in ascites, HE and SBP, the study by Kanwal \textit{et al}\textsuperscript{44} was the only one which studied association of patient- and physician-factors associated with guideline/QI concordance. The study assessed factors associated with concordance with eight different quality indicators, whereas this study looked at association of these factors only with one quality parameter (i.e. receiving outpatient therapy for ascites and HE).
In our ascites model, overweight patients had significantly lower odds of receiving diuretic therapy. Though not statistically significant, obese patients also had lower odds of receiving diuretic therapy. The negative association of being overweight and concordance with diuretic therapy is a surprising association and is unknown why a higher BMI would impact diuretic prescription. Physicians categorized as ‘others’ had significantly lower odds to prescribe diuretic therapy as compared to primary care physicians. This would be expected as their knowledge pertaining to ascites care would be anticipated to be more limited than a primary care physician or gastroenterology specialist. Surprisingly, though not significantly associated, gastroenterologists were less likely to prescribe diuretic therapy as compared to primary care physicians.

The logistic model for HE showed that obese patients and physicians categorized as ‘others’ were significantly less likely to receive and prescribe lactulose or lactulose and rifaximin, respectively. The association between obesity and lower odds of receiving HE therapy may be attributable to lack of other factors that could not be included in the model due to availability in the EMR and small sample size. Similar to the ascites model, physicians categorized as ‘others’ had significantly lower odds to prescribe (adhere to) HE therapy as compared to primary care physicians. This would be expected as their knowledge pertaining to HE care would be anticipated to be more limited than a primary care physician or gastroenterology specialist. Though not significantly associated, gastroenterologists were less likely to prescribe HE treatment as compared to primary care physicians. In this scenario, it can also be said that this may be observed as gastroenterologists may have considered a different treatment modality as these patients may not necessarily have new-onset hepatic encephalopathy, or have MHE/CHE and thus have other care needs.
Limitations

Study limitations must be considered when interpreting the results. The study data was obtained from EMR of an academic-based network of hospitals serving southwestern Pennsylvania, thus the study results may not be generalizable to the entire US population. Second, analysis was conducted using EMR data which might have limited quality due to recorder bias, incomplete data, coding errors. Data quality due to missing data was accounted for by using complete case analysis, however it might bias some of the results. Third, limited sample size was obtained for ascites, HE and specifically for SBP. Thus, a multivariable logistic model could not be developed for SBP. Fourth, in general, both the logistic models for ascites and HE did not reveal much about potential associations between the predictors and outcome. This can be attributable to missing variables in the EMR that could have better explained the outcome. Fifth, ascites, HE and SBP can be managed both on an outpatient and inpatient basis and the study looked at quality of care on an outpatient basis only. Inpatient care might have been provided to these patients instead of outpatient care based on clinical need. This however could not be ascertained and confirmed due to limited access to inpatient data. Sixth, reasons for observed concordance to care could not be identified and reported due to lack of access to patient charts. Finally, this study used a cross-sectional assessment of quality of care and quality care over time could not be assessed which would have provided a better estimation.

Study implications

The study findings have various implications for provision of quality care in a clinical setting. Based on study results, there may be opportunities to improve clinical care for patients with cirrhosis and complications. First, the study described the demographics and clinical characteristics of the population served by the network of hospitals providing the EMR. The
study provides a snapshot of the patient demographic and clinical characteristics that are prevalent in this population. This study used the CirCom score to identify comorbidity burden in these patients. This scoring can help physicians understand the burden of comorbidities in the liver cirrhosis population they serve as well as use it as a tool for future patients. Second, the study found that there was less than desirable concordance with clinical care guidelines. EMR are rich sources of data that can be used for providing efficient and quality care. Use of EMR for assessing patient history and providing the necessary care is important to achieve better outcomes in patients. In our study, we observed that there was poor documentation of lab values used to calculate the MELDNa score which is an important indicator of disease severity and indicator of prioritizing liver transplantation. Though, these values may have been documented on medical charts, it is important that they be documented in the EMR for understanding the condition of the patient and accordingly provide necessary care. In general, documentation of patient data in EMR can provide deep insight into patient’s condition and be used to provide patient-centered care based on evidence or established quality parameters. Lastly, evidence-based guidelines/quality parameters are increasingly used to guide patient care. The study assessed concordance with some of these and found that they might not be implemented in real-world clinical practice. Study results can be used by physicians to assess current practice patterns and accordingly modify them to provide more evidence-based care and eventually achieve better patient outcomes. The study results highlight need for protocol driven treatment, opportunities for physician education, and promoting coordinated team-based care to ensure delivery of quality care. Such approaches can be used effectively to create a systematic health system that provides the necessary evidence-based care using a structured established process.
Future directions

Based on the study results, less than desirable concordance with quality care parameters was observed, which may lead to poor quality of care. This study also tried to assess patient- and physician- factors associated with concordance with quality care but revealed limited results. Further research can focus on assessing patient- and physician- factors that govern quality care which did not yield rich results in this study. Our study mainly focused on outpatient care due to limited access to inpatient records. Further studies can assess concordance with quality parameters in an inpatient and outpatient setting and identify factors associated with quality care. Our study did not assess concordance with quality care and impact on outcomes which can be assessed by future studies. Liver cirrhosis and the associated complications involve coordinated care due to the complex nature of the disease. Studies using a prospective design can be used to assess impact of coordinated care on concordance with quality care and eventually outcomes.

Conclusion

Chronic liver diseases are the 12th leading cause of mortality in the United States. Liver cirrhosis and the associated complications have no cure and are solely based on management strategies to slow the disease progression and improve survival. Our study looked at concordance with various quality care parameters and patient- and physician- factors associated with concordance with certain parameters. Overall, we conclude that concordance with quality care was less than desirable. Study results assessing patient- and physician- factors associated concordance revealed limited information. The study results highlight lack of concordance with quality parameters and hence thereof improving care standards to provide quality care.
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