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Appendectomy for Appendicitis Has Worse Hospital Outcomes in Inflammatory Bowel Disease Patients

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Abstract

Background and Aims: Appendectomy is the choice of surgery for appendicitis but little is known about its outcomes in patients with Inflammatory Bowel Disease (IBD). We sought to compare hospital outcomes of appendectomy for appendicitis between patients with and without IBD. **Methods**: This is a cross-sectional study utilizing the Nationwide Inpatient Sample between 2009 and 2013. Patients with appendicitis undergoing appendectomy were identified using appropriate International Classification of Diseases codes. Primary outcomes of interest included length of stay (LOS), hospital costs, and post-surgical complications. Univariate and multivariate analyses were used to compare these outcomes between patients with and without IBD. **Results**: A total of 849,312 patients with appendicitis undergoing appendectomy were included in this study, of which 4261 patients had IBD. IBD patients had longer LOS and increased hospital costs. Crohn's disease (CD) patients were more likely to develop post-operative pulmonary embolism (adjusted odds ratio (aOR) 7.06, 95% Confidence Interval (CI) (2.19, 22.79)) and anemia (aOR 2.23, 95% CI (1.21, 4.10)), whereas ulcerative colitis patients were more likely to develop post-operative deep vein thrombosis (aOR 9.79, 95% CI (2.41, 39.75)). CD patients were more likely to have perforated appendicitis (aOR 1.37, 95% CI (1.67, 1.11)) and open appendectomy (aOR 1.56, 95% CI (1.96, 1.27)). **Conclusions**: Appendectomy for appendicitis in IBD patients is associated with adverse hospital outcomes. Focused attempts are needed to decrease the risk of DVT and PE in these patients. Treating patient's pre-surgical anemia and proactive venous thromboembolism prophylaxis in IBD patients

undergoing appendectomy for appendicitis might improve hospital outcomes.

Keywords

Ulcerative Colitis, Crohn's Disease, Inflammatory Bowel Disease, Appendicitis, Appendectomy, Outcomes

1. Introduction

Inflammatory Bowel Disease (IBD) consists of ulcerative colitis (UC) and Crohn's disease (CD), which are characterized by chronic inflammation with relapsing and remitting course involving the colonic mucosa and entire gastrointestinal tract, respectively [1] [2]. Both conditions result in decreased quality of life and increased morbidity [3] [4] [5]. Hospitalization due to IBD burdens the healthcare resource utilization system; the mean annual hospitalization cost for a CD patient was $2595 and $1895 for a UC patient between 2003 and 2004 [6].

Acute appendicitis is a common diagnosis with a lifetime incidence risk of about 8% among the general population [7]. The treatment of choice is laparoscopic appendectomy owing to less wound complications and faster recovery times [8]. Though it is one of the common emergent abdominal surgeries among hospitalized patients, not much is known about the hospital outcomes in IBD patients. Association of appendectomy with IBD has been studied previously, but there is paucity of research addressing the hospital outcomes of IBD patients undergoing appendectomy.

Thus we sought to compare hospital outcomes including in-hospital mortality, post-surgical complications, length of hospital stay and hospital costs between patients with and without IBD who underwent appendectomy for appendicitis.

2. Methods

2.1. Data Sources

All data were extracted from the Nationwide Inpatient Sample (NIS) between 2009 and 2013. NIS is the largest all-payer inpatient database in the United States. The database represents approximately a 20% sample of nonfederal, acute-care hospitals in the United States. The sampling frame includes community and general hospitals and academic medical centers comprising approximately 90% of all-hospital discharges in the United States. Each data entry includes a unique identifier, demographic variables (including age, gender and race/ethnicity), type of admission, source of admission, principal and secondary diagnoses, primary insurance payer, total hospital charges, and length of stay (LOS). Missing demographic information was summrized in **Supplementary Table S1**. Healthcare resource utilization included LOS and hospital costs. The comorbidity burden was stratified based on Elixhauser score <3 and ≥3 [9].

The "Data and Specimen Policy" and "Human Subjects Research Policy" at The Ohio State University does not require Institutional Review Board approval for population-based public data set [10].

2.2. Study Population and Definition of Variables

Our study consisted of all adult patients (≥18 years old) who had a principal discharge diagnosis of appendicitis and underwent appendectomy, identified by appropriate International Classification of Diseases, Ninth Revision, and Clinical Modification codes (ICD-9-CM) (**Appendix 1**). The patients were considered to have IBD if the secondary discharge diagnosis was either UC or CD. These criteria have been previously used and validated at a tertiary care academic center [9] [11]. Elective admissions and patients with discharge diagnoses of both UC and CD were excluded.

2.3. Outcomes

Our outcomes of interest were In-hospital Mortality, LOS, total hospital cost and incidence of post-surgical complications.

2.4. Statistics

Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC), employing appropriate survey estimation commands and strata weights. Continuous variables were summarized with means and confidence intervals. Categorical variables were summarized with frequencies and percentages. Differences between patients with and without IBD undergoing appendectomy were analyzed using X^2 tests or Student's t-tests, as appropriate. Multivariate logistic regression was used to calculate adjusted odds ratios and corresponding 95% confidence intervals for in-hospital mortality, incidence of post-surgical complications, and all other bivariate outcomes. Multivariate linear regression was used to analyze LOS and hospital cost. Each multivariate model was adjusted for patient demographics and hospital characteristics, sample size permitting. The models for LOS and hospital costs were additionally adjusted for type of appendicitis, surgery type and significant post-operative complications. The mortality and post-operative complications models were additionally adjusted for appendicitis type and surgery type.

3. Results

3.1. Demographic Characteristics of Patients and Hospitals

A total of 849,312 patients were included during the study period, of which there were 1845 patients with UC (0.22%), 2416 patients with CD (0.28%), and 845,051 patients with no IBD (99.50%) after 381,592 patients were excluded. Univariate analysis (**Table 1** and **Supplementary Table S2**) demonstrated that patients with UC were more likely to be olde0r and to have more comorbidities, including anemia, chronic blood loss, congestive heart failure, depression,

Table 1. Univariate analysis of non-inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC) patient and hospital characteristics.

	No IBD (n = 845,051)		CD (n = 2416)		p-value	UC (n = 1845)		p-value
Age (mean, SE)	41.44	0.08	41.46	0.72	0.967	44.99	0.81	<0.001
Sex					0.380			0.672
Male	446,401	53.31%	1235	51.30%		1000	54.43%	
Female	390,956	46.69%	1173	48.70%		837	45.57%	
Race					<0.001			<0.001
White	493,815	64.38%	1686	77.79%		1,424	83.39%	
Black	57,904	7.55%	185	8.52%		113	6.62%	
Hispanic	150,255	19.59%	184	8.47%		114	6.67%	
Other	65,104	8.49%	113	5.22%		57	3.33%	
Insurance					<0.001			<0.001
Medicare	102,771	12.20%	337	14.01%		284	15.40%	
Medicaid	103,107	12.24%	232	9.63%		140	7.59%	
Private	459,099	54.49%	1545	64.19%		1,259	68.24%	
Other	177,632	21.08%	293	12.17%		162	8.77%	
Income Quartile					0.491			<0.001
1	190,784	23.12%	511	21.52%		278	15.58%	
2	196,955	23.87%	549	23.14%		393	21.97%	
3	217,250	26.33%	608	25.60%		486	27.18%	
4	220,093	26.68%	706	29.73%		630	35.27%	
Elixhauser Comorbidity					<0.001			<0.001
<3	765,867	90.63%	2,082	86.15%		1,529	82.88%	
≥3	79,184	9.37%	335	13.85%		316	17.12%	
Hospital Bed Size					0.692			0.362
Small	116,963	13.92%	361	14.96%		239	13.00%	
Medium	222,620	26.50%	658	27.29%		437	23.82%	
Large	500,389	59.57%	1,393	57.76%		1,160	63.18%	
Hospital Type					0.360			0.323
Rural	94,489	11.25%	308	12.78%		179	9.74%	
Urban Non-Teaching	402,265	47.89%	1,187	49.22%		841	45.81%	
Urban Teaching	343,218	40.86%	917	38.00%		816	44.45%	
Hospital Region					0.019			0.007
Northeast	186,259	22.04%	544	22.52%		514	27.88%	
Midwest	145,426	17.21%	534	22.10%		369	19.99%	
South	287,006	33.96%	799	33.07%		539	29.23%	
West	226,361	26.79%	539	22.30%		423	22.90%	
Appendicitis Type					0.001			0.422
Perforated	231,732	27.42%	821	33.97%		472	25.59%	
Non-Perforated	613,320	72.58%	1596	66.03%		1,373	74.41%	
Surgery Type[1]					<0.001			0.486
Open	183,078	21.66%	744	30.80%		427	23.15%	
Laparoscopic	661,974	78.34%	1672	69.20%		1,418	76.85%	

[1]Patients with codes for both open and laparoscopic procedures were classified as open.

hypertension, liver disease, fluid and electrolyte disorders, valvular disease and weight loss when compared with patients without IBD. Patients with CD were more likely to have anemia, rheumatoid arthritis or collagen vascular disease, coagulopathy, fluid and electrolyte disorders, psychoses, and weight loss compared to patients without IBD.

Multivariate analysis adjusting for age, gender, race, insurance, income, Elixhauser score, and hospital size, type and region revealed that, UC patients were more likely to have non-perforated appendicitis (aOR 1.36, 95% CI (1.04, 1.79)) when compared with non-IBD patients (**Table 2**). CD patients were more likely to have perforated appendicitis (aOR 1.37, 95% CI (1.67, 1.11)) and require open appendectomies (aOR 1.56, 95% CI (1.96, 1.27)) (**Table 3**).

3.2. Outcomes

3.2.1. Mortality

In-hospital mortality was not different between CD and non-IBD patients after appendectomy and we were unable to compare the mortality between UC and non-IBD patients, as there were no deaths among the UC patients.

3.2.2. Hospital Resource Utilization (Length of Stay and Hospital Cost)

After adjusting for patient and hospital characteristics, appendicitis type (non-perforated versus perforated), surgery type (laparotomy versus open) and significant post-surgical complications, both UC and CD patients after appendectomy had longer LOS (adjusted coefficient, 0.45 days, 95% CI (0.11, 0.79); adjusted coefficient, 0.91 days, 95% CI (0.69, 1.14), respectively) when compared

Table 2. Univariate and multivariate analyses of length of stay (LOS), hospital costs, post-operative deep vein thrombosis, type of appendicitis and type of surgery between patients with UC and no IBD.

	Univariate			Multivariate		
	Odds ratio (OR)/Coefficient (95% CI)		p-value	Adjusted OR (aOR)/Coefficient (95% CI)		p-value
Length of Stay[1] (days)	0.72	(0.31, 1.12)	<0.001	0.45	(0.11, 0.79)	0.010
Cost[1] ($)	1473	(364, 2583)	0.009	902	(10, 1,794)	0.047
Deep Vein Thrombosis[2]	10.75	(2.63, 43.89)	<0.001	9.79	(2.41, 39.75)	0.001
Appendicitis Type[3]			0.432			0.026
Perforated		Reference			Reference	
Non-Perforated	1.10	(0.87, 1.38)		1.36	(1.04, 1.79)	
Surgery Type[3,4]			0.475			0.747
Open		Reference			Reference	
Laparoscopic	0.92	(0.72, 1.17)		0.96	(0.73, 1.25)	

[1]Adjusted for age, gender, race, insurance, income, Elixhauser score, hospital size, type, and region, appendicitis type, surgery type and deep vein thrombosis. [2]Adjusted for age, race, insurance, income, and Elixhauser score. [3]Adjusted for age, gender, race, insurance, income, Elixhauser score, hospital size, type, and region. [4]Patients with codes for both open and laparoscopic procedures were classified as open.

Table 3. Univariate and multivariate analyses of mortality, LOS, hospital costs, post-operative pulmonary embolism and anemia, type of appendicitis and type of surgery between patients with CD and no IBD.

	Univariate			Multivariate		
	Odds ratio (OR)/Coefficient (95% CI)		p-value	Adjusted OR (aOR)/Coefficient (95% CI)		p-value
Mortality[1]	2.16	(0.30, 15.35)	0.441	2.23	(0.29, 17.06)	0.441
Length of Stay[2] **(days)**	1.30	(1.00, 1.60)	<0.001	0.91	(0.69, 1.14)	<0.001
Cost[2] **($)**	2,575	(1818, 3332)	<0.001	1952	(1343, 2562)	<0.001
Pulmonary Embolism[3]	8.11	(2.55, 25.79)	<0.001	7.06	(2.19, 22.79)	0.001
Postoperative Anemia[2]	3.02	(1.84, 4.95)	<0.001	2.23	(1.21, 4.10)	0.010
Appendicitis Type[4]			0.001			0.003
Perforated	1.37	(1.64, 1.14)		1.37	(1.67, 1.11)	
Non-Perforated		Reference			Reference	
Surgery Type[4,5]			<0.001			<0.001
Open	1.61	(1.96, 1.32)		1.56	(1.96, 1.27)	
Laparoscopic		Reference			Reference	

[1]Adjusted for age, gender, race, insurance, Elixhauser score, hospital type, and region, appendicitis type, and surgery type. [2]Adjusted for age, gender, race, insurance, income, Elixhauser score, hospital size, type, and region, appendicitis type, surgery type, GI complications, hemorrhage, hematoma, seroma, pulmonary embolism and post-operative anemia. [3]Adjusted for age, gender, race, insurance, Elixhauser score, hospital region, appendicitis type, and surgery type. [4]Adjusted for, age, gender, race, insurance, income, Elixhauser score, hospital size, type, and region. [5]Patients with codes for both open and laparoscopic procedures were classified as open.

with non-IBD patients. Similarly, UC and CD patients had higher hospital costs (adjusted coefficient, $902, 95% CI (10, 1794); adjusted coefficient, $1952, 95% CI (1343, 2562), respectively) when compared with non-IBD patients (**Table 2** and **Table 3**).

3.2.3. Post-Surgical Deep Vein Thrombosis, Pulmonary Embolism, and Post-Operative Anemia

After adjusting for patient and hospital characteristics, appendicitis type, and surgery type, CD patients after appendectomy were more likely to develop pulmonary embolism (PE) (aOR, 7.06, 95% CI (2.19, 22.79)) and post-operative anemia (aOR, 2.23, 95% CI (1.21, 4.10)) compared to non-IBD patients, whereas UC patients were more likely to develop deep vein thrombosis (DVT) only (aOR, 9.79, 95% CI (2.41, 39.75)) (**Table 2** and **Table 3**).

4. Discussion

In this study of the nationwide inpatient database, patients with IBD undergoing appendectomy for appendicitis, although not incurring attributable mortality, was associated with increasing healthcare resource utilization with longer duration of hospitalization, and higher hospital costs. Further, IBD patients also in-

curred increased risk of post-surgical complications, specifically, DVT in UC patients and PE and post-operative anemia in patients with CD. Furthermore, patients with CD were more likely to have perforated appendicitis and open appendectomy compared to patients with no IBD. To our knowledge, this is the first population-based study evaluating hospital outcomes of IBD patients admitted with appendicitis.

While adult patients with non-perforated appendicitis can be safely discharged on the same day after laparoscopic appendectomy without high rates of complications [12], IBD patients in general have higher complexity, increased hospital costs and health resource utilization [13]. The study findings are similar to published data on IBD patients undergoing elective colectomy for colorectal cancer or diverticular disease where they contribute to higher healthcare resource utilization including prolonged hospitalization and higher hospital costs when compared with non-IBD patients [14]. Despite controlling for type of appendicitis and appendectomy, patients with UC and CD were associated with longer LOS and higher hospital costs. Compared to patients with UC, those with CD were more likely to have perforated appendicitis, which may be partially attributed to transmural inflammation associated with CD. Consequently, CD patients required more open appendectomies.

IBD patients undergoing appendectomy for appendicitis had increased risk of DVT or PE, which is in agreement with previous studies [15] [16]. Although chronic inflammation may play a role, DVT or PE could be an extra-intestinal manifestation of IBD as these are not associated with other inflammatory conditions like rheumatoid arthritis and celiac disease [17]. IBD patients have 2 - 3 fold-increased risk of venous thromboembolism [16] [18], particularly after surgery (19). Hence, pharmacologic DVT prophylaxis is recommended in all hospitalized patients with IBD unless contraindicated [18].

Patients with CD, but not UC, were more likely to have post-operative anemia compared to patients without IBD. Anemia is more prevalent in IBD patients due to iron deficiency, anemia of chronic disease, or vitamin B12 deficiency [19] with CD patients having higher incidence than UC patients [20]. In addition, perioperative blood transfusion has been shown to be associated with post-operative infection and worse hospital outcomes in CD [21]. Therefore, pre-operative optimization of anemia, for instance intravenous iron therapy, may improve outcomes of CD patients undergoing surgery [22].

We note that this study has several limitations. Accuracy of ICD-9-CM coding could not be verified by chart review, owing to privacy safeguards. However, the Agency for Healthcare Research and Quality has reviewed the NIS database and found good reliability [23]. In addition, any errors in administrative data should be distributed non-differentially across all groups [24]. Furthermore, administrative discharge codes have been previously used and validated for outcomes research in a variety of diseases [25] [26]. Due to the large number of patients included in the study, there is a risk of identifying statistically significant findings which are of no clinical significance. We reported ORs and 95% CIs to de-

termine the strength of the correlations and improve interpretation. There are no laboratory values or medication data in the NIS (*i.e.*, unable to determine use of immuno-modulators, or post-operative DVT prophylaxis), and no details about disease duration or distribution. This study demonstrated only an association between IBD and worse hospital outcomes in patients with appendicitis undergoing appendectomy. However, determination of causality would require a prospective study.

Despite the above limitations, our study also has several strengths. The NIS database provides a large number of patients with a discharge diagnosis of IBD who underwent appendectomy for appendicitis, which may not be possible from single center or multicenter studies. The benefit of using the NIS database is the results also represent the current national in-patient health-care utilization of IBD patients with appendicitis who underwent appendectomy.

5. Conclusion

IBD patients with appendicitis undergoing appendectomy had worse hospital outcomes when compared to non-IBD patients. Efforts should be made to give DVT prophylaxis for all IBD patients undergoing appendectomy as the risk of venous thromboembolism (DVT and PE) is very high. Pre-operative anemia in CD patients should be treated adequately with intravenous iron infusions as correcting anemia would improve surgical outcomes. Though laparoscopic approach is ideal for appendectomy, it is reasonable to have low threshold to convert to open appendectomy in CD patients, owing to increased association with perforated appendicitis.

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Appendix 1

Table A1. ICD-9 codes.

	Variable/Outcome	ICD-9 codes
IBD	Crohn's Disease (CD)	555, 555.0, 555.1, 555.2, and 555.9
	Ulcerative Colitis (UC)	556, 556.0, 556.1, 556.2, 556.3, 556.4, 556.5, 556.6, 556.8, 556.9
Appendicitis	Perforated	540.0, 540.1
	Non-Perforated	540.09, 541, 542
Appendectomy	Open	47.09
	Laparoscopic	47.01
Post-operative complications	Central Nervous System	997.0, 997.00, 997.01, 997.02, 997.09
	Cardiac	997.1
	Peripheral Vascular	997.2, 999.2
	Respiratory	512.1, 997.3, 997.31, 997.39
	Gastrointestinal	997.4, 997.49
	Genitourinary	997.5
	Hemorrhage, hematoma, or Seroma	998.1, 998.11, 998.12, 998.13, 998.2, 998.51
	Wound dehiscence, rupture, nonhealing, disruption	998.3, 998.83, 998.0, 998.31, 998.32, 998.33
	Postoperative Infection	998.5, 998.51, 998.59
	Deep Vein Thrombosis	453.4, 453.40, 453.41, 453.42
	Pulmonary Embolism	415.1, 415.11, 415.19
	Postoperative Anemia	285.1
	Foreign Object Retained After Surgery	998.4, 998.7
	Air Embolism	999.1
	Blood Incompatibility	999.6, 999.60, 999.61, 999.62, 999.63, 999.69
	Pressure Ulcer Stages II & IV	707.23, 707.24
	Falls and Trauma	800 - 829, 830 - 839, 850 - 854, 925 - 929, 940 - 949, 991 - 994
	Catheter-Associated UTI	996.64
	Vascular Catheter-Associated Infection	999.31
HAC	Manifestations of Poor Glycemic Control	250.10 - 250.13, 250.20 - 250.23, 251.0, 249.10 - 249.11, 249.20 - 249.21
	Surgical Site Infection, Mediastinitis, Following CABG	519.2 And one of the following procedure codes: 36.10 - 36.19
	Surgical Site Infection Following Certain Orthopedic Procedures	996.67, 998.59 And one of the following procedure codes: 81.01 - 81.08, 81.23, 81.24, 81.31 - 81.38, 81.83, 81.85
	Surgical Site Infection Following Bariatric Surgery for Obesity	539.01, 539.81, 998.59 And one of the following procedure codes: 44.38, 44.39, 44.95
	Deep Vein Thrombosis and Pulmonary Embolism Following Certain Orthopedic Procedures	415.11, 415.13, 415.19, 453.40 - 453.42 And one of the following procedure codes: 00.85-00.87, 81.51-81.52, 81.54

Supplementary

Table S1. Missing data.

	Percent Missing
Gender	0.94%
Race	9.37%
Income	2.33%
Type of insurance	0.28%
Hospital location/teaching status	0.61%
Hospital size	0.61%
Hospital region	0.00%

Table S2. Univariate analysis of Elixhauser comorbidities of non-inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC).

	No IBD (n = 845,051)		CD (n = 2416)		p-value	UC (n = 1845)		p-value
AIDS	1035	0.12%	0	0.00%	--	0	0.00%	--
Alcohol Abuse	9655	1.14%	51	2.10%	0.051	41	2.22%	0.057
Anemia	28,085	3.32%	195	8.06%	<0.001	147	7.98%	<0.001
Rheumatoid Arthritis/Collagen Vascular Disease	6884	0.81%	50	2.05%	0.003	30	1.64%	0.080
Chronic Blood Loss	1567	0.19%	≤10	0.17%	0.944	15	0.83%	0.005
Congestive Heart Failure	9821	1.16%	44	1.83%	0.169	45	2.44%	0.023
Chronic Lung Disease	63,243	7.48%	208	8.62%	0.354	186	10.08%	0.055
Coagulopathy	7256	0.86%	29	1.20%	0.415	30	1.62%	0.112
Depression	38,962	4.61%	185	7.64%	0.001	179	9.70%	<0.001
Diabetes Mellitus	54,488	6.45%	175	7.26%	0.459	166	9.02%	0.052
Diabetes with Chronic Complications	5907	0.70%	≤10	0.21%	0.195	≤10	0.54%	0.718
Drug Abuse	10,973	1.30%	30	1.23%	0.890	20	1.11%	0.747
Hypertension	180,280	21.33%	528	21.87%	0.769	537	29.10%	<0.001
Hypothyroidism	38,128	4.51%	145	6.02%	0.115	128	6.94%	0.031
Liver Disease	8805	1.04%	29	1.18%	0.755	69	3.73%	<0.001
Lymphoma	1279	0.15%	≤10	0.21%	0.753	0	0.00%	--
Fluid and Electrolyte Disorders	69,211	8.19%	374	15.47%	<0.001	293	15.90%	<0.001
Metastatic Cancer	1284	0.15%	≤10	0.21%	0.757	0	0.00%	--
Neurological Disease	14,172	1.68%	78	3.24%	0.007	30	1.64%	0.955
Obesity	70,452	8.34%	154	6.38%	0.113	149	8.10%	0.874
Paralysis	2418	0.29%	11	0.44%	0.532	0	0.00%	--
Peripheral Vascular Disease	8121	0.96%	20	0.82%	0.750	36	1.93%	0.058
Psychoses	12,536	1.48%	89	3.70%	<0.001	60	3.28%	0.005
Pulmonary Circulation Disorders	2531	0.30%	15	0.62%	0.206	≤10	0.46%	0.534
Renal Failure	13,371	1.58%	19	0.78%	0.144	41	2.20%	0.340
Solid Tumor without Metastasis	3755	0.44%	≤10	0.22%	0.472	18	0.98%	0.103
Peptic Ulcer Disease	68	0.01%	0	0.00%	--	0	0.00%	--
Valvular Disease	9206	1.09%	31	1.27%	0.708	52	2.84%	0.001
Weight Loss	5748	0.68%	83	3.42%	<0.001	45	2.46%	<0.001