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Outcomes associated with *Clostridium difficile* infection in patients with chronic liver disease

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Summary

Patients with chronic liver disease (CLD) have frequent exposure to *Clostridium difficile* infection (CDI) risk factors but the incidence and etiology of CDI on this population is poorly understood.

The aim of this study was to assess the incidence, disease presentation, and outcomes of CDI in patients with underlying CLD. The Health Care and Utilization Project National Inpatient Sample (HCUP-NIS) 2009 dataset was used to identify patients with CLD who developed CDI along with matched non-CLD patients with CDI. Using the NIS dataset, the incidence rate of CDI was 189.4 / 10,000 discharges in CLD patients versus 83.7 / 10,000 discharges in the non-CLD matched cohort (p<0.001). Compared to non-CLD, comorbidity-matched controls with CDI, CLD patients with CDI had higher likelihood of in-hospital mortality (8.8% vs 18.6%, p < 0.001), increased length of stay by 1.19 days (p < 0.001) and increased total costs by $8,632 (p<0.001). In separate analyses using a tertiary case database of hospitalized patients in Houston, Texas (2006–16) with CLD and CDI (n=41) compared to patients with CDI but not CLD (n=111), CLD patients had significantly higher Charlson comorbidity index (p<0.0001) but similar risk factors for CDI and CDI-related disease presentation compared to non-CLD patients. In conclusion, CDI-related risk factors were almost universally present in the CLD population. CDI resulted in worse outcomes in this population.

Keywords

Epidemiology; prospective; molecular epidemiology; anaerobic infection; chronic liver disease

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Introduction

Clostridium difficile infection (CDI) is the most common cause of diarrhea in hospitalized patients and the most common cause of death due to gastroenteritis in the USA.[1, 2] The pathogenesis of CDI includes disruption of the host microbiota, usually with broad-spectrum antibiotics, proliferation of toxins after germination of *C. difficile* in the colon, and lack of antibody response to the infection.[3] Patients with chronic liver disease (CLD) are especially prone to CDI due to altered immune dysfunction and frequent antibiotic use causing disturbances in gut microbiota.[4, 5] Patients with CLD tend to display less overt signs and symptoms of infection most likely due to underlying immune dysfunction.[6, 7] This may complicate treatment decisions as most severity risk stratification measures for CDI are based on host response to infection such as fever or leukocytosis.[8–10] Two previous studies have shown that CDI increases mortality, length of stay, and hospitalization costs in CLD patients.[11, 12] However, a comparator CDI population without CLD were not included in these previous studies. The purpose of this study was to assess resource utilization, mortality, and disease presentation among CLD patients with CDI. To accomplish these aims, we used data available from the nationwide inpatient sample and conducted a medical chart review at a tertiary care medical center with a large CLD population. In separate analyses, we assessed outcomes of CLD patients with CDI to comparator groups including CLD patients without CDI and CDI patients without CLD to better understand the impact of CDI on the CLD population.

Materials & Methods

Nationwide Inpatient Samples (NIS)

Data sources—Data from the 2009 Nationwide Inpatient Samples (NIS), the largest publicly available all-payer inpatient database in the USA was used to provide nationally representative estimates of CDI incidence, healthcare resource utilization, and mortality in the CLD population.[13] The NIS includes all discharges from 20% of community hospitals from participating short-term, non-Federal, general, and other hospitals. The sample is weighted to produce national estimates and represents over 97% of the US population. All data from NIS are de-identified.

Patient identification—The ICD-9 code 008.45 was used to identify patients with CDI.[14] Patients with CLD were identified using a previously validated set of ICD-9 codes and included one of the following diagnoses: hepatitis B virus, hepatitis C virus, alcohol-induced liver disease, Wilson’s disease, autoimmune hepatitis, and non-alcoholic fatty liver disease.[15] The Deyo Modification of the Charlson Comorbidity Index was used as a measure of chronic disease status.[16, 17]

Case and comparison groups—In separate analyses, patients with CDI and underlying CLD (study group) were compared to those with underlying CLD only (control group 1) and patients with CDI only (control group 2).

NIS dataset analysis plan—For statistical analysis of the NIS dataset, incidence rates and 95% confidence intervals for CLD and CDI vs. the entire NIS dataset population were calculated. Separate analyses were conducted to compare CLD patients with CDI vs. the two comparator groups (CLD patients without CDI and CDI patients without CLD). Demographic and comorbidity risk factors were assessed for patients with CLD and CDI vs. comparators. To determine the contribution of CDI to in-patient mortality, length of hospital stay, and hospital costs in patients with CLD vs. comparators, mixed-effect general linear models accounting for the hospital as a first-level variable and adjusting for demographic (age in decade-long intervals, gender, race) and socioeconomic characteristics (primary payer and income level) were constructed. In two separate analyses, patients with CLD and CDI were matched with each comparator group 1:1 based on age and Charlson Comorbidity Index using a nearest-neighbor greedy matching algorithm.[18] In this cohort, mixed effect general linear models were constructed as above and included CDI and an interaction term for CDI and CLD as independent variables. Odds ratios (aOR) were reported adjusting for demographic and socioeconomic differences. The reported difference refers to the β coefficient for the interaction term.

Tertiary care evaluation of patient presentation

Study Design: As the NIS dataset does not include certain types of granular data including disease presentation and treatment, a retrospective case-control observational analysis of patients with CDI, CLD, or both who were admitted to a 650-plus bed university-affiliated tertiary care hospital between 2006–2016 was conducted. Patients were identified utilizing pre-existing hospital and research databases.[19] Patient medical records were reviewed for demographic and hospitalization variables with a specific focus on disease presentation and treatment.

Tertiary care patient population: The study population consisted of adult hospitalized patients (≥18 years of age) with CLD and CDI. CDI was defined as diarrhea (≥ 3 stools in a 24-hour period) plus a positive *C. difficile* diagnostic test plus at least one of the following clinical parameters (diarrhea, fever, leukocytosis (WBC > 10,000 cells/ml^3), nausea, anorexia, or abdominal pain). *C. difficile* diagnostic test was ordered due to suspicion of CDI by the primary medical team. CLD was classified as at least one of the following: hepatitis B virus, hepatitis C virus, alcohol-induced liver disease, Wilson’s disease, autoimmune hepatitis, and non-alcoholic fatty liver disease. Patients with CDI and underlying CLD (study group) were compared to those with underlying CLD only (control group 1) and patients with CDI only (control group 2). Patients were excluded if they had CDI following liver transplantation, CLD due to drug-induced causes (except for alcohol consumption), or hemochromatosis. For patients with multiple occurrences of CDI, only data from the first episode was gathered. Leftover stool samples ordered as part of normal clinical care were collected after all clinical tests had been performed from all patients with CDI as previously described.[20] Briefly, *C. difficile* toxin-positive stool samples were plated onto cefoxitin-cycloserine-fructose agar plates and incubated anaerobically for 48–72 hours. The growth of toxigenic *C. difficile* was confirmed using multiplex PCR to determine the presence of toxins A (*tcdA)* and B (*tcdB)* and strain typed using fluorescent PCR ribotyping.[21] The study including analysis of both datasets was approved by the Committee for the Protection of Research Subjects at the University of Houston.

Statistical Analysis: SAS version 9.3 (SAS Institute, Cary, NC), Stata v13.1 (StataCorp, College Station, TX), or SPSS 24.0 software were used for all analyses. Continuous variables were expressed as means ± SD (normal distribution) or median and quartiles (non-normal distribution such as the Charlson Comorbidity index) and analyzed with the Student t-test/ANOVA or Mann-Whitney U/Kruskal-Wallis test, as appropriate. Chi-square or Fisher exact tests were utilized for categorical data. Univariate analysis was performed for each variable and those variables found to have a P-value of less than 0.2 was then included in the multiple regression analysis. Odds ratio (OR) with 95% confidence intervals were calculated from the regression analysis and P-value of <0.05 was considered to be statistically significant.

Results

NIS dataset results

Comparison of CLD patients with CDI vs. other patient populations with CDI— A total of 7,802,351 discharges were analyzed, of whom 114,108 (1.46%, 95%CI 1.39 – 1.53%) had CLD. The overall incidence rate of CDI was 85.2 / 10,000 discharges (95% CI 81.3 – 89.3). Among CLD patients, the CDI incidence rate was 189.4 / 10,000 discharges (95% CI 175.4 – 204.5) as compared to 83.7 / 10,000 (95% CI 79.9 – 87.7) in patients without CLD (p < 0.001). CLD patients with CDI had higher likelihood of inhospital mortality (18.6% vs. 8.8%; aOR 2.02, 95% CI 1.50 – 2.73; p = 0.003), longer hospital length of stay (1.19 days, 95% CI 0.39 – 2.00; p = 0.004), and increased total costs ($8,632, 95% CI $6,097 – $11,167; p < 0.001) compared to matched non-CLD with CDI.

Comparison of CLD patients with CDI vs. CLD patients without CDI

Compared to patients with CLD without CDI, patients with CLD and CDI were older (58.3 ± 13.2 vs. 60.4 ± 14.7; p<0.001), more likely to be female (44.0% vs. 38.6%; p<0.001) and had a statistically higher Charlson Comorbidity Index (4 (2–5) vs. 4 (3–5); median (IQR); p<0.001). CLD patients with CDI had significantly higher likelihood of inhospital mortality compared to matched CLD patients without CDI (aOR 2.29, 95% CI 1.90 – 2.76; p < 0.001). An average attributable increase in length of stay of 9.10 days (95% CI 8.55 – 9.65; p < 0.001) and $28,940 (95% CI $26,900 - $30,979; p < 0.001) in additional total cost were observed in CLD patients with CDI.

Tertiary care results

Comparison of CLD patients with CDI vs. other patient populations with CDI— A total of 225 hospitalized patients were identified including patients with both CLD and CDI (n=41), patients with CLD without CDI (n=73), and patients with CDI but not CLD (n=111). Patients with CLD averaged 59 ± 10 years (64% male) of which the most common etiology for the liver disease were hepatitis B or C virus (44%), alcohol-induced (31%), or non-alcoholic fatty liver disease (25%). The majority of patients had CLD-related complications including overt or medically-treated hepatic encephalopathy (70%), ascites

(64%), esophageal varices (57%), or prior spontaneous bacterial peritonitis (26%). The majority of CLD patients had risk factors related to CDI including previous use of antibiotics within the last 30-days (100%), current use of proton pump inhibitors (72%), and continued use of non-*C. difficile* antibiotics after diagnosis of CDI (69%). Demographics, etiology, CLD-related complications, or CDI-related risk factors did not differ between patients with CLD regardless of CDI status.

Comparison of CLD patients with CDI vs. CLD patients without CDI— Demographic, CDI-related risk factors, CDI-related severity variables, and CDI-related outcomes are shown in Table 1. Compared to patients with CDI but without CLD, patients with CDI and CLD had a significantly higher Charlson Comorbidity Index (p<0.0001). CDI-related risk factors were similar between the two groups. Ribotype data were available from 66 patients. Ribotype distribution was similar between the two groups which were most commonly ribotypes F014-020 (23%), F106 (14%), F002 (11%), F027 (5%), F056 (5%), and F103 (5%). CDI severity outcomes were also similar between the two groups with no differences noted for ICU admissions, increased creatinine, leukocytosis, or fever. Although not powered to show statistical significance, 30-day mortality was increased by approximately 2-fold in CLD patients who experienced CDI.

Discussion

CLD patients are at increased risk of bacterial infections including *C. difficile* infection due to underlying immunodeficiency and frequent hospitalizations. For CDI specifically, CLD associated immune dysfunction leads to an immunocompromised state due to altered immune response and dysbiosis of gut microbiota.[6, 7] Previous studies have shown that CDI in patients with CLD results in increases mortality, morbidity, and cost.[6, 11] This study confirms and extends these findings by demonstrating that mortality and cost are increased significantly in this patient population compared to patients with CDI without CLD. The observed worse outcomes in patients with CLD are likely due to a higher severity of underlying illness in this patient population compared to other chronically ill patients.

In a prior study using the NIS dataset from 2005, comparing CLD patients with or without CDI, CDI was associated with an approximate 2-fold increase in mortality, and significantly increased length of hospital stay and hospitalization charges.[11] In another study of the NIS datasets from 2008 to 2011 In patients with CLD due to alcoholic hepatitis, CDI was associated with mortality rates similar to hospitalized patients with urinary tract infections but CDI patients experienced longer length of stay and hospitalization costs.[12] CDI proportions in these two studies were 1.42% and 1.62%. Accounting for differences in the underlying patient population and time, similar results were observed in our study. The novel findings from our study centered on comparisons of CDI in patients with or without CLD. Using the NIS dataset and matching patients on comorbidity and age, CLD in patients with CDI was associated with higher likelihood of in-hospital mortality (8.8% vs. 18.6%), longer length of stay (1 day) and increased cost ($8,632). From our study, using our tertiary care database of patients with CDI, CLD patients had a high rate of CDI-related risk factors including previous antibiotic exposure and proton pump inhibitor use. Disease presentation was similar regardless of liver disease status suggesting that the immune dysfunction with

CLD does not dampen the presenting signs and symptoms of disease. Although underpowered, similar differences in mortality rates compared to the national-level NIS data were observed. Taken together, these data suggest that patients with CLD are (a) at high risk for CDI and (b) are especially prone to severe CDI disease consequences. These data can be used to help justify novel prevention or treatment approaches in this vulnerable patient population.[22–24]

This study has limitations. We used the NIS dataset to get national estimates of disease burden in this patient population. However, the NIS is limited to discharge characteristics and does not include granular data such as disease presentation, treatment, testing conditions, amongst others. We chose to use the NIS year 2009 as this was before wide-scale adoption of PCR diagnostics for CDI which may detect *C. difficile* colonization and not infection, potentially blunting the adverse impact of true CDI in this patient population.[25] Limitations of our single-center database include generalizability to other centers including different treatment and diagnostic approaches. However, the uniqueness of combining both datasets with each inherent limitation adds overall strength of applicability to this study. Due to inherent limitations with culture-based methodologies, we were not able to obtain ribotyping data on many of the patients in this study. Future analyses with a larger ribotyping database are planned. Moreover, optimal prevention and treatment strategies in this patient population will require further study.

In conclusion, CDI-related risk factors were almost universally present in the CLD population. In this population, worse CDI-related outcomes including mortality were observed compared to CDI patients without CLD.

Abbreviations

CDI	Clostridium difficile infection
CLD	Chronic liver disease
HCUP-NIS	Health Care and Utilization Project National Inpatient Sample

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Table 1

Patient demographics and baseline characteristics from tertiary care medical center analysis of patients with CDI and chronic liver disease compared to other hospitalized patients with CDI

Variable	**Chronic Liver Disease only (n=73)**	***C. difficile* only (n=111)**	***C. difficile* + Chronic liver disease (n=41)**	**P value***
Age, years (mean±SD)	58±11	64±20	60±9	0.014
Male g*ender* – n (%)	48 (66)	44 (40)	25 (61)	0.019
Race – n (%)				
African American/Black	11 (15)	25 (22.5)	9 (22)	0.26
Caucasian	41 (56)	70 (63.1)	21 (51)	
Hispanic	16 (22)	11 (9.9)	9 (22)	
Other	5 (7)	5 (4.5)	2 (5)	
Charlson's co-morbidity Index - median (25–75 quartile)	4 (3–5)	2 (1–4)	5 (3–6)	<0.0001
Etiology of CLD – n (%)				
Hepatitis B or C Virus	32 (44)	–	19 (46)	N/A
Alcohol-induced	21 (29)	–	14 (34)	
Non-Alcoholic Fatty Liver Disease	20 (27)	–	8 (20)	
Cirrhosis-related complications - (n%)				
Hepatic encephalopathy	56 (77)	–	24 (59)	N/A
Ascites	46 (63)	–	27 (66)	
Esophageal varices	43 (59)	–	22 (54)	
Prior spontaneous bacterial peritonitis	20 (27)	–	10 (24)	
CDI related variables				
Medication use - n(%)				
PPI	50 (68)	71 (64)	32 (78)	
Scheduled use of narcotics	25 (34)	26 (23)	13 (32)	
Continued use of non-CDI antibiotics	49 (67)	82 (74)	30 (73)	
Hospital onset CDI - n(%)	–	40 (36)	16 (39)	0.46
CDI severity variables				
ICU admit	–	33 (30)	13 (32)	0.81

Variable	**Chronic Liver Disease only (n=73)**	***C. difficile* only (n=111)**	***C. difficile* + Chronic liver disease (n=41)**	**P value***
Creatinine greater than 2.5	–	20 (19)	9 (22)	0.64
Leukocytosis greater than 15,000	–	28 (26)	8 (20)	0.41
Temperature greater than 100F	–	13 (12)	3 (7.5)	0.45
CDI outcome variables				
30-day mortality	–	11 (9.9)	7 (22)	0.22
Length of hospital stay (median (25–75 quartile))		7 (4–14)	8 (5–13)	0.55

* P value comparison between patients with *C. difficile* only and *C. difficile* + Chronic liver disease.

Tests between patients with Chronic Liver Disease only and *C. difficile* + Chronic liver disease were non-significant