1 *Original Article*

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3 **Trends of Hospitalization in Acute Pancreatitis in Patients in the United States from**
4 **2001-2014**

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12 **Abstract:** Background & Purpose: The prevalence of acute pancreatitis(AP) has increased
13 over time and is one of the most important gastrointestinal causes of frequent admissions
14 to hospital in the United States. The cost burden of AP has been steadily increasing. The
15 primary objective of our study was to analyze patient demographics, cost burden,
16 mortality and length of stay associated with AP hospital admissions.

17 Methods: Nationwide inpatient sample (NIS) database was used to identify AP
18 admissions in all patients from ≥18 years of age from 2001 to 2014 using ICD-9-CM code
19 577.0 as the principal discharge diagnosis

20 Results: The number of hospitalizations increased from 215,238 in 2001 to 279,145 in 2014.
21 In-hospital mortality decreased from 1.74% in 2001 to 0.66% in 2014. Mean length of
22 hospital stay has decreased from 6.1 days to 4.6 days during the same period, but the

mean hospital charges increased from \$19,303 in 2001 to \$35,728 in 2014. The proportion of males to females with acute pancreatitis is slowly trending up from 2001 to 2014.

Conclusion: The number of hospitalizations due to acute pancreatitis has been steadily increasing, and further research needs to be done on finding out the reasons for increased causes of hospitalization and ways to decrease the cost burden on patients and hospitals.

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Keywords: pancreatitis; epidemiology; etiology; risk factors; gallstones; alcohol

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32 1. Introduction

Acute pancreatitis (AP) is an inflammatory condition of the pancreas which is characterized by abdominal pain and elevated pancreatic enzymes in the blood.(1) AP may range from a mild self-limiting form to a more severe form (acute necrotizing pancreatitis). Gallstones and chronic alcoholism are the two most common etiological factors associated with AP. Other causes include drugs, infections, hyperlipidemia, trauma, hypercalcemia, HIV, neoplasms and idiopathic.(2)

The prevalence of acute pancreatitis (AP) has increased over time and is one of the most important gastrointestinal causes of frequent admissions to hospital in the United States. The cost burden of AP has been steadily increasing. The primary objective of our study was to analyze patient demographics, cost burden, mortality and length of stay associated with AP hospital admissions.

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45 2. Materials and Methods

46 Nationwide inpatient sample (NIS) database was used to identify AP admissions in all
47 patients from ≥ 18 years of age from 2001 to 2014 using ICD-9-CM code 577.0 as the
48 principal discharge diagnosis. NIS is the largest all-payer inpatient care database in the
49 United States, containing data on more than 7 million hospital stays. It has a large sample
50 size which is ideal for developing national and regional estimates.

51 We carried a literature search for etiology of acute pancreatitis using the online
52 databases of PubMed, Embase, Scopus, Google Scholar. We reviewed the pertinent articles
53 about acute pancreatitis and its etiology. The review is an attempt to provide a better
54 understanding of the possible various etiologic causes of acute pancreatitis.

55

56 3. Results

57 A total of 481,231,240 discharges with a diagnosis of AP were analyzed from 2001 to 2014
58 from the NIS database. Table 1 summarizes the data analyzed. The number of
59 hospitalizations increased from 215,238 in 2001 to 279,145 in 2014. In-hospital mortality
60 decreased from 1.74% in 2001 to 0.66% in 2014 (Figure 1). Mean length of hospital stay has
61 decreased from 6.1 days to 4.6 days during the same period, but the mean hospital charges
62 increased from \$19,303 in 2001 to \$35,728 in 2014. The proportion of males to females with
63 acute pancreatitis is slowly trending up from 2001 to 2014. Aggregate charges increased
64 from 4.15 billion dollars to 9.98 billion dollars.

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Figure 1. Trends in Mortality Rate of Acute Pancreatitis in the United States from 2001-2014.

Year	2014	2013	2012	2011	2010	2009	2008	2007	2006	2005	2004	2003	2002	2001
Sample Size, n	35,358,818	35,597,792	36,484,846	36,962,415	37,352,013	37,734,584	38,210,889	38,155,908	38,076,556	37,843,039	37,496,978	37,074,605	36,523,831	36,093,550
Acute pancreatitis, n	279,145	274,775	275,170	276,954	277,050	262,605	260,856	246,536	249,361	243,092	246,227	238,306	235,589	215,238
Males(%)	50.4	50.52	50.3	50.54	50.11	50.32	50.67	50.72	50.82	50.81	50.96	50.79	50.6	50.61
Females(%)	52.12	52.19	52.21	52.64	52.14	52.6	52.86	53.1	53.55	53.72	53.98	54.21	54.16	55.02
Mortality(%)	0.66	0.76	0.78	0.81	0.9	0.96	0.99	0.99	1.02	1.19	1.36	1.43	1.6	1.74
Mean LOS(d)	4.6	4.7	4.7	4.9	5	5.1	5.3	5.3	5.5	5.5	5.7	5.8	5.9	6.1
Mean hospital Charges(\$)	35,728	34,897	33,744	34,116	32,413	31,231	30,454	28,808	26,544	25,183	23,525	23,471	20,870	19,303
Aggregate Charges(Billion \$)	9.98	9.58	9.27	9.43	8.98	8.21	7.94	7.09	6.64	6.13	5.8	5.6	4.92	4.15

Table 1. Trends of Hospitalization in Acute Pancreatitis in Patients in the United States from 2001-2014

4. Discussion

Gallstones are the most common cause of AP accounting for about 40 to 70 percent of cases.(3, 4). The risk of developing AP in patients with gallstones is more significant in men. However, women have a higher prevalence of gallstones, and the incidence of gallstone

77 pancreatitis is higher in women. Patients with gallstones of size less than 5 mm are thought
78 to be at higher risk of gallstone pancreatitis.(5)

79 Alcohol intake is responsible for approximately 25 to 35 percent of cases of AP in the
80 United States.(6) Cigarette smoking might have an additive effect along with alcohol in
81 inducing pancreatitis. Alcohol may increase the secretion of lysosomal enzymes by acting
82 on the pancreatic acinar cells.(7) Although the exact pathogenesis of alcohol-induced AP is
83 still unclear.(8)

84 Serum triglyceride levels above 1000 mg/dL can cause AP.(9-11) Hypertriglyceridemia
85 accounts for about 1 to 14 percent of cases of AP.(12) Pancreatitis secondary to
86 hypertriglyceridemia is usually seen in the presence of one or more factors such as diabetes,
87 alcoholism in the presence of an underlying common genetic abnormality like familial
88 hypertriglyceridemia.(12, 13) Insulin and heparin along with other measures used for AP
89 have been proposed as the treatment for AP due to hypertriglyceridemia.(11)

90 Post-endoscopic retrograde cholangiopancreatography (ERCP) is associated with 3-5% of
91 cases with AP.(14) The risk of Post ERCP AP is also related to the type of ERCP procedure
92 being performed.(15) Studies have shown that patients undergoing ERCP for sphincter of
93 Oddi dysfunction are more to develop AP when compared to other ERCP related
94 procedures.(16)

95 Pancreatitis has been associated with multiple infections like Viruses (Mumps, hepatitis B,
96 cytomegalovirus, herpes simplex, human immunodeficiency virus), Bacteria (Mycoplasma,
97 Legionella, Salmonella), Fungi (Aspergillus) and Parasites (Toxoplasma, Ascaris).(17, 18)

98 Mutations in CTSC gene, CFTR gene, PRSS1 gene, SPINK1 have been implicated in
 99 pancreatitis etiology.(19) Patients with pancreatitis due to genetic mutations usually
 100 present as recurrent bouts of AP or childhood pancreatitis before it progresses to chronic
 101 pancreatitis and complications related to pancreatitis.

102 Drug-induced pancreatitis is rare and accounts for less than 5% of the cases.(20) Prognosis
 103 of drug-induced AP is good, and mortality is low. The diagnosis of drug-induced
 104 pancreatitis is difficult to establish as it is a diagnosis of exclusion.(21) Common drugs
 105 implicated in causing AP include aminosalicylates, sulfonamides, diuretics, valproic acid,
 106 didanosine, pentamidine, tetracycline, azathioprine, steroids.(22-24) Recently Glucagonlike
 107 peptide 1-based therapies have been increasingly implicated in etiology of drug-induced
 108 AP.(25)

109 Idiopathic causes can account up to 25% of the causes of AP. No etiology could be found on
 110 history, diagnostic tests or imaging. Research has shown recently that patient with
 111 idiopathic pancreatitis usually has complex genetic profiles.(26)

112 Other rare causes of pancreatitis include Pancreatic duct injury, Biliary obstruction,
 113 Hypercalcemia, Vascular disease, Biliary sludge and microlithiasis, Anatomic pancreatic
 114 anomalies.(27-33)

115

116 5. Conclusions

117 Etiology of AP can be established in most cases of AP. Although some cases can be
 118 challenging and in some patients, we may not find any etiology (idiopathic).
 119 Understanding the etiologic and risk factors of AP helps in formulating an appropriate

120 management plan and helps to decrease the length of stay and cost associated with
 121 hospitalizations due to AP and might also lead to decrease in mortality due to AP. Overall
 122 in-hospital mortality decreased but the number of hospitalizations and mean cost has
 123 increased over the years. This represents a significant cost burden on the healthcare system
 124 and patients. The decrease in mortality can be attributed to early diagnosis and early
 125 institution of aggressive treatments. The number of hospitalizations due to acute
 126 pancreatitis has been steadily increasing, and further research needs to be done on finding
 127 out the reasons for increased causes of hospitalization and ways to decrease the cost burden
 128 on patients and hospitals.

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130 **Author Contributions:** Conception and design: Roberto Argo, Albert Bianco, Kevin Casey,
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132 Analysis and interpretation, Drafting and Critical revision of the Article: Roberto Argo,
 133 Albert Bianco, Kevin Casey, Francesco Ricci, Daniele Costa.

134 Final approval of the article: Roberto Argo, Albert Bianco, Kevin Casey, Francesco Ricci,
 135 Daniele Costa.

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Mortality(%)	0.66	0.76	0.78	0.81	0.9	0.96	0.99	0.99	1.02	1.19	1.36	1.43	1.6	1.74
Mean LOS(d)	4.6	4.7	4.7	4.9	5	5.1	5.3	5.3	5.5	5.5	5.7	5.8	5.9	6.1
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