

Anxiety disorders and depression are associated with resistant hypertension

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Abstract

Background. Anxiety and depression can adversely affect the prognosis following cardiovascular diseases (CVDs) and may be associated with resistance to hypertension (HT) treatment. A better understanding of the complex biological substratum of resistant HT complicated by depression and anxiety is crucial for designing future primary care strategies.

Objectives. To evaluate the relationship between anxiety and depression and resistant HT, which will help to look at resistant HT from a broader perspective and aid the development of new strategies for diagnosis and treatment.

Materials and methods. We used a stratified random sampling method to select HT patients aged 18 and older in primary care setting. A total of 300 consecutive patients with persistent HT who were diagnosed with essential HT and uncontrolled blood pressure (BP) despite antihypertensive therapy were prospectively included in the study. Anxiety and depression were investigated, and scoring was evaluated using the Hospital Anxiety and Depression Scale (HADS).

Results. The study included 108 controlled and 91 uncontrolled HT patients. The HADS scales were higher in the controlled HT group compared to the uncontrolled HT group (6 (0–18) compared to 9 (0–20), $p = 0.001$; 5 (0–17) compared to 7 (0–16), $p < 0.001$, respectively). Body mass index (BMI) and C-reactive protein (CRP) were also significantly higher in the uncontrolled HT patients compared to the normotensive group. Anxiety was associated with a 2.18 times increased risk of HT and a 1.99 times increased risk of depression. Thus, anxiety and depression predicted resistant HT in both univariate and multivariate analyses.

Conclusions. During the treatment of HT, efforts should be made to improve the psychological and social functions of the patients beyond the primary therapy for control of the disease. As such, we hope to draw attention to the importance of psychological factors, especially anxiety and depression, in any field of medicine related to managing resistant HT.

Key words: depression, resistant hypertension, anxiety, hypertension, high blood pressure

Background

Hypertension (HT) is one of the most preventable risk factors for premature death and disability. Also, it has a high prevalence and serious adverse cardiovascular and renal effects, and is a current global health problem.¹ Despite numerous pharmacological treatment options, HT therapy does not always result in optimal blood pressure (BP) control. This observation led to the definition of resistant or refractory HT decades ago, a form of high BP that persists despite drug usage.² Although HT is one of the treatable diseases in primary care, chronic disease remains uncontrolled in many patients.³ There are differences in the definition of HT; thus, studies on the prevalence of resistant HT are limited, though it is estimated to be approx. 5–30%. However, the prevalence of resistant HT is almost less than 10% among treated patients when using a precise definition and excluding pseudo-resistant causes.⁴ A study in Turkey determined that the number of people with uncontrolled HT has decreased, though around 11 million people suffer from uncontrolled HT worldwide.⁵ Patients with resistant HT are at risk of chronic renal disease and early cardiovascular disease (CVD).⁶ Considering the end-organ damage in uncontrolled HT patients, the importance of visits and compliance with treatment draws attention. Therefore, patient management is crucial at all stages, from patient and clinician awareness, through treatment modalities and diagnosis, to invasive treatment strategies.^{7,8}

The pathophysiology of neurocognitive disorders is complex.^{9–11} Emotions play an important role as they motivate action in response to environmental changes and trigger adaptive behaviors to achieve variable goals. Moreover, the evidence shows that emotions affect metabolic processes and numerous cognitive abilities. It is vital to understand the central role of the prefrontal cortex to better comprehend how its impaired function can contribute to dysregulated behavioral responses and the development of mental dysfunctions, commonly associated with anxiety and depression.^{12,13} Chronic diseases can cause anxiety and depression, and also be caused by them, leading to a more severe disease course.^{14,15} Depression is quite common in patients with CVD, and leads to adverse cardiovascular outcomes and increased healthcare costs.^{16–18} Furthermore, the presence of anxiety disorders in HT individuals significantly affects the patient's response to treatment and increases the number of drugs used.¹⁹ In addition, the incidence of depression is higher in patients with coronary artery disease (CAD) and heart failure (HF) than in the general population.²⁰

There is a causative relationship between human mood and physical diseases such as HT. Patients with CVD commonly have anxiety and depression, both of which cause negative adverse cardiovascular outcomes and increased healthcare costs.⁸ A previous study in a heterogeneous

population of all ages showed that anxiety, depression and HT are clearly related.^{21,22} In the pathophysiological background of HT, at the molecular level, dynamic changes in the mitochondrial cycle may be linked to HT development, left ventricular hypertrophy, insulin resistance, obesity, and type 2 diabetes mellitus (T2DM).²³ Mitochondrial dynamics and factors involved in its regulation are critical for neuronal development, survival and optimal cell function. Moreover, mitochondrial dysfunction may be related to psychiatric symptoms such as depression, cognitive impairment, psychosis, and anxiety.²⁴ Endothelial dysfunction and inflammation also co-occur in HT. Accordingly, inflammatory cytokines are increased in depression, which may explain the serotonergic, noradrenergic and dopaminergic dysfunction of depression.^{25–28}

Hypertension, accompanied by anxiety and depression, was associated with adverse conditions such as lower treatment adherence, lower levels of daily functioning, poor health-related quality of life, and lower employment rate.²⁹ The relationship between depression and uncontrolled HT is still controversial. Data on this relationship are insufficient, especially those obtained from primary healthcare institutions.³⁰

The Hospital Anxiety and Depression Scale (HADS) is a readily obtainable anxiety-depression assessment instrument consisting of 14 items, with 7 items related to anxiety (HADS-A) and 7 items to depression (HADS-D). Although the score has been used to test compliance with treatment in CVDs, studies on patients with resistant HT did not demonstrate the impact of emotional status on the HT course.^{14,16} Therefore, this study aimed to assess the relationship between depression, HT and uncontrolled HT by evaluating the HADS in patients with resistant HT.

Objectives

This study was designed to investigate whether there is a relationship between resistant HT and anxiety and depression. As such, the study aimed to investigate the lack of BP control despite receiving optimal treatment, and reveal a relationship that may contribute to patient treatment and quality of life using an easily applicable test.

Materials and methods

Study population

This cross-sectional study included patients aged ≥ 18 who attended the family medicine and cardiology outpatient clinic at the Recep Tayyip Erdoğan University hospital (Rize, Turkey) between November 2021 and August 2022, and who completed the survey, which had a response

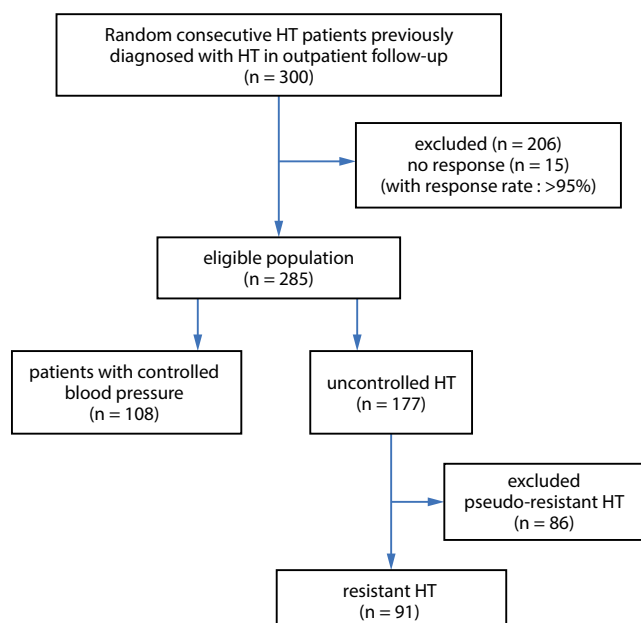


Fig. 1. The flowchart used for the screening and inclusion of patients
HT – hypertension.

rate >95%. Each patient had sociodemographic data and medical history recorded on admission. A cardiologist performed a detailed physical examination, and patients were referred to a psychiatric clinic for evaluation of anxiety and depression scores. A total of 300 patients with resistant HT diagnoses were prospectively included in this study. The control group comprised normotensive patients diagnosed with HT who received regular treatment. Patients with uncontrolled BP who did not use medication or used it tentatively were classified as pseudo-HT and excluded from the study (Fig. 1). Other information on comorbidities, demographics, behavioral lifestyle factors, and metabolic diseases such as dyslipidemia, diabetes, and CVDs and their complications, including stroke and CAD, was also obtained. This study was carried out in accordance with the Declaration of Helsinki and approved by Recep Tayyip Erdoğan University Ethical Committee (decision No. 2022/41).

Exclusion criteria

The study included patients diagnosed with essential HT who had uncontrolled BP despite antihypertensive therapy. Patients who did not want to fill out the questionnaire, those with dementia, and those receiving treatment for depression, anxiety or other psychiatric disorders, were not included in this study. Secondary HT, history of CAD, history of cerebrovascular disease, acute or chronic renal failure (estimated glomerular filtration rate (eGFR) <30 mL/1.7 m²/min), end-stage liver disease, malignancy, active inflammatory disease, endocrine diseases, and electrolyte disturbances were determined as exclusion criteria.

Blood pressure, plasma glucose and lipid measurements

An automatic sphygmomanometer (OMRON HBP-1300; OMRON, Kyoto, Japan) measured each patient's BP, with 3 measurements taken at 30-second intervals and the mean value of the 3 measurements used for the analysis. Also, trained professional healthcare providers measured each patient's height, weight and waist circumference. Body mass index (BMI) was calculated by dividing weight by the square of height (kg/m²). All patients fasted for ≥8 h, and 5-milliliter fasting blood samples were obtained and tested for fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) using standard methods.

Hypertension was defined as systolic BP (SBP) ≥ 140 mm Hg, diastolic BP (DBP) ≥ 90 mm Hg, and/or the use of antihypertensive agents within 2 weeks.⁴ Hypertensive patients receiving antihypertensive treatment and whose SBP/DBP was <140/90 mm Hg were identified and assigned to the control group. Resistant HT was diagnosed using the guidelines of the European Society of Cardiology (ESC).⁴ Treatment-resistant HT was diagnosed if lifestyle changes and recommended combination therapy did not reduce BP values under 140/90 mm Hg. Meanwhile, true resistant HT was defined when SBP was ≥140 mm Hg and/or DBP was ≥90 mm Hg while receiving treatment with the optimal or most tolerable doses of 3 or more drugs, including a diuretic, β-blocker, calcium channel blocker, and a renin-angiotensin-aldosterone antagonist.^{31,32} Uncontrolled BP was measured using ambulatory or home monitoring in all patients. We identified pseudo-resistant HT patients after classifying true resistant HT patients.^{33,34}

Evaluation and definition of anxiety and depression

Each subject completed the HADS questionnaire alone in a quiet environment. The HADS consists of 14 items, including 7 HADS-A and 7 HADS-D items.^{35–38} Each item was scored using a scale that separately evaluates anxiety and depression from 0 to 3 points to give a total score between 0 and 21. The scale classified patients as normal (0–7 points), borderline abnormal (8–10 points) or abnormal (11–21 points).

Statistical analyses

The Shapiro–Wilk test was used to evaluate the distribution normality of continuous variables, and continuous and categorical variables were expressed as mean ± standard deviation (M ± SD) and percentage (%), respectively. In addition, median values (Me) and interquartile ranges (IQRs) were used for non-normally distributed parameters. The Student's t-test compared continuous data with

a normal distribution, and a χ^2 test or Fisher's exact test were employed to compare categorical variables. Continuous variables without a normal distribution were evaluated using the Mann–Whitney U test, while logistic regression was employed to assess the relationship between HT groups (resistance compared to nonresistance) and anxiety and depression scores. The relationship between the predictors and HT groups was determined using odds ratio (OR) and 95% confidence intervals (95% CIs). Odds ratio and 95% CIs summarized the interquartile change for continuous predictors. To capture the nonlinear relationship between continuous predictors and HT groups, continuous predictors were entered into the model using restricted cubic spline transformation (with 3 knots). Multicollinearity was assessed using a variance inflation factor (VIF).³⁹ All statistical analyses were performed using R v. 3.5.6 software (R Foundation for Statistical Computing, Vienna, Austria). We built our model based on previous knowledge and biological plausibility.

Results

In this study, the mean age of 199 patients was 56.4 ± 11 years, and 105 (52.8%) were female. The mean HT treatment duration was 11.1 ± 6.4 years. There were no significant differences between groups in terms of age, gender, family history, and the number of drugs prescribed. The mean HADS-A score was 7.4 ± 4.8 , and the HADS-D score was 6.0 ± 4.0 . The HADS-A score (8.8 ± 5.1 compared to 6.3 ± 4.3 , $p < 0.001$) and HADS-D score (7.1 ± 4.3 compared to 5.0 ± 3.6 , $p = 0.001$) were higher in the uncontrolled HT patients compared to the controlled HT group. The BMI of the resistant HT group was higher than in the controlled HT group (24.9 ± 5.0 compared to 23.2 ± 3.0 , $p = 0.011$). C-reactive protein (CRP) level was higher in the uncontrolled group than in the controlled group (3.3 (0.40–10) mg/L compared to 2.2 (0.12–11) mg/L, $p = 0.045$) (Table 1).

Blood pressure monitoring findings differed between the groups (Table 2). In multivariable analysis, HADS-D score (OR: 1.88, 95% CI: 1.10–3.21, $p = 0.005$) and HADS-A score (OR: 1.89, 95% CI: 1.04–3.45, $p = 0.008$) were independent predictors of resistant HT. In addition, BMI (OR: 1.46, 95% CI: 0.98–2.18, $p = 0.027$) and CRP (OR: 3.06, 95% CI: 1.47–6.38, $p = 0.004$) predicted the presence of resistant HT (Table 3). The main study findings were that higher levels of anxiety and depression, as measured using HADS, were independent predictors of resistant HT. Additionally, higher BMI and CRP levels were associated with resistant HT.

Discussion

This study revealed that patients with uncontrolled HT exhibited higher levels of anxiety and depression compared

to those with controlled HT. In addition, the resistant HT patients had higher BMI and CRP levels. The multivariable analysis confirmed that anxiety and depression scores, BMI, and CRP levels independently predicted resistant HT. These findings suggest that psychological factors and inflammation may contribute to the course of resistant HT.

Hypertension is a common chronic disease that affects public health globally and is one of the most important preventable risk factors for CVDs.⁴⁰ The World Health Organization (WHO) reported in 2015 that approx. 25% of the adult population had HT, and around 40% of cardiovascular deaths were caused secondary to HT.⁴¹ Blacher et al. stated that every 10 mm Hg increase in BP causes increasingly severe CVD complications and increases the risk of death by nearly 20%.⁴² Considering these high mortality and morbidity rates, it can be concluded that uncontrolled and resistant HT represents a more complicated status. Moreover, patients with resistant HT have a twofold increased risk for CVDs than patients without resistant HT, so those with resistant HT are a critical population that needs further evaluation.⁴³

Recently, it has been frequently emphasized that anxiety and depression increase the risk of CVDs and eventually complicate their treatment.^{44,45} Although the etiopathogenesis of resistant HT is heterogeneous, conditions that increase the activity of the sympathetic nervous system, including chronic stress and chronic pain, appear to be particularly responsible factors.⁴⁶ It has been known for more than 50 years that oxidative stress and inflammation have a crucial role in the pathogenesis of HT. Biomarkers of inflammation, including high-sensitivity CRP, numerous cytokines and various products of the complement pathway, are elevated in patients with HT.⁴⁷ Long-term inflammatory responses and pro-inflammatory factors also play a critical role in the pathogenesis of anxiety and depression and are central to HT, while the activation of certain enzymes by stress hormones such as cortisol and inflammatory cytokines is well known. Moreover, genotypic variations contribute to inflammation, which in turn may lead to the development of various diseases.⁴⁸ In this study, CRP was higher in resistant HT patients than in control patients, compatible with the current literature. These findings predicate that chronic inflammation arising from anxiety and depression contributes to the pathogenesis of resistant HT.

The negative effects of dietary habits and being overweight are well known in HT.⁴⁹ In this study, BMI was significantly higher in resistant HT patients compared to the control group, which also shows that it has a deleterious effect on controlling HT in the normal range.

The relationship between psychosocial stress and HT is complex, with multiple mechanisms involved. The 2 main mechanisms are behavioral responses and pathophysiological responses. Maladaptive behavioral responses include smoking, poor activity and dietary habits thought to contribute to resistant HT over time.⁴⁴ Physiological

Table 1. Baseline clinical and laboratory characteristics of patients

Variable		Study population			
		overall (n = 199)	group 1 (n = 108)	group 2 (n = 91)	p-value
Age [years]		56 (35–81)	57.5 (36–81)	55 (35–78)	0.242*
Female sex, %		52.8	54	60	0.413 ^a
Diabetes, %		12.6	11	13	0.676 ^a
Duration of HT [years]		11.1 ±6.4	11.7 ±6	10.5 ±6	0.159 [#]
Smoking, %		11.1	12	10	0.665 ^a
Dyslipidemia, %		18.6	20	18	0.756 ^a
Family history of HT		18	17	18	0.592 ^a
CV disease, %		10	9	11	0.653 ^a
HADS-Anxiety score		7 (0–20)	6 (0–18)	9 (0–20)	0.001*
HADS-Depression score		5 (0–17)	5 (0–17)	7 (0–16)	<0.001*
C-reactive protein [mg/dL]		2.7 (0.12–11)	2.2 (0.12–11)	3.3 (0.40–10)	0.045*
Hemoglobin [g/dL]		13 (8–16)	13 (8–16.5)	14 (10.2–16.6)	0.444*
Fasting glucose [mg/dL]		98 (83–242)	100 (83–242)	97 (83–213)	0.520*
Total cholesterol [mg/dL]		217 ±46	214 ±50	220 ±39	0.280 [#]
LDL cholesterol [mg/dL]		126 (31–257)	121 (31–257)	131 (41–257)	0.123*
HDL cholesterol [mg/dL]		39 (16–59.8)	39 (16–59.8)	39 (16–59.3)	0.941*
Triglyceride [mg/dL]		180 (93–603)	185 (99–603)	171 (93–392)	0.252*
GFR [mL/min]		58 (40–100)	56 (40–98)	60 (40–100)	0.163*
BMI [kg/m ²]		23.4 (16–39)	22.7 (16.3–35.7)	23.8 (16.3–39)	0.040*
Medications, %	aspirin	8.8	10.2	7.4	0.603 ^a
	statin	13.6	13.9	12	0.685 ^a
	ACE-inhibitors	41.7	38	44.4	0.407 ^a
	ARB	29.1	26.9	29.2	0.763 ^a
	CCB	34.2	34.3	33.3	0.100 ^a
	β-blocker	15.6	18.5	13	0.262 ^a
	alfa-adrenergic receptor blocker	9	6.5	10.2	0.325 ^a
	diuretic	78.4	60.2	100	<0.001 ^a
combined pill		61.8	60.2	63.9	0.670 ^a

Normally distributed continuous variables are presented as mean ± standard deviation (M ±SD). Categorical variables are presented as percentage (%). Non-normally distributed variables are presented as median (Me) (interquartile range (IQR)). group 1 – patients with regulated blood pressure; group 2 – resistant hypertensive patients; HT – hypertension; HADS – Hospital Anxiety and Depression Scale; CV – cardiovascular; BMI – body mass index; GFR – glomerular filtration rate; LDL – low-density lipoprotein; HDL – high-density lipoprotein; ACE – angiotensin converting enzyme; ARB – angiotensin II receptor blocker; CCB – calcium channel blocker; * Mann–Whitney U test; [#] Student's t-test; ^a Pearson's χ^2 test.

Table 2. 24-hour blood pressure monitoring findings in the patients

Variable	Group 1 (n = 108)	Group 2 (n = 91)	p-value	test value
Mean daytime systolic	116 (95–170)	160 (108–172)	<0.001*	U: 1731
Mean daytime diastolic	75 (62–123)	97 (67–112)	<0.001*	U: 1954
Mean night systolic	70 (55–115)	140 (94–150)	<0.001*	U: 1680
Mean night diastolic	105 (74–148)	85 (60–101)	<0.001*	U: 1850

Non-normally distributed variables are presented as median (Me) (interquartile range (IQR)). group 1 – patients with regulated blood pressure; group 2 – resistant hypertensive patients; * Mann–Whitney U test.

pathways, such as the hypothalamus–pituitary–adrenal (HPA) axis, sympathetic activation, vagal withdrawal, and immune responses, mediate the pathophysiological response.⁴⁹ The HPA axis releases corticotropin-releasing factor (CRF) from the hypothalamus, and subsequently,

adrenocorticotrophic hormone (ACTH) is released into the systemic circulation and reaches the adrenal cortex. Glucocorticoid synthesis is stimulated by the adrenal cortex, which ultimately contributes to the development of HT.⁵⁰ The sympathetic nervous system is also thought

Table 3. Association of depression and anxiety with resistant hypertension (HT) tested using multivariable binary logistic regression

Variable	Predictors of patients with resistant HT			
	univariable analysis		multivariable analyzes	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Model 1			Nagelkerke R ² = 0.243	
HADS-Depression score (from 3 to 8.5)	1.99 (1.26–3.15)	0.002	1.88 (1.10–3.21)	0.005
BMI (from 20.9 to 26.5)	1.30 (0.91–1.86)	0.040	1.46 (0.98–2.18)	0.027
CRP (from 1.4 to 5.6)	3.00 (1.56–5.79)	0.001	3.06 (1.47–6.38)	0.004
Age (from 47 to 66)	0.73 (0.46–1.17)	0.115	0.63 (0.37–1.07)	0.218
Male sex	1.28 (0.73–2.23)	0.395	1.46 (0.78–2.74)	0.239
Model 2			Nagelkerke R ² = 0.237	
HADS-Anxiety score (from 3 to 11)	2.18 (1.26–3.75)	0.002	1.89 (1.04–3.45)	0.008
BMI (from 20.9 to 26.5)	1.30 (0.91–1.86)	0.031	1.47 (1.00–2.17)	0.046
CRP (from 1.4 to 5.6)	3.00 (1.56–5.79)	0.001	3.19 (1.58–6.46)	0.003
Age (from 47 to 66)	0.73 (0.46–1.17)	0.115	0.67 (0.39–1.14)	0.183
Male sex	1.28 (0.73–2.23)	0.395	1.50 (0.80–2.82)	0.208

HADS – Hospital Anxiety and Depression Scale; OR – odds ratio; 95% CI – 95% confidence interval; CRP – C-reactive protein; BMI – body mass index.

to play a vital role in the pathophysiological response of HT to stress. Furthermore, decreased vagal tone is thought to be a reliable indicator of new-onset HT, and fluctuations in vagal tone can be as imperative to psychology-related BP increases as sympathetic nerves and the HPA systems. The role of the parasympathetic system in recovery and restoration is also essential, and those who cannot relax under chronic stress are more likely to develop premature coronary events.⁵¹ Overall, individuals with hyperactive HPA and sympathetic systems, and decreased vagal tone, aggravated by chronic stress, are at greater risk of developing HT.

Most disorders have a different pathophysiological basis, though concomitant depression and anxiety may be seen in all patients attending the clinic and presenting with fluctuating symptoms. Furthermore, psychiatric symptoms can serve as prodromal indicators of a particular condition.⁵² It is thought that emotional and psychosocial stress takes on an important role in HT development, and BP is negatively affected by anxiety and depression.⁵³ On the other hand, patients experience emotional deterioration after HT diagnosis. As such, evaluating emotional status would be beneficial for detecting resistance to HT treatment. Accordingly, it can be asserted that emotional status assessment, even after resistant HT development, would be beneficial to prevent HT progression and provide a response to treatment. In parallel with our study, Lane et al. demonstrated that depression is an independent predictor of uncontrolled HT.¹⁶ Indeed, anxiety and depression levels were higher in patients with resistant HT than in control patients, and both were independent predictors of HT. In this respect, if there is no identifiable secondary cause, anxiety and depression play a critical role in uncontrolled development of HT.

Our study may shed light on better defining emotional disturbances that have a negative impact on the course

of chronic diseases in future large-scale studies. A general overview of the pathogenesis, biochemical markers, preclinical evidence, and translational research on anxiety and depression, which may be common in chronic diseases, could provide insight into the discovery of new therapeutic targets. In resistant HT management, it may be essential to address psychological and lifestyle factors, such as weight management and inflammation, as suggested by these findings.

Healthcare providers should consider screening for anxiety and depression in patients with HT, as these conditions may contribute to poor BP control. Furthermore, implementing strategies to address psychological lifestyle factors, such as weight management and inflammation reduction, may be vital in managing resistant HT.

Limitations of the study

First, we could not establish a causative relationship between depression and uncontrolled HT due to the cross-sectional study design. More studies and clinical trials are necessary to determine the effects of depression and anxiety on uncontrolled HT. Second, the HADS questionnaire assessed depression and anxiety, and a psychiatrist did not evaluate the scores. Third, we were unable to collect reliable information on adherence to the HT treatment used. Blood pressure levels and antihypertensive treatment benefits may affect BP control in HT patients, and our results may be biased for this reason.

Conclusions

The study found that high anxiety and depression scores were independent predictors for true resistant HT in patients with uncontrolled BP. Thus, we can use the HADS

score to assess risks in HT patients with uncontrolled BP. Emotional status is mostly neglected by medical doctors in general practice, although it might be the basis of uncontrolled but treatable HT. This oversight may cause undesirable outcomes and waste time dedicated to HT. Therefore, it is essential to screen for anxiety and depression in primary healthcare facilities while diagnosing and during follow-up in patients with arterial HT to identify high-risk groups, improve treatment strategies and prevent future adverse events.

Supplementary data

The supplementary materials are available at <https://doi.org/10.5281/zenodo.7916433>. The package contains the following files:

Supplementary Fig. 1. HADS-A was positively correlated with mean daytime systolic blood pressure ($p < 0.001$, $r = -0.235$).

Supplementary Fig. 2. HADS-A was positively correlated with mean daytime systolic blood pressure ($p = 0.001$, $r = -0.227$).

Supplementary Table 1. Mann–Whitney U, χ^2 and Student's t-test of presented statistical values.

Supplementary Table 2. Mann–Whitney U test values.

Supplementary Table 3. Multivariable binary logistic regression analysis and Nagelkerke R^2 values.

Supplementary Table 4. Shapiro–Wilk test results.

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