Hypertension But Not Heart Failure or Coronary Artery Disease is Associated with Mental Disorders

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Abstract

Background: Previous studies have emphasized the significant association between depression, anxiety, and stress and hypertension (HTN), heart failure (HF), and coronary artery disease (CAD). However, among included patients with HF or CAD in those studies, there were considerable proportions of patients with concomitant HTN and vice versa leading to some possible bias in final estimations. Therefore, we aimed to exclude those patients with concomitant diseases and reassess the association between these three prevalent cardiovascular diseases with three important psychological disorders.

Methods: In this cross-sectional study, 300 patients were evaluated, including 100 with HTN (without a history or concomitant HF or CAD), 100 with HF (without HTN or CAD), and 100 with CAD (without HTN or HF). Moreover, 100 healthy volunteers were considered as the control group. Depression Anxiety Stress Scale 21 was used to measure the magnitude of depression, anxiety, and stress.

Result: The average scores of 4.6, 9.1, 3.7, and 4.4 for depression, 3.9, 11.1, 4.1, and 3.6 for anxiety and 6.5, 13.6, 5.2, and 5.4 for stress were detected in control, HTN, CAD, and HF groups, respectively. The depression, anxiety, and stress scores of HTN group were significantly higher than the control ($p<0.05$), CAD ($p<0.05$) and HF ($p<0.05$) groups; this is while these scores were not significantly different between other study groups ($p>0.05$).

Conclusion: Our study demonstrated a significantly higher magnitude of psychological disorders in patients with HTN. However, their magnitude in patients with HF and CAD without concomitant HTN were similar to those in healthy participants.

Introduction:

Despite promising advances in healthcare and therapeutics, Cardiovascular Diseases (CVDs) remain the leading cause of mortality and disability worldwide (1, 2). It has been reported that CVDs cause a number of over 18 million mortalities per year, which will rise up to 23.3 million till 2030 (3). CVDs impose a heavy social and financial burden on the global economy particularly in low- and middle-income countries (4). Aging, obesity, inadequate preventive strategies, and suboptimal management of risk factors increase the burden of CVDs (4). However, it is noteworthy that classical cardiac risk factors such as aging and obesity can explain only a half of the clinical CVDs (5). A growing number of studies have emphasized the significant role of psychological disorders especially depression, anxiety states including panic disorder, post-traumatic psychological symptoms, and mental stress in development of CVDs (6–9). The relatively poorer outcomes of patients with CVDs and concomitant psychological diseases have made them the subjects of many recent studies (10, 11). Depression in patients with congestive Heart Failure (HF) has an independent prognostic role in patients' outcome and can bring about 2 to 3-fold higher rates of rehospitalization and mortality (10, 11). Also, anxiety is reported to be significantly associated with mortality in patients with Coronary Artery Disease (CAD) (12). Likewise, higher states of psychological stress such as social-isolation or work-related stress can bring about poorer prognosis in patients with

established CAD (13). Although the mechanisms are not well-defined, studies using both electrophysiological and neurochemical techniques, demonstrated that the sympathetic nervous system activation in psychological disorders seems to have an important role in development of CVDs (5).

A high prevalence of psychological disorders is reported among hypertensive patients and the numbers vary greatly among previous studies (14–17). In addition, the proportions of patients with HF or CAD suffering from concomitant psychological disorders have been variedly reported. However, it should be noted that among included patients with HF or CAD in those studies, there were considerable proportions of patients with concomitant Hypertension (HTN) (18–20). Considering that HTN patients have high rate of psychological disorders (21, 22), the possibility of this bias exists that due to presence of HTN patients in the study samples, the prevalence of psychological disorders of patients with HF and CAD has been intrusively reported higher than normal (23, 24). Therefore, we aimed to exclude those patients with HF and CAD that have a history of or concomitant HTN and reassess the association between these three prevalent CVDs with three important psychological disorders.

Patients And Methods:

This study was designed as a cross-sectional study on patients with the age of 18 years and above, who were referred to the outpatient clinics of university hospitals of (the name of the city was blinded for double blinded peer review), from January 2018 to January 2019. An overall number of 100 healthy volunteers were considered as the control group and 300 patients were consecutively included, of whom 100 patients had HTN (without a history or concomitant HF or CAD), 100 patients had HF (without a history or concomitant HTN or CAD), and 100 patients had CAD (without a history or concomitant HTN or HF). Informed consent for participation was obtained and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

The diagnosis of HF, HTN, and CAD was assigned by an attending cardiologist. HF was diagnosed based on Framingham criteria and if the patients meet at least two major criteria or one major and two minor criteria and ejection fraction was below 40 percent were included in the HF group (25). Patients whose blood pressures were consistently ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic or were under treatment with antihypertensive drugs were considered hypertensive according to the Eighth Joint National Committee (JNC 8) guideline (26). CAD was diagnosed based on a history of confirmed myocardial infraction or a previous angiography report demonstrating more than 50 percent luminal narrowing of coronary arteries (25).

Demographic data including age, sex, marital status, place of residence, education, number of children, and occupation status were recorded for each study sample. The average amount sleeping hours, self-reported sleep disorders and incidence of spontaneous cry were asked from each sample as well. *Depression Anxiety Stress Scale 21* (DASS-21) was used as a measure of the magnitude of the three traits of depression, anxiety, and stress. DASS-21 scale consists 21 questions, each question needs to be

answered on a 4-point scale by the patient rating the extent of each 21 statements applied over the past week. The Internal consistency scores for this scale in terms of Cronbach's alpha scores rate are high (of 0.96 to 0.97 for Depression, 0.84 to 0.92 for Anxiety, and 0.90 to 0.95 for Stress) (27–31).

Interpretation of the patients' scores was performed by converting them to z-scores and comparing them to the normative values contained in the DASS manual. The scores from this version of DASS (DASS-21) were converted to the DASS normative data by multiplying the scores by two. A z-score of 0.5 was considered as normal, 0.5 to 1.0 was mild, 1.0 to 2.0 was moderate, 2.0 to 3.0 was severe, and z-scores over 3 were considered as extremely severe depression, anxiety, or stress. The validity and reliability of Persian translation of DASS-21 have also been verified by Sahebi et al. (Cronbach Alphas of 0.77, 0.79 and 0.78 for the depression, anxiety and stress subscales, respectively). Also, a significant correlation of DASS-21 with well-known measures such as Beck's Depression Inventory ($r = 0.70$), Zung's Anxiety Inventory ($r = 0.67$) and Perceived Stress Inventory ($r = 0.49$) have been demonstrated.

Normal distribution of all variables was tested by the Kolmogorov-Smirnov test. Mean and standard deviation or median and interquartile range of quantitative variables and frequency and percentage of qualitative variables were calculated. Student's t-test or Mann-Whitney U were used to compare quantitative variables between two groups and one-way ANOVA or the Kruskal-Wallis to compare means of more than two groups. Chi-square test was used for qualitative variables.

SPSS version 24 was used for all analyses. A P-value of less than 0.05 was considered significant.

Results:

An overall 400 participants including 213 women (53.2%) and 187 men (46.8%), with a mean age of 55.1 ± 14.1 years old were included. The majority of the participants were married (95.8%) illiterate (34.7%), urban residences (80.5%) and employed (77%). Also, the participants had a median number of 3 children (0–11). The demographic characteristics of participants within each study group are summarized in Table 1; regarding the demographic characteristics, the study groups were significantly different in age ($p < 0.05$), gender ($p < 0.05$), marriage status ($p < 0.05$), children number ($p < 0.05$), education ($p < 0.05$), residence place ($p < 0.05$) and occupation ($p < 0.05$).

Table 1
The demographics of participants (n = 400)

	Study Groups				P-value
	Control (n = 100)	HF (n = 100)	HTN (n = 100)	CAD (n = 100)	
Age (years)*	43.5 (13.0)	62.8 (11.5)	55.8 (12.3)	58.3 (12.3)	0.000≠
Sex ¥					
Male	37 (37.0)	66 (66.0)	21 (21.0)	63 (63.0)	0.000∂
Female	63 (63.0)	34 (34.0)	79 (79.0)	37 (37.0)	
Marriage Status ¥					
Married	89 (89.0)	100 (100)	95 (95.0)	99 (99.0)	0.000∂
Unmarried	11 (11.0)	0	5 (5.0)	1 (1.0)	
Children (number) §	2 (0–8)	4 (1–11)	3 (0–10)	3 (0–9)	0.000¤
Education ¥					
Illiterate	13 (13.0)	59 (59.0)	31 (31.0)	36 (36.0)	0.000∂
Middle School	22 (22.0)	35 (35.0)	35 (35.0)	34 (34.0)	
Diploma	24 (24.0)	6 (6.0)	15 (15.0)	16 (16.0)	
University Degree	41 (41.0)	0	19 (19.0)	14 (14.0)	
Residence Place ¥					
Urban	90 (90.0)	61 (61.0)	90 (90.0)	81 (81.0)	0.000∂
Rural	10 (10.0)	39 (39.0)	10 (10.0)	19 (19.0)	
Occupation ¥					
Unemployed	6 (6.0)	28 (28.0)	5 (5.0)	7 (7.0)	0.000∂
Employee	21 (21.0)	0	11 (11.0)	12 (12.0)	
Businessman	25 (25.0)	34 (34.0)	9 (9.0)	29 (29.0)	
Retired	10 (10.0)	6 (6.0)	11 (11.0)	19 (19.0)	
Housekeeper	38 (38.0)	32 (32.0)	64 (64.0)	33 (33.0)	

	Study Groups				P-value
	Control (n = 100)	HF (n = 100)	HTN (n = 100)	CAD (n = 100)	
*Data are presented as Mean (SD)					
¥Data are presented as n (%)					
§Data are presented as Median (min-max)					
≠Analysis of variance (ANOVA)					
∂Fisher's exact test					
¤Kruskal-Wallis test					

Following the findings in Table 2, the study groups were significantly different in sleep duration ($p < 0.05$) and sleep disorder ($p < 0.05$). While 70% of participants in the control group reported having an adequate daily sleep (defined as 6–8 hours of sleep), respectively 49%, 63%, and 62% of patients in HTN, CAD, and HF groups reported having an adequate daily sleep (Table 2). Although only 38% of participants in control were suffering from sleep disorder, the disorder was as frequents as 71% in HTN group, 43% in CAD group, and 57% in HF group (Table 2). In addition, the status of spontaneous crying was significantly different between the groups ($p < 0.05$), as 12% control participants, 53% HTN patients, 20% CAD patients, and 10% HF patients reported to have spontaneous crying (Table 2). In general, insufficient daily sleep, sleep disorder, and spontaneous crying were more common among HTN patients compared to other participants.

Table 2
The sleeping and crying status of participants (n = 400)

	Study Groups				P-value≠
	Control (n = 100)	HF (n = 100)	HTN (n = 100)	CAD (n = 100)	
Sleep Duration (hour)*					
6–8	70 (70.0)	62 (62.0)	49 (49.0)	63 (63.0)	0.035
3–6	28 (28.0)	38 (38.0)	48 (48.0)	35 (35.0)	
< 3	2 (2.0)	0	3 (3.0)	2 (2.0)	
Sleep Disorder*	38 (38.0)	57 (57.0)	71 (71.0)	43 (43.0)	0.000
Spontaneous Crying*	12 (12.0)	10 (10.0)	53 (53.0)	20 (20.0)	0.000
*Data are presented as N (%)					
≠Fisher's exact test					

The individuals' scores of depression, anxiety and stress were classified by the normative values contained in the DASS manual. Regarding the depression levels, the frequency of normal versus (vs) severe levels in control, HTN, CAD, and HF groups were 90% vs 1%, 43% vs 9%, 91% vs 1%, and 94% vs 2%, respectively. The prevalence of normal vs severe levels of anxiety in control, HTN, CAD, and HF groups were 86% vs 1%, 24% vs 44%, 85% vs 2%, and 92% vs 2%, respectively. Finally, the prevalence of normal vs severe levels of stress in control, HTN, CAD, and HF groups were 92% vs 2%, 54% vs 10%, 94% vs 1%, and 96% vs 2%, respectively (Table 3).

Table 3
The levels of depression, anxiety and stress in study groups (n = 400)

	Study Groups			
	Control (n = 100)	HF (n = 100)	HTN (n = 100)	CAD (n = 100)
Depression Level				
Normal	90 (90.0)	94 (94.0)	43 (43.0)	91 (91.0)
Mild	8 (8.0)	4 (4.0)	28 (28.0)	5 (5.0)
Moderate	1 (1.0)	0	20 (20.0)	3 (3.0)
Severe	1 (1.0)	0	7 (7.0)	1 (1.0)
Very Severe	0	2 (2.0)	2 (2.0)	0
Anxiety Level				
Normal	86 (86.0)	92 (92.0)	24 (24.0)	85 (85.0)
Mild	7 (7.0)	2 (2.0)	7 (7.0)	6 (6.0)
Moderate	6 (6.0)	4 (4.0)	25 (25.0)	7 (7.0)
Severe	1 (1.0)	0	25 (25.0)	1 (1.0)
Very Severe	0	2 (2.0)	19 (19.0)	1 (1.0)
Stress Level				
Normal	92 (92.0)	96 (96.0)	54 (54.0)	94 (94.0)
Mild	4 (4.0)	2 (2.0)	16 (16.0)	1 (1.0)
Moderate	2 (2.0)	0	20 (20.0)	4 (4.00
Severe	2 (2.0)	2 (2.0)	9 (9.0)	1 (1.0)
Very Severe	0	0	1 (1.0)	0
Data are presented as N (%)				

The overall scores of depressions in study groups had an average of 4.6 in the control group, 9.1 in HTN group, 3.7 in CAD group, and 4.4 in HF group (Table 4, Fig. 1). The depression scores between the study groups were significantly different ($p < 0.05$, Table 4), as the depression scores of HTN patients were significantly higher than the control participants ($p < 0.05$), CAD patients ($p < 0.05$) and HF patients ($p < 0.05$); this is while the depression scores were not significantly different between other study groups (Table 5).

Table 4
The comparison of depression, anxiety and stress scores between study groups (n = 400)

	Study Groups				
	Control (n = 100)	HF (n = 100)	HTN (n = 100)	CAD (n = 100)	P-value≠
Depression Score*	4.6 (4.0–5.4)	4.4 (3.5–5.3)	9.1 (7.8–10.5)	3.7 (3.1–4.5)	0.000
Anxiety Score*	3.9 (3.3–4.6)	3.6 (3.0–4.2)	11.1 (9.6–12.8)	4.1 (3.5–4.8)	0.000
Stress Score*	6.5 (5.5–7.6)	5.4 (4.7–6.2)	13.6 (12.2–15.1)	5.2 (4.5–6.0)	0.000

*Data are presented as Geometric Mean (95% Confidence Interval)

≠Adjusted for patients' demographics, sleep duration, sleep disorder, spontaneous crying with analysis of covariance (after logarithmic transformation)

Table 5
The post-hoc differences of depression, anxiety and stress scores among the study groups (n = 400)

Variable	Study Groups	MD (95% CI)¥	P-value≠
Depression Score			
	HF vs Control	0.5 (-1.7–2.7)	0.935
	HTN vs Control	5.7 (3.7–7.7)	0.000
	CAD vs Control	0.3 (-1.6–2.3)	0.967
	HTN vs HF	5.2 (3.1–7.3)	0.000
	CAD vs HF	-0.1 (-2.0–1.7)	0.997
	CAD vs HTN	-5.3 (-7.3 – -3.4)	0.000
Anxiety Score			
	HF vs Control	1.2 (-0.9–3.3)	0.466
	HTN vs Control	8.7 (6.8–10.6)	0.000
	CAD vs Control	1.5 (-0.4–3.4)	0.171
	HTN vs HF	7.5 (5.5–9.5)	0.000
	CAD vs HF	0.3 (-1.4–2.1)	0.966
	CAD vs HTN	-7.2 (-9.0 – -5.3)	0.000
Stress Score			
	HF vs Control	1.6 (-0.9–4.1)	0.362
	HTN vs Control	7.9 (5.6–10.1)	0.000
	CAD vs Control	1.0 (-1.3–3.3)	0.675
	HTN vs HF	6.3 (3.8–8.7)	0.000
	CAD vs HF	-0.6 (-2.7–1.5)	0.888
	CAD vs HTN	-6.9 (-9.1 – -4.6)	0.000

¥MD (95% CI): Mean Difference (95% Confidence Interval)

≠ The post-hoc Tukey test

≠The significant comparisons are reported only

The estimations for scores of anxiety revealed overall averages of 3.9, 11.1, 4.1, and 3.6 for control, HTN, CAD, and HF groups, respectively (Table 4). The study groups were significantly different in anxiety score

($p < 0.05$, Table 4); the significant differences of anxiety scores were among the HTN patients vs the patients in other groups (all: $p < 0.05$, Table 5), as HTN patients showed higher anxiety scores than others.

Regarding the overall scores of stress in study groups, which was significantly different between the groups ($p < 0.05$), the overall averages of 6.5, 13.6, 5.2, and 5.4 were estimated for control, HTN CAD, and HF groups, respectively (Table 4). Similar to depression and anxiety scores, the stress scores of HTN patients were significantly higher than the ones in other groups ($p < 0.05$), while the other inter-groups scores were not significantly different (Table 5).

Discussion:

Our results demonstrated a significantly higher prevalence of psychological problems including anxiety, depression, and stress among HTN patients. Also, a great proportion of HTN patients had sleeping disorders and spontaneous crying and few had enough sleep. However, HF and CAD patients' results were similar to the results of healthy participants in terms of status of anxiety, stress, sleep duration, sleep disorders, and spontaneous crying except for depression which was even lower in HF patients as compared to control group.

Our study confirms and extends the findings of previous studies that demonstrated a significant association between psychological disorders and HTN (14–17). Ginty et al. revealed a significant association between symptoms of depression and anxiety and a diagnosis of hypertension assessed 5 years later (9). Maatouk et al. in a recent study, have also confirmed the relationship between depression and a higher risk of HTN (14). However, some other studies have recently questioned these findings, proposing that, depression and anxiety can even lead to lower BP (16, 17, 32). Thus, two other studies tried to explain these discrepancies and suggested that this association have an age-related pattern as it is more evident in middle-aged patients, but not in young or elderly patient (6, 33). HTN group in our study mostly consisted of middle-aged patients (half of the patients aged between 48 to 65 years). The underlying mechanism of this age-related pattern of this association remains to be determined. However, different possible explanations of the mechanism underlying the association between psychological disorders and HTN have been proposed. Both unhealthy behaviors and physiological dysregulation in patients with psychological disorders are imagined to contribute to development of HTN. Some of the possible physiological dysregulations that are previously suggested include altered hypothalamic–pituitary–adrenal axis (34), deregulated autonomic function (35), altered brain activity (i.e. hypometabolism of dorsal cortical regions and ventral limbic structures) (36). An increased postganglionic sympathetic fibers activation passing to blood vessels of skeletal muscle results in vasoconstriction and increased blood pressure in patients with borderline or established hypertension (5, 37, 38).

Previous studies postulated that there are associations between HF and CAD with psychological disorders but we found no such association (18–20). One possible explanation could be that the association between HF and CAD with psychological disorders in previous studies is due to the inclusion

of HF/CAD patients with concomitant HTN. Garfield et al. reported significant association of anxiety disorders and depression with incident heart failure. Although the results of this study was adjusted to HTN at baseline, HTN due to depression/anxiety disorders over the course of study were not considered in final analysis as a confounding factor (18). Also, some other studies did not consider controlling the confounding effect of HTN in the evaluation of depression in HF patients (19, 39). Abramson et al. revealed that depression can lead to two-fold higher rate of heart failure in patients with HTN (24). Therefore, HTN may play a role in this association. Thus, it can be imagined that although the prevalence of depression is high among HF patients, this phenomenon is not related to the pathophysiology of HF, instead, it is related to HTN. Accordingly, when we excluded HTN patients from HF patients, no higher rate of depression was found. Similar bias can be found within those studies evaluating the association of anxiety and stress and heart failure (18, 39, 40).

Although the cross-sectional design of current study may prevent us to argue about causation relationship between psychological disorders and HTN, low rate of psychological disorders among HF and CAD patient without concomitant HTN leads us to suppose that it is unlikely that psychological disorders in HTN be merely an emotional response to having HTN, instead it is more likely that HTN is a physical response to these damaging psychological disorders. However, this issue needs to be confirmed by future longitudinal and preventive interventional studies.

Our study had some limitations that worth mentioning. First, this study was designed as a cross-sectional study rather than a cohort study. Yet, we included a control group in order to be able to compare the results. Second, analysis of demographic characteristics demonstrated significant differences among study groups that was due to consecutive inclusion of patients without considering their demographic characteristics. A previous study in Iran demonstrated that there was no significant associations between DASS-21 scale scores and demographic variables (i.e. age, gender, education, and marital status) (41). Therefore, differences in demographic characteristics may not prevent us to use our data for comparing the results of DASS-21 between HTN, HF, and CAD patients. Moreover, possible confounding effects of these variables were controlled in final analysis.

Conclusion:

Our study demonstrated a significantly higher rate of psychological disorders (including stress, anxiety, and depression) among patients with HTN. However, the rate of psychological disorders in patients with HF and CAD without concomitant HTN were similar to those in healthy participants. Therefore, we can conclude that first, the confounding effect of HTN needs to be considered in future studies that evaluate association of psychological disorders and HF and CAD. Second, due to higher rate of psychological disorders among HTN patients and their negative consequences, more attention should be paid on psychological disorders in these patients. Third, considering that we found higher rates of psychological disorders among HTN patients but not among HF and CAD patients, it can be imagined that, these psychological disorders may have a role in pathophysiology of HTN, rather than being an emotional

response to a distressing and unwell physical condition. However, this issue needs to be confirmed by future longitudinal studies.

Declarations

Ethics approval: The protocol of this study was approved by medical ethics committee of our institution.

Consent to participate: Informed consent was obtained from the participants.

Consent for publication: Consent for publication was granted.

Availability of data and materials: All Data and material collected during this study are available from the corresponding author upon reasonable request.

Conflicts of interest/Competing interests: None declared.

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Authors' contributions: Conceptualization: HN, SRSE; Methodology: HN, FJ, DE; Formal analysis and investigation: RZ, SRSE; Writing - original draft preparation: SRSE; Writing - review and editing: HN, RZ, SRSE; Funding acquisition: HN; Resources: FJ, DE, Supervision: HN

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Figures

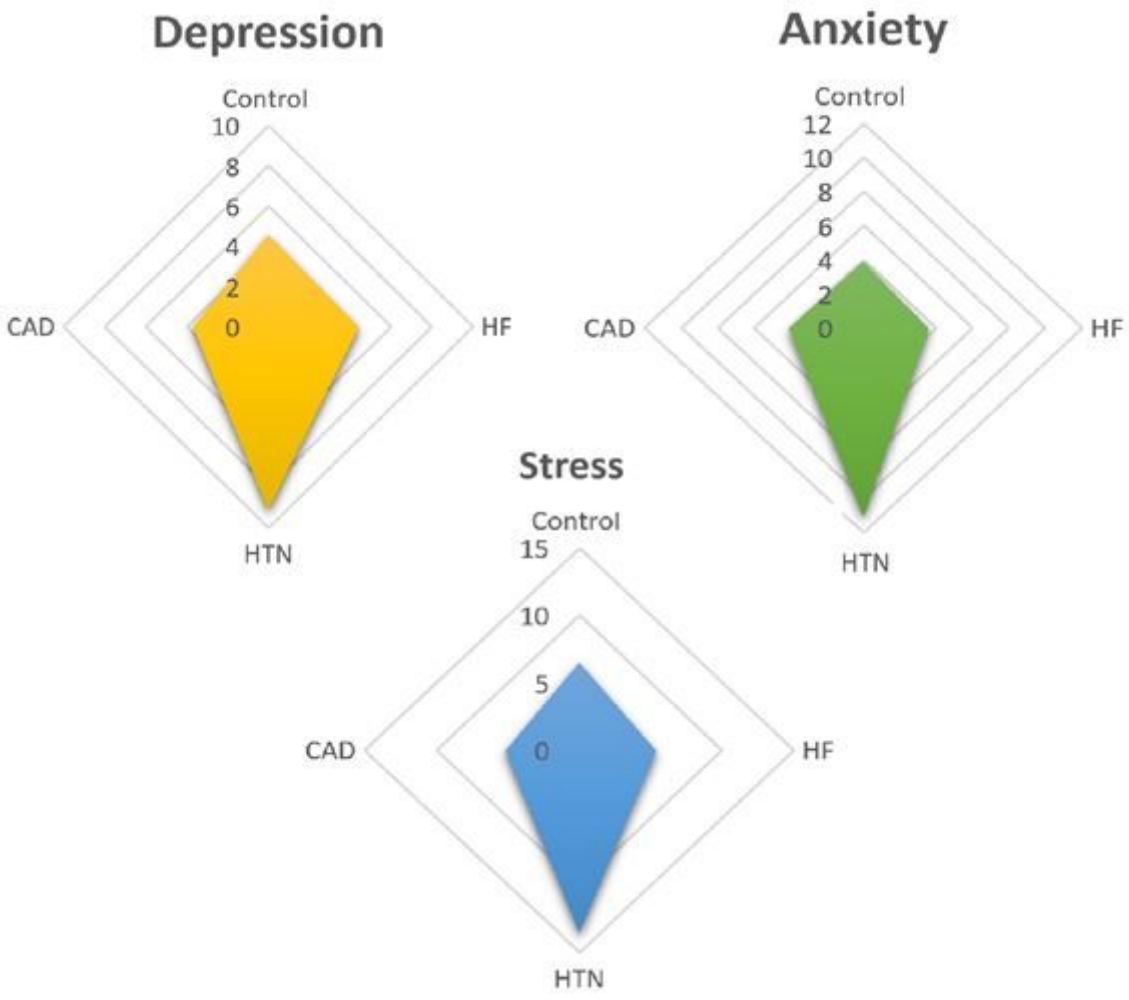

Figure 1

The results of three dimensions of DASS-21 including depression, anxiety, and stress in four study groups (HTN, hypertension; HF, heart failure; CAD, coronary artery disease; and control groups).