

Prevalence and risk factors for secondary hypertension among young Korean men

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Screening for secondary hypertension (HTN) is recommended for early-onset HTN. However, there have been few studies on secondary HTN in young adults. We aimed to investigate the prevalence and risk factors for secondary HTN in young male military personnel. In this retrospective cross-sectional study, hypertensive men (age, 19-29 years) were identified using the electronic medical records (EMR) database between 2011 and 2017. Among them, patients with secondary HTN were confirmed through a review of the EMR. Using clinical characteristics and laboratory findings, independent predictors associated with secondary HTN were identified by binary logistic regression analysis. Secondary HTN was confirmed in 140 of 6373 participants (2.2%). Overall, the most common causes were polycystic kidney disease ($n = 47$, 0.74%) and renal parenchymal diseases ($n = 24$, 0.38%). The independent predictors of secondary HTN were abnormal thyroid function test (TFT) (odds ratio [OR]: 9.50, 95% confidence interval [CI]: 4.84-19.45, $P < 0.001$), proteinuria (\geq trace) (OR: 6.13, 95% CI: 2.97-12.99, $P < 0.001$), hematuria (\geq trace) (OR: 4.37, 95% CI: 2.15-9.01, $P < 0.001$), severe HTN ($\geq 180/110$ mmHg) (OR: 3.07, 95% CI: 1.42-6.65, $P = 0.004$), and non-overweight (OR: 3.03, 95% CI: 1.69-5.26, $P < 0.001$). However, there were no significant differences in the family history of HTN, headache, total cholesterol, and diabetes between patients with primary and secondary HTN. Therefore, to ensure cost-effectiveness, screening for secondary HTN in young hypertensive men should be performed selectively considering abnormal TFT, proteinuria, hematuria, severe HTN, and non-overweight.

Keywords

Epidemiology; hypertension; military personnel; prevalence; young adult

1. Introduction

Secondary hypertension (HTN) is defined as HTN with an identifiable cause, which may be treatable with specific interven-

tions. If the underlying cause is identified and treated before the age of 30-40 years, blood pressure (BP) is likely to normalize. However, if the cause is treated later in life, HTN may persist because long-standing high BP results in damage to the arterial system and other organs (Streeten et al., 1990). Therefore, the guidelines from North America and Europe suggest screening for secondary HTN in patients with early-onset (age < 30 -40 years) HTN, particularly without other risk factors (such as obesity, metabolic syndrome, and family history) (Rimoldi et al., 2014; Unger et al., 2020; Whelton et al., 2018; Williams et al., 2018). Common causes of secondary HTN are known to be renal parenchymal disease, primary aldosteronism, renal artery stenosis, obstructive sleep apnea, pheochromocytoma, Cushing's syndrome, and thyroid disease. Thus, screening tests for secondary HTN could include renal ultrasound or computed tomography (CT), overnight dexamethasone suppression test (DST) or 24-h urinary free cortisol (UFC), and thyroid function test (TFT), and evaluation of plasma aldosterone/renin ratio (ARR) and plasma metanephrines (Rimoldi et al., 2014; Unger et al., 2020; Whelton et al., 2018; Williams et al., 2018). However, screening should be individualized, and history taking and physical examinations should guide the choice of investigations rather than all patients requiring these excessive investigations.

The prevalence of secondary HTN in hypertensive patients is reportedly 5%-15% (Anderson et al., 1994; Danielson and Dammström, 2009; Omura et al., 2004; Sinclair, 1987). Unlike the prevalence of primary HTN, which increases with age, (Chow, 2013; Jago, 2006; Zhou et al., 2017) the prevalence of secondary HTN is the highest in preschool children (51%), (Gupta-Malhotra et al., 2015) the lowest in younger adults aged < 30 years (5.6%), and increases gradually in patients aged up to ≥ 70 years (17.4%) (Anderson et al., 1994). Although there have been many studies on secondary HTN over the decades, the prevalence and predictive factors of secondary HTN in young adults aged < 30 years are not well known. Considering the rarity and importance of secondary HTN, it is necessary to screen individuals who are more likely to have this condition. Although there are general clinical characteristics suggestive of secondary HTN, (Mancia et al., 2013) it is not easy for practitioners to arrive at a decision on screening a pa-

tient with early-onset secondary HTN. There are several reasons for this: (1) secondary causes are diverse, and clinical manifestations range from asymptomatic to severe; (2) some patients are reluctant to undergo additional investigations including 24-h urine collection because such tests are uncomfortable, costly, and time consuming; and (3) little is known about the predictors of secondary HTN, especially in young adults.

In South Korea, men aged 18–35 years are obligated to complete a 2-year military service. All recruits undergo medical checkups to confirm eligibility at the time of enlistment. Men are exempted from military service if their height is < 146 cm or body mass index is < 14 or ≥ 50 kg/m², or if they have a serious illness or disability (Table S1 in the Supplementary Materials). During military service, military personnel undergo annual medical examinations, including BP measurements. When HTN is suspected, they are referred to a military hospital for appropriate examinations and treatment. If the referred patients are suspected of secondary HTN based on screening tests, they are referred again to the Armed Forces Capital Hospital, a tertiary referral hospital, and are examined by a multidisciplinary team of cardiologists, nephrologists, and endocrinologists.

There have been many studies on secondary HTN so far, but little is known about secondary HTN in young adults aged < 30 years. Therefore, we aimed to investigate the prevalence and predictors of secondary HTN in relatively healthy young men aged 19–29 years using recent data from South Korean military hospitals. This study could increase cost-effectiveness by selectively screening for secondary HTN in young adult hypertensive patients.

2. Materials and methods

2.1 Study design and setting

This retrospective cross-sectional study was conducted to investigate the prevalence and predictors of secondary HTN in young male military personnel. This study used data from the Defense Medical Information System (DEMIS) database between January 2011 and June 2017.

2.2 Data collection and management

Patients who had a diagnosis of primary and secondary HTN were identified from the DEMIS database. The DEMIS database includes electronic medical records (EMR), imaging data, and laboratory data from 19 military hospitals and about 1200 medical corps in South Korea from 1997 till date. The diagnoses were coded according to the International Classification of Diseases 10th revision (ICD-10).

Collecting primary HTN cases is relatively easy and simple using ICD-10 code 'I10'; however, this is not the case for secondary HTN. Although ICD-10 code 'I15' is assigned to secondary HTN, a significant number of cases with a secondary cause only have a diagnostic code for the secondary cause without ICD-10 code 'I15', at the physician's discretion. Therefore, we first collected all possible cases of secondary HTN with ICD-10 code 'I15' or other codes for causative diseases (Table S2 in the Supplementary Material). Subsequently, through meticulous reviews of EMR, we eliminated inappropriate cases according to the exclusion criteria. Exclusion criteria were designed to remove cases that failed to meet the diagnostic criteria, those with an obvious preceding cause such as trauma or sepsis, and those that failed to meet the diagnostic criteria for HTN (Fig. 1) (Mancia et al., 2013). Subse-

quently, patient characteristics including clinical and demographic information and laboratory and imaging data were extracted from DEMIS directly into the electronic database by the author.

HTN was defined as a systolic BP ≥ 140 mmHg and/or a diastolic BP ≥ 90 mmHg and classified according to the 2018 European Society of Hypertension/European Society of Cardiology guidelines (Mancia et al., 2013). White coat HTN was diagnosed when a patient had a clinic BP of $\geq 140/90$ mmHg in at least three visits but had an average BP of < 130/80 mmHg in 24-h ambulatory BP monitoring (ABPM).

2.3 Clinical guidelines and standards for tests

To confirm the diagnosis of primary aldosteronism (PA), test values of plasma aldosterone concentration (PAC), plasma renin activity (PRA), and plasma ARR were obtained. Patients taking any antihypertensive medication had to undergo a medication washout period before undergoing screening tests to avoid interference with the renin-angiotensin-aldosterone system (RAAS). Dihydropyridine calcium channel blockers, β -blockers, angiotensin-converting enzyme inhibitors, and angiotensin-II receptor blockers should be stopped at least 2 weeks before testing. Diuretics and aldosterone antagonists should be withdrawn for at least 4 weeks. If needed, slow-release verapamil and/or doxazosin can be prescribed instead. When PA was confirmed in the saline loading test, bilateral adrenal venous sampling should be performed for subtype classification (Funder et al., 2016). For Cushing's syndrome, the test results of 24-h UFC and 1-mg overnight DST were assessed (Guignat and Bertherat, 2010). Patients with positive results should be referred to the Armed Forces Capital Hospital, a tertiary referral hospital, and re-examined by an endocrinologist.

The diagnostic criteria for subclinical hypercortisolism remain controversial and uncertain. Considering the sensitivity and specificity of previous studies, we diagnosed subclinical hypercortisolism if the 24-h UFC was > 90 μ g/day and (1) serum cortisol was repeatedly > 1.8 μ g/dL after 1-mg overnight DST, (2) serum cortisol was > 1.8 μ g/dL after a 4-mg low-dose DST, or (3) serum cortisol was > 5 μ g/dL after a 1-mg overnight DST (Chiodini, 2011; Martins et al., 2012).

For autosomal dominant polycystic kidney disease (ADPKD), the presence of three or more renal cysts (unilateral or bilateral) was considered sufficient for diagnosis in patients with a family history. Without a family history, the presence of ≥ 10 renal cysts in each kidney was considered sufficient for the diagnosis of ADPKD (Chapman et al., 2015; Pei et al., 2015).

2.4 Biochemical measurements and analyses

All urine or blood samples for hormone tests except TFT were sent from 19 military hospitals across the country to Green Cross Laboratories, Korea's leading clinical laboratory, for analyses. PAC, PRA, and 24-h UFC were assessed using radioimmunoassay. Plasma metanephrine and normetanephrine levels were analyzed using liquid chromatography coupled with tandem quadrupole mass spectrometry, whereas 24-h urine metanephrine, normetanephrine, catecholamines, and vanillylmandelic acid levels were measured using high-performance liquid chromatography.

2.5 Sample size calculation

The number of patients needed to obtain a confidence level of 95% and such that the real value is within $\pm 0.6\%$ of the surveyed

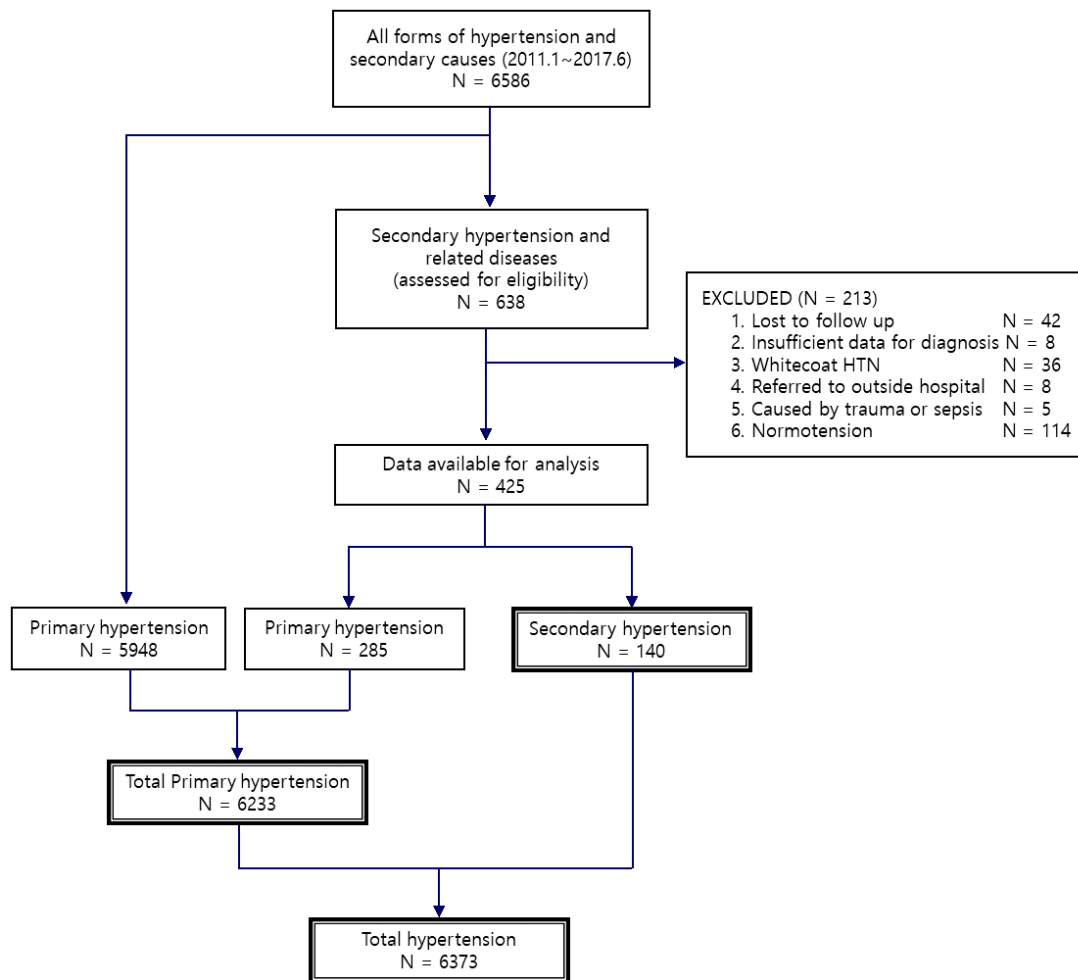


Fig. 1. Patient flowchart. searching, assessment, and exclusion. HTN, hypertension. Among the 6586 cases, there were 638 cases of 'possible' secondary HTN with a diagnostic code associated with secondary HTN. After excluding 213 cases according to the exclusion criteria, 140 cases were confirmed to have secondary HTN through a meticulous review of EMR. In contrast, the remaining 285 cases were of primary HTN, despite having diagnostic codes associated with secondary HTN.

value was 5069. This was calculated assuming a secondary HTN prevalence of 5%.

2.6 Statistical analysis

Data are presented as median (interquartile range) for continuous variables with a non-normal distribution and as frequency (percentage) for categorical variables. The Shapiro-Wilk normality test was used to assess normal distribution. The Wilcoxon rank sum test with continuity correction was used to compare continuous variables with a non-normal distribution. The chi-square test (χ^2) or Fisher's exact test was used to compare categorical variables.

We imputed missing data using multivariate imputation via the chained equations package in R program under missing-at-random assumptions. Binary logistic regression analysis was performed to identify independent variables associated with an increased risk for the diagnosis of secondary HTN. We included overweight/obese, family history of HTN, hypokalemia, hematuria, proteinuria, ALT, prediabetes/diabetes, TFT, and severe HTN in binary form in the first model. Multicollinearity of independent variables was checked using the variance inflation factor (VIF). A VIF value > 5 was considered indicative of multi-

collinearity. For the multivariable logistic regression model, stepwise backward elimination based on likelihood ratios was used, with $P < 0.10$ for entry and $P > 0.05$ for removal. Odds ratios (ORs) were computed together with their 95% confidence intervals (CIs). $P < 0.05$ was considered statistically significant. The goodness of fit of the model was tested using the Hosmer-Lemeshow test. Prediction accuracy was assessed using Nagelkerke's R -square and classification table. Statistical analyses were performed using SPSS version 20.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) and R version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria).

2.7 Ethics statement

Approval for the study was obtained from the institutional review board of the Armed Forces Medical Command (institutional review board approval number: AFMC-16057-IRB-16-045). The requirement for written informed consent was waived because the data were anonymous and retrospectively analyzed. The study was designed in accordance with the ethical guidelines of the Declaration of Helsinki.

Table 1. Prevalence of secondary causes (n = 140) among hypertensive men.

Cause of secondary HTN	N (% of total HTN)
Autosomal dominant polycystic kidney disease	47 (0.74)
Renal parenchymal disease	24 (0.38)
Chronic glomerulonephritis	19 (0.30)
Atrophic kidney	2 (0.03)
Solitary kidney	2 (0.03)
Tubulointerstitial nephritis	1 (0.02)
Hyperthyroidism	23 (0.36)
Subclinical hypercortisolism	12 (0.19)
Without adrenal adenoma	9 (0.14)
With adrenal adenoma	3 (0.05)
Pheochromocytoma/paraganglioma	10 (0.14)
Renal artery stenosis	9 (0.14)
Idiopathic	4 (0.06)
Fibromuscular dysplasia	3 (0.05)
Takayasu's arteritis	2 (0.03)
Cushing's syndrome	5 (0.08)
Hypothyroidism	3 (0.05)
Primary aldosteronism	3 (0.05)
Aldosterone-producing adenoma	2 (0.03)
Idiopathic hyperaldosteronism	1 (0.02)
Acromegaly	2 (0.03)
Hyperparathyroidism	2 (0.03)
Coarctation of the aorta	1 (0.02)
Total HTN	6373 (100)

HTN, hypertension.

3. Results

3.1 Prevalence of secondary HTN among hypertensive patients

We initially collected 6586 cases of primary and 'possible' secondary HTN from the DEMIS database using ICD-10 diagnostic codes assigned to primary HTN (I10), secondary HTN (I15), and various diagnoses related to secondary HTN (Table S2 in Supplementary Material). Among the 6586 cases, there were 638 cases of 'possible' secondary HTN with a diagnostic code associated with secondary HTN. Of the 638 cases, 425 cases of 'possible' secondary HTN were identified and analyzed after 213 cases were excluded according to the exclusion criteria. Finally, 140 cases (2.2% of all 6364 hypertensive cases) were confirmed to have secondary HTN through a meticulous review of EMR. In contrast, the remaining 285 cases were of primary HTN, despite having diagnostic codes associated with secondary HTN (Fig. 1).

Hormone tests for hyperaldosteronism, Cushing's syndrome, pheochromocytoma, and thyroid disease screening were performed in 4311/6373 (67.6%) hypertensive patients. Imaging studies such as abdominal CT or ultrasonography were conducted for 3817/6373 (59.9%) patients to eliminate the presence of intra-abdominal mass, ADPKD, renal atrophy, or renal artery stenosis (Table S3 in the Supplementary Materials).

The most common causes of HTN were ADPKD (n = 47/6373, 0.74%) and renal parenchymal diseases (n = 24/6373, 0.38%), followed by hyperthyroidism (n = 23/6373, 0.36%) and subclinical hypercortisolism (n = 12/6373, 0.19%). Other endocrinologic

causes, including pheochromocytoma/paraganglioma (n = 10/6373, 0.14%) and PA (n = 3/6373, 0.05%), were very rare (Table 1).

3.2 Comparison of baseline characteristics between primary and secondary HTN

The demographic, clinical, and laboratory characteristics of patients with primary HTN (n = 285) and secondary HTN (n = 140) are summarized in Table 2. The median (interquartile range) age of patients with primary and secondary HTN was 20.0 (20.0-21.0) years and 21.0 (20.0-22.0) years, respectively. Both groups had few comorbidities, such as chronic kidney disease, diabetes, and hypercholesterolemia.

Patients with secondary HTN were more likely to be hypokalemic (6.5%, n = 9/139, vs. 1.1%, n = 3/273, $P = 0.009$), and to have hematuria (\geq trace) (31.3%, n = 42/134, vs. 5.9%, n = 15/256, $P < 0.001$), proteinuria (\geq trace) (35.8%, n = 48/134, vs. 5.8%, n = 15/257, $P < 0.001$), lower levels of alanine aminotransferase (22.0 [16.0; 35.0], vs. 25.0 [17.0; 44.0], $P = 0.045$), abnormal TFT (36.8%, n = 39/136, vs. 6.2%, n = 16/259, $P < 0.001$), and severe HTN (\geq 180/110 mmHg) (18.6%, n = 26/140, vs. 6.8%, n = 19/282, $P < 0.001$), than those with primary HTN. In contrast, patients with secondary HTN were less likely to be overweight (81.4%, n = 182/224 vs. 64.6%, n = 82/127, $P = 0.001$). However, there were no significant differences in smoking history, family history of HTN (first-degree relatives), headache, total cholesterol level, diabetic state, and in-office heart rate between the two groups.

Among the nine patients with hypokalemia in the secondary HTN group, there were three patients with renal artery stenosis, two patients with ADPKD, and one patient with subclinical hypercortisolism in addition to three patients with PA.

3.3 Prediction of secondary HTN

In multiple logistic regression analyses, six major clinical parameters were identified as predictors of secondary HTN (Table 3): abnormal TFT (OR: 9.50, 95% CI 4.84-19.45, $P < 0.001$), proteinuria (\geq trace) (OR: 6.13, 95% CI 2.97-12.99, $P < 0.001$), hematuria (\geq trace) (OR: 4.37, 95% CI 2.15-9.01, $P < 0.001$), hypokalemia (OR: 3.79, 95% CI 0.85-17.98, $P = 0.082$), severe hypertension (OR: 3.07, 95% CI 1.42-6.65, $P = 0.004$), and non-overweight (BMI $<$ 23 kg/m²) (OR 3.03, 95% CI 1.69-5.26, $P < 0.001$). However, there were no significant differences in the family history of HTN, headache, total cholesterol, and diabetes between the groups.

The VIF values for predictive factors were $<$ 1.1, which indicated that there was no multicollinearity. The model fit the data well (Hosmer-Lemeshow $\chi^2 = 1.07$, $P = 0.998$), and the amount of explained variance was estimated at 42% (Nagelkerke's R -square = 0.42). Although the sensitivity (60.0%) and positive predictive value (PPV, 24.3%) were low, the specificity (90.5%) and negative predictive value (NPV, 82.2%) were good, with an overall accuracy of 80.5%.

4. Discussion

In this study, we found that secondary HTN was very rare (2.2%, n = 140/6373) among hypertensive military males aged $<$ 30 years. The most common causes of secondary HTN were ADPKD (0.74%, n = 47/6373) and renal parenchymal diseases (0.38%, n = 24/6373), with other endocrinologic causes such as

Table 2. Demographic, clinical, and laboratory characteristics of study subjects.

Clinical characteristics	Secondary HTN (n = 140)	Primary HTN (n = 285)	P-value
Age [range], years	21.0 [20.0; 22.0]	20.0 [20.0; 21.0]	0.018
Body mass index (BMI) [range], kg/m ²	24.5 [22.3; 27.2]	26.0 [23.7; 29.1]	0.001
Underweight (BMI < 18.5 kg/m ²)	2 (1.6%)	0 (0.0%)	
Normal (18.5 ≤ BMI < 23 kg/m ²)	43 (33.9%)	42 (18.8%)	
Overweight/Obese (BMI ≥ 23 kg/m ²)	82 (64.6%)	182 (81.2%)	
Smoking, number (%)			0.289
Never	65 (55.1%)	109 (52.9%)	
Past	15 (12.7%)	17 (8.3%)	
Current	38 (32.2%)	80 (38.8%)	
History of HTN in first-degree relatives, number (%)	66 (49.6%)	138 (57.3%)	0.19
Headache, number (%)	39 (29.8%)	73 (32.3%)	0.705
BUN [range], mg/dL	13.8 [11.4; 16.5]	13.2 [11.6; 14.7]	0.018
Creatinine [range], mg/dL	0.9 [0.8; 1.1]	1.0 [0.9; 1.1]	0.005
Serum potassium, no. (%)			0.009
Hypokalemia (K ⁺ ≤ 3.5 mEq/L)	9 (6.5%)	3 (1.1%)	
Normokalemia (3.5 < K ⁺ ≤ 5 mEq/L)	125 (89.9%)	260 (95.2%)	
Hyperkalemia (K ⁺ > 5 mEq/L)	5 (3.6%)	10 (3.7%)	
Hematuria, number (%)			< 0.001
Absent (-)	92 (68.7%)	241 (94.1%)	
Trace (+/-)	16 (11.9%)	7 (2.7%)	
Mild (1+)	4 (3.0%)	5 (2.0%)	
Moderate to severe (≥ 2+)	22 (16.4%)	3 (1.2%)	
Proteinuria, number (%)			< 0.001
Absent (-)	86 (64.2%)	242 (94.2%)	
Trace (+/-)	25 (18.7%)	13 (5.1%)	
Mild (1+)	7 (5.2%)	1 (0.4%)	
Moderate to severe (≥ 2+)	16 (11.9%)	1 (0.4%)	
Alanine aminotransferase (ALT) [range], IU/L	22.0 [16.0; 35.0]	25.0 [17.0; 44.0]	0.045
Total cholesterol [range], mg/dL	170.0 [145.0; 197.0]	176.0 [154.0; 198.0]	0.066
Diabetes, number (%)			0.096
Non-diabetic	117 (84.8%)	200 (91.7%)	
Prediabetic	17 (12.3%)	16 (7.3%)	
Diabetic	4 (2.9%)	2 (0.9%)	
Thyroid function test (TFT), number (%)			< 0.001
Normal	67 (63.2%)	243 (93.8%)	
Subclinical hypothyroidism (high TSH)	1 (0.9%)	6 (2.3%)	
Subclinical hyperthyroidism (low TSH)	5 (4.7%)	8 (3.1%)	
Hypothyroidism	4 (3.8%)	0 (0.0%)	
Hyperthyroidism	23 (21.7%)	0 (0.0%)	
Other abnormal TFT	6 (5.7%)	2 (0.8%)	
Office heart rate [range], rate/min	82.0 [74.0; 94.5]	82.0 [72.0; 95.0]	0.745
Classification of office BP* - no. (%)			< 0.001
High normal (≥ 130/85 mmHg)	6 (4.3%)	5 (1.8%)	
Grade 1 (≥ 140/90 mmHg)	67 (47.9%)	166 (58.9%)	
Grade 2 (≥ 160/100 mmHg)	41 (29.3%)	92 (32.6%)	
Grade 3 (≥ 180/110 mmHg)	26 (18.6%)	19 (6.7%)	
Isolated systolic HTN	51 (36.4%)	121 (43.1%)	0.231

Hypertension (HTN), blood urea nitrogen (BUN), thyroid-stimulating hormone (TSH), blood pressure (BP).

*Office BP and heart rate values are the average of measurements before taking antihypertensive drugs. Hypertension was defined and classified according to the 2018 European Society of Hypertension/European Society of Cardiology guidelines:

High normal: systolic 130-139 mmHg and/or diastolic 85-89 mmHg.

Grade 1: systolic 140-159 mmHg and/or diastolic 90-99 mmHg.

Grade 2: systolic ≥ 160-179 mmHg and/or diastolic 10-109 mmHg.

Grade 3: systolic ≥ 180 mmHg and/or diastolic ≥ 110 mmHg.

Isolated systolic HTN: ≥ 140 mmHg and diastolic < 90 mmHg.

Table 3. Major predictive factors of secondary HTN.

Logistic regression Variables	Univariate analysis				Multivariable analysis		
	Unadjusted OR	95% CI	P-value	VIF	Adjusted OR	95% CI	P-value
Abnormal TFT	8.50	4.69-16.13	< 0.001	1.04	9.50	4.84-19.45	< 0.001
Proteinuria (≥ trace)	9.93	5.51-18.80	< 0.001	1.09	6.13	2.97-12.99	< 0.001
Hematuria (≥ trace)	7.74	4.36-14.30	< 0.001	1.06	4.37	2.15-9.01	< 0.001
Hypokalemia (K ⁺ ≤ 3.5)	4.83	1.54-18.08	0.010	1.02	3.79	0.85-17.98	0.082
Severe HTN*	3.02	1.63-5.69	< 0.001	1.03	3.07	1.42-6.65	0.004
Non-overweight [†]	2.38	1.52-3.70	< 0.001	1.07	3.03	1.69-5.26	< 0.001

Thyroid function test (TFT), hypertension (HTN), odds ratio (OR), confidence interval (CI), variance inflation factor (VIF).

*Severe HTN was defined as systolic ≥ 180 mmHg and/or diastolic ≥ 110 mmHg.

†In the Asian criteria, overweight is defined as BMI ≥ 23 kg/m² (in the World Health Organization criteria, overweight is defined as BMI ≥ 25 kg/m²).

aldosteronism (0.05%, n = 3/6373) being very rare.

A previous study conducted from 1974 to 1991 in the United States reported that secondary causes were noted in 5.6% of patients aged 18-29 years who were referred for severe HTN (Cohen, 2017). Another study conducted from 1995 to 1999 in Japan demonstrated that the prevalence of secondary HTN was 9.1% among 1020 hypertensive patients in an outpatient clinical setting (Omura et al., 2004). However, the study did not describe in detail the age-related prevalence of secondary HTN. To the best of our knowledge, there has been no previous study on the prevalence of secondary HTN in young adults < 30 years of age.

The main reasons for the lower prevalence of secondary HTN in this study could be explained by the following two reasons. First, most of the 1200 medical corps in South Korea are in charge of primary care; however, they do not have antihypertensive drugs and cannot perform screening tests for secondary HTN. Therefore, in most cases where hypertensive patients are identified by a primary physician in the medical corps, patients are referred to a nearby military hospital for screening and treatment. This peculiarity of military medical systems makes the denominator large in calculating the prevalence of secondary HTN, hence the low prevalence. Second, as new recruits undergo multiple tests at the time of enlistment, a significant number of cases of secondary HTN would have been newly detected, and the affected individuals would be exempted from military service (Table S1 in the Supplementary Appendix). This could have reduced the number of patients with secondary HTN and increased the total number of hypertensive patients, resulting in a lower prevalence of secondary HTN.

Previous studies have reported that renal disease was the most common cause of secondary HTN (Anderson et al., 1994; The Japanese Society of Hypertension, 2014). However, most of them did not specify ADPKD as an important single disease entity. ADPKD is the most common hereditary kidney disease and accounts for about 10% of end-stage renal disease (ESRD) cases requiring renal replacement therapy (Spithoven et al., 2014). Early detection of ADPKD and rigorous BP control are associated with improvement in clinical markers and delay in the onset of ESRD (Schrier et al., 2014, 2003). Surprisingly, however, a previous study on HTN in young adults with ADPKD revealed that only 7% of the subjects had been screened for ADPKD (Kelleher et al., 2004). Normal findings in routine laboratory tests are not a basis for excluding ADPKD, and ultrasound has a low diagnostic sensi-

tivity for ADPKD screening in individuals aged < 30 years (Pei et al., 2009). In this study, ADPKD was found to be the most common cause of HTN, which could be attributed to the fact that CT was performed in up to 56.9% of all subjects.

Recent studies have shown that PA is more prevalent in patients with severe or resistant HTN than previously thought (Fagugli and Taglioni, 2011). According to a recent systematic review, however, there were wide variations in prevalence and large heterogeneity in primary care settings (3.2%-12.7%, I² = 57.6% [0%-78%]) and referral centers (1.0-29.8%, I² = 97.1% [96.7-97.5%]) (Käyser et al., 2016). In addition, a population-based study documented that positive screening results for PA were obtained in 0.2-7.0% of the general hypertensive population, which was less than that reported in a previous study on referred hypertensive patients (Hannemann et al., 2012). Although hypokalemia is a characteristic finding in PA, it can also manifest in renal artery stenosis, ADPKD, and subclinical hypercortisolism as a result of RAAS activation (Schrier et al., 2014; The Japanese Society of Hypertension, 2014). Such cases are differentiated from PA by high renin levels and low ARR. Monticone et al. reported that of 1672 general hypertensive patients (age, 46 ± 9.2 years) from Italy, 232 patients (13.8%) had an ARR > 30 together with a PAC > 10 ng/dL, and 99 patients (5.9%) were diagnosed with PA (Monticone et al., 2017). According to the result of the Bussolengo study, the prevalence of elevated ARR (≥ 32) increased with age from 15% (age 35-44 years) to 38% (age 55-74) (Olivieri et al., 2004). From this, it could be inferred that the prevalence of elevated ARR may be lower in younger age groups.

In the present study, of the 6373 hypertensive patients, only 5 patients (0.08%) had an ARR > 30, together with a PAC > 10 ng/dL, and 3 patients (0.05%) were diagnosed with PA. Of the 3 patients with PA, the ARR was 182.7; 170.0 in 2 patients with aldosterone-producing adenoma (APA) and 24.0 in 1 patient with idiopathic hyperaldosteronism (IHA). There are three possible explanations for why the prevalence of PA in this study is much lower than that reported in other studies. First, the subjects of this study were much younger (mean age, 21 years) than those of other studies. Second, although IHA is usually more than twice as common as APA, ARR is not very high in patients with IHA; thus, it could have been under detected. Most importantly, as noted above, it is possible that a significant number of patients with secondary HTN were excluded from the study population owing to health checkups at the time of enlistment (Table S1 in the Supplementary Material).

Subclinical hypercortisolism had not been determined as a cause of HTN in previous reports until its prevalence was reported to be 1.0% of all hypertensive patients in 2004 (Omura et al., 2004). Although the diagnostic criteria are complex and controversial, subclinical hypercortisolism should be considered as a cause of resistant HTN, as it is associated with increased comorbidities and mortality (Martins et al., 2012). In this study, subclinical hypercortisolism was the fourth most common cause of secondary HTN (0.19%).

Multiple logistic regression analysis revealed five major predictive factors for secondary HTN. Abnormal TFT results had the strongest association with secondary HTN (Table 3). TFT is important for the diagnosis of hyperthyroidism or hypothyroidism as a cause of HTN, and other abnormal TFT findings were also more prevalent in secondary HTN. Further studies will be required to ascertain the correlation between other abnormal TFT results and secondary causes of HTN.

Abnormal findings in urine dipstick tests for blood and protein can occur transiently and functionally for various reasons, especially in young patients. In this study, however, these were much more prevalent in patients with secondary HTN, mainly due to renal parenchymal diseases and ADPKD. Of note, even trace amounts of proteinuria or hematuria were suggestive of secondary HTN.

Being overweight/obese ($BMI \geq 23 \text{ kg/m}^2$) appeared to be a protective factor against secondary HTN (OR: 0.33, 95% CI 0.19-0.59, $P < 0.001$). The accumulation of excess adipose tissue introduces a cascade that elevates BP, causing obesity-induced hypertension (Cohen, 2017; Leggio et al., 2017). Thus, it is presumed that overweight/obese hypertensive patients are less likely to have secondary causes of HTN even in young individuals, as obesity itself may cause primary HTN.

Although the sensitivity and PPV of the model were unsatisfactory, the specificity (90.5%) and NPV (82.2%) were satisfactory with an accuracy of 80.5%. In other words, if hypertensive patients do not have any predictive factors, it is likely that they will not need to undergo further tests for secondary HTN.

4.1 Study limitations and strengths

This study has some limitations. First, as this was a retrospective study, there was a lack of unique, predefined criteria for screening secondary HTN. Second, 24-h ABPM was performed in only 31.6% of all hypertensive patients. Thus, it is possible that the total number of hypertensive patients was exaggerated by white coat HTN. Third, the EMR of only 638 patients with 'possible' secondary HTN were reviewed among the 6373 hypertensive patients. Fourth, obstructive sleep apnea, one of the most common causes of secondary HTN (Pedrosa et al., 2011), was not evaluated in most patients. As obesity is a typical finding in patients with obstructive sleep apnea, if it was screened as a cause of HTN in this study, excessive weight might have been a positive predictor rather than a negative predictor of secondary HTN. Lastly, the existence of selection bias should be considered when interpreting the results of this study, as the study population consisted of relatively healthy young male military personnel.

Despite these limitations, our study has several strengths. First, this is the largest prevalence study on secondary HTN among young hypertensive men. The study population comprised a certain, well-defined, homogeneous demographic group. In South

Korea, nearly all men are obligated to serve in the army in their 20s, and most of them are examined in military hospitals when suspected of having HTN. Second, as medical services at military hospitals are free of charge, individuals can undergo screening tests for secondary HTN without concerns about the cost. This was key to enabling screening for secondary HTN in up to two-thirds of general hypertensive patients. Third, all urine or blood specimens for hormone tests were analyzed at a single institution, thus increasing confidence in the test results. Therefore, our findings could be applied to an unselected hypertensive population in their early 20s without severe comorbidities, especially in military personnel.

Secondary HTN is rare in relatively healthy hypertensive patients aged < 30 years. Therefore, in this population, screening for secondary HTN should be considered in the presence of any predictive factors, such as abnormal TFT findings, proteinuria, hematuria, severe HTN, or non-overweight, to ensure cost-effectiveness.

Authors' contributions

Conceptualization: Kihyun Kim, Se-Joong Rim Data collection and analysis: Kihyun Kim Methodology: Eui-Young Choi, Hyuck Moon Kwon Draft: Kihyun Kim Revision: Jong-Youn Kim, Eui-Young Choi, Hyuck Moon Kwon, Se-Joong Rim.

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Conflict of Interest

The authors declare no conflicts of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at <https://rcm.imrpress.com/EN/10.31083/j.rcm.2020.04.121>.

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