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Incidence and Risk Factors Associated with Readmission After Surgical Treatment for Adrenocortical Carcinoma

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Abstract

Background—Adrenocortical carcinoma (ACC) is a rare disease with a poor prognosis. Given the lack of data on readmission after resection of ACC, the objective of the current study was to

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define the incidence of readmission, as well as identify risk factors associated with readmission among patients with ACC who underwent surgical resection.

Methods—Two hundred nine patients who underwent resection of ACC between January 1993 and December 2014 at 1 of 13 major centers in the USA were identified. Demographic and clinicopathological data were collected and analyzed relative to readmission.

Results—Median patient age was 52 years, and 62 % of the patients were female. Median tumor size was 12 cm, and the majority of patients had an American Society of Anesthesiologists (ASA) class of 3–4 (n=85, 56 %). The overall incidence of readmission within 90 days from surgery was 18 % (n=38). Factors associated with readmission included high ASA class (odds ratio (OR), 4.88 (95 % confidence interval (CI), 1.75–13.61); P=0.002), metastatic disease on presentation (OR, 2.98 (95 % CI, 1.37–6.46); P=0.006), EBL (>700 mL: OR, 2.75 (95 % CI, 1.16–6.51); P=0.02), complication (OR, 1.91 (95 % CI, 1.20–3.05); P=0.007), and prolonged length of stay (LOS; ≥9 days: OR, 4.12 (95 % CI, 1.88–9.01); P<0.001). On multivariate logistic regression, a high ASA class (OR, 4.01 (95 % CI, 1.44–11.17); P=0.008) and metastatic disease on presentation (OR, 3.44 (95 % CI, 1.34–8.84); P=0.01) remained independently associated with higher odds of readmission.

Conclusion—Readmission following surgery for ACC was common as one in five patients experienced a readmission. Patients with a high ASA class and metastatic disease on presentation were over four and three times more likely to be readmitted after surgical treatment for ACC, respectively.

Keywords

Adrenocortical carcinoma; Surgery; Readmission

Introduction

Adrenocortical carcinoma (ACC) is a difficult disease to study due to its overall low incidence. In fact, there are only about 0.5–2 ACC cases per million adults in the USA each year.[1] While rare, ACC can be associated with a poor prognosis with 5-year survival as low as 30 % among patients with advanced disease.[2] Most information on ACC in the literature is derived from small, single-institution case series.[2–9] In addition, most studies have focused exclusively on examining treatment strategies, as well as long-term outcome such as survival.[10–13] More recently, other metrics of surgical quality have become an increasing topic of interest. In particular, unplanned hospital readmission has been emphasized as an area for quality improvement.[14–16] Readmission can lead to adverse medical outcomes, lower patient satisfaction,[17] as well as increased health care costs.[18] The Centers for Medicare and Medicaid Services has targeted readmission as a quality metric and will financially penalize those hospitals with excess readmission in the future.

The incidence and risk factors associated with readmission have been reported by several investigators.[19–22] In particular, using the American College of Surgeons National Surgical Quality Improvement Program, Lucas et al. reported on readmission after general, vascular, and thoracic surgery.[20] In this study, the authors noted that length of stay (LOS) and American Society of Anesthesiologists (ASA) class could be used to predict readmission

with moderate accuracy among a broad variety of patients. Other investigators have focused more on disease-specific populations and reported factors associated with readmission among patients with pancreatic, liver, cholangiocarcinoma, as well as gastric cancer.[23–30] Data on readmission following surgery for ACC remains not defined. Information on ACC may be particularly interesting as readmission might be affected by patient presentation (e.g., age, comorbidities, etc.), tumor factors (e.g., size, functional vs. non-functional tumor, etc.), as well as perioperative considerations (e.g., operative approach, blood loss, complications, etc.). To our knowledge, no previous study has examined readmission after resection of ACC. Given this knowledge gap, the objective of the current study was to define the incidence of readmission after surgery for ACC. In particular, using a large, multicenter collaborative dataset, we sought to identify risk factors associated with a higher risk of readmission among patients with ACC who underwent surgical resection.

Methods

Study Population

All patients who underwent resection for ACC at 1 of 13 centers between 1993 and 2014 were identified. The medical centers included Johns Hopkins Hospital, Baltimore, MD; Emory University, Atlanta, GA; Stanford University, Palo Alto, CA; Washington University, St. Louis, MO; Wake Forest University, Winston-Salem, NC; University of Wisconsin, Madison, WI; The Ohio State University, Columbus, OH; Medical College of Wisconsin, Milwaukee, WI; New York University, New York, NY; University of California at San Diego, San Diego, CA; University of California at San Francisco, San Francisco, CA; University of Texas Southwestern Medical Center, Dallas, TX; and Vanderbilt University Medical Center, Nashville, TN). The institutional review board of the participating institutions approved the study. Only patients with complete data on hospital course and postdischarge status were included in the cohort (n=209).

Baseline characteristics and demographic data were collected, including age, race, sex, ASA class, comorbidities, as well as body mass index (BMI). Clinical data such as tumor size, laterality of tumor (i.e., left, right), function of tumor (i.e., hormone-secreting, non-secreting), the presence or absence of capsular invasion, and final T, N, and M stage of disease were also collected. In addition, surgical approach (open abdominal or posterior, minimally invasive surgery (MIS), thoracoabdominal surgery), estimated blood loss (EBL), as well as overall length of stay (LOS), postoperative complications, and in-hospital mortality. Perioperative morbidity was classified according to the Clavien–Dindo classification system: grades 1 and 2 were categorized as minor complications, while grades 3 and 4 were categorized as major complications.[31] Readmission was defined as rehospitalization within 90 days of discharge of the index hospitalization.[25]

Statistical Analysis

Categorical variables were reported as total frequencies and proportions; median and interquartile range (IQR) were used to describe continuous variables. Discrete variables were compared using the Chi-square and Fisher’s exact tests, where appropriate. The Wilcoxon test was used to compare continuous data variables, as well as to assess parametric

and non-parametric data. For the univariate and multivariate models, logistic regression was utilized to evaluate the relationships between relevant baseline and/or clinicopathological characteristics and the odds of readmission. Variables significant on univariate analysis (P<0.05), as well as those deemed to be clinically important, were entered into the multivariate regression model. For multivariate logistic regression, variables with missing data were subjected to the multiple imputation method for missing values. Odds ratios (OR) were presented with 95 % confidence intervals (95 % CI) and P values, respectively. Collinearity was assessed using variance inflated factor (VIF). A sensitivity analysis was carried out to compare multivariate logistic regression models before and after multiple imputation, which showed similar results. For all statistical analysis, P<0.05 was considered statistically significant. All analyses were carried out using STATA®, version 13.1 (StataCorp, LP, College Station, Texas, USA).

Results

Patient Characteristics

A total of 209 patients who underwent resection of ACC met inclusion criteria and were included in the study group (Table 1). Median patient age was 52 years (IQR, 44–62), and most patients were female (n=130, 62.2 %). Most patients had at least one comorbidity, as the majority of patients had an ASA class of 3 or 4 (n=85, 55.9 %). In most patients, the ACC tumor was non-functioning (n=111, 55.5 %), while a subset had a tumor that was functional (glucocorticoid: n=50, 25.0 %; virilizing/feminizing: n=28, 14.0 %; mineralocorticoid hormone secreting: n=10, 5.0 %). Preoperatively, most ACC tumors were evaluated by computed tomography (CT; n=129, 62.3 %), while a subset of patients had both a CT and magnetic resonance imaging (MRI; n=61; 29.5 %); only a few patients (n=15, 7.3 %) had only an MRI. Median tumor size was 11.8 cm (IQR, 8.8–15.0), with tumors being roughly equally distributed on the right (n=93, 44.9 %) and left (n= 114, 55.1 %) side.

Most patients underwent surgery with an open abdominal or posterior approach (n=136, 66.3 %), while a smaller subset of patients had a minimally invasive approach (n=32, 15.6 %). The median operative time was 240 min (IQR, 159–330); median EBL was 700 mL (IQR, 200–1900) and 35.7 % patients received a blood transfusion with a median of 5 units transfused (IQR, 2–10). Postoperatively, 71 patients experienced a complication for an overall morbidity of 39.4 %. Most complications were minor (n=44, 24.4 %), while 27 (15.0 %) patients had a major complication. The median overall hospital LOS for the index hospitalization was 6 days (IQR, 4–9).

Readmission Analysis

Within 90 days of discharge from the index hospitalization, 38 patients were readmitted for a 90-day all-cause readmission rate of 18.0 %. Perhaps as expected, there were differences in the baseline characteristics of patients who were and were not readmitted (Table 1). For example, most readmitted patients (n=24, 82.8 %) had a perioperative ASA class of 3–4 compared with non-readmitted patients (n=61, 49.6 %; P=0.001). The median operative time for patients who were readmitted was 298 min (IQR, 186–364) compared with a median operative time of 231 min (IQR, 155–318). In addition, patients who experienced a

readmission were more likely to have had a complication during their index hospitalization (readmitted, 62.8 % vs. non-readmitted, 33.8 %; P=0.002). Of note, the incidence of minor (grades 1–2) vs. major (grades 3–4) complications was comparable among readmitted and non-readmitted patients (both P>0.05). Patients who experienced a readmission did have an initial longer index LOS (median, 9 days; IQR 6–13) compared with patients who were not readmitted (median, 6 days; IQR, 4–8). The percent of patients who experienced a readmission, stratified by LOS and complication grade, is shown in Fig. 1; of note, 34 % of patients with an extended LOS were readmitted within 90 days. Among patients who experienced a grades 1–2 or grades 3–4 complications during index hospitalization, 31.8 and 29.6 % were readmitted, respectively, while only 11.9 % of patients who did not have a complication were readmitted within 90 days (Fig. 1).

On univariate analysis, patient-level and tumor-related factors such as sex, age, race, tumor size, T stage, or N stage were not associated with readmission (all P>0.05) (Table 2). On the other hand, patients with a higher pre-operative comorbidity index (ASA 3–4: OR, 4.88 (95 % CI, 1.75–13.61); P=0.002) and patients with more advanced disease (M1 disease: OR, 2.98 (95 % CI, 1.37–6.46); P=0.006) had higher odds of being readmitted. While various surgical factors such as operative time were not associated with risk of readmission (OR, 2.22 (95 % CI, 0.93–5.29); P=0.07), other factors such as high EBL increased the odds of being readmitted (EBL >700 mL: OR, 2.75 (95 % CI, 1.16–6.51); P=0.02). Patients who experienced complications also had higher odds of readmission (OR, 1.91 (95 % CI, 1.20–3.05): P=0.007) compared with patients who did not have a complication. Specifically, patients with either grades 1–2 complications (OR, 3.45 (95 % CI, 1.46–8.14); P=0.005) or grades 3–4 complications (OR, 3.11 (95 % CI, 1.13–8.53); P=0.03) had a higher odds of readmission vs. patients with no complications. In addition, prolonged LOS ≥9 days (OR, 4.12 (95 % CI, 1.88–9.01); P<0.001) during the index hospitalization was associated with readmission. On multivariate logistic regression, after controlling for competing risk factors, ASA classes 3–4 (OR, 4.01 (95 % CI, 1.44–11.17); P=0.008) and M1 disease (OR, 3.44 (95 % CI, 1.34–8.84); P=0.01) remained independently associated with higher odds for readmission.

The most common causes of readmission were postoperative infections (n=10, 29.4 %); specifically, four (11.8 %) patients had a superficial wound infection, while four (11.8 %) had a deep organ site collection/abscess. Other causes of readmission included gastrointestinal (n=9, 26.5 %), pulmonary (n=2, 5.9 %), or cardiac (n=5, 14.7 %) issues (Fig. 2). The median LOS for the second hospitalization was 9.5 days (IQR, 7–12).

Discussion

Hospital readmission has become a standard measure for quality of care in healthcare.[16] Unplanned readmission not only drives up health care costs but also can adversely impact patient satisfaction and safety.[14,16,17] While several studies have reported on factors associated with readmission for patients undergoing a variety of disease-specific procedures, little data exist on readmission following surgery for ACC. In fact, information regarding outcomes related to ACC treatment is scarce due to the rarity of this cancer.[6,10,32] Data on readmission following surgery for ACC is particularly uncommon, as no previous study has

specifically examined this topic. As such, the current study is important because it was the first to define the incidence of readmission following surgery for ACC, as well as characterize factors associated with readmission. Specifically, the incidence of readmission rate was 18.0 %—indicating that nearly one in five patients undergoing surgery for ACC was readmitted within 90 days. Factors most associated with readmission among patients with ACC included a high ASA class and prolonged LOS.

Most previous studies on ACC have focused exclusively on long-term outcomes such as survival. In these reports, several factors were identified as being associated with poor prognosis. In particular, increasing patient age, tumor size, and nodal status were each predictive of worse long-term outcome.[10,32] Interestingly, in the current study, none of these patient or tumor-related factors were associated with readmission. Gratian et al. noted that outcomes for patients with ACC were associated with hospital case volume.[10] While treatment at high-volume centers was associated with more aggressive surgical resection and chemotherapy use, overall survival was no different at high- vs. low-volume centers.[10] More germane to the current paper, Gratian and colleagues similarly noted that 30-day readmission was the same at high- (4 %) vs. low-(3.9 %) volume centers. In the current study, only high-volume centers were included in the collaborative. However, the overall incidence of readmission was considerably higher (18 %) compared with the readmission rate reported by Gratian et al. The reasons for these disparate results are probably several fold. First, unlike the current study, Gratian and colleagues utilized a large, national administrative dataset, which may have been subject to underreporting. In addition, Gratian et al. only reported readmission within the first 30 days from surgery, while the current study reported events 90 days after discharge and therefore was more likely to capture all readmissions following surgery.

The two factors most strongly associated with readmission following surgery for ACC included ASA classification and LOS. Specifically, patients with a high ASA class had a fourfold increased odds of readmission, while a prolonged LOS was similarly associated with a higher risk of readmission. A high ASA class has been reported to be an important factor associated with readmission in several disease-specific specialties including orthopedics,[33,34] thoracic-vascular surgery,[20] and urology.[35] In fact, similar to findings in the current study, Lucas et al. reported that ASA class and LOS were among the two strongest predictors of readmission.[20] In fact, a simple integer-based score based on ASA class and LOS alone could predict risk of readmission with moderate accuracy (area under the receiver operator curve (0.702).[20] Interestingly, we also noted that the presence of metastatic disease was associated with a higher likelihood of readmission. Others studies have similarly linked metastatic disease to an increased odds of readmission among patients with cancer.[36,37]

The current study had several limitations. Despite the participation of 13 major centers in the USA, the sample size was still relatively small (n~200). As such, some analyses were limited by sample size and may have been subject to a type II statistical error. In addition, due to the manner in which data on readmission were collected, information on the specific timing of readmission was not available. Moreover, while every attempt was made to account for patients readmitted to non-index hospitals (i.e., different hospital from where the

surgery was performed), it is possible that some patients may have been readmitted to a different hospital without being detected. In turn, this would have led to an underreporting of readmission in the current study. Finally, analyses from the current study were based on data from large, experienced medical centers. As such, data herein presented on ACC and readmission may not be applicable to community hospitals that only operate on the occasional ACC patient.

In conclusion, data from the current study are among the first to evaluate specifically the incidence and risk of readmission among patients undergoing surgery for ACC. The results demonstrated that roughly one out of five patients were readmitted following resection of ACC. Factors most strongly associated with readmission included LOS, ASA class, and the presence of metastatic disease. Future research should aim to better understand and target areas of quality improvement to decrease unnecessary readmissions among patients with ACC.

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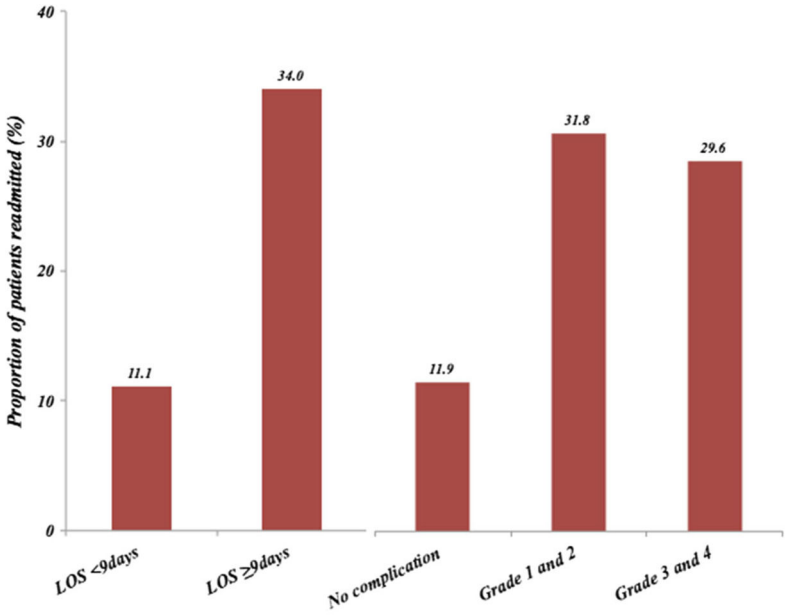

Fig. 1.
Proportion of patients readmitted, stratified by LOS and complication grades

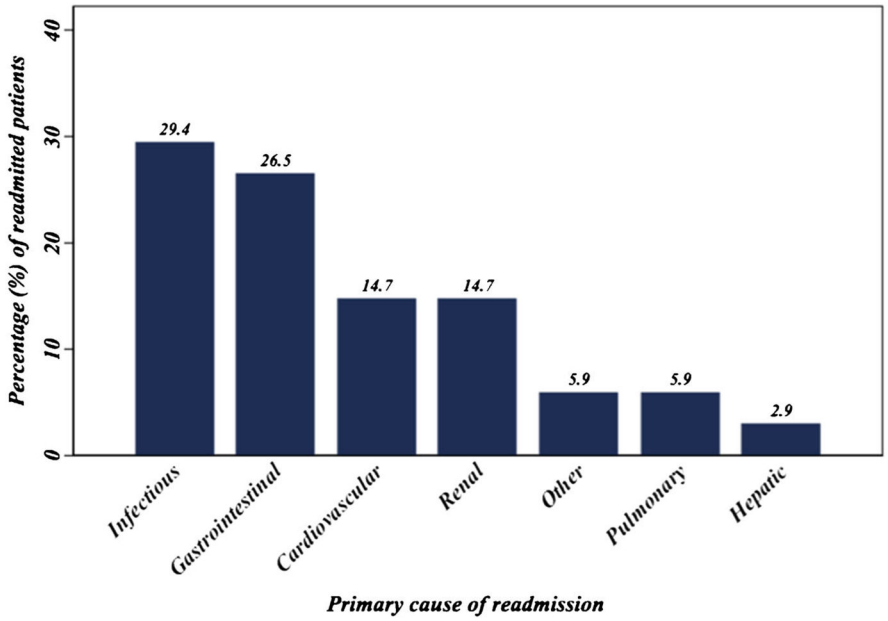

Fig. 2.
Primary cause of readmission among patients undergoing surgical resection for ACC

Table 1

Baseline characteristics of patients underwent surgical resection for ACC

	All (*n*=209)	Readmission (*n*=38)	No readmission (*n*=171)	*P* value
Age (years, median (IQR))	52 (44–62)	55 (49–64)	51 (44–61)	0.15
Caucasian race	161 (79.7)	30 (78.9)	131 (79.9)	0.89
Female gender	130 (62.2)	23 (61.0)	107 (63.0)	0.81
ASA Class (*n*=152)				
1 and 2	67 (44.1)	5 (17.2)	62 (50.4)	0.001
3 and 4	85 (55.9)	24 (82.8)	61 (49.6)	
Comorbidities				
CAD	18 (8.7)	5 (13.9)	13 (7.6)	0.23
CHF	9 (4.4)	4 (11.1)	5 (2.9)	0.03
COPD	13 (6.3)	4 (10.8)	9 (5.3)	0.21
Liver disease	6 (2.9)	1 (2.7)	5 (2.9)	0.93
Chronic renal insufficiency	12 (5.8)	5 (13.5)	7 (4.1)	0.03
DM	37 (17.9)	9 (24.3)	28 (16.4)	0.26
BMI (kg/m^2, median (IQR; *n*=161)	27 (24–33)	29 (23–37)	27 (24–33)	0.66
Laterality				
Left	114 (55.1)	22 (57.9)	92 (54.4)	0.70
Right	93 (44.9)	16 (42.1)	77 (45.6)	
Tumor functionality				
Non-secreting	111 (55.5)	17 (48.6)	94 (57.0)	0.14
Glucocorticoid	50 (25.0)	9 (25.7)	41 (24.9)	
Mineralocorticoid	10 (5.0)	0	10 (6.1)	
Virilizing/feminizing	28 (14.0)	9 (25.7)	19 (11.5)	
Capsular invasion	91 (59.5)	15 (56.6)	76 (60.8)	0.67
T stage				
I	9 (4.5)	1 (2.8)	8 (4.9)	0.88
II	82 (40.8)	16 (44.4)	66 (40.0)	
III	76 (37.8)	12 (33.0)	64 (38.8)	
IV	33 (16.4)	7 (19.4)	26 (15.8)	
N stage				
N0	48 (23.5)	9 (25.0)	39 (23.2)	0.16
N1	24 (11.8)	8 (22.2)	16 (9.52)	
N*x*	131 (64.2)	19 (52.8)	112 (66.7)	
Metastasis at presentation	42 (20.1)	14 (36.8)	28 (16.4)	0.004
Preop imaging				
CT	129 (62.3)	23 (62.2)	106 (62.3)	0.85
MRI	15 (7.3)	2 (5.4)	13 (7.7)	
Both	61 (29.5)	12 (32.4)	49 (28.8)	
Tumor size (cm, median (IQR))	11.8 (8.8–15.0)	12.2 (10.5–15.0)	11.3 (8.5–15.0)	0.31
Surgical approach				

	All (*n*=209)	Readmission (*n*=38)	No readmission (*n*=171)	*P* value
Open surgery	136 (66.3)	29 (80.6)	107 (63.3)	0.10
MIS	32 (15.6)	2 (5.6)	30 (17.8)	
Thoracoabdominal	37 (18.1)	5 (13.9)	32 (18.9)	
OR time (min, median (IQR; *n*=135))	240 (159–330)	298 (186–364)	231 (155–318)	0.051
EBL (mL, median (IQR; *n*=158))	700 (200–1900)	1000 (600–2300)	600 (200–1500)	0.008
LOS (days, median (IQR; *n*=194))	6 (4–9)	9 (6–13)	6 (4–8)	<0.001
Complication during hospitalization (*n*=180)				
Grades 1 and 2	44 (24.4)	14 (40.0)	30 (20.7)	0.007
Grades 3 and 4	27 (15.0)	8 (22.8)	19 (13.1)	
No complication	109 (60.6)	13 (37.1)	96 (66.2)	
Death during hospitalization	5 (2.4)	0	5 (2.9)	0.31

ASA American Society of Anesthesiology, *CAD* coronary artery disease, *CHF* chronic heart failure, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *BMI* body mass index, *OR* operating room, *EBL* estimated blood loss, *LOS* length of stay

Variables with >5 % missing values indicate their total *n* next to their names

Table 2

Univariate and multivariate analyses of factors associated with readmission

Variable	Univariate analysis		Multivariate analysis	
Prognostic factor	**OR (95 % CI)**	***P* value**	**OR (95 % CI)**	***P* value**
Age ≥65 years	1.32 (0.57–3.07)	0.51	–	
Female sex	0.92 (0.45–1.89)	0.81	–	
Caucasian race	0.94 (0.40–2.25)	0.90	–	
ASA				
1–2	1.00 (Reference)		1.00 (Reference)	
3–4	4.88 (1.75–13.61)	0.002	4.01 (1.44–11.17)	0.008
EBL >700 mL	2.75 (1.16–6.51)	0.02	1.48 (0.53–4.15)	0.76
OR time ≥4 h	2.22 (0.93–5.29)	0.07	–	
Surgical approach				
MIS	1.00 (Reference)		1.00 (Reference)	
Open	3.67 (0.84–16.11)	0.09	1.99 (0.38–10.47)	0.42
Tumor size ≥13 cm	1.28 (0.61–2.69)	0.51	–	
N stage				
N0	1.00 (Reference)			
N1	2.17 (0.71–6.61)	0.18	–	
T stage				
T1	1.00 (Reference)			
T2	1.94 (0.23–16.64)	0.55	–	
T3	1.50 (0.17–13.11)	0.71	–	
T4	2.15 (0.23–20.23)	0.50	–	
Tumor functionality				
Non-secreting	1.00 (Reference)		1.00 (Reference)	
Secreting	1.42 (0.68–2.95)	0.35	0.74 (0.29–1.84)	0.51
Metastasis on presentation	2.98 (1.37–6.46)	0.006	3.44 (1.34–8.84)	0.01
LOS				
<9 days	1.00 (Reference)		1.00 (Reference)	
≥9 days	4.12 (1.88–9.01)	<0.001	0.99 (0.97–1.07)	0.98
Complications				
No complication	1.00 (Reference)		1.00 (Reference)	
Any complication	1.91 (1.20–3.05)	0.007	1.50 (0.77–2.91)	0.24