

Retrospective Study

Hospitalization for esophageal achalasia in the United States

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Abstract

AIM: To assess the outcome of different treatments in patients admitted for esophageal achalasia in the United States.

METHODS: This is a retrospective analysis using the Nationwide Inpatient Sample over an 8-year period (2003-2010). Patients admitted with a primary diagnosis of achalasia were divided into 3 groups based on their treatment: (1) Group 1: patients who underwent Heller myotomy during their hospital stay; (2) Group 2: patients who underwent esophagectomy; and (3) Group 3: patients not undergoing surgical treatment. Primary outcome was in-hospital mortality. Secondary outcomes included length of stay (LOS), discharge destination and total hospital charges.

RESULTS: Among 27141 patients admitted with achalasia, nearly half (48.5%) underwent Heller myotomy, 2.5% underwent esophagectomy and 49.0% had endoscopic or other treatment. Patients in group 1 were younger, healthier, and had the lowest mortality when compared with the other two groups. Group 2 had the highest LOS and hospital charges among all groups. Group 3 had the highest mortality (1.2%, $P < 0.001$) and the lowest home discharge rate (78.8%) when compared to the other groups. The most frequently performed procedures among group 3 were esophageal dilatation (25.9%) and injection (13.3%). Among patients who died in this group the most common associated morbidities included acute respiratory failure, sepsis and aspiration pneumonia.

CONCLUSION: Surgery for achalasia carries exceedingly low mortality in the modern era; however, in complicated patients, even less invasive treatments are burdened by

significant mortality and morbidity.

Key words: Esophageal achalasia; Outcomes; Myotomy

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Core tip: We aimed to assess the outcomes of different treatments in patients hospitalized for esophageal achalasia in the United States. We queried the Nationwide Inpatient Sample database from 2003 to 2010. Patients admitted with a primary diagnosis of achalasia were divided into 3 groups, based on treatment, and compared. About half of the patients did not actually undergo a surgical procedure; yet, they had the highest mortality and lowest home discharge rate. Our data suggest that when achalasia has gone too far and previous treatments have been untimely or ineffective, patients may face non-negligible mortality and morbidity even with endoscopic treatment or supportive care.

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INTRODUCTION

Achalasia is a chronic, progressive disease characterized by loss of peristalsis of the distal esophagus, failure of the lower esophageal sphincter to completely relax with deglutition, and elevated baseline intraluminal esophageal pressure^[1]. The pathophysiology of the impaired peristalsis is represented by the progressive degeneration and destruction of a subpopulation of inhibitory neuronal ganglion cells of the Auerbach myenteric plexus of the esophagus^[2]. The resulting long lasting contraction of the lower esophageal sphincter (LES) causes stasis of food within the esophageal lumen until the rising intraesophageal pressure overcomes the obstacle represented by the cardiac spasm and the bolus slowly transits into the stomach. The outflow obstruction inevitably leads, over time, to progressive esophageal dilation and tortuosity, if the condition is left untreated.

The treatment of achalasia is substantially palliative and aims to relieve symptoms and to contrast the natural history of the disease through improvement of passive esophageal transit. The distal esophageal obstacle to food progression can be eliminated with endoscopic pneumatic dilation or surgical myotomy, both with similar short-term success of about 80%-90% and a long-term control of symptoms of approximately 50% with dilation, and 80%-90% with myotomy^[3-6].

The therapeutic options for achalasia also include endoscopic botulin toxin injection, especially for the high-risk patients or those patients with contraindications to pneumatic dilation or surgery; this procedure, however,

is burdened by high long-term costs, short lasting results and a high recurrence rate^[7]. Pharmacological treatment of achalasia, targeted to induce LES relaxation with nitrates and calcium channel blockers, has been shown to yield unsatisfying results with poor control of symptoms^[8,9].

We believe that the severity of the disease is often underestimated, especially in more advanced stages, due to its slow progression and to its common classification as a benign condition. We therefore queried the Nationwide Inpatient Sample (NIS), in order to assess the outcome of different treatments in patients admitted for esophageal achalasia in the United States.

MATERIALS AND METHODS

Data source and study population

A retrospective review was performed using the NIS database from 2003-2010. NIS consists of 20% stratified sample of all United States hospitals, and it provides discharge weights to produce a 95% of all discharges in the United States^[10]. International Classification of Diseases, ninth revision (ICD-9) coding was used to establish the desired study population. All patients admitted with a primary diagnosis of achalasia (ICD-9 diagnosis code of 530.0) were included in the study. These patients were divided into 3 groups based on their in-hospital treatment: (1) Group 1: Achalasia patients who underwent Heller myotomy during their hospital stay (ICD-9 procedure code of 42.7); (2) Group 2: Achalasia patients who underwent esophagectomy (ICD-9 procedure codes of 150, 150.1, 150.2, 150.3, 150.4, 150.5, 150.8, 151); and (3) Group 3: Achalasia patients not undergoing surgical treatment. This study was limited to adult patients (> 17 years old) without a diagnosis of esophageal cancer (ICD-9 diagnosis codes of 150, 150.1, 150.2, 150.3, 150.4, 150.5, 150.8, 151). This study was granted exempt status by the Johns Hopkins Medicine Institutional Review Board.

Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes included length of stay (LOS), discharge destination (home/transfer), total hospital charges (TOTCHG), and complications such as, pneumonia, urinary tract infection (UTI), shock/sepsis, and pulmonary compromise. These complications were obtained by using previously validated ICD-9 diagnosis codes (1-2) (Table 1). Total hospital charges were adjusted for inflation to reflect 2011 United States dollars.

Statistical analysis

All statistical analyses were performed using STATA/MP, version 11.2 (Stata Corp, College Station, Texas). Weighting strategy was applied prior to conducting statistical analysis. Adjusted Wald test and Pearson's χ^2 were used for continuous and categorical variables, respectively. Multivariable logistic regressions were performed to compare odds of each outcome while

Table 1 International Classification of Disease, ninth revision procedure and diagnosis codes used to determine surgical procedure categories and complications

	ICD-9 code
Achalasia	530
Heller ¹	427
Esophagectomy ¹	42.4, 42.41, 42.42, 42.5, 42.51-59, 42.6, 42.61-69
Esophageal cancer	150, 150.1, 150.2, 150.3, 150.4, 150.5, 150.8, 151
Complications	
Pneumonia	481, 482.0-482.4, 482.8-482.9, 483, 484, 485, 486, 507.0, 482.40, 482.41, 482.42, 482.49
Urinary tract infection	997.5, 599.0-599.9
Shock/sepsis	998.0, 995.9, 995.90, 995.91, 995.92, 038
Pulmonary compromise	514, 518.4, 518.5, 518.81, 518.82

¹Indicates procedure codes. ICD-9: International Classification of Disease, ninth revision.

adjusting for age, gender, and Charlson Index score. Adjusted TOTCHG and LOS were obtained from a multiple regression, while adjusting for age, gender, and Charlson Index score. A level of significance was set at $\alpha = 0.05$.

RESULTS

Baseline demographic and clinical characteristics

A total of 31769 achalasia patients met the study criteria, including, 15567 Heller patients (49.0%), 785 esophagectomy patients (2.5%), and 15417 non-surgical patients (48.5%) (Table 2). The overall mean age was 59 (median 59), with 54.3% females, and 70.8% white patients. Heller group was the youngest (median age of 51) and the healthiest (mean Charlson score of 0.34). While the non-surgical group was the oldest (median age 72) with the highest comorbidity (mean Charlson score of 0.93). Among the most common procedures performed for patients who underwent non-surgical treatment of achalasia (group 3) were: esophagogastroduodenoscopy (65.2%), dilation of esophagus (26.9%), and injection of therapeutic/prophylactic substance-including botulism antitoxin (17.3%) (Table 3).

Unadjusted outcomes

The overall in-hospital mortality was 0.65%, with the highest unadjusted mortality seen in the esophagectomy group (1.96%) (Table 4). There was no significant difference between the in-hospital mortality for the esophagectomy group vs non-surgical group. The esophagectomy group stayed in the hospital the longest (median LOS of 13 d) and had highest total hospital charges (median TOTCHG of \$134670.40). Achalasia patients undergoing Heller myotomy were the most likely to be discharged home (97.2%) and were less likely to acquire pneumonia, UTI, shock/sepsis, and pulmonary compromise (3.3%, 2.0%, 0.3%, and 1.6%, respectively). Pneumonia, shock/sepsis, and pulmonary compromise were the most common complications in the esophagectomy group. Mean LOS, TOTCHG,

and pneumonia were significantly different across all three groups (even when the pairwise comparison was applied).

Adjusted outcomes

Multivariable logistic regression was performed for the two surgical groups vs the non-surgical group, while adjusting for age, gender, and Charlson Index score.

Heller vs non-surgical group

The likelihood of in-hospital mortality was more than four times higher in the non-surgical group (OR = 4.73, 95%CI: 1.16-19.31, $P = 0.03$), and the chance to develop pneumonia and UTI was doubled (OR = 1.91, 95%CI: 1.42-2.58, $P < 0.001$; OR = 2.31, 95%CI: 1.67-3.18, $P < 0.001$, respectively) when compared to the Heller group. Moreover, the non-surgical group was significantly more likely to be transferred (OR = 3.76, 95%CI: 2.85-4.97, $P < 0.001$). The non-surgical achalasia patients paid \$14594.24 less ($P < 0.001$) in TOTCHG and stayed in the hospital about one day longer ($P < 0.001$) than the Heller patients (Table 5).

Esophagectomy vs non-surgical group

The esophagectomy group was seven times as likely to have an in-hospital mortality (OR = 7.28, 95%CI: 2.06-25.79, $P = 0.002$) and nearly twice as likely to be transferred compared to the non-surgical group (OR = 1.84, 95%CI: 1.16-2.94, $P = 0.01$). Achalasia patients who underwent esophagectomy had also higher complications such as pneumonia, shock/sepsis, and pulmonary compromise (OR = 3.68, 95%CI: 2.40-5.64, $P \leq 0.001$; OR = 16.53, 95%CI: 6.36-42.96, $P < 0.001$; OR = 37.97, 95%CI: 22.85-63.07, $P < 0.001$, respectively). Esophagectomy patients stayed in the hospital twelve days longer ($P < 0.001$) and paid \$181167.90 more ($P < 0.001$) than the non-surgical patients (Table 6).

DISCUSSION

Our study shows that more than 30000 patients were hospitalized over an 8-year period for the treatment of esophageal achalasia in the United States. It would be intuitive to assume that most patients were admitted to undergo surgery, since endoscopic treatment is commonly performed in the outpatient setting. Only half of them underwent a surgical procedure instead, thus suggesting that the natural history of the disease can potentially lead to complications severe enough to require admission.

As broadly demonstrated in previous studies, we confirmed that patients treated with Heller myotomy benefit from low mortality, morbidity and LOS. The most frequent procedures performed among the non-surgical group were endoscopic pneumatic dilatation (25.9%) and endoscopic drugs injection (13.3%). It is common and widespread practice to elect non-surgical,

Table 2 Baseline demographic and clinical characteristics of patients among the three groups, Nationwide Inpatient Sample, 2003-2010 *n* (%)

	Total 31769	Group 1 Heller 5567 (49.00)	Group 2 Esophagectomy 785 (2.47)	Group 3 Non-surgical 15417 (48.53)	<i>P</i>
Age, mean (median)	59 (59)	51.2 (51)	53.8 (54)	67.1 (72)	< 0.001
Age category					< 0.001
18-44	8041 (25.31)	5576 (35.82)	251 (31.97)	2214 (14.36)	
45-64	10554 (33.22)	6330 (40.66)	308 (39.24)	3916 (25.40)	
65-74	4746 (14.94)	2254 (14.48)	141 (17.96)	2351 (15.25)	
≥ 75	8428 (26.53)	1407 (9.04)	85 (10.83)	6936 (44.99)	
Gender ¹					< 0.001
Male	14429 (45.73)	7883 (51.21)	371 (47.41)	6175 (40.17)	
Female	17120 (54.27)	7510 (48.79)	412 (52.59)	9198 (59.83)	
Race ²					0.002
White	17663 (70.77)	8662 (71.64)	403 (65.96)	8598 (70.15)	
Black	3662 (14.67)	1533 (12.68)	75 (12.27)	2054 (16.76)	
Other	3633 (14.56)	1896 (15.68)	133 (21.77)	1604 (13.09)	
Charlson score	0.63	0.34	0.48	0.93	0.036
0	21147 (64.53)	11681 (75.04)	508 (64.71)	7958 (51.62)	< 0.001
1	7390 (22.55)	3015 (19.37)	206 (26.24)	4169 (27.04)	
≥ 2	4232 (12.91)	871 (5.59)	71 (9.05)	3290 (21.34)	

¹Missing data for 220 patients; ²Missing data for 6811 patients.

Table 3 Most common procedure types for patients who underwent non-surgical treatment of achalasia

ICD-9 code	Procedure type	Group 3 Non-surgical 15417
45.13 and 45.16	Esophagogastroduodenoscopy	65.15%
42.92	Dilation of esophagus	26.94%
99.57 and 99.29	Injection of therapeutic/prophylactic substance-including botulism antitoxin	17.32%
98.02	Removal of intraluminal foreign body from esophagus without incision	6.44%
43.11	Percutaneous endoscopic gastrostomy percutaneous transabdominal gastrostomy	5.73%
29.31	Cricopharyngeal myotomy	2.77%

ICD-9: International Classification of Diseases, ninth revision.

Table 4 Observed unadjusted rates of outcomes across the three patient groups, Nationwide Inpatient Sample, 2003-2010 *n* (%)

	Total 31769	Group 1 Heller 15567 (49.00)	Group 2 Esophagectomy 785 (2.47)	Group 3 Non-surgical 15417 (48.53)	<i>P</i>
In-hospital mortality	206 (0.65)	16 (0.1)	15 (1.96)	180 (1.17)	< 0.001
Disposition					
Home ¹	27916 (87.87)	15130 (97.19)	637 (81.15)	12149 (78.80)	< 0.001
Transfer ²	3504 (11.03)	416 (2.67)	133 (16.89)	2955 (19.17)	< 0.001
Pneumonia	1959 (6.17)	509 (3.27)	150 (19.11)	1300 (8.43)	< 0.001
UTI	1462 (4.60)	311 (2.00)	50 (6.37)	1101 (7.14)	< 0.001
Shock/sepsis	171 (0.54)	50 (0.32)	46 (5.86)	75 (0.49)	< 0.001
Pulmonary compromise	813 (2.56)	241 (1.55)	245 (31.21)	327 (2.12)	< 0.001
Median LOS (d)	3	2	13	4	< 0.001
Median TOTCHG	\$26299.41	\$30118.12	\$134670.40	\$21175.23	< 0.001

¹Home is discharge to home with and without home health care; ²Transfer is discharge to short term hospital, skilled nursing facility, intermediate care and other type of facilities. LOS: Length of hospital stay; TOTCHG: Total hospital charges; UTI: Urinary tract infection.

thus less invasive, treatment as the best option for high-risk patients. This phenomenon can be indeed observed in demographics of group 3, which included the oldest patients and those with highest comorbidity. Nevertheless, it is interesting to remark that, even after adjusting for age, gender, and Charlson Index score, the non-surgical group was more than four times as likely to have in-hospital mortality, and twice as likely

to have pneumonia and UTI compared to the Heller group. This finding, which might appear counterintuitive at first glance, finds a logical explanation when recalling that non-surgical treatment of achalasia is usually administered in the outpatient setting. The youngest and most fit patients undergoing non-surgical treatment were therefore likely not captured by this analysis focusing on hospitalized patients. Conversely, many of

Table 5 Adjusted odds ratios of outcomes and complications for the non-surgical group (in comparison to the Heller group)

	OR	P	95%CI
In-hospital mortality	4.73	0.03	1.16-19.31
Disposition			
Home	0.24	< 0.001	0.19-0.31
Transfer	3.76	< 0.001	2.85-4.97
Pneumonia	1.91	< 0.001	1.42-2.58
Urinary tract infection	2.31	< 0.001	1.67-3.18
Shock/sepsis	1.18	0.726	0.47-2.97
Pulmonary compromise	0.83	0.413	0.54-1.29

All the analyses were adjusted for age, gender, and Charlson Index score.

the patients of our group 3 were probably complicated patients, such as subjects affected by advanced stage, recurrent or refractory achalasia, or individuals at high risk for surgery. In addition, our analysis is likely to have included in group 3 also those patients who faced serious complications of endoscopic treatments. Pneumatic dilation, although offering fast recovery and low overall complication rate, is burdened by a tangible risk of esophageal full-thickness perforation, especially when the procedure is repeated multiple times to maintain satisfactory results^[11,12].

Heller myotomy is usually performed laparoscopically and an antireflux procedure is commonly added; randomized studies have in fact confirmed its efficacy in decreasing postoperative gastroesophageal reflux disease^[13,14]. It is reasonable to hypothesize that the ongoing technical advancements in minimally invasive surgery, along with the widespread of advanced laparoscopic skills to an increasing number of surgeons, will strengthen the role of Heller myotomy as the safest and most durable choice for the treatment of achalasia.

The findings of our analysis outline the potential risks resulting from the insidious, slowly progressive nature of achalasia. When the disease has gone too far and previous treatments have been untimely or ineffective, patients may face non-negligible mortality and morbidity even with endoscopic treatment or supportive care. We therefore think that Heller myotomy should be strongly considered early in patients with esophageal achalasia and should be offered to all patients as the first therapeutic option, in absence of absolute contraindications to surgery.

This recommendation might change in the future, once the long term outcomes of patients treated with per-oral endoscopic myotomy (POEM) will become available. POEM, in fact, represents the cutting edge of minimally invasive treatment for achalasia and offers comparable early outcomes to Heller myotomy with the adjunctive benefit of being performed endoscopically^[15,16]. Therefore, if randomized studies will demonstrate long-term outcomes similar to those of laparoscopic Heller procedure, POEM might become the new gold standard for the treatment of esophageal achalasia.

Table 6 Adjusted odds ratios of outcomes and complications for the esophagectomy group (in comparison to the non-surgical group)

	OR	P	95%CI
In-hospital mortality	7.28	0.002	2.06-25.79
Disposition			
Home	0.54	0.009	0.35-0.86
Transfer	1.84	0.010	1.16-2.94
Pneumonia	3.68	< 0.001	2.40-5.64
Urinary tract infection	1.28	0.507	0.62-2.67
Shock/sepsis	16.53	0.001	6.36-42.96
Pulmonary compromise	37.97	< 0.001	22.85-63.07

All the analyses were adjusted for age, gender, and Charlson Index score.

Pulmonary symptoms as well as functional abnormalities have been demonstrated to be present in a significant percentage of patients with achalasia and are readily apparent in the poor pulmonary outcomes of our non-surgical group^[17]. Respiratory complications represent one of the most frequent causes of morbidity in patients with achalasia, if the natural history of the disease is not radically modified by treatment. In addition, radiological pulmonary abnormalities in the form of consolidation, ground glass opacities, nodular opacities, air trapping, fibrotic changes and bilateral alveolar findings that resemble aspiration pneumonia have been widely described in achalasia patients^[18]. Data in the literature support the hypothesis that surgery could not only improve the symptoms, but also lead to regression of the functional and radiological pathologic findings^[17,18].

The results of our analysis confirm that esophagectomy, as previously shown, is an operation burdened by significant mortality and morbidity. It has been reported that laparoscopic myotomy may still play a role and improve outcomes in patients with stage IV disease, even when a remarkable esophageal dilation is present; this is particularly true for patients with an enlarged but linear esophagus^[19].

However, about 5% of all patients with achalasia will eventually require esophagectomy and it is our belief that this procedure remains a reasonable option and a precious last resort in patients with end stage disease^[20-22]. Moreover, we have previously shown that operative outcomes, including mortality, overall morbidity, and LOS are comparable between patients undergoing esophagectomy for achalasia and for esophageal cancer^[23].

Our study presents some limitations worth mentioning. First of all, NIS is an administrative database, which is prone to errors due to missing or inaccurately entered ICD-9 codes. This database does not include any outpatient information, therefore patients that may have been treated by pneumatic dilation and sent home the same day are not captured. In addition, ICD-9 coding system is not perfect and specific procedures might be difficult to identify using the current ICD-9 procedure codes. For example, there is no specific

code for pneumatic balloon dilation, but there exists an ICD-9 code (42.92) for dilation of esophagus. There is no way to know if these dilations were merely routine dilations vs true pneumatic dilations with a 30 mm balloon. This fact, together with a small number of patients in the endoscopic injection group, did not allow us to meaningfully compare treatment subgroups among the non-surgical patients. No information is given on symptomatic relief and functional outcomes with this database, nor there is trace of postoperative events occurred after patients' discharge. Finally, it is not possible to know the stage of patients' disease at admission or if previous treatments for achalasia had been attempted.

That said, this study provides a useful general overview of the trends and outcomes of achalasia management and, in particular, it sheds light over the less studied populations of non-surgical patients who nonetheless needed hospitalization.

In conclusion, it is important to remark that the common labeling of achalasia as "benign condition" can be misleading and delay referral for definitive treatment. If left untreated or if treated with less than optimal approach, the disease will progress and can lead to complications, which will significantly affect patients' quality of life or potentially become life threatening. Although this database does not allow us to compare outcomes between endoscopic and surgical treatment of achalasia, the analysis of our data suggests that a timely and effective relief of esophageal obstruction may avoid future complications brought by the natural history of the disease.

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COMMENTS

Background

Achalasia is a chronic, progressive disease characterized by loss of peristalsis of the distal esophagus, failure of the lower esophageal sphincter to completely relax with deglutition, and elevated baseline intraluminal esophageal pressure. The treatment of achalasia is substantially palliative and aims to relieve symptoms and improve passive esophageal transit. The authors believe that the severity of the disease is often underestimated, especially in more advanced stages, due to its slow progression and to its common classification as a benign condition. Comparing the outcomes after different treatments in patients hospitalized for achalasia can help provide additional clinical insights for providers who care for these patients.

Research frontiers

Early intervention and modification of the history of achalasia is paramount, since the disease is prone to an insidious and burdensome progression, as evidenced by several studies, including the authors'. Awareness should be raised and efforts focused on early diagnosis and treatments. Surgical treatment remains the gold standard for improving symptoms, however less invasive procedures, like per-oral endoscopic myotomy (POEM), are being frequently used. Studies of POEM's long-term outcomes is a current hotspot in

the field.

Innovations and breakthroughs

This study takes an innovative approach, since it focuses on a different population than most other publications. It provides data and analysis of patients that were hospitalized for traditional treatments for achalasia in addition to patients that were admitted for complications of achalasia itself.

Applications

The data raises awareness for the common misconception in considering achalasia a benign condition. It is, in fact, an insidious disease that can lead to non-negligible mortality and morbidity when treated late or not incisively. This becomes apparent when analyzing the outcomes and characteristics in the authors' non-surgical group.

Peer-review

The authors have provided a valuable review on surgical treatment options in achalasia. The study design, discussion and conclusion are fine.

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