Original Research Article

Association between CHA2DS2-VASc Score and Right Ventricular Dysfunction in Patients with Acute Pulmonary Embolism

Abstract

Background: Acute right ventricular dysfunction (RVD) is a leading cause of death in the setting of acute pulmonary embolism (PE). Therefore, several studies investigated the predisposing factors of RVD. However, at present, little is known about the clinical predictors of RVD in the patients presented with acute PE.

Objective: To assess the association of CHA_2DS_2-VASc Score with the PE severity, RVD and the in-hospital mortality in patients presented with acute PE.

Methods: This study was conducted on 50 patients admitted with acute PE at Tanta University Hospitals. We studied the association of different variables including demographic data, common risk factors, clinical presentation, management and the in-hospital mortality with the PE clinical subgroups (massive, sub-massive and non-massive) based on the severity of clinical presentation and also the association of these variables with the thromboembolic risk (high, moderate and low) based on the CHA2DS2-VASc scores. The independent predictors of the RVD were then investigated by the univariate and multivariate regression analyses.

Results: The massive PE presentation was associated with higher CHA2DS2-VASc scores (P value = 0.02). Also, the incidence of RVD was higher among the high risk group of patients (CHA2DS2-VASc scores ≥3) with P value = 0.009. TAPSE, MPI, FAC**,** and E`/A` ratio were found to be more significant in the high risk group (P value = 0.032, 0.002, 0.007 and 0.001), respectively. The independent predictors of RVD were demonstrated to be tachycardia, lower systolic blood pressure and CHA2DS2-VASc score (P value = 0.022, 0.007, 0.021), respectively. The CHA2DS2-VASc score predicted the presence of RVD with 66.7 % sensitivity and 78.6% specificity as demonstrated by the receiver operating characteristic (ROC) analysis, with area under the curve (AUC) of 0.776 (CI 0.636-0.882, P value < 0.001). This study demonstrated no statistically significant difference between the different risk groups regarding the in-hospital mortality.

Conclusion: Being independent of other factors, the CHA2DS2-VASc score can be used as a new, simple, and reliable tool to predict the development of RVD in patients with acute PE.

Key words: Acute pulmonary embolism, Right ventricular dysfunction, CHA2DS2-VASc score.

1. Introduction

Venous thromboembolism includes deep vein thrombosis and pulmonary embolism (PE), both together constitute one of the "big three" cardiovascular diseases, the other two being myocardial infarction and stroke [(1)]. It is the third common cause of cardiovascular death with an overall annual incidence of 100–200 per 100 000 inhabitants.[(2)]

PE is a clinical phenomenon presenting with a spectrum of findings, ranging from small emboli causing mild hemodynamic dysfunction to massive emboli leading to cardiogenic shock, and it can be sometimes fatal.[3] Due to pulmonary vascular bed obstruction, PE can result in acute right ventricular dysfunction (RVD) which is a life-threatening condition. Because most patients ultimately die within the first hours of presentation, early diagnosis is of utmost importance.[4]

In clinical practice, echocardiography is the modality of choice for the assessment of morphology and function of the right ventricle (RV) as it is non-invasive, widely available, relatively inexpensive, and has no side effects.[5] Echocardiographic findings indicating RVD have been reported in about 25% of patients with PE, including RV dilation, increased RV-LV diameter ratio, hypokinesia of the RV free wall, increased velocity of the jet of tricuspid regurgitation and decreased tricuspid annulus plane systolic excursion.[6]

The development of RVD in the setting of acute PE has been related to several specific clinical and laboratory variables, such as diabetes, advanced age, and female gender. These risk factors are also included in the CHA2DS2-VASc score.[7],[8]

CHA2DS2-VASC score (C: congestive heart failure or left ventricular systolic dysfunction, H: hypertension, A: age of $\geq$ 75 years, D: diabetes mellitus, S: previous stroke, V: vascular disease, A: age between 65 and 74 years, Sc: female gender) is a clinical prediction rules which are used to determine the thromboembolism risk and to manage the anticoagulation treatment in patients with non-valvular atrial fibrillation.[9] Because of its effectiveness in treatment and follow up processes in patients with AF, CHA2DS2-VASc score has been involved in several studies concerned with other diseases as well, such as PE, chronic obstructive pulmonary disease, heart failure and coronary artery disease.[10–15]

In this study, we aimed to assess the association of CHA_2DS_2-VASc Score with the PE severity, RVD and the in-hospital mortality in patients presented with acute PE.

2. Material and methods

2.1. Patient population

This study was conducted to 50 patients with proven acute pulmonary embolism that were admitted at cardiology department of Tanta university hospital in a period of six months starting from June 2019.

2.2. Inclusion criteria

All patients presented with symptoms suggesting acute pulmonary embolism as shortness of breath, haemoptysis, syncope and/or chest pain, positive D-dimer test and visualization of the pulmonary embolus by CT pulmonary angiography were included.

2.3. Exclusion criteria

All other conditions that can affect the right ventricular function other than PE, such as:

- Previous right ventricular dysfunction.
- Valvular heart diseases.
- Congenital heart diseases.
- Sepsis or septic shock.
- Serious pericardial effusion.

- Nephrotic syndrome.
- Acute renal failure.

2.4. Methods

All patients were subjected to full history taking with emphasis on demographic data involving age and sex, predisposing factors of pulmonary embolism, the main presenting symptom of the patients including shortness of breath, chest pain, cough, haemoptysis, syncope and unilateral lower limb pain, full clinical examination to define hemodynamic status at time of admission, calculation of pre-test probability of each patient by using both Wells score and Revised Geneva score, resting 12 leads ECG upon admission and during hospital stay regarding presence of sinus tachycardia and signs of RV strain, baseline laboratory tests especially Troponin and D-dimer, Duplex ultrasound on the venous system of both lower limbs for detection of deep vein thrombosis (DVT) and CT pulmonary angiography which is the modality for confirmation of the diagnosis we used.

Transthoracic echocardiography

All studies were performed using (a GE vivid seven Cardiac ultrasound phased array system with tissue Doppler imaging using M4S transducer 4 M.HZ.) for assessment of RV systolic and diastolic function.

The RV systolic function was assessed using:

- **Tricuspid annular plane systolic excursion (TAPSE) (mm):** represents a measure of RV longitudinal function, measured in 2-dimensional M-mode echocardiograms from the apical 4-chamber view, positioning the cursor on the lateral tricuspid annulus near the free RV wall and aligning it as close as possible to the apex of the heart. RVD is suggested by TAPSE values of <17 mm.[16]
- **Pulsed Doppler velocity at the annulus (cm/s) or S` wave:** measuring peak systolic velocity of the tricuspid annulus by pulsed wave tissue Doppler imaging (TDI) (cm/s) by placing cursor over lateral annulus of tricuspid valve then Pulsed Wave Doppler and TDI and then Identify maximum systolic velocity above the baseline (S` wave). RVD is suggested by S′ wave velocity of <9.5 cm/s.[16]
- **Myocardial performance index (MPI) or Tei index:** an index of global (systolic and diastolic) RV performance. The isovolumic contraction time (IVCT), the isovolumic relaxation time (IVRT), and ejection time (ET) intervals were measured from the same heartbeat using either PW Doppler or TDI velocity of the lateral tricuspid annulus.
MPI= (IVRT + IVCT)/ET = (TCO "Tricuspid valve closure–to–opening time" - ET)/ET.
MPI > 0.43 by PW Doppler and > 0.54 by DTI indicate RVD. [16]
- **Fractional area change (FAC):** a 2D measure of RV global systolic function, obtained from the apical four-chamber view, optimized to obtain a RV focused view showing clearly the border of the endocardium and the RV free wall in particular. It was then calculated as the difference in end-diastolic area (EDA) and end-systolic area (ESA) divided by the end-diastolic area. RV FAC < 35% indicates RV systolic dysfunction.[17]

The RV diastolic function was assessed using:

Doppler examination of the tricuspid inflow and tissue Doppler interrogation of the lateral tricuspid valve annulus, then the E` (cm/s), A` (cm/s), E`/A` and E/E` ratios were measured.

The acute pulmonary embolism cases were then assigned to 3 clinical subgroups, according to their hemodynamic and radiological characteristics: [18]

- **Massive PE group:** including the hemodynamically unstable patients (developing hypotension, shock, or cardiovascular arrest) and acute RVD detected by echocardiogram.
- **Sub-massive PE group:** including the patients with stable hemodynamics but with RVD detected by echocardiogram.
- **Non-massive PE group:** including the patients with stable hemodynamics with no RVD confirmed by echocardiogram.

The simplified Pulmonary Embolism Severity Index (sPESI) scores of the patients were then calculated and patients with sPESI risk scores of were accepted to have low sPESI scores and the patients with sPESI scores of 1 were accepted to have high sPESI scores.[19] Then all patients were risk stratified depending on presence of hemodynamic instability or not, result of sPESI score, cardiac troponin level and presence of RVD detected by transthoracic echocardiography and categorized according to the risk for 30-day mortality into high risk, intermediate high, intermediate low and low risk patients.[20]

The CHA2DS2-VASc score was calculated for each patient. The components of the CHA2DS2-VASc score were calculated as follows: congestive heart failure (1 point), hypertension (1 point), age (>75 years [2 points]), diabetes mellitus (1 point), history of stroke or transient ischemic attacks (2 points), history of vascular disease (1 point), age (>65 years [1 point]), and female gender (1 point). and the patients were then classified into 3 groups as follows: [21]

- **Low-risk group:** with scores between 0 and 1.
- **Moderate risk group:** with scores of 2.
- **High-risk group:** with scores of 3 and more.

Treatment lines were given for each patient regarding the type of parenteral anticoagulation (UFH, LMWH or Fondaprinux), whether the patient was given fibrinolytic therapy or not and the type of long-term anticoagulation prescribed upon discharge (warfarin, Non-Vitamin K Antagonist Oral Anticoagulants (NOACs) or LMWH). The in-hospital outcome documented according to occurrence of in hospital death and bleeding complications. Finally, the association between the CHA2DS2-VASc score and the clinical subgroups of PE, RVD and in-hospital mortality in patients with acute PE was investigated.

2.5. Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 26. The distribution of continuous numerical data was assessed using the Shapiro-Wilk test for normality. Data following the normal distribution were summarized as mean ± standard deviation (SD); and compared using one way ANOVA test (for three groups, followed by post-hoc test if significant). [22] Data not following the normal distribution were summarized as median and interquartile range (IQR); and Kruskal-Wallis test was used to compare among three groups (followed by post-hoc test if significant). Categorical data were presented as frequencies (count and percentage). Pearson's Chi square test was used for independence, Fisher's exact test or Fisher-Freeman-Halton exact test were used to examine the association between two categorical variables as appropriate. The p-value was adopted at 0.05 to interpret the results of statistical tests. [22]

3. Results and Discussion

A total of 50 patients with acute PE were included in the study. They were assigned to 3 groups, namely massive PE (n= 20), sub-massive PE (n = 14) and non-massive PE (n = 16) based on their hemodynamic characteristics. The associations of the variables with the PE subgroups are summarized in Table 1. The mean age was 54.3 ±14.8 with 31 females and 19 males. Of all risk factors, only the history of abdominal or pelvic surgery within one month was statistically significantly higher in the massive PE subgroup (P value= 0.02). Tachycardia, hypotension and tachypnea were manifested more among the massive group of patients with (P value < 0.001, < 0.001 and 0.01), respectively. Hypoxia was detected more among the massive and sub-massive groups of patients with (P value = 0.002).

Concerning ECG findings on admission, only sinus tachycardia (P value= 0.002) with heart rate >100 beat per minute and RBBB (P value= 0.014) showed statistically significant difference among the PE clinical subgroups. Both had higher prevalence in the massive group of patients compared to another group. ECG findings of studied population in relation to PE clinical subgroups are summarized in Table 2.

The incidence of the positive troponin was detected to be significantly higher (95.0%) in the massive PE group (P value= 0.001), also the D-dimer level was significantly higher in the massive PE group (P value < 0.001) with median [IQR] of 6.3 [6.0-8.5] compared to other groups as shown in Table 3.

Echocardiographic assessment of RV function

Assessment of RV systolic function using TAPSE as well as S` wave were found to be more significant among patients in the massive and sub-massive groups compared to the non-massive group, with (P value < 0.001) for both. Pulsed Doppler MPI and Tissue Doppler MPI were more significant among the massive group of patients with (P value < 0.001) for both. Also, fractional area change (FAC) was found to be more significant among the massive group of patients with mean ± SD (28.1 ± 3.6) and (P value < 0.001). Additionally, RV diastolic function was assessed using the E`/A` and E/E` ratios. E`/A` was significant among the massive and sub-massive groups compared to the non-massive group, with (P value < 0.001), while E/E` ratio was found to be more significant among the massive group (P value < 0.001). Moreover, Analysis of RVD regarding its presence or absence in different PE clinical subgroups was found to be statistically significant (P value <0.001). 36 patients (72%) presented with RVD. There was higher incidence of RVD in massive and sub-massive groups (100%), compared to the non-massive group of patients (12.5%). Echocardiographic assessment of RV function is summarized in Table 4.

In the current work, calculation of CHA2DS2-VASc score for each patient revealed a significant correlation between CHA2DS2-VASc score and the PE clinical subgroups (P value = 0.01). The patients were classified according to CHA2DS2-VASc scores into 3 risk groups the low-risk group (N = 11) had a score between 0 and 1, the moderate risk group (N = 12) had a score of 2 and the high-risk group (N = 27) had a score of 3 or more. There was statistically significant difference between different risk groups of CHA2DS2-VASc scores and PE clinical subgroups (P value = 0.02). The massive PE group of patients had the highest risk (80%) compared to other groups.

The elderly patients were common with higher rates in the high risk group, mean ± SD (59.6 ± 13.8) and (P value = 0.017). Among different risk factors for acute PE, there were only three risk factors that were found to be correlated to the different risk group of CHA2DS2-VASc score. Estrogen use had a higher prevalence among the patient with low risk (P value = 0.017). In contrast, the percentage of hypertensive patients was higher in the

moderate and high-risk group (P value = 0.01). Additionally, the percentage of patients with previous DVT was higher in the high-risk group (P value = 0.011).

Concerning the presenting symptoms, dyspnea and unilateral lower limb pain were correlated with the high risk group of patients (P value = 0.001 and 0.04), respectively. Additionally, small percentage of patients presented with hemoptysis (10.0%), however, it was prevalent among the moderate risk group of patients (P value = 0.02). Hypotension, tachypnea and hypoxia were more prevalent among the high risk group of patients with P value = 0.009, 0.001 and 0.003, respectively. The association between CHA2DS2-VASc Score and various variables is summarized in Table 5.

The incidence of the positive troponin was significantly higher (81.5%) in the high risk group (P value= 0.016), also the D-dimer level was significantly higher in the high risk group (P value = 0.026) with median [IQR] of 6.0 [4.7-7.0] compared to other groups. Importantly, patients in the high-risk group of CHA2DS2-VASc score had a higher pre-test probability according to wells score (Mean 6.4 ± 1.6, P value < 0.001) and Revised Geneva score (Mean 9.6 ± 3.7, P value < 0.001).

Echocardiographic assessment of RV function in relation to CHA2DS2-VASc score

The incidence of RVD was higher among the high risk group of patients (P value = 0.009). Regarding RV systolic function, TAPSE (P value = 0.032), pulsed and tissue Doppler MPI (P value = 0.002) as well as FAC (P value = 0.007) were more significant in the high risk group. And as regard to RV diastolic function, E`/A` ratio was found to be more significant among patients in high risk group (P value = 0.001), while E/E` ratio showed no statistically significant difference between different risk groups (P value = 0.106). These data are summarized in Table 6 and Figures (1-5).

It was also noted that, the incidence of receiving thrombolytic treatments was detected to be higher (59.3%) in the high-risk group with (P value = 0.004) compared to other groups (Figure 6). And despite the higher percent of deaths among the high-risk group of patients compared to other groups, the in-hospital mortality rates were not significantly associated with any of the risk groups (P value =0.772) as shown in Figure 7.

Univariate and multivariate regression analysis (Table 7) were performed to investigate the possible predictors of RVD in patients with acute PE in the study population. Accordingly, higher heart rates (OR 1.044, P value = 0.022), lower systolic blood pressure (OR 0.948, P value = 0.007) and CHA2DS2-VASc score (OR 2.507, P value = 0.021) were demonstrated to be independent predictors of RVD. It was also demonstrated by the receiver operating characteristic (ROC) analysis that the CHA2DS2-VASc score predicted the presence of RVD with 66.7 % sensitivity and 78.6% specificity, the area under the curve (AUC) was 0.776, 95% confidence interval (CI) 0.636-0.882, P value < 0.001 and with cutoff value CHA2DS2-VASc score more than 2 as shown in Figure 8.

	Acute Pulmonary Embolism			
Variable	**Massive (n = 20)**	**Sub-massive (n = 14)**	**Non-massive (n =16)**	**P Value**
Age (Mean ±SD)	55.9 ±17.1	55.1±13.6	51.7 ±13.0	0.687
Sex				0.321
Female	11 (55.0%)	11 (78.6%)	9 (56.3 %)	
Male	9 (45.0%)	3 (21.4%)	7 (43.8%)	
Predisposing factors				
Estrogen use	2 (10.0 %)	4 (28.6%)	4 (25.0%)	0.367
Autoimmune disease	2 (10.0%)	3 (21.4%)	2 (12.5%)	0.689
Active DVT	6 (30.0%)	4 (28.6%)	1 (6.3%)	0.181
Abdominal and pelvic surgery within one month	6 (30.0%)	1 (7.1%)	0 (0.0%)	0.020*
Active cancer	1 (5.0%)	4 (28.6%)	3 (18.8%)	0.179
bed rest > 3 days	6 (30.0%)	5 (35.7%)	2 (12.5%)	0.335
Clinical presentation				
Chest pain	9 (45.0%)	9 (64.3%)	8 (50.0%)	0.531
Dyspnea	19 (95.0%)	11 (78.6%)	14 (87.5%)	0.349
Hemoptysis	1 (5.0%)	3 (21.4%)	1 (6.3%)	0.357
Syncope	3 (15.0%)	2 (14.3%)	2 (12.5%)	1.000
Calf pain	6 (30.0%)	4 (28.6%)	2 (12.5%)	0.453
Heart rate (Mean ± SD)	122.7 ±13.7	104.6 ±16.0	104.6 ±13.9	<0.001*
SBP (Mean ± SD)	77.5 ± 15.5	117.1 ±12.7	116.6 ±11.9	<0.001*
Respiratory rate (Mean ± SD)	29.2 ± 4.5	24.2 ±5.0	24.0 ±6.9	0.010*
O2 saturation (Mean ± SD)	88.2 ± 2.9	89.6 ±2.8	91.9 ±3.3	0.002*
Right ventricular dysfunction	20 (100%)	14 (100%)	2 (12.5%)	<0.001*
CHA2DS2-VASc score				
Low (0 – 1)	2 (10.0%)	3 (21.4%)	6 (37.5%)	0.021*
Moderate (2)	2 (10.0%)	4 (28.6%)	6 (37.5%)	
High (≥3)	16 (80.0%)	7 (50.0%)	4 (25.0%)	
Parenteral anticoagulation				
UFH	12 (75%)	9 (64.3%)	8 (50%)	0.53
LMWH	4 (25%)	5 (35.7%)	7 (43.8%)	
Fondaprinux	0 (0.0%)	0 (0.0%)	1 (6.3%)	
Thrombolytic therapy	19 (95%)	0 (0.0%)	0 (0.0%)	<0.001*
In-hospital mortality	5 (25.0%)	3 (21.4%)	0 (0.0%)	0.083

Table 1: The association of variables with acute pulmonary embolism subgroups.
N number; SD standard deviation; *Significance is adopted at P<0.05; DVT deep venous thrombosis; SBP systolic blood pressure; UFH unfractionated heparin; LMWH low molecular weight heparin.

Table 2: ECG findings of studied population in relation to PE clinical subgroups

ECG findings		Massive (N = 20)		Sub-massive (N = 14)		Non-massive (N = 16)		P
Sinus tachycardia >100 b/min	No	0	0.0%	6	42.9%	6	37.5%	0.002*
	Yes	20	100.0%	8	57.1%	10	62.5%	
RBBB	No	13	65.0%	12	85.7%	16	100.0%	0.014*
	Yes	7	35.0%	2	14.3%	0	0.0%	
Right axis deviation	No	18	90.0%	12	85.7%	14	87.5%	1.000
	Yes	2	10.0%	2	14.3%	2	12.5%	
S1Q3T3	No	9	45.0%	10	71.4%	9	56.3%	0.311
	Yes	11	55.0%	4	28.6%	7	43.8%	
T wave inversion in V1-V3	No	14	70.0%	5	35.7%	10	62.5%	0.124
	Yes	6	30.0%	9	64.3%	6	37.5%	

*** Significance at P<0.05; RBBB right bundle branch block.**

Table 3: Comparison between PE subgroups and Laboratory data on admission

		Massive (N = 20)		Sub-massive (N = 14)		Non-massive (N = 16)		P
D-dimer level Median [IQR]		6.3 [6.0 - 8.5]		3.8 [2.5 - 5.0]		2.8 [2.1 - 4.5]		<0.001*
Troponin	Negative	1	5%	7	50%	9	56.3%	0.001*
	Positive	19	95%$	7	50%	7	43.8%	

	CHA2DS2-VASc score			
Variable	Low (0 -1) (N = 11)	Moderate (2) (N = 12)	High (≥3) (N = 27)	P Value
Age (Mean ±SD)	46.4 ± 14.8	49.7 ± 12.8	59.6 ± 13.8	0.017*
Sex				0.927
Female	7 (63.6%)	8 (66.7%)	16 (59.3 %)	
Male	4 (36.4%)	4 (33.3%)	11 (40.7%)	
Predisposing factors				
Estrogen use	5 (45.5 %)	3 (25.0%)	2 (7.4%)	0.017*
Hypertension	0 (0.0%)	5 (41.7%)	13 (48.1%)	0.010*
Autoimmune disease	3 (27.3%)	2 (16.7%)	2 (7.4%)	0.236
Prior DVT	0 (0.0%)	0 (0.0%)	9 (33.3%)	0.011*
Active DVT	0 (0.0%)	2 (16.7%)	9 (33.3%)	0.073
Abdominal and pelvic surgery within one month	0 (0.0%)	2 (16.7%)	5 (18.5%)	0.415
Active cancer	3 (27.3%)	1 (8.3%)	4 (14.8%)	0.455
bed rest > 3 days	1 (9.1%)	3 (25.0%)	9 (33.3%)	0.359

Clinical presentation				
Chest pain	7 (63.6%)	7 (58.3%)	12 (44.4%)	0.495
Dyspnea	10 (90.9%)	7 (58.3%)	27(100.0%)	0.001*
Hemoptysis	2 (18.2%)	3 (25.0%)	0 (0.0%)	0.020*
Syncope	1 (9.1%)	1 (8.3%)	5 (18.5%)	0.756
Calf pain	0 (0.0%)	2 (16.7%)	10 (37.0%)	0.040*
Heart rate (Mean ± SD)	109.8 ± 17.8	103.9 ± 17.3	116.2 ± 15.2	0.095
SBP (Mean ± SD)	109.5 ± 14.6	113.8 ± 14.9	92.0 ± 26.2	0.009*
Respiratory rate (Mean ± SD)	20.9 ± 4.3	26.1 ± 5.8	28.3 ± 5.3	0.001*
O2 saturation (Mean ± SD)	90.8 ± 3.0	92.0 ± 2.6	88.4 ± 3.2	0.003*
Right ventricular dysfunction	5 (45.5 %)	7 (58.3%)	24 (88.9)	0.009*
CHA2DS2-VASc score				
Massive	2 (18.2%)	2 (16.7%)	16 (59.3 %)	0.021*
Sub-massive	3 (27.3%)	4 (33.3%)	7 (25.9%)	
Non-massive	6 (54.5%)	6 (50.0%)	4 (14.8%)	
Parenteral anticoagulation				
UFH	7 (63.6%)	5 (45.5%)	17 (70.8%)	0.363
LMWH	4 (36.4%)	5 (45.5%)	10 (37.0%)	
Fondaprinux	0 (0.0%)	2 (16.7%)	0 (0.0%)	
Thrombolytic therapy	1 (9.1%)	2 (16.7%)	16 (59.3 %)	0.004*
In-hospital mortality	2 (18.2%)	1 (8.3%)	5 (18.5%)	0.083

*** Significance at P<0.05**

Table 4: Echocardiographic assessment of RV function in relation to PE subgroups

	Massive (N = 20)	Sub-massive (N = 14)	Non-massive (N = 16)	P
RV systolic function				
TAPSE (cm) Mean ± SD (Min -Max)	1.4 ± 0.1 (1.2 - 1.6)	1.5 ±0.1 (1.3 - 1.8)	2.1 ±0.2 (1.7 - 2.4)	<0.001*
S` wave Mean ± SD (Min -Max)	7.7 ± 0.7 (7.0 - 9.0)	8.3 ±0.7 (7.0 - 9.8)	12.4 ±1.7 (10.0 - 16.0)	<0.001*
Pulsed Doppler MPI Mean ± SD (Min -Max)	0.52 ± 0.04 (0.44 - 0.59)	0.45 ±0.03 (0.40 - 0.49)	0.34 ±0.06 (0.26 - .50)	<0.001*
Tissue Doppler MPI Mean ± SD (Min -Max)	0.62 ± 0.05 (0.50 - 0.70)	0.55 ±0.03 (0.49 - 0.59)	0.45 ±0.07 (0.36 - .62)	<0.001*
Fractional area change (FAC) Mean ± SD (Min -Max)	28.1 ± 3.6 (22.0 - 37.0)	33.1 ±2.6 (28.0 - 37.0)	40.4 ±2.8 (36.0 - 45.0)	<0.001*
RV diastolic function				
E`/A` ratio Mean ± SD (Min -Max)	0.43 ± 0.04 (0.37 - 0.51)	0.49 ±0.03 (0.39 - 0.52)	0.70 ±0.14 (0.52 - .90)	<0.001*
E/E` ratio Mean ± SD (Min -Max)	7.0 ± 0.3 (6.0 - 7.6)	6.4 ± 0.3 (5.9 - 7.0)	5.1 ±0.4 (4.5 - 5.7)	<0.001*

*** Significance at P<0.05; RV right ventricle; TAPSE tricuspid annular plane systolic excursion; MPI myocardial performance index**

Table 5: The association between CHA2DS2-VASc Score and various variables

N number; SD standard deviation; *Significance is adopted at P<0.05; DVT deep venous thrombosis; SBP systolic blood pressure; UFH unfractionated heparin; LMWH low molecular weight heparin.

Table 6: Echocardiographic assessment of RV function in relation to CHA2DS2-VASc risk groups

	Massive (N = 20)	Sub-massive (N = 14)	Non-massive (N = 16)	P
RV systolic function				
TAPSE (cm) **Mean ± SD** **(Min -Max)**	1.8 ± 0.3 (1.4 - 2.1)	1.8 ± 0.4 (1.3 - 2.4)	1.5 ± 0.3 (1.2 - 2.4)	0.032*
S` wave **Mean ± SD** **(Min -Max)**	10.6 ± 2.8 (7.5 - 16.0)	9.9 ± 2.6 (7.0 -14.0)	8.6 ± 1.9 (7.0 - 14.0)	0.082
Pulsed Doppler MPI **Mean ± SD** **(Min -Max)**	0.38 ± 0.08 (0.28 - 0.51)	0.4 ±0.08 (0.29 - 0.53)	0.48 ± 0.08 (0.26 - 0.59)	0.002*
Tissue Doppler MPI **Mean ± SD** **(Min -Max)**	0.48 ± 0.08 (0.36 - 0.60)	0.52±0.09 (0.38 - 0.64)	0.58 ± 0.07 (0.37 - 0.70)	0.002*
Fractional area change (FAC) **Mean ± SD** **(Min -Max)**	35.5 ± 6.9 (22.0 - 45.0)	36.9 ± 5.7 (28.0 - 45.0)	31.1 ± 4.9 (23.0 - 41.0)	0.007*
RV diastolic function				
E`/A` ratio **Mean ± SD** **(Min -Max)**	0.66 ± 0.19 (0.43 - 0.90)	0.55 ± 0.12 (0.37 - 0.80)	0.47 ± 0.09 (0.37 - 0.83)	0.001*
E/E` ratio **Mean ± SD** **(Min -Max)**	6.0 ± 0.9 (4.7 - 7.4)	5.9 ± 1.0 (4.7 - 7.6)	6.5 ± 0.8 (4.5 - 7.3)	0.106

*** Significance at P<0.05; RV right ventricle; TAPSE tricuspid annular plane systolic excursion; MPI myocardial performance index**

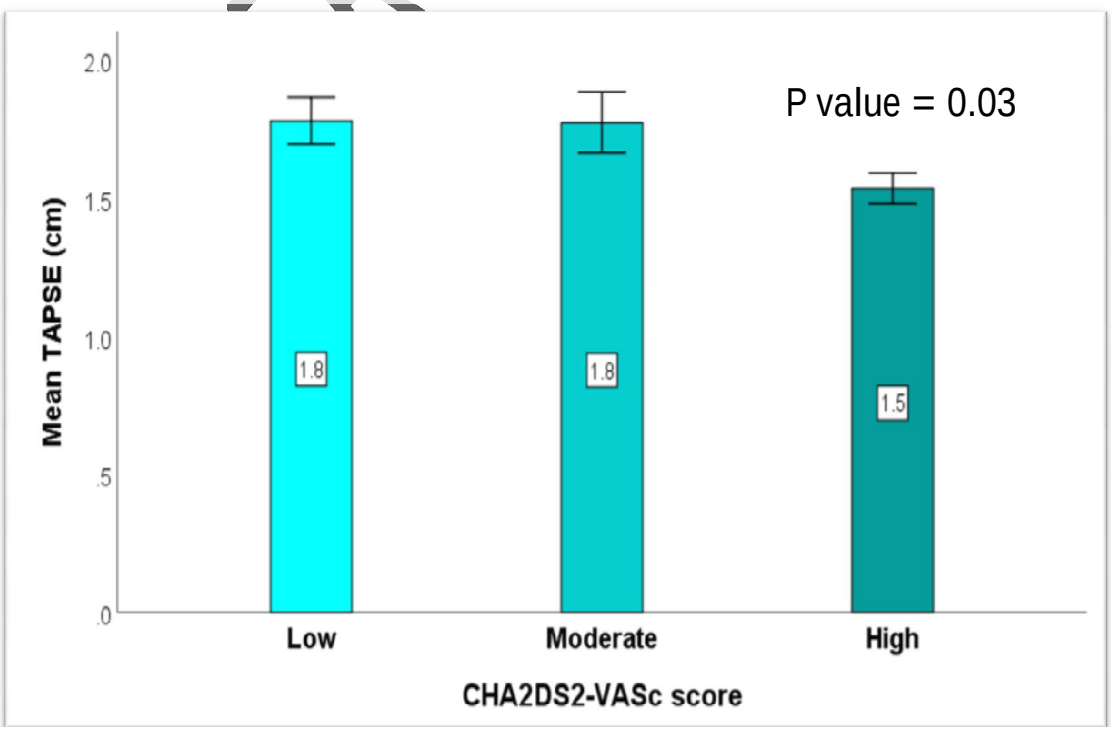

Figure 1: TAPSE in relation to CHA2DS2-VASc risk groups

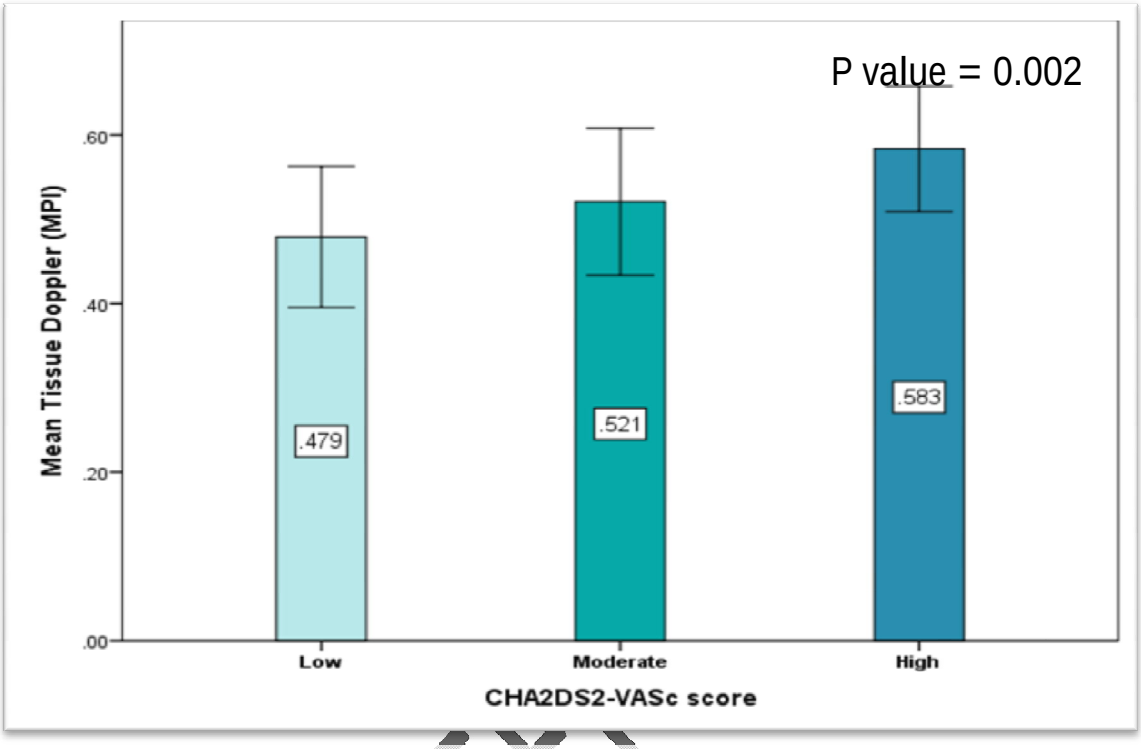

Figure 2: Tissue doppler MPI in relation to CHA2DS2-VASc risk groups

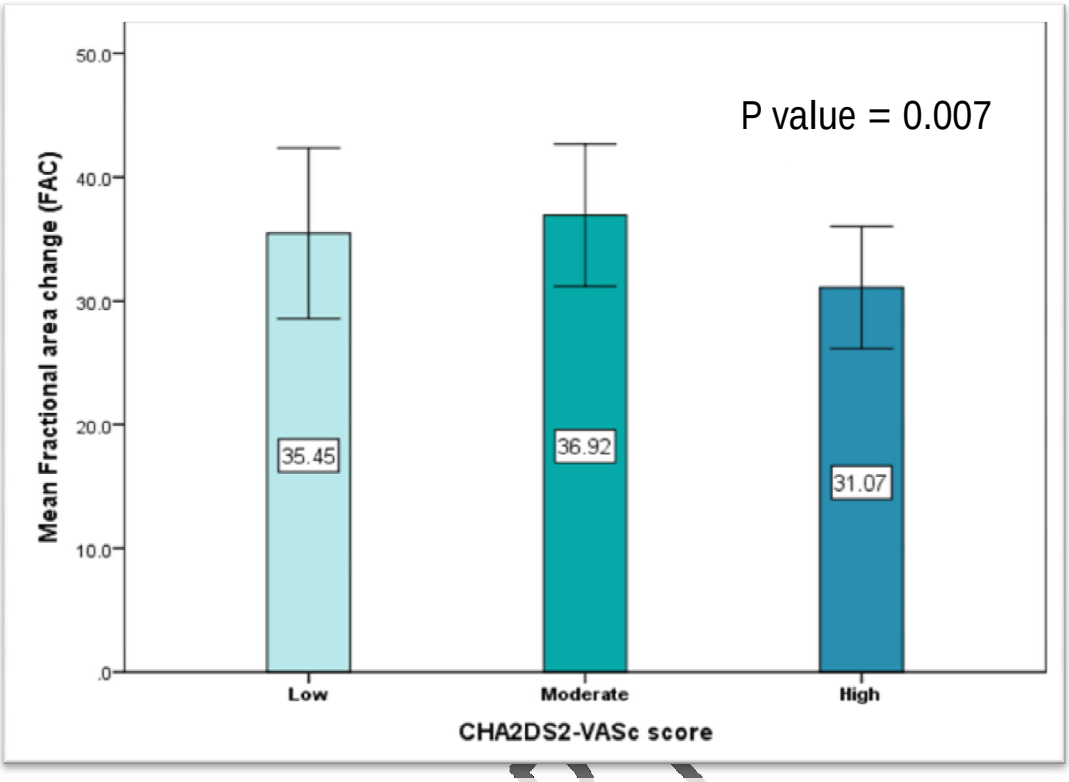

Figure 3: FAC in relation to CHA2DS2-VASc risk groups

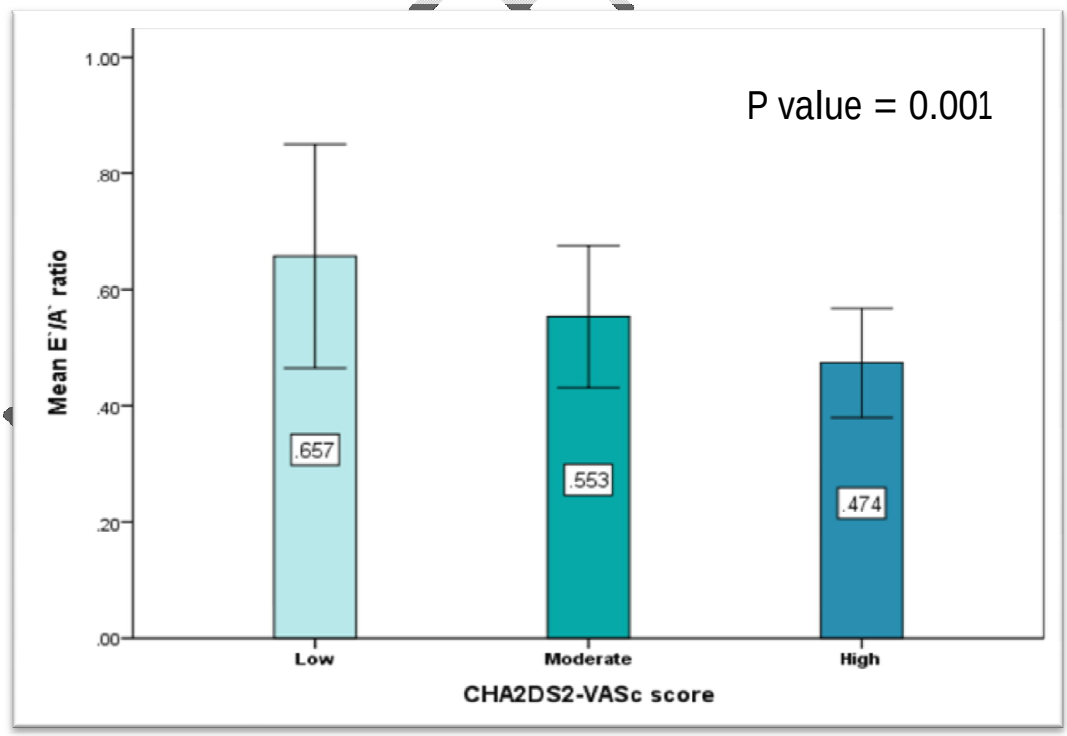

Figure 4: E`/A` in relation to CHA2DS2-VASc risk groups

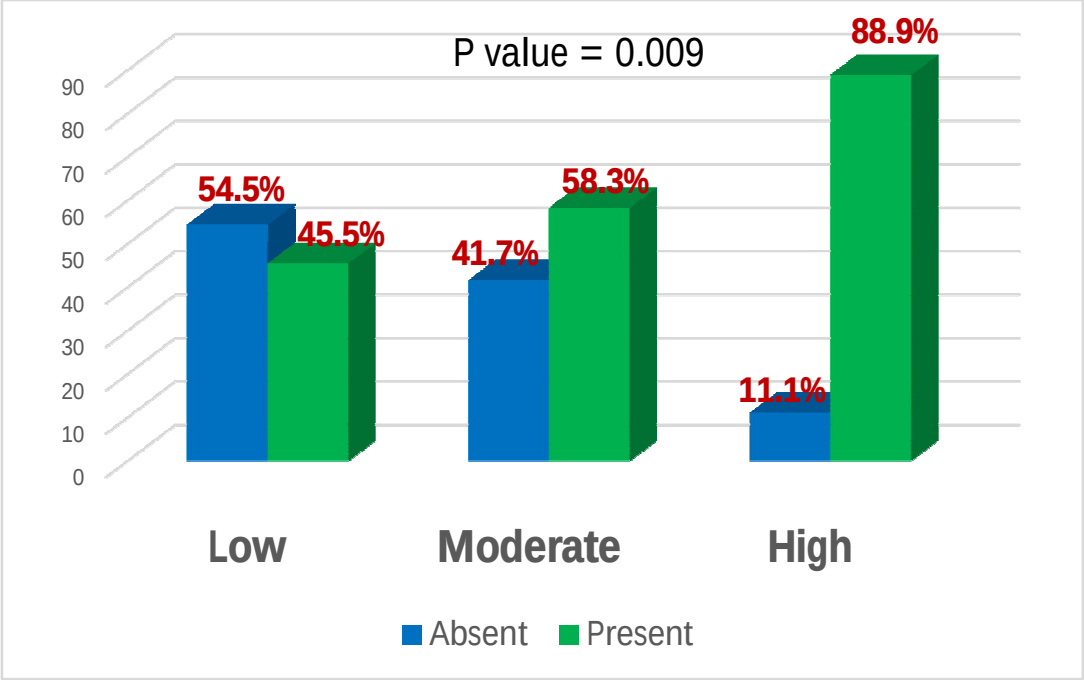

Figure 5: RVD in relation to CHA2DS2-VASc risk groups

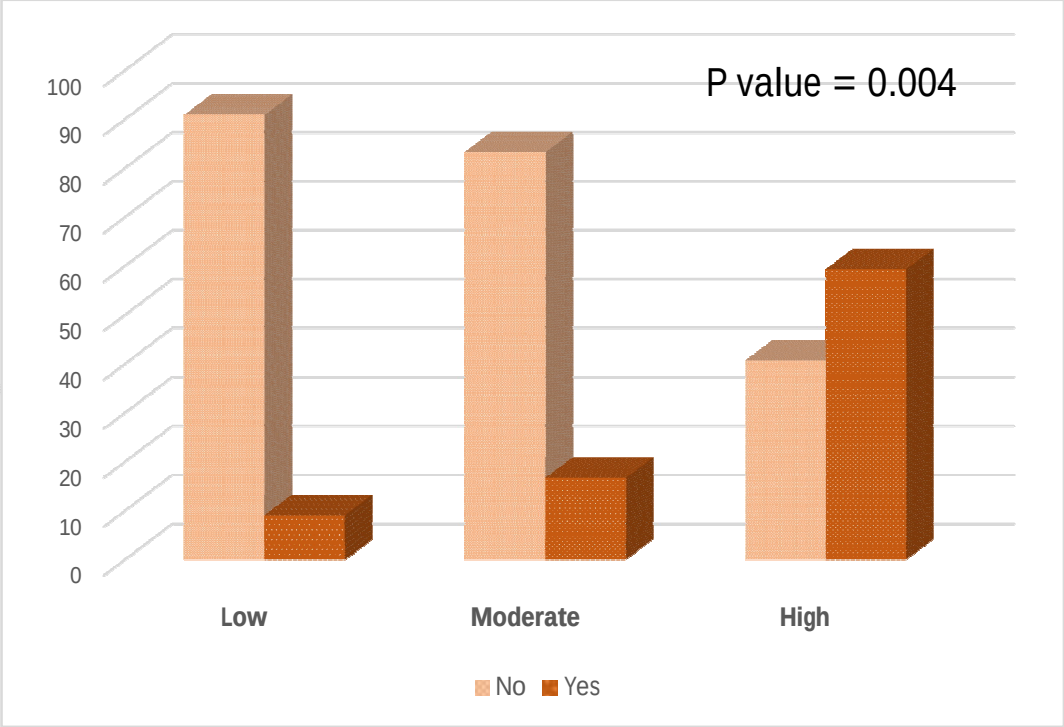

Figure 6: Comparison between CHA2DS2-VASc risk groups regarding Thrombolytic therapy

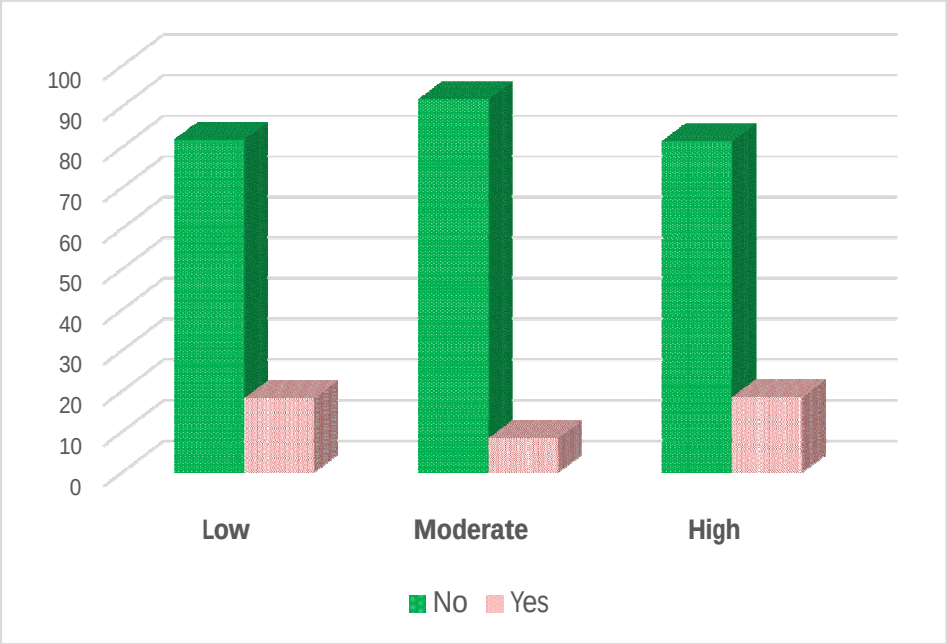

Figure 7: Correlation between CHA2DS2-VASc risk groups and the in-hospital mortality

Table 7: Univariate and Multivariate analysis for predictors of right ventricular dysfunction in patients with acute PE

Right ventricular dysfunction	Univariate			Multivariate		
	p	OR	95% C.I. for OR	p	OR	95% C.I. for OR
Age	0.459	1.016	0.974 - 1.060			
Male Sex	0.659	0.754	0.214 - 2.652			
Smoking	0.221	0.444	0.121 - 1.631			
Estrogen use	0.350	0.500	0.117 - 2.139			
Autoimmune disease	0.971	0.968	0.165 - 5.682			
Prior stroke	0.832	0.765	0.064 - 9.169			
Active DVT	0.144	5.000	0.576 - 43.388			
Prior DVT	0.238	3.714	0.420 - 32.872			
Active cancer	0.517	0.591	0.121 - 2.894			
bed rest>3 days	0.251	2.640	0.504 - 13.835			
Heart rate (beat/min)	0.029*	1.051	1.005 - 1.100	0.022*	1.044	1.006 - 1.084
Systolic blood pressure (mmHg)	0.008*	0.947	0.910 - 0.986	0.007*	0.948	0.912 - 0.985
Respiratory rate (breath/min)	0.029*	1.156	1.015 - 1.317	0.136	1.042	0.987 - 1.099
O2 saturation (%)	0.012*	0.736	0.579 - 0.935	0.922	1.005	0.926 - 1.088
Chest pain	0.860	1.118	0.325 - 3.844			
Dyspnea	0.518	0.477	0.051 - 4.492			
Cough	0.185	4.333	0.495 - 37.928			
Syncope	0.971	0.968	0.165 - 5.682			
D-dimer level	0.005*	1.790	1.195 - 2.681	0.929	1.028	0.554 - 1.909
Troponin	0.142	2.600	0.725 - 9.319			
CHA2DS2-VASc score	0.006*	2.492	1.293 - 4.804	0.021*	2.507	1.152 - 5.456
Wells score	0.028*	1.695	1.058 – 2.715	0.058	2.459	0.971 – 6.230

CI confidence interval; N number; OR odds ratio: SD standard deviation; *Significance is adopted at P<0.05; DVT deep venous thrombosis; SBP systolic blood pressure; UFH unfractionated heparin; LMWH low molecular weight heparin.

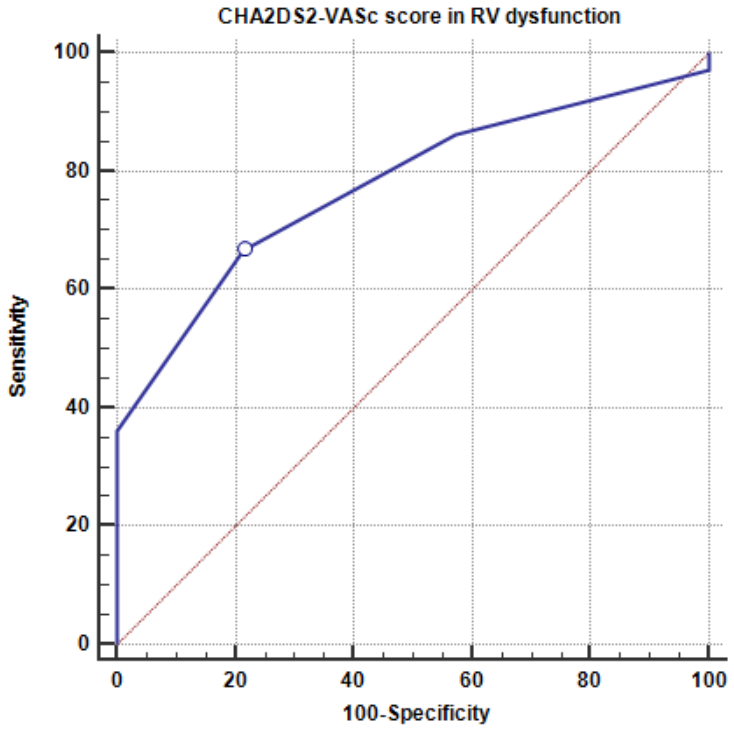

Figure 8: The CHA2DS2-VASc score in the receiver operating characteristics (ROC) curve to predict the right ventricular dysfunction

RV dysfunction	AUC	95%CI	P	Cut off value	Sensitivity	Specificity
	0.776	0.636 - 0.882	<0.001*	>2	66.7%	78.6%

AUC area under the curve; CI confidence interval; * significant at P<0.05

4. Discussion

The incidence of acute pulmonary embolism (PE) has been increasing over the last 20 years and it has significant negative impacts on the quality of life, healthcare costs, and longevity. It is one of the major causes of mortality, morbidity, and hospitalization worldwide [(3)]. The clinical course of acute PE is highly variable ranging from asymptomatic to massive embolism with hemodynamic instability and death. Right ventricular dysfunction (RVD) is one of the most common causes of death in the setting of acute PE.[(23)] Therefore, several studies investigated the predisposing factors of the RVD. However, at present little is known about the clinical predictors of RVD in the patients presented with acute PE.

In this study we aimed to evaluate the association of CHA_2DS_2-VASc Score with the PE severity, RVD and the in-hospital mortality in patients presented with acute PE. For that, we reported demographics, baseline clinical presentation, management and the in-hospital mortality in 50 patients with acute PE presented to Tanta university hospital over six months. First, we studied the association of all variables with the PE clinical subgroups based on the

severity of clinical presentation. Next, we studied the association of these variables with the risk of thromboembolism based on the CHA_2DS_2-VASc Scores. And finally, we investigated the predictors of the RVD using univariate and multivariate analyses.

Patients were assigned to 3 clinical subgroups, according to their hemodynamic and radiological characteristics, including massive (n=20), sub-massive (n=14) and non-massive PE (n=16). The classification of the cases with PE as such is very important as it affects the treatment decision. While the thrombolytic therapy is at the forefront of the treatment in massive PE, anticoagulants are the treatment of choice in the other clinical presentations.[24] The patients were also classified according to CHA_2DS_2-VASc scores into 3 risk groups the low-risk (n=11), moderate risk (n=12) and high risk (n=27) groups.

Among all risk factors, only the history of abdominal or pelvic surgery within one month was statistically significantly higher in the massive PE subgroup (P value= 0.02). This was consistent with the study of D Jiménez et al. which included 23,858 patients with acute PE enrolled in the RIETE registry between 2001 and 2013.[25] Additionally, the IPER registry and P Hariharan et al. reported a significant association between recent major surgery and massive PE.[26],[27]

We also found that tachycardia, hypotension and tachypnea were manifested more among the massive group of patients, while hypoxia was detected more among the massive and sub-massive groups of patients. These results came in agreement with N Kucher et al. as well as D Jiménez et al., a study conducted on 2096 presented with acute PE, they reported that tachycardia, hypotension and hypoxia were correlated with the severity of PE.[28],[29] In contrast, the PREP study, D Aujesky et al. and S Garvey et al. that was conducted on 1121 patients presented with acute PE, they demonstrated that tachypnea had no significant correlation with the PE severity.[30],[31],[32]

As regards ECG findings on admission, our data demonstrate that only sinus tachycardia and RBBB showed statistically significant difference among the PE clinical subgroups with higher prevalence in the massive group of patients compared to the other groups. A meta-analysis conducted by Shopp JD et al. after reviewing 10 studies on 3007 patients with acute PE and also in a study conducted by Kukla P et al. on 614 patients presented with acute PE, they reported that heart rate > 100 beats/min and complete RBBB were associated with massive PE. On the other hand, they also demonstrated that S1Q3T3 pattern and inverted T waves in V1-V4 were also associated with massive presentation.[33],[34]

In a study conducted by W Ghanima et al. on 495 consecutive patients, they demonstrated a correlation of D-dimer level and troponin with the clinical severity of PE.[35] Additionaly, in a prospective study conducted by M Lankeit et al. on 156 consecutive normotensive patients with confirmed PE and also in A Kaeberich et al., conducted on 682 consecutive normotensive patients, they reported that troponin was a predictor of severity and worse prognosis. [36],[37] These data are similar to our findings that higher levels of D-dimer (P value < 0.001) and positive troponin were significantly correlated with the massive PE group of patients. On the other hand, by S Yilmaz et al., a study conducted on 79 patient presented with acute PE, and also in the PREP study, they reported that D-dimer level and troponin had no significant correlation with the PE severity.[30],[38]

Another finding in our study is the higher incidence of RVD in massive and sub-massive groups compared to the non-massive group of patients. This result came in agreement with several studies, conducted by M Gök et al. and Y Chen et al. on 286 patients presented with

acute PE.[24],[39] Similarly, RVD were correlated with the severity of clinical presentation and worse prognosis in studies conducted by M Tuzovic et al. on 51 patients, A Weekes et al. on 123 patients and P Pruszczyk et al. on 490 patients presented with acute PE. [40],[41],[42]

In the present study RV systolic function was assessed by TAPSE, S` wave, Pulsed and tissue Doppler MPI and RV FAC. TAPSE and S` wave were found to be more significant in the massive and sub-massive groups compared to the non-massive group. Pulsed and tissue Doppler MPI as well as FAC were more significant among the massive group of patients. These findings are consistent with published data by S Hsiao et al. that was conducted on 150 patient and reported a significant correlation of TAPSE, S` wave and MPI with the severity of PE. [43] Also, TAPSE had a significant correlation with the PE severity in S Alerhand et al. and M Paczynska et al.[44],[45] Similarly, S` wave had a significant correlation with the PE severity in A Rodrigues et al. [46], and FAC had a significant correlation with the PE severity in A Terluk et al. [47] Additionally, in a study conducted by T Dahhan et al. [48] on 135 patients presented with acute PE, they reported that MPI was a significant predictor of RVD as well as PE severity.

It is to be noted that the MPI is a combinative index of ventricular systolic and diastolic function. In patients with PE, the higher RV MPIs, due almost entirely to the prolonged RV isovolumic relaxation time, may indicate that RV diastolic dysfunction is more severe in acute RV overload than in chronic pulmonary hypertension.[43]

As regard RV diastolic function, it was assessed by E`/A` ratio and E/E` ratio, both were found to be significantly correlated with clinical severity of PE (P value <0.001). It was noted that only few studies were concerned with the assessment of RV diastolic function in the setting of acute pulmonary embolism. Our findings are discordant to the data reported by A Rodrigues et al. [46] in which E/E` ratio had no significant correlation with PE severity.

Importantly, our study demonstrated a significant difference between different risk groups of CHA_2DS_2-VASc scores and PE clinical subgroups (P value = 0.02). The massive PE group of patients had the highest risk (80%) compared to other groups. Several studies had suggested the relationship between CHA_2DS_2-VASc score and PE severity. In concordance with our study, a study conducted by W Saliba et al. on 73,541 subjects with atrial fibrillation. They have emphasized that CHA_2DS_2-VASc score was directly correlated with the incidence, severity and prognosis of PE.[12] Similarly, in a study conducted by T Onuk et al. on 277 PE patients, they reported that CHA2DS2-VASc score was significantly related to PE severity.[13]

Dyspnea, being the most prevalent symptom in our study, it was found to be correlated with the high risk group of patients. This result came in agreement with the data published by ***S*** Grifoni et al. [49]. Also, unilateral lower limb pain was also found to be significantly correlated to the high risk group of patients, similar data were reported in Kucher et al.[28]. Additionally, small percentage of patients presented with hemoptysis (10.0%), however, it was more prevalent in the moderate risk group of patients. This result came in agreement with the study of M Gök et al. [24], but it contrasted with the study of F Casazza et al.[26]

In our study, hypotension, tachypnea and hypoxia were more prevalent among the high risk group of patients. Regarding hypoxia and hypotension, our observation came in line with the studies conducted by D Jiménez et al.[29], IPER registry [26], N Kucher et al. [28] and S Garvey et al [32]. On the other hand, as regard tachypnea, our study contrasted with result of the PREP Study [30] and D Aujesky et al.[31]

In the present study, higher levels of D-dimer (P value = 0.026) and positive troponin (P value = 0.016) were significantly higher in the high risk group. Our observation was concordant with the study of W Ghanima et al. [35]. Also, the studies of M Lankeit et al. and A Kaeberich et al. reported that positive troponin was significant between the high risk group of patients.[37] Similarly, D-dimer was found to be significant in the high risk group of patients in the studies conducted by M Gök et al. and Y Yamashita et al.[24],[50]

Moreover, it was found that the incidence of RVD was higher among the high risk group of patients (P value = 0.009). This finding was consistent with the data published by Y Chen et al.[39]. Regarding RV systolic function, TAPSE, pulsed and tissue Doppler MPI as well as FAC were found to be more significant in the high risk group, on the other hand, the S′ wave showed no statistically significant difference between different risk groups. These results, regarding TAPSE and MPI, were concordant with the study of S Hsiao et al.[43]. Similarly, A Terluk et al. [47] reported a significant correlation of FAC with the high risk group of patients. In contrast with the current study, S` wave was significantly lower in the high risk group in A Rodrigues et al. [46]. And as regard to RV diastolic function, E`/A` ratio was found to be more significant among patients in high risk group, while E/E` ratio showed no statistically significant difference between different risk groups. These data was concordant with a that of A Rodrigues et al. [46] in which E/E` ratio had no significant correlation with the thromboembolic risk groups.

Interestingly, our data reported that the incidence of receiving thrombolytic therapy was higher (59.3%) in the high risk group compared to other groups. A meta-analysis conducted by C Marti et al. reported similar data.[51] Conversely, T Onuk et al. didn't demonstrate a significant correlation between thrombolytic therapy and different risk groups.[13]

Despite the higher percent of deaths among the high-risk group of patients, our study reported that there was no statistically significant difference between patients in the different risk groups regarding the in hospital mortality (P value =0.772). This result came in agreement with a study conducted by T Onuk et al. [13] and M Gök et al.[24]. On the other hand, the in hospital mortality as well as the risk of 30 days and long-term mortality were correlated with the high risk group of patients in the studies of F Casazza et al. [26], the PREP Study [30] and D Jiménez et al.[29].

As regard the predictors of RVD in patients with acute PE, univariate and multivariate regression analysis were performed to investigate the possible predictors of RVD in patients with acute PE in the study population. In univariate regression analysis, heart rate, systolic blood pressure, respiratory rate, O2 saturation, D-dimer level, wells score and CHA2DS2-VASc score were correlated with RVD.

Variables with a significant P value in univariate analysis were included into multivariate regression analysis and accordingly, ***higher heart rate (OR 1.044, P value = 0.022), lower systolic blood pressure (OR 0.948, P value = 0.007) and CHA2DS2-VASc score (OR 2.507, P value = 0.021)*** were demonstrated to be independent predictors of RVD.

It was also demonstrated by the receiver operating characteristic (ROC) analysis that the CHA2DS2-VASc score predicted the presence of RVD with a 66.7 % sensitivity and 78.6% specificity, the area under the curve (AUC) was 0.776, 95% confidence interval (CI) 0.636-0.882, P value < 0.001) and with cutoff value CHA2DS2-VASc score more than 2. The validity of CHA2DS2-VASc score to predict the RVD in the setting of acute PE was also

demonstrated in the study of W Saliba et al. [12], T Onuk et al. [13], and also in the study of M Gök et al. [24].

The importance of the RVD is more significant in patients presenting with the clinical signs and symptoms of sub-massive PE rather than those presenting with massive PE as detecting RVD in these patients or predicting the development of it during the follow-up will prompt the thrombolytic treatment option. The development of RVD in the settings of acute PE has been related to several specific clinical and laboratory variables, such as diabetes, advanced age, and female gender [7],[8]. These risk factors for RVD in patients with PE are also included in the CHA2DS2-VASc score. This study demonstrated that the CHA2DS2-VASc score can be used as a new, simple, and reliable tool to predict the development of RVD in patients with acute PE.

5. Study limitations

This is a single-center experience study and represents only patients presented to cardiology department of Tanta university hospital during the study period. In addition to that, our analysis involved a simple baseline determination at a single time point that may not reflect the patient status over long periods. Also, small number of patients was included in this study, so our findings cannot be generalized to all populations.

6. Conclusion

Being independent of other factors, the CHA2DS2-VASc score can be used as a new, simple, and reliable tool to predict the development of RVD in patients with acute PE.

Ethical Approval and consent:

The study protocol was formally reviewed and approved by the ethics committee for human research at Tanta Faculty of Medicine and an informed consent was obtained from all participants prior to commencement of the study after thorough explanation of the study objectives.

References:

1. **Raskob GE, Angchaisuksiri P, Blanco AN, Büller H, Gallus A, Hunt BJ, et al.** Thrombosis: A Major Contributor to Global Disease Burden. Semin Thromb Hemost. 2014;

2. **Wendelboe AM, Raskob GE**. Global Burden of Thrombosis: Epidemiologic Aspects. Circ Res. 2016;33(44):345.

3. **Konstantinides S V., Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al.** 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. European Heart Journal. 2014. p. 122.

4. **Bělohlávek J, Dytrych V, Linhart A**. Pulmonary embolism, part I: Epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. Exp Clin Cardiol [Internet]. 2013 [cited 2021 Nov 15];18(2):129. Available from: /pmc/articles/PMC3718593/

5. **Jurcut R, Giusca S, La Gerche A, Vasile S, Ginghina C, Voigt J-U, et al.** The echocardiographic assessment of the right ventricle: what to do in 2010? Eur J Echocardiogr.

2010;11(2):81–96.

6. **Coutance G, Cauderlier E, Ehtisham J, Hamon M, Hamon M**. The prognostic value of markers of right ventricular dysfunction in pulmonary embolism: a meta-analysis. Crit Care [Internet]. 2011 Mar 28 [cited 2022 May 20];15(2):R103. Available from: /pmc/articles/PMC3219376/

7. **Rendina D, de Bonis S, Gallotta G, Piedimonte V, Mossetti G, de Filippo G, et al.** Clinical, historical and diagnostic findings associated with right ventricular dysfunction in patients with central and non-massive pulmonary embolism. Intern Emerg Med [Internet]. 2010 Feb 25 [cited 2020 Dec 6];5(1):53–9. Available from: http://www.ministerosalute.it/

8. **Keller K, Beule J, Schulz A, Coldewey M, Dippold W, Balzer JO**. Gender-specific differences in hemodynamically stable patients with acute pulmonary embolism [in German]. Dtsch Medizinische Wochenschrift [Internet]. 2014 Nov 1 [cited 2020 Dec 6];139(46):2329–34. Available from: https://pubmed.ncbi.nlm.nih.gov/25369042/

9. **Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM, Andresen D, et al.** Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on atrial fibrillation. Chest. 2010 Feb 1;137(2):263–72.

10. **Kurtul A**. Usefulness of the CHA2DS2-VASc Score in Predicting In-Stent Restenosis Among Patients Undergoing Revascularization With Bare-Metal Stents. Clin Appl Thromb [Internet]. 2018 May 1 [cited 2020 Dec 5];24(4):589–95. Available from: /pmc/articles/PMC6714711/?report=abstract

11. **Kurtul A, Acikgoz SK**. Validation of the CHA2DS2-VASc Score in Predicting Coronary Atherosclerotic Burden and In-Hospital Mortality in Patients With Acute Coronary Syndrome. Am J Cardiol [Internet]. 2017 Jul 1 [cited 2020 Dec 5];120(1):8–14. Available from: http://www.ajconline.org/article/S0002914917306379/fulltext

12. **Saliba W, Rennert G**. CHA2DS2-VASc score is directly associated with the risk of pulmonary embolism in patients with atrial fibrillation. Am J Med [Internet]. 2014;127(1):45–52. Available from: http://dx.doi.org/10.1016/j.amjmed.2013.10.004

13. **Onuk T, Karataş MB, Ipek G, Güngör B, Akyüz Ş, Çanga Y, et al.** Higher CHA2DS2-VASc Score Is Associated with Increased Mortality in Acute Pulmonary Embolism. Clin Appl Thromb [Internet]. 2017 Sep 1 [cited 2020 Dec 3];23(6):631–7. Available from: https://pubmed.ncbi.nlm.nih.gov/26759374/

14. **Hu WS, Lin CL**. CHA 2 DS 2 -VASc score for ischaemic stroke risk stratification in patients with chronic obstructive pulmonary disease with and without atrial fibrillation: A nationwide cohort study. Europace [Internet]. 2018 Apr 1 [cited 2020 Dec 6];20(4):575–81. Available from: https://academic.oup.com/europace/article/20/4/575/3605215

15. **Temizer O, Açar B, Yayla, Ünal S, Ertem AG, İpek EG, et al.** The association between CHA2DS2-VASc score and mortality in patients with heart failure with reduced ejection fraction. Acta Cardiol Sin [Internet]. 2017 Jul 1 [cited 2020 Dec 6];33(4):429–35. Available from: /pmc/articles/PMC5534423/?report=abstract

16. **Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al.** Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr [Internet]. 2015 Jan 1 [cited 2021 Oct

11];28(1):1-39.e14. Available from: http://www.onlinejase.com/article/S0894731714007457/fulltext

17. **Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al.** Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography: Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and . J Am Soc Echocardiogr [Internet]. 2010 Jul 1 [cited 2021 Oct 11];23(7):685–713. Available from: http://www.onlinejase.com/article/S0894731710004347/fulltext

18. **Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, et al.** Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: A scientific statement from the american heart association. Circulation. 2011;2(4):77.

19. **Verschuren F, Meyer G, Quentin-Georget S, Soulie C, Thys F, Roy P-M**. Comparison of the unstructured clinician gestalt, the wells score, and the revised Geneva score to estimate pretest probability for suspected pulmonary embolism. Ann Emerg Med. 2013;22(33):234.

20. **Konstantinides S V., Meyer G, Becattini C, Bueno H, Geersing G-J, Harjola V-P, et al.** 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Respir J. 2019;3(4):123.

21. **Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM, Andresen D, et al.** Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on atrial fibrillation. Chest [Internet]. 2010;137(2):263–72. Available from: http://dx.doi.org/10.1378/chest.09-1584

22. **Hinkle DE**. Applied statistics for behavioral sciences, + workbook, 5th ed. 2002;

23. **Piazza G, Goldhaber SZ**. Venous thromboembolism and atherothrombosis: An integrated approach. Circulation. 2010. p. 78.

24. **Gök M, Kurtul A, Harman M, Kara M, Süleymanoglu M, Ornek E**. Relationship Between CHA2DS2-VASc Score and Right Ventricular Dysfunction in Patients With Acute Pulmonary Thromboembolism. Clin Appl Thromb [Internet]. 2018 Dec 1 [cited 2020 Dec 6];24(9_suppl):56S-62S. Available from: http://journals.sagepub.com/doi/10.1177/1076029618785771

25. **Jiménez D, De Miguel-Díez J, Guijarro R, Trujillo-Santos J, Otero R, Barba R, et al.** Trends in the Management and Outcomes of Acute Pulmonary Embolism Analysis from the RIETE Registry. J Am Coll Cardiol. 2016;4(5):67.

26. **Casazza F, Becattini C, Bongarzoni A, Cuccia C, Roncon L, Favretto G, et al.** Clinical features and short term outcomes of patients with acute pulmonary embolism. the Italian Pulmonary Embolism Registry (IPER). Thromb Res. 2012;4(6):123.

27. **Hariharan P, Giordano N, Muzikansky A, Kabrhel C**. Clinical factors associated with massive pulmonary embolism and PE-related adverse clinical events. Int J Cardiol. 2021 May 1;330:194–9.

28. **Kucher N, Rossi E, De Rosa M, Goldhaber SZ**. Massive pulmonary embolism. Circulation [Internet]. 2006 Jan 31 [cited 2021 Nov 15];113(4):577–82. Available from: https://www.ahajournals.org/doi/abs/10.1161/circulationaha.105.592592

29. **Jiménez D, Bikdeli B, Barrios D, Morillo R, Nieto R, Guerassimova I, et al.** Management appropriateness and outcomes of patients with acute pulmonary embolism. Eur Respir J. 2018;3(4):66.

30. **Sanchez O, Trinquart L, Caille V, Couturaud F, Pacouret G, Meneveau N, et al.** Prognostic Factors for Pulmonary Embolism The PREP Study, A Prospective Multicenter Cohort Study. [cited 2021 Nov 17]; Available from: www.atsjournals.org

31. **Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, et al.** Derivation and Validation of a Prognostic Model for Pulmonary Embolism. https://doi.org/101164/rccm200506-862OC [Internet]. 2012 Dec 20 [cited 2021 Nov 16];172(8):1041–6. Available from: www.atsjournals.org

32. **Garvey S, Dudzinski DM, Giordano N, Torrey J, Zheng H, Kabrhel C**. Pulmonary embolism with clot in transit: An analysis of risk factors and outcomes. Thromb Res. 2020;2(3):44.

33. **Shopp JD, Stewart LK, Emmett TW, Kline JA**. Findings from 12-lead electrocardiography that predict circulatory shock from pulmonary embolism: Systematic review and meta-analysis. Acad Emerg Med. 2015;24(34):367.

34. **Kukla P, Kosior DA, Tomaszewski A, Ptaszyńska-Kopczyńska K, Widejko K, Długopolski R, et al.** Correlations between electrocardiogram and biomarkers in acute pulmonary embolism: Analysis of ZATPOL-2 Registry. Ann Noninvasive Electrocardiol. 2017;3(5):59.

35. **Ghanima W, Abdelnoor M, Holmen LO, Nielssen BE, Ross S, Sandset PM**. D-dimer level is associated with the extent of pulmonary embolism. Thromb Res. 2006;120:281–8.

36. **Lankeit M, Friesen D, Aschoff J, Dellas C, Hasenfuß G, Katus H, et al.** Highly sensitive troponin T assay in normotensive patients with acute pulmonary embolism. Eur Heart J. 2010;1(2):33.

37. **Kaeberich A, Seeber V, Jiménez D, Kostrubiec M, Dellas C, Hasenfuß G, et al.** Age-adjusted high-sensitivity troponin T cut-off value for risk stratification of pulmonary embolism. Eur Respir J [Internet]. 2015 May 1 [cited 2021 Nov 18];45(5):1323–31. Available from: https://pubmed.ncbi.nlm.nih.gov/25614162/

38. **Yilmaz S, Yaylali YT, Kuyumcu MS, Ünal S, Senol H, Tufekcioglu O**. Relationship between cha2ds2-vasc and chads2 scores with pulmonary hypertension in patients with acute pulmonary embolism. Adv Respir Med. 2019;87(6):203–8.

39. **Chen YL, Wright C, Pietropaoli AP, Elbadawi A, Delehanty J, Barrus B, et al.** Right Ventricular Dysfunction is Superior and Sufficient for Risk Stratification by a Pulmonary Embolism Response Team. J Thromb Thrombolysis [Internet]. 2020 Jan 1 [cited 2021 Nov 18];49(1):34. Available from: /pmc/articles/PMC6954969/

40. **Tuzovic M, Adigopula S, Amsallem M, Kobayashi Y, Kadoch M, Boulate D, et al.** Regional right ventricular dysfunction in acute pulmonary embolism: relationship with clot burden and biomarker profile. Int J Cardiovasc Imaging [Internet]. 2016 Mar 1 [cited 2021 Nov 18];32(3):389–98. Available from: https://www.researchgate.net/publication/282437159_Regional_right_ventricular_dysfunction_in_acute_pulmonary_embolism_relationship_with_clot_burden_and_biomarker_profile

41. **Weekes AJ, Johnson AK, Troha D, Thacker G, Chanler-Berat J, Runyon M**. Original

Contribution PROGNOSTIC VALUE OF RIGHT VENTRICULAR DYSFUNCTION MARKERS FOR SERIOUS ADVERSE EVENTS IN ACUTE NORMOTENSIVE PULMONARY EMBOLISM. [cited 2021 Nov 18]; Available from: http://dx.doi.org/10.1016/j.jemermed.2016.09.002

42. **Pruszczyk P, Kurnicka K, Ciurzyński M, Hobohm L, Thielmann A, Sobkowicz B, et al.** Defining right ventricular dysfunction by echocardiography in normotensive patients with pulmonary embolism. Polish Arch Intern Med. 2020 Sep 30;130(9):741–7.

43. **Hsiao SH, Chang SM, Lee CY, Yang SH, Lin SK, Chiou KR**. Usefulness of Tissue Doppler Parameters for Identifying Pulmonary Embolism in Patients With Signs of Pulmonary Hypertension. Am J Cardiol. 2006 Sep 1;98(5):685–90.

44. **Alerhand S, Hickey SM**. Ultrasound in Emergency Medicine TRICUSPID ANNULAR PLANE SYSTOLIC EXCURSION (TAPSE) FOR RISK STRATIFICATION AND PROGNOSTICATION OF PATIENTS WITH PULMONARY EMBOLISM Clinical Scenario 2. J Emerg Med [Internet]. 2020 [cited 2021 Nov 18];58(3):449–56. Available from: https://doi.org/10.1016/j.jemermed.2019.09.017

45. **Paczynska M, Sobieraj P, Burzynski L, Kostrubiec M, Wisniewska M, Bienias P, et al.** Tricuspid annulus plane systolic excursion (TAPSE) has superior predictive value compared to right ventricular to left ventricular ratio in normotensive patients with acute pulmonary embolism. Arch Med Sci [Internet]. 2016 [cited 2021 Nov 18];12(5):1008–14. Available from: https://www.researchgate.net/publication/308773854_Tricuspid_annulus_plane_systolic_excursion_TAPSE_has_superior_predictive_value_compared_to_right_ventricular_to_left_ventricular_ratio_in_normotensive_patients_with_acute_pulmonary_embolism

46. **Rodrigues ACT, Cordovil A, Monaco C, Guimarães L, Cury A, Naccarato GAF, et al.** Right ventricular assessment by tissue-Doppler echocardiography in acute pulmonary embolism. Arq Bras Cardiol [Internet]. 2013 Jun [cited 2021 Nov 18];100(6):524–30. Available from: https://pubmed.ncbi.nlm.nih.gov/23657266/

47. **Terluk AD, Trivedi SJ, Kritharides L, Chow V, Chia E-M, Byth K, et al.** Echocardiographic Predictors of Long-Term Mortality in Patients Presenting With Acute Pulmonary Embolism. 2019 [cited 2021 Nov 18]; Available from: www.ajconline.org0002-9149/

48. **Dahhan T, Siddiqui I, Tapson VF, Velazquez EJ, Sun S, Davenport CA, et al.** Clinical and echocardiographic predictors of mortality in acute pulmonary embolism.

49. **Grifoni S, Olivotto I, Cecchini P, Pieralli F, Camaiti A, Santoro G, et al.** Short-Term Clinical Outcome of Patients With Acute Pulmonary Embolism, Normal Blood Pressure, and Echocardiographic Right Ventricular Dysfunction. Circulation [Internet]. 2000 Jun 20 [cited 2020 Dec 6];101(24):2817–22. Available from: https://www.ahajournals.org/doi/10.1161/01.CIR.101.24.2817

50. **Yamashita Y, Morimoto T, Amano H, Takase T, Hiramori S, Kim K, et al.** Deep vein thrombosis in upper extremities: Clinical characteristics, management strategies and long-term outcomes from the COMMAND VTE Registry. Thromb Res. 2019;33(5):345.

51. **Marti C, John G, Konstantinides S, Combescur C, Sanchez O, Lankeit M, et al.** Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J [Internet]. 2015 Mar 7 [cited 2021 Nov 20];36(10):605–14. Available from: https://pubmed.ncbi.nlm.nih.gov/24917641/