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Missed diagnosis of cirrhosis in the inpatient setting

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Abstract

Cirrhosis accounts for a large amount of deaths in the United States (US) and worldwide leading to an increasing burden on the healthcare system. Cirrhosis is however a progressive disease with different potential complications related to liver dysfunction and portal hypertension. Often, patients may present with complications of cirrhosis without having been diagnosed previously. It is pertinent that clinicians recognize these signs to put patients on an appropriate course of management to help delay or avoid further disease progression while avoiding deleterious outcomes and unnecessary utilization. We will discuss the epidemiology of liver disease, cirrhosis, and its complications (hepatic encephalopathy, ascites, and varices). Following, we will discuss the rationale and impact of missing these diagnoses on the healthcare system and patient.

Keywords

Missed diagnosis; Cirrhosis; Healthcare costs; Inpatient; Hospitalization

Introduction

Cirrhosis accounts for at least 44,000 deaths in the United States and 2 million deaths worldwide each year, leading to an increase in healthcare utilization and burden.[1] In the US in 2014, cirrhosis accounted for over 1,000,000 outpatient and 325,000 ED visits (40% increase in ED visits since 2006).[1] Common etiologies include hepatitis B (HBV), hepatitis

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C (HCV), non-alcoholic fatty liver disease (NAFLD), and alcohol-related liver disease (ALD). There is a shift in cause as there is increasing vaccination and treatment for HBV and HCV, while we experience an obesity epidemic leading to metabolic syndrome and fatty liver disease and increasing rates of alcohol misuse.[1]

As cirrhosis progresses, patients develop complications related to liver dysfunction and portal hypertension. Approximately 4–12% of patients with cirrhosis develop a decompensation event annually with the most common being ascites, variceal hemorrhage, and hepatic encephalopathy (HE).[1] The personal and public health impact of cirrhosis is largely driven by the burden of decompensations. Cirrhosis related hospitalization has been increasing every year with increasing inpatient costs. The mean hospitalization cost in 2016 for cirrhosis was >$20,000 for 1 or more cirrhosis related complications.[2] Annual inpatient costs for cirrhosis increased from $4.8 billion in 2001 to $14.9 billion in 2016.[1, 2, 3] Readmissions are very common, as high as 24.2% within 30 days and 35.9% within 90 days. Presence of hepatic encephalopathy was strongly associated with readmission.[4] (Table 1)

Hospital Medicine and the inpatient setting is a place where many patients with decompensated cirrhosis present. Often the diagnosis of cirrhosis or its complications have not yet been made. Accordingly, the astute clinician needs the skills and knowledge required to make timely diagnoses that can improve the outcomes of patients with cirrhosis. It is imperative that in these situations the hospitalists and hepatologist/GI physicians take ownership over these patients and put them on an appropriate course of management to help delay or avoid further disease progression and mitigate against deleterious outcomes and unnecessary utilization. Below we will describe the rationale and impact of missed diagnosis of liver disease, cirrhosis, and its complications.

Methods

We conducted a review of literature regarding cirrhosis and complications of cirrhosis. Literature searching included key terms: cirrhosis, epidemiology, etiology, healthcare cost, alcohol use disorder, hepatic encephalopathy, ascites, and varices. Electronic database searches of PubMed of English-language articles published between 2001 and 2022. We also reviewed current guidelines from relevant societies and references of included articles.

We selected articles for review based on information derived from the title, abstract, and keywords. If the title, abstract, and keywords did not yield enough information, we then reviewed the full paper. We evaluated for measurements or values that would quantify the impact of cirrhosis and related disorders on the healthcare system.

Diagnostic clues suggesting cirrhosis

When compensated, medical history and physical examination by themselves are often insufficient to detect cirrhosis.[5, 6] Stereotypical findings such as jaundice, ascites, and encephalopathy are absent, as are substantial changes in the albumin, bilirubin, and INR levels.[6] However, there are numerous clues that can be extracted from the history, laboratory values, and imaging. First, the probability of cirrhosis is elevated amongst patients with risk factors such as a known history of viral hepatitis and alcohol-use disorder. (Table 2) At

this early stage, patients may not show signs or symptoms of cirrhosis. While no algorithm exists, it may be appropriate to link high risk patients to effective care.[7] Nonalcoholic fatty liver disease (NAFLD) is becoming an increasingly common underlying etiology of cirrhosis and accordingly patients with longstanding diabetes, obesity, and other components of the metabolic syndrome are at increased risk of cirrhosis.[1, 8]

Second, there are a variety of indirect serologic markers of cirrhosis. It is common to observe longitudinal changes in the ratio of aminotransferases. With the exception of severe alcohol use disorder, among persons with chronic liver disease, levels of alanine aminotransferase (ALT) exceed aspartate aminotransferase (AST) until cirrhosis develops, likely due to decreased AST clearance and decreased ALT production.[9–12] The most sensitive indicator of cirrhosis, however, is thrombocytopenia. The platelet level integrates multiple streams of information reflecting cirrhosis physiology including diminished liver function and thus thrombopoietin production, portal hypertension (splenic sequestration), and platelet destruction.[6] A platelet count <100 is a strong indicator of cirrhosis among people with chronic liver disease. A simplified index called the Fibrosis-4 (FIB-4) includes the AST and ALT ratio, platelet count and age. It yields a continuous value that is trichomotized into low, indeterminate, and high risk. While cutoffs are optimized for specific etiologies, generally values <1.3 are suggestive of low risk and those >3.25 are high risk.[13] Depending on the specific etiology and risk stratification, sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio can range from 33–91%, 71–98%, 2.1–18.3, and 0.12–0.76, respectively.[13] False negatives are possible and false positives are common, particularly hematologic causes of thrombocytopenia or increased AST levels from alcohol abuse or extrahepatic sources (e.g. muscle injury) are mistakenly attributed to cirrhosis.

Third, it is possible to suspect cirrhosis with standard imaging tests. Ultrasounds often report on liver nodularity. However, this sign is inadequate for diagnosis with a sensitivity and specificity for cirrhosis of 12.5%−87.5% and 78–95%.[14] Positive likelihood ratio was 11.6 and negative likelihood ratio was 0.68.[15] Sensitivity can be enhanced when markers of portal hypertension are detected (e.g. splenomegaly, recanalized umbilical vein or varices, and subclinical ascites). While cross-sectional imaging increases sensitivity for ascites and varices, the sensitivity for cirrhosis overall is not much higher than ultrasound and it also suffers for lack of inter-rater reliability.[16] Ultrasound and cross-sectional imaging may be used as initial imaging to evaluate the liver while inpatient before the patient follows up outpatient with more dedicated imaging.

Finally, while elastography is not performed in the hospital for the purpose of diagnosing cirrhosis, liver elastography provides more accurate assessments of advanced fibrosis than imaging tests and if previously performed is important to understand for interpretation. There are two key methods: Vibration Controlled Transient Elastography (VCTE, Fibrosis) and MR-Elastography (MRE) (Figure 1). These techniques assess liver stiffness by passing mechanical/vibratory shear waves through the liver and measuring wave speed which has been correlated with liver fibrosis. In general, elastography offers excellent negative likelihood ratios (0.07–0.30) for advanced fibrosis but much lower positive likelihood ratios (4.1–14.4).[13] Other variables such as passive congestion (heart failure) and severe inflammation (high ALT) can raise liver stiffness.[17] In general, values from VCTE of ≥15.0

kilopascals and MRE of ≥5.0 kilopascals are suggestive of cirrhosis.[13, 18] The validity of MRE cutoffs is more uncertain. VCTE values of >25 kilopascals suggest a higher risk of portal hypertension.

Early diagnosis of alcohol-related liver disease (ALD)

Epidemiology—In 2018, 130,000 patients presented to the ED with ALD as their principal diagnosis, 614,000 as a secondary problem, and a rate of 40/100,000 persons.[3] Of these, 75% of patients were admitted as their principal problem, and 90% as secondary problem, and a rate of 32.9/100,000 persons.[3] The median LOS in 2014 was 4 days and median cost $8552.[19] Alcohol is estimated to account for approximately 20–36% of cirrhosis cases.[1]

Early detection—Patients can have subtle but detectable clues that may suggest an alcohol use disorder. In the outpatient setting, patients can be screened with an AUDIT (Alcohol Use Disorders Identification Test) to identify unhealthy alcohol use and risky/hazardous behavior. Similarly, patients when hospitalized may show signs of alcoholic liver disease without symptoms. AST and ALT may be elevated and typically in a 2:1 ratio.

Linkage to care—When patients are hospitalized whether alcoholic liver disease is the primary problem, it is an opportunity to optimize patient care. Many patients with alcohol use disorder may have compensated cirrhosis. Hospitalizations for other alcohol-related harms – intoxication, trauma, etc. – often precede the incidence of decompensation.[20] Patients can be started on therapy (naltrexone, gabapentin, or baclofen) to assist with alcohol cravings.[21] Patients can also be connected to social work and community resources. SBIRT (screening, brief intervention, referral, and treatment) has shown a reduction in alcohol use, negative consequences, and ED repeat visits in the ED setting.[22]

Early diagnosis of hepatic encephalopathy

Epidemiology—Among cirrhosis complications, the most morbid is hepatic encephalopathy (HE). It is a spectrum of neurocognitive deficits ranging from limitations in executive function (attention, coordination, and processing speed) to coma. It is unique for lacking a diagnostic test and is therefore often missed. In 2018, HE accounted for 55,000 ED visits as the principal diagnosis and 197,000 as secondary problems with a rate of 17/100,000 persons.[3] Of these, nearly 90% of patients were admitted with a principal diagnosis and over 95% of patients had HE as a secondary diagnosis with a rate of 15.3/100,000. The median length of stay (LOS) in 2014 was 4 days with a median cost of $6354.[19] HE is associated with a median survival of 0.95 and 2.5 years for those ≥ 65 or < 65 years old.[23] Given the high mortality risk, hepatic encephalopathy should not be missed and further evaluated.

HE triggers—Identifying and treating HE appropriately may reduce readmission. HE is best viewed as a marker of serious underlying triggers. These include infection, gastrointestinal hemorrhage, dehydration, and hypokalemia. Accordingly, the presentation of HE demands a careful history and examination as well as a thorough evaluation for infection including diagnostic paracentesis, basic laboratory testing, urine and blood culture

testing. Hospitalization is often the result of inadequate therapy.[24] Lactulose is first-line therapy, however lactulose is frequently not prescribed at discharge even for hospitalizations due to HE, a key quality gap.[25] Rifaximin is indicated for patients with HE on lactulose. Rifaximin use reduces readmissions substantially.[23] Efforts to increase rifaximin use using electronic decision supports have been associated with reduced readmissions at hospitals in Massachusetts and Michigan.[26, 27]

The disutility of ammonia testing—HE is a clinical diagnosis. It should be suspected when patients present with apathy, disorientation, changes in behavior, and falls. Patients with HE are often tested for ammonia levels. In a study from 2007 to 2015 in patients with noncirrhotic chronic liver disease and cirrhosis, there was an increase in ammonia testing doubling from 2013 to 2015, attributed to the transition to electronic health records in 2013 and increased ease of ordering despite guidelines not recommending routine testing.[28] A study looking at 8 hospitals over 5 years from 2015 to 2019 looked at their ammonia test ordering pattern, resulting in a cost that ranges, depending on the test price, from $342,170 up to $2.3 million over that 5 year period.[29]

AASLD guidelines do not recommend routine ammonia level testing in HE.[30] It is possible to have HE with normal serum ammonia levels and thus an ammonia level should not be used to diagnose or exclude HE. Although a normal value is felt to warrant reevaluation for other etiologies of encephalopathy (particularly when the patient is comatose), there is no known diagnostic cutoff.[30] Ammonia levels can be low when patients present with infections as the triggering event – more than 40% of patients with HE and low ammonia levels have infections as a trigger.[31] Ammonia levels may also remain elevated after resolution of HE.[28] In a single center study in 2020 evaluating ammonia ordering in the emergency department, 50 ammonia orders were evaluated and 26% were ordered prior to seeing the patient. Clinicians were interviewed on their pre-test probability and if it would affect their decision making. Among patients with a low probability of HE, ammonia testing led to overuse of lactulose and for those deemed to be high probability, it did not change decision making.[32]

Early diagnosis of ascites

Epidemiology—In 2018, 54,000 patients presented to the ED with ascites as their principal diagnosis, 431,000 as a secondary problem, and with a rate of 16/100,000 persons.[3] Of these, a quarter of patients were admitted as their principal problem, 90% as secondary problem, and a rate of 3.8/100,000 persons.[3] The median LOS in 2014 was 3 days and median cost $6073.[19]

Opportunities to improve care—When patients re-present for symptomatic ascites, it is an opportunity to evaluate for what could be improved. Readmission for symptomatic ascites may be improved depending on factors affecting readmission such as education regarding salt restriction, calling clinics during business hours, and availability and access to outpatient paracentesis services.[24]

Focus on spontaneous bacterial peritonitis (SBP)—SBP is a morbid and often fatal complication that is best diagnosed with a timely diagnostic paracentesis according to a total ascitic neutrophil count >250. AASLD guidelines recommend performing a diagnostic paracentesis on patients with ascites due to cirrhosis when emergently admitted to the hospital since up one third of patients with SBP are asymptomatic or lack signs of infection.[33] In light of this, diagnostic paracentesis may be delayed or deferred when done by housestaff in a residency center that requires supervision or if the procedure is referred to radiologists.[24, 34] Inoculating ascitic fluid directly into blood culture bottles increased the sensitivity of the culture to >90% in the diagnosis of SBP.[33] It is also important to collect the culture prior to the first administration of antibiotics. While 3rd generation cephalosporins are used frequently, the prevalence of multidrug resistant (MDR) organisms is increasing. At a liver unit in Spain, the prevalence of MDR bacteria doubled from < 10% between 1998 and 2000 to 23% between 2010 and 2011.[35] The prevalence across Europe, North America, and Asia was 11–45%.[35]

Alternative causes of ascites—The cause of ascites also requires thorough evaluation. Collecting ascitic fluid and sending it for analysis to calculate a serum-ascites albumin gradient (SAAG) and total protein may assist differentiating the cause of ascites. When the SAAG is ≥ 1.1 and total protein is low (< 2.5), the etiology is most likely cirrhosis and portal hypertension. When the SAAG is ≥ 1.1 and total protein is high (≥ 2.5), the etiology is usually cardiac.[36]

Early diagnosis of varices

Epidemiology—Esophageal varices (EV) and variceal hemorrhage is a significant morbid complication of cirrhosis and portal hypertension. Gastrointestinal (GI) hemorrhage account for a large amount of health care costs per year, particularly upper GI bleeding. In 2018, there were 431,000 ED visits with upper GI hemorrhage as a principal diagnosis, 1 million as a secondary problem, and a rate of 132/100,000 persons.[3] Of these, three quarters of patients were admitted for upper GI hemorrhage inclusive of variceal bleed, three quarters as a secondary problem, and a rate of 97.6/100,000 persons.[3] Looking specifically at esophageal varices, there has been a rise in hospitalizations for esophageal varices with and without bleeding. From 2001 to 2011, hospitalizations with a discharge diagnosis of EV with and without bleeding increased from 19,167 to 45,578.[37] There was a 221% increase in hospitalization with EV without hemorrhage and 7% increase in hospitalizations with hemorrhage. The overall in-hospital mortality rate was 3.4% for patients with EV without hemorrhage and 8.7% for patients with EV with hemorrhage.[37] With the increasing number of esophageal varices, there would be an increase in number of endoscopies to intervene on the varices. The average hospital cost for variceal bleed was $6612, and if there were complications or rebleeding, the cost increased to $23,207.[38]

Management—Prevention of variceal hemorrhage can reduce significant patient harms and healthcare costs. Patients with medium or large varices are recommended to start non-selective beta blockers (NSBB).[39] The preferred agent at this time is carvedilol, dosed once daily from 6.25–25mg.[40] NSBB are used for primary prophylaxis after finding varices but are increasingly started for patients with evidence of portal hypertension. NSSB is

also recommended after patients experience their first variceal hemorrhage as secondary prevention with esophageal variceal ligation.[39] As long as the patient's blood pressure can tolerate NSBB, it would be beneficial to patients. NSBB should be used with caution in patients with systolic blood pressures <100 to avoid renal injury and orthostasis. This level of risk vs. benefit assessment is required before initiating therapy with NSBB, due to downstream impact of cirrhosis complications from varices.

Conclusion

It behooves us as healthcare professionals to diagnose complicated liver disease appropriately early its course, manage compensated liver disease to prevent decompensated liver disease and the complications described above. The inpatient setting is an opportunity for healthcare professionals to put patients on a proper trajectory to meet the above goals and optimize their management. This is an optimal time to ensure patients are on therapy for HE on discharge, NSBB to prevent further variceal bleeds, set up with outpatient paracentesis clinics to prevent further readmissions, and address the root of alcohol use disorder. Patient education and compliance is paramount to facilitating goals. Equity and access to care is fundamentally important for these patients requiring interdisciplinary collaboration to utilize local resources.

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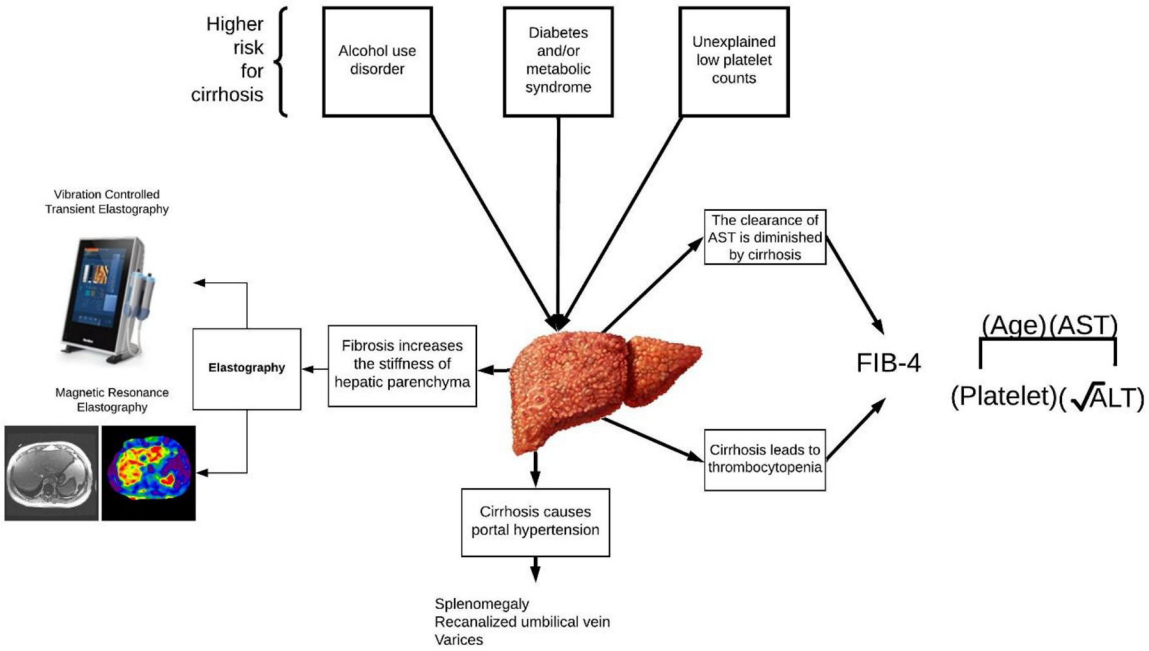

Figure 1.

Noninvasive assessment of cirrhosis

Three of the major ways that cirrhosis can be detected noninvasively are using radiological signs of portal hypertension, indirect serological signs, and liver elastography.

AST = Aspartate Aminotransferase, ALT = Alanine Aminotransferase

Table 1.

Emergency department visits and hospital admissions for complications of cirrhosis in 2018. Length of stay and cost of hospitalizations in 2014

	ED visits[1]			Admitted[1]				
	Principal problem	**Secondary problem**	**Rate per 100,000 persons**	**Principal problem**	**Secondary problem**	**Rate per 100,000 persons**	**Length of stay (median) in days[2]**	**Cost (median) in USD[2]**
Alcohol-related liver disease	130,154	613,948	40	104,920	548,940	32.9	4	8,552
Hepatic encephalopathy	54,589	196,699	17	48,765	189,945	15.3	4	6,354
Ascites	53,873	431,043	16	12,025	395,410	3.8	3	6,073
Varices	431,141	1,009,733	132	311,015	786,470	97.6	3	6612–23207[3]

1. Peery et al 2022

2. Peery et al 2019

3. Adam et al 2008

Table 2.

High Risk Population for Cirrhosis

High Risk Population	Common Presentations	Additional tools for case finding
Alcohol-use disorder	Intoxication and withdrawal, falls and other trauma, Pancreatitis, atrial fibrillation	AUDIT-C
Metabolic syndrome	Cardiovascular events, diabetic complications such as nephropathy and wounds	n/a
Viral hepatitis	n/a	Hepatitis C Antibody * Hepatitis B Surface Antigen **

(* CDC recommends one-time testing for all adults, **consider testing high risk groups such as persons with prior intravenous drug use, immigration from endemic area, men who have sex with men)