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Neutrophil-Lymphocyte and Platelet-Lymphocyte Ratio as Predictors of Disease Specific Survival After Resection of Adrenocortical Carcinoma

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Abstract

Background—The systemic inflammatory response may be associated with tumor progression. We sought to analyze the impact of neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) on recurrence-free survival (RFS) and disease-specific survival (DSS) among patients who underwent surgery for adrenocortical carcinoma (ACC).

Methods—Patients undergoing surgery for ACC were identified from a multi-center database. Cut-off values of 5 and 190 were defined as elevated NLR and PLR, respectively, and long-term outcome was assessed.

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Results—Among 84 patients with ACC, 29 (34.%) had NLR >5 while 32 (40.5%) had PLR >190. NLR and PLR were associated with larger tumors (NLR >5: ≤ 5 cm, 0% vs. >5 cm, 39.7%; PLR >190: ≤ 5cm, 0% vs. >5 cm, 45.7%), as well as need to resect of other organs (NLR >5: other organ resected 48.8% vs. not resected 20.9%; PLR >190: other organ resected 25.0% vs. not resected 56.4%)(all $P<0.05$). Five-year RFS was associated with an elevated NLR (NLR ≤ 5, 14.2% vs. NLR>5, 10.5%) and PLR (PLR ≤190: 19.4% vs. PLR >190: 5.2%) (both $P<0.05$). On multivariate survival analyses, PLR remained a predictor of RFS (HR 1.72), while NLR was associated with both DSS (HR 2.21) and RFS (HR 1.99) (both $P<0.05$).

Conclusions—Immune markers such as NLR and PLR may be useful to stratify patients with regards to prognosis following surgery for ACC.

Keywords

adrenocortical carcinoma; prognosis; neutrophil-lymphocyte ratio; platelet-lymphocyte ratio

INTRODUCTION

Adrenocortical carcinoma (ACC) is a very rare endocrine cancer with an annual incidence of 1–2 patients per million [1]. About 40–60% of ACC are functional with hormonal hyper-secretion that can be characterized by several well-defined clinical presentations (e.g., Cushing's syndrome, feminization/masculinization, and hyperaldosteronism) [2]. Other ACC tumors are non-functional and typically can present with abdominal pain, weight loss, and other constitutional symptoms or incidentally [3]. In fact, with the increasing use of cross-sectional imaging, a growing number of patients have asymptomatic and nonfunctioning ACC that are discovered during exams performed for other unrelated medical reasons [4,5]. When discovered, surgery remains the only possible curative treatment for patients with ACC [6,7]. Despite several studies suggesting an improved survival over the last 20 years, the prognosis of patients after surgical resection is not well defined with overall 5-year survival ranging widely from 16% to 77% [8–11]. Currently, the most commonly utilized scheme to predict prognosis for patients with ACC is the AJCC tumor, node, metastasis (TNM) staging system [12]. While several tumor specific morphologic factors have been associated with prognosis (e.g., tumor size), other prognostic factors are not well defined, largely because of the small sample size of most studies [13,14]. Several studies have examined prognostic factors including patient- and tumor-specific characteristics, but the impact of other constitutional factors such as the immune system have not been investigated among patients with ACC [10,13,15,16].

The role of chronic inflammation in promoting tumor progression has been a topic of increasing interest. In fact, the systemic inflammatory response has been associated with outcomes in several types of cancer including gastric, liver, pancreatic, colorectal, and breast cancer [17–20]. The complex interaction between inflammation and cancer involves multiple elements of the immune system as myeloid, T-, and B-cells exert either pro- or anti-tumor proprieties [21]. In particular, chronically activated leukocytes have been demonstrated to supply direct and indirect growth factors such as epidermal growth factor (EGF), transforming growth factor-β (TGFβ), tumor necrosis factor-α (TNF-α), fibroblast growth factors (FGF), and interleukins (ILs 4, 8, 10, and 13) stimulating vascular

angiogenesis, proliferation of cancers, and stromal tissue [22,23]. Recently, several studies have reported that peripheral blood-derived inflammation-based scores, such as the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), may be associated with long-term outcomes in patients undergoing surgical treatments for solid cancers [24,25]. To our knowledge, however, the patient's inflammatory status has not been investigated as a predictor of survival after surgery for ACC. As such, the aim of the present study was to analyze the impact of NLR and PLR on postoperative outcomes, recurrence free survival (RFS), and disease-specific survival (DSS) among patients who underwent surgical resection for ACC.

METHODS

Patient Population and Data Collection

A multi-institutional database consisting of 265 patients with ACC who underwent surgery from 1993 to 2013 at 13 major surgery centers in the United States (Johns Hopkins Hospital; Emory University Hospital; Medical College of Wisconsin Medical Center; New York University Medical Center; Ohio State University Wexner Medical Center; Stanford University Medical Center; University of Wisconsin Hospital; University of California San Diego Medical Center; University of California San Francisco Medical Center; University of Texas Southwestern Medical Center; Vanderbilt University Medical Center; Wake Forest Baptist Medical Center; Washington University Medical Center) was used for this study. The institutional review board of each participating institution approved this study. Only patients with a complete blood count including a white blood cell differential count performed within 30 days before the date of surgery were included in this study. Exclusion criteria were signs of active infection or sepsis at the time of surgery and coexisting inflammatory conditions such as hematological or autoimmune disorders.

Patient demographic and clinicopathological data were collected on all patients. In particular age, gender, American Society of Anesthesiologist (ASA) status, and coexisting comorbidity data were collected. Data regarding ACC clinical presentation included type of diagnosis (incidentaloma or symptomatic disease), functional status, hormonal hypersecrection, and tumor size defined as the maximal diameter of the lesion in the resected specimen. AJCC staging system 7th edition was used to classify ACC according to tumor (T), nodes (N), and metastatic (M) status [12]. Type of surgery (adrenalectomy and resection extended to other organs), major vascular resection (inferior vascular exclusion), and margin status were also collected. Data on short-term outcomes included incidence of complication and readmission within 90 days of surgery. Variables regarding postoperative treatment were also collected including systemic chemotherapy, specific mitotane-based chemotherapy, and radiotherapy.

The primary outcome was RFS calculated the time from operation to the date of recurrence. Time was censored at the date of last follow-up assessment for patients who did not relapse. The secondary outcome was DSS calculated from the time of operation to the date of death related to ACC. Time was censored at the date of the last follow-up for the patients who were still alive or at the date of death for patients who died from causes other than ACC.

NLR and PLR were calculated by dividing the absolute number of neutrophils or platelets by the absolute number of lymphocytes measured within 30 days before surgery as part of the routine preoperative workup of patients. Cut-off values of 5 and 190 were used as a threshold to define an elevated NLR and PLR accordingly to previous data reported in the literature [19].

Statistical Analysis

Continuous variables were reported as the median and interquartile range (IQR) and as whole number and percentages for categorical variables. The distributions of categorical and numerical variables between independent groups were compared using Fisher's exact test and the Mann–Whitney U-test, respectively. Survival was estimated using the Kaplan–Meier method and differences between curves were determined using the log-rank test. Statistically significant variables in the univariate analysis ($P<0.05$) were included in the multivariate analysis using a Cox proportional hazard regression model with backward elimination method (likelihood-ratio test). A *P*-value of 0.10 was the threshold used for the selection of variables in multivariate models. Point estimates were reported as a hazard ratio (HR) with a 95% CI only for the variables selected with the elimination method. All analyses were performed with STATA version 12.0 (StataCorp LP, College Station, Texas).

RESULTS

Patient Cohort Characteristics

After excluding patients who did not have a complete blood count within 30 days of surgery, as well as patients who had signs of active infection, 84 patients who underwent surgery for ACC were included in the study cohort. The majority of patients were female (n = 48, 56.5%) and older than 50 years (n =48, 56.6%) with a median age at diagnosis of 51.5 years. Forty-eight (56.5%) patients had an ASA status of 3–4 and the most frequent comorbidities were diabetes mellitus (n =13, 15.5%), coronary artery disease (n =8, 9.5%), and chronic obstructive pulmonary disease (n =8, 9.5%). ACC was an incidental finding on imaging done for other medical reasons in 36 (42.8%) patients. The ACC tumor was functional in 44 (52.4%) cases with most hormonal symptoms related to excess glucocorticoids (n =21, 25.0%), followed by androgens/estrogens (n =18, 21.5%) or mineralocorticoids (n =5, 5.9%). The vast majority of patients (n =73, 86.9%) had a tumor >5 cm. At the time of surgery, most patients had an open approach (n =67, 79.7%), while a minority underwent minimally invasive adrenalectomy (n =17, 20.3%). Forty-one (48.8%) patients underwent a resection of other organs involved by the ACC. The incidence of complications and readmission within 90 days of surgery were 30.9% and 22.6%, respectively. On final pathology, according to the AJCC staging system, 40 (47.6%) patients had T 3–4 disease, 14 (16.7%) N1 disease, and 22 (26.2%) had distant metastasis (M1). Fifty-one (60.7%) patients received peri-operative systemic chemotherapy; 38 (45.2%) patients received postoperative mitotane.

Table I shows the association of clinicopathological characteristics with NLR and PLR. Preoperatively, NLR was >5 in 29 (34.5%) patients while PLR was >190 in 32 (40.5%) patients. In assessing patient comorbidity and ACC clinical presentation, an elevated NLR

(>5) was associated with chronic renal insufficiency (present 100% vs. not present 31.6%; P =0.005), diabetes mellitus (present 69.2% vs. not present 28.6%; P =0.005), and functional ACC tumor status (functional 50.0% vs. non-functional 20.6%; P =0.008). Furthermore, an elevated NLR was more common among patients with larger tumors (≤5 cm 0% vs. >5 cm 39.7%; P =0.037); therefore, perhaps not surprisingly, those patients who required concomitant resection of other organs involved by the ACC were more likely to have an elevated NLR (other organ resected 48.8% vs. not resected 20.9%; P =0.007). NLR was also associated with an advanced AJCC tumor stage (OR 2.72, 95%CI 1.03–7.20; P =0.04) and a positive surgical margin (OR 3.61, 95%CI 1.29–10.1; P =0.01). Similarly, an elevated PLR (>190) was associated with tumor size (≤5 cm 0% vs. >5 cm 45.7%; P =0.019) and with resection of other organs involved by ACC (other organ resected 25.0% vs. not resected 56.4%; P =0.004). In the post-operative period, an elevated NLR was associated with both the incidence of post-operative complications (occurrence 53.9% vs. not occurrence 25.0%; P =0.015) and readmission within 90 postoperative days (readmission 63.2% vs. not readmission 28.8%; P =0.007). In contrast, PLR was not associated with either postoperative complications or readmission (both P >0.05).

Long-Term Outcome: Recurrence Free Survival

The median RFS for the entire cohort was 11.0 months (IQR, 3.8–40.4) and the1-,3-, and 5-year RFS were 44.1%, 25.4%, and 12.9%, respectively. On univariate analysis, factors associated with shorter RFS were functional status, AJCC T, N, and M stage, peri-operative complications, as well as NLR and PLR (Table II). Specifically, patients with an NLR ≤5 had a median RFS of 13.8 months compared with 5.3 months for patients with an NLR >5. The 1-, 3-, and 5-year RFS for patients with a NLR <5 was 52.7%, 27.7%, and 14.2%, respectively, compared with 26.1%, 20.9%, and 10.5% for patients with a NLR >5 (P =0.022; Fig. 1a). Similarly, median survival of patients with a PLR ≤190 was 11.5 months compared with 5.7 months among patients with an elevated PLR >190. The 1-, 3-, and 5-year RFS for patients with a PLR ≤190 was 49.6%, 32.4%, and 19.4% versus 34.8%, 15.5%, and 5.2% for patients with a PLR >190 (P =0.021; Fig. 1b). On the multivariate analysis, in additional to functional tumor status (HR 1.74, 95%CI 0.95–3.20), AJCC T stage (HR 2.09, 95% 1.11–3.94), and PLR (HR 1.72, 95%CI 0.96–3.09) remained an independent predictor of a shorter RFS (all P <0.10; Table II). In contrast, after controlling for other competing risk factors, NLR was not associated with RFS (HR 1.28, 95%CI 0.65–2.51; P =0.474).

Long-Term Outcome: Disease Specific Survival

The median DSS for the entire cohort was 31.7 months (IQR, 11.4–90.9) and the 1-, 3-, and 5-year DSS was 74.7%, 48.3%, and 40.3%, respectively. On univariate analysis, diabetes, AJCC stage (T, N, and M status), positive surgical margins, peri-operative complications, and readmission were all associated with DSS (Table III). In addition, NLR >5 was associated with long-term outcome. Specifically, the 1-, 3-, and 5-year DSS for patients with a NLR ≤5 was 88.3%, 57.7%, and 49.4% versus 50.8%, 32.6%, and 24.4% for patients with a NLR >5 (P <0.001; Fig. 2a). Conversely, PLR was not associated with DSS as the median DSS for patients with a PLR ≤190 was 24.0 months versus 36.5 months for patients with a PLR >190 (P =0.756; Fig. 2b). On the multivariate analysis, AJCC T (HR 3.91, 95% 1.76–

8.73) and M status (HR 2.42, 95%CI 1.10–5.35), as well as NLR (HR 2.21, 95%CI 1.10–4.43) remained independent predictors of a shorter DSS (all P <0.05; Table III).

DISCUSSION

There is increasing evidence that the presence of a systemic inflammatory response may be associated with outcomes among patients with a variety of solid tumors [27]. For example, a high C-reactive protein (CRP) concentration has been associated with tumor progression in colorectal cancer [28,29], as well as worse OS among patients with pancreatic [30], rectal [31], gastric [32], and lung cancer [33]. Furthermore, the modified Glasgow Prognostic Score (mGPS), which combines data about peripheral blood albumin level with CRP, has been utilized to stratify cancer patients accurately with regards prognosis [34]. In fact, a large retrospective study demonstrated that the mGPS was able to separate patients with a wide array of malignant diseases into three distinct prognostic groups [35]. More recently, NLR and PLR have been investigated as possible markers of a patient's immune status and predictors of long-term survival. NLR and PLR have intuitive appeal, as these blood values are easy to obtain and are often routinely measured in the peri-operative period. While several studies have noted an association of NLR and PLR with RFS and DSS for several cancers including HCC [36], ovarian cancer [37], and vulva carcinoma [38], no previous study has evaluated the impact of NLR and PLR on short-term and long-term outcomes of patients undergoing surgical resection for ACC. As such, the current study is important because it examined the association of NLR and PLR on outcome among ACC patients using a large, multi-center database. Of note, an elevated NLR >5 was associated with worse short-term outcomes such as an increased risk of perioperative complications (OR 3.5) and readmission (OR 4.2). Furthermore, we found that a PLR >190 was associated with tumor recurrence after surgery. Specifically, an elevated PLR was associated with a 1.8-fold increased risk of recurrence, while NLR was associated with a 2.2-fold risk of disease related death. As such, the data strongly suggest that NLR and PLR may be helpful in stratifying the post-operative prognosis of patients with ACC.

The functional relationship between inflammation and cancer has long been a topic of much interest [22,23]. Virchow first hypothesized that cancer occurred at sites of chronic inflammation with immune cells releasing factors that stimulate proliferation of tumor cells, while Coley successfully treated sarcomas with bacterial mixtures leading to tumor regression mediated by acutely activated cytotoxic immune cells [39,40]. The contrasting properties of the immune systems are due, in part, to functional plasticity of myeloid and lymphoid-linage cells that likely exert both pro- or anti-tumor effects [41,42]. For example, macrophages exposed to interleukin-4 (IL-4) enhance angiogenesis in mammary carcinoma and derivative metastasis by secreting vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) [43]. In contrast, when macrophages are activated through CD40 (a tumor necrosis factor [TNF] receptor superfamily member), these cells exert an anti-tumor effect and deplete tumor stroma enabling other immune cells and cytotoxic drugs access to the tumor [44]. In the clinical setting, NLR and PLR have been demonstrated to be relevant preoperative markers of a patient's immune status and to correlate to the long-term prognosis of many patients undergoing surgical resection of solid tumors [45,46]. In patients with cancer, neutrophilia may be associated with the production of inflammatory cytokines

(IL-6 and TNF-α) [47], growth factors [48], and granulocyte colony stimulating factor [49], indicating the presence of cancer-related inflammation. Similarly, tumor cells secreting VEGF and cytokines (IL-1 and IL-6) can stimulate megakaryocytes differentiation leading to thrombocytosis [50]. Both tumor-associated neutrophils and platelets may promote tumor proliferation, facilitate metastatic disease by releasing pro-angiogenic mediators (VEGF), and lead to more aggressive tumors by inhibiting the function of cytotoxic lymphocytes [19,51]. Specifically, TNF-α and angiogenesis factors have been noted to be potent regulators of steroidogenesis and cell viability of adrenocortical cells [52,53].

In the present study, more than 30% of patients had an elevated preoperative NLR (>5), and almost 40% had an elevated PLR (>190). Interestingly, patients with a high NLR and PLR had a larger tumor (>5 cm) and were more likely to require an extended surgical resection that included other surrounding organs invaded by the ACC lesion. Interestingly, both NLR and PLR levels were also associated with long-term outcomes. While PLR was a strong predictor of RFS, NLR had a prognostic role for both RFS and DSS. Specifically, patients who had an elevated NLR >5 had an increased risk developing a recurrence versus patients with a NLR ≤ 5 (HR 1.9) (Fig. 1a). Similarly, patients with a PLR >190 had a shorter 5-year RFS compared with patients who had a PLR ≤ 190, with this association remaining significant on multivariate analysis (HR 1.7) (Table Ib). In contrast, only NLR was associated with an increased odds of death (DSS, HR 2.2) on multivariate survival analysis.

Results from the current study are consistent with those reported by Templeton et al. in a large meta-analysis that included a wide array of solid tumors such as gastro-esophageal, pancreatic, hepatocellular, renal, and lung cancer [25]. Our report expands on this previous work by demonstrating that NLR and PLR were also associated with adverse DSS for patients with ACC. Of note, while NLR was associated with RFS on univariate analysis, NLR did not remain significant in the multivariate survival model for RFS. The reasons for this are undoubtedly multifactorial and may have been influenced by limited sample size. It is interesting to note, however, that Spolverato et al. reported a similar phenomenon for patients with hepatopancreaticobiliary malignancy: NLR was a strong predictor of OS but not RFS [19]. Taken together, these data suggest that NLR, and perhaps PLR to a lesser degree, are indicators of a perioperative inflammatory state and can be used to predict long-term prognosis after surgery.

Our study had several limitations that need to be considered. Given its retrospective design, the current study was subject to possible selection bias, as well as diagnostic bias. Moreover, despite including data from 13 major centers across the United States, the sample size remained relatively small due to the rarity of ACC. This limited our ability to perform a certain statistical analyses and increased the risk of a type II statistical error. However, it is important to note that the results of NLR and PLR for ACC patients were similar to those reported in the literature for other types of cancer, providing some degree of external validity.

In conclusion, immune markers such as NLR and PLR may be useful to stratify patients with regards to prognosis following surgery for ACC. In the current study, we demonstrated that an elevated preoperative NLR and PLR were associated with long-term outcome. While

PLR was associated with only RFS, an elevated NLR was associated with both a worse RFS and DSS among patients undergoing surgery for ACC. NLR and PLR are easily determined using preoperative labs and therefore may be helpful in determining prognosis of patients following surgery for ACC.

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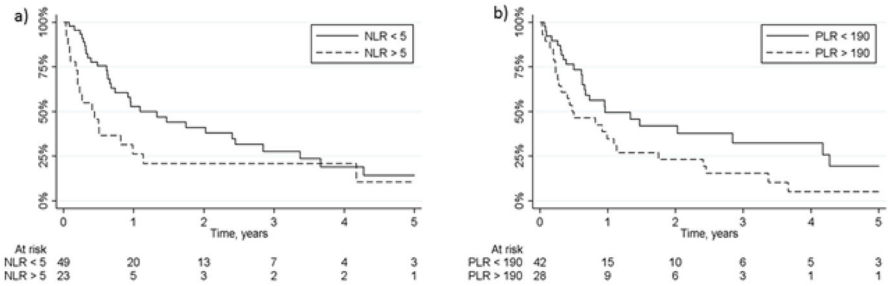

Figure 1.

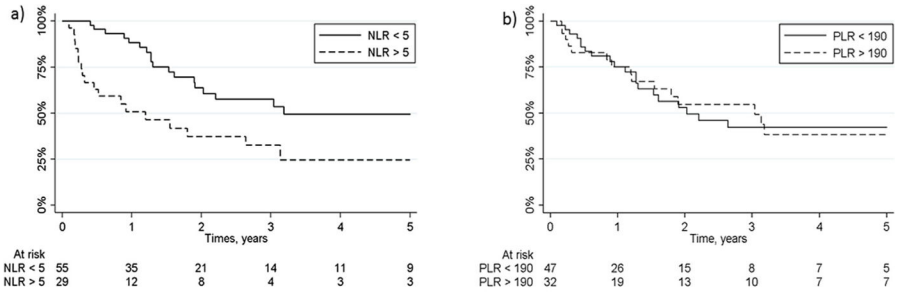

Fig. 2.

Disease Specific Survival (DSS) Kaplan-Meier curves for patients who underwent surgery for adrenal cortical carcinoma stratified by (a) NLR and (b) PLR.

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TABLE I

Baseline Characteristics Stratified by NLR and PLR

	NLR (n =84)			PLR (n =79)		
	≤5	**>5**	***P*-value**	**≤190**	**>190**	***P*-value**
Gender			0.260			0.091
Female	29 (60.4%)	19 (39.6%)		31 (67.4%)	15 (32.6%)	
Male	26 (72.2%)	10 (27.8%)		16 (48.5%)	17 (51.5%)	
Age			0.260			0.467
<50 years	26 (72.2%)	10 (27.8%)		23 (63.9%)	13 (36.1%)	
≥50 years	29 (60.4%)	19 (39.6%)		24 (55.8%)	19 (44.2%)	
ASA physical status			0.174			0.936
1–2	17 (80.9%)	4 (19.1%)		13 (68.4%)	6 (31.6%)	
3–4	31 (64.6%)	17 (35.4%)		31 (67.4%)	15 (62.6%)	
NA	7	8		5	11	
Coronary artery disease			0.320			0.806
No	50 (67.6%)	24 (32.4%)		40 (57.9%)	29 (42.1%)	
Yes	4 (50.0%)	4 (50.0%)		5 (62.5%)	3 (37.5%)	
NA	1	1		2	0	
Chronic heart failure			0.965			0.072
No	50 (65.8%)	26 (34.2%)		40 (55.6%)	32 (44.4%)	
Yes	4 (66.7%)	2 (33.3%)		5 (100%)	0 (0%)	
NA	1	1		2	0	
Chronic obstructive pulmonary disease			0.333			0.564
No	51 (67.1%)	25 (32.9%)		43 (60.6%)	28 (39.4%)	
Yes	4 (50.0%)	4 (50.0%)		4 (50.0%)	4 (50.0%)	
Chronic renal insufficiency			**0.005**			0.708
No	55 (68.4%)	25 (31.6%)		45 (59.5%)	30 (40.5%)	
Yes	0 (0%)	4 (100.0%)		2 (50.0%)	2 (50.0%)	
Diabetes mellitus			**0.005**			0.680
No	51 (71.4%)	20 (28.6%)		40 (60.0%)	26 (40.0%)	
Yes	4 (30.8%)	9 (69.2%)		7 (53.8%)	6 (46.2%)	

	NLR (n =84)			PLR (n =79)		
	≤5	>5	*P*-value	≤190	>190	*P*-value
Incidentaloma			0.788			0.802
No	30 (63.8%)	17 (36.2%)		26 (57.8%)	19 (42.2%)	
Yes	24 (66.7%)	12 (33.3%)		20 (60.6%)	13 (39.4%)	
NA	1	0		1	0	
Functional status			**0.008**			0.990
No	27 (79.4%)	7 (20.6%)		19 (59.4%)	13 (40.6%)	
Yes	22 (50.0%)	22 (50.0%)		25 (59.5%)	17 (40.5%)	
NA	6	0		3	2	
Hormonal hypersecretion			0.201			0.826
Glucocorticoid	8 (38.1%)	13 (61.9%)		13 (61.9%)	8 (38.1%)	
Androgens/Estrogens	10 (55.6%)	8 (50.0%)		10 (62.5%)	6 (37.5%)	
Mineralocorticoid	4 (80.0%)	1 (20.0%)		2 (40.0%)	3 (60.0%)	
Tumor size			**0.037**			**0.019**
≤5 cm	7 (100.0%)	0 (0%)		7 (100.0%)	0 (0%)	
>5 cm	44 (60.3%)	29 (39.7%)		38 (54.3%)	32 (45.7%)	
NA	4	0		2	0	
Preoperative chemo-radiotherapy			0.196			0.796
No	51 (63.7%)	29 (36.3%)		45 (59.2%)	31 (40.8%)	
Yes	3 (100.0%)	0 (0%)		2 (66.7%)	1 (33.3%)	
NA	1	0		0	0	
Other organ resected			**0.007**			**0.004**
No	34 (79.1%)	9 (20.9%)		30 (75.0%)	10 (25.0%)	
Yes	21 (51.2%)	20 (48.8%)		17 (43.6%)	22 (56.4%)	
IVC exclusion			0.189			
No	52 (67.5%)	25 (32.5%)		44 (61.1%)	28 (38.9%)	
Yes	3 (42.9%)	4 (57.1%)		3 (42.8%)	4 (57.2%)	0.348
AJCC tumor status			**0.040**			0.210
T stages I–II	30 (76.9%)	9 (23.1%)		24 (66.7%)	12 (33.3%)	
T stages III–IV	22 (55.0%)	18 (45.0%)		21 (52.5%)	19 (47.5%)	
NA	3	2		2	1	

	NLR (n =84)			PLR (n =79)		
	≤5	>5	*P*-value	≤190	>190	*P*-value
AJCC node status			0.340			0.446
N0	12 (75.0%)	4 (25.0%)		7 (46.7%)	8 (53.3%)	
N1	7 (50.0%)	7 (50.0%)		6 (54.5%)	5 (45.5%)	
Nx	36 (66.7%)	18 (33.3%)		34 (64.1%)	19 (35.9%)	
AJCC metastasis status			0.209			0.699
M0	43 (69.3%)	19 (30.6%)		37 (60.7%)	24 (39.3%)	
M1	12 (54.5%)	10 (45.5%)		10 (55.6%)	8 (44.4%)	
Margin status			**0.012**			0.537
R0	34 (75.6%)	11 (24.4%)		27 (61.4%)	17 (38.6%)	
R1/R2	12 (46.1%)	14 (53.8%)		14 (53.8%)	12 (46.2%)	
NA	9	4		6	3	
Complications			**0.015**			0.880
No	33 (75.0%)	11 (25.0%)		23 (56.1%)	18 (43.9%)	
Yes	12 (46.1%)	14 (53.9%)		13 (54.2%)	11 (45.8%)	
NA	10	4		11	3	
Readmission within 90 days			**0.007**			0.662
No	42 (71.2%)	17 (28.8%)		33 (58.9%)	23 (41.1%)	
Yes	7 (36.8%)	12 (63.2%)		9 (52.9%)	8 (47.1%)	
NA	6	0		5	1	
Post-operative chemotherapy			0.695			0.072
No	43 (67.2%)	21 (32.8%)		35 (55.6%)	28 (44.4%)	
Yes	8 (61.5%)	5 (38.5%)		10 (83.3%)	2 (16.7%)	
NA	4	3		2	2	
Post-operative mitotane			0.371			0.873
No	24 (70.6%)	10 (29.4%)		19 (57.6%)	14 (42.4%)	
Yes	23 (60.5%)	15 (39.5%)		22 (59.5%)	15 (40.5%)	
NA	8	4		6	3	
Post-operative radiation			0.521			0.991
No	40 (63.5%)	23 (36.5%)		38 (62.3%)	23 (37.7%)	
Yes	6 (75.0%)	2 (25.0%)		5 (62.5%)	3 (37.5%)	

	NLR (n =84)			PLR (n =79)		
	≤5	>5	*P*-value	≤190	>190	*P*-value
NA	9	4		4	6	

NA, not available; ASA, American Society of Anesthesiologist; IVC, inferior vena cava. *P*-values ≤ 0.05 are reported in bold and indicate statistically significant results.

TABLE II

Predictors of Recurrence Free Survival (RFS) for Patients With Adrena Cortical Carcinoma Who Underwent Surgical Resection

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	***P*-value**	**HR (95%CI)**	***P*-value**
Gender		0.652		
Female	Ref.			
Male	1.14 (0.62–2.11)			
Age		0.950		
<50 years	Ref.			
≥50 years	1.00 (0.98–1.08)			
ASA physical status		0.132		
1–2	Ref.			
3–4	1.83 (0.83–4.03)			
Coronary artery disease		0.557		
No	Ref.			
Yes	1.32 (0.51–3.43)			
Chronic heart failure		0.498		
No	Ref.			
Yes	0.19 (0.03–1.36)			
Chronic obstructive pulmonary disease		0.147		
No	Ref.			
Yes	2.17 (0.76–6.22)			
Chronic renal insufficiency		0.052		
No	Ref.			
Yes	4.33 (0.98–18.9)			
Diabetes mellitus		0.268		
No	Ref.			
Yes	1.59 (0.69–3.61)			
Incidentaloma		0.270		
No	Ref.			
Yes	0.72 (0.39–1.29)			
Functional status		**0.050**		0.075
No	Ref.		Ref.	
Yes	1.84 (1.00–3.38)		1.74 (0.95–3.20)	
Tumor size		0.242		
≤5 cm	Ref.			
>5 cm	1.15 (0.91–1.45)			
Preoperative chemo-radiotherapy		0.705		
No	Ref.			
Yes	0.68 (0.09–4.90)			
Other organ resected		0.118		

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	***P*-value**	**HR (95%CI)**	***P*-value**
No	Ref.			
Yes	1.59 (0.88–2.87)			
IVC exclusion		0.110		
No	Ref.			
Yes	2.05 (0.84–4.95)			
AJCC tumor Status		**0.002**		**0.022**
T stages I–II	Ref.		Ref.	
T stages III–IV	2.67 (1.41–5.03)		2.09 (1.11–3.94)	
AJCC node status		**0.027**		
N0	Ref.			
N1	1.50 (1.04–2.15)			
AJCC metastasis status		**0.011**		0.061
M0	Ref.		Ref.	
M1	2.58 (1.24–5.38)		2.04 (0.97–4.29)	
Margin status		0.100		
R0	Ref.			
R1/R2	1.68 (0.90–3.16)			
Complications		**0.049**		
No	Ref.			
Yes	1.87 (1.00–3.51)			
Readmission within 90 days		0.090		
No	Ref.			
Yes	1.75 (0.91–3.35)			
NLR		**0.022**		
≤5	Ref.			
>5	1.99 (1.10–3.59)			
PLR		**0.021**		0.067
≤190	Ref.		Ref.	
>190	1.93 (1.11–3.38)		1.72 (0.96–3.09)	
Post-operative chemotherapy		0.630		
Not performed	Ref.			
Performed	0.79 (0.21–2.02)			
Post-operative radiotherapy		0.748		
Not performed	Ref.			
Performed	0.84 (0.30–2.37)			
Post-operative chemotherapy with mitotane		0.220		
Not performed	Ref.			
Performed	1.45 (0.79–2.64)			

ASA, American Society of Anesthesiologist; IVC, inferior vena cava; *P*-values ≤ 0.05 are reported in bold and indicate statistically significant results.

TABLE III

Predictors of Disease Specific Survival (DSS) for Patients With Adrena Cortical Carcinoma Who Underwent Surgical Resection

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	***P*-value**	**HR (95%CI)**	***P*-value**
Gender		0.893		
Female	Ref.			
Male	0.96 (0.50–1.81)			
Age		0.347		
<50 years	Ref.			
≥50 years	0.99 (0.97–1.01)			
ASA physical status		0.092		
1–2	Ref.			
3–4	2.13 (0.88–5.17)			
Coronary artery disease		0.205		
No	Ref.			
Yes	1.86 (0.71–4.87)			
Chronic heart failure		0.309		
No	Ref.			
Yes	0.35 (0.05–2.61)			
Chronic obstructive pulmonary disease		0.164		
No	Ref.			
Yes	1.95 (0.76–5.05)			
Chronic renal insufficiency		0.074		
No	Ref.			
Yes	3.86 (0.88–17.0)			
Diabetes mellitus		**0.002**		
No	Ref.			
Yes	3.36 (1.55–7.28)			
Incidentaloma		0.788		
No	Ref.			
Yes	0.92 (0.48–1.74)			
Functional status		0.229		
No	Ref.			
Yes	1.50 (0.77–2.93)			
Tumor size		0.987		
≤5 cm	Ref.			
>5 cm	0.99 (0.78–1.26)			
Preoperative chemo-radiotherapy		0.149		
No	Ref.			
Yes	2.91 (0.68–12.5)			
Other organ resected		0.074		

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	***P*-value**	**HR (95%CI)**	***P*-value**
No	Ref.			
Yes	1.79 (0.94–3.41)			
IVC exclusion		0.064		
No	Ref.			
Yes	2.51 (0.95–6.63)			
AJCC tumor status		<**0.001**		
T stages I–II	Ref.		Ref.	
T stages III–IV	4.54 (2.07–9.99)		3.91 (1.76–8.73)	**0.001**
AJCC node status		**0.008**		
N_0	Ref.			
N_1	1.63 (1.13–2.35)			
AJCC metastasis status		**0.004**		**0.028**
M0	Ref.		Ref.	
M1	2.84 (1.39–5.79)		2.42 (1.10–5.35)	
Margin status		<0.001		
R0	Ref.			
R1/R2	3.83 (1.88–7.77)			
Complications		**0.004**		
No	Ref.			
Yes	2.90 (1.40–6.01)			
Readmission within 90 days		**0.039**		
No	Ref.			
Yes	2.06 (1.03–4.09)			
NLR		**0.002**		**0.025**
≤5	Ref.		Ref.	
>5	2.85 (1.49–5.47)		2.21 (1.10–4.43)	
PLR		0.757		
≤190	Ref.			
>190	0.90 (0.47–1.73)			
Post-operative chemotherapy		0.438		
Not performed	Ref.			
Performed	1.42 (0.58–3.52)			
Post-operative radiotherapy		0.893		
Not performed	Ref.			
Performed	1.07 (0.37–3.07)			
Post-operative chemotherapy with mitotane		0.372		
Not performed	Ref.			
Performed	1.38 (0.67–2.81)			

IVC, inferior vena cava; *P*-values ≤ 0.05 are reported in bold and indicate statistically significant results.