Hispanic Ethnicity and Steatohepatitis are associated with increased risk of peptic ulcer disease in the cystic fibrosis population: a national database study

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Abstract

Background

Although cystic fibrosis (CF) is widely considered a lung disease, the prevalence of CF-specific gastrointestinal symptoms and diseases has continued to rise. Peptic ulcer disease (PUD) has not been well-studied among people with CF (PwCF) and may be a common cause of abdominal symptoms. In PwCF, impaired bicarbonate secretion and unbuffered gastric acid production have been attributed to the development of ulcers, although ulcers remain uncommon. The objective of this study was to evaluate the prevalence of PUD in PwCF and assess for possible contributing factors.

Methods

This study utilized the National Inpatient Sample (NIS) database. All patients 18 years or older with CF were identified from 2014 to 2019. Relevant patient characteristics and procedures were identified using ICD-9 and ICD-10 codes. Linear trend, bivariate analyses, and multiple regression analysis were performed. The outcomes of interest were peptic ulcer disease, pancreatic insufficiency, and nonalcoholic steatohepatitis or NASH. All analyses accounted for complex sampling scheme of the NIS.

Results

The total prevalence of PwCF in the National Inpatient Sample (NIS) database was 0.08%, and the number was stable year to year from 2014 to 2019. Hispanic patients were more likely to be diagnosed with PUD than other white (aOR 1.802 [1.311,2.476]). Multiple regression analysis indicated that PUD in PwCF was strongly associated with a diagnosis of NASH (aOR 2.421[1.197, 4.898]). PUD patients were less likely to have pancreatic insufficiency compared to the non-PUD group (aOR 0.583 [0.455, 0.745]). All outcomes were adjusted for the use of proton pump inhibitors, H2 blockers, and NSAIDs.

Conclusion

Although cystic fibrosis has been historically known as a disease of childhood, advancements in therapy have led to prolonged life expectancy and higher prevalence for cystic fibrosis-related digestive diseases. This study revealed a low prevalence of PUD in PwCF. Hispanics and those with NASH are more likely to develop peptic ulcers. To validate these findings, additional multi-center prospective studies are warranted.

Introduction

Cystic fibrosis (CF) is the most common lethal autosomal recessive disease in white populations, with an incidence estimated at 1 in 2500–3000 live births (1, 2). This multisystem disorder is characterized by a

gene mutation on chromosome 7 resulting in dysfunctional chloride ion transport across epithelial surfaces (2, 3). This subsequently results in the formation of viscous mucus, causing disease in the pancreas, lungs, and other mucus-secreting organs (4). Due to significant advancements in care over the past three decades, a child diagnosed with CF during infancy can anticipate a lifespan extending well into their sixth decade (5, 6). With the rise of life expectancies, there is an apparent increase in the prevalence of gastrointestinal (GI) manifestations in CF, highlighting the necessity for focused and prioritized care (7, 8). Proper knowledge of the GI manifestations related to CF may allow for higher rates of detecting undiagnosed CF in young patients and appropriate characterization and subsequent management for a rapidly increasing adult population with CF.

Peptic ulcer disease (PUD) refers to acid-induced mucosal damage in the upper gastrointestinal (GI) tract, typically occurring in the stomach or proximal duodenum. PUD impacts four million individuals globally each year (9) with an estimated lifetime prevalence ranging from 5–10% in the general population (10). Leading causes of PUD include *Helicobacter pylori* (H.pylori) infection and excessive use of non-steroidal anti-inflammatory drugs (11). Factors such as age, alcohol consumption, smoking, and obesity exhibit a strong association with PUD (12). In addition, growing body of evidence support an association between metabolic dysfunction associated steatotic liver disease (MASLD; previously known as nonalcoholic fatty liver disease or NAFLD) and PUD (13).

The association between CF and PUD has not been well-studied among adults, although it may be a common cause of abdominal symptoms in this population. Prior literature has centralized the discussion of PUD in persons with CF (PwCF) around the notion of the ‘CF paradox’ (4, 14). The ‘CF paradox’ suggests that despite impaired HCO3-secretion and subsequent lack of alkalinization of gastric acids, the development of ulcer disease in this population is uncommon (1). As the body of literature grows, the validity of this concept has been further questioned (1). This study aims to address the rates of PUD in CF. Furthermore, we also performed a comparative analysis between PUD and non-PUD PwCF to assess for possible contributing factors.

Methods

This study utilized the National Inpatient Sample (NIS) database to derive a population-based assessment of national trends related to CF. The NIS database is the largest publicly accessible all-payer inpatient database in the United States. It serves as a repository of information on hospital inpatient discharges which can be used to generate national estimates of hospital utilization, cost, quality and access (15). The database’s large sample size ensures a broad representation of the general US population and statistical integrity. To identify cases of CF, the NIS database was queried for hospital data encompassing all patients discharged with primary diagnosis codes of CF diagnosis (ICD-9-CM 277.0x; ICD-10-CM E84.x) (CF and associated manifestations) spanning the years 2014 to 2019.

Variables recorded: All patients 18 years or older with CF were identified. Relevant patient demographics including age, gender and race were identified. Payer status for all admissions was collected and

classified into categories such as Medicare, Medicaid, private insurance, self-payer or other. NIS database uses the quartile classification by NIS to estimate median household income of residents in patient's ZIP code. Quartiles were identified by values of 1 to 4, indicating the poorest to most prosperous populations, respectively (15). The primary outcome of interest was diagnosis of peptic ulcer disease based on the discharge diagnoses (ICD-9-CM: 531, 532, 533, 534, 578.0, 578.1, 578.9; ICD-10-CM: K25, K26, K27, K28, K92.0, K92.1, K92.2). Patients were further stratified based on two underlying conditions – pancreatic insufficiency and non-alcoholic steatohepatitis (NASH).

Statistical methods

The percentage of patients in patient's demographic and clinical characteristics were determined in the entire sample and then by the status of PUD. A linear trend was determined for the frequency of discharges among PwCF and those with PUD. Bivariate analyses were conducted using Chi-square tests for categorical variables and t-tests for continuous measures. All analyses accounted for the complex sampling scheme of the NIS. A multiple regression adjusting for the use of proton pump inhibitors, H2 blockers, and NSAIDs, was included to account for potential confounding factors. Adjusted odds ratio (aOR) of risk factors were reported with 95% confidence intervals (CI). P-values less than 0.05 were considered statistically significant.

Results

Between 2014 and 2019, the prevalence of adults with CF in the National Inpatient Sample (NIS) database was 0.08%. The count of these patients within the database remained consistent from year to year. A trend analysis is presented in Fig. 1.

Demographic and clinical characteristics of adult persons with cystic fibrosis

Most of the hospitalized CF patients fell within the range of 19 and 35 years old (50.8%), followed by those age less than 18 years old (27%). Subsequently, individuals between 36 and 45 years accounted for 9.4%, while those older than 65 constituted 2.5%. Among PwCF, 54.1% were females and 45.9% were males. Regarding racial distribution, 78.5% of people with CF were identified as white, 8.8% as Hispanic, 4.5% as black and 8.1% as others, mixed or unknown race. In terms of insurance coverage, a majority of PwCF had private insurance (41.6%), followed by Medicaid (33.5%), Medicare (19%) and 5.9% were self-payers. When categorized by quartiles of estimated median household income based on the patient's ZIP Code according to NIS classification (15), 26.9% of PwCF were classified in quartile 2 (Q2), 26.5% quartile 3 (Q3), 24.3% were quartile 1 (Q1), and 22.3 were quartile 4 (Q4).

Peptic ulcer disease in persons with cystic fibrosis

The prevalence of PUD among NIS persons with CF was 1.19%. Within this group, 215 (51.9%) were males, 308 (74.4%) were identified as white, while 12.6% were Hispanic, 5.8% were black, and 7.2% were

categorized as other, mixed or unknown races. The majority of those with PUD were hospitalized between the ages of 19 to 35 (48.6%) and had private insurance coverage (35.3%).

Compared to PwCF without PUD, female PwCF had lower odds of developing PUD based on the results of the multiple regression analysis (aOR 0.78 [0.640, 0.951] (Table 2). Hispanic patients were more likely to have PUD ($p = 0.026$) (Table 1). Using a multiple regression model, this difference was found statistically significant (aOR 1.802 [1.311,2.476)]) (Table 2). Within the PUD group, 2.2% had comorbid non-alcoholic steatohepatitis (NASH), whereas only 0.9% in the non-PUD group had NASH ($p = 0.01$) (Table 1). Multiple regression analysis indicated that PUD in PwCF was strongly associated with a diagnosis of NASH (aOR 2.421[1.197, 4.898]) (Table 2). PUD patients were less likely to have pancreatic insufficiency (22.2%) compared to the non-PUD group (32.6%) ($p < 0.0001$) (Table 1). This finding was confirmed by the multiple regression model (aOR 0.583 [0.455, 0.745]) (Table 2).

Table 1
Demographic and clinical characteristics of adult people with cystic fibrosis

	No Ulcer	Ulcer	All CF Diagnosed	
N	34276	414	34690	
Weighted N	171380	2070	173450	
	%	%	%	p value
Age at hospitalization, years				< .0001
0–18	27.2	13.8	27.0	
19–35	50.8	48.6	50.8	
36–45	9.4	11.8	9.4	
46–64	7.4	16.4	7.5	
≥ 65	2.4	6.8	2.5	
Unknown	2.8	2.7	2.8	
Sex				0.0145
Male	45.8	51.9	45.9	
Female	54.2	48.1	54.1	
Race				0.0268
White	78.6	74.4	78.5	
Black	4.5	5.8	4.5	
Hispanic	8.7	12.6	8.8	
Other/mixed/unknown	8.2	7.2	8.1	
Primary payer				< .0001
Medicare	18.9	27.8	19.0	
Medicaid	33.5	30.2	33.5	
Private	41.7	35.3	41.6	
Self-pay or other	5.9	6.8	5.9	
Median household income for patient's ZIP Code				0.1801
Quartile 1	24.3	24.5	24.3	
Quartile 2	26.8	30.6	26.9	

	No Ulcer	Ulcer	All CF Diagnosed	
Quartile 3	26.6	22.1	26.5	
Quartile 4	22.3	22.8	22.3	
Comorbidities				
MASH	0.9	2.2	0.9	0.0105
Pancreatic insufficiency	32.6	22.2	32.5	< .0001
Quartiles 1 to 4 represent the lowest to highest incomes				

Table 2
Multiple logistic regression analysis on risk factors for Peptic ulcer disease in persons with cystic fibrosis

	aOR (95% CI)	p value
Age at admission, years		
0–17 vs 46–64	0.221 (0.148,0.330)	< .0001
18–35 vs 46–64	0.434 (0.321,0.586)	0.05
36–45 vs 46–64	0.568 (0.393,0.821)	0.6567
≥65 vs 46–64	1.060 (0.654,1.716)	0.0005
Unknown vs 46–64	0.395 (0.178,0.878)	0.3539
Female sex	0.780 (0.640,0.951)	0.0142
Race/Ethnicity		
Black vs White	1.298 (0.838,2.010)	0.8056
Hispanic vs White	1.802 (1.311,2.476)	0.0055
Other vs White	1.024 (0.711,1.475)	0.1926
Primary payer		
Medicaid vs Private	1.201 (0.923,1.563)	0.8578
Medicare vs Private	1.162 (0.882,1.531)	0.8724
Other vs Private	1.397 (0.922,2.117)	0.2618
ZIP-specific income of patient in quartile of national average		
Q2 vs Q1	1.137 (0.854,1.516)	0.252
Q3 vs Q1	0.839 (0.615,1.147)	0.177
Q4 vs Q1	1.049 (0.763,1.442)	0.6834
Unknown vs Q1	0.980 (0.424,2.268)	0.9604
Bedsize of hospital		
Medium vs Large	0.949 (0.718,1.254)	0.8758
Small vs Large	0.858 (0.606,1.214)	0.4753
Location and teaching status of hospital		
Rural vs Urban teaching	1.068 (0.606,1.881)	0.9497
Urban nonteaching vs Urban teaching	1.099 (0.734,1.644)	0.7984

	aOR (95% CI)	p value
Age at admission, years		
Region of hospital		
Midwest vs Northeast	1.094 (0.800,1.497)	0.1463
South vs Northeast	0.927 (0.685,1.254)	0.654
West vs Northeast	0.842 (0.603,1.176)	0.1835
Concurrent clinical conditions		
Obesity	0.959 (0.504,1.822)	0.8972
NASH	2.421 (1.197,4.898)	0.0139
Pancreatic Insufficiency	0.583 (0.455,0.745)	< .0001
Long-term Use of Anti-Coagulants	0.689 (0.339,1.400)	0.303
Year of admission		
2015 vs 2014	1.149 (0.788,1.673)	0.9548
2016 vs 2014	0.918 (0.635,1.328)	0.0561
2017 vs 2014	1.180 (0.820,1.698)	0.8655
2018 vs 2014	1.640 (1.157,2.323)	0.0012
2019 vs 2014	1.175 (0.819,1.685)	0.8911

Discussion

In this national database study, we observed a low prevalence of PUD in the adult CF population at 1.19%, as compared to previous studies. To our knowledge, this study represents the first large-sample study to examine the prevalence of PUD in adult PwCF. Historically, data on the prevalence of PUD in people with CF have been limited by small sample sizes, making comparisons to our data challenging. In 1962, an evaluation of 115 patients with cystic fibrosis found a prevalence of 22% for peptic ulcers while an autopsy review in 1975 of 146 patients found a prevalence of 8% for peptic ulcers (16, 17). The PUD rate in our CF population was lower than that of the general population (5–10%), this can be attributable to the “CF paradox”, which remains a subject of controversy in the CF population (1). The prevalence of PUD in PwCF has significantly declined. This decline in CF patients parallels that of the general population and can be attributed to the widespread use of PPI for acid suppression and advancements in H. pylori eradication (18, 19).

Prior studies have shown that Hispanics have a higher prevalence of PUD associated with H. pylori (18.7%) compared to the white population (14%) (20). Despite CF being more prevalent in white populations, there has been an increase in people with CF identifying as Hispanic since 2006, with 9.8% of patients identifying as Hispanic in 2001, which is consistent with our results (8.8%) (21). Multiple disparities affect the Hispanic CF population leading to increased mortality compared to their non-Hispanic counterparts even after adjusting for socioeconomic status and clinical severity (22, 23). Hispanic populations also exhibit decreased pulmonary function, an important predictor of life expectancy in CF (24). McGarry et. al list factors such as lack of representation in clinical trials, implicit bias during care and late diagnosis due to low CFTR mutation detection rates in newborn screening panels as contributors to these disparities (22). The increased rates of PUD in Hispanic CF population could be multifactorial, given the extensive literature on disparities in CF and PUD.

Non-alcoholic steatotohepatitis (NASH, recently renamed metabolic dysfunction-associated steatohepatitis (MASH)) was associated with increased PUD in this population. NASH is a subtype of non-alcoholic fatty liver disease (NAFLD, recently renamed metabolic dysfunction-associated liver disease (MASLD)). Hepatic steatosis has a prevalence of 20–60% and is the most common hepatic manifestation observed in people with CF (25, 26). The mechanism of hepatic steatosis in CF is not well characterized and is appears to be independent of the CFTR mutation (27). A retrospective study of 114 CF patients revealed that 14.9% had steatohepatitis with significant association with overweight status and no association with CF related liver disease (26). PUD is also frequently seen among those with liver cirrhosis; however, there is currently a lack of data on PUD prevalence in MASLD associated hospitalizations. A recent study by Dahiya et al. also observed a rise in inpatient mortality in MASLD hospitalizations with concomitant PUD (13). The noted rise in inpatient mortality in MASLD with PUD, coupled with our findings of increased prevalence of steatohepatitis in PUD, raises concerns about the significance of the relationship between these two diseases. This understanding is crucial for identifying individuals at the highest risk of adverse outcomes and complications, in the prevention of increased morbidity and mortality.

Growing evidence also supports an association between MASLD and H. pylori, one of the most important environmental factors for PUD (28). Possible underlying mechanisms by which H. pylori contributes to MASLD encompass various pathways including insulin resistance (IR), inflammation cytokines and gut dysbiosis (28). First, it is well known that IR is pivotal in MASLD development, and emerging research indicates that H. pylori infection may function as a causative factor for IR through inducing chronic inflammation and activating certain signaling pathway (29). Second, H. pylori infection may trigger chronic low-grade systemic inflammation, leading to elevated levels of inflammatory cytokines such as IL-6 and TNF-α (30). This, in turn, activates the IKK/NF-KB pathway, inducing insulin resistance. Additionally, H. pylori infection may impede the release of leptin from adipose tissue, enhancing the activity of liver stearoyl-CoA desaturase and expediting the production of very-low-density lipoprotein cholesterol (VLDL-C) and fatty deposits in liver tissue (28). Third, the interaction between the stomach and intestines, influenced by H. pylori infection, may contribute to gastrointestinal dysbiosis. Gut dysbiosis has been associated with the development of MASLD (31, 32).

There was a steady increase in the number of admissions associated with CF from 2014 to 2019 (21). According to data from the CF registry (21), the patient count in 2021 stood at 32,100, a notable increase compared to the approximately 15,000 recorded in 1986. This is in line with an earlier investigation conducted by Agrawal et al., examining the NIS database spanning from 2003 to 2013 and revealing a rise in the number of inpatient discharges associated with CF during that period. The majority of these admissions were due to pulmonary examinations (33). These findings are primarily from advancements in therapies like CFTR modulators and improved mucociliary clearance, but also to the adoption of the care center model endorsed by the Cystic Fibrosis Foundation (CFF). These interventions have resulted in fewer pulmonary complications, improved FEV1, and enhanced quality and quantity of life in the CF population. The median predicted survival reached 53.1 in 2021, a significant increase from the mere 16 years observed in 1970 (21). As the CF population ages, managing their gastrointestinal manifestations becomes crucial to continued expansion of life expectancy.

Another pertinent finding is that, concerning payer status, a majority of PwCF were covered by private health insurance compared to other insurance types. This aligns with previous findings from the CFF (21). Medicaid-covered patients might be less inclined to seek care at the onset due to concerns about limited healthcare access (34). Socioeconomic disparities among insured people with CF can impact care, with Medicaid-covered patients having a 3.7-fold higher risk of death compared to those without Medicaid (35). The low number of uninsured patients is promising because CF patients lacking health insurance have been shown to have higher mortality rates.

Our study has several limitations primarily associated with the characteristics of the NIS database and the study's design. First, our results likely underestimate the true numbers of people with CF hospitalized since the NIS database was designed as an administrative dataset reflecting the coding practices unique to each institution. Therefore, a discharge coded with an alternative diagnosis might not have been reflected in the dataset. The dataset is also devoid of controls for data entry errors. Second, the NIS dataset lacks details about patients, essential to assess for symptoms and signs of PUD, metabolic risk factors that are usually associated with MASLD, and other laboratory and clinical signs of fatty liver disease. As such, this precludes the study of temporal relationship between conditions. Although our study controlled for the use of PPIs, NSAIDS and H2 blockers, one limitation was the inability to identify if the patients diagnosed with PUD were also positive for *H. Pylori*, another risk factor for peptic ulcer disease. While coinfection is a possibility, current literature suggests that the rates of H. Pylori in cystic fibrosis patients remain the same as the general population making it less likely to be a confounding factor in our study (1).

Conclusion

Cystic fibrosis poses a substantial public health challenge, placing a significant burden on the United States healthcare system. Although cystic fibrosis has been historically known as a disease of childhood, advancements in therapy have led to prolonged life expectancy and higher prevalence for cystic fibrosis-related digestive diseases. There exists a substantial knowledge gap regarding peptic ulcer disease and

associated risk factors in the CF population. This study revealed a low prevalence of peptic ulcers in the CF population from a multi-institutional observational cohort based in the United States. Hispanics and those with MASH are more likely to develop peptic ulcers. Although peptic ulcers are uncommon in CF, we believe that cystic fibrosis in association with MASH, and possibly other associated metabolic risk factors may be associated with a higher risk of developing peptic ulcers. To validate these findings, additional multi-center prospective studies are warranted.

Declarations

Conflict of Interests:

None

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Author Contribution

MM participated in the study concept, data interpretation and drafted the articleEN conceptualized the study, reviewed and revised the manuscriptZZ participated in data acquisition and statistical analysis, reviewed the manuscriptRT and NM drafted the initial manuscriptIM prepared the figures and reviewed the manuscript WS and CB critically reviewed and revised the manuscriptCH conceptualized and supervised the study, critically reviewed and revised the manuscript

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Figures

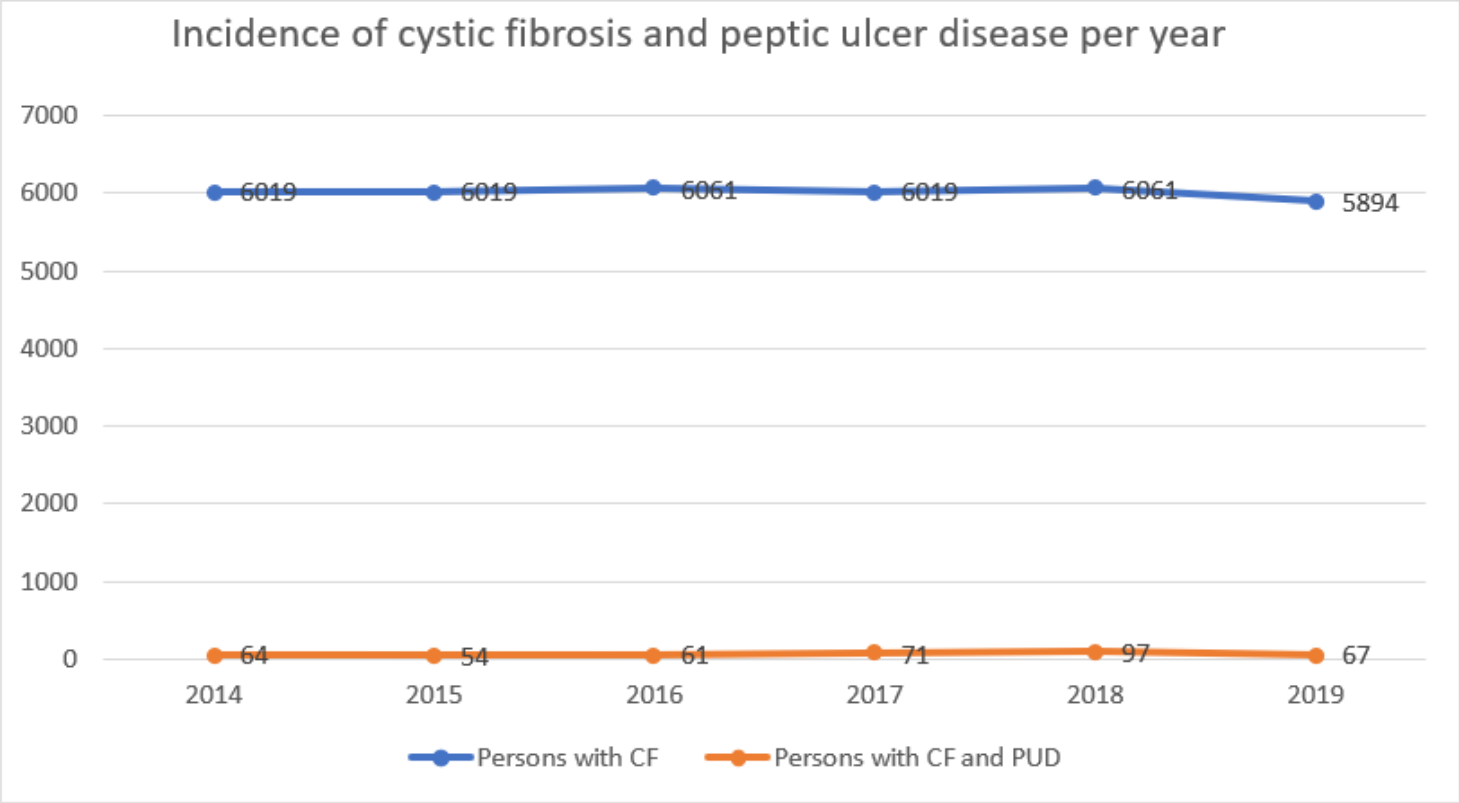

Figure 1

Trends in national cystic fibrosis hospitalization from the National Inpatient Sample