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Clinical Research Article

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Epidemiology and Comorbidity of Adrenal Cushing Syndrome: A Nationwide Cohort Study

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Abbreviations: ACTH, adrenocorticotropic hormone; CI, confidence interval; CRH, corticotropin-releasing hormone;CS, Cushing syndrome;CT, computed tomography;HPA, hypothalamic-pituitary-adrenal;KNHANES, Korean National Health and Nutrition Examination Survey;NHIS, National Health Insurance Services;OR, odds ratio.

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Abstract

Context: Adrenal Cushing syndrome (CS) is a major subtype of CS and has a high surgical cure rate. However, only a few studies have investigated the epidemiology and long-term outcomes of adrenal CS.

Objective: We aimed to investigate the nationwide epidemiology, long-term prognosis, and postoperative glucocorticoid replacement therapies of adrenal CS in Korea.

Design: Retrospective cohort study.

Setting: A nationwide claim database.

Patients: Adrenal CS patients who were defined as having undergone adrenalectomy, a diagnosis code of CS, and not having pituitary gland surgery.

Main Outcome Measures: Crude incidence and age-standardized incidence rates, long-term mortality, comorbidities diagnosed preoperatively or developed postoperatively, and the pattern of postoperative glucocorticoid replacement therapy.

Results: From 2002 to 2017, there were a total of 1199 new adrenal CS patients, including 72 patients with adrenocortical carcinoma (malignant adrenal CS), in Korea. The crude and age-standardized incidence rates were 1.51 and 1.27 per million person-years, respectively. The overall standardized mortality ratio was 3.0 (95% confidence interval [CI], 2.4-3.7) for benign adrenal CS and 13.1 (95% CI, 7.6-18.6) for malignant adrenal CS. Adrenal CS patients had a high risk of having coronary artery disease, stroke, metabolic diseases, and depression. A similar proportion of patients were diagnosed with these comorbidities both preoperatively and postoperatively, suggesting a significant residual risk even after adrenalectomy. The median time of postoperative glucocorticoid

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replacement therapy was 10.1 months, and the major types of glucocorticoids used were prednisolone (66.6%) and hydrocortisone (22.4%).
Conclusions: Adrenal CS is associated with multiple comorbidities even after treatment, which necessitates meticulous postoperative care.

Key Words: adrenal Cushing syndrome, epidemiology, comorbidity, postoperative glucocorticoid replacement

Cushing syndrome (CS) is a syndrome characterized by glucocorticoid excess and leads to various complications and mortality. Endogenous CS cases are categorized as adrenocorticotropic hormone (ACTH)-dependent CS and ACTH-independent CS. ACTH-dependent CS can be caused by ACTH-producing pituitary adenoma (Cushing disease) or ectopic ACTH or corticotropin-releasing hormone (CRH) secretion (ectopic CS). ACTH-independent CS is almost exclusively caused by excess glucocorticoid secretion from the adrenal gland (adrenal CS). The most common subtype of endogenous CS is Cushing disease, which accounts for 70% of endogenous CS cases in Western countries (1). Adrenal CS accounts for 20% to 25% of endogenous CS cases, and the remaining cases are ectopic CS (1). The underlying pathologies of adrenal CS include cortisol-producing adrenal adenoma, adrenal cortical carcinoma, and bilateral hyperplasia of the adrenal gland.

Although adrenal CS is the major subtype of endogenous CS, there are only a limited number of studies that have comprehensively studied the epidemiology and long-term prognosis of adrenal CS. The long-term survival of adrenal CS patients varied across previous studies. The standardized mortality ratio of adrenal CS ranged from 1.7 to 7.5 (2-6). However, these studies included only small numbers of patients (ranging from 16 to 84 patients). The long-term prognosis of adrenal CS needs to be determined with a sufficient number of patients and a sufficient follow-up duration.

CS is also associated with various complications, including metabolic diseases, cardiovascular diseases, osteoporosis, thrombotic diseases, and mental illnesses. The resolution of hypercortisolemia can improve the metabolic profile and halt the progression of these comorbidities. However, the risk of several complications remains elevated, even after the remission of CS (2, 7). Thus, the long-term follow-up data of various complications after the surgical treatment of adrenal CS can be useful for determining the optimal follow-up strategy for adrenal CS.

After the treatment of CS, patients experience postoperative adrenal insufficiency resulting from chronic suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Glucocorticoid replacement therapy is required until the HPA axis recovers. A previous study reported that the recovery time varied between patients with CS of different etiologies (8). In this study, adrenal CS had a longer recovery time than did Cushing disease and ectopic CS. Furthermore, approximately 40% of adrenal CS patients still exhibited adrenal insufficiency over the mean follow-up period of 8.5 years (8). However, other previous studies on adrenal CS reported recovery times of 12 months (9) and 15 months (10), but these studies included only small numbers of patients.

Herein, we aimed to investigate the national epidemiology, comorbidities, postoperative glucocorticoid replacement therapies, and long-term prognosis of adrenal CS in Korea using nationwide data based on the National Health Insurance Service.

Methods

Data sources

We used the National Health Insurance Services (NHIS) database in Korea. The insurance system was established by the Korean government and covered approximately 97.2% of Korean residents in all age groups. The NHIS database contains data on all forms of healthcare services reimbursed by the insurance system, including demographics, diagnoses, prescriptions, diagnostic or surgical procedures, and medical costs associated with the claims. The diagnoses were classified by the 10th version of the International Classification of Diseases (ICD-10). The data used for this study comprised all NHIS databases from 2002 to 2018. The incidence of adrenal CS was investigated from 2002 to 2017, and the comorbidities and survival rate were analyzed from 2002 to 2018 for at least 1 year of follow-up data.

Operational definition of adrenal CS

Adrenal CS was defined as any patients fulfilling all 3 following criteria: (i) a procedural code for unilateral or bilateral adrenalectomy (P4571, P4572), (ii) ICD-10 code of CS (E240, E248, E249, E270), and (iii) the absence of procedural codes for pituitary gland surgery (S4633, S4743). The number of patients fulfilling the above criteria was 1230. Patients with a diagnostic code of C741 (malignant neoplasm of adrenal gland medulla) were excluded (n = 21). Given that ectopic or pituitary CS patients can be

treated with bilateral adrenalectomy, patients with a diagnostic code of ectopic CS (E243) or pituitary CS (E240) and underwent bilateral adrenalectomy (P4572) were also excluded (n = 10). As a result, a total of 1199 patients were included in the final analysis. Among all adrenal CS patients, those with the ICD-10 code of the neoplasm of the adrenal gland (C740, C749) were classified as malignant adrenal CS patients, and the remaining patients were classified as benign adrenal CS patients.

Validation of the definition of adrenal CS

To validate the operational definition of adrenal CS, we checked the false-positive rate and false-negative rate of the operational definition using our institution's database. To estimate the false-positive rate, we identified patients fulfilling the above definition of adrenal CS at our institution from January 2010 to September 2019. A total of 88 patients fulfilled the criteria. The medical records of these patients were reviewed, and 86 (97.7%) patients were confirmed as having true adrenal CS. The remaining 2 patients were those with Cushing disease who underwent bilateral adrenalectomy due to uncontrolled hypercortisolemia despite having undergone pituitary-directed treatments. To estimate the false-negative rate, we applied the above definition to our institution's cohort of 61 proven adrenal CS patients who were prospectively enrolled in a registry of adrenal tumors. Among these patients, 58 (95.1%) fulfilled the criteria. The remaining 3 patients did not have either the diagnosis code of CS or a procedural code for adrenalectomy. From these analyses, the false-positive and false-negative rates of the adrenal CS definition were estimated to be 2.3% and 4.9%, respectively.

Comorbidities of adrenal CS

Comorbidities were considered to exist if the following diagnostic codes for at least 2 principal or secondary diagnosis were present. The comorbidities examined were depressive disorder (F32, F33, F34), psychotic disorder (F20-F29), osteoporosis (M80, M81, M82), fracture (M843, M844, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02), tuberculosis (A15-A19), other bacterial infection (A20-A28, A30-A49, A50-A64), coronary artery disease (I20-I25), ischemic stroke (I63, I64, I693, I694, G45), hemorrhagic stroke (I60-I62, I690, I692), pulmonary embolism (I26), diabetes mellitus (E11, E12, E13, E14), dyslipidemia (E78), and hypertension (I10-I13, I15). If comorbidities existed before adrenalectomy, the comorbidities were classified as "preoperative comorbidities." Based on the time of the first appearance of each diagnosis code, each comorbidity was classified as being present at more than 1 year before adrenalectomy (>1 year preoperatively) and within 1 year before adrenalectomy (within 1 year preoperatively). For preoperative comorbidities, the proportion of patients who were preoperatively diagnosed with each comorbidity among all patients is shown. To assess the risk of having preoperative comorbidities in adrenal CS patients, we compared the prevalence of each comorbidity in adrenal CS patients with that in a control population. The control population comprised age- and sex-matched (1:2) individuals to the adrenal CS patients selected from the 2015 Korean National Health and Nutrition Examination Survey (KNHANES) database. The KNHANES is a nationally representative cross-sectional survey that included approximately 10 000 individuals (11). In the KNHANES database, information on depressive disorder, osteoporosis, tuberculosis, coronary artery disease, stroke, diabetes mellitus, dyslipidemia, and hypertension were available, but information on fracture, bacterial infection, psychotic disorder, aortic disease, and pulmonary embolism were not available. The odds ratios (ORs) for having these comorbidities were calculated.

If comorbidities were newly diagnosed after adrenalectomy, they were classified as "postoperative comorbidities." For postoperative comorbidities, we calculated the proportion of patients who were diagnosed with each comorbidity postoperatively among those without the comorbidity at the time of surgery. To explore the time interval to the diagnosis of comorbidities from adrenalectomy, we also assessed the results according to the time of the first diagnosis code of each comorbidity as follows: within 3 months after adrenalectomy (within 3 months postoperatively), within 3 months to 1 year after adrenalectomy (3 months to 1 year postoperatively), and more than 1 year after adrenalectomy (>1 year postoperatively). The median time to diagnosis from adrenalectomy was analyzed for each comorbidity.

Analysis of postoperative glucocorticoid replacement therapy

We examined the type of glucocorticoid used for postoperative replacement therapy and the duration of glucocorticoid replacement after adrenalectomy. Considering that the type of oral glucocorticoid can be modified for each patient during postoperative replacement therapy, the type of oral glucocorticoid used for the longest time after adrenalectomy by each patient was recorded as the representative type. The date of the last glucocorticoid replacement therapy was determined as the last day of any oral glucocorticoid prescription, with more than a 1-year glucocorticoid-off period.

Statistical analysis

Subjects' demographic characteristics were summarized as the means ± standard deviations for interval variables and numbers (%) for categorical variables. The median time and interquartile range are presented for the follow-up and time to diagnosis of each comorbidity. The crude incidence rate and age-standardized incidence rate of adrenal CS were calculated. The WHO world standard population (12) was used to calculate the age-standardized incidence rate. The Kaplan-Meier survival curves of malignant adrenal CS (adrenal CS due to adrenocortical carcinoma) and benign adrenal CS (adrenal CS due to noncarcinoma diseases) were compared by the log-rank test. The Cox proportional hazards model was used to evaluate the impact of age, sex, comorbidities of CS, and having bilateral adrenalectomy on mortality. A P value of <0.05 was considered statistically significant. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC, USA), and R, version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical considerations

The Institutional Review Board of Seoul National University Hospital (IRB No. 1811-007-982 and 1801-010-911) approved the study protocol. Informed consent was waived since personal information was anonymously encrypted in the NHIS and KNHANES databases.

Results

Incidence and prevalence of adrenal CS in Korea

From 2002 to 2017, 1199 patients were newly diagnosed with adrenal CS in Korea. The mean age was 44.9 ± 13.4 years, with the peak age between 36 and 55 years (Table 1 and Fig. 1A). Patients were predominantly female, with a male:female ratio of 1:3.2. The prevalence of adrenal CS was 23.4 per million people. The overall crude incidence rate of adrenal CS was 1.51 per million person-years, and the age-standardized incidence rate was 1.27 per million person-years (Fig. 1B). Among the total adrenal CS patients, 72 (6.0%) had malignant adrenal CS. The mean age of the patients with malignant adrenal CS was similar to that of all the patients with adrenal CS (47.8 ± 16.3 years, Table 1). The peak age was 56 to 60 years, which was slightly higher than that of all the patients with adrenal CS. There was also a female predominance in the patients with malignant adrenal CS (male:female ratio of 1:1.8).

Mortality of adrenal CS

During the follow-up period, which had a median duration of 9.7 (4.7-12.5) years, 96 patients (74 benign adrenal CS and 22 malignant adrenal CS patients) died. The 5-year survival rates of benign adrenal CS and malignant adrenal CS were 96.3% (95% confidence interval [CI]: 95.2-97.5%) and 68.6% (95% CI, 55.8-79.2%), respectively (Fig. 2). The overall standardized mortality ratio was 3.0 (95% CI, 2.4-3.7) for benign adrenal CS and 13.0 (95% CI, 7.6-18.6) for malignant adrenal CS. The most mortality (21/22) occurred during the first 5 years after adrenalectomy in the malignant adrenal CS patients, while mortality occurred steadily for 10 years after adrenalectomy in the benign adrenal CS patients (Fig. 2). In survival analysis, older age (HR 1.06; 95% CI, 1.04-1.08), bilateral adrenalectomy (2.92, 1.25-6.81), stroke (3.56, 1.95-6.52), and diabetes (1.95, 1.21-3.15) were independently associated with higher mortality in addition to the malignant adrenal CS (Table 2). These factors were still independent risk factors of mortality in patients with benign adrenal CS.

Comorbidities of adrenal CS

We investigated the preoperative and postoperative comorbidities of adrenal CS, which were categorized on the basis of whether the comorbidity was diagnosed before or after the treatment of adrenal CS. The most common

Table 1. Demographics of the Adrenal Cushing Syndrome Patients

	Total	Benign adrenal CS	Malignant adrenal CS	Age and sex-matched control population
Total N	1199	1127	72	2404
Age, years	44.9 ± 13.4	44.8 ± 13.3	47.8 ± 16.3	45.1 ± 13.6
Sex				23.5 ± 3.6
Male	287 (23.9%)	261 (23.2)	26 (36.1%)	
Female	912 (76.1%)	866 (76.8)	46 (63.9%)	580 (24.1%)
Surgical treatment				1824 (75.9%)
Unilateral adrenalectomy	1161 (96.8%)	1092 (96.9%)	69 (95.8%)	NA
Bilateral adrenalectomy	38 (3.2%)	35 (3.1%)	3 (4.2%)	NA

The data are shown as the mean ± SD or n (%). Abbreviations: CS, Cushing syndrome; NA, not applicable.

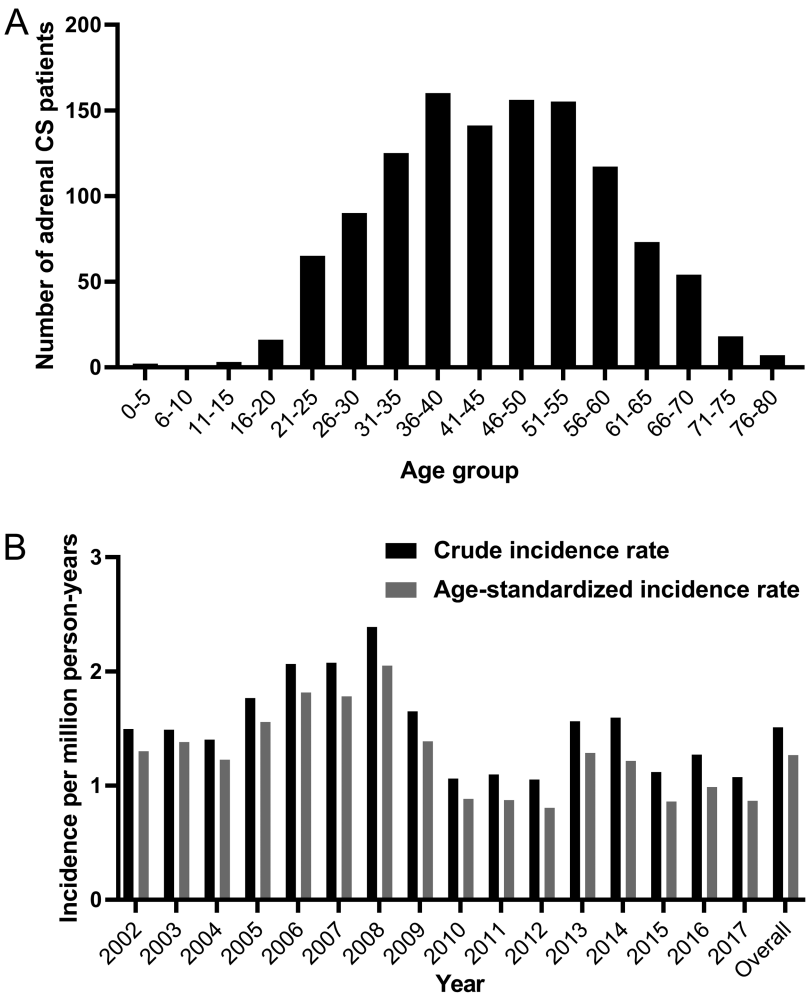

Figure 1. Age distribution and incidence of adrenal CS. (A) Age distribution of adrenal CS patients and (B) annual crude and age-standardized incidence rates of adrenal CS.

preoperative comorbidities were hypertension (67.6%), dyslipidemia (56.3%), and diabetes (37.9%), in order of prevalence (Table 3). All preoperative comorbidities were diagnosed mostly within 1 year before adrenalectomy. We compared the risk of preoperative comorbidities in adrenal CS patients with that in the age- and sex-matched KNHANES control population. Adrenal CS patients had a clearly increased risk of having coronary artery disease (OR 17.5; 95% CI, 11.8-26.0), stroke (OR 14.4; 95% CI, 8.9-23.1), dyslipidemia (OR 10.6; 95% CI, 8.9-12.6), diabetes (OR 9.6; 95% CI, 7.8-11.8), hypertension (OR 9.2; 95% CI, 7.9-10.8), osteoporosis (OR 5.0; 95% CI, 3.9-6.3), and depression (OR 4.6; 95% CI, 3.6-6.0) (Fig. 3A). Various comorbidities also commonly occurred postoperatively (Table 3). The median time to diagnosis of the postoperative comorbidities after adrenalectomy ranged from 0 to 4.2 years. Hypertension, dyslipidemia, diabetes, coronary artery disease, and ischemic and hemorrhagic stroke were more commonly noted as preoperative comorbidities than as postoperative comorbidities (Fig. 3B). However, only hypertension was more commonly noted as a preoperative comorbidity by more than 2-fold, whereas other comorbidities were noted as a postoperative comorbidity after adrenalectomy in a considerable proportion of patients. Osteoporosis, bacterial infection, and pulmonary embolism were more commonly noted as postoperative comorbidities. These findings suggest that adrenal CS patients still have a significant residual risk for these comorbidities, even after adrenalectomy. All comorbidities were diagnosed within 1 year before or after adrenalectomy in more than half of the patients, suggesting that this perioperative 2-year period is a high-risk period for developing various comorbidities.

Postoperative glucocorticoid replacement therapy

Among 1161 patients who had unilateral adrenalectomy, 973 (83.8%) patients were prescribed postoperative oral glucocorticoids. The most common type of glucocorticoid

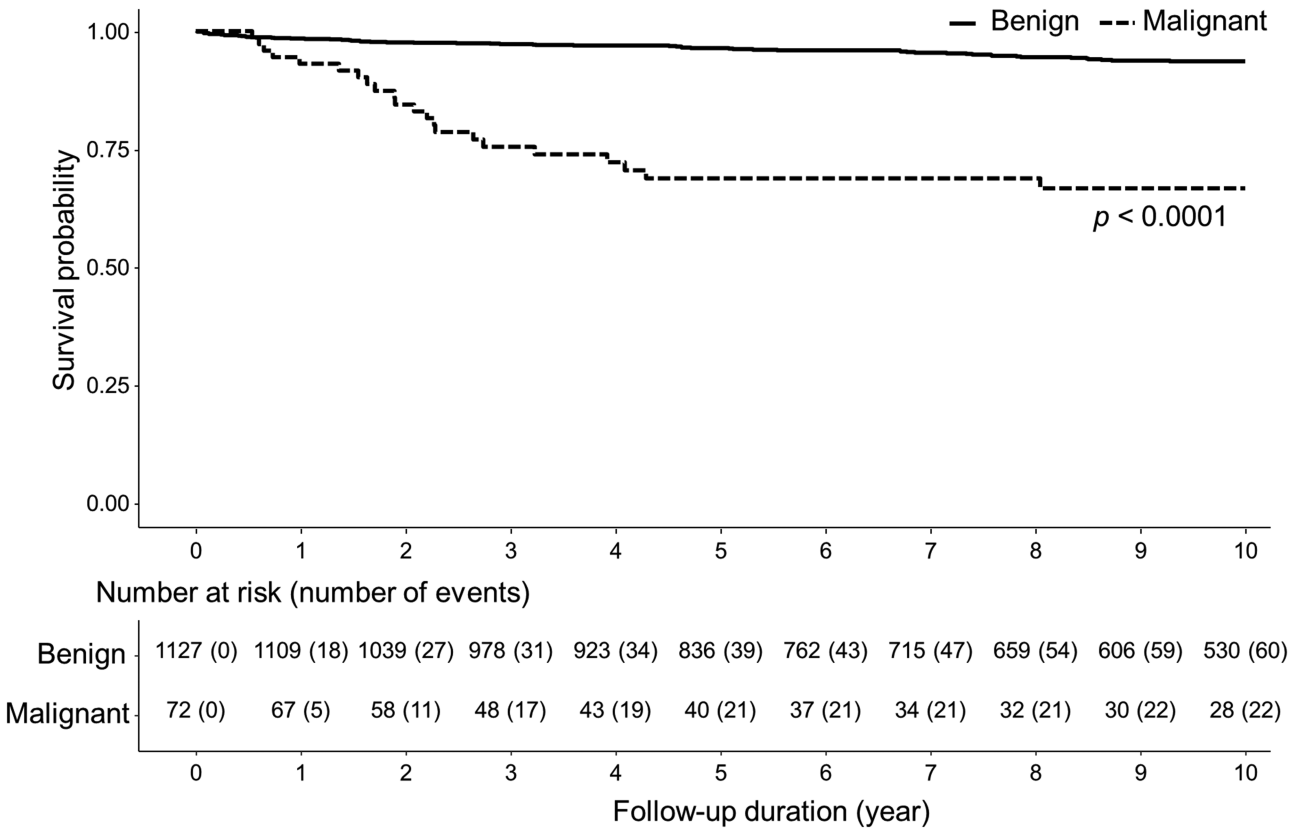

Figure 2. Kaplan-Meier survival curves of benign and malignant adrenal CS after adrenalectomy. $P < 0.001$ according to the log-rank test.

Table 2. Factors Associated With Higher Mortality in Adrenal CS Patients

	All adrenal CS[a]				Benign adrenal CS[b]			
	Unadjusted HR[c]	*P* value	Adjusted HR[d]	*P* value	Unadjusted HR[c]	*P* value	Adjusted HR[d]	*P* value
Female sex	0.69 (0.43-1.10)	0.116	1.07 (0.66-1.74)	0.795	0.78 (0.44-1.38)	0.395	1.06 (0.59-1.90)	0.854
Age (year)	1.07 (1.05-1.09)	<0.001	1.06 (1.04-1.08)	<0.001	1.07 (1.05-1.1)	<0.001	1.06 (1.04-1.09)	<0.001
Bilateral adrenalectomy	2.53 (1.10-5.80)	0.029	2.92 (1.25-6.81)	0.013	3.69 (1.59-8.59)	0.002	3.97 (1.66-9.50)	0.002
Coronary artery disease	1.15 (0.57-2.30)	0.694	0.52 (0.25-1.07)	0.075	1.25 (0.57-2.74)	0.585	0.59 (0.26-1.34)	0.206
Stroke	4.41 (2.52-7.72)	<0.001	3.56 (1.95-6.52)	<0.001	5.22 (2.83-9.65)	<0.001	3.26 (1.67-6.33)	0.001
Diabetes	2.48 (1.60-3.82)	<0.001	1.95 (1.21-3.15)	0.006	3.27 (1.95-5.48)	<0.001	2.10 (1.02-3.66)	0.009
Hypertension	1.93 (1.15-3.26)	0.013	1.05 (0.59-1.85)	0.880	2.14 (1.14-4.03)	0.018	0.88 (0.45-1.73)	0.714
Fracture	1.58 (0.82-3.07)	0.173	1.43 (0.72-2.85)	0.311	1.93 (0.95-3.91)	0.070	1.31 (0.63-2.72)	0.470
Depression	1.33 (0.67-2.67)	0.415	0.99 (0.48-2.03)	0.970	1.85 (0.91-3.75)	0.090	1.12 (0.54-2.35)	0.757
Malignant adrenal CS	6.72 (4.12-10.96)	<0.001	8.36 (4.94-14.13)	<0.001	NA	NA	NA	NA

Abbreviations: CS, Cushing syndrome; HR, hazard ratio; NA, not applicable.
[a]A Cox proportional hazards model was applied for all 1199 adrenal CS patients.
[b]A Cox proportional hazards model was applied for 1127 benign adrenal CS patients.
[c]Unadjusted hazard ratio was calculated for each factor in univariate Cox proportional hazards model.
[d]Adjusted hazard ratio was calculated in multivariate Cox proportional hazards model including all factors.

used was prednisolone (66.6%). Hydrocortisone (22.4%), methylprednisolone (5.3%), and dexamethasone (4.9%) were also used (Fig. 4A). The median duration of postoperative glucocorticoid replacement was 10.1 months (interquartile range: 4.7-20.2) (Fig. 4B). Among various types of glucocorticoid, the median duration of postoperative glucocorticoid replacement was 7.5 (3.6-18.8) months for hydrocortisone and 11.4 (5.5-21.0) months for prednisolone or methylprednisolone ($P = 0.02$). Postoperative glucocorticoid replacement continued until 1, 2, and 5 years after adrenalectomy in 47.0%, 23.6%, and 10.8% of the patients, respectively.

Table 3. Preoperative and Postoperative Comorbidities in the Adrenal Cushing Syndrome Patients

	Preoperative comorbidities[a]		Postoperative comorbidities[b]			
	>1 y preoperatively	Within 1 y preoperatively	Within 3 mos postoperatively	3 mos to 1 y postoperatively	>1 y postoperatively	Median time to diagnosis postoperatively [c] (y)
Hypertension	220 (18.3%)	590 (49.2%)	64 (5.3%)	5 (0.4%)	20 (1.7%)	0.0 (0.0-0.8)
Dyslipidemia	151 (12.6%)	524 (43.7%)	70 (5.8%)	30 (2.5%)	161 (13.4%)	1.7 (0.3-5.5)
Diabetes	123 (10.3%)	332 (27.7%)	98 (8.2%)	19 (1.6%)	93 (7.8%)	0.6 (0.1-3.8)
Osteoporosis	99 (8.3%)	137 (11.4%)	103 (8.6%)	31 (2.6%)	117 (9.8%)	0.9 (0.2-3.0)
Fracture	51 (4.3%)	178 (14.8%)	25 (2.1%)	17 (1.4%)	118 (9.8%)	3.0 (1.0-6.2)
Coronary artery disease	45 (3.8%)	166 (13.8%)	25 (2.1%)	5 (0.4%)	73 (6.1%)	2.5 (0.7-6.0)
Depression	44 (3.7%)	145 (12.1%)	48 (4.0%)	24 (2.0%)	86 (7.2%)	1.3 (0.4-4.6)
Bacterial infection	18 (1.5%)	84 (7.0%)	14 (1.2%)	10 (0.8%)	83 (6.9%)	4.2 (1.5-6.5)
Ischemic stroke	14 (1.2%)	87 (7.3%)	10 (0.8%)	8 (0.7%)	43 (3.6%)	3.3 (0.9-5.4)
Hemorrhagic stroke	10 (0.8%)	18 (1.5%)	2 (0.2%)	2 (0.2%)	10 (0.8%)	2.8 (1.0-3.6)
Tuberculosis	6 (0.5%)	18 (1.5%)	6 (0.5%)	2 (0.2%)	9 (0.8%)	1.6 (0.2-4.1)
Psychotic disorder	3 (0.3%)	9 (0.8%)	2 (0.2%)	1 (0.1%)	7 (0.6%)	3.2 (0.9-5.4)
Aortic disease	2 (0.2%)	4 (0.3%)	2 (0.2%)	0 (0.0%)	3 (0.3%)	1.3 (0.5-5.0)
Pulmonary embolism	1 (0.1%)	3 (0.3%)	6 (0.5%)	0 (0.0%)	3 (0.3%)	0.1 (0.0-3.5)

[a]The data are expressed as n (percentage among total adrenal CS patients).
[b]The data are expressed as n (percentage among adrenal CS patients without each comorbidity at the time of surgery).
[c]The median time from adrenalectomy to the diagnosis of each comorbidity was analyzed for postoperative comorbidities. Median time (interquartile range).

Discussion

Current nationwide analysis based on the NHIS claim database demonstrated that the prevalence of adrenal CS was 23.4 per million people, and the age-standardized incidence rate was 1.27 per million person-years in Korea. This is the first epidemiologic study of adrenal CS in Korea. Adrenal CS is the second most common subtype of endogenous CS. In the nationwide analysis in Denmark that was performed on the basis of the national registry database, the incidence of adrenal CS with adrenal adenoma and adrenocortical carcinoma was 0.6 per million person-years and 0.2 per million person-years, respectively (3). In New Zealand, according to the medical records of 4 main endocrinology centers, the incidence of endogenous CS was estimated to be 1.8 per million person-years, and 18.2% of these cases were caused by adrenal adenoma (2). Thus, the incidence was calculated to be 0.3 per million person-years for benign adrenal CS in New Zealand. Another study in western Sweden reported the incidence of adrenal CS to be 0.7 per million person-years for benign CS and 0.2 per million person-years for malignant adrenal CS (13). Our study showed a higher incidence of adrenal CS in Korea than in Western countries. The Korean guideline for adrenal incidentaloma is similar to other guidelines (14, 15). The 1 mg overnight dexamethasone suppression test is recommended as a screening test for adrenal incidentaloma (16). Additionally, late-night salivary cortisol, midnight serum cortisol, and 24-hour urinary free cortisol can be used for the diagnosis of endogenous CS. Although the salivary cortisol test is not available in Korea, a combination of other available tests could accurately diagnose CS patients in most cases.

The inconsistency between the incidence of adrenal CS in Korean and Western countries might be due to the differences in databases used; the national claim database was used in our study, and the national registry database was used in other studies. However, the operational definition of adrenal CS had a balanced rate of false positives and false negatives in our validation analysis. The operational definition of adrenal CS may have a minimal influence, if any. Thus, it is possible that the incidence of adrenal CS is higher in Korea than in Western countries. Although it was conducted almost 20 years ago, a previous Korean national survey reported that the etiology of endogenous CS was Cushing disease for 43.3% of cases and adrenal CS for 41.7% of cases (17). A single-center study in Korea also reported that adrenal CS (62.0%, n = 57) was more prevalent than Cushing disease (38.0%, n = 35) (18). Adrenal CS can have a higher incidence in Korea than in Western countries and comprises a higher proportion of endogenous CS cases. Another explanation of the higher incidence of adrenal CS in Korea is that the use of computed tomography (CT) has increased over the recent decades (19). This increased use of CT might have led to an increased detection rate of adrenal adenomas and, eventually, cortisol-producing

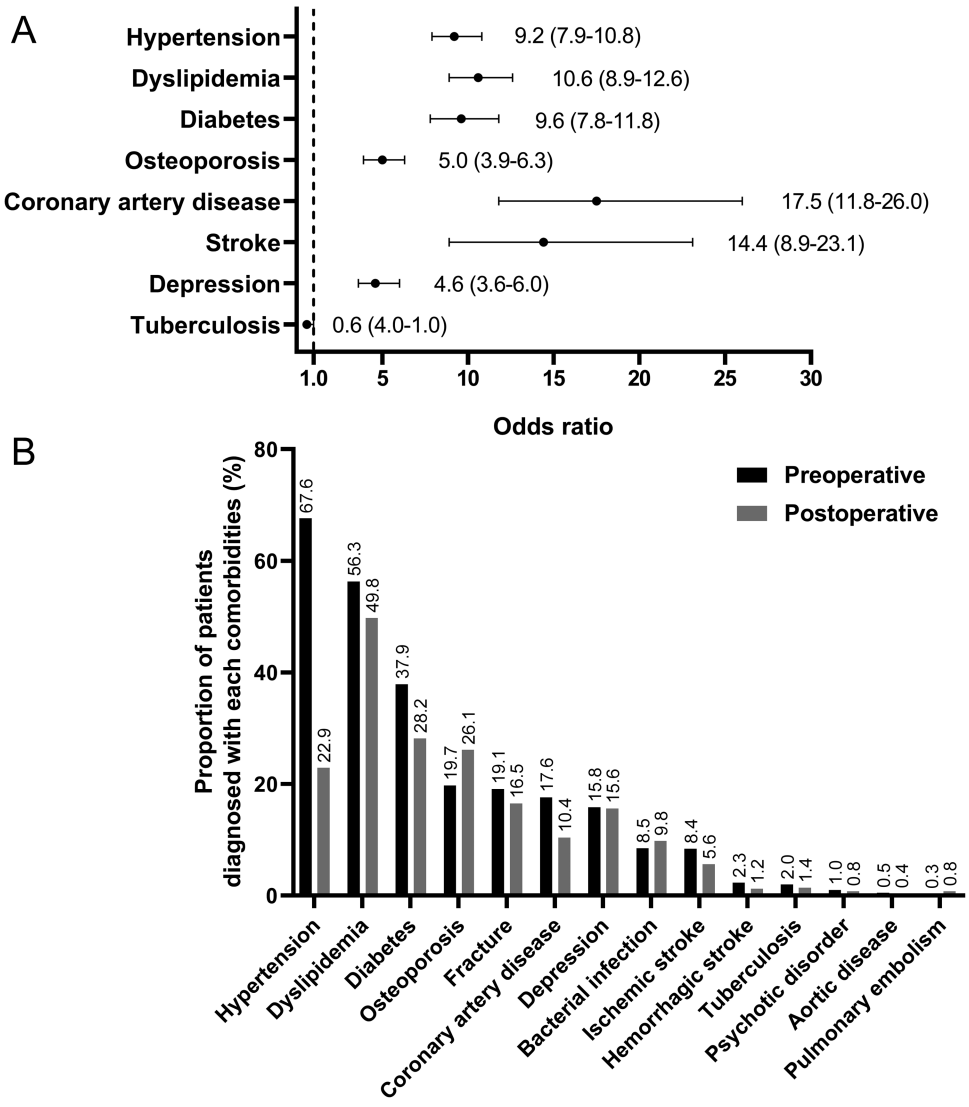

Figure 3. Comorbidities of adrenal CS patients. (A) Odds ratios of the preoperative comorbidities in the adrenal CS patient population compared with the control population and (B) proportion of the patients who were diagnosed with each comorbidity preoperatively or postoperatively. Data are odds ratios with 95% confidence intervals in (A).

adenomas. However, these patients who presented with adrenal incidentalomas would have subclinical CS rather than overt CS. It is necessary to investigate the nationwide data of other CS subtypes in future studies.

Benign adrenal CS patients had a more than 3-fold higher mortality rate than did the standard population. Although the number of deaths was small, mortality occurred steadily for 10 years after adrenalectomy in the benign adrenal CS patients. Due to limited access to data, we were unable to present the cause of death for adrenal CS patients. However, we demonstrated that a risk of cardiovascular disease remained even after adrenalectomy in adrenal CS patients, which could contribute to the higher mortality in adrenal CS patients. Clayton et al also showed that the increased cardiovascular mortality of CS patients, even after biochemical remission, can increase the overall mortality of benign adrenal CS patients (20). Most deaths occurred during the first 5 years after surgery in the malignant adrenal CS group. This finding is probably attributed to the prognosis of adrenocortical carcinoma (21).

Various comorbidities were prevalent at the presentation of adrenal CS. The most prevalent comorbidities were hypertension, dyslipidemia, and diabetes. Atherosclerotic cardiovascular diseases were also highly prevalent, and these patients had a 17-fold and 14-fold increased risk of coronary artery disease and stroke compared with the control population. Cardiovascular disease is the leading cause of death in CS patients (22). CS patients have multiple cardiovascular risk factors. Moreover, hypercortisolemia itself can directly cause myocardial hypertrophy (23) and vascular damage (24). The cardiovascular mortality remained elevated, even after the

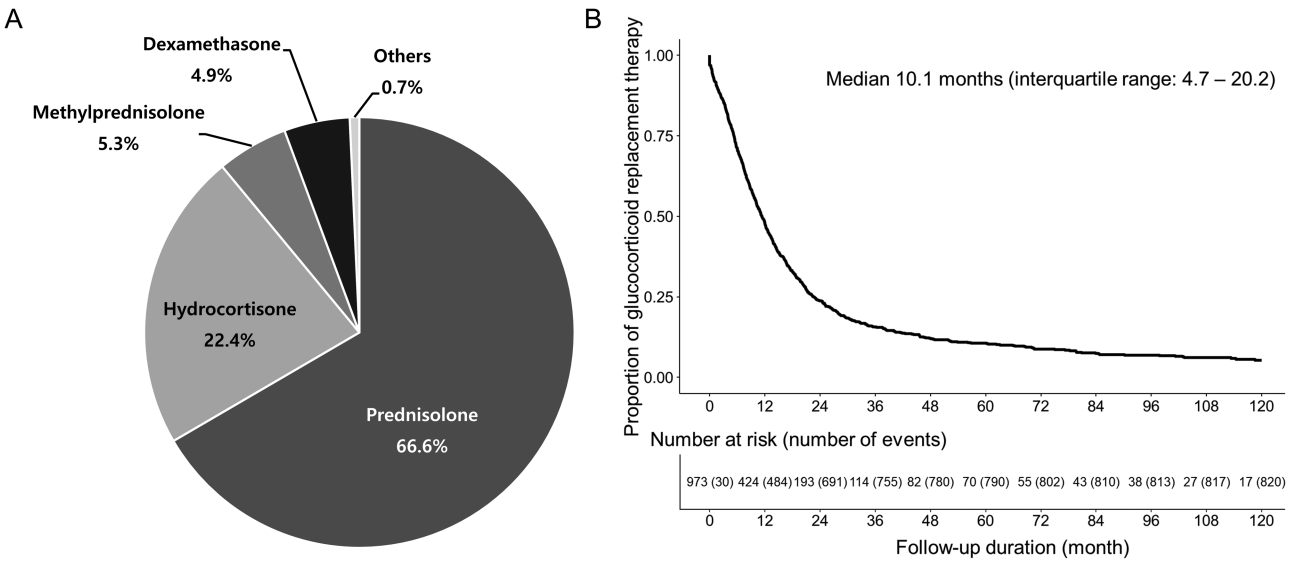

Figure 4. Postoperative glucocorticoid replacement therapies for adrenal CS. (A) Type of postoperative glucocorticoid replacement administered after adrenalectomy. (B) A Kaplan-Meier curve for the proportion of patients continuing postoperative glucocorticoid replacement therapy.

biochemical remission of CS (20). The cardiovascular risk factors, including a high body mass index, hyperglycemia, and dyslipidemia, also remained elevated at 5 years after the remission of Cushing disease (7). In our study, for all the comorbidities, considerable proportions of patients were diagnosed with postoperative comorbidities after adrenalectomy, suggesting a significant residual risk for these comorbidities, even after the treatment of adrenal CS. Interestingly, pulmonary embolism was mostly diagnosed within 3 months after adrenalectomy (46.2% of all pulmonary embolism cases were diagnosed within 3 months after adrenalectomy). A previous study also reported that the risk of venous thromboembolism was remarkably high (hazard ratio of 59.9) in the 3-month period after the surgical treatment of CS (25). High thrombotic diathesis occurs in CS patients (22). Thus, the perioperative period is the period in which CS patients are at the highest risk for thromboembolism. Special consideration should be taken for the early detection and proper management of these comorbidities during the follow-up of adrenal CS patients after adrenalectomy.

After the curative resection of adrenal CS, the remaining adrenal gland becomes atrophied and requires glucocorticoid replacement therapy until the HPA axis is recovered. It has been reported that the recovery time of the HPA axis differs according to the etiology of CS (8). The recovery time was longest for adrenal CS cases, followed by Cushing disease and ectopic CS cases, with median recovery times of 2.5, 1.4, and 0.6 years, respectively (8). However, a more recent study reported a shorter recovery time of 11.4 months for severe CS and 2.8 months for moderate CS, which were defined based on the number of clinical features of CS presented in the patient (26). In our study, the median duration of postoperative glucocorticoid replacement was 10.1 months. However, approximately 10% of patients received glucocorticoid replacement therapy, even after 5 years. The more worrisome finding was that the main type of glucocorticoid replacement used was prednisolone, not hydrocortisone. Prednisolone has a longer action duration and higher glucocorticoid receptor binding affinity, which results in more suppression of CRH secretion from the hypothalamus and ACTH secretion from the pituitary gland. Among the patients who underwent unilateral adrenalectomy, 188 (16.2%) patients did not receive postoperative glucocorticoid replacement therapy. This may be attributed to bilateral macronodular adrenal hyperplasia or subclinical CS in these patients. Furthermore, since we only included postoperative glucocorticoid that was prescribed regularly, those patients who took postoperative glucocorticoid as needed were not included in the analysis on postoperative glucocorticoid replacement. However, considering the extremely high risk of adrenal insufficiency that exists after the treatment of CS (27), these patients could suffer from adrenal insufficiency after adrenalectomy. More attention is warranted for optimal glucocorticoid replacement therapy after adrenalectomy in adrenal CS patients.

The strength of our study is that the NHIS database has nationally representative data that covers nearly 97% of the whole population. Our study investigated long-term prognosis and comorbidities without any patients being lost to follow-up. The treatment of adrenal CS, when the diagnosis is definitive, is surgical resection of adrenal pathology for all adrenal CS patients.

Thus, the operational definition of adrenal CS was validated in our institution and had low false-positive and negative rates.

Our study also has several limitations. First, we could not retrieve data on the cause of death. Second, we categorized adrenal CS cases as only either benign or malignant. Among the benign adrenal CS cases, bilateral macronodular or micronodular adrenal hyperplasia was not distinguishable from adrenal adenoma, because it was not indicated by a diagnostic code. Bilateral macronodular adrenal hyperplasia may have different postoperative course from adrenal adenoma. Third, because our study was based on a claim database, the results of biochemical, imaging, and pathologic exams could not be obtained. Thus, patients with subclinical CS and overt CS could not be differentiated in our study. In addition, we could not precisely evaluate the recovery of the HPA axis using biochemical tests. Last, the definition of comorbidities was solely based on the diagnosis codes, which could have been imprecise in some cases. We could not differentiate newly developed postoperative comorbidities from preexisting comorbidities that were only diagnosed postoperatively.

In summary, the prevalence of adrenal CS was 23.4 per million people, and the age-standardized incidence rate of adrenal CS was 1.27 per million person-years in Korea. Approximately 6.0% of adrenal CS cases were caused by adrenocortical carcinoma. Benign adrenal CS patients had a 3-fold higher mortality than did the standard population. Various comorbidities, including metabolic diseases, cardiovascular diseases, osteoporosis, and mental illness, were already prevalent at the presentation of adrenal CS, and a residual risk remained after the treatment of adrenal CS. The early detection and management of these comorbidities are necessary to optimally follow-up adrenal CS patients. More attention should also be paid to have optimal postoperative glucocorticoid replacement therapies based on the physiologic regimens.

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Data Availability: This study used National Health Information Database (NHIS-2019-4-007) made by National Health Insurance Service (NHIS). Restrictions apply to all the availability of data generated or analyzed during this study to preserve patient confidentiality. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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