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Celiac disease hospitalizations: an emerging challenge in the United States

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Abstract

Background This study aimed to assess the trends and characteristics of celiac disease (CeD) hospitalizations in the United States (US).

Methods The National Inpatient Sample was analyzed from 2007-2017 to identify all adult hospitalizations with a primary discharge diagnosis of CeD. Demographic trends, associations, and other aspects of CeD hospitalizations were analyzed. SAS 9.4 was used for statistical analysis and P-values ≤0.05 were considered statistically significant.

Results From 2007-2017, we noted an increasing trend of CeD hospitalizations from 19,385 in 2007 to 38,395 in 2017 (P-trend <0.001). The mean age was 57.85 years, with a declining trend. Females and patients with a Charlson Comorbidity Index score ≥3 had a rising trend of CeD hospitalizations from 70.68% in 2007 to 73% in 2017 (P-trend <0.001) and from 16.96% in 2007 to 26.59% in 2017 (P-trend <0.001), respectively. Additionally, a White predominance was seen in the study cohort. Furthermore, for CeD hospitalizations, all-cause inpatient mortality increased from 1.30% in 2007 to 1.58% in 2017 (P-trend <0.001) and the mean total hospital charge increased from $26,299 in 2007 to $49,282 in 2017 (P-trend <0.001). However, we noted a decline in the mean length of stay (LOS) from 4.88 days in 2007 to 4.59 days in 2017 (P-trend=0.0015) and rates of esophagogastroduodenoscopy performed from 2.09% in 2007 to 1.89% in 2017 (P-trend <0.001).

Conclusion We noted a rising trend in hospitalizations, inpatient mortality, and hospital costs for CeD hospitalizations in the US; however, inpatient EGDs performed and mean LOS showed a decline.

Keywords Celiac disease, National Inpatient Sample, trends, mortality, esophagogastroduodenoscopy

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Conflict of Interest: None

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Introduction

Celiac disease (CeD), also known as celiac sprue, is an autoimmune disease characterized by chronic inflammation of the small intestine. It is precipitated by the ingestion of dietary gluten in genetically susceptible individuals [1]. Gluten is commonly present in cereals such as wheat, barley, rye, spelt, and Kamut® [2]. CeD is believed to be multifactorial in origin, as it comprises both an environmental component (gluten consumption) and a genetic component: human leukocyte antigen (HLA)-DQ2 and HLA-DQ8, numerous non-HLA loci, and the auto-antigen tissue transglutaminase (tTG) [3]. Consumption of gluten in these genetically susceptible individuals, through a complex, multifactorial pathogenic

mechanism, may lead to villous atrophy of the intestinal mucosa [4]. This damage can cause severe compromise in the intestinal function and clinical features of malabsorption, along with other heterogeneous symptoms. Initially thought to be a rare disorder, the perception of CeD has changed significantly in recent years, with studies predicting a global prevalence of around 1.4% via serological testing and 0.7% based on intestinal biopsy [5]. Although the exact reason for the rising incidence and prevalence of CeD, particularly in American and European populations, is currently unknown, some studies have postulated that it may be attributable to increased awareness and improved diagnostic tests for the disease [6]. Since its first description by Samuel Gee in 1888, there have been significant strides in the identification of the epidemiology, pathogenesis and treatment of CeD in the general population [7]. However, in an inpatient setting, CeD has not been thoroughly investigated. Therefore, in this study, we identified the biodemographic characteristics and trends of hospitalizations for CeD in the United States (US). We also focused on the association of CeD with other comorbidities and the adverse outcomes associated with CeD hospitalizations.

Materials and methods

Design and data source

This retrospective study used the National Inpatient Sample (NIS), the largest publicly available, multi-ethnic, all-payer database in the US. It consists of inpatient admissions derived from billing data submitted by hospitals across the US to state-wide data organizations covering more than 97% of the population [8]. It approximates a 20% stratified sample of discharges from US community hospitals, excluding rehabilitation and long-term acute-care hospitals. This dataset is weighted to obtain national estimates [9]. Additionally, based on hospital location, the NIS groups all hospitals in the US into 4 major regions: the Northeast, Midwest, South, and West [8]. The information in the database is stored using the International Classification of Diseases (ICD) coding system. For our study period, ICD-9 and ICD-10 codes were used to identify the target population. For data analysis from the NIS, diagnoses were divided into principal diagnosis and secondary diagnoses. A principal diagnosis was the main ICD-9/10 code for the hospitalization, whereas the secondary diagnoses were any ICD-9/10 codes other than the principal diagnosis. Further information on the acquisition of the NIS data files is available at: https://www.hcup-us.ahrq.gov/nisoverview.jsp.

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Study population

This study included all adult (≥18 years) hospitalizations with a primary discharge diagnosis of CeD, identified using the ICD-9 and ICD-10 codes from the NIS for 2007-2017. Patients aged <18 years were excluded from the study. Additionally, for the same study period, all adult non-CeD hospitalizations were also identified to serve as controls to compare the association with comorbidities.

Outcome measures

The outcomes included biodemographic characteristics, hospitalization trends, associations with other comorbidities, number of esophagogastroduodenoscopies (EGDs) performed and the inpatient mortality for CeD hospitalizations. We also estimated the burden of the disease on the US healthcare system in terms of hospital costs and stays for these hospitalizations. The mean total hospital charge (THC) was not adjusted for inflation, in an attempt to provide gastroenterologists and healthcare systems with the real-world cost estimates of managing CeD hospitalizations for individual years and the study period in the US.

Statistical analysis

The statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC). All analyses were conducted using the weighted samples for national estimates in accordance with Healthcare Cost and Utilization Project regulations for use of the NIS database. The age group distribution utilized in the study was available within the NIS database. Descriptive statistics were provided, which included the mean for continuous variables and the count (percentage) for categorical variables. To test for the trend for proportions of binary variables in years, the Cochran-Armitage trend test was implemented. The trend for the averages of continuous variables was examined using linear regression. The Rao-Scott design-adjusted chi-square test, which takes the stratified survey design into account, was used to examine the association between 2 categorical variables. All of the analytical results were considered to be significant when the P-value was ≤0.05.

Ethical considerations

As the NIS database lacks patient identifiers, our study was exempt from Institutional Review Board (IRB) approval as per guidelines put forth by our institutional IRB for clinical research using inpatient databases.

Results

Biodemographic characteristics of hospitalizations

There was a rising trend for total CeD hospitalizations from 19,385 in 2007 to 38,395 in 2017 (P-trend <0.001). The mean age for the study period was 57.85 years, with a trend towards decreasing mean age from 59.84 in 2007 to 56.57 years in 2017 (P-trend <0.001). We noted a rising trend of CeD hospitalizations in the 18-34 age group, from 2,584 in 2007 to 7,390 in 2017 (P-trend <0.001), while a decline was seen for the 35-49, 65-79, and ≥80 age groups (Table 1). Additionally, CeD hospitalizations had female predominance (254,750 females vs. 101,373 males) for the study period, with a rising trend from 13,701 in 2007 to 28,030 in 2017 (P-trend <0.001).

From a race perspective, Whites made up 90.18% of all CeD hospitalizations for the study period, with a trend towards increasing hospitalizations from 13,092 in 2007 to 32,830 in 2017 (P-trend <0.001). Other races, such as Blacks, Hispanics and Asians, were also noted to have a significant trend towards increasing CeD hospitalizations (Table 1).

Comorbidities associated with CeD hospitalizations

From 2007-2017, patients with a Charlson Comorbidity Index score ≥3 had a rising trend of CeD hospitalizations, from 16.96% in 2007 to 26.59% in 2017 (P-trend <0.001). Compared to the non-CeD cohort, CeD hospitalizations were noted to have a higher proportion of patients with weight loss (2.20 vs. 0.67%, P<0.001), Type 1 diabetes mellitus (T1DM) (5.48 vs. 1.07%, P<0.001), peripheral vascular disease (4.12 vs. 3.53%, P<0.001), anemia (32.26 vs. 23.82%, P<0.001), hypothyroidism (22.35 vs. 11.22%, P<0.001), inflammatory bowel disease (3.34 vs. 0.94%, P<0.001), microscopic colitis (2.74 vs. 0.89%, P<0.001), liver cirrhosis (2.91% vs. 1.65%, P=0.002), and chronic pancreatitis (1.44 vs. 0.50%, P<0.001), among others (Table 2). Furthermore, dermatitis herpetiformis (DH) was seen in 2,510 (0.70%) CD hospitalizations. Additionally, higher proportions of patients with autoimmune conditions, such as Addison's disease, autoimmune hepatitis (AH), vitiligo, rheumatoid arthritis (RA), juvenile arthritis, Sjögren's syndrome, systemic lupus erythematosus (SLE), psoriasis, and sarcoidosis were observed in the CeD cohort compared to the non-CeD cohort (Table 2).

Disposition and inpatient mortality for CeD hospitalizations

For the study period, a majority (68.17%) of CeD hospitalizations were discharged home, with a trend towards decreasing home discharges from 69.01% in 2007 to 67.83% in 2017 (P-trend <0.001). However, we noted an increasing trend for transfers to other facilities (skilled nursing facilities and intermediate care facilities), discharge with home healthcare and discharges against medical advice (Table 1).

We noted an increasing trend of inpatient mortality from 1.30% in 2007 to 1.58% in 2017 (P<0.001) for CeD hospitalizations (Fig. 1). Furthermore, a trend towards increasing inpatient mortality was observed for both sexes, and for patients in the 34-49, 50-64, and 65-79 age groups (Table 3). From a race perspective, there was a trend towards increasing inpatient mortality for Whites while a decreasing trend was noted for Blacks (Table 3).

Burden of CeD hospitalizations on the US healthcare system

For CeD hospitalizations, the mean THC increased from $26,299 in 2007 to $49,282 in 2017 (P-trend <0.001), while the mean length of stay (LOS) decreased from 4.88 days in 2007 to 4.59 days in 2017 (P-trend=0.0015). Additionally, inpatient EGDs performed decreased from 2.09% in 2007 to 1.89% in 2017 (P-trend <0.001). Urban teaching hospitals had the highest number of CeD hospitalizations, with a trend towards increasing hospitalizations from 8,897 in 2007 to 27,355 in 2017 (P-trend <0.001).

Discussion

CeD is a well-known autoimmune enteropathy that presents with a wide range of intestinal and extraintestinal symptoms. Establishing a diagnosis of CeD is primarily based on a combination of serological testing (anti-tTG antibodies, anti-endomysium antibodies, and deamidated gliadin peptide antibodies) and duodenal biopsies in patients who consume a gluten diet [10]. Although there is an abundance of literature on CeD, there is a significant paucity of data on various aspects of the disease entity in an inpatient setting. Therefore, in this study, we focused on CeD hospitalizations.

In the US, prospective population-based studies have reported the prevalence of CeD to be 0.71%, similar to the figure reported in European countries [11]. For 2009-2014, it was estimated that about 1.76 million Americans had CeD and that the prevalence of CeD had remained stable in the general adult population [12]. However, in our study, CeD hospitalizations increased from 19,385 in 2007 to 38,395 in 2017, with a trend towards rising hospitalizations (Table 1). The lower prevalence rate for CeD hospitalizations compared to the prevalence of CeD in the general population was expected, as

Table 1 Demographic and hospitalization characteristics for CeD hospitalizations in the United States from 2007-2017

Epidemiological variable	Year												Trend and P-value
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2007-2017 (Overall)	
Total number of CeD hospitalizations	19,385	23,633	26,230	30,016	33,598	34,255	36,470	36,655	38,280	39,285	38,395	356,202	Increase (P<0.001)
Mean age (years)	59.84	59.53	59.07	58.64	58.41	57.67	57.45	57.46	57.01	56.88	56.57	57.85	Decrease (P<0.001)
Age group (years)													
18-34	2,584 (13.33%)	3,271 (13.84%)	3,697 (14.10%)	4,633 (15.44%)	5,344 (15.90%)	5,850 (17.08%)	6,370 (17.47%)	6,555 (17.88%)	7,130 (18.63%)	7,310 (18.61%)	7,390 (19.25%)	60,133 (16.88%)	Increase (P<0.001)
35-49	3,391 (17.49%)	4,154 (17.57%)	4,540 (17.31%)	5,234 (17.44%)	5,819 (17.32%)	5,990 (17.49%)	6,045 (16.58%)	6,115 (16.68%)	6,610 (17.27%)	6,252 (16.61%)	6,685 (17.41%)	61,107 (17.16%)	Decrease (P<0.001)
50-64	4,422 (22.81%)	5,548 (23.47%)	6,397 (24.39%)	7,111 (23.69%)	7,916 (23.56%)	8,280 (24.17%)	9,045 (24.80%)	8,860 (24.17%)	8,865 (23.26%)	9,490 (24.16%)	9,000 (23.44%)	84,934 (23.84%)	No Trend (P=0.2074)
65-79	5,478 (28.26%)	6,447 (27.28%)	7,243 (27.61%)	7,889 (26.28%)	8,974 (26.71%)	8,600 (25.11%)	9,260 (25.39%)	9,165 (25.00%)	9,600 (25.08%)	10,305 (26.23%)	9,460 (24.64%)	92,421 (25.95%)	Decrease (P<0.001)
≥80	3,510 (18.11%)	4,215 (17.83%)	4,352 (16.59%)	5,150 (17.16%)	5,546 (16.51%)	5,535 (16.16%)	5,750 (15.77%)	5,960 (16.26%)	6,075 (15.87%)	5,655 (14.39%)	5,860 (15.26%)	57,607 (16.17%)	Decrease (P<0.001)
Sex													
Male	5,684 (29.32%)	6,964 (29.47%)	7,533 (28.72%)	8,944 (29.80%)	9,558 (28.46%)	9,605 (28.04%)	10,500 (28.79%)	10,365 (28.28%)	10,525 (27.51%)	11,330 (28.88%)	10,365 (27.00%)	101,373 (28.47%)	Decrease (P<0.001)
Female	13,701 (70.68%)	16,669 (70.53%)	18,697 (71.28%)	21,073 (70.20%)	24,031 (71.54%)	24,650 (71.96%)	25,970 (71.21%)	26,290 (71.72%)	27,735 (72.49%)	27,905 (71.12%)	28,030 (73.00%)	254,750 (71.53%)	Increase (P<0.001)
Race													
White	13,092 (91.06%)	17,155 (91.15%)	20,250 (91.97%)	23,488 (90.19%)	26,974 (90.06%)	28,350 (88.83%)	30,115 (89.92%)	30,745 (90.40%)	31,925 (90.49%)	33,190 (89.76%)	32,830 (89.72%)	288,113 (90.18%)	Increase (P<0.001)
Black	446 (3.10%)	504 (2.67%)	602 (2.73%)	867 (3.33%)	1055 (3.52%)	1,065 (3.34%)	1,165 (3.48%)	940 (2.76%)	1,080 (3.06%)	1,275 (3.45%)	1,035 (2.83%)	10,031 (3.14%)	Increase (P<0.001)
Hispanic	467 (3.25%)	718 (3.81%)	646 (2.93%)	923 (3.54%)	1,217 (4.06%)	1,340 (4.20%)	1,335 (3.97%)	1,440 (4.23%)	1,405 (3.98%)	1,495 (4.04%)	1,605 (4.39%)	12,590 (3.94%)	Increase (P<0.001)
Asian	51 (0.35%)	96 (0.51%)	105 (0.48%)	108 (0.41%)	147 (0.49%)	180 (0.56%)	211 (0.62%)	206 (0.60%)	231 (0.65%)	235 (0.64%)	215 (0.59%)	1,779 (0.56%)	Increase (P<0.001)
Native American	53 (0.36%)	65 (0.35%)	134 (0.60%)	169 (0.65%)	87 (0.29%)	185 (0.58%)	90 (0.27%)	96 (0.28%)	101 (0.28%)	110 (0.30%)	165 (0.45%)	1,251 (0.39%)	Decrease (P=0.0118)
Other	271 (1.88%)	285 (1.51%)	283 (1.28%)	492 (1.89%)	473 (1.58%)	796 (2.49%)	575 (1.72%)	585 (1.72%)	540 (1.53%)	670 (1.81%)	740 (2.02%)	5,707 (1.79%)	Increase (P<0.001)

(Contd...)

Table 1 (*Continued*)

Epidemiological variable	Year												Trend and P-value
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2007-2017 (Overall)	
Charlson comorbidity index (CCI)													
CCI=0	7,791 (40.19%)	9,820 (41.55%)	10,223 (38.97%)	11,658 (38.84%)	12,571 (37.41%)	12,775 (37.29%)	13,045 (35.77%)	13,210 (36.04%)	13,245 (34.60%)	13,640 (34.72%)	12,970 (33.78%)	130,947 (36.76%)	Decrease (P<0.001)
CCI=1	5,363 (27.67%)	6,284 (26.59%)	6,957 (26.52%)	7,886 (26.27%)	8,753 (26.05%)	8,930 (26.07%)	9,640 (26.43%)	9,040 (24.66%)	9,945 (25.98%)	10,160 (25.86%)	9,690 (25.24%)	92,648 (26.01%)	Decrease (P<0.001)
CCI=2	2,943 (15.18%)	3,535 (14.96%)	4,083 (15.57%)	4,584 (15.27%)	5,075 (15.11%)	4,985 (14.55%)	5,610 (15.38%)	5,635 (15.37%)	5,850 (15.28%)	5,770 (14.69%)	5,525 (14.39%)	53,595 (15.05%)	Decrease (P=0.0026)
CCI≥3	3,287 (16.96%)	3,995 (16.91%)	4,968 (18.94%)	5,889 (19.62%)	7,199 (21.43%)	7,565 (22.08%)	8,175 (22.42%)	8,770 (23.93%)	9,240 (24.14%)	9,715 (24.73%)	10,210 (26.59%)	79,013 (22.18%)	Increase (P<0.001)
Hospital location and teaching status													
Rural	2,642 (13.64%)	2,512 (10.65%)	2,591 (10.01%)	3,384 (11.38%)	3,575 (10.74%)	3,445 (10.06%)	3,575 (9.80%)	3,025 (8.25%)	2,965 (7.75%)	3,170 (8.07%)	2,790 (7.74%)	33,853 (9.53%)	Decrease (P<0.001)
Urban nonteaching	7,824 (40.41%)	10,028 (42.50%)	11,190 (43.24%)	13,098 (44.06%)	13,583 (40.80%)	12,760 (37.25%)	13,390 (36.72%)	9,235 (25.19%)	9,595 (25.07%)	9,460 (24.08%)	8,070 (21.02%)	118,234 (33.29%)	Decrease (P<0.001)
Urban teaching	8,897 (45.95%)	11,054 (46.85%)	12,100 (46.75%)	13,245 (44.56%)	16,132 (48.46%)	18,050 (52.69%)	19,505 (53.48%)	24,395 (66.55%)	25,720 (67.19%)	26,655 (67.85%)	27,355 (71.25%)	203,107 (57.18%)	Increase (P<0.001)
Esophagogastro-duodenoscopy	405 (2.09%)	575 (2.43%)	627 (2.39%)	607 (2.02%)	791 (2.35%)	721 (2.10%)	780 (2.14%)	831 (2.26%)	771 (2.01%)	771 (1.96%)	726 (1.89%)	7,597 (2.13%)	Decrease (P<0.001)
Length of stay (days)	4.88	4.90	4.99	4.86	4.90	4.94	4.74	4.81	4.78	4.67	4.59	4.81	Decrease (P=0.0015)
Total hospital charge (USD)	26,299	30,033	32,796	34,066	37,162	38,909	41,125	43,396	44,311	46,885	49,282	39,886	Increase (P<0.001)
Disposition													
Routine (home)	13,377 (69.01%)	16,806 (71.17%)	18,303 (69.78%)	20,546 (68.47%)	23,081 (68.91%)	23,455 (68.48%)	24,715 (67.79%)	24,250 (66.20%)	25,635 (67.00%)	26,435 (67.37%)	26,025 (67.83%)	242,628 (68.17%)	Decrease (P<0.001)
Transfer to short-term hospital	425 (2.19%)	539 (2.28%)	517 (1.97%)	680 (2.27%)	710 (2.12%)	660 (1.93%)	685 (1.88%)	826 (2.25%)	751 (1.96%)	685 (1.75%)	605 (1.58%)	7,078 (1.99%)	Decrease (P<0.001)
Transfer to another type of facility (includes skilled nursing facility and intermediate care facility)	2,703 (13.95%)	3,111 (13.17%)	3,675 (14.01%)	4,051 (13.50%)	4,803 (14.34%)	4,915 (14.35%)	5,440 (14.92%)	5,570 (15.21%)	5,605 (14.65%)	5,495 (14.00%)	5,450 (14.20%)	50,818 (14.28%)	Increase (P<0.001)
Home healthcare	2,527 (13.04%)	2,670 (11.31%)	3,198 (12.19%)	4,088 (13.63%)	4,187 (12.50%)	4,485 (13.09%)	4,860 (13.33%)	5,100 (13.92%)	5,295 (13.84%)	5,625 (14.33%)	5,320 (13.87%)	47,356 (13.30%)	Increase (P<0.001)
Discharge against medical advice	93 (0.48%)	156 (0.66%)	180 (0.68%)	225 (0.75%)	255 (0.76%)	271 (0.79%)	275 (0.75%)	375 (1.02%)	416 (1.08%)	410 (1.04%)	360 (0.94%)	3,012 (0.85%)	Increase (P<0.001)

CeD, celiac disease

Table 2 Comorbidities associated with celiac disease hospitalizations in the United States from 2007-2017

Co-morbidities	Celiac disease hospitalizations	Non-celiac disease hospitalizations	P-value
Total hospitalizations	356,202	345,784,226	
Type 1 diabetes mellitus	19,537 (5.48%)	3,703,598 (1.07%)	<0.001
Type 2 diabetes mellitus	52,369 (14.70%)	79,461,702 (22.98%)	<0.001
Hypertension	120,079 (33.71%)	129,996,800 (37.59%)	<0.001
Myocardial infarction	7,776 (2.18%)	10,741,210 (3.11%)	<0.001
Cardiomyopathy	7,982 (2.24%)	10,698,206 (3.09%)	<0.001
Congestive heart failure	35,426 (9.95%)	48,646,715 (14.07%)	<0.001
Pericarditis	119 (0.03%)	71,303 (0.02%)	0.0208
Obesity	30,484 (8.56%)	39,652,934 (11.47%)	<0.001
Weight loss	7,825 (2.20%)	2,316,645 (0.67%)	<0.001
Hyperlipidemia	87,382 (24.53%)	94,811,918 (27.42%)	<0.001
Peripheral vascular disease	14,690 (4.12%)	12,199,714 (3.53%)	<0.001
Anemia	116,342 (32.66%)	82,380,108 (23.82%)	<0.001
Hypothyroidism	79,594 (22.35%)	38,813,910 (11.22%)	<0.001
Inflammatory bowel disease	11,900 (3.34%)	3,263,584 (0.94%)	<0.001
Microscopic colitis	9,765 (2.74%)	3,067,159 (0.89%)	<0.001
Autoimmune hepatitis	1411 (0.40%)	170,046 (0.05%)	<0.001
Liver cirrhosis	10,381 (2.91%)	5,715,070 (1.65%)	0.002
Acute pancreatitis	7,814 (2.19%)	4,774,129 (1.38%)	<0.001
Chronic pancreatitis	5,115 (1.44%)	1,744,205 (0.50%)	<0.001
Enteropathy-associated T-cell lymphoma	201 (0.06%)	13,341 (0.00%)*	<0.001
Chronic obstructive pulmonary disease	39,668 (11.14%)	48,446,764 (14.01%)	<0.001
Acute renal failure	35,897 (10.08%)	35,723,844 (10.33%)	0.0436
Chronic kidney disease	37,448 (10.51%)	44,865,392 (12.98%)	<0.001
Addison's disease	4,281 (1.20%)	994,187 (0.29%)	<0.001
Dermatitis herpetiformis	2510 (0.70%)	5,027 (0.00%)*	<0.001
Alopecia areata	68 (0.02%)	7,091 (0.00%)*	<0.001
Vitiligo	303 (0.09%)	71,913 (0.02%)	<0.001
Dermatomyositis	347 (0.10%)	85,538 (0.02%)	<0.001
Rheumatoid arthritis	10,650 (2.99%)	5,469,600 (1.58%)	<0.001
Juvenile arthritis	352 (0.10%)	65,979 (0.02%)	<0.001
Sjögren's syndrome	4,031 (1.13%)	457,817 (0.13%)	<0.001
Systemic lupus erythematosus	6,184 (1.74%)	1,961,324 (0.57%)	<0.001
Thyroiditis	3,424 (0.96%)	316,889 (0.09%)	<0.001
Psoriasis	3,847 (1.08%)	1,523,768 (0.44%)	<0.001
Sarcoidosis	1,593 (0.45%)	856,160 (0.25%)	<0.001
Immune thrombocytopenic purpura	1,300 (0.36%)	574,005 (0.17%)	<0.001
Multiple sclerosis	2,889 (0.81%)	1,584,008 (0.46%)	<0.001

*As percentages are reported only to 2 decimal places, 0.00% signifies a low percentage (<0.01) of individuals with the comorbidity among all non-celiac disease hospitalizations

not all patients with CeD were admitted to hospital. Per current literature, CeD is known to occur at any age, with a median age at diagnosis reported to be 45 years [11]. In our study, the mean age for CeD hospitalizations was 57.85 years, with a decreasing trend. Interestingly, CeD hospitalizations for the 18-34 age group showed a rise. This may, in part, be due to early diagnosis

Table 3 Trends of in-patient mortality for celiac disease hospitalizations in the United States from 2007-2017

Outcome	Year											2007-2017 (Overall)	Trend and P-value
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017		
Inpatient mortality	1.30%	1.41%	1.34%	1.28%	1.34%	1.33%	1.33%	1.37%	1.46%	1.50%	1.58%	4,996 (1.40%)	Increase (P<0.001)
Sex-specific inpatient mortality													
Male	1.77%	1.66%	1.78%	1.86%	1.63%	2.08%	1.91%	1.93%	2.04%	1.86%	2.27%	1,932 (1.91%)	Increase (P=0.0017)
Female	1.10%	1.31%	1.17%	1.03%	1.23%	1.03%	1.10%	1.14%	1.24%	1.36%	1.32%	3,034 (1.19%)	Increase (P=0.0061)
Race-specific inpatient mortality													
White	1.61%	1.30%	1.41%	1.23%	1.32%	1.41%	1.21%	1.38%	1.46%	1.54%	1.59%	4,049 (1.41%)	Increase (P=0.0041)
Black	1.17%	0.85%	0.85%	1.72%	2.21%	0.47%	1.29%	1.60%	0.93%	0.39%	0.48%	108 (1.08%)	Decrease (P=0.0062)
Hispanic	0%	2.67%	0.88%	0.51%	1.87%	0.37%	1.50%	1.04%	1.07%	2.01%	0.31%	143 (1.13%)	No trend (P=0.2320)
Asian	11.67%	0%	0%	0%	3.88%	0%	2.38%	4.88%	0%	0%	4.65%	37 (2.06%)	No trend (P=0.4570)
Native America	0%	0%	0%	0%	5.71%	5.41%	0%	0%	0%	0%	6.06%	25 (2.00%)	Increase (P=0.0093)
Others	0%	3.56%	1.66%	3.03%	1.68%	0%	1.74%	0.85%	0%	0.75%	2.70%	78 (1.36%)	No trend (P=0.1931)
Age group-specific inpatient mortality													
18-34	0%	0.14%	0.13%	0.45%	0.47%	0%	0.47%	0.31%	0.14%	0.27%	0.07%	141 (0.23%)	No trend (P=0.1967)
34-49	0.16%	0.46%	0.11%	0.08%	0.33%	0.50%	0.50%	0.33%	0.68%	0.23%	0.52%	228 (0.37%)	Increase (P<0.001)
50-64	0.70%	1.31%	1.02%	1.48%	0.95%	0.91%	1.49%	1.47%	1.07%	1.48%	1.33%	1,044 (1.23%)	Increase (P=0.0014)
65-79	1.33%	1.15%	1.80%	1.75%	1.52%	1.80%	1.46%	1.42%	2.14%	1.94%	2.33%	1,597 (1.73%)	Increase (P<0.001)
≥80	4.05%	3.87%	3.39%	2.22%	3.53%	3.52%	2.70%	3.36%	3.37%	3.81%	3.84%	1,957 (3.40%)	No trend (P=0.2407)

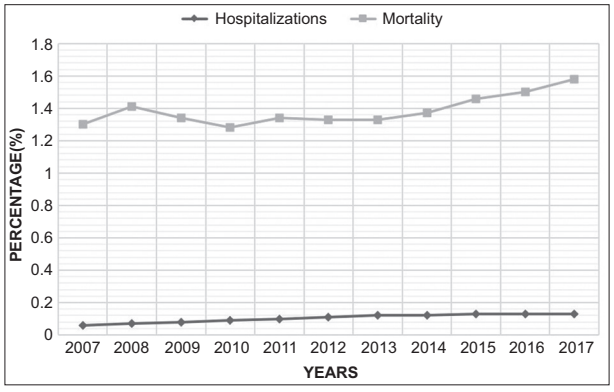

Figure 1 Hospitalization and inpatient mortality trends for celiac disease hospitalizations in the United States from 2007-2017

of CeD in younger adults because of increased awareness and the widespread availability of serological testing. Furthermore, it has been well established that CeD is primarily seen in the Caucasian population [13]. Similarly, in our study, Whites made up 90.18% of the study population, with an increasing trend for hospitalizations. We also noted a trend towards increasing hospitalizations for the Black, Hispanic, and Asian populations (Table 1). The exact reason for this increasing trend is currently unknown, but it may be postulated that an increase in the consumption of dietary gluten may have a key role to play within these subset racial populations. Nonetheless, these findings warrant further investigation through larger studies.

From a hospital perspective, urban teaching hospitals were noted to have the most hospitalizations for CeD, with a trend

towards increasing hospitalizations. This may, in part, be due to the fact that these hospitals are usually tertiary referral centers that accept patients from widespread geographical areas, and hence have an abundance of resources and specialists to further manage CeD and its complications.

In our study, a higher proportion of CeD hospitalizations were found to have weight loss and anemia compared to the non-CeD cohort. This may be secondary to the malabsorption seen in patients with CeD due to villous atrophy. DH, a classical feature of CeD characterized by the presence of multiple intensely pruritic papules and vesicles that occur in grouped arrangements, was seen in only 0.70% of these hospitalizations. However, literature reports a DH prevalence of up to 10% in patients with CeD [14]. The exact reason for the significantly lower rates of DH is unknown, but may be explained by an overall low hospitalization rate for CeD in our study. Furthermore, we noted a higher proportion of patients with autoimmune conditions such as T1DM, Addison's disease, AH, vitiligo, RA, juvenile arthritis, Sjögren's syndrome, SLE, psoriasis, and sarcoidosis for CeD hospitalizations compared to the non-CeD cohort (Table 2). These findings were in line with the current literature.

According to the guidelines issued by the American College of Gastroenterology, the management of CeD is primarily focused around patient education, dietary counseling, lifelong adherence to a gluten-free diet, treatment of underlying nutritional deficiencies and long-term annual follow up, preferably by a multidisciplinary team [10,15]. In an inpatient setting, a majority of patients with CeD may have mild complications, such as electrolyte disturbances secondary to diarrhea, pre-renal fluid responsive acute kidney injury, and nutritional deficiencies. After correction of these disturbances, initiation of supplements for nutritional deficiencies and rigorous counseling, these patients are usually sufficiently stable to be discharged home. Strict adherence to a gluten-free diet and regular follow up with a care provider may prevent future hospitalizations and the development of complications [16]. In our study, from 2007-2017, a majority (68.17%) of the CeD hospitalizations were deemed stable enough to be discharged home; however, we noted a trend towards decreasing home discharges and an increasing trend for transfers to other facilities, such as skilled nursing facilities and intermediate care facilities, and discharge home with home healthcare. This may be explained by the fact that a majority of the CeD hospitalizations in our study were ≥65 of age. This older demographic may require additional resources and support prior to discharge. Additionally, we noted an increasing trend for discharges against medical advice (Table 1).

From a mortality standpoint, a study of the Swedish population from 1969-2017 reported that a diagnosis for CeD was associated with a small, but statistically significant increase in the mortality risk compared to the general population [17]. This relative increase in the mortality risk was noted in all age groups; however, it was most prominent in the 18-39 age group [17]. Our study somewhat mirrors these findings. We observed an increase in all-cause inpatient mortality for CeD hospitalizations from 1.30% in 2007 to 1.58% in 2017, with a trend towards increasing inpatient mortality. There was a rising trend of inpatient mortality for both sexes, Whites and for the 34-49, 50-64 and 65-79 age groups (Table 3). Interestingly, we did not find a statistically significant trend of inpatient mortality for the 18-34 and ≥80 age group. The exact rationale for this increasing trend of inpatient mortality is currently unknown, but it is postulated that it may be secondary to a state of persistent chronic inflammation leading to severe complications, and the association of CeD with other comorbidities. Nonetheless, we advocate for the need of additional, large, multicenter prospective studies to further investigate this trend and identify the exact causes of inpatient mortality.

It is well established that CeD is associated with a significant financial burden, on both individuals and the US healthcare system [18]. A study of the Olmsted County population in Minnesota from 1989-2006 revealed that undiagnosed and untreated CeD patients had higher 4-year medical care costs by $4,000 compared to non-CD patients [19]. This difference was noted to be even more prominent in men, who had incurred on average $10,000 more in medical costs compared to men in the non-CeD cohort [19]. Another study from 2008-2015 in Sweden reported that the mean healthcare costs for CeD patients were higher by $1,075 for the <18 age group, $715 for the 18-64 age group and $1,010 for individuals ≥65 years of age compared to those without CeD, and hospitalization for CeD was cited as an important factor attributing to these increased costs [20]. Although numerous studies have attempted to estimate the economic impact of CeD, there continues to be a substantial knowledge gap. Additionally, it is difficult to estimate the financial impact of a gluten-free diet, strict adherence to which may reduce CeD hospitalizations and in turn healthcare costs. In our study, we noted a rising trend of mean THC from $26,299 in 2007 to $49,282 in 2017. This may be attributed to a combination of increasing hospitalizations of CeD, need for additional investigations to establish diagnosis, given the wide spectrum of clinical presentations, early gastroenterology consultation and inflation. Interestingly, we noted a declining trend for EGDs performed in an inpatient setting, which may, in part, be because more of these patients had been scheduled for outpatient EGDs for histological diagnosis. Furthermore, we observed a trend towards decreasing mean LOS from 4.88 days in 2007 to 4.59 days, reflecting early diagnosis and improved management strategies for CeD and its complications.

This study has several strengths and limitations. A key strength of this study is the study population, derived from one of the largest, publicly available, multi-ethnic databases in the US, developed through a Federal-State-Industry partnership. It contains data on inpatient admissions from hospitals across the US. Therefore, the outcomes are applicable to most of these hospitals. Moreover, through the study design and analysis, this study focuses primarily on the epidemiology, hospitalization characteristics and adverse outcomes associated with CeD. We also compared

the frequency of comorbidities between the CeD and non-CeD hospitalizations, which serve as a control. This allows for an extremely comprehensive analysis that adds meaningful information to the current literature.

However, we do acknowledge the limitations of our study. The NIS database does not contain data on the severity of the disease, time from hospital admission to diagnosis, information on serological testing and seroprevalence in hospitalized patients, treatment aspects, laboratory investigations, and hospital course of CeD. Additionally, as the NIS database lacks data on the indications for all inpatient procedures, we were unable to determine the exact indication for EGDs in CeD hospitalizations. Furthermore, given the retrospective nature of the study and the use of the NIS database, which only captures inpatient admissions, we were unable to calculate the prevalence of CeD in the general population. Moreover, all biases associated with retrospective studies are applicable to this study. The hospitalizations identified in the study were based on a diagnosis of CeD rather than individual patients. Hence, individuals admitted numerous times for the same diagnosis may have been included several times within the data set. Lastly, NIS is an administrative database that uses specific codes to gather and store information; therefore, the possibility of coding errors and missing data cannot be excluded. Despite these limitations, we believe that the large sample size, study design and comprehensive analysis technique help us better understand the topic in question. Through this study we aim to encourage intellectual conversation and promote future research on CeD.

In conclusion, CeD is a complex autoimmune gluten-mediated enteropathy in genetically susceptible individuals. The literature reports a rising incidence and prevalence of CeD worldwide. In this study, we observed a trend towards increasing hospitalizations for CeD. The mean age was noted to be 57.85 years. A rising trend of CeD hospitalizations was observed for a younger demographic (18-34 age group), which may reflect increased awareness about the disease, the widespread availability of serological screening, and a rise in the seroprevalence. Additionally, a female and White predominance was seen throughout the study period. CeD places a significant burden on the US healthcare system, as there was a trend towards increasing mean THC from $26,299 in 2007 to $49,282 in 2017. However, the mean LOS decreased from 4.88 days in 2007 to 4.59 days in 2017, reflecting early diagnosis and treatment of CeD and its complications. Interestingly, there was a declining trend for EGDs performed in an inpatient setting. All-cause inpatient mortality for CeD hospitalizations was observed to have an increasing trend and was noted to be 1.58% in 2017. The exact reason for this is unknown, but it may be secondary to a state of persistent chronic inflammation and the association of CeD with other comorbidities. In general, patients with CeD have an excellent response to a gluten-free diet, which may help reduce hospitalizations, healthcare costs, and adverse outcomes. Hence, these patients need extensive dietary counseling and regular outpatient follow up.

Summary Box

What is already known:

- The global prevalence of celiac disease is around 1.4% via serological testing and 0.7% based on intestinal biopsy
- The incidence and prevalence of celiac disease is on the rise in the United States (US), possibly because of increased awareness of the disease and the widespread availability of diagnostic testing
- Celiac disease is associated with a significant financial burden on both individuals and the US healthcare system

What the new findings are:

- There was a rising trend for celiac disease hospitalizations in the US from 19,385 in 2007 to 38,395 in 2017, with a significant White predominance
- Inpatient mortality for celiac disease hospitalizations increased from 1.30% in 2007 to 1.58% in 2017
- Although the mean length of stay and rates of esophagogastroduodenoscopy performed both decreased—from 4.88 days in 2007 to 4.59 days in 2017 and from 2.09% in 2007 to 1.89% in 2017, respectively—the mean total hospital charge increased from $26,299 in 2007 to $49,282 in 2017

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