Supplemental Material

Data S1.

Identification of primary aldosteronism from the National Health Insurance Research Databases

Material and Methods

Our population-based retrospective cohort study is based on data from the National Health Insurance Research Databases (NHIRD) dating between 1997 and 2009. The NHIRD has been implemented in Taiwan since 1995 and is one of the largest and most comprehensive databases in the world, having been used extensively in various studies.[1-3] The National Health Insurance (NHI) covers almost all of the 23.7 million people living in Taiwan and contains medical information about outpatient visits, hospital admissions, prescriptions, interventional procedures, disease profiles, and vital status.[4, 5] The NHI Administration (NHIA) routinely checks for data accuracy and thus reliability.[6-8]

We have proved the abovementioned hypothesis of such identification of PA diagnosis by using multi-center medical records as the "gold standard" and matched with the TNHI reimbursement records.[2] The diagnosis of PA is according to clinical judgment. In order to increase the diagnostic specificity, we used validated algorithm to enroll PA patients. Our strategy, based on a combination of PA ICD-9 codes, and spironolactone claim, had the highest positive predictive value (PPV) for the identification of patients with PA. Using 3 out-patient visits or one inpatient has higher PPVs than one outpatient or one inpatient record. PPVs varied with different algorithms with PA code: PPV for antihypertensive drugs in use (PPV= 66.9%, 95%CI = 63.0%-70.6%), claims with hypokalemia and antihypertensive drug in use (PPV= 89.4%, 95%CI = 85.4%-93.0%), and final decisions of clinical certainty of PA with spironolactone in use[2] (PPV= 93.4%, 95%CI = 89.4%-97.0%). By searching the procedure codes, we analyzed the ratio of image study, adrenal venous sampling (AVS), and postural stimulation tests among the PA patients in this study. Since the diagnostic and procedure codes were for insurance reimbursement, they were recorded with high accuracy, and it reflected the 'real-world practice' to identify aldosteronism in Taiwan during the past decade (Table S1). In order to validate the diagnostic tests from the NHI database, we scrutinized the database of TAIPAI (the patients in the database of TAIPAI are included as a fraction of the whole NHI database; but more detailed clinical parameters of the patients are available from TAIPAI than from NHI database, because the former is a multicenter quality-control data registry, while the latter is a population-base health insurance data registry). The TAIPAI study group included two medical centers (National Taiwan University

Hospital (NTUH), Taipei, Taiwan; Taipei University Hospital , Taipei, Taiwan), and five regional hospitals (Cardinal Tien Hospital, New Taipei City, Taiwan; Taipei Tzu Chi Hospital, New Taipei City, Taiwan; Yun- Lin Branch of NTUH, Douliou City, Taiwan; Hsin-Chu Branch of NTUH, Hsin-Chu City, Taiwan; Zhongxing Branch of Taipei City Hospital, Taipei, Taiwan). Because there is no specific ICD-9 diagnosis of aldosterone producing adenoma, PA patients with the diagnosis of adrenal tumor (ICD-9 code =227, 227.0, 239.7) were further analyzed as a specificity test.

Results

131I-6β-Iodomethyl-19-Norcholesterol SPECT/CT (NP-59 SPECT/CT) plays an important ancillary role, especially among those patients for whom AVS was unavailable and CT showed a unilateral adrenal mass. Currently iodocholesterol scintigraphy is no longer used in some countries, like the United States (U.S.), but remains available in Taiwan, Japan and other countries. It has the ability similar to conventional visual scale (VS) in differentiating APA from IAH, and yet an excellent ability to predict postsurgical outcomes of adrenalectomy[9].

CT scan, postural stimulation and AVS were the leading procedures to identify APA from our two datasets[3] (the NHI dataset of the current article and the TAIPAI dataset) (Table S2). Salt loading test is the most commonly used diagnostic procedure to identify PA form the TAIPAI database. From TAIPAI cohort, we notice that the diagnostic utility of AVS and posture stimulation tests was almost the same as that from the NHI database. Most of the hospitals form the TAIPAI group were equipped with the capacity of NP-59 SPECT/CT, and therefore the diagnostic utility of NP-59 SPECT/CT was higher than that from the NHI database.

In Taiwan, patients who received captopril tests showed a sensitivity of 66.2% and a specificity of 89.1%.[10] According to our previous validation, the NP-59 for Primary Aldosteronism patients showed an accuracy of 77.4% for predicting pathological change of aldosteronism[11]; However NP-59 semi-quantification in differentiating APA could reach the accuracy of 85.7%.[9]

The result of our AVS among the TAIPAI dataset showed that 44.7% of PA patients were found to have lateralized hypersecretion of aldosterone (i.e.: APA; including 32.7% with lateralization towards the right and 12% with lateralization towards the left), and no lateralization could be identified among the other 55.3% PA patient; i.e.: idiopathic adrenal hyperplasia).

For the comparison between patients with aldosterone producing adenoma who were treated with surgery versus MRA, PA patients with the diagnosis of adrenal tumor (ICD-9 code =227, 227.0, 239.7) were further analyzed as a specificity test

from TAIPAI cohort. In our dataset, among the patients who underwent adrenalectomy and had the ICD-9 record of an adrenal tumor, there was a very high positive predictive value (96%) of APA. Furthermore, in the specificity test of this study we chose- only to include those confirmed APA patients to run the test, which although sacrificed some sensitivity, increased the positive predictive rate. In such a conservative way, we are confident to report the beneficial effects of adrenalectomy on the all-cause mortality among these APA patients.

Among the patients who underwent AVS we further identified those patients with incidentaloma (not APA) and contralateral adrenal aldosteronism, and compared them with the previously mentioned combo coding of PA and adrenal tumor. The result showed a high incidence of such discrepancy (99.2%) and indirectly confirmed the high specificity of coding about adrenal adenoma among PA patients as APA.[8]

Table S1. The details of diagnostic procedures from national health insurance data[12]

	Before Match			*After Match**		
	No Operation (n=2516)	**Operation (n=846)**	***p***	**No Operation (n=822)**	**Operation (n=822)**	***p***
Male sex	1188 (47.2%)	369 (43.6%)	0.073	358 (43.6%)	360 (43.8%)	0.960
Age (year)	52.91 ± 15.44	46.6 ± 10.85	<0.001	46.9± 13.7	46.9 ± 10.8	0.447
Age < 35 y/o	292 (11.6%)	114(13.5%)	0.161	140(17.0%)	107(13.0%)	0.027
Age < 40 y/o	521(20.7%)	226(26.7%)	<0.001	256(31.1%)	208(25.3%)	0.010
Subtype						
CT	1481(58.9%)	539(63.7%)	0.017	529(64.4%)	520(63.3%)	0.692
MRI	808(32.1%)	283(33.5%)	0.391	267(32.5%)	278(33.8%)	0.289
AVS	471(18.7%)	190(22.5%)	0.023	151(18.4%)	195(23.7%)	0.020
NP-59	304(12.1%)	113(13.4%)	0.186	99(12.0%)	129(12.9%)	0.343
Posture	1085(43.1%)	413(48.8%)	0.336	379(46.1%)	399(48.5%)	0.421

AVS, adrenal venous sampling, CT, computer tomography, MRI, Magnetic Resonance Imaging, NP-59, 131I-6β-Iodomethyl-19-Norcholesterol SPECT/CT

Table S2. Details of diagnostic procedures from TAIPAI database[12].

Total 563 patients	**No Operation (n=330)**	**Operation (n=233)**	**P**
Male sex	159(48.2%)	111(47.6%)	0.932
Age (in year)year)	56.1 ± 12.5	52.2 ± 11.8	<0.001
Age <35 year old	24 (7.2%)	28 (12.0%)	0.096
Age <40 year old	52(15.8%)	56(24.0%)	0.026
Confirmation test			
Capoten test	109(33.0%)	55(23.6%)	0.018
Salt loading test	205(62.1%)	134(57.5%)	0.294
Subtype			
CT	307(93.0%)	212(91%)	0.426
MRI	63(19.1%)	46(19.7%)	0.914
AVS	82(24.8%)	61(26.2%)	0.423
NP-59	66(20.0%)	52(22.3%)	0.256
Posture	158 (47.9%)	105 (45.1%)	0.398

Detailed information regarding to comparison of PA and EH

Table S3 showed baseline characteristics of all study population. Of the 2,391 newly diagnosed PA patients enrolled in this study, 1,307 (54.7%) were female. 151 (6.3%) patients in the PA group had new-onset CHF and 279 patients (11.7%) in the PA group died. After targeted treatment, the incidence of new onset CHF was of 11.8 per 1000-person year in the PA group. The incidence of mortality and CHF were lower among the PA group after targeted treatment than that of the EH group (Incidence rate of CHF, EH vs. PA = 13.7 vs. 11.8; incidence rate of Mortality, EH vs. PA = 24.1 vs. 20.8, Table S2). Regarding to comparison of PA/EH (Table S4), in the comparison of PA and EH group, the risk of CHF was not significantly different between both groups (adjusted hazard ratio (HR)=0.87, CI: 0.73-1.03, p = 0.109, Table S2), but the risk of all-causes mortality was lower in PA group (adjusted hazard ratio (HR)=0.87, CI: 0.76-0.099, p = 0.35, Table S2).

Table S3. Baseline Characteristics of all Study Population.

Variables	Matched PA/EH			
	EH (n = 9564)	PA (n = 2391)	p	StD
Propensity score	-4.04 ± 1.58	-4.04 ± 1.58	0.997	0.000
Sex				
Women	5013 (52.42%)	1307 (54.66%)	0.050	-0.045
Men	4551 (47.58%)	1084 (45.34%)		-0.045
Age	49.98 ± 13.98	49.98 ± 13.98	0.999	0.000
Urbanization level				

Urban	4428 (46.30%)	1124 (47.01%)		-0.008
Suburban	2543 (26.59%)	644 (26.93%)	0.581	-0.006
Rural	2593 (27.11%)	623 (26.06%)		0.022
Monthly income, n (%)				
<NT$19100	5637 (58.94%)	1443 (60.35%)		-0.014
NT$19100–NT$41999	3240 (33.88%)	789 (33.00%)	0.397	0.013
≥NT$42000	687 (7.18%)	159 (6.65%)		0.021
Comorbidity				
Cerebrovascular disease	630 (6.59%)	178 (7.44%)	0.145	0.034
CKD	175 (1.83%)	54 (2.26%)	0.182	0.030
COPD	445 (4.65%)	123 (5.14%)	0.308	0.023
Coronary artery disease	51 (0.53%)	14 (0.59%)	0.756	0.007
Dementia	55 (0.58%)	10 (0.42%)	0.437	-0.022
Diabetes Mellitus	1140 (11.92%)	307 (12.84%)	0.220	0.028
Hemiplegia	52 (0.54%)	18 (0.75%)	0.231	0.026
Liver disease	566 (5.92%)	127 (5.31%)	0.282	-0.026
Peptic Ulcer	715 (7.48%)	182 (7.61%)	0.828	0.005
Peripheral vascular disease	59 (0.62%)	9 (0.38%)	0.222	-0.034
RA	50 (0.52%)	7 (0.29%)	0.183	-0.036
Solid tumor	236 (2.47%)	60 (2.51%)	0.883	0.003
SLE	20 (0.21%)	6 (0.25%)	0.629	0.009
Atrial fibrillation	69 (0.72%)	17 (0.71%)	0.999	-0.001
Dyslipidemia	1376 (14.39%)	336 (14.05%)	0.695	-0.010
Parkinson disease	48 (0.50%)	15 (0.63%)	0.432	0.017
Medication for hypertension				
Alpha-Blocker	566 (5.92%)	155 (6.48%)	0.313	0.023
ACEI or ARB	3723 (38.93%)	918 (38.39%)	0.639	-0.011
Beta-Blocker	4495 (47.00%)	1080 (45.17%)	0.114	-0.037
Calcium-Channel Blocker	5793 (60.57%)	1439 (60.18%)	0.743	-0.008
Diuretic	3934 (41.13%)	992 (41.49%)	0.763	0.007
Other Medication				
Aspirin	527 (5.51%)	140 (5.86%)	0.517	0.015
Clopidogrel	120 (1.25%)	29 (1.21%)	0.918	-0.004
Ticlopidine	85 (0.89%)	24 (1.00%)	0.630	0.012
Warfarin	60 (0.63%)	16 (0.67%)	0.775	0.005

PPI	343 (3.59%)	90 (3.76%)	0.669	0.009
H2 blocker	854 (8.93%)	214 (8.95%)	0.968	0.001
Statin	801 (8.38%)	205 (8.57%)	0.742	0.007
NSAID	4566 (47.74%)	1151 (48.14%)	0.731	0.008
Steroid	874 (9.14%)	224 (9.37%)	0.722	0.008
SSRI	244 (2.55%)	55 (2.30%)	0.511	-0.016
Nitrate	17 (0.18%)	7 (0.29%)	0.303	0.024
Outcome of interests				
CHF	671 (7.02%)	151 (6.32%)	0.240	-0.028
Mortality	1257 (13.14%)	279 (11.67%)	0.056	-0.045

ACEI: Angiotensin-Converting-Enzyme Inhibitor; APA: Aldosterone Producing Adenoma; ARB: Angiotensin Receptor Blocker; CHF: Congestive Heart Failure; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; EH: Essential Hypertension; H2 blocker: Histamine-2 receptor antagonist; NT$: New Taiwan dollar; NSAID: NonSteroidal Anti-Inflammatory Drug; PA: Primary Aldosteronism; PPI: Proton-Pump Inhibitor; RA: Rheumatoid Arthritis; SLE: Systemic Lupus Erythematous; SSRI: Selective Serotonin Reuptake Inhibitors

Table S4. Incidence rate of CHF, Mortality and HRs (PA and EH).

Variables	Events	Person-Years	Incidence Rate*	Events	Person-Years	Incidence Rate*
	EH			**PA**		
CHF	671	49133	13.7	151	12830	11.8
Mortality	1257	52191	24.1	279	13408	20.8
Comparison of PA and EH						
	HR	p	Adjusted HR	p	HR Competing with mortality	p
PA/EH						
CHF	0.87 [0.73,1.04]	0.136	0.87 [0.73,1.03]	0.109	0.88 [0.74,1.05]	0.150
Mortality	0.87 [0.76,0.99]	<0.031	0.87 [0.76,0.99]	0.035		

*: Per 1000 Person-Years

APA: aldosterone producing adenoma; CHF, congestive heart failure; EH, essential hypertension; HR, hazard ratio; PA, primary aldosteronism

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