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Original Article

The Effect of COVID-19 Infection on Heart Rate Variability: A Cross-sectional Study

Fatih Levent, Ahmet Tutuncu, Gokhan Ozmen, Dogan Ormanci, Fahriye Vatansever, Mustafa Ahmet Huyut[1]

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Abstract

Introduction and Objectives: Heart rate variability (HRV) measurement is a non-invasive procedure used to evaluate autonomic nervous system (ANS) activity. We aimed to investigate the coronavirus disease 2019 (COVID-2019) infection effects on time-domain and frequency-domain HRV parameters to determine COVID-19 effects on the ANS. **Materials and Methods:** From the registry of the COVID-19 outpatient clinics between July 2020 and October 2021, 6127 patients with polymerase chain reaction (PCR) results positive for COVID-19 in real-time PCR (RT-PCR) test were obtained. Eighty-seven patients with at least 24 h of Holter electrocardiogram (ECG) recording with at least 90% normal–normal interval analysis referred to as the first Holter ECG analysis. Those patients underwent follow-up for the second Holter ECG analysis within 3 months following the first positive RT-PCR tests. The HRV time and frequency domain parameters by means of six standard time domain measures: standard deviation (SD) of all normal sinus RR intervals over 24 h (SDNN), mean of the SDs of all normal sinus RR intervals for all 5-min segments (SDNN index), root-mean-square of successive normal sinus RR interval difference (rMSSD), low-frequency (LF) band, high-frequency (HF) band, and LF/HF ratios were recorded from both the first and second Holter ECG analyses. Moreover, the third Holter ECG analysis was planned for patients if any statistically significant differences were observed among the first and the second Holter ECGs. **Results:** After COVID-19 infection with the second Holter ECG analysis, we found a significant decrease in SDNN, SDNN index, and a significant increase in LF/HF ratio ($P < 0.05$). Moreover, with the third Holter ECG analysis, which was performed in 48 of the 87 patients after 3 months following the second Holter ECG analysis, we have shown that those decreases in SDNN and SDNN index were reversed, and we found a significant increase in LF band and a non-significant decrease in LF/HF ratio ($P = 0.052$). **Conclusion:** The reversal in the changes of HRV parameters that occurred within the first 3 months following COVID-19 diagnosis may be an indicator of acute autonomic dysfunction due to COVID-19 infection.

Keywords: Autonomic nervous system, coronavirus disease 2019 infection, heart rate variability

Introduction

Heart rate variability (HRV) is a physiological phenomenon indicating the variation in the time intervals between consecutive heartbeats referred to as beat-to-beat intervals. HRV measurement is a non-invasive procedure commonly used to evaluate the effects of the autonomic nervous system (ANS) on heart rate (HR).[1] Non-invasive HRV measurement methods are divided into four main categories: time domain, spectral or

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frequency domain, geometric, and non-linear methods. Other methods of HRV measurement are baroreflex sensitivity and HR turbulence. The measurements can be calculated over either a short time as a 5-min electrocardiogram (ECG) recording or as a 24-h long-term ECG recording based on the chosen parameter.[2]

The stability of the selected time domain analysis (such as SDNN, SDNN index, and rMSSD) parameters over time in healthy individuals makes them preferable for the evaluation of ANS function.[3] Increased sympathetic nervous system (SNS) or decreased parasympathetic nervous system (PNS) activity decreases HRV, whereas increased PNS or decreased SNS activity increases HRV.[4]

Moreover, low HRV values have also been used as a risk marker for many cardiac or non-cardiac conditions.[5-8] Aging and psychiatric disorders can lead to reduced HRV, and gender variations have also been shown in HRV.[9,10]

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is the agent virus of coronavirus disease-2019 (COVID-19), has spread worldwide in the past 2 years causing serious morbidity and mortality in millions of patients.[11,12] Two recent clinical trials have suggested that COVID-19 may be associated with autonomic symptoms due to ANS dysfunction.[13,14]

In a recently published case report, reduced HRV was observed in a patient during COVID-19 infection.[15] To the best of our knowledge, no clinical study has yet investigated the effect of COVID-19 on HRV changes. Therefore, this study aimed to determine whether COVID-19 infection decreased HRV acutely due to ANS involvement.

Materials and Methods

This cross-sectional study was conducted in the cardiology department of a high-volume training and research hospital. The study protocol was approved by the local ethics committee of the hospital in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all the study participants.

Patient selection

From the registry of the COVID-19 outpatient clinics between July 2020 and October 2021, 6127 patients with polymerase chain reaction (PCR) results positive for COVID-19 in real-time PCR test of upper respiratory specimens were obtained. All were aged >18 years. Of those patients, 304 had a 24-h Holter ECG recording (Pathfinder, Spacelabs Healthcare, Snoqualmie, WA, USA) at least 6 months before their first positive PCR results were determined from hospital records. The Holter ECG recordings had been ordered due to symptoms of heart palpitation. Exclusion criteria were defined as: a rhythm other than sinus rhythm, diagnosis of sinoatrial atrioventricular conduction defect, use of beta-blockers, diltiazem, digoxin, or other anti-arrhythmic drugs that could cause significant changes in HRV values, any infectious disease diagnosed during Holter ECG recording, use of any medication for a psychiatric disorder, active smoking, a history of thyroid disease, cancer, autoimmune disease, hypertension, diabetes, peripheral neuropathy, metabolic disorders, chronic bronchitis, or asthma (documented or newly diagnosed after referral to internal medicine or neurology outpatient clinics),[16-19] computed tomography (CT) findings of pulmonary involvement in COVID-19, the clinical presentation with at least one symptom (eg, breathlessness, ankle swelling, or fatigue) and/or at least one sign (eg, elevated jugular venous pressure, pulmonary crackles, or peripheral edema) of heart failure.[20] After implementation of the exclusion criteria, 151 patients were eligible for the study.

The 24-h Holter ECG recordings of those 151 patients' data were collected. Only 87 patients with at least 24 h of Holter ECG recording with at least 90% normal–normal interval analysis referred to as the first Holter ECG analysis were accepted as suitable for HRV measurement. Those 87 patients were invited to participate in the study within 3 months following the positive PCR (after completing 14 days in quarantine) and included for analysis [Figure 1].

Time and frequency domain measures of heart rate variability in 24-h Holter electrocardiogram monitoring

The 24-h Holter ECG monitoring of all 87 patients was made using the same recording devices. These 87 ECG recordings, referred to as the second Holter ECG analysis, were found to be sufficient for HRV measurement. The mean HR, three main time-domain standard HRV parameters (standard deviation [SD] of all normal RR [NN] intervals [SDNN], mean of the SDs of all normal sinus RR intervals for all 5-min segments [SDNN index], and the root-mean-square of successive differences between NN intervals [rMSSD]), and three frequency-domain HRV parameters (low-frequency [LF] band, high-frequency [HF] band, and LF/HF ratio) were automatically calculated by the recording devices. All the

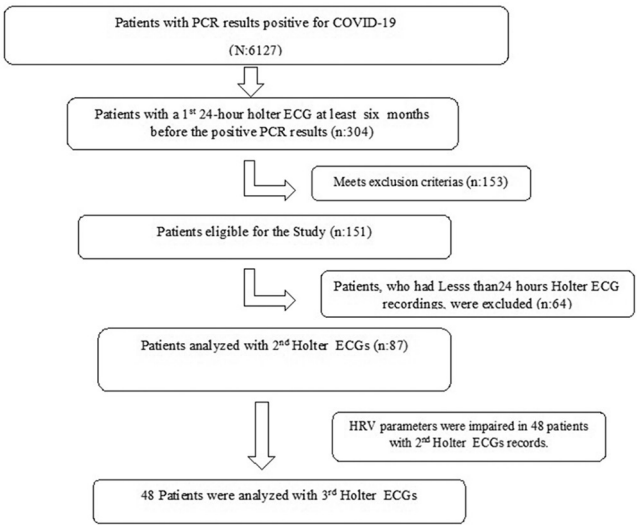


Figure 1: Patient selection criteria for the study

parameters from the first Holter ECG analysis and the second Holter ECG analysis were obtained by a clinician blinded to the characteristics of the patients. A third Holter ECG analysis was planned if any statistically significant differences were observed among the first and the second Holter ECGs.

Each patient's demographic characteristics, clinical characteristics, chronic medications, treatments for COVID-19 (favipiravir, oseltamivir, remdesivir, antibiotics, heparin, and hydroxychloroquine), and laboratory measurements for COVID-19 (creatinine level, white blood cell count, D-dimer level, ferritin level, BNP/proBNP [N-terminal prohormone of brain natriuretic peptide], troponin level, and C-reactive protein level) were collected. In addition, all the patients included in the study were assessed for orthostatic hypotension (OH) using a manual blood pressure cuff. OH was defined as a fall of >20 mmHg systolic and >10 mmHg diastolic after standing for 3 min.[21]

Statistical analysis

All statistical analyses were performed using IBM (SPSS Inc., Chicago, IL, USA) Statistics 25 software. The variables were stated as mean ± SD values when the distribution was normal according to the Kolmogorov–Smirnov test, otherwise as median and minimum–maximum values. Fisher's exact test was used to compare the categorical variables. For comparisons of the repeated measurements (HRV parameters, mean HR, and Holter ECG recording durations), the paired samples *t*-test was applied. $P < 0.05$ was considered statistically significant.

Ethical statement

This study was approved by the University of Health Sciences Turkey, Bursa Yuksek Ihtisas Training and Research Hospital Non-Interventional Health Sciences Research Ethics Committee with the decision number 2011-KAEK-25 2021/04-11, dated 28/04/2021.

Results

The patients comprised 26 (29.9%) males and 61 (70.1%) females, with a mean age of 43.39 ± 14.12 years (minimum: 19 and maximum: 73). None of the patients had syncopal episodes, whereas 11 (%12.6) of the patients stated at least an episode of dizziness that occurs after COVID-19 positivity. The demographic characteristics and chronic medications of the patients are shown in Table 1.

The median time interval between the date of the positive PCR test and the date of the second Holter ECG analysis was 36 days (minimum: 15 and maximum: 83). The laboratory measurements and treatments for COVID-19 are shown in Table 2.

The mean edited Holter ECG recording duration was similar in the first Holter ECG analysis and the second Holter ECG analysis (23.45 ± 0.91 h vs. 23.46 ± 0.87 h, $P = 0.17$). The second Holter ECG analysis showed that there was a significant decrease in SDNN and SDNN index, and an increase in LF/HF ratio ($P < 0.05$). The HF band was decreased but not at a significant level ($P = 0.092$) [Table 3].

Table 1: Demographic, clinical characteristics, and medications of the patients (*n*=87)

Variables	Results
Age (years), mean±SD	43.39±14.12
Male, *n* (%)	26 (29.9)
Hyperlipidemia, *n* (%)	4 (4.6)
CAD, *n* (%)	6 (6.9)
Kidney damage*, *n* (%)	3 (3.4)
ASA, *n* (%)	18 (20.7)
Furosemide, *n* (%)	3 (3.4)
Statins, *n* (%)	7 (8.0)
Syncope, *n* (%)	0
Dizziness, *n* (%)	11 (12.6)
OH, *n* (%)	6 (6.9)

*Glomerular filtration rate <60 ml/min/1.73 m^2. SD: Standard deviation, ASA: Acetylsalicylic acid, CAD: Coronary artery disease, OH: Orthostatic hypotension

Table 2: Laboratory measurements and treatments for coronavirus disease 2019

Variables	Results
Favipiravir, *n* (%)	87 (100)
Hydroxychloroquine, *n* (%)	17 (19.5)
Cephalosporin, *n* (%)	6 (6.9)
Macrolide antibiotic, *n* (%)	2 (2.3)
Quinolone antibiotic, *n* (%)	3 (3.4)
Heparin, *n* (%)	9 (10.3)
WBC, $\times 10^9$/L, mean±SD (*n*=45)	6.36±2.47
Neutrophils, $\times 10^9$/L, mean±SD (*n*=45)	3.38±1.43
Lymphocytes, $\times 10^9$/L, mean±SD (*n*=45)	2.48±0.93
D dimer, mg/L, mean±SD (*n*=45)	0.37±0.05
Hs-CRP, mg/L, median (minimum-maximum) (*n*=45)	10.5 (3.11-53.20)
Hs-cTn-T, ng/L, mean±SD (*n*=45)	3.51±0.76
Ferritin, ng/ml, median (minimum-maximum) (*n*=45)	128.90 (12-574)
BUN, mg/dl, mean±SD (*n*=45)	16.77±6.29
Creatinine, mg/dl, mean±SD (*n*=45)	0.86±0.18
Potassium, mmol/L, mean±SD (*n*=45)	4.65±0.47

WBC: White blood cell, BUN: Blood urea nitrogen, Hs-CRP: High-sensitivity C-reactive Protein, Hs-cTn-T: High-sensitive cardiac troponin T, SD: Standard deviation

To determine whether the changes in the HRV parameters recovered with time, 24-h Holter monitoring was repeated 3 months after the second Holter ECG analysis (third Holter ECG analysis). After implementation of the exclusion criteria and manual removal of artifacts and extra beats, 48 of the third Holter ECG analysis were eligible for comparison with the second Holter ECG analysis. In the comparison, a significant increase was observed in SDNN and SDNN index, and a significant decrease in the LF band ($P < 0.005$). The decrease in LF/HF ratio was not found to be statistically significant ($P = 0.052$) [Table 4].

Table 3: Comparisons of heart rate variability parameters in first Holter electrocardiogram analysis and second Holter electrocardiogram analysis

	First Holter ECG analysis (n=87)	Second Holter ECG analysis (n=87)	P
SDNN, ms, mean±SD	138.77±25.28	129.86±33.18	0.006
SDNN index, ms, mean±SD	42.53±9.08	40.68±10.83	0.032
rMSSD, ms, mean±SD	33.32±7.81	33.72±9.65	0.713
LF, ms^2, mean±SD	1168.97±222.65	1199.60±238.79	0.108
HF, ms^2, mean±SD	454.65±72.74	440.55±79.82	0.092
LF/HF, mean±SD	2.39±0.46	2.56±0.13	0.021
HR bpm, mean±SD	79.68±9.80	78.90±8.78	0.405

SD: Standard deviation, HF: High frequency, HR: Heart rate, LF: Low frequency, rMSSD: Root-mean-square of successive differences between NN intervals, SDNN: SD of all normal RR (NN) intervals, ECG: Electrocardiogram

Table 4: Comparisons of heart rate variability parameters between second Holter electrocardiogram analysis and third Holter electrocardiogram analysis in time interval <3-month group

	Second Holter ECG analysis (n=25)	Third Holter ECG analysis (n=25)	P
Holter ECG duration hours, mean±SD	23.64±0.80	23.30±0.69	0.102
SDNN, ms, mean±SD	130.60±37.97	145.71±38.64	0.013
SDNN index, ms, mean±SD	41.55±11.15	45.85±11.73	0.006
rMSSD, ms, mean±SD	35.89±10.92	37.54±14.71	0.356
LF, ms^2, mean±SD	1141.83±238.31	1073.00±196.18	0.018
HF, ms^2, mean±SD	445.04±81.30	476.93±129.20	0.070
LF/HF, mean±SD	2.56±0.12	2.34±0.50	0.052
HR bpm, mean±SD	79.64±9.32	78.07±10.25	0.209

SD: Standard deviation, HF: High frequency, HR: Heart rate, LF: Low frequency, rMSSD: Root-mean-square of successive differences between NN intervals, SDNN: SD of all normal RR (NN) intervals, ECG: Electrocardiogram

Discussion

The study revealed that a significant decrease was determined in the mean SDNN and SDNN index, a significant increase in LF/HF ratio, and a non-significant decrease in HF band in the patients who had a positive PCR result for COVID-19 within the past 3 months. The third Holter ECG analysis showed that the decrease in SDNN and SDNN index and the increase in LF/HF ratio were reversed 6 months after the second Holter ECG analysis. Moreover, a significant decrease in the LF band was observed.

SDNN, which is the SD of all normal RR (NN) intervals, is the most widely used time-domain HRV parameter. When calculated over 24 h, it indicates all the cyclic components which contribute to HRV.[22-24] A reduced SDNN value mostly refers to sympathetic overactivity or reduced vagal tonus or both.[25] LF band refers to oscillations of HR in the 0.04–0.15 Hz frequency range. It denotes both parasympathetic and sympathetic activities. The LF/HF ratio is another parameter indicating the sympathovagal balance.[26] It expresses the ratio of LF band to HF band which includes 0.16–0.4 Hz oscillations of HR. An increased LF/HF ratio indicates depressed vagal activity.[27,28] The current study findings that the decrease in SDNN and SDNN index and the increase in LF/HF ratio were reversible and may be associated with ANS dysfunction in COVID-19 favoring sympathetic overactivity or reduced vagal tonus for a short period. Similarly, Mittal *et al*.[29] showed that all the HRV parameters were decreased in the early stages of human immunodeficiency virus infection, in which autonomic dysfunction is relatively common.[30] In another clinical trial, the onset of autonomic symptoms occurred within a short interval after COVID-19 symptoms (median: 7 days).[14] In parallel with the results of the third Holter ECG analysis in this study, Asarcikli *et al*.[31] reported that post-COVID patients were more likely to have SDNN >60 msn, RMSSD >40 msn, and low LF/HF ratio compared to healthy individuals, indicating parasympathetic overtones in the post-COVID period.

Previous reports have shown that COVID-19 may cause Guillain–Barré syndrome or other types of peripheral neuropathy.[32,33] Neurological symptoms have been mostly observed in cases with severe COVID-19 infection. Direct viral invasion of the peripheral nervous system by the SARS-Cov-2 virus and/or immune-mediated damage to peripheral nerves have been considered two possible mechanisms of peripheral neuropathy in patients with COVID-19.[34]

The release of cytokines, which are tiny circulating peptides that act as mediators of the inflammatory response, is the primary host reaction in sepsis.[35] The pathophysiology of the systemic inflammatory response syndrome is thought to be an imbalance between the pro- and anti-inflammatory effects of cytokines.[36] Cytokines have wide-ranging impacts on signal transduction mechanisms and can hamper the sympathetic and PNSs on the regulation of HR.[35] For instance, the cytokines of tumor necrosis factor-alpha, interleukin (IL)-1b, and IL-6

increase HR. However, they can also blunt HR responses to beta-adrenergic agonists.[35]

IL-6 levels in the blood have been found to significantly associate with measures of reduced HRV in a variety of clinical situations, according to epidemiological research.[36] The indices of reduced HRV in systemic inflammation showed the highest connection with IL-6 among the cytokines. Gholami *et al*.[36] showed that on BALB/c mice, IL-6 receptor (gp130) is expressed in mouse atria, and incubation of isolated atria with recombinant IL-6 impaired the negative chronotropic response to cholinergic stimulation. Because cytokines could potentially blunt beta-adrenergic signaling, it has been proposed that cytokine overexpression and subsequent loss of beta-adrenergic responsiveness may contribute to the decrease in HRV during inflammation.[37] As a result, there is insufficient evidence to support the hypothesis that impaired responsiveness to the beta-adrenergic system contributes to changes in HRV indexes during systemic inflammation.[38] We did not measure plasma concentrations of catecholamines and cytokines in the study population. Further, studies are needed to elucidate whether COVID-19 affects the ANS in the same way as it affects the peripheral nervous system.

Study limitations

This study had several limitations, primarily that it was conducted in a single center, it was retrospective in design, and the female predominance may have affected the results. Second, anxiety disorders due to COVID-19 disease were not evaluated in the study and these may have contributed to the decrease in HRV values by increasing SNS activity. Third, we did not measure plasma concentrations of cytokines in the study population. Finally, coincident infectious diseases may have affected the results, so it is not possible to state definitively that the findings were specific to COVID-19.

Conclusion

The reversal in the changes of HRV parameters that occurred within the first 3 months following COVID-19 diagnosis may be an indicator of acute autonomic dysfunction due to COVID-19 infection.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

The Relationship between H2FPEF Score and Thrombus Burden in Patients with ST Elevation Myocardial Infarction

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Abstract

Background and Aim: The presence of intracoronary thrombus (ICT) is known to be associated with poor clinical outcomes, including death, in patients diagnosed with ST-segment elevated myocardial infarction (STEMI). Despite this, the predictors of ICT are still uncertain. The aim of our study was to investigate the relationship between thrombus burden (TB) and obesity (H), hypertension (H), atrial fibrillation (F), pulmonary hypertension (P), an age >60 years (E), and E/e' > 9 (F) (H2FPEF) score in STEMI patients. **Methods:** One hundred consecutive STEMI patients were included in the study. Patients were divided into two groups according to the low TB (grades 0–3) and high TB (HTB) (grades 4 and 5) in comparison with the TB grade before percutaneous coronary intervention in coronary angiographic imaging. H2FPEF score was calculated for all patients. **Results:** The H2FPEF score was higher in the HTB group (2.94 ± 1.68 vs. 1.62 ± 1.15, $P < 0.001$). In STEMI patients, the red cell distribution width (odds ratio [OR]: 2.443, 95% confidence interval [CI]: 1.382–4.316; $P = 0.002$) and H2FPEF score (OR: 2.360, 95% CI: 1.447–3.847; $P = 0.001$) were independent predictors of HTB. H2FPEF score above a cutoff level of two predicted HTB with a sensitivity of 78% and a specificity of 50%. **Conclusion:** H2FPEF score may be used as a useful score in predicting HTB in STEMI patients.

Keywords: H2FPEF score, ST-segment elevated myocardial infarction, thrombus burden

Introduction

Increased cardiac risk factors cause an increase in the incidence of ST-elevated myocardial infarction (STEMI).[1] Although primary percutaneous coronary intervention (PCI) is applied in most centers, STEMI is still a common cause of death worldwide.[2] Early risk classification of patients will have positive effects on risk reduction with appropriate therapeutic options in future.[3] The Synergy between Percutaneous Coronary Intervention (SYNTAX) score is useful in predicting the success of the revascularization (surgical or percutaneous invasive intervention) planned to be performed according to the angiographic anatomical results of the patients and the prognosis of the patients. Furthermore, it provides information about the prevalence and complexity of coronary artery disease (CAD).[4] Although there are plans for treatment strategies, the presence of an intracoronary thrombus (ICT) is a risk factor for stent thrombosis and recurrent infarctions in the short and long term, as well as complications such as spasm in the coronary arteries, lack of flow, and distal embolization in patients with an angiographic thrombus.[5]

While the H2FPEF score is current, it is useful in the etiological distinguishing of unexplained shortness of breath (preserved ejection fractionated heart failure or non-cardiac causes). The H2FPEF score consists of a combination of clinical and echocardiographic data (left ventricular (LV) filling and pulmonary artery systolic pressure indicators) such as obesity, hypertension (HT), age, and atrial fibrillation (AF).[6] Several

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studies conducted separately with these parameters have shown the severity and complexity of CAD and its association with adverse events.[7-9]

As far as we know, there is no study investigating the relationship between the thrombus burden (TB) and the H2FPEF score in STEMI patients. Therefore, in our study, we aimed to investigate the relationship between TB and H2FPEF scores in STEMI patients.

Methods

Patient population

One hundred consecutive patients who underwent coronary angiography with the diagnosis of STEMI were included in the study. The diagnosis of STEMI was made in patients consulting with chest pain in at least two adjacent derivations and patients with ST-segment elevation measured from the J point in 12-lead electrocardiography (ECG) (≥2.5 mm in males <40 years of age in V2-V3 derivations, ≥2 mm in males over 40 years of age, ≥1.5 mm in females over 40 years of age, and/or ≥1 mm in other derivations (in the absence of LV hypertrophy or left bundle branch block).[10]

Patients with a history of coronary artery bypass grafting (CABG), valve surgery, PCI, or diagnosed heart failure with reduced LV function (LV ejection fraction [LVEF] ≤40%), history of stroke, chronic kidney disease (estimated glomerular filtration rate <30 (ml/min/1.73 m^2), an active infection, known coagulopathy, malignancy, chronic pulmonary embolism, diagnosis of pulmonary HT, regular alcohol use (>20 g/day), chronic obstructive pulmonary disease, permanent heart pacemaker or mitral annular calcification, moderate heart valve disease, mitral valve repair or a prosthetic valve, thyroid dysfunction, pre-PCI resuscitation, upper segment elevation or depression in the aVR lead, and receiving thrombolytic therapy or under 18 years of age were not included in the study.

The hospital's electronic medical records were used to obtain the data on patients' laboratory values. This study received the ethical committee's approval (decision no: 2022-YÖNP-0019), and it was conducted according to the Declaration of Helsinki.

Blood analysis

Blood samples were taken from antecubital peripheral veins at the time of admission. All hematological parameters were studied using a Mindray BC-6000 (Mindray Co., Shenzhen, China) hematology device. Biochemical parameters were studied using a Roche COBAS c 701 (Roche Diagnostics, GmbH, Mannheim, Germany) device. The lipid profile was studied within the first 24 h following 12 h of fasting.

Echocardiographic imaging protocol

Blood pressure (BP) levels were measured just before starting echocardiographic imaging. Echocardiographic examinations were performed following the patients' BP measurements. All patients underwent echocardiographic examinations by connecting simultaneous ECG using a Vivid 7 Pro device (GE, Vingmed, Horten, Norway). Echocardiographic measurements were performed in the left lateral position. The LVEF was calculated using the modified Simpson formula. Systolic pulmonary artery pressure (sPAP) was calculated using the formula sPAP = 4 × (highest tricuspid regurgitation rate)^2 + right atrial pressure. LV filling pressures were obtained by the ratio of early mitral flow rate (E) to early diastolic mitral annular tissue rate (e ').[11]

H2FPEF score

When calculating the H2FPEF score, six parameters were used, and the calculation was made as in the literature (obesity 2 points, AF 3 points, and other parameters 1 point).[12]

1 – Obesity (body mass index >30 kg/m^2)
2 – Age >60
3 – AF
4 – Use of 2 or more antihypertensive drugs
5 – Pulmonary artery systolic pressure >35 mmHg
6 – E/e ' >9.

Coronary angiography and thrombus burden classification

Coronary angiographies (GE Healthcare Innova 2100, New Jersey, USA) were performed by an experienced cardiologist using the standard Judkins technique and iobitridol (Xenetix-350, Guerbet BP, France) with the femoral or radial approach. Angiographic images were evaluated by two experienced cardiologists with the digital system for a quantitative analysis of images obtained from at least two different angles.

The angiographic TB was classified as in the literature:[13] grade 0: No thrombus, grade 1: A possible thrombus (turbidity, irregular lesion contour, and reduced contrast intensity), grade 2: The presence of a thrombus with a vessel diameter of <½ in multiple angiographic projections, grade 3: The presence of a thrombus with vessel diameter of >½ and <2 in multiple angiographic projections, grade 4: The presence of a thrombus with vessel diameter of >2 in multiple angiographic projections, and grade 5: Obstruction of the entire thrombus and vessel. The patients were divided into two groups according to low-TB (LTB) (grades 0–3) and high-TB (HTB) groups (grades 4 and 5).

Statistical analysis

An SPSS 19.0 (SPSS Inc., Chicago, IL, USA) application was used for statistical analysis. The distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test. Data were presented as mean ± standard deviation or median (interquartile range). Categorical variables are expressed as percentages and numbers. A *t*-test and the Mann–Whitney U-test or Kruskal–Wallis tests were used to compare normal and nonnormally distributed parameters, respectively. The Chi-square or Fisher's exact tests were used to compare the probability ratios of categorical variables. Single and multiple logistic regression analyses were performed to predict HTB in STEMI patients. The Hosmer–Lemeshow test was used to evaluate the model fit. Receiver operating characteristic (ROC) curves were created for HTB of H2FPEF, and cutoff values were determined. *P* values were found statistically significant <0.05.

Ethical statement

The study approval was obtained from the Ethics Committee of Clinical Research of Canakkale Onsekiz Mart University (Date: 2022.04.27 and Decision no: 2022-YÖNP-0019). The study was performed in accordance with the Declaration of Helsinki.

Results

Our study consisted of a total of 100 patients diagnosed with STEMI, 76 males and 24 females. The mean age was 63.98 ± 9.18 years in the HTB group, the mean age was 62.20 ± 10.25 years in the LTB group. A high red cell distribution width (RDW) (14.69 ± 1.25 vs. 13.92 ± 0.99, $P = 0.001$) and a high H2FPEF score (2.94 ± 1.68 vs. 1.62 ± 1.15, $P < 0.001$) were found in the HTB group. Our study groups mostly had proximal left anterior descending coronary artery (LAD) lesions. The number of our patients with LAD bifurcation lesions was three patients and it was not statistically significant. As shown in Table 1, there were no statistical differences between the groups in terms of other routine serum biomarkers. The demographic and laboratory data of the patients are shown in Table 1.

As shown in Table 2, a statistically significant relationship was observed between the H2FPEF score and TB ($P < 0.001$). When the H2FPEF score was divided into three groups according to low (0–1), medium (2–5), and high (≥6) scores, it was seen that 35, 60, and five patients were distributed among the groups, respectively [Table 2].

As a result of the univariate analysis of the variables for predicting HTB, RDW (odds ratio [OR]: 1.989, 95% confidence interval [CI]: 1.1269–3.116; $P = 0.003$), Killip status (OR: 11.294, 95% CI: 2.435–52.379; $P = 0.002$), and the H2FPEF score were found as (OR: 1.937, 95% CI: 1.371–2.738; $P < 0.001$), whereas RDW (OR: 2.443, 95% CI: 1.382–4.316; $P = 0.002$) and the H2FPEF score (OR: 2.360, 95% CI: 1.447–3.847; $P = 0.001$) were found to be significant in multivariate analysis. In the Hosmer–Lemeshow test ($\chi^2 = 9.60$, $P = 0.294$), there was a good model fit [Table 3]. The H2FPEF score was significantly higher in patients with a HTB (2.94 ± 1.68 vs. 1.62 ± 1.15; $P < 0.001$) [Figure 1].

ROC curve analysis was performed to evaluate the H2FPEF score in predicting HTB. The cutoff value of HTB ≥2 (area under the curve: 0.724, 95% CI 0.626–0.822, $P < 0.001$ with 78% sensitivity and 50% specificity) [Figure 2].

A significant increase in H2FPEF score was observed for the responsible lesion LAD or RCA ($P < 0.001$) and right coronary artery (RCA) or circumflex artery (CX) ($P = 0.037$) differentiation [Figure 3].

Discussion

The important findings of our study related to the TB of the H2FPEF score in STEMI patients were as follows: (1) higher H2FPEF score values were found in the HTB group; (2) the H2FPEF score and RDW were found to be independent predictors of HTB in STEMI patients; (3) the H2FPEF score had a sensitivity of 78%, a specificity of 50%, and an AUC of 0.72 for predicting a HTB.

Early PCI is the recommended revascularization method in STEMI patients.[14] Emergency revascularization plays a key role in the perfusion of myocardial tissue since inadequate perfusion can be presented with various clinical outcomes ranging from an increase in infarction sizes to heart failure.[15,16] STEMI is a process that continues with the formation of a thrombus following the rupture or erosion of the atherosclerotic plaque in the epicardial coronary arteries.[17] An ICT burden is associated with poor clinical outcomes including decreased ventricular functions, increased infarction dimensions, stent

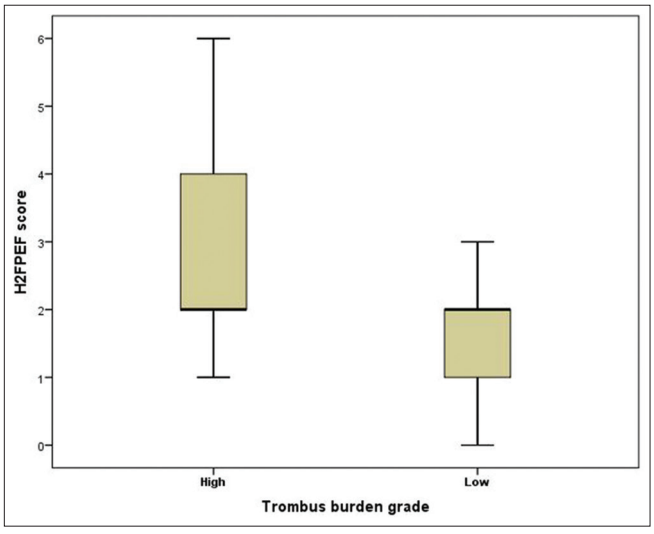


Figure 1: H2FPEF score values according to thrombus burden grade

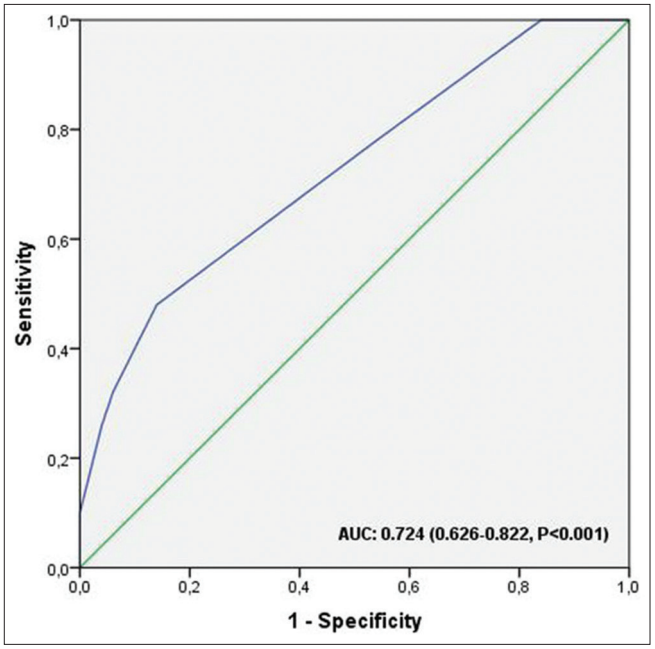


Figure 2: Receiver operating characteristic curves for H2FPEF score values for the prediction of thrombus burden grade

Table 1: Demographic, clinical, laboratory, and angiographic features of patients

	HTB (*n*=50), *n* (%)	LTB (*n*=50), *n* (%)	*P*
H2FPEF score	2.94±1.68	1.62±1.15	<0.001
Age (years)	63.98±9.18	62.20±10.25	0.363
Gender (male/female)	39/11	37/13	0.640
BMI (kg/m^2)	24.88±1.46	25.14±1.52	0.387
Smoking	18 (36)	20 (40)	0.680
Hypertension	27 (54)	29 (58)	0.687
Diabetes mellitus	15 (30)	14 (28)	0.826
Family history of CAD	8 (16)	3 (6)	0.110
SBP (mmHg)	104.58±19.42	107.44±20.71	0.478
DBP (mmHg)	81.66±7.71	80.60±7.80	0.521
Laboratory data			
Glucose (mg/dl)	113 (922.25-172)	105.5 (91-125.2)	0.387
Creatinine (mg/dl)	0.86±0.15	0.81±0.14	0.091
Hemoglobin (g/dl)	12.69±2.29	13.17±1.89	0.252
WBC count (10^9/L)	8.03±2.15	8.31±2.15	0.522
Platelet count (10^9/L)	259.12±93.33	252.82±56.68	0.685
Red cell distribution width (%)	14.69±1.25	13.92±0.99	0.001
LDL-cholesterol (mg/dl)	113.4 (77.9-160)	114.3 (83.7-142.9)	0.962
HDL-cholesterol (mg/dl)	41.80±13.10	41.67±10.50	0.956
Triglyceride (mg/dl)	106.15 (84.1-136.9)	118.5 (99.1-149.7)	0.152
Cardiac Tn (ng/L)	43.5 (22-63)	39.2 (23.5-73.3)	0.588
Angiographic data			
IRA			
LAD	33 (66)	38 (76)	0.403
LCX	5 (10)	2 (4)	
RCA	12 (24)	10 (20)	
Killip II-IV	11 (22)	7 (14)	0.298
Pain to balloon time (min)	275 (133.75-354.75)	200 (120-320)	0.141
Echocardiographic data			
LVEF (%)	48.3±4.88	49.9±6.84	0.187
LVEDD (mm)	39.9±9.3	40.3±9.2	0.830
LVESD (mm)	27.6±6.2	28±6.1	0.710
LA (mm)	28.8±5.4	29.9±5.49	0.327
RA (mm)	24±7.51	22.6±6.08	0.310
IVS (mm)	11.8±1.1	11.4±1.3	0.211
PW (mm)	8.3±0.8	8.5±0.9	0.441
Medical therapy before admission			
Aspirin	28 (56)	25 (50)	0.548
Antiplatelet	3 (6)	2 (4)	0.646
Beta-blocker	4 (8)	9 (18)	0.137
Statin	6 (12)	4 (8)	0.505
ACEI/ARB	10 (20)	4 (8)	0.084

BMI: Body mass index, CAD: Coronary artery disease, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, WBC: White blood cell, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, Tn: Troponin, IRA: Infarct-related artery, LAD: Left anterior descending artery, LCx: Left circumflex artery, RCA: Right coronary artery, LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, LA: Left atrium, RA: Right atrium, IVS: Interventricular septum, PW: Posterior wall, ACEI: Angiotensinogen converting enzyme inhibitor, ARB: Angiotensin receptor blocker, LTB: Low thrombus burden, HTB: High thrombus burden, H2FPEF: Obesity (H), hypertension (H), atrial fibrillation (F), pulmonary hypertension (P), an age >60 years (E), and E/e' > 9 (F)

thrombosis, and increased mortality. In addition, a HTB is associated with increased 30-day mortality in STEMI patients.[18,19] The pathogenesis of ICT development has not been fully understood. It is known that inflammation, in particular, triggers plaque rupture and thrombus formation.[20] HTB may cause distal embolization as well as undesirable complications due to decreased epicardial blood flow and lead to a decrease in the success of the procedure. In addition to all these, RDW, which was simply obtained from hemogram values, was shown to be associated with TB in STEMI patients, and similar results were obtained in our study results.[21] In a study of STEMI and non-ST-segment elevation myocardial infarction (NSTEMI) patients, basal troponin values were shown to be predictive of TB,[22] and similar results could not be obtained in our study.

We consider that the most important reason why similar results could not be obtained in our study may be that only STEMI patients were included in our study. Although LVEF decreases are less common in acute coronary syndrome (ACS) patients after primary PCI, as seen in our study, we think that the higher decrease in H2FPEF score LVEF values in STEMI patients will be a stimulant for the clinician in terms of TB.

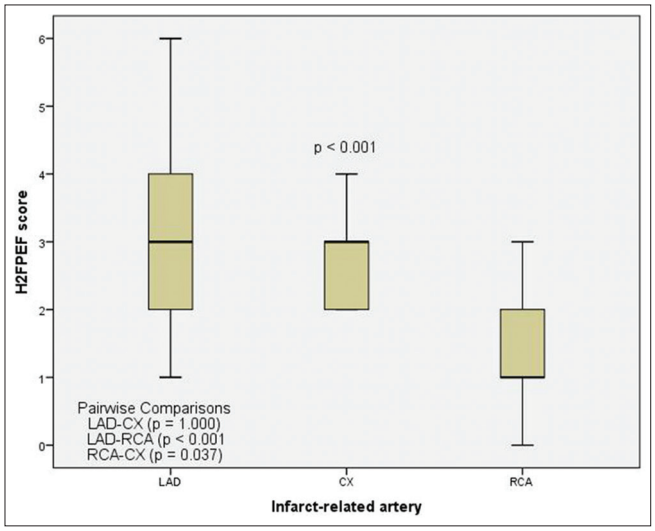


Figure 3: Relationship between culprit vessels and H2FPEF score

Table 2: Association of the total H2FPEF score and high and low thrombus burden result

H2FPEF score (*n*=100)	HTB (*n*=50), *n* (%)	LTB (*n*=50), *n* (%)	*P*
Low 0-1 (*n*=35)			
0	0	8 (16)	<0.001
1	11 (22)	15 (30)	
Intermediate 2-5 (*n*=60)			
2	15 (30)	20 (40)	
3	8 (16)	4 (8)	
4	3 (6)	1 (2)	
5	8 (16)	2 (4)	
High ≥6 (*n*=5)			
6	5 (10)	0	

LTB: Low thrombus burden, HTB: High thrombus burden, H2FPEF: Obesity (H), hypertension (H), atrial fibrillation (F), pulmonary hypertension (P), an age >60 years (E), and E/e' > 9 (F)

Studies have shown that those with HTB are older compared to those with a LTB, and the frequency of HT is more common in HTB patients.[23,24] The lack of similar results in our study supports the position that the pathogenesis of ICT development is not clear.

It has been shown that there may be significant differences in age values in patients with a diagnosis of STEMI, depending on the infarct-related artery (IRA).[25] As seen in our study, the H2FPEF score, including the age component, was found to be associated with the IRA.

The H2FPEF score is the current score used to distinguish unexplained shortness of breath from preserved ejection fractional heart failure or non-cardiac causes. However, the H2FPEF score has been shown to predict nephropathy after revascularization in patients diagnosed with ACS.[26] In another current study, its relationship between H2FPEF and SYNTAX scores was shown in patients with NSTEMI.[27] As can be understood from the examples in the literature, the H2FPEF score helps the clinician with various issues besides its main purpose. In addition, as seen in our study, the H2FPEF score was associated with HTB in STEMI patients.

Study limitations

One of the limitations of our study was the relatively low number of cases and the fact that it was a single center after the wide exclusion criteria. In our study, TB was decided by evaluating angiographic images, and since STEMI patients needed urgent revascularization, specific imaging methods such as intravascular ultrasound and optical coherence tomography were not used. In addition, data obtained in our study evaluating the H2FPEF score in newly diagnosed STEMI patients were short-term follow-up data; the long-term usability of such data has not been investigated, and multicenter studies are needed to confirm the H2FPEF score results and cutoff values in STEMI patients.

Conclusions

TB can be easily predicted in STEMI patients with an H2FPEF score. The H2FPEF score may be helpful in TB management

Table 3: Univariate and multivariate analysis for prediction of high thrombus burden

Variables	Univariate OR (95% CI)	*P*	Multivariate OR (95% CI)	*P*
Family history of CAD	1.194 (0.371-3.841)	0.766	0.595 (0.126-2.814)	0.512
Smoking	0.844 (0.376-1.894)	0.680	0.540 (0.184-1.583)	0.261
Previous statin use	1.568 (0.414-5.935)	0.508	0.723 (0.114-4.597)	0.731
Triglyceride	0.997 (0.987-1.006)	0.520	0.993 (0.981-1.005)	0.278
Cardiac Tn	0.196 (0.980-1.004)	0.196	0.986 (0.971-1.002)	0.085
Red cell distribution width	1.989 (1.269-3.116)	0.003	2.443 (1.382-4.316)	0.002
Killip status, ≥II	11.294 (2.435-52.379)	0.002	2.970 (0.682-12.937)	0.147
Pain to balloon time	1.001 (0.998-1.003)	0.617	1.003 (1.000-1.007)	0.060
H2FPEF score	1.937 (1.371-2.738)	<0.001	2.360 (1.447-3.847)	0.001

CAD: Coronary artery disease, Tn: Troponin, OR: Odds ratio, CI: Confidence interval, H2FPEF: Obesity (H), hypertension (H), atrial fibrillation (F), pulmonary hypertension (P), an age >60 years (E), and E/e' > 9 (F)

for high-risk patients and to avoid undesirable clinical outcomes that may occur due to TB. According to the current guidelines, additional medical treatments such as glycoprotein IIb/IIIa inhibitors are recommended in STEMI patients in the presence of a massive thrombus or in cases where a sufficient flow degree cannot be achieved during revascularization. The H2FPEF score can be helpful in medical treatment management such as the use of a glycoprotein IIb/IIIa inhibitor and thus can be used in the treatment management of high-risk individuals.

Declaration of patient consent

Both verbal and written informed consents were obtained from the participants.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Evaluation of the Heart Rate Variability in Cardiogenic Vertigo Patients

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Abstract

Background: The detection of documented cardiac arrhythmias during vertigo attacks and vertigo resolution through the treatment of arrhythmias is defined as cardiogenic vertigo (CV). **Aim and Objective:** We evaluate the impact of arrhythmias on vertigo and assess the types of arrhythmias and heart rate variability using 24-h ambulatory electrocardiogram (Holter) monitoring. **Patients and Methods:** The study included 70 patients with CV. Demographic, clinical, and laboratory data were analyzed. Holter monitoring and echocardiography were conducted, and the results were analyzed. **Results:** The average age of the patient group was 46.7 ± 8.6 years, and the number of female patients (65.7%) was almost twice that of the number of male patients. Clinical features, such as thyroid dysfunction (4.2%), diabetes mellitus (22%), dyslipidemia (27.1%), hypertension (34%), iron deficiency anemia (5.7%), and smoking status (21.4%), were identified. Vertigo manifested in the presence of syncopal episodes in 18 (25.7%) patients, and 47 (67.1%) patients presented with spinning during the episodes. Most of the vertigo attacks were induced by standing in 27 patients (38.6%) and lasted for only a few seconds in 52 (74.2%) patients. In terms of the Holter monitoring records, tachycardia-bradycardia was the syndrome that was observed the most. The computed average low-to-high frequency ratio was 2.24 ± 1.6. **Conclusion:** This study showed that arrhythmias could increase the risk of vertigo attacks in patients with no known history of heart disease. The patients had significant autonomic nervous system dysfunction in favor of the sympathetic system.

Keywords: Arrhythmia, heart rate variability, Holter monitoring, syncope, vertigo

Introduction

Vertigo is the most typical cause of dizziness brought on by cardiovascular diseases.[1] Vertigo can sometimes be accompanied by syncope. Cardiovascular disorders are the second most frequent cause of syncope.[2] Since cardiac syncope causes morbidity and mortality, the underlying causes need to be treated.[3]

If vertigo attacks are accompanied by syncope, diagnosing cardiogenic vertigo (CV) can be difficult.[4] Short recurrent rotatory vertigo may be the first presentation of arrhythmia.[5] When this condition is accompanied by syncope, serious problems can occur, ranging from trauma to cardiac death.

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In this study, we assessed the clinical characteristics of patients with CV caused by arrhythmias and evaluate the types of arrhythmias and heart rate variability (HRV) using Holter monitoring.

Patients and Methods

Selection of participants

The study was conducted retrospectively between 2018 and 2022. The study comprised patients who were referred to cardiology with dizzy complaints by otolaryngologists, neurologists, and psychiatrists. Recurrent episodes of spontaneous reversion or nonreturning vertigo, onset

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over 18 years of age, vertigo duration <1 min, documentation of heart diseases during an attack of vertigo, response to appropriate treatments for heart disease, and inability to be better explained by another diagnosis were defined as diagnostic criteria of CV according to the classification of the Bárány Society (2015). Patients with valvular heart disease, coronary artery disease, cardiomyopathy, acute coronary syndrome, using beta-blockers due to arrhythmia, hypertension and diabetes patients who are unstable despite drug use, no vertigo attack during rhythm recording, and whose data could not be accessed were excluded from the study. Seventy patients who had been diagnosed with CV were included in the study.

Study protocol

Routine blood tests were performed, along with echocardiography using a Philips brand ultrasonography device (Model HD7 X E). The patients were also evaluated by a cardiologist who was not aware of the study by performing a 24-h standard 3-channel (leads V1, V2, and V5) Holter electrocardiogram (ECG). After manually adjusting the intervals of consecutive R waves, all recordings were analyzed using a Century 2000/3000 hV Package System. According to the North American Society of Pacing and Electrophysiology, the recordings were taken as the mean of five different 5-min periods.[6] Low frequency (LF) (0.04–0.15 Hz) and high frequency (HF) (0.16–0.4 Hz) components were defined as the power between 0.003 MHz and 0.40 Hz on the heart rate spectrum.

Ethical statement

The study protocol was authorized by the Local Ethics Committee (Gazi Yasargil Training and Research Hospital; no. 2022-109, June 11, 2022), and it followed the Declaration of Helsinki's ethical guidelines for human testing (2013).

Statistical methods

All analyses were carried out using the SPSS program (version 24.0, Chicago, IL, USA). According to the data distribution, the initial continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range). Frequencies and percentages are used to express categorical variables. The Kolmogorov–Smirnov or Shapiro–Wilk tests were used to determine whether the variables' distributions were normal. To compare continuous variables, the Student's *t*-test or the Mann–Whitney *U* tests were employed, and to compare nominal variables, the Chi-squared or Fisher's exact tests were used. The level of significance was set at $P < 0.05$.

Results

The average age of the patient group was 46.7 ± 8.6 years, with nearly twice as many female patients (65.7%) as male patients. Clinical features, such as thyroid dysfunction (4.2%), diabetes mellitus (22%), dyslipidemia (27.1%), hypertension (34%), iron deficiency anemia (5.7%), and smoking status (21.4%) were identified. The mean values for left atrium diameter 3.64 ± 0.19 cm, left ventricle diastolic diameter 4.89 ± 0.31 cm, left ventricle systolic diameter 2.53 ± 0.40 cm, and ejection fraction 61.8% ±5.5% were measured during the echocardiographic examinations. Measurements were also taken for hemoglobin 13.3 ± 2.4 g/dl, glucose 105.1 ± 34.2 mg/dl, fe 64.8 ± 28.7 ml/ng, thyroid-stimulating hormone 2.39 ± 1.1 mIU/L, free triiodothyronine 3 2.49 ± 1.0 pg/ml, low-density lipoprotein 112.0 ± 30.9 mg/dl, and high-density lipoprotein 40.3 ± 8.5 mg/dl [Table 1]. Vertigo occurred without syncopal attacks in 18 (25.7%) patients. The duration of the symptoms of patients with recurrent isolated vertigo ranged from days (22.9%) to years (8.6%), and 47 (67.1%) patients presented with spinning during the episodes. The majority of the vertigo attacks were induced by standing (*n* = 27; 38.6%), fatigue (*n* = 16; 22.9%), walking (*n* = 16; 22.9%), and eating (*n* = 11; 15.7%). Palpitations (*n* = 48; 68.6%), arm twitching (*n* = 11; 15.7%), and dyspnea (*n* = 11; 15.7%) were found to be an associated symptoms [Table 2]. Figure 1 shows the Holter-ECG findings in patients with vertigo. For the HRV, SD of the NN (R-R) intervals (SDNN) 103.4 ± 46.7 ms, root mean square of the successive differences (RMSSD) 33.7 ± 23.5 ms, the proportion of NN50 divided by the total number of NN (R-R) intervals (pNN50) 10.7% ±8.6%, LF 67.3 ± 17.5 nu, HF 31.7 ± 9.2 nu, and LF/HF 2.24 ± 1.6 were measured [Table 3].

Table 1: Clinical characteristics, echocardiography, and laboratory test of vertigo patients

Parameters	Case (*n*=70), *n* (%)
Age	46.7±8.6
Sex (female)	46 (65.7)
Thyroid dysfunction	3 (4.2)
Diabetes mellitus	16 (22)
DL	19 (27.1)
Hypertension	24 (34)
Iron deficiency anemia	4 (5.7)
Smoking	15 (21.4)
Echocardıography	
LAD (cm)	3.64±0.19
LVDD (cm)	4.89±0.31
LVSD (cm)	2.53±0.40
EF (%)	61.8±5.5
Laboratory	
Hemoglobin (g/dl)	13.3±2.4
Glucose (mg/dl)	105.1±34.2
Fe (ml/ng)	64.8±28.7
TSH (mIU/l)	2.39±1.1
fT3 (pg/ml)	2.49±1.0
LDL (mg/dl)	112.0±30.9
HDL (mg/dl)	40.3±8.5

Values are presented as mean±SD as appropriate. DL: Dyslipidemia, LAD: Left atrium diameter, LVDD: Left ventricle diastolic diameter, LVSD: Left ventricle systolic diameter, EF: Ejection fraction, TSH: Thyroid-stimulating hormone, fT3: Free triiodothyronine, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, SD: Standard deviation

Table 2: Characteristics of vertigo patients

Vertigo	Case (n=70), n (%)
Spinning nature	47 (67.1)
Syncope	18 (25.7)
Frequency	
Day	16 (22.9)
Week	42 (60)
Month	6 (8.6)
Year	6 (8.6)
Duration	
3-5 s	27 (38.6)
5-10 s	25 (35.7)
>10 s	9 (12.9)
A few minute	9 (12.9)
Trigger factors	
Eating	11 (15.7)
Standing	27 (38.6)
Fatigue	16 (22.9)
Walking	16 (22.9)
Accompanying symptoms	
Palpitation	48 (68.6)
Arm twitching	11 (15.7)
Dyspnea	11 (15.7)

Table 3: Heart rate variability of vertigo patients

	Case (n=70)
SDNN (ms)	103.4±46.7
RMSSD (ms)	33.7±23.5
pNN50 (%)	10.7±8.6
LF (Nu)	67.3±17.5
HF (Nu)	31.7±9.2
LF/HF	2.24±1.6

Values are expressed as mean±SD as appropriate. SD: Standard deviation, SDNN: SD of the NN (R-R) intervals, RMSSD: Root mean square of the successive differences, pNN50: The proportion of NN50 divided by the total number of NN (R-R) intervals, LF: Low frequency, HF: High frequency

Discussion

This study revealed that patients suffering from arrhythmias can develop vertigo, which is generally induced by standing. In addition, the patients had significant autonomic nervous system dysfunction in favor of the sympathetic system.

Vertigo occurs at a rate of 2.4% throughout life and accounts for 17.1% of all complaints of dizziness in the general population but nearly half of the complaints of dizziness in the elderly.[7,8] It develops mainly after arrhythmia in younger people.[9] The number of patients without cardiovascular disease who complained of palpitations during vertigo attacks is not small. The importance of early CV diagnosis in decreasing morbidity and mortality from arrhythmia complications such as cardiac arrest, syncope, and embolic stroke is crucial.[10]

When structural heart diseases are excluded, problems such as underlying cardiac conduction system diseases, diabetes,

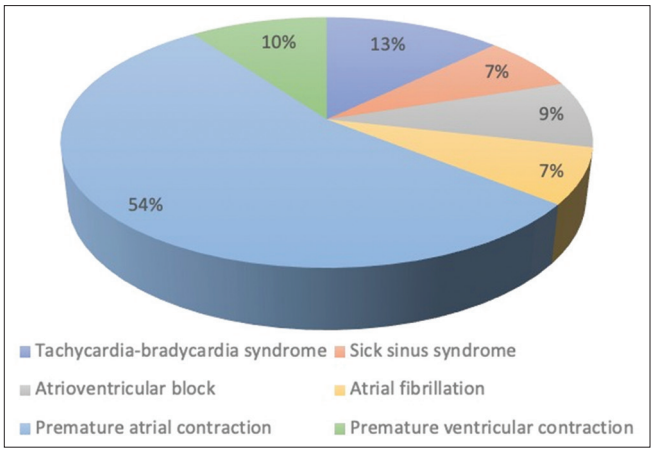


Figure 1: Holter ECG findings in patients with vertigo. ECG = Electrocardiogram

thyroid dysfunction, and iron deficiency may predispose the patient to arrhythmia. When the heart does not provide enough cardiac output, the brain suffers from hypoperfusion and malfunctions, resulting in syncope. In bradyarrhythmias, the heart beats too slowly to generate enough flow, resulting in cerebral hypoperfusion, whereas tachyarrhythmias cause the heart to beat too fast, resulting in inadequate ventricular filling and poor cardiac output.[11] We can expect isolated vertigo without loss of consciousness as a result of the temporary or moderate reduction in brain perfusion induced by arrhythmias.[12] CV can develop in isolation or with syncope, depending on a variety of factors including the duration or severity of brain hypoperfusion, individual differences in the cerebral vasculature, and individual vulnerability to decreased perfusion.

The attacks were generally spontaneous, and vertigo could be also provoked by standing, fatigue, walking, or eating. Other cardiac or neurological symptoms, such as palpitation, arms twitching, and dyspnea, are frequently associated with CV.[13] Remarkably, CV lasted only a few seconds or minutes, meeting the diagnostic criteria for vestibular paroxysmia.[14] In our study, most of the vertigo attacks were induced by standing in 27 patients (38.6%) and lasted for only a few seconds in 52 (74.2%) patients.

Holter monitoring is the most basic method for determining whether a particular type of arrhythmia causes vertigo. In our study, 54% premature atrial contraction, 10% premature ventricular contraction, 7% sick sinus syndrome, 9% atrioventricular block, 13% tachycardia-bradycardia syndrome, and 7% atrial fibrillation were observed. After COVID-19 infection, premature atrial contraction arrhythmias may occur as a consequence of autonomic dysfunction caused by excessive catecholamine release. Malayala *et al*.[15] reported that patients with COVID-19 developed vertigo due to arrhythmia a few weeks after treatment.

Sympathoneural dysfunctions are frequent in patients with posttreatment vertigo. Residual vertigo could be caused

by sympathoneural autonomic dysfunction.[16] HRV can be used to detect sympathetic-parasympathetic balance in the autonomic nervous system.[17] It is shown that HF, RMSSD, and pNN50 are parasympathetic activity markers, whereas LF and SDNN are sympathetic activity markers.[18] Hayano *et al*.[19] reported that fatal arrhythmias developed in patients with SDNN <50 ms. SDNN <70 ms in patients undergoing percutaneous coronary intervention was associated with premature contractions.[20] In some studies, RMSSD values of more than 28 ms and pNN50 values of more than 5.5% were associated with bradycardia.[21,22] Increased cardiac sympathetic activity was reported to be associated with high LF and LF/HF ratios.[23] In our study, tachycardia-bradycardia syndrome and high LF/HF ratio were observed.

Variations in HRV time (pNN50, RMSSD, SDNN) and frequency (LF, HF) domain indices have frequently been seen in chronic diseases, such as diabetes and hypertension, and have been linked to cardiac autonomic dysfunction.[24] A reduction in HRV is a measure of decreased parasympathetic and increased sympathetic tone and has long been considered to be having a detrimental effect on the prognosis of cardiovascular disease.[25] Sympathetic overactivation and autonomous imbalance play important roles in the pathogenesis of hypertension.[26] Abnormal HRV was demonstrated in hypertensive patients in previous studies.[27] Sheng *et al*.[28] found that the LF/HF ratio was higher in white-coat patients than in sustained hypertension patients. Menezes Ada *et al*.[29] reported that LF power decreased and LF/HF increased before treatment and regressed to normal after treatment. After 12 months of anti-hypertensive medication, Maciorowska *et al*.[30] observed a considerable improvement in SDNN, pNN50, and RMSDD. On the other hand, excessive autonomic fluctuation, represented by higher HRV in patients with hypertension, was associated with an increased risk of atrial fibrillation.[31] It was observed at a low rate (7%) in our study. Controlling hypertension has a beneficial effect on HRV and could prevent arrhythmias.

In a meta-analysis, patients with diabetes were found to have considerably lower HRV values.[32] Patients who were exercising and under the control of medications demonstrated higher HRV values.[21] Agashe and Petak.[33] reported that autonomic dysfunction in diabetes patients can be determined more easily by calculating the frequency domains of HRV. Martinez and Okoshi.[34] did not include healthy controls in their study. They suggested that there would be no significant differences in terms of HRV time domain between the patients under treatment and the healthy controls. Patients' frequency domain of HRV was only calculated. As a result, they defined an LF/HF ratio >1 as a sympathetic system dysfunction. In our study, this ratio was found to be higher.

Study limitations

Our study was retrospective and relatively small. Holter monitoring was only 24-h. In the future, an implantable loop recorder could be used to identify whether there are different rhythms during vertigo attacks. Electrophysiological studies were not conducted. Cardiac magnetic resonance imaging was not performed. In addition, the absence of control patients is one of the limitations of this study.

Conclusion

This study showed that arrhythmias could increase the risk of vertigo attacks in patients with no known history of heart disease. Standing-induced attacks were the most and lasted only a few seconds. The patients had significant autonomic nervous system dysfunction in favor of the sympathetic system. Additional studies are needed to determine the role of autonomic nerve dysfunction as a prognostic indicator in patients with CV.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Association of Serum Pleiotrophin Levels with Acute Coronary Syndrome

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Abstract

Background and Aim: Pleiotrophin (PTN) is known as a multifunctional cytokine and a neurite outgrowth-promoting factor and appears as an angiogenic response to numerous processes such as ischemic injury affecting a region of the heart and the brain. We evaluated the serum concentration of PTN in clients with acute coronary syndrome (ACS), besides assessing the clients with no visible stenosis (NVS) in elective invasive coronary angiography (ICA). **Materials and Methods:** Through conducting a prospective research, we compared 110 consecutive patients with ACS referred for ICA with 47 stable patients with NVS. **Results:** We determined that ACS group had higher PTN levels than NVS group (244.94 ± 89.09 vs. 199.46 ± 70.71, $P < 0.001$). Based on the multivariate analysis, besides older age, smoking, and white blood cell, PTN ≥207.66 ng/ml remained independently associated with ACS. **Conclusion:** The serum concentration of PTN in clients was determined to have an association with ACS. The potential diagnostic and prognostic impact of PTN in ischemic heart disease may deserve to be further evaluated. PTN may also be studied as an angiogenic therapeutic factor in patients with ACS in additional studies.

Keywords: Acute coronary syndrome, angiogenesis, pleiotrophin

Introduction

Acute coronary syndrome (ACS) is considered a significant factor that leads to morbidity and mortality worldwide, affecting more than 1 million patients admitted annually to hospitals in the United States.[1] Despite recent advances in drug therapy and interventional techniques, the survivors of ACS can suffer from repetitive infarction and experience the risk of mortality at least five or six times higher than the population who are not affected by the coronary artery disease (CAD).[2] Alternative treatments are investigated for ACS besides resorting to traditional strategies. Angiogenesis occurs with the remodeling of new blood vessels growing out of the existing vasculature. Numerous cells secrete pro-angiogenic agents under the conditions of ischemia and hypoxia. Therapeutic vascular growth stimulated by proteins or genes is asserted to potentially enhance blood flow to ischemic tissue by inducing angiogenesis and vasculogenesis.[3] Supporting the infarcted myocardium by supplying blood through angiogenesis can strengthen the performance of heart muscles subsequent to myocardial infarction. Numerous preclinical and clinical researches have scrutinized the effect of angiogenic agents on therapeutic angiogenesis when adequate blood flow to the myocardium is obstructed. Despite the fact that vascular endothelial growth factor (VEGF) represents an essential growth factor for angiogenesis, as tested in lab analysis, VEGF may result in unpleasant effects such as atherosclerotic lesions and hemangiomas.[4]

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Being a cytokine which constitutes a group of heparin-binding proteins along with midkine (MK),[5] pleiotrophin (PTN) serves as a neurite outgrowth-promoting factor and emerges as an angiogenic response to numerous processes such as ischemic injury affecting a region of the heart and the brain.[4] It has been confirmed that PTN has a chemoattractant effect on endothelial progenitor cells, much the same as VEGF and stromal cell derived factor 1 alpha (SDF-1α).[6] Moreover, Sharifi discovered that PTN can stimulate monocytes to transdifferentiate into functional endothelial cells.[7] Christman *et al*.[8] reported that delivery of PTN plasmid increases neovasculature formation, unlike the control group. The capillary and arteriole density was observed to be much higher in the PTN plasmid-injected patients in comparison to that of the control group. Besides, the group supported with the PTN plasmid was observed to show no sign of developing macroscopic or histological risk of forming tumors.[8]

Türker Duyuler *et al*.[9] reported that serum PTN levels had a close correlation with maintaining coronary collateral circulation in clients who suffer from angina pectoris. However, serum PTN levels were not identified in clients with ACS. As an objective of our research, we assessed the serum levels of PTN in clients with ACS and patients with no visible stenosis (NVS) through applying elective invasive coronary angiography (ICA).

Materials and Methods

This single-center prospective study enrolled 110 consecutive clients having the symptoms of ACS referred for ICA within 24 h of symptom onset and 47 stable patients with NVS. NVS was defined as complete absence of stenosis or plaque formation in coronary arteries.[10]

Exclusion criteria were applied for the participants who experienced CAD, peripheral arterial disease, cerebrovascular disease, cancer, myocardial infarction with non-obstructive coronary arteries (MINOCA), severe congestive heart failure, atrial fibrillation, severe valvular disease, hypertrophic cardiomyopathy, or severe renal or liver failure.

Diabetes mellitus was determined as a fasting plasma glucose level >126 mg/dl or currently on antidiabetic treatment. Hyperlipidemia was detected as a fasting serum low-density lipoprotein (LDL), with the cholesterol level >130 mg/dl or currently being treated with lipid-lowering drugs. Patients with resting blood pressure ≥140/90 mmHg on at least two measurements or currently taking antihypertensive medication were deemed to have hypertension.

Data collection

Patient gender, age, medical history, comorbidities, 12-lead electrocardiography, and transthoracic echocardiography were collected from the medical records of our hospital.

Laboratory tests

We collected blood samples for biochemistry parameters and complete blood count after 12-h of fasting. Tests such as complete blood count, serum urea, creatinine, triglyceride, total cholesterol, high-density lipoprotein cholesterol, LDL cholesterol, and glucose levels were performed via routine laboratory techniques. We drew venous blood sample for PTN testing before ICA in the ACS group and after ICA in the NVS group. We centrifuged the venous blood samples in the biochemical tubes of 3000 g for 10 min to deliver serum samples, followed by storing them at the freezing temperature of –80°C. Levels of PTN were calculated by means of a commercial PTN Enzyme-linked immunosorbent assay Kit (*SunRed Biotechnology Company*, *Shanghai SunRed Biological Technology Co., Ltd. Hu Tai Road, Baoshan District, Sanghani, China*), adhering to the instructions recommended in the owner's manual.

Invasive coronary angiography

The indication for ICA in acute and elective conditions was decided according to the guidelines.[11,12] ICA was performed by means of the Judkins coronary catheter via radial or femoral access. Four experienced invasive cardiologists interpreted the ICA recordings, and the therapeutic approach was determined by taking into consideration guidelines of 2018 ESC/EACTS on myocardial revascularization.[13]

Statistical analysis

Sample size calculations were performed using G*Power 3.1. All data were analyzed via SPSS software (ver. 22.0; SPSS Inc., Chicago, IL, USA), whereas continuous data were demonstrated as the mean ± standard deviation and analyzed with the *t*-test. Pearson's Chi-square was preferred to analyze qualitative variables. The area under the receiver operating characteristic curve was used to measure the cutoff point of PTN for ACS. Univariate and multivariate logistic regression was used to predict the markers of ACS in clients without history of CAD. We applied two-tailed tests for both the groups, as the $P < 0.05$ was assessed to be statistically significant.

Ethical Statement

All patients were referred for ICA between February 2022 and June 2022. Prepared in line with the principles of the Declaration of Helsinki, version 1975, the research protocol was confirmed by the local ethics committee of Ankara City Hospital (E1-22-2375, dated February 9, 2022).

Results

We analyzed 110 patients with ACS (n = 110, 71.8% of males, mean age = 61.47 ± 11.00 years) and 47 patients with NVS (n = 47, 51.1% of males, mean age = 54.53 ± 9.06 years). Table 1 summarizes their demographic, clinical, and laboratory data. Smoking (59.1% vs. 34.0%, $P = 0.004$) was more prevalent in the group with ACS in comparison to the group with NVS.

We determined that ACS (+) group had higher PTN levels than NVS group (244.94 ± 89.09 vs. 199.46 ± 70.71, $P < 0.001$). The cutoff value of PTN for ACS was 207.66. PTN ≥207.66 ng/ml predicted ACS with a sensitivity of 79.1% and specificity of 59.6% (area under the curve: 0.697 [0.598–0.797], 95% confidence interval, $P < 0.001$]) [Figure 1].

According to the findings of univariate logistic regression analysis, older age, male gender, smoking, and PTN ≥207.66 ng/ml predicted ACS. In the multivariate analysis, besides older age, smoking and white blood cell (WBC), PTN ≥207.66 ng/ml remained independently associated with ACS [Table 2].

Discussion

In this research, we concluded that PTN levels were higher in ACS patients when compared to NVS patients, and the PTN cutoff point for ACS was 207.66 ng/dl. Presumably, our research is the first attempt applied on people in terms of revealing an association between high levels of PTN serum and ACS.

Table 1: Demographic and clinical data of study population

	NVS (*n*=47)	ACS (*n*=110)	*P*
Age (year)	54.53±9.06	61.47±11.00	<0.001
Gender (male), *n* (%)	24 (51.1)	79 (71.8)	0.012
Comorbidities, *n* (%)			
DM	12 (25.5)	41 (37.3)	0.154
HT	20 (42.6)	46 (41.8)	0.932
Smoking	16 (34.0)	65 (59.1)	0.004
Laboratory findings			
Creatinine, mg/dl	0.77±0.20	0.83±0.26	0.172
Uric acid, mg/dl	5.47±2.00	5.60±2.00	0.280
HDL-C, mg/L	47.09±17.22	43.04±10.30	0.07
LDL-C, mg/L	124.00±33.00	126.00±47.25	0.068
WBC, 10^3/uL	8.20±2.30	9.40±3.93	0.001
Neutrophil 10^3/uL	5.23±1.54	7.08±2.73	<0.001
Lymphocyte 10^3/uL	2.17±0.73	1.95±1.09	0.157
Hb, g/dl	14.00±2.40	13.90±2.20	0.802
Plt, 10^3/uL	252.43±58.13	248.83±66.95	0.749
Pleiotrophin, ng/ml	199.46±70.71	244.94±89.09	<0.001
Echocardiographic findings			
LVEF, %	59.64±4.57	43.98±9.03	<0.001

ACS=Acute coronary syndrome, DM=Diabetes mellitus, Hb=Hemoglobin, HDL-C=High-density lipoprotein cholesterol, HT=Hypertension, LDL-C=Low-density lipoprotein cholesterol, LVEF=Left ventricular ejection fraction, Plt=Platelet, NVS=No visible stenosis, WBC=White blood cell

ACS involves a wide range of clinical syndromes occurring in the form of instability or rupture of coronary atherosclerotic plaque and microvascular occlusion developing in the coronary artery, which is mostly experienced as coronary thrombosis. Despite the improvements in interventional and medical therapeutic approaches, ACS is still considered a major cause of morbidity and mortality all around the world. Sufficient supply of blood to the ischemic region can remarkably prevent the myocardial injury, which contributes to the improvement of heart function and maintenance of healthy of life.

Angiogenesis is the growth of new blood vessels from adjacent vasculature providing collateral blood supply of the tissues subject to chronic ischemia. By this way, the viability of the ischemic tissue may be maintained. An adequately coordinated angiogenic response is linked by promising results in animal models of acute MI as proved by tiny infarct scars, minor remodeling, and diastolic heart failure. Similarly, Fang *et al*.[4] demonstrated in a study with mice that delivery of myoblast mediated *PTN* gene could enhance blood distribution and protect tissues in the ischemic hindlimb muscle. We detected an increase in PTN level in acute ischemia of myocardium.

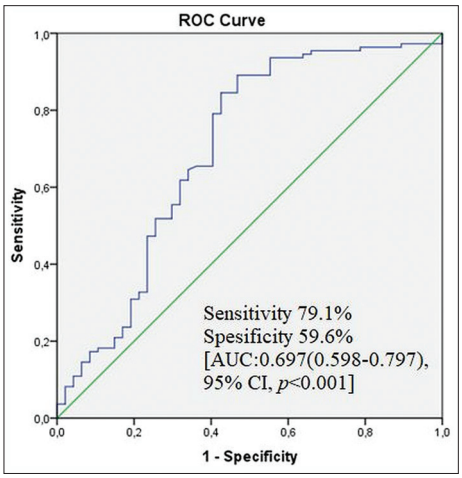


Figure 1: ROC curves for PTN associated with ACS. ROC = Receiver operating characteristic, PTN = Pleiotrophin, ACS = Acute coronary syndrome

Table 2: Univariate and multivariate logistic regression analysis showing the independent predictors of acute coronary syndrome

	Univariate		Multivariate	
	Odds ratio 95% CI	*P*	Odds ratio 95% CI	*P*
Age, year	1.064 (1.028-1.102)	<0.001	1.106 (1.052-1.163)	<0.001
Gender, male	2.442 (1.204-4.952)	0.013	1.457 (0.516-4.109)	0.477
Smoking	1.799 (1.372-5.710)	0.005	3.358 (1.138-9.913)	0.028
Hypertension	0.970 (0.486-1.937)	0.932		
Creatinine	2.956 (0.619-14.117)	0.174		
HDL-C	0.976 (0.949-1.004)	0.096		
WBC	1.306 (1.112-1.534)	0.001	1.390 (1.137-1.700)	0.001
PTN ≥207.66 ng/ml	5.574 (2.654-11.707)	0.014	3.994 (1.649-9.676)	0.002

HDL-C=High-density lipoprotein cholesterol, PTN=Pleiotrophin, WBC=White blood cell, CI=Confidence interval

This increase in PTN level in the acute phase of myocardial infarction may affect angiogenesis and by this way may reduce ischemia in the myocardium. Our study is the first to demonstrate the increase of PTN in the acute phase of myocardial infarction in humans. Promoting angiogenesis in the ischemic area may evolve as a novel approach to ACS treatment.[14] Early treatment with angiogenic factors in ACS may help rescue the jeopardized ischemic myocardium. Further studies are warranted for the effect of angiogenic factors like PTN in the treatment of ACS patients.

Obama *et al*.[15] studied the expression of MK in the mouse heart due to experimental myocardial infarction. As detected via IHC staining, myocytes and endothelial cells in the non-infarcted cardiac area produced dense immunoreactivity of MK 6 h after ligation of the left anterior descending coronary artery.[15] Similarly, our study demonstrated the increased level of PTN in the acute phase of myocardial infarction. We made a comparison between the clients with ACS and those with NVS. PTN has also been reported at increased levels in stable patients with good coronary collateral compared to poor collateral patients. No study has been designed comparing ACS with chronic coronary syndrome patients. The increased level of PTN in good collateral stable patients suspends PTN from being a diagnostic marker for ACS patients. Nonetheless, additional studies are required for evaluating PTN as a diagnostic marker in ACS.

Yeh *et al*.[16] designed a study to discover a proof that PTN can enhance tissue recovery. They examined PTN's expression pattern after designing focal cerebral ischemia model in rats and demonstrated that both the endothelial cells in neovasculature and the cells that are associated with the sites of angiogenesis exhibit intense PTN mRNA signals, initially at day 3 and continued up to day 14. Our study revealed that PTN level increased in the acute phase of myocardial ischemia. If we had scrutinized the patients' PTN levels included in our study on the 7th day, perhaps we would have seen even higher PTN values. In addition, there may be a difference in PTN levels between patients with ACS who are revascularized and those who are followed up medically.

Apoptosis is defined as cell death and removal without activating an inflammatory process based on DNA and cellular fragmentation. Abrupt reduction in coronary blood flow leads to hypoxia and hypoperfusion of the myocardium, generally resulting in cell death. Hence, therapeutic modulation on cardiac myocyte apoptosis may be a good target for the treatment of ACS patients. Several treatment strategies such as pharmacological and genetic interventions to modulate ion channels, nitric oxide, growth factors, and downstream signaling molecules have been studied to reduce apoptotic cell damage.[17] None of them have been shown to be useful clinically until now. It has been suggested that PTN signaling provides a strong anti-apoptotic effect. Bowden *et al*.[18] demonstrated that PTN through its receptor anaplastic lymphoma kinase could provide a survival signal for epithelial and fibroblast cells. However, Li *et al*.[19] demonstrated that PTN was released from cardiomyocytes in response to cell stress and can potentiate cardiomyocyte apoptosis through inhibition of protein kinase B (AKT) signaling. Du *et al*.[20] showed that suppression of PTN activity promoted apoptosis of cell lines in leukemia patients. PTN may have different effects on apoptosis in various cell lines through diverse signaling pathways. The effects of increase in PTN levels in ACS patients may be a subject of further studies.

Study limitations

While study population is limited in number, patients were included according to their statements relating subjective symptoms. Actual time of initiation of symptoms may be different. Our study population consisted of unstable angina, non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction patients. This might have led to a heterogeneous study group in terms of biomarker kinetics. Amount of PTN in the tissue levels may vary with respect to the serum level, since we only measured serum PTN levels.

Conclusion

We determined that the serum PTN level had an association with ACS. Furthermore, older age, smoking, WBC, and PTN ≥207.66 ng/ml were independent predictors of ACS. The potential diagnostic and prognostic impact of PTN in ischemic heart disease may deserve to be further evaluated. PTN may also be studied as an angiogenic therapeutic factor in patients with ACS in additional studies.

Declaration of patient consent

We obtained written informed consent from each client before enrolling them in the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Cardiac Comorbidities Impact on the Outcomes in Severe COVID-19 Infection

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Abstract

Background: COVID-19 is now a global pandemic, with the officially recorded number of affected individuals approaching 4 billion patients. **Aim of the Work:** Our purpose is to study the effect of cardiac comorbidities on the outcomes of severely infected COVID-19 patients. **Patients and Methods:** This study included 147 patients with severe COVID-19. All data were analyzed regarding demographic risk factors, associated diseases, mode of oxygen therapy administration, and echocardiography. **Results:** The death rate (DR) in patients with severe COVID-19 and no comorbidities was 7.7%. In patients who had only one risk factor as smoking, hypertension (HTN), or diabetes mellitus (DM), the DR was 16.7%, 33.3%, and 8.3%, respectively. The addition of one risk factor to HTN increased DR in the case of DM (36.8%) and in the case of smoking (40%). Regarding the outcomes, the percentage of the patients affected was as follows: impaired left ventricular ejection fraction (LVEF) <50% (19.7%), dilated right ventricular (RV) basal dimension (12.2%), decreased tricuspid annular plane systolic excursion <17 mm (8.2%), increased SPAP >30 mmHg (53.7%), and pericardial effusion (23.1%). Patients were subclassified according to the presence of HTN. The hypertensive group had increased LV wall thickness and LV end-systolic dimension and impaired LVEF and fraction of shortening than normotensive patients. DR for females and males treated by high-flow nasal cannula was (3.3% vs. 6.9%), continuous positive airway pressure (0% vs. 3.2%), and mechanical ventilation (100% vs. 90.5%). The suggested score was significantly higher in the death group ($P < 00001$). The DR increased markedly with the incremental rising score. **Conclusions:** Comorbidities, age, and delayed presentation with decreased oxygen saturation had a cumulative risk that can predict the outcome of COVID-19 patients. The presence of HTN alone or associated with other risk factors had a higher DR than other risk factors.

Keywords: Comorbidity score, COVID-19, echocardiography, hypertension, oxygen saturation, ventricular function

Introduction

The coronavirus disease (COVID-19) has been declared a global pandemic by the WHO. With 80% of the patients having mild illness, 14% severe illness, and 6% critical illness.[1] Outbreaks caused by coronaviruses are considered a more recent phenomenon; the first reported outbreak was caused by severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) in 2003[2] and the most recent is the still ongoing pandemic caused by SARS-CoV-2.[3] Outbreaks related to coronavirus infections are a global concern, but the dynamics of these outbreaks and their effects on mortality are still being studied.[4]

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Patients and Methodology

This study is a retrospective cross-sectional study that included 147 patients who were admitted to our University Hospital from December 2020 to June 2021. The current study was approved by the Research Ethics Committee; (FMG-IRB); ID: 1167 and was performed following the Helsinki declaration. Patients were diagnosed to have documented severe COVID-19. All their data in the files were analyzed regarding

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demographic risk factors (smoking, hypertension [HTN], diabetes mellitus [DM], ischemic heart disease [IHD], and associated diseases [bronchial asthma, cerebral, and chronic kidney disease (CKD)]). Their treatment in the intensive care unit was documented regarding methods of oxygen therapy or mechanical ventilation. Medical therapies were performed according to the Egyptian Ministry of Health protocol.

Severe COVID-19 cases were defined according to the clinical and radiographic criteria, including respiratory rate >30 and computed tomography (CT) chest revealing CORADs 4–5 and/or low O2 saturation (<92%). Only intrahospital mortality due to confirmed COVID-19 was considered COVID-19-related mortality.

During admission, all patients were examined clinically; CT chest and laboratory results were collected for analysis. All patients underwent full echocardiographic examination, including left ventricular (LV) dimensions, fraction of shortening (FS), LV ejection fraction (EF), right ventricular basal dimension (RVBd), tricuspid annular plane systolic excursion (TAPSE) and estimated systolic pulmonary artery pressure (SPAP), and the presence of mitral or aortic regurgitation and pericardial effusion. The diagnosis of impaired LVEF if <50%, RVBd dilatation if >41 mm, increased SPAP >30 mmHg, and abnormal TAPSE if <17 mm.

The medical status at admission was analyzed in all patients and according to several classifications: first, according to gender. The second was according to the presence of HTN or not in each gender.

Statistical analysis

Numerical variables were expressed as mean and standard deviation. The Social Science Statistical (SSS) calculators were used:

- t-test calculator for two independent means when data are normally distributed
- Mann–Whitney *U*-test calculator was used to compare two independent groups or conditions or treatments to be compared without making the assumption that values are normally distributed. The data are continuous or the scale of measurement should be ordinal, interval, or ratio
- Statistical significance was set at a level of $P < 0.05$, and ≤0.001 is highly significant
- Qualitative measures (categorical) data, either nominal or ordinal, were expressed as percent for comparison. Odds ratios (ORs), 95% confidence interval (CI), and *P* values are calculated using MedCalc statistical software
- Multivariate logistic regression analysis using stats.Blue calculator.

Ethical statement

The current study was approved by the Research Ethics Committee Al-Azhar University; (FMG-IRB); ID:1167.

Results

The study included 147 patients. The study population included 65 males representing 44.2% and 82 females representing 55.8%. Age ranged from 19 years to 86 years old. The mean age was 61.6 ± 12.5 and 58.9 ± 15.7 years for male and female patients, respectively, with no significant difference. The total deaths were 44 (29.9%) patients; 23 (15.6%) females and 21 (14.3%) males, with no significant difference.

Individual risk factors were recorded among the studied patients, whether as a sole comorbidity or combined risk factors, and the death rate (DR) for each risk factor represented in Table 1.

Regarding age (<40 years, 41–60 years, and ≥61 years), the DR was 6.7%, 19.2%, and 41.3%, respectively. Logistic regression analysis of outcomes and age was statistically significant ($P \leq 0.01$).

Regardless of age, the COVID patients with no comorbidities had a DR of 7.7%. Smokers had a DR of 16.7%. Hypertensive patients had a higher DR than diabetic patients (33.3% vs. 8.3%, respectively). DRs in hypertensive patients with the addition of one other risk factor such as DM or smoking were 36.8% and 40%, respectively.

Echocardiographic parameters showed a decrease of LVEF <50% in 29 (19.7%) patients, dilated RV basal dimension >41 mm in 18 (12.2%) patients, decreased TAPSE <17 mm in 12 (8.2%) patients, pericardial effusion in 34 (23.1%) patients, and increased SPAP >30 mmHg in 79 (53.7%) patients.

Classification of the male and female groups according to the presence and absence of hypertension

The female group included 82 patients, of which 36 were hypertensives and 46 normotensives. The male group included 65 patients, of which 31 were hypertensives and 34 normotensives. Hypertensive and normotensive female patients showed no significant difference regarding age, length of stay (LOS), and oxygen saturation (O_2%) at admission.

Hypertensive and normotensive males showed no significant difference regarding LOS and oxygen saturation (O_2%) on admission, but the mean age of normotensive male patients was significantly younger ($P < 0.005$).

Table 1: Age, risk factors (single or combined), and death percentage among each group

Risk factors in (n=147) patients	Total number	Death number	Death (%)
Age≤40 years	15	1	6.7
Age 41-60 years	52	10	19.2
≥61 years	80	33	41.3
No risk factors/other diseases	26	2	7.7
HTN	6	2	33.3
DM	12	1	8.3
CKD	4	2	50
Smoking	12	2	16.7
HTN + DM	19	7	36.8
HTN + smoking	5	2	40

HTN: Hypertension, DM: Diabetes mellitus, CKD: Chronic kidney disease

Echocardiographic parameters showed that both hypertensive males and females had increased interventricular septum (IVS) thickness ($P < 0.00001$), posterior wall thickness ($P < 0.00001$), increase of left ventricular end-systolic dimension (LVESd) ($P < 0.002$ for females and $P < 0.008$ for males), and LV systolic functions were significantly lower in hypertensive groups.

Pericardial effusion was detected in hypertensive patients more than in normotensive. The OR was 2.77 and 95% CI: 1.24–6.15 ($P \leq 0.0123$) [Table 2].

CT chest findings regarding CORADs scores were reported in female and male patients, and the number of deaths and their percent in each CORADs level are summarized in Table 3. CT chest and CORADs scores revealed no significant difference in DR between female and male groups in CORADs 4 and CORADs 5 ($P = 0.97$ and $P = 0.358$, respectively).

The lower O_2% at admission was related to a higher DR in all patients (males and females). Multivariate logistic regression analysis of outcomes and O_2% was highly significant ($P \leq 0.0001$), and the multivariate logistic regression and CKD were also significant ($P \leq 0.037$). The number of patients who required mechanical ventilation was 42 (representing 28.6% of the study population); all of them were admitted with O_2% <71%. The DR among them was 95.2%. DR for patients treated by high-flow nasal cannula was 3.3% in females and 6.9% in males, whereas treatment by Continuous positive airway pressure was associated with 0% mortality versus 3.2% mortality in males and females, respectively [Table 3].

Our suggested COVID scores [Table 4] depended on the analysis of all data and variables at the time of admission. The associated comorbidities had a cumulative risk for prediction of outcome with COVID infection. These risks include age,

Table 2: Comparison between hypertension and non-hypertension groups in female and male gender

	Females ($n=82$)			Males ($n=65$)		
	HTN ($n=36$)	Non-HTN female ($n=46$)	*t*-test *P*	HTN ($n=31$)	Non-HTN male ($n=34$)	*t*-test *P*
Age (years)	62±12	56.3±17	0.297	65.9±9.3	57.5±13.7	0.005
LOS (days)	7.3±5.5	6±5.1	0.382	7.65±7.2	6.68±5.5	0.544
O_2%	84.8±9.2	84±11.5	0.523	83.4±9.9	83.7±11.4	0.913
IVS (mm)	13.2±1.2	10.7±1.7	0.00001**	13.3±1.7	10.5±1	0.00001*
LVEDd (mm)	50.6±5.7	48.3±4.9	0.054	53.1±5.3	50.5±5.3	0.045*
PWT (mm)	11.8±0.9	9.5±1.9	0.00001**	12.3±0.9	9.6±1.1	0.0001**
LVESd (mm)	34.5±7.9	29.3±7	0.002*	37.4±6.6	32.9±7.3	0.008*
FS (%)	32.5±7.8	40±6.8	0.00005**	30.3±7.3	36.3±10	0.002*
EF (%)	60.1±11	68.8±8.1	0.0001**	56.5±11.4	63.1±10.1	0.01*
RVBd (mm)	37.8±4.4	35.7±3.4	0.0138	37.9±3.5	36.8±3.4	0.21
TAPSE (mm)	19.6±3.1	21±2.5	0.033*	18.7±2.1	19.5±2.9	0.22
SPAP (mmHg)	36.0±8.4	31.7±8.3	0.021*	35.1±7.1	32.7±6.3	0.18

*Statistically significant, **Statistically high significant. LOS: Length of stay, O_2%: Oxygen saturation, IVS: Interventricular septum thickness, LVEDd: Left ventricular end-diastolic dimension, PW: Posterior wall thickness, LVESd: Left ventricular end-systolic dimension, FS: Fraction of shortening, EF: Ejection fraction, RVBd: Right ventricular basal dimension, TAPSE: Tricuspid annular plane systolic excursion, SPAP: Systolic pulmonary artery pressure, HTN: Hypertension

Table 3: Death rate in relation to computed tomography chest COVID-19 reporting and data system, oxygen saturation, and methods of oxygen supply

	Female ($n=82$)			Male ($n=65$)		
	Patients number	Deaths number Total ($n=23$)	Percentage of death	Patients number	Death number Total ($n=21$)	Percentage of death
CT chest findings at admission						
CORADs 4	52	14	27.5	54	16	29.6
CORADs 5	30	9	30	11	5	45.5
O_2% at admission						
≤80	21	13	61.9	18	13	72.2
81-90	35	9	25.7	36	8	22.2
≥91	26	1	3.8	11	0	0
Methods of oxygen supply						
High-flow nasal cannula	30	1	3.3	29	2	6.9
CPAP	31	1	3.2	15	0	0
Mechanical ventilation	21	21	100	21	19	90.5

CORADs: COVID-19 reporting and data system, CPAP: Continuous positive airway pressure, O_2%: Oxygen saturation

O_2% at admission, smoking, HTN, DM, IHD, PE, CKD, and rescue from cardiac arrest or shock.

The calculated COVID score for patients is summarized in Table 5 and its correlation with the DR. The mean ± standard deviation of the total score was 5.86 ± 2.04 in the patients who died, whereas it was 3.7 ± 2.02 in the patients who survived (P < 00001). The logistic regression analysis of outcomes and COVID score was highly significant (P < 0.0001).

Discussion

Although acute respiratory complications are common in COVID-19, cardiovascular complications are increasingly being recognized. These include acute myocardial injury, arrhythmias, and heart failure (HF). Therefore, there is a need for a high index of suspicion of cardiovascular complications since there is an overlap in the symptoms and signs.[5] In the previous epidemics, it was noted that coexisting cardiovascular disease (CVD) with or without myocardial injury was associated with higher mortality.[6] Data from Europe and the US have confirmed the disturbing relationship between diabetes, HTN, CVD, and COVID-19 outcomes.[7,8] A study including 5700 patients reported a similar message that HTN (56.6%), obesity (41.7%), diabetes (33.8%), coronary artery disease (11.1%), and congestive HF (6.9%) were the most common comorbidities.[9]

Table 4: COVID score for prediction of death outcome

Risk	Score
Age (years)	
<40	0
41-60	1
>61	2
O_2% at admission (%)	
≥91	0
90-81	1
80-71	2
≤70	3
Presence of risk factors	
Smoking	1
HTN	1
DM	1
IHD	1
Other diseases	
Pericardial effusion	1
CKD	1
Rescue of cardiac arrest/shock	2

HTN: Hypertension, DM: Diabetes mellitus, IHD: Ischemic heart disease, CKD: Chronic kidney disease, O_2%: Oxygen saturation

Table 5: Estimated COVID score for COVID admitted patients and the death rate

The score	Total patients		
	Patient number	Death number	Death (%)
0	14	0	0
1			
2	43	4	9.3
3			
4	50	16	32
5			
6	27	15	55.5
7			
8	13	9	69.2
9			
10			
Total	147	44	29.9

Case fatality rates vary by country from <0.1% to >20% and are influenced by testing strategies that define the infected population, economics, health-care resources, comorbidity rates, demographics, and politics.[10] Our admitted patients were severe cases only and their CORADs were 4 and 5. DR in different age categories (<40 years, 41–60 y, and ≥61 years) was 6.7%, 19.2, and 41.3%, respectively. However, the estimated case fatality ratio was 0.32 in patients aged <60 years in comparison with 6.4% in patients aged >60 years.[11] In Italy, case fatalities ranged from 0% below age 30 years to 3.5% for ages 60–69 years and 20% above age 80 years.[12] The relative risk of fatal outcomes in young patients with HTN, diabetes, and CVD was higher than in elderly patients.[13]

Gender has no significant difference regarding the mean of age, LOS, and oxygen saturation at admission. Despite the higher rate of HTN, DM, smoking, IHD, CKD, and DR in the male gender, the OR revealed no significant difference between the male and female gender except for smoking due to the higher prevalence of smoking among males (P < 0.0001).

The DR among COVID-19 patients with no comorbidities or other diseases was 7.7%. The presence of one risk factor as HTN, DM, or smoking was associated with an increase of DR to 33.3%, 8.3%, and 16.7%, respectively. DRs in hypertensive patients with the addition of one other risk factor as diabetes or smoking were 36.8% and 40%, respectively.

Echocardiography was performed for all patients included in our study population although it has been recommended that performing echocardiograms would be only limited to cases where the derived information is likely to produce clinical benefit.[14,15] In our study, echocardiography was done for all admitted patients with complete personal protective equipment worn by the medical staff. The echo-derived data helped to understand COVID-19 impact on the heart and was also of additive value for follow-up.

In our study, decreased LV systolic function (LVEF <50%) was detected in 19.7% of patients. Hypertensive patients had significantly increased both LVEDd and LVESd with a decrease both EF and FS. Echocardiography variables were compared in both genders according to the presence of HTN or not, because of the impact of HTN on myocardial structure

and function. In the hypertensive group, there was a highly significant increase of IVS, PW thickening, and LVESd in both genders. LVEDd was higher in hypertensive males. The systolic functions (EF and FS) were reduced significantly in both male and female hypertensive groups.

Although it was mentioned that SARS-CoV infection was found to be associated with cardiomyopathy.[16] Other studies recorded reversible cardiomegaly without HF in 10.7% of the cases.[17] Transient atrial fibrillation is an uncommon feature.[17]

The incidence of acute HF was 23% (44 out of 191 patients with COVID-19) and that multiple precipitating etiologies, including acute coronary syndrome, cardiac arrhythmias, stress-induced cardiomyopathy, and fulminant myocarditis, might result in acute HF or cardiogenic shock in patients with COVID-19.[18] Although COVID-19 is predominantly a respiratory illness,[19] this may be secondary to lung disease since acute lung injury itself leads to increased cardiac workload and can be problematic, especially in patients with preexisting HF.[20]

The unique pathophysiology of COVID-19 places the RV at higher risk of failure.[21] In our study, dilated RV basal dimension >41 mm was present in 18 (12.2%) patients, decreased TAPSE <17 mm in 12 (8.2%) patients, pericardial effusion in 34 (23.1%) patients, and increased SPAP >30 mmHg in 79 (53.7%) patients.

Pericardial effusion was detected in hypertensive patients more than in normotensives. The OR of pericardial effusion was significantly higher.

In our study, analysis of CT chest and CORADs grading revealed no significant difference regarding DR between female and male groups at CORADs 4 and 5 ($P = 0.97$ and $P = 0.358$, respectively). Moreover, there was no significant difference between hypertensive and non-hypertensive patients regarding CORADs grading. The P values for CORADs 4 and 5 were $P = 0.148$ and $P = 0.93$, respectively.

Factors associated with outcomes in 187 patients with COVID-19 were previously noted and recorded, up to 35% had underlying CVD (HTN, coronary heart disease, or cardiomyopathy), and 28% showed evidence of acute myocardial injury (defined as elevated troponin T).[22] However, a number of chronic diseases are associated with an increased frequency of elevated troponin, including systemic HTN, left ventricular hypertrophy, HF, pulmonary HTN, and CKD.[23]

In our hypertensive females, the mean of RVBd was dilated, TAPSE was decreased, and SPAP was increased significantly, reflecting the COVID effect on the lungs and their impact on the right ventricle. The male gender had the same changes but did not reach statistical significance.

The identification of factors that may influence the heterogeneity of COVID-19 onset and outcome can optimize care services. In this regard, advanced age and preexisting chronic diseases, two strictly related aspects, have shown to substantially affect the COVID-19 prognosis, leading to dramatic increases in case fatality rates.[12,24] However, they assigned no weight to individual conditions, although the differing impact of multimorbidity depending on the severity of the disorders has been previously acknowledged. Weighting is particularly useful if the purpose of the measurement is to predict future outcomes such as mortality.[24]

Our suggested COVID score included several points, patient's age, oxygen saturation at admission, and comorbidities including smoking, HTN, DM, IHD, pericardial effusion, CKD, and rescue from cardiac arrest or shock. The mean score was significantly lower in recovered patients than in dead patients. Moreover, logistic regression of the outcome and score was highly significant ($P < 0.0001$). The DR increased markedly with the incremental rising score.

Study limitations

The study comprised a small number of patients suffering from severe COVID-19 only. In addition, the number of patients who had isolated comorbidities such as IHD and CKD alone was small for analysis.

Conclusions

Comorbidities had a cumulative risk that can predict the outcome of COVID-19 patients. Applying the suggested score at the time of admission can predict the danger of death and the need for mechanical ventilation. Patients who have high scores should attract attention for special medical care and treatment from the start.

The presence of HTN risk factors alone or associated with other risk factors has a higher DR than others. The suggested score needs to be evaluated in a prospective study with a large number of patients

Complications in hypertensive patients are significantly higher as dilated LV, decreased systolic function, and development of pericardial effusion. Long-term follow-up of those patients who may proceed to HF in future is essential.

Consents

The written informed consent was obtained from all patients at admission and all required consents according to the hospital by law.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Authors' Contributions

This research is a collaboration between 4 departments in 2 universities.

The researchers from 1 to 4 contributed by data collection.

The fifth researcher contributed by scientific data analysis, paper writing, revision and publication.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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