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Factors predicting secondary hypertension in young adults with hypertension: a retrospective study

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Abstract

Background Hypertension in young adults is often due to secondary causes, and investigating these can be resource-intensive. This study aimed to identify clinical and biochemical markers that could suggest secondary hypertension in individuals under 40 years.

Materials and methods A 6-year retrospective observational cohort study included 207 young adults with hypertension who were assessed for secondary causes such as hyperthyroidism, primary aldosteronism, Cushing's syndrome, pheochromocytoma, and renovascular disease. Multivariable logistic regression was used to identify significant predictors, with a significance level set at $p < 0.05$.

Results Secondary hypertension was diagnosed in 7 patients (3.4%). The most common diagnoses were primary aldosteronism and hyperthyroidism. Three significant clinical and biochemical predictors were identified: female (OR 4.56, $p = 0.020$), systolic blood pressure > 160 mmHg at the time of diagnosis (OR 1.44, $p = 0.010$), and serum potassium < 3.5 mEq/L (OR 3.69, $p = 0.019$).

Conclusion Several easy-to-obtain clinical and biochemical markers can help identify secondary hypertension in young adults. Individuals who do not have any of these predictors may have a lower likelihood of secondary hypertension; however, these markers should always be used in conjunction with a thorough clinical assessment and are not intended to serve as definitive criteria for diagnosis.

Clinical trial number Not applicable.

Keywords Young-onset hypertension, Secondary hypertension, Hypertension, Predictive factors

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Introduction

Hypertension is a primary modifiable risk factor for cardiovascular diseases and premature mortality. It affects approximately 1 billion individuals aged 30 to 79 years globally, with prevalence rates increasing with advancing age [1]. Over the past several decades, hypertension in young adults has emerged as a significant public health concern globally [2]. The prevalence of hypertension in young adult were reported to be approximately 7–11% [3, 4]. The relationship between blood pressure and adverse cardiovascular outcomes in young adults is reported to be similar to that observed in middle-aged and older individuals [5, 6]. However, having hypertension at a young age raises the risk of cardiovascular events in middle age [7]. It leads to an earlier development of multiple cardiovascular conditions such as coronary heart disease, heart failure, stroke, and transient ischemic attacks [8].

The definition of hypertension in young adults differs across various guidelines, with age thresholds commonly set at below 30, 40, or 50 years [9–11]. If hypertension occurs in young adults, it is important to identify any secondary causes. Approximately 5–8% of young adult patients are found to have secondary causes of hypertension [12]. Commonly documented secondary causes of hypertension in young adults include hypothyroidism, renovascular disease (such as fibromuscular dysplasia or atherosclerosis), renal insufficiency, primary aldosteronism, Cushing syndrome, and pheochromocytoma [12].

Persistent high blood pressure in young adults can result in irreversible damage to cardiovascular organs. Therefore, identifying secondary causes of hypertension and to understand etiology of hypertension in young adults is essential, as it can guide targeted treatment strategies, enhance blood pressure control, and potentially cure hypertension in this population. Many young individuals with hypertension may not present with classic risk factors, making it challenging to diagnose secondary causes without thorough assessment. Integrating these aspects, healthcare providers can enhance early detection of hypertension in young adults, ultimately leading to improved long-term health outcomes and a reduction in the incidence of cardiovascular diseases later in life.

To date, most studies related to young-onset hypertension have been epidemiological in nature [13, 14]. One study focused exclusively on young adult males with hypertension to identify significant predictors of secondary causes of hypertension in this population [15]. Investigating secondary hypertension can require significant resources and may not be feasible in all institutions. This study aimed to identify clinical and biochemical factors that could indicate secondary causes of hypertension in young adults (aged < 40 years), with the goal of reducing the need for referrals to specialized testing and avoiding unnecessary investigations.

Materials and methods

A 6-year retrospective observational cohort study was conducted using data from electronic medical record of adult patients who visited outpatient department unit at a university hospital in Thailand during January 2017 to January 2023. The study protocol was approved by the Faculty of Medicine, Chiang Mai University, Ethical Committee (Ethical number: EXEMPTION 0237/2566, Date of approval: 14 June 2023). Informed consent was waived by ethical committee as this was a retrospective study. The study was carried out following the Declaration of Helsinki. The authors did not have access to any information that could identify individual participants during or after data collection, as all data were anonymized. The inclusion criteria comprised adult patients aged 20–40 years with an office blood pressure exceeding 140/90 mmHg, those diagnosed with hypertension, or individuals currently on antihypertensive medications who had been evaluated for secondary causes of hypertension. Exclusion criteria included patients diagnosed with malignancies, pregnant women, or those with incomplete laboratory results for secondary hypertension.

Information gathered from medical records comprised of demographic details such as age and sex, medical history including comorbid conditions like diabetes mellitus, dyslipidemia, cerebrovascular disease, chronic kidney disease (CKD), and obesity. Histories of alcohol consumption, tobacco use, and family history of hypertension were also documented. Additionally, anthropometric data such as weight, height, and body mass index (BMI) were recorded, along with measurements of systolic and diastolic blood pressure at the time of hypertension diagnosis. Baseline biochemical parameters were also documented. The final diagnosis of hypertension was classified as either secondary hypertension (including hyperthyroidism, primary aldosteronism, Cushing's syndrome, pheochromocytoma, or renovascular hypertension) or essential hypertension.

Screening for secondary causes of hypertension

At our institution, young adults aged < 40 years diagnosed with hypertension are routinely screened for secondary causes. The investigations typically include assessments for hyperthyroidism, primary aldosteronism, Cushing's syndrome, pheochromocytoma and/or paraganglioma and renovascular disease.

Screening for hyperthyroidism was conducted using thyroid function tests, including serum TSH, free triiodothyronine (T3), and free thyroxine (T4). Primary aldosteronism was evaluated through measurements of serum potassium, serum bicarbonate, plasma aldosterone

concentration (PAC), and plasma renin activity (PRA) levels. Cushing's syndrome was assessed using the 1-mg overnight dexamethasone suppression test. Pheochromocytoma and/or paraganglioma were investigated with 24-hour urine metanephrine and normetanephrine tests. Renovascular hypertension was screened using renal Doppler ultrasound.

Definitions of secondary causes of hypertension

Hyperthyroidism was defined as having higher FT3 and/or FT4 levels than the normal ranges, with TSH levels lower than the normal range. The diagnosis of primary aldosteronism followed the Endocrine Society Guideline 2016 [16]. Positive screening results for primary aldosteronism included: (1) an aldosterone/renin ratio (ARR) > 20 (ng/dL)/(ng/mL/hr), (2) PAC levels > 15 ng/dL, and (3) PRA < 1.0 ng/mL/hr. Those meeting all screening criteria proceeded to confirmation tests for primary aldosteronism unless they had either: (1) spontaneous hypokalemia, undetectable PRA, and PAC > 20 ng/dL, or (2) ARR > 100 (ng/dL)/(ng/mL/hr). A normal saline suppression test was used for confirmation, and those with PAC levels greater than 6 ng/mL were diagnosed with primary aldosteronism. For Cushing's syndrome, individuals with 8 AM cortisol levels greater than 1.8 µg/dL after a 1-mg overnight dexamethasone suppression test were diagnosed with the condition. Elevated 24-hour urine metanephrine and/or normetanephrine levels more than three times the upper normal range, combined with positive anatomical imaging, indicated a diagnosis of pheochromocytoma or paraganglioma. Renovascular hypertension was diagnosed in those with positive findings of renal artery stenosis via renal Doppler ultrasound. CKD was not included as a secondary cause of hypertension in the present study. Patients who tested negative for all the previously mentioned conditions were diagnosed with essential hypertension.

Statistical analysis

The data were analyzed using STATA version 17.0. Statistical significance was determined using a two-tailed p-value threshold of < 0.05. Counts and percentages were reported for categorical variables, while means and standard deviations (SD) were used for normally distributed continuous variables. For non-normally distributed continuous variables, medians with interquartile ranges (IQR) were presented. Univariable analysis for continuous data involved the independent t-test for normally distributed variables and the Wilcoxon rank-sum test for non-normally distributed variables. Additionally, multivariable logistic regression analyses were conducted to identify predictive factors in young hypertensive adults with secondary causes of hypertension, with results reported as odds ratios (OR) and 95% confidence intervals (CI). The adjusted model accounted for covariates that either exhibited statistically significant differences between young adults with essential hypertension and those with secondary causes of hypertension in univariable analysis or were considered clinically significant and likely to impact the outcomes. Additionally, the adjusted model was analyzed in clusters based on obesity status, categorized by a BMI of < 25 kg/m^2 or ≥ 25 kg/m^2, as obstructive sleep apnea (OSA), which is associated with obesity, was not included as a cause of secondary hypertension in this study. To determine the sample size for the multivariable analysis, an empirical rule was applied, estimating 10 observations per independent variable included in the model. Given the plan to incorporate at least 14 predictors, and assuming that 25% of patients would have secondary causes of hypertension identified during the follow-up period and about 5% would have incomplete data, a minimum of 200 patients was required to accurately identify the significant predictors.

Results

A study involving 207 young adults with hypertension found that 3.4% (7/207) had secondary causes of hypertension. Among these, 85.7% had primary aldosteronism, and 14.3% had hyperthyroidism. Of the total participants, 57.5% (119/207) were male. The overall median age was 31 years, with an IQR of 27–35 years. There were no significant differences in baseline BMI, blood pressure, pulse rate, smoking and alcohol consumption status, or family history of hypertension. Significantly higher levels of estimated glomerular filtration rate (eGFR) was observed in individuals with secondary causes of hypertension compared to those with essential hypertension. Baseline characteristics are shown in Table 1.

Predictive factors associated with secondary causes of hypertension in young adults

Serum creatinine was excluded from the final multivariable model due to redundancy with eGFR. To facilitate interpretation, continuous predictive variables were transformed into categorical variables. Three clinical and biochemical predictors were significantly associated with secondary causes of hypertension in young adults with hypertension. These predictors included being female (OR 4.56, 95% CI 2.79–7.28, $p = 0.020$), systolic blood pressure > 160 mmHg at the time of diagnosis (OR 1.44, 95% CI 1.38–1.53, $p = 0.010$), and serum potassium < 3.5 mEq/L (OR 3.69, 95% CI 1.24–8.95, $p = 0.019$). Other factors, including age, sex, BMI, family history of hypertension, diastolic blood pressure, pulse rate, smoking status, hematocrit level, serum glucose, serum bicarbonate, eGFR, and LDL levels, were not significantly associated

Table 1 Baseline characteristics ($n=207$)

Baseline characteristics	Secondary hypertension ($n=7$)	Essential hypertension ($n=207$)	*p*-value
Demographic data			
Age, IQR (years)	31 (28–36)	31 (27–35)	0.852
Male, *n* (%)	2 (28.5)	117 (58.5)	0.115
Body mass index, IQR (kg/m^2)	25.9 (21.6–33.6)	27.1 (22.1–32.4)	0.752
Systolic blood pressure at the time of diagnsosis, IQR (mmHg)	158 (153–180)	158 (148–169)	0.444
Diastolic blood pressure at the time of diagnosis, IQR (mmHg)	106 (95–112)	100 (92.5-109.5)	0.660
Pulse rate, IQR (beat per minute)	102 (73–114)	90 (83–101)	0.184
Smoker, *n* (%)	0 (0)	20 (10.4)	0.810
Alcohol drinking, *n* (%)	0 (0)	59 (30.7)	0.080
Underlying disease, *n* (%)			
• Diabetes mellitus	0 (0)	13 (6.5)	0.486
• Dyslipidemia	1 (14.2)	14 (7.0)	0.465
• Cerebrovascular disease	0 (0)	10 (6.5)	0.544
• Chronic kidney disease	0 (0)	6 (3.0)	0.642
• Obesity	0 (0)	4 (2.0)	0.706
• Obstructive sleep apnea	3 (42.9)	46 (23.0)	0.224
Family history of hypertension, *n* (%)	1 (14.3)	66 (33)	0.298
Final diagnosis, *n* (%)			
• Hyperthyroidism	1 (14.3)	-	
• Primary aldosteronism	6 (85.7)	-	
Biochemical data			
Hematocrit, IQR (%)	41.9 (41.8–43.3)	41.5 (33.9–45.2)	0.416
Creatinine, IQR (g/dL)	0.74 (0.53–0.89)	1.0 (0.74–6.05)	0.147
eGFR, IQR (mL/min/1.73m^2)	109.5 (105-135.2)	95.1 (10.5-115.1)	0.026
Plasma glucose, IQR (g/dL)	92 (90–96)	95 (88–109)	0.524
Serum sodium, IQR (mEq/L)	139 (137–141)	139 (137–141)	0.862
Serum potassium, IQR (mEQ/L)	3.9 (3.5-4)	3.9 (3.7–4.3)	0.135
Serum bicarbonate, IQR (mEq/L)	24 (23–29)	24 (22–26)	0.212
Total cholesterol, IQR (mg/dL)	240 (204–246)	197.5 (176–225)	0.216
LDL, IQR (mg/dL)	172 (129–179)	132 (109–154)	0.230
Triglyceride, IQR (mg/dL)	99 (85–153)	138 (103–199)	0.456

Table 2 Multivariable analysis of predictive factors of secondary hypertension in patients with hypertension in the young*

Predictors	Odds ratio	95% confidence interval	*p*-value
Female	4.56	2.79–7.28	0.020
Systolic blood pressure > 160 mmHg at the time of diagnosis	1.44	1.38–1.53	0.010
Serum potassium < 3.5 mEq/L	3.69	1.24–8.95	0.019

*Adjusted for age, sex, family history of hypertension, systolic and diastolic blood pressure at the time of diagnosis, pulse rate, smoking status, serum bicarbonate, eGFR, and LDL levels and clustered by obesity status

with secondary causes of hypertension. The data are shown in Table 2.

Discussion

The key finding in this study was the identification of three easily obtainable clinical and biochemical factors that could predict secondary causes of hypertension in young hypertensive adults. These factors can assist clinicians in determining which patients should undergo further investigation or be referred to other institutions for additional evaluation of secondary hypertension. In practical terms, clinical data such as sex and systolic blood pressure at the time of hypertension diagnosis, along with baseline biochemical tests like serum potassium, should be collected. While individuals lacking these predictors may be at a lower risk for secondary hypertension, these markers should be used alongside a comprehensive clinical evaluation and are not meant to serve as definitive diagnostic criteria.

The present study reported a prevalence of secondary causes of hypertension (3.4%), compared to other studies which reported a prevalence ranging from 2 to 8% [12, 15]. This study did not include CKD as a secondary cause of hypertension because routine serum creatinine screening is performed for all patients presented with hypertension at our institution. Instead, the study aimed to identify predictors of secondary hypertension that are challenging to investigate and for which tests, such as plasma aldosterone, renin levels, and metanephrines levels, are not readily available in some smaller institutions.

The predictors identified in this study are explained by the underlying physiology of secondary hypertension. The present study found that females were more likely to have secondary hypertension. Two causes of secondary hypertension were identified in this study: primary aldosteronism and hyperthyroidism. A previous study reported no significant difference in the prevalence of primary aldosteronism between males and females [17]. However, regarding primary hyperthyroidism, another study revealed that females were twice as likely as males to have primary hyperthyroidism [18]. Therefore, in young females presenting with hypertension, thyroid function tests should be performed to exclude this condition.

Regarding the link between blood pressure levels and secondary causes of hypertension, this study found that patients with a systolic blood pressure above 160 mmHg at the time of diagnosis were more likely to have secondary hypertension, consistent with findings from previous research [15]. Additionally, experts suggest that screening for secondary causes of hypertension is particularly indicated in patients with resistant or severe hypertension, with a focus on identifying primary aldosteronism, which was the most common secondary cause of

hypertension in the present study [19]. Also, there was a study reported that severe or resistant hypertension is more frequently observed in individuals with secondary hypertension, particularly due to primary aldosteronism [20]. Currently, the 2024 European Society of Cardiology guidelines for the management of hypertension recommend that all hypertensive patients be screened for primary aldosteronism [11]. Therefore, primary aldosteronism should be considered in patients with severe hypertension.

Another significant predictor of secondary hypertension identified in the present study was a serum potassium level below 3.5 mEq/L. This finding can be attributed to the high prevalence of primary aldosteronism in the cohort, as hypokalemia is a hallmark sign in 30% of patients with this condition [21]. However, the normal potassium levels do not eliminate the diagnosis of primary hyperaldosteronism.

The strengths of this study included that all significant predictors of secondary causes of hypertension identified in young adults were explainable by underlying physiology and supported by evidence. All potential confounding factors were adjusted for in the multivariable analysis, reducing the likelihood of bias. Additionally, all young adults with hypertension in this study were investigated using specialized tests for all possible secondary causes. Unlike previous studies that focused solely on young adult males with hypertension, this study examined significant predictors in both young adult males and females [15].

This study had several limitations. First, as a retrospective study, it may introduce selection and referral bias, as the enrollment rate remained low despite the flexible inclusion and exclusion criteria. Second, as a single-center study, the findings might not be fully generalizable to other institutions and the results may require either internal or external validation before being extrapolated to other populations. Third, the absence of ambulatory blood pressure monitoring in this study may have led to an overestimation of hypertension prevalence in young adults due to white-coat hypertension introducing inclusion bias. Fourth, not all secondary causes of hypertension were identified in this cohort, as no cases of pheochromocytoma or Cushing's syndrome were observed. Therefore, the predictors identified in this study may not fully represent all secondary causes of hypertension. Fifth, although the sample size was calculated based on empirical rule, it remained relatively small. Future studies including a broader range of diagnosis should be conducted. Due to several limitations, these factors do not serve as definitive criteria for diagnosing secondary hypertension.

Conclusion

Several easily obtainable clinical and biochemical predictors, such as sex, systolic blood pressure, and serum potassium levels, could aid in identifying secondary causes of hypertension in young adult patients. Utilizing these predictors may reduce the need for specific referrals and avoid unwarranted investigations. A prospective, multi-center study that includes a broader range of diagnoses is recommended for future research.

Author contributions

NP performed the data curation, data validation, analyzed and wrote the original draft of manuscript. WM designed the study, supervised the study, analyzed and interpreted the data and was the major contributor in writing and editing the manuscript. BH, MW and PC performed the data curation of the study. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Faculty of Medicine, Chiang Mai University, Ethical Committee (Ethical number: EXEMPTION 0237/2566, Date of approval: 14 June 2023).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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