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Marginal ulcer continues to be a major source of morbidity over time following gastric bypass

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Abstract

Background Marginal ulcerations (MU) are a common and concerning complication following Roux-en-Y gastric bypass (RYGB) surgery. The aim of the present study was to examine the progression of MU and identify risk factors for the need for surgical intervention in patients with MU following RYGB.

Methods A New York state longitudinal administrative database was queried to identify patients who underwent RYGB between 2005 and 2010 and who were followed for at least 4 years for the development of MU using ICD-9 and CPT codes. Patients with perforation as their first presentation of MU were excluded. Multivariable Cox proportional hazard model was built to identify risk factors for surgical intervention. Hazard ratios (HR) with 95% confidence intervals (CI) were reported.

Results We identified 35,075 patients who underwent RYGB. Mean age was 42.47 ± 10.90 years and most were female (81.08%). There were 2201 (6.28%) patients with MU, of which 204 (9.27% of MU; 0.58% of RYGB overall) required surgery. The estimated cumulative incidence of having surgical intervention 1, 2, 5, and 8 years after MU diagnosis was 6% (95% CI 5–7%), 8% (95% CI 7–9%), 13% (95% CI 11–14%), and 17% (95% CI 13–20%), respectively. At time of MU diagnosis, younger age (HR 0.93 every 5 years, 95% CI 0.87–0.99), white race (HR 1.60, 95% CI 1.15–2.23), and weight loss (HR 2.82, 95% CI 1.62–4.88) were independent risk factors for subsequent surgical intervention for MU. Estimated cumulative incidence of MU recurrence was 15% (95% CI 9–22%) and 24% (95 CI% 15–32%) at 6 and 12 months after surgical intervention.

Conclusions The need for surgical intervention for MU after RYGB is uncommon. Young age, white race, and marked weight loss are risk factors for surgical intervention. Such patients may benefit from early intensive medical therapy at the time of MU diagnosis.

Keywords Marginal ulcer · Gastric bypass · Anastomotic ulcer

In response to rising obesity epidemic in the United States, bariatric surgery has emerged as the most effective means of achieving sustained weight loss and offers substantial amelioration of its related comorbidities [1, 2]. Of the estimated 216,000 bariatric procedures performed in 2016 in the United States, 40,392 (18.7%) were Roux-en-Y gastric bypasses (RYGB) [3]. Marginal ulcerations (MU), which are ulcers that develop at the gastrojejunal anastomosis, are a common and concerning complication following RYGB surgery. Symptoms of MU may include heartburn, abdominal pain, nausea, and diarrhea, but up to 61% of patients are asymptomatic [4]. The reported incidence of marginal ulcers varies between 0.6 and 16% [5, 6], likely due to differences in how MU is defined and diagnosed as well as the methods used to screen for them [7].

The etiology of MU is likely multifactorial. Identified risk factors for the development of marginal ulcers include nonsteroidal anti-inflammatory drug use, corticosteroid use, nicotine use, foreign body reactions to staples or suture material, and *Helicobacter pylori* infection [5, 8]. The

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clinical impact and optimal treatment of MU remain unclear. Some patients with MU undergo surgical intervention due to persistence of symptoms despite medical therapy or in the setting of complications such as intestinal perforation, which has a reported incidence of 0.83% [9]. Given the wide variation in disease severity, ranging from asymptomatic diagnosis to recurrent MU requiring multiple reinterventions, the clinical impact of this complication remains poorly understood. The aim of the present study was to examine the progression of MU and identify risk factors for subsequent surgical intervention in patients with non-perforated MU following RYGB, so these risks may be mitigated through changes in future practices.

Materials and methods

This study was approved by the Institutional Review Board (IRB) at the Stony Brook University Medical Center and the New York State Department of Health Data Governance Committee. We searched the Statewide Planning and Research Cooperative System (SPARCS) longitudinal database for all patients who underwent RYBG between 2005 and 2010 in the state of New York and who were followed for at least 4 years for the development of MU using ICD-9 and CPT codes. Patients with perforation as their first presentation of MU were excluded due to the fact that these patients almost universally require immediate surgical intervention.

For all inpatient records and outpatient records before 2008, the primary procedure code column contains the ICD-9 code either 44.31 or 44.39 (open RYGB), or 44.38 (laparoscopic RYGB) and primary diagnosis code of either 278.00, 278.01, or 278.02. For outpatient records after 2008, either of the 7 CPT code column contains 43,644 or 43,645 and primary diagnosis codes of either 278.00, 278.01, or 278.02. For all patients who had multiple RYGB records found during the study period, only their first records were used as initial RYGB. In addition, if a patient's earliest RYGB record had a diagnosis code of v4586, this patient was viewed as having a revision procedure as the first record and hence was excluded in the analysis. Any patients records with age < 18, having in-hospital death, having unknown insurance type, or without exact unique patient identification were excluded.

With the use of a specific identifier, patients were followed across the state for subsequent diagnosis of MU and surgical intervention. Surgical intervention included repair (procedure codes: 44.41, 44.69, 44.6, 44.61, 44.62, 44.63, 44.4, 44.40, 44.41, 44.49, 44.74, 44.73, 44.79) or revision (procedure code: 44.5, 44.31, 44.38, 44.39, 43.89, 44.96, 43.7, 43.81, 43.9, 43.91, 43.99, 46.93). Twenty-seven patients who had revision and repair at the same time were treated as revision.

Multivariable Cox proportional hazard (PH) model was built to identify risk factors for surgical intervention. Hazard ratios (HR) with 95% confidence intervals (CI) were reported as indicated. Univariate Cox PH models were utilized to examine the marginal association between the risk of having surgical intervention after first-time non-perforated MU diagnosis and patients' characteristics, comorbidities at the time of having MU diagnosis, and complications at the time of their original RYGB procedure. Any factors with p value < 0.1 based on univariate Cox PH models were further considered in the multivariable Cox PH model. Comorbidities and complications that afflicted < 10 patients were not considered as possible predictors. Statistical significance level was set at 0.05. Descriptive analysis and Cox PH models were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC); cumulative incidence results were performed using R packages "cmprsk" based on R 3.3.1.

Results

Between 2005 and 2010, we identified 35,075 patients who underwent initial RYGB in the state of New York, with follow-up to 2014. Mean patient age was 42.47 ± 10.90 years, and most were female (81.08%). There were 2201 (6.28%) patients diagnosed with MU and 204 (9.27% of MU; 0.58% of entire RYGB cohort) required a surgical intervention 248 days (interquartile range 51–824 days) after MU diagnosis. The demographic characteristics of the population are listed in Table 1. The estimated cumulative incidence of having surgical intervention at 1, 2, 5, and 8 years after MU diagnosis was 6% (95% CI 5–7%), 8% (95% CI 7–9%), 13% (95% CI 11–14%), and 17% (95% CI 13–20%), respectively (Fig. 1).

At the time of MU diagnosis, young age (HR 0.93 for every 5 year increase in age, 95% CI 0.87–0.99), white race (HR 1.60, 95% CI 1.15–2.23), and profound weight loss (HR 2.82, 95% CI 1.62–4.88) were independent risk factors for subsequent surgical intervention for MU after adjusting for hypertension, diabetes, chronic blood loss anemia, and tobacco use, while patients with chronic blood loss anemia (HR 0.22, 95% CI 0.05–0.88) were less likely to have surgical intervention for MU after adjusting for other confounding factors (Table 2). Estimated cumulative incidence of MU recurrence following surgical intervention was 15% (95% CI 9–22%) and 24% (95% CI 15–32%) at 6 and 12 months after surgical intervention (Table 3). The estimated incidence of MU recurrence following repair was 17% (95% CI 1.3–33%) and 23% (95% CI 4.4–41%) at 6 and 12 months after surgical intervention.

Table 1 Descriptive statistics of patient characteristics, comorbidities, and complications comparing patients who underwent surgical intervention for MU with those who did not

Variable	Level	Total	Not having surgical intervention for MU	Having surgical intervention for MU	*p* value*
Patient characteristics					
Age group	18–24	54 (2.45%)	46 (85.18%)	8 (14.82%)	0.0019
	25–34	366 (16.63%)	334 (91.26%)	32 (8.74%)	
	35–44	640 (29.08%)	558 (87.19%)	82 (12.81%)	
	45–54	598 (27.17%)	544 (90.97%)	54 (9.03%)	
	≥ 55	543 (24.67%)	515 (94.84%)	28 (5.16%)	
Gender	Female	1738 (78.96%)	1568 (90.22%)	170 (9.78%)	0.1564
	Male	463 (21.04%)	429 (92.66%)	34 (7.34%)	
Race/ethnicity	White	1519 (69.01%)	1361 (89.60%)	158 (10.40%)	0.0031
	Non-white	682 (30.99%)	636 (93.25%)	46 (6.75%)	
Insurance	Medicaid/Medicare	377 (17.13%)	333 (88.33%)	44 (11.67%)	0.4856
	Commercial	1803 (81.92%)	1645 (91.24%)	158 (8.76%)	
	Other	21 (0.95%)	19 (90.48%)	2 (9.52%)	
Time from bypass to MU	1997 vs 204	863.55 ± 840.91	882.62 ± 852.37	676.84 ± 693.70	0.8393
Comorbidities					
Any comorbidity	No	809 (36.76%)	725 (89.62%)	84 (10.38%)	0.1926
	Yes	1392 (63.24%)	1272 (91.38%)	120 (8.62%)	
Congestive heart failure	No	2179 (99.00%)	1975 (90.64%)	204 (9.36%)	–
	Yes	22 (1.00%)	22 (100.00%)	0 (0.00%)	
Valvular disease	No	2177 (98.91%)	1974 (90.67%)	203 (9.33%)	0.5414
	Yes	24 (1.09%)	23 (95.83%)	1 (4.17%)	
Peripheral vascular disease	No	2184 (99.23%)	1980 (90.66%)	204 (9.34%)	–
	Yes	17 (0.77%)	17 (100.00%)	0 (0.00%)	
Hypertension	No	1553 (70.56%)	1397 (89.95%)	156 (10.05%)	0.0468
	Yes	648 (29.44%)	600 (92.59%)	48 (7.41%)	
Paralysis	No	2195 (99.73%)	1991 (90.71%)	204 (9.29%)	–
	Yes	6 (0.27%)	6 (100.00%)	0 (0.00%)	
Other neurological disorders	No	2151 (97.73%)	1950 (90.66%)	201 (9.34%)	0.4803
	Yes	50 (2.27%)	47 (94.00%)	3 (6.00%)	
Chronic pulmonary disease	No	1947 (88.46%)	1768 (90.81%)	179 (9.19%)	0.9221
	Yes	254 (11.54%)	229 (90.16%)	25 (9.84%)	
Diabetes	No	1823 (82.83%)	1646 (90.29%)	177 (9.71%)	0.0596
	Yes	378 (17.17%)	351 (92.86%)	27 (7.14%)	
Hypothyroidism	No	2023 (91.91%)	1834 (90.66%)	189 (9.34%)	0.7345
	Yes	178 (8.09%)	163 (91.57%)	15 (8.43%)	
Renal failure	No	2165 (98.36%)	1964 (90.71%)	201 (9.29%)	0.9276
	Yes	36 (1.64%)	33 (91.67%)	3 (8.33%)	
Liver disease	No	2167 (98.46%)	1966 (90.72%)	201 (9.28%)	0.8820
	Yes	34 (1.54%)	31 (91.18%)	3 (8.82%)	
Peptic ulcer disease × bleeding	No	2135 (97.00%)	1939 (90.82%)	196 (9.18%)	0.3452
	Yes	66 (3.00%)	58 (87.88%)	8 (12.12%)	
Metastatic cancer	No	2197 (99.82%)	1993 (90.72%)	204 (9.28%)	–
	Yes	4 (0.18%)	4 (100.00%)	0 (0.00%)	
Solid tumor w/out metastasis	No	2195 (99.73%)	1991 (90.71%)	204 (9.29%)	–
	Yes	6 (0.27%)	6 (100.00%)	0 (0.00%)	
Rheumatoid arthritis/collagen vas	No	2173 (98.73%)	1972 (90.75%)	201 (9.25%)	0.6557
	Yes	28 (1.27%)	25 (89.29%)	3 (10.71%)	

Table 1 (continued)

Variable	Level	Total	Not having surgical intervention for MU	Having surgical intervention for MU	*p* value*
Coagulopathy	No	2174 (98.77%)	1971 (90.66%)	203 (9.34%)	0.5014
	Yes	27 (1.23%)	26 (96.30%)	1 (3.70%)	
Weight loss	No	2137 (97.09%)	1947 (91.11%)	190 (8.89%)	< 0.0001
	Yes	64 (2.91%)	50 (78.13%)	14 (21.87%)	
Fluid and electrolyte disorders	No	1935 (87.91%)	1755 (90.70%)	180 (9.30%)	0.8746
	Yes	266 (12.09%)	242 (90.98%)	24 (9.02%)	
Chronic blood loss anemia	No	2117 (96.18%)	1915 (90.46%)	202 (9.54%)	0.0342
	Yes	84 (3.82%)	82 (97.62%)	2 (2.28%)	
Deficiency anemias	No	1997 (90.73%)	1810 (90.64%)	187 (9.36%)	0.8451
	Yes	204 (9.27%)	187 (91.67%)	17 (8.33%)	
Alcohol abuse	No	2147 (97.55%)	1943 (90.50%)	204 (9.50%)	–
	Yes	54 (2.45%)	54 (100.00%)	0 (0.00%)	
Drug abuse	No	2164 (98.32%)	1963 (90.71%)	201 (9.29%)	0.8019
	Yes	37 (1.68%)	34 (91.89%)	3 (8.11%)	
Psychoses	No	2143 (97.36%)	1946 (90.81%)	197 (9.19%)	0.4134
	Yes	58 (2.64%)	51 (87.93%)	7 (12.07%)	
Depression	No	1939 (88.10%)	1761 (90.82%)	178 (9.18%)	0.4103
	Yes	262 (11.90%)	236 (90.08%)	26 (9.92%)	
Tobacco use	No	1847 (83.92%)	1681 (91.01%)	166 (8.99%)	0.0933
	Yes	354 (16.08%)	316 (89.27%)	38 (10.73%)	
Complications (at the time of bypass)					
Any complication	No	1944 (88.32%)	1765 (90.79%)	179 (9.21%)	0.8678
	Yes	257 (11.68%)	232 (90.27%)	25 (9.73%)	

*p value was based on univariate Cox PH model

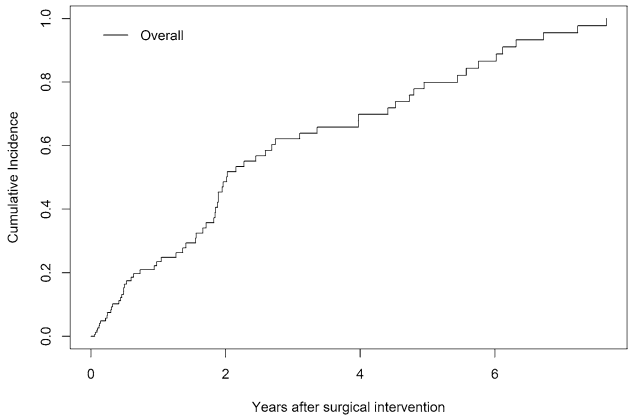

Fig. 1 Cumulative incidence of surgical intervention for MU after initial non-performed MU diagnosis

The estimated incidence of MU recurrence following revision was 15% (95% CI 7.4–22%) and 24% (95% CI 14–33%) at 6 and 12 months after surgical intervention.

Discussion

Our study shows that the estimated cumulative incidence of having surgical intervention 8 years after non-perforated MU diagnosis was 17%. This falls within the wide range of 9–31% seen in the previous literature [10–12]. However, the true burden of refractory MU is revealed by the considerable recurrence rate following surgical intervention. El-Hayek et al. found that 33% of patients had recurrence of MU after surgical intervention [11]. Our study showed similar MU recurrence rate of 15% and 24% at 6 and 12 months after surgical intervention. Importantly, MU recurrence is very common after surgical intervention, and patients may possibly benefit from prolonged or even lifelong medical prophylaxis.

MU following RYGB, while often asymptomatic, has the potential to incur significant morbidity including intractable abdominal pain, fistula formation, persistent bleeding, and perforation. While the majority of patients with non-emergent complications of MU can be managed medically with proton pump inhibitors, sucralfate, and avoidance of causative factors, some patients will go on to undergo surgical intervention. Studies suggest that the most common indications for surgical intervention for

Table 2 Independent risk factors associated with surgical intervention for MU based on a multivariable Cox PH model

Variable	Level	HR	95% CI	*p* value*
Age	By 5 years	0.929	0.87–0.99	0.0222
Race/ethnicity	White vs non-white	1.600	1.15–2.23	0.0054
Hypertension	Yes vs no	0.904	0.63–1.29	0.5787
Diabetes	Yes vs no	0.814	0.52–1.27	0.3635
Weight loss	Yes vs no	2.815	1.62–4.88	0.0002
Chronic blood loss anemia	Yes vs no	0.219	0.05–0.88	0.0328
Tobacco use	Yes vs no	1.199	0.84–1.72	0.3195

*p value was the Type-3 p value from multivariable Cox PH model

Table 3 Estimated cumulative incidences and corresponding 95% CI of having recurrence of MU at month 3, 6, 9, and 12 after surgical intervention among all patients having surgical intervention

Group	3rd month	6th month	9th month	1st year
Overall	7.4% (2.9–12%)	15% (8.6–22%)	21% (13–29%)	24% (15–32%)
Repair	13% (1.2–26%)	17% (1.3–33%)	23% (4.4–41%)	23% (4.4–41%)
Revision	6.2% (1.7–11%)	15% (7.4–22%)	21% (12–29%)	24% (14–33%)

MU include perforation, refractory disease, presence of gastrogastric fistula, and active bleeding [10–16]. A retrospective review of 2535 patients who underwent RYGB identified MU in 59 patients (2.3%), and of these, surgical intervention was required in 26 patients (44.1%) [12]. Of the 26 operative cases, 12 (20.3%) were performed for perforation, seven (13.5%) for chronic and refractory ulcers, five (8.5%) for associated gastrogastric fistula, and two (3.4%) for active bleeding [12].

While the need for surgical intervention for MU after RYGB is uncommon, with an incidence of < 1% in our study, once MU is diagnosed, the rate of surgical intervention is considerable. Risk factors for subsequent surgical intervention for MU have not been previously delineated. Based on our data, patients of younger age, white race, and those with marked weight loss are at higher risk for surgical intervention, and may potentially benefit from early intensive medical therapy at the time of initial MU diagnosis.

The limitations of the study include the retrospective nature of the design, the fact that there were no endoscopic diagnoses, and the fact that the medical therapy could not be controlled for as it was an unknown entity in this study. Our study is also limited by the absence of information about operative time and technique for both primary RYGB as well as for subsequent surgical interventions when indicated. Importantly, the SPARCS database is a hospital-based data source. Patients who are diagnosed and managed solely in the outpatient setting would be missed using this design. It is therefore likely that the recurrence rate following surgical intervention and the true incidence of MU at baseline are higher than what we report herein.

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Compliance with ethical standards

Disclosures Dr. Aurora Pryor receives honoraria for speaking for Ethicon, Medtronic, Stryker, and Gore, and is a consultant for Medicines Company, Merck, Intuitive, BAROnova, Obalon Therapeutics. Dr. Pryor also has ownership interest in Transenterix. Dr. Konstantinos Spaniolas is on the advisory board for Mallincktodt and received a research grant from Merck. Donglei Yin, Drs. Owen Pyke, Jie Yang, Tyler Cohn, Salvatore Docimo, Andrew Bates, and Mark Talamini have no conflicts of interest or financial ties to disclose.

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