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Novel insights into myocardial injury, diastolic pathology, and in-hospital mortality: the impact of H₂FPEF score in COVID-19 patients

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ABSTRACT

Aims: H₂FPEF score is a reliable tool for diagnosing heart failure with preserved ejection fraction (HFpEF) linked to diastolic dysfunction. Our objective was to explore the correlation between H₂FPEF score and in-hospital mortality, as well as parameters previously identified in association with COVID-19, among hospitalized COVID-19 patients.

Methods: This prospective, single-center observational study included 205 consecutive COVID-19 hospitalized patients. Data regarding patients' clinical status, comorbidities, and drug therapy were extracted from medical histories and records. Afterward, we calculated H₂FPEF score for each patient and subsequently grouped them based on the following score categories: low (0-1), medium (2-5), and high (6-9). Logistic regression and Kaplan-Meier survival curve analyses were conducted to assess in-hospital mortality and the presence of an intermediate-to-high H₂FPEF score.

Results: Death occurred in 46 (22.4%) patients. 79 participants (38.5%) fell into the low-risk category (0-1 points), 108 (52.7%) were classified as intermediate-risk (2-5 points), and the remaining 18 (8.8%) were in the high-risk category (6-9 points). Age, heart rate, body mass index, and co-morbidities exhibited a rising trend with increasing H₂FPEF scores ($p<0.05$ for all). Moreover, an escalation in the H₂FPEF category correlated with deteriorated echocardiographic parameters. Multivariable logistic regression analysis revealed that heart rate per minute (OR=1.048, p=0.022), H₂FPEF score (OR=1.396, p=0.018), and current smoker (OR=4.569, p=0.050) were independent determinants of in-hospital mortality. ROC curve indicated that the H₂FPEF score, with a threshold of ≥2, exhibited good discriminative capacity, demonstrating 80.4% sensitivity and 69.2% specificity (AUC=0.777, $p<0.001$). The pairwise comparison of ROC curves analysis demonstrated that troponin (AUC=0.819) exhibited better discriminative abilities than both D-dimer (AUC=0.737, p=0.029) and hemoglobin (AUC=0.691, p=0.007) in determining an intermediate-to-high H₂FPEF score.

Conclusion: COVID-19, recognized for its association with myocardial damage, could emerge as a significant risk factor for the onset of HFpEF. H₂FPEF score presents as a straightforward tool for rapid risk assessment upon hospitalization, potentially aiding in the evaluation of the risk for HFpEF development. Its utilization may facilitate early intervention, thereby contributing to a reduction in poor outcomes.

Keywords: COVID-19, heart failure with preserved ejection fraction, H₂FPEF score, in-hospital mortality, cardiac injury

INTRODUCTION

The coronavirus disease 2019 (COVID-19) remains a substantial challenge, contributing to widespread morbidity and mortality globally. It presents a complex clinical scenario with frequent cardiac symptoms and multi-organ involvement, and evidence suggests that heart damage is linked to increased major adverse cardiovascular events among individuals infected with COVID-19.[1]

Heart failure with preserved ejection fraction (HFpEF) has emerged as the predominant form of heart failure (HF) globally, closely linked to the aging of the general population and the escalating prevalence of obesity, diabetes, and hypertension.[2] HFpEF is characterized as a clinical syndrome hemodynamically associated with a heart incapable of pumping sufficient blood without elevated cardiac filling pressures. Currently, no universally accepted treatment modifies the clinical

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course of HFpEF.[3] Recent studies have demonstrated associations between COVID-19 and both systolic and diastolic dysfunction, as well as HF.[4,5]

The H2FPEF score is a simple scheme primarily developed for diagnosing HFpEF. A severe H2FPEF score includes obesity, atrial fibrillation, age >60, more than two antihypertensive treatments, an echocardiographic E/e' ratio >9, and echocardiographic pulmonary artery systolic pressure >35 mmHg. Moreover, correlations between this score, its constituent parameters, and various coronary phenomena have been demonstrated.[6] Notably, many parameters constituting this score have been associated with mortality in COVID-19. Thus, the scheme may elucidate the connection between COVID-19 and cardiac diastology and prove valuable in predicting poor prognosis. This study aims to assess the distribution and prognostic value of the HFpEF clinic and the H2FPEF score among patients with COVID-19.

METHODS

The study complied with the principles stated in the Helsinki Declaration, and the study protocol received approval from the local ethics committee and the Ministry of Health. Written informed consent was obtained from all participating patients. The Ethics Committee of Adana City Training and Research Hospital approved the study (Date: 24.03.2022, Decision No: 1860).

Study Population

This observational and prospective single-center study included 205 consecutive patients hospitalized with a diagnosis of COVID-19-associated pneumonia between February 2022 and June 2022.

The detection of SARS-CoV-2 RNA was conducted through a real-time reverse transcription polymerase chain reaction after collecting oropharyngeal and nasal samples following the protocols recommended by the Ministry of Health. Patient monitoring adhered to the COVID-19 treatment management guidelines specified by the Ministry of National Health of the Republic of Turkiye. Exclusions were made for patients with HF and reduced left ventricular ejection fraction, severe valvular disease, significant liver or kidney disease, hereditary coagulation disorders, active cancer or undergoing chemotherapy-radiotherapy, rheumatologic disease, and those below 18 years of age. A standard blood sample was uniformly collected from the antecubital vein for all patients. Comprehensive data regarding patients' clinical status, comorbidities, and drug therapy were directly extracted from their medical histories and records. Subsequently, H2FPEF score was calculated for each patient, and they were categorized into groups based on low (0-1), medium (2-5), and high (6-9) scores.

Transthoracic Two-dimensional Echocardiography

Echocardiographic parasternal and apical images, including 2D, M-mode, and Doppler echocardiography, were obtained in the in-patient clinics during hospitalization. The imaging occurred with patients in the left lateral decubitus position under stable conditions, utilizing the X5 transducer probe (Philips Epiq7; Philips Healthcare, Inc., Andover, MA, USA). The imaging was performed by three experienced cardiac sonographers who were blinded to the study data. Echocardiographic images were acquired employing four standard views (long-axis parasternal, short-axis parasternal, two-chamber apical, and four-chamber apical) following the techniques recommended by the American Society of Echocardiography. The assessment of left ventricular systolic function involved the calculation of the left ventricular ejection fraction from the apical two- and four-chamber views using Simpson's method. The end-diastolic and end-systolic endocardial borders were manually monitored.[7] Additionally, the left atrial diameter was measured at the end of systole from the parasternal long-axis window.

Tissue Doppler was utilized to measure the ratio of early transmitral flow velocity to early diastolic mitral annular velocity (E/e') and the ratio of early transmitral flow velocity (E) to late transmitral flow velocity (A). Tricuspid annulus plane systolic excursion (TAPSE) was performed using M-Mode, positioned opposite the lateral tricuspid valve annulus in a 4-chamber window. The assessment of right ventricular function involved the measurement of TAPSE. The estimated pulmonary artery systolic pressure was derived by summing the estimated right atrial pressure, determined from the size and collapse of the inferior vena cava during inspiration, with the peak velocity of the tricuspid regurgitation jet. The latter was obtained using continuous wave Doppler and applying the modified Bernoulli equation.

H2FPEF score

Throughout their hospitalization, two cardiologists, blinded to patient survival data, calculated each patient's H2FPEF score following the method described by Reddy et al.[8] This score integrates four clinical features and two echocardiographic parameters, including: (i) obesity (Body Mass Index >30 kg/m²- Heavy) (H); (ii) use of ≥2 antihypertensive drugs- Hypertensive (H); (iii) atrial Fibrillation (F); (iv) Pulmonary hypertension (Doppler echocardiographic estimated pulmonary artery systolic pressure >35 mmHg) (P); (v) age >60 years- Elder (E); and (vi) Filling pressure (Doppler echocardiographic E/e' >9) (F). Atrial fibrillation was assigned 3 points, obesity 2 points, and other variables 1 point each. The total score ranged from 0 to 9 points (**Table 1**). According to this scoring system, a score of 0-1 excludes the diagnosis of HFpEF. Scores between 2 and 5 indicate a moderate probability of HFpEF, while patients with a score of 6-9 are deemed to have a high probability of being diagnosed with HFpEF.

Table 1. The risk factors used in the H2FPEF score

H2FPEF score	H2	F	P	E	F
Clinical Variable	Heavy Hypertensive	Atrial Fibrillation	Pulmonary Hypertension	Elder	Filling Pressure
Values	-Body mass index>30 kg/m² -2 or more antihypertensive drugs	-Paroxysmal or persistent	-Doppler echocardiographic Estimated pulmonary systolic artery pressure>35mm Hg	-Age>60 years	-E/e'>9
Points Sum (0-9)	2 1	3	1	1	1

Statistical Analysis

Data analyses were conducted using IBM SPSS Statistics for Windows, Version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables with a normal distribution were presented as mean ± standard deviation, while those with a non-normal distribution were expressed as median (interquartile range25-75). Categorical variables were reported as numbers (n) and percentages (%). Student's t-test or one-way ANOVA was employed for normally distributed parameters, and the Mann-Whitney U test or Kruskal-Wallis test was used for non-normally distributed parameters. The chi-square test or Fisher's exact test was applied to compare categorical variables. Univariable and multivariable logistic regression analyses were conducted to assess in-hospital mortality and the presence of an intermediate-to-high H2FPEF score (≥2). Variables with a significance value of p<0.05 in the univariable analysis were included in the multivariable analysis. Receiver operating characteristic (ROC) curve analysis was utilized to assess the predictive accuracy and performance of H2FPEF for in-hospital mortality and to identify intermediate-to-high H2FPEF score. The Youden index was utilized to determine the cut-off for the H2FPEF score in predicting in-hospital mortality. The DeLong method was employed for pairwise comparison of ROC curves. Survival analysis against the H2FPEF score was conducted using Kaplan-Meier analysis, and the log-rank test was employed for comparisons. Statistical significance was set at p<0.05.

RESULTS

Baseline Characteristics

The study included two hundred and five consecutive hospitalized patients with COVID-19 (52% male, mean age 51 years). According to the H2FPEF score, 79 participants (38.5%) fell into the low-risk category (0-1 points), 108 (52.7%) were classified as intermediate-risk (2-5 points), and the remaining 18 (8.8%) were in the high-risk category (6-9 points). The mean age (p<0.001), heart rate (p=0.014), and body-mass index (p<0.001) demonstrated an upward trend with increasing H2FPEF score categories. The prevalence of comorbidities, including coronary artery disease (p<0.001), diabetes mellitus (p<0.001), hypertension (p<0.001), hyperlipidemia (p<0.001), and chronic obstructive pulmonary disease (COPD) (p<0.001), also increased proportionally with the score category. Additionally, in the evaluation of echocardiographic parameters, left ventricular ejection fraction (p<0.001), resting E/A ratio (p<0.001), septal E/e' (p<0.001), and TAPSE (p<0.001) exhibited a gradual decrease, while interventricular septum thickness (p<0.001), end-systolic and end-diastolic diameters (p<0.001 for both), and left atrial anteroposterior diameter (p<0.001) showed a gradual increase.

In laboratory findings, hemoglobin and albumin levels were lower in the high H2FPEF score category, while white blood cell (WBC), C-reactive protein, D-dimer, and high-sensitive troponin T (hsTnT) values were higher (p<0.001 for all). Platelet count remained similar across the groups. Table 2 provides detailed information on the baseline, echocardiographic, and laboratory parameters of the study population based on the categorized H2FPEF score.

In-hospital Mortality and Determinants

Among the COVID-19 patients, 46 individuals (22.4%) experienced in-hospital mortality. In comparison to the survivors, the deceased cohort was characterized by advanced age (46 vs. 69 years, p<0.001) and a higher prevalence of smoking (p=0.002), coronary artery disease (p=0.001), diabetes mellitus (p=0.001), and COPD (p=0.047). Additionally, those who succumbed to the illness exhibited a statistically significant increase in the H2FPEF score (1.8 vs. 4.0 points, p<0.001). Furthermore, the individual parameters contributing to the H2FPEF score were also elevated in the deceased group (p<0.05 for all), except body mass index (p=0.452).

In terms of laboratory findings, the deceased group exhibited lower levels of hemoglobin (p<0.001), platelets (p=0.004), and albumin (p<0.001), while WBC count, C-reactive protein, D-dimer, and hsTnT levels were higher (p<0.001 for all). Table 3 provides an overview of the demographic and laboratory parameters, as well as H2FPEF score details, based on in-hospital mortality status.

Multivariable logistic regression analysis revealed that heart rate per minute (OR=1.048, 95% CI 1.007-1.091, p=0.022), H2FPEF score (OR=1.396, 95% CI 1.060-1.839, p=0.018), and current smoking status (OR=4.569, 95% CI 1.001-20.917, p=0.050) were independent determinants of in-hospital mortality among patients hospitalized for COVID-19 (Table 4).

Table 2. Baseline characteristics of the study population by the H2FPEF score

	All patients (n=205)	Low score (0-1 points) (n=79)	Intermediate score (2-5 points) (n=108)	High score (6-9 points) (n=18)	p-value*
Age, years	51.4±19.5	34.4±11.8	60.6±15.7	70.6±10.0	<0.001
Male gender, n (%)	107 (52.2)	44 (55.7)	57 (52.8)	6 (33.3)	0.227
Systolic BP, mm Hg	119.1±16.1	113.8±10.0	122.2±16.9	126.6±26.8	0.001
Diastolic BP, mm Hg	71.3±9.5	69.6±7.4	72.3±10.0	73.6±13.7	0.110
Heart rate, beats per minute	86.5±15.3	82.6±11.9	88.6±16.3	90.6±18.8	0.014
BMI, kg/m²	28.2±5.1	25.1±2.6	29.3±4.7	34.8±6.5	<0.001
Coronary artery disease, n (%)	30 (14.6)	2 (2.5)	20 (18.5)	8 (44.4)	<0.001
Diabetes mellitus, n (%)	41(20)	3 (3.8)	29 (26.9)	9 (50.0)	<0.001
Atrial fibrillation, n (%)	8 (3.9)	0 (0)	0 (0)	8 (44.4)	<0.001
Hypertension, n (%)	75 (36.6)	2 (2.5)	55 (50.9)	18 (100)	<0.001
Hyperlipidemia, n (%)	30 (14.6)	0 (0)	20 (18.5)	10 (55.6)	<0.001
COPD, n (%)	15 (7.3)	0 (0)	9 (8.3)	6 (33.3)	<0.001
Cerebrovascular accident, n (%)	2 (1)	0 (0)	1(0.9)	1(5.6)	0.096
Cancer, n (%)	4(2)	1 (1.3)	3 (2.8)	0 (0)	0.626
Current smoker, n (%)	32 (15.6)	14 (17.7)	12 (11.1)	6 (33.3)	0.045
LVEF, %	58.9±6.9	62.5±3.0	57.5±6.3	51.9±12.7	<0.001
IVS, mm	10.3±2.4	8.7±1.3	11.0±2.2	13.2±2.7	<0.001
LVDd, mm	47.0±4.2	44.7±3.2	48.1±4.0	50.3±4.9	<0.001
LVDs, mm	30.8±5.4	27.7±4.6	32.3±4.7	35.6±6.0	<0.001
LAD, mm	38.4±5.6	34.0±4.9	40.7±4.5	44.4±5.9	<0.001
E/A at rest	1.07±0.45	1.43±0.36	0.88±0.33	0.71±0.40	<0.001
E/e' septal	11.7±5.6	7.3±3.6	14.2±5.0	16.0±4.0	<0.001
sPAP, mm Hg	29.2±7.8	24.0±4.7	31.2±7.2	40.5± 5.7	<0.001
TAPSE, mm	19.8±5.1	23.1±4.1	18.4±4.5	14.1±3.6	<0.001
Hemoglobin, mmol/L	12.8±1.9	14.5±1.6	13.5±1.9	13.0±2.3	<0.001
WBC, ×10³/ul	6.8±3.3	6.2±2.0	6.8±3.4	9.1±5.6	0.004
Platelet count, ×10³/Ul	213.1±65.6	220.8±57.5	211.3±69.7	190.2±70.9	0.187
Albumin, g/L median, IQR	3.8 (3.5-4.1)	4.0 (3.8-4.3)	3.6 (3.2-4.0)	3.6 (2.9-3.9)	<0.001
C-reactive protein, nmol/L, median, (IQR)	1.00 (0.21-6.28)	0.22 (0.10-0.70)	2.01 (0.52-13.88)	5.48 (1.19-21.95)	<0.001
D-dimer, µg/ml, median, (IQR)	0.25 (0.06-0.97)	0.10 (0.0-0.26)	0.42 (0.11-4.23)	0.61 (0.17-8.19)	<0.001
hsTnT, pg/ml, median, (IQR)	2.8 (1.6-9.1)	1.7(1.3-2.5)	4.4 (2.3-15.8)	19.5 (6.9-99.0)	<0.001

Data are given as mean± standard deviation (SD), median (IQR25-75), or n (%). P value was calculated using one-way ANOVA test or Kruskal-Wallis test for continuous variables and a chi-squared test for categorical variables, as appropriate. *A p-value <0.05 was considered significant. Abbreviations: BMI, body mass index; BP, blood pressure; COPD, Chronic obstructive pulmonary disease; hsTnT, high-sensitive Troponin T; LAD, left atrium diameter; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; IVS, interventricular septum; IQR, interquartile range; sPAP, Systolic pulmonary artery pressure; TAPSE, Tricuspid annular plane systolic excursion; WBC, White blood count.

H2FPEF Score and Survival

The analysis of ROC curve indicated that the H2FPEF score, with a threshold of ≥2, exhibited good discriminative capacity, demonstrating 80.4% sensitivity and 69.2% specificity (AUC=0.777, 95% CI 0.710-0.844, p<0.001, Figure 1). Kaplan-Meier curve analysis, stratified by the H2FPEF score using this cut-off determined by the Youden index, revealed a higher in-hospital mortality rate among individuals with scores ≥2 (log-rank p<0.001, Figure 2).

The results of the multivariable logistic regression analysis aimed at identifying parameters associated with an intermediate-to-high H2FPEF score (≥2) revealed that diabetes (OR=5.775, 95% CI 1.534-21.735, p=0.010), hemoglobin (OR=0.782, 95% CI 0.637-0.961, p=0.019), D-dimer (OR=0.993, 95% CI 0.985-1.000, p=0.050), and hsTnT (OR=1.126, 95% CI 1.013-1.251, p=0.027) were associated with an increased H2FPEF score (Table 5). The pairwise comparison of ROC curves analysis demonstrated that hsTnT (AUC=0.819) exhibited better discriminative abilities than both D-dimer (AUC=0.737, p=0.029) and hemoglobin (AUC=0.691, p=0.007) in determining an intermediate-to-high H2FPEF score (Figure 3).

Table 3. Comparison of baseline characteristics among COVID-19 patients based on their mortality status

Variable	Survivor (n=159)	Non-survivors (n=46)	p
Age	46.3±18.0	69.0±13.4	<0.001
Male gender, n (%)	77 (48.4)	29 (63.0)	0.081
Systolic BP, mm Hg	117.6±13.1	127.3±25.08	0.058
Diastolic BP, mm Hg	70.7± 8.2	74.6± 14.2	0.163
Heart-rate, beats per minute	83.5± 10.9	96.9±22.3	<0.001
H_2FPEF score	1.8±2.0	4.0±2.1	<0.001
H_2FPEF score components			
BMI >30 kg/m²	39 (27.1)	15 (33.3)	0.452
E/e' >9	67 (45.9)	41 (91.1)	<0.001
Age >60, n (%)	39 (24.5)	38 (82.6)	<0.001
Hypertension	41 (28.8)	34 (73.9)	<0.001
SPAP>35 mm Hg, n (%)	36 (22.6)	28 (60.9)	<0.001
Atrial fibrillation, n (%)	3 (1.9)	5 (10.9)	0.015
H_2FPEF score point			<0.001
0- 1 (low)	77 (48.4)	2 (4.3)	
2-5 (intermediate)	73 (45.9)	35 (76.1)	
6-9 (high)	9 (5.7)	9 (19.6)	
Diabetes mellitus, n (%)	20 (12.6)	21 (45.7)	
Current smoker, n (%)	18 (11.3)	14 (30.4)	0.002
Coronary artery disease, n (%)	12 (7.5)	18 (38.1)	<0.001
Cerebrovascular accident, n (%)	0 (0)	2 (4.3)	0.049
COPD, n (%)	8 (5.0)	7 (15.2)	0.047
Cancer, n (%)	2 (1.3)	2 (4.3)	0.218
Hemoglobin, mmol/L	14.2±1.6	12.5±2	<0.001
WBC, $\times 10^3$/ul	6.1±2.4	9.0±4.8	<0.001
Platelet count, $\times 10^3$/ul	220.1± 60.3	188.9±77.2	0.004
Albumin, g/L, median, (IQR)	3.9 (3.6-4.2)	3.2 (2.6-3.6)	<0.001
C-reactive protein, nmol/L, median, (IQR)	0.51 (0.20-1.70)	22.15 (10.27-112.95)	<0.001
D-Dimer, µg /ml, median, (IQR)	0.13 (0.02-0.36)	441.50 (0.98-1842.50)	<0.001
hsTnT, pg/ml, median, (IQR)	2.3 (1.5-4.5)	24.0 (7.6-159.0)	<0.001

The data are expressed as number (%), mean ± standard deviation (SD), or median (IQR25-75). Statistical comparisons were performed using an independent samples t-test or the Mann-Whitney U-test for continuous variables, while categorical variables were analyzed using a chi-squared test or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant. Abbreviations: BMI, Body Mass Index; BP, blood pressure; COPD, Chronic obstructive pulmonary disease; hsTnT, high-sensitive Troponin T; WBC, White Blood Count.

Table 4. Univariable and multivariable logistic regression analysis of in-hospital mortality

Variable	Univariable analysis		Multivariable analysis+	
	OR (95% CI)	p value*	OR (95% CI)	p value*
Heart rate	1.064 (1.037-1.091)	<0.001	1.048 (1.007-1.091)	0.022
H_2FPEF score	1.573 (1.325-1.868)	<0.001	1.396 (1.060-1.839)	0.018
Diabetes mellitus	5.838 (2.769-12.308)	<0.001	2.591 (0.807-8.320)	0.110
Current Smoker	3.427 (1.545-7.604)	0.002	4.569 (1.001-20.917)	0.050
Coronary artery disease	7.875 (3.418-18.146)	<0.001	0.878 (0.220-3.509)	0.854
COPD	3.388 (1.158-9.914)	0.026	1.191 (0.219-6.474)	0.840
Hemoglobin	0.612 (0.498-0.754)	<0.001	0.796 (0.570-1.113)	0.183
WBC	1.274 (1.144-1.419)	<0.001	1.055 (0.863-1.289)	0.603
Platelet count	0.992 (0.986-0.997)	0.005	0.992 (0.983-1.002)	0.123
Albumin	1.087 (0.965-1.223)	0.169	-	-
C-reactive protein	1.048 (1.024-1.072)	<0.001	1.020 (0.999-1.043)	0.067
D-dimer	1.260 (1.125-1.412)	<0.001	1.080 (0.984-1.186)	0.107
hsTnT	1.087 (0.990-1.192)	0.079	-	-

*p-value <0.05 was considered significant. +Nagelkareke R square =0.656, -2log-likelihood=103, Omnibus tests of model coefficients p<0.001, Hosmer-Lemeshow test p=0.437 Abbreviations: CI, Confidence Interval; COPD, Chronic obstructive pulmonary disease; hsTnT, high-sensitive troponin T, OR, Odds Ratio; WBC, white blood cell.

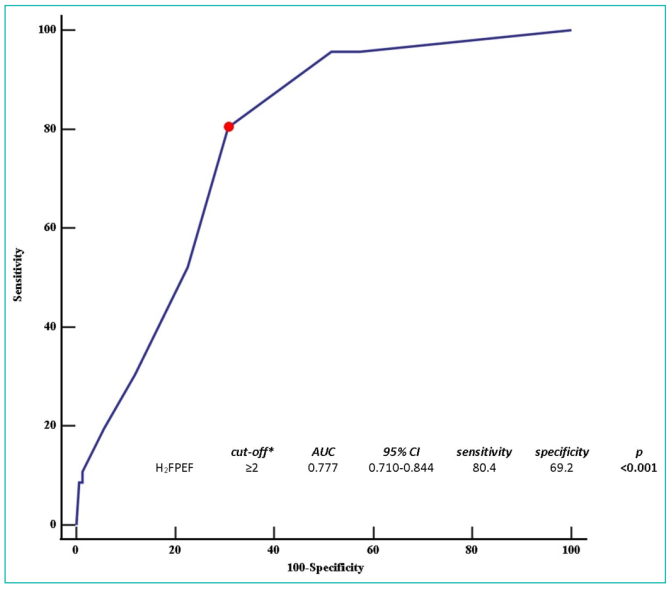

Figure 1. Receiver Operating Characteristic curve that illustrates the predictive ability of the H2FPEF score in identifying in-hospital mortality Abbreviations: AUC, Area Under the Curve; CI, Confidence Interval. *The threshold was determined using the Youden Index.

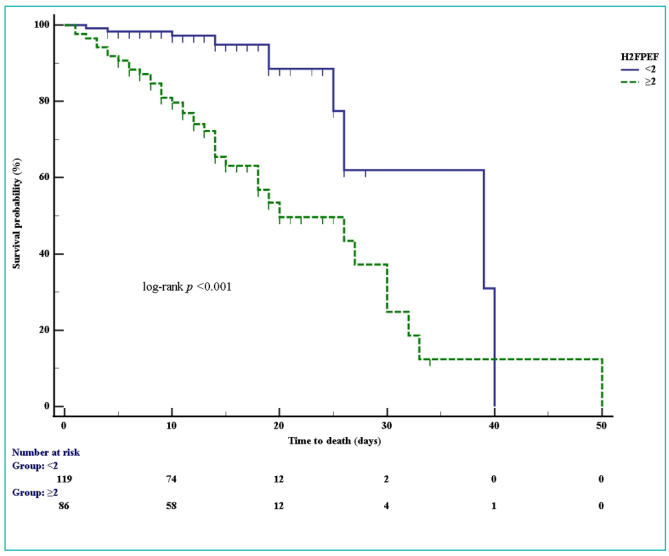

Figure 2. Kaplan-Meier survival curves of in-hospital mortality by H2FPEF score

DISCUSSION

Our objective was to explore the impact of the H2FPEF score on the distribution and clinical outcomes of COVID-19 patients. The H2FPEF score, designed as a straightforward tool for diagnosing HFpEF, was considered relevant given the occurrence of a clinical presentation resembling HFpEF in individuals affected by COVID-19. The key findings of our investigation are as follows: I) A substantial proportion of COVID-19 patients fell into the intermediate- and high-risk categories for HFpEF development. II) Non-survivors of COVID-19 exhibited significantly elevated H2FPEF scores compared to survivors (p<0.001). III) H2FPEF, heart rate, and smoking were established as independent

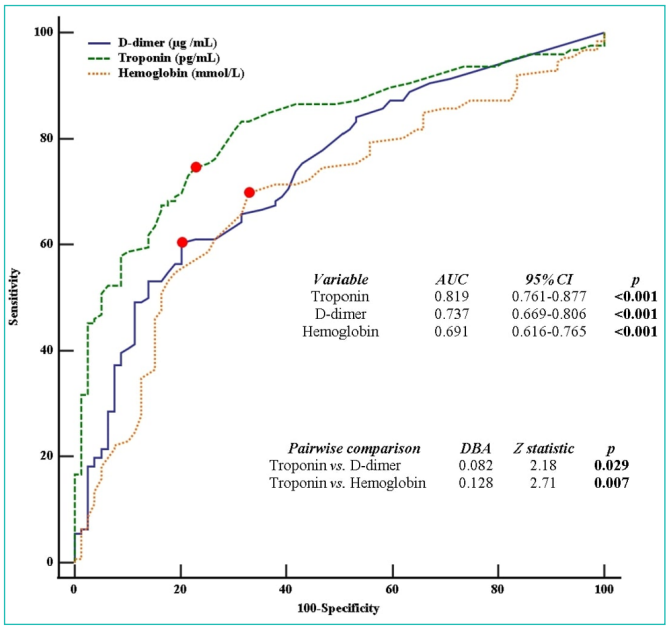

Figure 3. The results of the Receiver Operating Characteristic curve analysis that demonstrate the predictive accuracy of high-sensitivity cardiac troponin T, hemoglobin, and D-Dimer in the detection of intermediate-to-high H2FPEF scores (≥2) and the pairwise comparison of curves Abbreviations: AUC, Area Under the Curve; CI, Confidence Interval; DBA, Difference Between Areas. Note that the pairwise comparison analysis was conducted utilizing the DeLong method

determinants of in-hospital mortality. IV) Kaplan-Meier survival analysis revealed a significant increase in mortality among patients with an intermediate-to-high H2FPEF score (p<0.001 by log-rank test).

The activation of neurohormones and markers of myocyte necrosis, particularly in septic patients, has demonstrated a robust association with HFPEF.[9] Myocardial relaxation abnormalities in these patients could range from asymptomatic increases in cardiac filling pressures to clinical manifestations of classical HFpEF. COVID-19 has the potential to induce myocardial damage through inflammation and/or a cytokine storm, especially in cases with a severe course and pre-existing chronic diastolic dysfunction. This damage may further compromise myocardial relaxation, particularly in situations involving the administration of large volumes of intravenous fluids, ultimately leading to severe pulmonary involvement and concealed pulmonary edema beneath acute respiratory distress syndrome.[10] Consequently, it has been suggested that COVID-19 may contribute to HFpEF development through direct viral damage or autoimmune mechanisms.[5]

Research on the HFpEF clinic in COVID-19 patients is notably limited in the literature. The initial study, conducted with the most substantial patient cohort comprising 64 individuals, was the first to report a significant proportion of COVID-19 patients demonstrating a high risk of HFpEF. Correspondingly,

over half of the patients in this study were categorized into the clinically intermediate and high-risk groups for HFpEF, mirroring findings similar to ours.[11] Given this context, we believe that our study, including the largest number of patients on this subject, may provide a crucial contribution to the existing literature.

Elevated H2FPEF scores were linked to unfavorable clinical outcomes in our study. Moreover, the H2FPEF score exhibited robust performance in ROC analysis for determining in-hospital mortality among COVID-19 patients. Notably, the risk factors included in the H2FPEF score align with factors already recognized to be associated with COVID-19-related deaths. While our findings may not be entirely surprising in this context, the prevalence of moderate and high scores in our patient cohort, accounting for 61.5% of patients, underscores the substantial clinical risk for HFpEF. We posit that adjustments in the treatment strategy, considering HFpEF, could be beneficial in mitigating mortality in this patient group. Atrial fibrillation,[12] hypertension,[13] pulmonary hypertension,[14] and diastolic filling disorder,[15] all of which have established mortality associations in COVID-19 patients, render the H2FPEF score with its concise scoring system particularly pertinent in this patient group, alongside the documentation of advanced age and obesity.[16]

Notable increases were observed in both age and the prevalence of chronic diseases, corresponding to the escalation of the H2FPEF score in the present study. Furthermore, the H2FPEF score was significantly elevated in the non-survivor group. It is well-established that mortality rates in COVID-19 are higher among the elderly and individuals with significant comorbidities.[17,18] Remarkably, populations with poorer prognoses typically manifest at least one comorbidity, with hypertension, diabetes, chronic obstructive pulmonary disease, and heart disease ranking among the most prevalent.[19] We also found that the H2FPEF score appears to serve as a valuable predictor of morbidity and mortality, shedding light on the risk profile of the HFpEF clinic in COVID-19 patients. Furthermore, multivariable regression analysis revealed that, in addition to a high H2FPEF score, a high heart rate, and current smoker were independent determinants of in-hospital mortality. Similar to our findings, sinus tachycardia, the presence of diabetes mellitus, and a low platelet count have consistently emerged as independent risk factors for mortality in COVID-19, as demonstrated in numerous studies.[20-22]

A notable percentage (20% to 35%) of COVID-19 patients admitted to hospitals display elevated levels of cardiac biomarkers, such as hsTnT and natriuretic peptides.[23] Myocardial injury, defined by increased hsTnT values, has been linked to a more severe disease course and even death in COVID-19 patients.[24] Elevated D-dimer levels at admission are significantly associated with the severity of COVID-19 pneumonia and may serve as a predictor of mortality in hospitalized patients.[25,26] Serum CRP levels can effectively gauge disease severity and predict outcomes in patients with COVID-19.[27] In our study, patients with biochemical evidence of myocardial injury had higher H2FPEF scores, and it was observed that D-dimer, CRP, and particularly high-sensitive hsTnT levels, which impact COVID-19 severity and mortality, are robust predictors of high H2FPEF score. Therefore, increased hsTnT levels, especially in COVID-19 patients, may aid in identifying cardiac diastolic abnormalities caused by COVID-19.

Limitations

It is crucial to highlight that despite the prospective design of our study, it was conducted with a relatively small patient cohort. Nevertheless, conducting detailed echocardiograms in such a sizable sample of COVID-19-infected patients lends significance to the study. Another limitation of the study is the absence of certain laboratory parameters, such as N-terminal proB-type brain natriuretic peptide, and the lack of information on treatment protocols that could potentially influence the study outcomes. The majority of our patients presented with pneumonia necessitating hospitalization, and they exhibited a high risk of mortality during follow-up. Consequently, our findings may not fully represent the entire COVID-19 population, particularly those requiring outpatient treatment. Given that our study focused on the acute phase of COVID-19, additional investigations are warranted to elucidate the development of HFpEF in COVID-19 survivors during the chronic phase of recovery.

CONCLUSION

COVID-19 may emerge as a novel risk factor for HFpEF development, potentially triggered by systemic inflammation and autoimmune activation. It is advisable to conduct comprehensive assessments, including biomarkers and echocardiographic evaluations for HFpEF, in high-risk COVID-19 patients. In this context, the H2FPEF score may be valuable for rapid risk assessment upon hospital admission, providing insights to guide early treatment and facilitate close follow-up.

List of Abbreviations

A: Late transmitral flow velocity; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; E: Early transmitral flow velocity; E/e': Early transmitral flow velocity to early diastolic mitral annular velocity; HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; hsTnT: high-sensitive troponin; TAPSE: Tricuspid annulus plane systolic excursion.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Adana City Training and Research Hospital Clinical Researches Ethics Committee. (Date:24.03.2022, Decision No: 1860)

Informed Consent

Written informed consent was obtained from all participating patients.

Referee Evaluation Process

Externally peer reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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