Operational Definition of Adrenal diseases: Enhancing Precision and Reproducibility in Observational Data

Suhyun Kim[1], Seung Shin Park[2, 3], Seung hun Lee[4], Kwangsoo Kim[1], Jung Hee Kim[2, 3]

[1]Transdisciplinary Department of Medicine & Advanced Technology, Seoul National University Hospital, Seoul, Republic of Korea.

[2]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea.

[3]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea.

[4]Division of Endocrinology and Metabolism, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

Background

The rare incidence of adrenal disease[1] prompts the conduct of research in the field of observational research. However, relying solely on diagnosis codes may not provide sufficient granularity and accuracy in capturing the complexity of adrenal disease, so the false positive rate increases when patients are defined simply using diagnosis codes (e.g. ICD-10 or SNOMED).[2] Therefore, this study proposes operational definitions for six adrenal diseases, and report on the positive predictive values (PPVs) of the proposed phenotypes to validate.

Methods

In this study, Seoul National University Hospital (SNUH) CDM database was used to develop operational definitions of six adrenal diseases, and prospectively constructed registry data were utilized for validation. Clinical information captured in the condition, drug, procedure, and measurement domains was utilized to construct operational definitions of each adrenal disease (Table 1). Registry data served as the golden standard, allowing for the construction of an accurate operational definition.

Results

This is ongoing research. The operational definition framework successfully identified and classified different adrenal diseases. Specifically, six adrenal diseases were characterized: primary aldosteronism, adrenal Cushing syndrome, pheochromocytoma and paraganglioma, adrenal cortical carcinoma, nonfunctioning adrenal adenoma, and mild autonomous cortisol secretion. The operational definition steps for each disease were established, combining various criteria such as admission history, outpatient department visits, specific lab values, and relevant medical procedures.

Conclusion

The operational definitions of the six adrenal diseases we present in this study will be further validated for accuracy. We also plan to acquire additional data partners to robustly evaluate the generalizability to operational definitions.

Table 1. The operational definition steps of 6 adrenal diseases.

Adrenal Disease	Cohort Criteria
Primary aldosteronism	**Cohort Start Criteria** • At least 1 day Admission or 2 days outpatient department of Hyperaldosteronism (195213) | Renal hypertension (443771) | Hypertension secondary to endocrine disorder (4110948) • No history of Secondary hyperaldosteronism (437836) any days prior **Additional Criteria** • Adrenalectomy (4137462) or at least 180 days of Spironolactone (970250) | Amiloride (991382) cummulative prescription • The minimum lab value of Aldosterone [Mass/volume] in Serum or Plasma (3011337) > 10 microgram per deciliter (8837; ug/dL) at the same prescription day of Sodium chloride (967823)
Adrenal Cushing syndrome	**Cohort Start Criteria** • At least 1day Admission OR 2 outpatient department of Pituitary dependent hypercortisolism (4096185) | Hypercortisolism (195212) | Adrenocortical hyperfunction (438123) • No history of Primary malignant neoplasm of adrenal medulla (4162859) | Hypercortisolism due to nonpituitary tumor (4269053) |Pituitary dependent hypercortisolism (4096185) | Primary malignant neoplasm of adrenal cortex (4162115) | Primary malignant neoplasm of adrenal gland (198104) **Additional Criteria** • Has Adrenalectomy (4137462) • No history of Operation on lesion of pituitary gland (4034810) • ODST (Overnight Dexamethasone Suppression Test)* ≥ 1.8 microgram per deciliter (8837; ug/dL) or LDST (Low Dose Suppression Test)** ≥ 1.8 microgram per deciliter or Cortisol [Mass/time] in 24 hour Urine (3017275) > 75 microgram per 24 hours (8906; ug/24hr) *ODST: the minimum lab value of Cortisol [Mass/volume] in Serum or Plasma (3009682) after 365 days within 548 days of Dexamethasone (1518254) 1 milligram (8576; mg) prescription **LDST: the minimum lab value of Cortisol [Mass/volume] in Serum or Plasma within 4 days of Dexamethasone 0.5 milligram prescription
Pheochromocytoma and Paraganglioma	**Cohort Start Criteria** • At least 1 day Admission or 2 days outpatient department of Benign neoplasm of adrenal gland (192273) | Neoplasm of uncertain behavior of adrenal gland (196365) | Hypertension secondary to endocrine disorders (45596189) | Primary malignant neoplasm of adrenal cortex (4162115) | Primary malignant neoplasm of adrenal gland (198104) | Benign neoplasm of paraganglion (444463) | Neoplasm of uncertain behavior of carotid body (4314634) | Neoplasm of uncertain behavior of paraganglia (27516) | Neoplastic disease of uncertain behavior (432582) | Primary malignant neoplasm of paraganglion (442122) **Additional Criteria** • Has at least one sugery of Adrenalectomy (4137462) | Excision of carotid body tumor (4051038) | Excision from retroperitoneum (4004044) | Transurethral resection of bladder neoplasm (4305077) | Excision of mediastinal tumor (4084965) • EPINEPHrine [Mass/time] in 24 hour Urine (3017018) > 17 |

	Norepinephrine [Mass/time] in 24 hour Urine (3011657) > 370 or < 62 | Normetanephrine [Mass/volume] in Serum or Plasma (3016851) > 341 or < 52 | Metanephrine [Mass/volume] in Serum or Plasma (3015200) > 930 or < 90 | Normetanephrine [Mass/volume] in Serum or Plasma (3016851) > 2300 or < 100
Adrenal cortical carcinoma	**Cohort Start Criteria** • At least 1 day Admission or 2 days outpatient department of Primary malignant neoplasm of adrenal cortex (4162115) | Primary malignant neoplasm of adrenal gland (198104) **Additional Criteria** • Dehydroepiandrosterone sulfate (DHEA-S) [Mass/volume] in Serum or Plasma (3015884) > 2.5% to 97.5% percentiles vary by age and sex | 17-Ketosteroids [Mass/time] in 24 hour Urine (3020027) > 25 mg/day (4120731) for male 14 mg/day for female
Nonfunctioning adrenal adenoma	**Cohort Start Criteria** • At least 1 day Admission or 2 days outpatient department of Benign neoplasm of adrenal gland (192273) | Neoplasm of uncertain behavior of adrenal gland (196365) **Additional Criteria** • ODST ≤ 1.8 microgram per deciliter or LDST ≤ 1.8 microgram per deciliter
Mild autonomous cortisol secretion	**Cohort Start Criteria** • At least 1 day Admission or 2 days outpatient department of Benign neoplasm of adrenal gland (192273) | Neoplasm of uncertain behavior of adrenal gland (196365) **Additional Criteria** • ODST ≥ 1.8 microgram per deciliter or LDST ≥ 1.8 microgram per deciliter

References

1. Kim, J. H., Kim, M. J., Lee, J. H., Yoon, J. W., & Shin, C. S. (2020). Nonfunctioning adrenal incidentalomas are not clinically silent: a longitudinal cohort study. *Endocrine Practice*, 26(12), 1406-1415.
2. Cho, S. W., Kim, J. H., Choi, H. S., Ahn, H. Y., Kim, M. K., & Rhee, E. J. (2023). Big data research in the field of endocrine diseases using the Korean National Health Information Database. *Endocrinology and Metabolism*, 38(1), 10-24.