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Nationwide analysis of adrenocortical carcinoma reveals higher perioperative morbidity in functional tumors

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ABSTRACT

Background: Current adrenalectomy outcomes for functional adrenocortical carcinoma (ACC) remain unclear. This study examines nationwide in-hospital post-adrenalectomy outcomes for ACC.
Methods: A retrospective analysis of the Nationwide Inpatient Sample database (2006–2011) to identify unilateral adrenalectomy patients for functional or nonfunctional ACC was performed. Patient demographics, comorbidities and postoperative outcomes were evaluated by *t*-test, Chi-square and multivariate regression.
Results: Of 2199 patients who underwent adrenalectomy, 87% had nonfunctional and 13% had functional ACC (86% hypercortisolism, 16% hyperaldosteronism, 4% hyperandrogenism). Functional ACC patients had significantly more comorbidities, and experienced certain postoperative complications more frequently including wound issues, adrenocortical insufficiency and acute kidney injury with longer hospital stay compared to nonfunctional ACC ($P < 0.01$). On multivariate analysis, functional ACC was an independent prognosticator for wound complications (28.1, 95%CI 4.59–176.6).
Conclusion: Patients with functional ACC manifest significant comorbidities with certain in-hospital complications. Such high-risk patients require appropriate preoperative medical optimization prior to adrenalectomy.
Synopsis: Patients with functional adrenocortical carcinoma (ACC) have significant preoperative comorbidities and experience higher rates of certain postoperative complications including wound complications, hematoma formation, adrenal insufficiency, pulmonary embolism and acute kidney injury. Functional ACC patients also necessitate longer hospitalizations. These patients should undergo appropriate preoperative counseling in preparation for adrenalectomy.

1. Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive endocrine tumor of the adrenal gland with a reported annual incidence of approximately 1–2 cases per million individuals per year.[1,2] The clinical presentation may be characterized by functional symptoms related to adrenal hormone overproduction, including hypercortisolism, hyperaldosteronism and hyperandrogenism and/or by local symptoms due to compression by the tumor mass. Approximately 40% of ACC do not secrete hormones and therefore, may present as large nonfunctional tumors causing local mass effect.[3] As a result, most patients present with advanced disease, and have a median survival time of <12 months.[3]

Complete surgical excision with curative intent remains the mainstay of treatment for this aggressive endocrine malignancy.[4] While surgical resection offers the best chance to achieve long-term survival, ACC is still associated with a 5-year survival ranging from 16% to 45%, largely due to disease recurrence.[2,3] Surgical evaluation for primary ACC should determine the appropriate extent of resection for each patient amenable to surgical treatment. Depending upon variables such as functional status and hormone secretion profile, tumor size, location and patient anatomy, optimal surgical treatment may vary from radical adrenalectomy to complex *en bloc* multi-organ resection.[2,5]

Unfortunately, disease rarity has restricted the assessment of large numbers of patients with ACC. Given the scarcity of studies

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with robust patient sample size, perioperative outcomes after adrenalectomy for functional ACC remain unclear. This study is one of the first in the literature to examine nationwide in-hospital outcomes after adrenalectomy for ACC. Based on surgeon experience and current literature, the authors hypothesize that functional ACC may be associated with worse perioperative outcomes as compared to nonfunctional ACC.

2. Methods

A retrospective cross-sectional analysis using data from the Healthcare Cost and Utilization Project's Nationwide Inpatient Sample (HCUP-NIS) from 2006 to 2011 was performed. This large sample size allows for analysis of rare conditions such as ACC stratified by tumor functionality. Clinical and pathologic data of 2199 consecutive patients with ACC who underwent adrenalectomy were analyzed. Patients were initially identified by a primary procedure involving unilateral adrenalectomy using International Classification of Diseases, Ninth Revision (ICD-9) codes 07.21, 07.22 and 07.29. Patients with a primary diagnosis of ACC (ICD-9194.0) were included and stratified based on diagnosis of functional (hormonally active) compared to nonfunctional ACC. The functional ACC group included patients with Cushing's syndrome (ICD-9255.0), Conn's syndrome (ICD-9255.12) or primary hyperaldosteronism (ICD-9255.10) and hyperandrogenism (ICD-9255.2). All remaining patients were classified as having nonfunctional ACC.

Patients with metastases to the adrenal gland from secondary malignancies (ICD-9198.7) were excluded. Patients with a diagnosis of pheochromocytoma (ICD-9255.6) were also excluded given that these patients represent a separate diagnostic entity from ACC. All operative cases listing nephrectomy as the primary procedure performed were excluded (ICD-9 55.4/55.54/55.52). Lastly, laparoscopy was found only in a limited subset of nonfunctional patients and therefore, excluded given lack of a comparative group in patients with a functional adrenal tumor.

Patient characteristics including demographic, socioeconomic and comorbidities were recorded and compared between the aforementioned cohorts. Variables available from HCUP-NIS included age, sex, race, payer type, admission status (elective versus non-elective) and hospital characteristics such as urban versus rural location, and teaching versus non-teaching hospital. Hospital annual adrenalectomy volume was also calculated using unique NIS hospital identifiers assigned to each case. Hospitals were then stratified into quartiles by annual adrenalectomy volume. Comorbidities including history of diabetes mellitus type 2, hypertension, congestive heart failure, chronic lung disease, kidney failure, liver disease, obesity, coagulopathy and peripheral artery disease were also recorded. A modified version of the Charlson Comorbidity Index was calculated for each patient and compared between groups.[6]

Dependent postoperative variables included in-hospital complications and length of stay. Perioperative complications were identified using ICD-9 diagnostic codes largely based on a previously published model with exception of in-hospital death that is reported in HCUP-NIS.[7] Perioperative complications analyzed included intraoperative vascular, spleen or liver injury, blood transfusion and hematoma formation. Wound complications analyzed included surgical site infections, seroma, dehiscence, and delayed healing. Endocrine complications included adrenocortical insufficiency. Medical complications included pulmonary embolism, renal, cardiovascular and pulmonary adverse events. All complications listed refer to in-hospital events, as there is no post-discharge data in the HCUP-NIS database.

Of note, on multivariate analysis, each row represents a multivariable logistic regression model with biochemical functional status as the main predictor variable. Models also include: age (years), gender (woman, man), race (Asian, Black, Hispanic, White, others), insurance (Medicare, Medicaid, private, uninsured/other), medical comorbidities (congestive heart failure, chronic lung disease, coagulopathy, hypertension, obesity, liver disease, renal failure, peripheral vascular disease, diabetes mellitus), admission status (elective, emergent/urgent), hospital location/teaching status, and hospital annual adrenalectomy volume quartile.

Statistical analyses were performed using SPSS Statistical Package version 22 (IBM, Chicago, IL). Categorical data were analyzed using Chi-squared tests, and Student t-tests were used for normally distributed continuous variables. Risk-adjusted multivariate logistic regression models for each of the primary outcomes included the primary predictor group (functional ACC versus nonfunctional ACC), in addition to co-variables including demographic characteristics, insurance status, comorbidities and admission status. Adjusted odds ratios (OR) with corresponding 95% confidence intervals (95% CI) along with *P* values and area under the curve (AUC) for each model were calculated. A $P < 0.05$ was considered statistically significant for all analyses. This study of de-identified patient data was exempt from review by the Institutional Review Board (IRB) at the University of Miami Leonard M. Miller School of Medicine.

3. Results

Of 2199 consecutive patients with ACC who underwent unilateral adrenalectomy, 13% (n = 276) had functional ACC compared to 87% (1923) of patients with nonfunctional ACC (Table 1). Among patients with functional ACC, 86% had hypercortisolism and 16% (n = 44) had hyperaldosteronism. Hyperandrogenism was found in 4% (n = 10) of all functional ACC patients. On average, patients with functional ACC were younger (51 vs. 55 years, respectively; $P < 0.01$) and more likely to be women (63% vs. 54%, respectively; $P < 0.01$) than those patients with nonfunctional ACC. There were no statistically significant differences in terms of race and insurance type between groups. All patients included in this study underwent open resection for ACC. Adrenalectomies were performed during emergent hospital admission 24% and 16% of the time in functional and nonfunctional ACC groups, respectively ($P < 0.01$). Furthermore, the majority of patients in each group underwent adrenalectomy at an urban hospital (100% vs. 95%, respectively; $P < 0.01$) and teaching institution (85% vs. 77%, respectively; $P < 0.01$). Patients with functional ACC were more likely to undergo adrenalectomy at hospitals in the highest quartile for adrenalectomy volume (37% vs. 29%, respectively; $P < 0.01$) (Table 1).

Overall, functional ACC patients had a significantly higher rate of several preoperative comorbidities including diabetes mellitus type 2 (33% vs. 19%, respectively; $P < 0.01$), hypertension (81% vs. 58%, respectively; $P < 0.01$), congestive heart failure (11% vs. 4%, respectively; $P < 0.01$), obesity (31% vs. 11%, respectively; $p < 0.01$), and coagulopathy (9% vs. 3%, respectively; $P < 0.01$) compared to nonfunctional ACC. The functional ACC group was also more likely to be associated with a Charlson comorbidity index of ≥ 2 as compared to the nonfunctional group (21% vs. 17%, respectively; $P < 0.01$) (Table 2).

Overall, perioperative complication rates were higher in patients with functional ACC compared to patients with nonfunctional ACC, but did not reach significance (46% vs. 41%, respectively; $P = 0.16$). While rate of in-hospital death was similar between both cohorts (2% vs. 2%, respectively; $P = 0.77$), certain perioperative adrenalectomy complications were more prevalent in the functional ACC group of patients. Functional ACC patients were significantly more likely to incur a postoperative wound complication (5% vs. 1%, respectively; $P < 0.01$), adrenocortical insufficiency (10%

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