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High prevalence of primary aldosteronism in a tertiary care hospital in Lebanon

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Abstract

Primary aldosteronism (PA) is a frequent cause of secondary hypertension. Studies on the prevalence of PA are lacking in the Middle East region. To determine the proportion of patients with high aldosterone-to-renin ratio (ARR) among Lebanese patients with hypertension screened for PA and to compare their clinical and biological characteristics with patients with essential hypertension. A retrospective review of medical charts of patients with hypertension undergoing sampling of serum aldosterone and plasma renin concentration at a tertiary care center between October 2022 and 2023 was conducted. Of 144 patients with hypertension screened for PA, 23 (16%) had an ARR higher than 3.7 ng/dL/mU/L and serum aldosterone above 15 ng/dL. The mean age of the screened population was 51 ± 15 years, 56% were men. The median duration of hypertension was 4 years and the median number was 2 of antihypertensive medications. Patients with a positive screening test were mostly men (88%, $P = .0001$), and more frequently had diabetes (50%, $P < .0001$) than those with essential hypertension. Only 22% had hypokalemia. Of the 23 patients, 11 underwent intravenous saline suppression testing; PA was confirmed in all of them. The high frequency of PA in our center is comparable to other countries. More studies are needed to determine how to reduce healthcare disparities and overcome the barriers to appropriate diagnosis and treatment.

Abbreviations: AAR = aldosterone-to-renin ratio, PA = primary aldosteronism, SST = saline suppression test.

Keywords: adrenal disorders, hypertension, Lebanese prevalence, primary aldosteronism

1. Introduction

Primary aldosteronism (PA) is characterized by a renin-independent excessive secretion of aldosterone.[1] It is the most frequent cause of secondary hypertension. Until the end of the 1990s, PA was suspected solely in the presence of spontaneous hypokalemia, with an estimated prevalence of only 1% to 2%.[2] Since the use of the aldosterone-to-renin ratio (ARR) as a screening test in patients with hypertension, the prevalence of PA was multiplied by 5 to 15 times.[3,4] Depending on the characteristics of the selected population, whether from primary care or hypertension clinics, the proportion of patients with PA varies between 1% and 29.8%.[5,6] It remains however an underdiagnosed disease, and the prevalence of its 2 major subtypes—adrenal adenoma and bilateral adrenal hyperplasia—are underestimated.[7,8] PA is strongly associated with the progression of cardiovascular and cerebrovascular diseases, as well as metabolic syndrome independently of blood pressure management and this is probably due to an independent deleterious effect of elevated aldosterone levels.[9] Therefore, missing the diagnosis, even in patients with controlled blood pressure could have major health consequences.[10,11] According to the Endocrine Society's guidelines, the diagnosis of PA requires 3 steps: screening test by ARR measurement, confirmatory test by mainly using a saline suppression test (SST), and subtype classification by performing an adrenal imaging or adrenal venous sampling. The last step is necessary to distinguish the 2 most common subtypes of PA: unilateral adenoma and bilateral adrenal hyperplasia, and therefore to determine the appropriate treatment modality: either unilateral adrenalectomy or medical treatment with mineralocorticoid receptor antagonists.[12] The importance of extending the indication to screen for PA in patients with hypertension remains a matter of debate especially in underdeveloped countries. Many authors concur that Conn syndrome is merely the tip of the iceberg, and what was once considered a rare disease now represents a broad spectrum of PA. This condition is increasingly recognized as a common contributor to significant cardiovascular morbidity, yet it remains underdiagnosed.[13] Some researchers suggest that even these high prevalence rates in resistant hypertension are underestimated, as they exclude milder forms of PA that may not meet the classical diagnostic thresholds of screening tests.[1]

IJ and RK contributed to this article equally.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Although hypertension affects 36.9% of the Lebanese population,[14] data on the prevalence of PA are lacking in our country. The present study aimed to determine the proportion of patients with elevated ARR at a tertiary care center in Beirut, analyze the characteristics of this population, and demonstrate that PA is prevalent in Lebanon, similar to other parts of the world. This study seeks to increase awareness of milder forms of PA and improve patient care.

2. Methods

2.1. Study design

This study was conducted in a tertiary care center at Hotel-Dieu de France Hospital. Patients with hypertension who were screened for PA between October 2022 and October 2023 were included in the study. Data were retrospectively collected from the clinic files of cardiologists and endocrinologists, and included the duration of hypertension, number of antihypertensive medications, and presence of cardiovascular disease or diabetes. The values of potassium, creatinine, serum aldosterone, and plasma renin concentration were noted. Only patients who were on spironolactone, eplerenone, and amiloride were excluded from the study. The screening test was considered positive if the ARR was higher than 3.7 ng/dL/mU/L, in addition to a plasma aldosterone ≥15 ng/dL (or ≥410 pmol/L). This is in concordance with the Endocrine Society guidelines.[1] Patients with an elevated ARR underwent confirmatory testing with an intravenous SST. They received 2 L of saline perfusion (0.9%) over 4 hours while being in a seated position. A plasma aldosterone above 10 ng/dL (288 pmol/L) at the end of the test confirmed PA. The project was approved by the ethics committee of Hotel-Dieu de France Hospital (reference CEHDF 1992). No informed consent was needed since the study is retrospective.

2.2. Biochemical measurements

The blood samples for aldosterone and renin were drawn in the morning between 7 and 9 AM at the laboratory of Hotel-Dieu de France University Hospital in Beirut. The patients had been up (sitting, standing, or walking) for about 1 to 2 hours and seated for 5 to 15 minutes before sampling, according to the recommendations of the Endocrine Society.[1] Aldosterone was measured by using the chemiluminescent immunoassay in solid phase ALDOCTK-2 (DiaSorin, Saluggia, Italy). The analytical sensitivity for aldosterone is 2.8 ng/dL. Renin was measured by using the kit RENCTK RIA (DiaSorin) in accordance with the manufacturer's instructions. The analytical sensitivity is 0.1 mU/L

2.3. Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk) and GraphPad Prism 8 (La Jolla). The Kolmogorov–Smirnov test was employed to determine the distribution of the data. Results for continuous variables with a normal distribution were expressed as mean ± standard deviation, while results for nonnormal distributions were presented as median (interquartile range [IQR]). For nonnormally distributed data, the Kruskal–Wallis test and Mann–Whitney *U* test were used to assess significance between groups. One-way analysis of variance followed by the Bonferroni post hoc test was used to compare quantitative variables between groups. The χ^2 test or Fisher exact test was used to compare qualitative variables between groups. Results were considered statistically significant if the *P* value was ≤.05, with a confidence interval of 95%.

3. Results

3.1. Characteristics of the population

During the study period, a screening test for PA was performed in 144 patients with hypertension. The mean age was 51 ± 15 years, and 44% were women. The mean body mass index was 30 ± 7 kg/m^2, 35% were smokers and 22% had diabetes. The median duration of hypertension was 4 years with a range of 1 to 32 years. The median number of antihypertensive drugs was 2 with a range of 1 to 5 drugs (Table 2).

Table 1

Proportions of patients with elevated plasma aldosterone to plasma renin ratio according to different cutoffs.

	Number of patients (%)
ARR, ng/dL/mIU/L	
≥2.4	44 (31)
≥3.7	30 (21)
≥4.9	21 (15)
ARR ≥ 3.7 and plasma aldosterone level	
≥9 ng/dL	29 (20)
≥15 ng/dL	23 (16)

ARR = aldosterone-to-renin ratio.

Table 2

Clinical and biochemical characteristics of the participants.

Characteristics	Total cohort	PA	No PA	*P*
Number of patients (%)	144 (100%)	23 (16%)	121 (84%)	
Age (yr), average (SD)	51 (15)	53 (13)	51 (15)	.680
Gender (women) %	44%	22%	48%	**<.001**
Weight (kg), average (SD)	88 (20)	84 (17)	90 (20)	.465
Height (cm), average (SD)	173 (9)	172 (7)	173 (9)	.962
BMI (kg/m^2), average (SD)	30 (7)	25 (5)	31 (7)	.198
Smoker (%)	35%	29%	37%	.23
Diabetic (%)	22%	50%	16%	**<.001**
Duration of hypertension (yr), average (min–max)	4 (1–32)	10 (1–32)	3 (1–24)	**.018**
Number of antihypertensive drugs, average (min–max)	2 (1–5)	3 (1–5)	2 (1–5)	**.011**
Potassium (mEq/L), average (SD)	4.3 (0.5)	3.78 (0.82)	4.4 (0.38)	**.005**
Creatinine (mg/dL), average (SD)	0.88 (0.47)	1.15 (0.49)	0.84 (0.31)	.125
Aldosterone (ng/dL), average (IQR)	14.1 (9.4–21.2)	38.3 (21.1–49.5)	12.8 (8.9–17.6)	**<.001**
Renin (mIU/L), average (IQR)	12.8 (5.1–35.5)	3.4 (0.9–6)	17.6 (7.5–42)	**<.001**
Aldosterone/renin ratio (ng/dL/mIU/L), average (min–max)	1 (0.32–2.84)	12.4 (4.8–44.1)	0.7 (0.26–1.48)	**<.001**

The differences between the 2 groups were tested by the Mann–Whitney test or *t* test for continuous data and the χ^2 squared test for categorical data with a $P < .05$. Bold values mean that the results are statistically significant because the $P < .05$.

BMI = body mass index, IQR = interquartile range, min–max = minimum–maximum, PA = primary aldosteronism, SD = standard deviation.

3.2. Proportion of patients with a positive screening test for PA

Using 3 different cutoffs, the proportion of patients with an elevated ARR ranged from 15% to 31 % (Table 1). With a threshold of 3.7 ng/dL/mU/L, 30 patients out of 144 (21%) had a positive ARR. Of those 30 patients, 29 (20%) had an aldosterone level above 9 ng/dL and 23 (16%) had an aldosterone level above 15 ng/dL(Table 1).

3.3. Confirmation of PA and subtype classification

A confirmatory test using the intravenous SST was performed in 11 of the 23 patients who had an ARR ≥3.7 ng/dL/mU/L and a serum aldosterone ≥15 ng/dL. All of them failed to suppress their aldosterone levels below 10 ng/dL. The remaining 12 patients were lost to follow-up. The least prevalence of PA in our study is 7.6%—a slight underestimation since it was not performed on the 23 patients who had a positive screening test. Subtyping and treatment of the patients who had a follow-up are summarized in Figure 1.

3.4. Comparison between individuals with elevated ARR and normal ARR

For the rest of the article, we categorized individuals with elevated ARR as the PA group, and those with a negative screening test as the non-PA group. Subjects in the PA group were mostly men (78%) compared with the individuals in the patients without PA group (52%) ($P < .001$) (Table 2). There was a significantly higher prevalence of patients with diabetes among patients with PA compared with those without PA (50 % vs 16%, $P < .001$). Moreover, the duration of hypertension was significantly greater in patients with PA than in those without PA, with a median duration of 10 years compared with 3 years ($P = .018$). The median number of antihypertensive drugs per patient was 3 in the PA group versus 2 in the group without PA ($P = .011$). Finally, the mean potassium level in patients with PA was 3.78 mEq/L, which was significantly lower than the mean potassium in patients without PA (4.4 mEq/L) ($P = .005$) (Table 2). Only 5 out of the 23 patients who screened positive for PA (22%) had hypokalemia (potassium below 3.5 mEq/L). There were no significant differences in age, body mass index, or creatinine levels between the 2 groups ($P = .680$, .198, and .125, respectively).

3.5. Patients' hormonal profile

Patients in the PA group had a median plasma aldosterone level of 38.3 ng/dL with a minimum value of 15.6 ng/dL, a maximum value of 265 ng/dL, and an IQR of 21.1 to 49.5 ng/dL. The median aldosterone level of patients in the patients without PA group was 12.8 with a minimum value of 1.3 ng/dL, a maximum value of 42.2 ng/dL, and an IQR of 8.9 to 17.6 ng/dL. Aldosterone levels in the PA group were significantly higher than those in the patients without PA group with a $P < .001$ (Fig. 2). Similar results were found when comparing plasma renin concentrations. Patients in the PA group had a median renin of 3.4 mIU/L with a minimum value of 0.5 mIU/L, a maximum value of 10.2 mIU/L, and an IQR of 0.9 to 6 mIU/L. The median renin level of the patients without PA group was significantly higher: 17.6 with a minimum value of 2.2 mIU/L, a maximum value of 487 mIU/L, and an IQR of 7.5 to 42. Finally, the median ARR in the PA group was significantly higher than the median in the patients without PA group (12.4 vs 0.7; Fig. 2).

4. Discussion

Identifying PA in patients with hypertension is important to prevent CV and renal complications[15] although the cost-effectiveness of this approach has been debated. The high

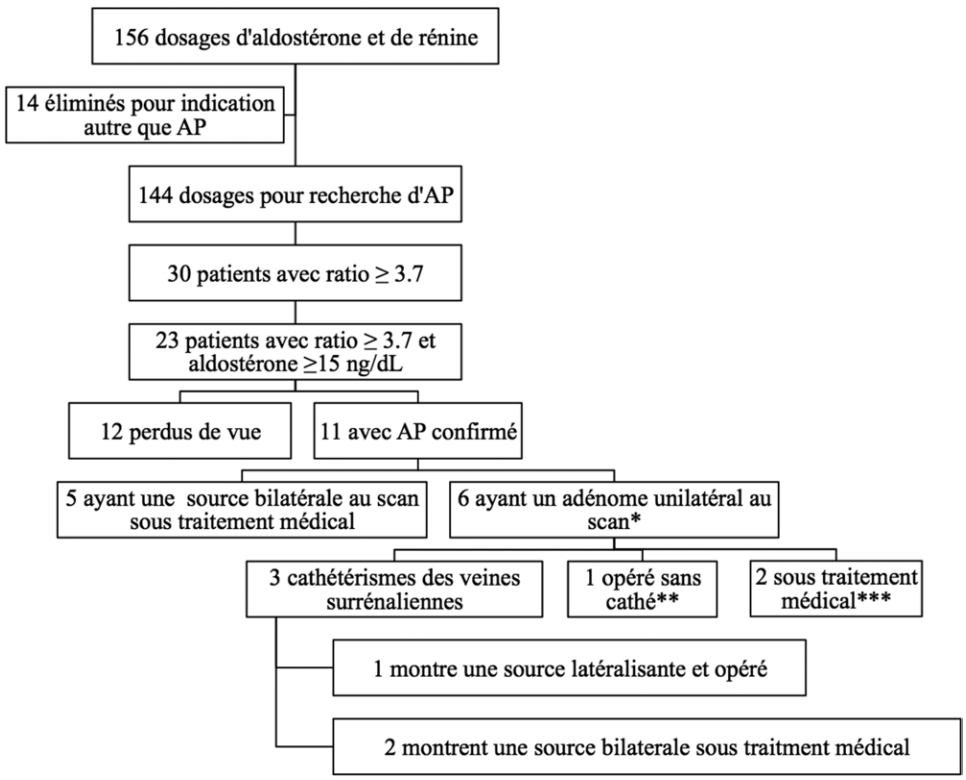

Figure 1. Study flowchart. ARR = aldosterone-to-renin ratio, AVS = adrenal vein sampling, CT = computed tomography, PA = primary aldosteronism, UA = unilateral adenoma.

prevalence of this disease as well as the potential for hypertension remission, particularly in patients with unilateral adenoma, justify the need to identify this condition. A study by Ruiz-Sanchez et al[16] has shown that the greater the number of indications for PA investigation, the higher its prevalence. Indeed, the prevalence of PA in this study was as high as 46 because the 2016 Endocrine Society guidelines recommendations were rigorously implemented. In our study, 16% of Lebanese patients with hypertension had an ARR >3.7 ng/dL/mU/L combined with an aldosterone level of over 15 ng/dL. After the intravenous SST confirmatory test, this prevalence dropped to 7.6%. However, this percentage is probably underestimated since half of the patients with a positive ARR test did not undergo a confirmatory test. This is consistent with several other studies where a confirmatory test was not performed for all patients.[17–21] These findings highlight the importance of confirmatory testing for the appropriate diagnosis of PA. While PA prevalence varies geographically, our results align with those reported in the literature (Table 3). Screening frequently yields a prevalence of 10% to 25%, which typically falls to 5% to 15% after confirmation.[8,17–27] This is not systematically true, however, and depends on the stringency of screening criteria. In an Indian study, the prevalence only fell from 18.8% to 17.8%.[28] The variation in prevalence between countries can be attributed to several factors, including the lack of standardization in the ARR thresholds and the different confirmatory tests, as well as the way of recruitment of patients with hypertension (e.g., specialized hypertension clinics vs primary care).

In our study, only 22% of patients with PA were women, while the male-to-female ratio in patients without PA was close to 1. Data found in the literature are discordant. In one study, a male predominance among 175 patients with confirmed PA was found, with 64% of men and 36% of women.[29] In another study, no significant difference in gender distribution between PA and patients without PA was noted.[30] In a third study, PA was more common in women than in men.[31] In addition, adenomas have been reported to be more common in women. This may be attributed to a higher frequency of "driver" mutations in the *KCNJ5* gene that favor the development of these autonomous adenomas.[32]

Half of our diagnosed patients with PA had elevated blood pressure for more than 10 years. This contrasts with the median duration of 3 years for our non-PA patients with hypertension. Since the average age between the 2 groups is similar, this suggests that patients with PA develop high blood

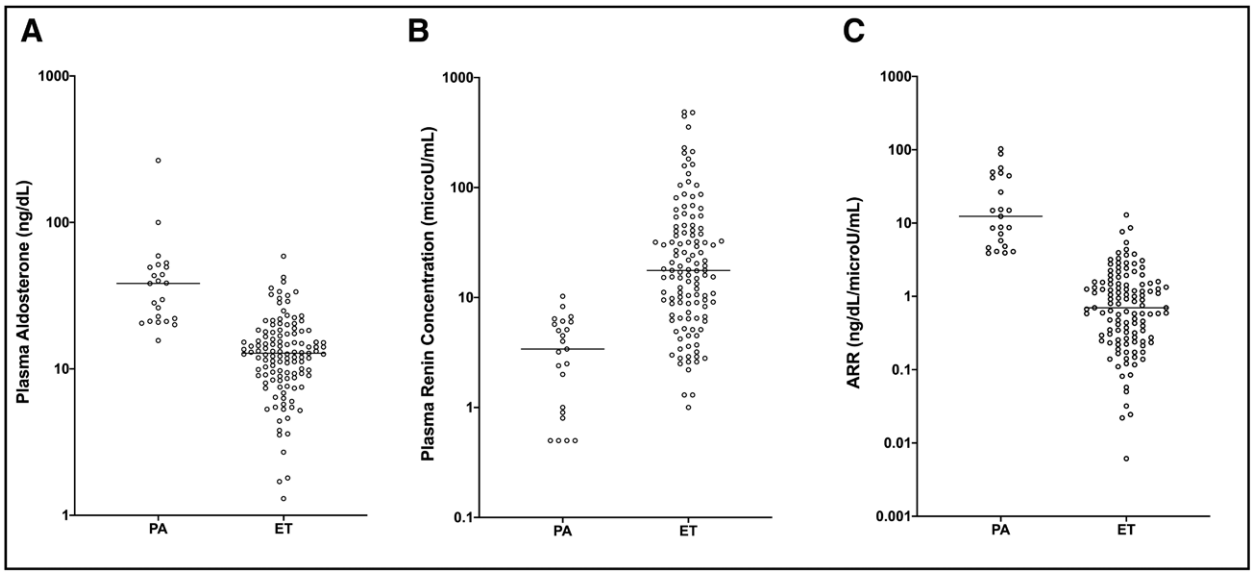

Figure 2. Hormonal profile of the patients with hypertension. (A–C) Plasma aldosterone concentration, plasma renin concentration, and ARR in patients with PA versus patients with essential hypertension. ARR = aldosterone-to-renin ratio, ET = essential hypertension, PA = primary aldosteronism.

Table 3

Various studies reporting the prevalence of primary aldosteronism in different countries around the world.

Study	Type of study	Country	Centre	Number of patients	Prevalence, %	After confirmation
Xu et al[17]	Prospective	China	Centre for cardiovascular diseases	7594	8.12	3.3%* (251/367 not 617)
Ribeiro et al[18]	Prospective	Brazil	Cardiology outpatient clinics	105	8.5	0.96%* (1/8 not 9)
Mosso et al[22]	Cross-sectional	Chile	Primary care	609	10.3	6.1%
Omura et al[23]	Prospective	Japan	Cardiology outpatient clinics	1020	11.7	8.1%
Gordon et al[3]	Cross-sectional	Australia	Newspaper announcement	52	12	12%
Rossi et al[15]	Prospective	Italy	General practice	1046	12.8	6.3%
Monticone et al[24]	Prospective	Italy	Primary care	1672	13.9	5.9%
Loh et al[19]	Prospective	Singapore	Primary care	350	18	4.5%* (16/56 not 63)
Asbach et al[20]	Prospective	Germany	Primary care	200	21	5.5%* (11/33 not 42)
Strauch et al[25]	Prospective	Czech Republic	Hypertension unit	402	21.6	19%
Käyser et al[5]	Cross-sectional	The Netherlands	Primary care	343	21.6	2.6%
Chen et al[21]	Prospective	China	Cardiology outpatient clinics	1329	26.2	12.2%* (163/175 not 348)

Preconfirmation prevalence represents the number of patients with a positive screening test divided by the total number of patients. Postconfirmation prevalence represents the number of patients who had a diagnostic confirmation divided by the total number of patients.

*These percentages are actually an underestimation since the confirmation test was not performed on all patients with a positive screening test.

pressure at a younger age compared to those with essential hypertension. On the other hand, in clinical practice, PA is generally suspected after several years of hypertension. This diagnostic delay has already been reported in the literature. In fact, the Indian prospective study previously discussed found a median duration of hypertension before PA diagnosis of 10.5 years (3.5–18 years).[28] Another recent study revealed a delay of at least 5 years between the onset of hypertension and the diagnosis of PA in one-third of the cohort. This is particularly concerning since many patients had already suffered from preventable organ damage at the time of diagnosis.[33] In our study, patients with PA were on an average taking 3 antihypertensive medications, compared with 2 for patients without PA. This finding highlights that most of the patients with PA diagnosed in our cohort have stage 3 hypertension or resistant hypertension. Average potassium levels in our study were significantly lower in patients with PA than in patients without PA: 3.78 versus 4.4 mEq/L.[34] Only 5 out of our 23 (22%) patients with PA had a potassium level below the lower limit. This is concordant with a large retrospective multicentric study, where hypokalemia was only found in 9% to 37% of patients with PA.[35] This confirms the fact that hypokalemia is not an essential criterion to suspect PA. More specifically, there is growing evidence demonstrating the association between hypokalemia and a more severe course of the disease in terms of cardiovascular and metabolic morbidity and mortality.[36] Indeed, in 1 study, the prevalence of cardiovascular events—including arrhythmias, heart failure, and stroke—was significantly higher in patients with hypokalemia than in those with normal potassium levels: 10.7% versus 6.3% with a $P < .001$. The prevalences of renal failure, diabetes, metabolic syndrome, left ventricular hypertrophy, and microalbuminuria were also higher.[37] Therefore, waiting for the development of hypokalemia to search for PA negatively impacts the long-term prognosis of patients.

Moreover, half of the patients with PA in our study had diabetes, similar to the findings of Conn et al[38] who reported diabetes in nearly half of the patients with PA of his cohort. PA is indeed associated with glucose intolerance and an increased risk of type 2 diabetes. Aldosterone has been recently shown to directly impair insulin secretion in isolated murine pancreatic islets, while genetic aldosterone deficiency significantly increases insulin secretion in mice. Similarly, short-term stimulation of the renin–angiotensin–aldosterone system during sodium restriction has been found to affect insulin secretion in humans.[39] Another factor that may contribute to glucose intolerance in patients with PA is the presence of mild autonomous cortisol secretion. It is therefore recommended to screen for it in patients with PA by performing an overnight 1 mg dexamethasone suppression test.[40] In addition, studies have shown a high prevalence of PA in patients with both hypertension and type 2 diabetes,[41] sometimes reaching ≈30%.[42,43] Thus, it would be beneficial to screen for diabetes in patients with PA and to suspect PA in patients with hypertension with diabetes.

The main limitations of our study reside in its retrospective nature, the small sample size, and the referral bias. Indeed, our hospital is a tertiary care center recruiting patients that might present with a more resistant hypertension therefore overestimating the prevalence of PA. Furthermore, we used the ARR to screen patients, a test that has been found to have low sensitivity for PA, and therefore does not effectively rule out PA. Indeed, authors now emphasize individual components (plasma aldosterone concentration and renin) rather than reliance on ARR for the diagnosis of PA.[24] However, the study has several strengths. Notably, it is the first to investigate the prevalence of PA in Lebanon. In addition, all patients were evaluated in the same laboratory, ensuring consistent testing procedures and cutoffs as recommended by the Endocrine Society. Our findings align closely with the existing literature, validating our results and demonstrating that PA is a prevalent disease.

5. Conclusion

Our study shows a high frequency of PA in a Lebanese tertiary care center that is comparable to Western countries.

Given the high prevalence of hypertension in Lebanon,[14] screening for PA is justified not only in patients with resistant hypertension but also in newly diagnosed patients and individuals with mild hypertension. Raising awareness about PA among healthcare professionals, especially in third world countries is essential to optimize treatment outcomes and to reduce the long-term consequences of this disease.

Author contributions

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