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The impact of COVID-19 on coronary heart failure patients and co-morbid diseases

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Abstract
Objective: The objective of this study was to evaluate the risk of serious adverse outcomes in patients with Chronic Coronary Heart Failure (CHF) related COVID-19 by stratifying the co-morbidity status.
Subjects and Methods: This is a prospective cohort study based on 1,264 male and female aged 25-75 years old patients and 1,007 (74%) patients gave consent to participate. Demographics, clinical, biochemistry and microbiology information, the presence of disease.
Results: There was a significant difference between CHF versus controls with respect to age groups ($p< 0.001$), gender (p =0.039), BMI (p = 0.047), smoking cigarette (p = 0.022), nargile-sheesha smoking (p =0.033), Metabolic-Syndrome(ATP III) (p = 0.038), Metabolic-Syndrome(IDF) (p = 0.018), infection (p = 0.015), hypertension ($p< 0.001$), stroke ($p< 0.001$), COPD ($p< 0.001$), malignite (p = 0.006), diabetes (p = 0.032), cerebrovascular disease (CVD) (p = 0.010), and vitamin D levels (p = 0.027) respectively. Additionally, there were highly statistically significant differences between CHF versus control subjects regarding, hemoglobin ($p< 0.001$), HbA1C ($p< 0.001$), glucose (p= 0.008), vitamin D (mmol/L) (p = 0.011), vitamin B12 (p= 0.023), urea (mmol/L) ($p< 0.001$), albumin (p=0.033), total cholesterol (p=0.019), HDL, uric acid ($p< 0.001$), ferritin ($p< 0.001$), Fe (p = 0.006), TSH (p = 0.008), Creatinine Kinase -CK (p = 0.005), CK-MB (p= 0.022) , hematocrit ($p< 0.001$), monocytes (p = 0.021), Neutrophil (/mm^3), (p = 0.034), Lymphocyte (p = 0.023), Platelet ($p< 0.001$), apartate transaminase-AST (p= 0.009), and alanine transaminase-ALT (p= 0.002), respectively. The regression analysis indicated that Systolic BP mmHg ($p< 0.001$), hypertension ($p< 0.001$), hematocrit ($p< 0.001$), Lymphocyte ($p< 0.001$), platelet ($p< 0.001$), uric acid ($p< 0.001$), ferritin (p = 0.003), infection (yes) (p = 0.007), Metabolic-Syndrome (IDF) (p = 0.008), vitamin D (p = 0.011)and BMI (p = 0.019), vitamin B12 (p = 0.023) and smoking (Yes) (p = 0.024) were considered as risk predictors of the CHF among COVID-19 patients.
Conclusion: This study determined that CHF disease was the most prevalent with co-morbidity hypertension, COPD and diabetes disease among COVID-19 patients. The history of CHF identifies patients with COVID-19 who are at high risk of in-hospital admission, due to complications and comorbid.

Keywords: COVID-19, coronary, heart failure, co-morbid

Introduction
Severe acute respiratory syndrome coronavirus COVID-19 constitutes a serious threat for patients with particularly those with coronary heart failure (CHF) [1-4], also several studies reported that CHF is the most common in COVID-19 patients [1-10]. The situation is worsening rapidly with increasing case counts and deaths worldwide [7-8]. The risk of COVID-19 in patients with CHF has been reported under estimate [2, 9-10] although most recently studies have stated an increased risk of severe COVID-19 and increased morbidity and mortality among CHF patients [4-7]. The clinical occurrence and distribution of COVID-19 patients with CHF are vary from place to place according latest reports [1-6, 9-18]. CHF significantly associated with COVID-19 related hospital admission and mortality and morbidity [8-14]. In addition, CHF is associated with a high prevalence of comorbidities such as cardiovascular disease, hypertension, diabetes, Coronary Heart Failure-CHF and old age in population [4-6, 11-15]. During the COVID-19 pandemic, reduced physical activities, socioeconomic condition, social isolation, and sleeping disturbances may induce CHF unstability and cause more complications [2-6]. In addition to older age, chronic comorbidities increase the risk of CHF and severe COVID-19 infection as well as its fatality [4, 9-11].

The aim of the present study was to determine and to evaluate the risk and prevalence of patients with CHF among coronavirus disease COVID-19 patients by stratifying the co-morbidity status.

Subjects and Methods

This is a prospective cohort study conducted on the patients screened and diagnosed with COVID-19 at Istanbul Medipol University based on several Medipol Hospitals and Research Hospitals. The study included Accident Emergency Department, Departments of Internal Medicine, Cardiology and Infectious Diseases, Clinical Biochemistry and Microbiology between periods from January to August 2021. The study included age, gender, presence of CHF, COPD, hypertension, stroke, The study protocol was approved by the Istanbul Medipol University and Faculty of Medicine Institutional Review Board (IRB) Ethics Research Committee. (Research Protocol and IRB #E-10840098-772.02-1411).

This is a cross-sectional design study conducted among residential population of Istanbul. The sample size was based on previous prevalence reported (25% to 30%) of co-morbid [5, 9, 16] among visited patients as sample proportion likely to be considered 30%, assuming 99% confidence interval with 3% error of estimation sample size needed to be 1,364 subjects and 1007 (74%) male and female and aged 25-75 years agreed and gave consent to participate in this research during January to December 2021.

Socio-demographic data, clinical biochemistry and microbiology, the presence of co-morbid symptoms and signs, treatment, and outcomes were collected and evaluated by consultant team of physicians. RT-PCR results of nasopharynx and throat samples were analyzed by Medipol Hospitals COVID-19 diagnosis laboratory which was authorized and assessed by the Ministry of Health. The routine blood sample investigation and influenza polymerase chain reaction testing was also performed for all patients.

We have conducted cardiac imaging equipment refers to non-invasive imaging of the heart using ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), or nuclear medicine (NM) imaging with positron emission tomography (PET) electrocardiography (ECG) exercise cardiac stress test or stress echocardiography.

The significance differences between two independent groups the Student's t-test was conducted. Chi-square analysis was performed to test for differences in proportions of categorical variables between two or more groups. Multivariate stepwise regression analysis method was used to predict risk factors for the COPD and co-morbid. The level $p< 0.05$ was considered as the cut-off value for significance.

Results

Table 1 shows socio-demographic characteristics of comparison between CHF and control subjects. There was a significant difference between CHF versus controls with respect to age groups ($p< 0.001$), gender (p =0.039), BMI (p = 0.047), smoking cigarette (p = 0.022), nargile-sheesha smoking (p =0.033), respectively.

Table 2 gives co-morbidity comparison of CHF versus control subjects as common diseases. As can be seen from Table 2 there significance differences between CHF patients and control subjects regarding Metabolic Syndrome (ATP III) (p = 0.038), Metabolic Syndrome (IDF) (p = 0.018), infection (p = 0.015), hypertension ($p< 0.001$), stroke ($p< 0.001$), COPD ($p< 0.001$), malignite (p = 0.006), diabetes (p = 0.032), CVD (p = 0.010), and vitamin D levels (p = 0.027) respectively.

Table 3 presents clinical biochemistry data values by CHF versus control subject comparison among COVID-19 positive patients. There were highly statistically significant differences between CHF versus control subjects regarding , hemoglobin ($p< 0.001$), HbA1C ($p< 0.001$), glucose (p= 0.008), vitamin D (mmol/L) (p = 0.011), vitamin B12 (p= 0.023), urea (mmol/L) ($p< 0.001$), albumin (mmol/L) (p=0.033), total cholesterol (mmol/L) (p=0.019), HDL(mmol/L), uric acid (mmol/L) ($p< 0.001$), ferritin (mmol/L) ($p< 0.001$), Fe (mmol/L) (p = 0.006), TSH (p = 0.008), Creatinine Kinase -CK (ug/L) (p = 0.005), CK-MB (ug/L) (p= 0.022) , hematocrit (ug/L) ($p< 0.001$), monocytes ((/mm^3) (p = 0.021), Neutrophil (/mm^3), (p = 0.034), Lymphocyte (/mm^3) (p = 0.023), Platelet (10^3/ mm^3) ($p< 0.001$), apartate transaminase-AST (U/L) 2 (p= 0.009), and alanine transaminase-ALT (U/L) B12 (p= 0.002), respectively.

Table 4 presents impact of COVID-19 positive on the CHF and predictor risk factors using multivariate stepwise regression analysis. The regression analysis indicated that total Systolic BP mmHg ($p< 0.001$), hypertension ($p< 0.001$), hematocrit (ug/L) ($p< 0.001$), Lymphocyte (/mm^3) ($p< 0.001$), platelet(/mm^3) ($p< 0.001$), uric acid (mmol/L) ($p< 0.001$), ferritin ug/L (p = 0.003), infection (yes) (p = 0.007), Metabolic Syndrome (IDF) (p = 0.008), vitamin D mmol/L (p = 0.011)and BMI kg/m^2 (p = 0.019), vitamin B12 mmol/L (p = 0.023) and smoking (Yes) (p = 0.024) were considered as risk predictors of the CHF among COVID-19 patients after adjusting for age and gender.

Discussion

The world is currently suffering and struggle with the coronavirus disease COVID-19 as major public health problem in human history. The current prospective cohort study suggests that patients hospitalized with COVID-19 who has CHF and hypertension and COPD may have worse outcomes than those without these co-morbid conditions. COVID-19 mostly affects the elderly and males patients with chronic diseases such as hypertension, COPD and diabetes [9-11]. The risk of COVID-19 in patients with CHF was not recognized clearly earlier [1-6], surprisingly, most recently studies reported as an increased risk of severe COVID-19 morbidity and mortality rate among CHF patients [4, 9-11].

Several studies reported that males and an old patients with CHF increases morbidity and mortality in-hospital admission [4, 9, 11-14]. Recently a study indicated that CHF medical condition is associated with poor prognosis, particularly CHF patients with severe complications if infected with COVID-19 may lead toincrease rate of morbidity and mortality [5].

The current study revealed co-morbid of CHF (26%), infection (31.2%), stroke (35.7%), COPD (27.8%), hypertension (38.0%), diabetes (20.7%) and CVD (20.3%). Several studies have reported COVID-19 patients that have been increased with severity such as CHF, hypertension, COPD and diabetes COVID-19 [4-7, 18, 20-21]. Those results are confirmative with current study outcome. CHF is mainly caused by smoking and the inflammatory profile is known

in developed countries. The current study revealed that 22.8% of CHF patients reported being smokers and 19.8% nargile smokers. Most recently a study reported the proportion of mortality was higher among comorbidities disease patients who were hospitalized with COVID-19 in Jazan region, Saudi Arabia [19]. The affect of COVID-19 on CHF can increase the high risk of in-hospital admission, due to multiple complications and co-morbid [18]. This is consistent with the recent our study reported that CHF mostly occurs in males, an old age and cigarette smokers. Also, WHO report declared that smoking could be a risk factor for the prognosis of COVID-19 pandemic [20].

We assume that the prevalence of patients with CHF disease is under-diagnosis and considered higher than reported. Furthermore, during COVID-19 pandemic CHF patients had experienced more respiratory symptoms, higher viral load and increased markers of inflammation than before [4, 6-9, 11].

The vulnerable populations with CHF and COVID-19 diseases are at high risk, and their routine follow-up care cannot be done adequately. Therefore, perhaps remote monitoring offers a low cost and safe solution for their daily lives activities and function [21]. The clinical public health leader role are to formulate work guidance, providing medical care, re-commendations, and advice to frontline medical staff prevention during the pandemic.

Furthermore, the outbreak of the severe COVID-19 pandemic highlighted the serious problems of the mental and physical health of patients as a worldwide. More recently a study conducted by Wankowicz *et al*. [21] in Poland reported that CHF, hypertension, diabetes, coronary artery disease, circulatory failure, COPD disease which are strongly correlated with mental health condition. Similar study conducted in Turkey [16, 22-23] also reported impact of COVID-19 pandemic on the mental health fatigue, sleeping, depression, anxiety and stress symptoms.

More recently, some authors findings indicated that hypertension is one of the commonest and highest occur as comorbidities in patients with COVID-19 [4-6, 21]. This is consistent with the current obtained results. Meanwhile, unfortunately, the size of morbidity and mortality rate of COVID-19 patients in Turkey is alarming according to the WHO situation report [10]. Some studies confirmed strong an association between CHF and COVID-19 [1-9-11-18]. The current conducted is confirmed with the previous reported study as well.

Finally, it seems in over 2 years, the COVID-19 pandemic caused over 5.69 million deaths and 350 million infection cases [24]. Patients with CHF who contract COVID-19 infection are at a higher risk, but vaccination remains the most effective global therapy approach for controlling this disease [25]. Some measures should be allowed for not delaying vaccination against COVID-19, meanwhile need to continue use of facemasks, social distancing and hand hygiene.

The current study has several limitations. Firstly, this is a a prospective cohort design, which may not describe cause-effect relation. Second, the study may not reach to the target patient as considered bias. Third, many patients have a history of CHF, but radiological data are not always included therefore, patients may not been properly diagnosed of CHF. Fourth, the clinical investigation and assessment used for the co-morbidity in relation to COVID-19 may not be accurate; therefore the results must be interpreted with caution.

Table 1: Socio-demographic characteristics of subjects CHF vs Control comparison among COVID-19 positive patients (N = 1007)

Variables	CHF = 266 n (%)	Control= 741 n (%)	*p*-Value Significance
Age groups in Years			
<50	35 (17.6)	225 (21.8)	0.001
50-59	53 (26.9)	185 (26.1)	
60-69	48 (24.5)	174 (24.6)	
=>70	61 (31.0)	124 (17.5)	
Gender			
Males	90 (45.7)	356 (50.3)	0.254
Females	107 (54.3)	352 (49.7)	
BMI			
Normal (<25 kg/m^2)	52 (26.4)	227 (321.1)	0.010
Overweight (29-30 kg/m$^{2)}$	75 (38.1)	292 (41.2)	
Obese (>30 kg/m^2)	70 (35.5)	189 (26.7)	
Smoking cigarette			
Yes	45 (22.8)	77 (10.9)	0.001
No	152 (77.2)	631 (89.1)	
Nargile smoking			
Yes	39 (19.8)	93 (13.1)	0.019
No	158 (80.2)	615 (86.9)	
	Mean ± SD	**Mean ± SD**	
Systolic Blood Pressure mmHg	139.42±8.51	130.60±5.61	0.001
Diastolic Blood Pressure mmHg	79.90±10.01	77.72±6.72	0.001

Table 2: Clinic characteristics and morbidities of CHF vs Control comparison among COVID-19 positive patients (N = 1007)

Co-morbidities variables		CHF = 266 n (%)	Control= 741 n (%)	*p*-Value Significance
Metabolic Syndrome (ATP III)	Yes	78 (29.3)	176(22.9)	0.038
	No	188(70.7)	571(778.1)	
Metabolic Syndrome (IDF)	Yes	86(32.3)	184 (24.8)	0.018
	No	1804(67.7)	557(75.2)	

Infection	Yes	83 (31.2)	175(23.6)	0.015
	No	183 (68.8)	566(76.4	
Thyroid	Yes	57 (21.4)	149 (20.1)	0.647
	No	209 (78.6)	592 (79.9)	
Hypertension	Yes	61(38.0)	106 (14.3)	0.001
	No	165 (62.0)	635 (85.7)	
Stroke	Yes	95 (35.7)	96 (13.0)	0.001
	No	171(64.3)	635 (87.0)	
Chronic Obstructive Pulmonary Disease (COPD)	Yes	74 (27.8)	155 (20.9)	0.021
	No	192 (72.2)	586 (79.1)	
Malignite	Yes	36 (13.5)	58 (7.8)	0.001
	No	230 (86.5)	6835 (92.2)	
Diabetes	Yes	55 (20.7)	111 (15.0)	0.032
	No	211 (79.33	630 (85.0)	
Cerebrovascular disease	Yes	51 (20.3)	94 (12.7)	0.010
	No	215 (79.7)	647 (87.3)	
Vitamin D Levels	Deficiency <20 ng/ml	159 (59.8)	374 (50.5)	
	Insufficiency 20 -29 ng/ml	77 (28.9)	251 (33.9)	0.027
	Sufficiency>30 ng/ml	30 (11.3)	1164(15.7)	

COPD = Chronic Obstructive Pulmonary Disease

Table 3: Clinical biochemistry CHF vs Control comparison among COVID-19 patient (N=1007)

Variables	CHF ;N = 266 Mean ± SD	Control ;N= 741 Mean ± SD	P value
Hemoglobin (g/dL)	11.10± 2.38	11.85± 2.33	0.001
HbA1c	5.99±076	5.73±0.75	0.001
Glucose (mg/dL)	126.42±58.67	116.23±50.72	0.008
Vitamin D (mmol/L)	18.80±7.62	20.16±7.40	0.011
Vitamin B12	258.68±121.86	277.66±131.30	0.023
Calcium (mmol/L)	8.54±0.84	8.55±0.81	0.984
Urea (mg/dL)	52.92±5.92	42.03±4.32	0.001
Phosphor (mmol/L)	3.69±1.27	3.65±1.11	0.652
Creatinine (mmol/L)	75.08±24.84	75.92±30.42	0.683
Albumin (mmol/L)	3.42±0.58	3.51±0.58	0.033
Total Cholesterol (mmol/L)	172.01±53.02	164.32±41.80	0.019
HDL (mmol/L)	39.23±11.79	36.02±11.69	0.040
LDL (mmol/L)	147.19±86.39	204.96±79.20	0.001
Triglyceride (mmol/L)	164.30±140.63	155.06±123.64	0.328
Uric Acid (mmol/L)	5.88±1.87	5.36±1.73	0.001
Ferritin (ug/L)	246.99±140.80	387.92±136.00	0.001
Fe (ug/L)	54.58±28.64	60.56±30.98	0.006
TSH	1.79±1.10	1.70±1.15	0.989
Creatine kinase (ug/L)	39.63± 20.01	36.01± 17.39	0.005
Creatine kinase-myocardial band; (ug/L)	14.11± 6.92	13.12± 5.77	0.022
D-dimer (ug/L)	1650.8±615.00	1104.5±655.00	0.001
Hematocrit (ug/L)	37.41± 5.74	35.43± 5.81	0.001
White blood cell (/mm^3)	7508±1533	7666±1475	0.137
Neutrophil (/mm^3)	6.08±3.52	5.62±2.85	0.034
Lymphocyte (/mm^3)	1.72±0.95	1.53±0.86	0.023
Monocyte(/mm^3)	1.74±0.84	1.60±0.83	0.021
Platelet (103/mm^3)	244.5±104.00	216.12±100.72	0.001
Aspartate transaminase; (U/L)	24.36±17.33	28.50±23.47	0.009
Alanine transaminase (U/L)	18.97±11.78	23.753±13.80	0.002
Folate (U/L)	8.05±4.56	8.02±5.04	0.952
C-reactive protein (mg/L)	21.24±11.73	22.78±13.34	0.348
Procalcitonin (ug/L)	0.24±0.10	0.23±0.10	0.665

Table 4: The impact of COVID-19 positive on the Coronary Heart Failure Disease patients and their predictor risk factors using multivariate stepwise regression analysis (N= 1107)

Independent variables	Regression coefficient	Standard Error	Standardized Coefficients Beta	t-test value	p-value significance
Systolic Blood Pressure mmHg	-1.012	0.110	-0.302	-10.323	0.001
Hypertension	-0.311	0.040	-0.636	-7.816	0.001
Hematocrit (ug/L)	-0.010	0.002	-0.138	-4.884	0.001
Lymphocyte (/mm^3)	0.187	0.039	0.387	4.769	0.001
Platelet (/mm^3)	-0.708	0.189	-0.119	-3.787	0.001
Uric Acid (mmol/L)	-0.263	0.070	-0.106	-3.738	0.001
Ferritin ug/L	0.098	0.032	0.091	3.069	0.003
Infection (Yes)	0.078	0.029	0.077	2.694	0.007
Metabolic Syndrome (IDF)	0.263	0.098	0.182	2.683	0.008
Vitamin D mmol/	0.508	0.196	0.080	2.559	0.011
BMI kg/m^2	-0.007	0.003	-0.067	-2.353	0.019
Vitamin B12	0.168	0.074	0.072	2.270	0.023
Smoking (Yes)	0.080	0.035	0.064	2.266	0.024

Conclusion

The present study indicated that over one-fourth of the population have co-morbid symptoms during the COVID-19 outbreak. This study determined that CHF disease was the most prevalent with co-morbidity hypertension, COPD and diabetes disease among COVID-19 patients. The history of CHF identifies patients with COVID-19 who are at high risk of in-hospital admission, due to complications and comorbid.

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