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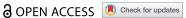
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ORIGINAL ARTICLE



Saddle versus non-saddle pulmonary embolism: differences in the clinical, echocardiographic, and outcome characteristics

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ABSTRACT

The central location, the size, and instability of saddle pulmonary embolism (PE) have raised considerable concerns regarding its hemodynamic consequences and the optimal management approach. Sparse and conflicting reports have addressed these concerns in the past. We aimed to evaluate the clinical presentation, hemodynamic and echocardiographic effects, as well as the outcomes of saddle PE, and compare the results with those of non-saddle type. This was a retrospective study of 432 adult patients with saddle and non-saddle PE. Overall, 432 patients were diagnosed with PE by computed tomography pulmonary angiography (CTPA). Seventy-three (16.9%) had saddle PE, and 359 had non-saddle PE. Compared to those with non-saddle PE, patients with saddle PE presented more frequently with tachycardia (68.5% vs. 46.2%, P= .001), and tachypnea (58.9% vs. 42.1%, P= .009) on admission, required more frequent intensive care unit (ICU) admissions (45.8% vs. 26.6%, P= .001) and thrombolysis/thrombectomy use (19.1% vs. 6.7%, P= .001), and were at more risk of developing decompensation and cardiac arrest after their initial admission (15.3% vs. 5.9%, P= .006). On echocardiography, right ventricular (RV) enlargement (60% vs. 31.1%, P= .000), RV dysfunction (45.8% vs. 22%, P= .000), and RV systolic pressure (RVSP) of greater than 40 mmHg (61.5% vs. 39.2%, P= .003) were significantly more observed with saddle PE. The two groups did not differ concerning the rates of hypotension (17.8% vs. 18.7%, P= .864) and hypoxemia (41.1% vs. 34.3%, P= .336) on admission and mortality rates. A logistic regression model indicated that the use of oral contraceptive pills (OCP), RVSP > 40 mmHg, and development of hypotension and decompensation following admission were associated with an increased likelihood of having saddle embolus. Saddle PE accounts for a higher proportion among all PE cases than previously reported. Patients with saddle PE tend to present more frequently with adverse hemodynamic and echocardiographic changes and decompensate after their initial presentation. OCP use, development of hypotension, and decompensation following admission and RVSP > 40 mmHg are significant predictors of saddle PE. These characteristics should not be overlooked when managing patients with saddle PE.

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Pulmonary embolism; saddle pulmonary embolism; hemodynamics; echocardiography

1. Introduction

Acute PE is a potentially life-threatening condition and represents the third most common cause of cardiovascular death after myocardial infarction and stroke [1]. Some reports estimated an overall mortality rate from acute PE that exceeded 10% [1]. Historically, pulmonary angiography and nuclear planar V/Q-imaging were the main imaging methods used to diagnose PE. While it was considered the gold-standard method for PE diagnosis, pulmonary angiography is an invasive technique and involves right heart catheterization. V/Q-imaging has also its important limitation because of the indeterminate PE probability that is seen in as many as 65% of cases [2-4]. The introduction of fast-speed helical CT in

the early nineties has revolutionized the diagnostic techniques of PE. CTPA has replaced conventional pulmonary angiography as the gold-standard method for diagnosing PE. Besides being minimally invasive, CTPA provides a high level of image quality resulting in a diagnostic performance that equals or surpasses that of conventional pulmonary angiography, with sensitivity and specificity varying between 83%-100% and 89%–96%, respectively [4–7]. Furthermore, CTPA allows identifying the exact anatomic locations of PE. These anatomical locations are based on the levels of proximal extension and include central, lobar, segmental, and sub-segmental [8]. Saddle PE is defined as a visible thromboembolus straddling the bifurcation of the

main pulmonary artery trunk [9-11]. The central location, the size, and instability of the saddle clot have raised considerable concerns regarding the hemodynamic consequences and the optimal management approach of this condition. Nevertheless, only sparse and conflicting reports have addressed these concerns. On one hand, some reports considered saddle PE to represent an unstable clinical situation that may be complicated by a transient aggravation of pulmonary vascular obstruction causing syncope, or by rupture of the embolus causing sudden circulatory arrest and advocated elective pulmonary embolectomy as a treatment option [12]. On the contrary, other reports found no major differences in its clinical presentation and hemodynamic effects as compared to non-saddle PE and suggested no justification for aggressive therapy [13]. This study aimed to evaluate the clinical presentation, hemodynamic and echocardiographic effects, as well as the outcomes of saddle PE, and compare the results with those of non-saddle type.

2. Methods

2.1. Study design, setting, and participants

This was a retrospective study of adult patients (aged >14 years) who were admitted to Hamad General Hospital (HGH) (the largest tertiary hospital in the State of Qatar) for acute PE during the study period from 1 January 2014 to 31 December 2018. Based on a careful analysis of CTPA imaging, the cases were divided into saddle and non-saddle PE groups. The Qatari health system classifies patients aged ≤14 years as 'pediatric'. This age group is normally admitted to pediatric hospitals and hence, excluded from this study.

2.2. Data collection and study definitions

Patients were identified using the registers of the services. We performed an extensive search in patients' electronic medical records to confirm the consistency and completeness of the information. The diagnosis of PE was defined by the identification of a thrombus in the pulmonary artery or any of its branches using CTPA, direct visualization of the emboli in the right heart chambers or central pulmonary arteries via echocardiography, or high-probability V/Q (lung scintigraphy)] scan along with high clinical probability for PE. Saddle PE was defined by the presence of a visible thromboembolus straddling the bifurcation of the main pulmonary artery trunk on CTPA [9-11]. Tachycardia was defined as a pulse rate of > 100 beats per minute and tachypnea as a respiratory rate of > 20 breaths per minute. PErelated hypotension was defined as the presence of a systolic blood pressure <90 mmHg or vasopressors

required to achieve a BP ≥90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion, in the presence of a pulmonary clot [14]. In our institution, thrombectomy is usually a catheter-based procedure (Angiojet) performed in the interventional radiology department. Administration of a thrombolytic agent directly into the lumen of the artery to accelerate lysis of the embolus is frequently utilized during the procedure unless there is a contraindication. Furthermore, for echocardiographic assessment, transthoracic echocardiography is usually used in our instituation. Transesophageal echocardiography is reserved to the cases in which image quality is poor. 2D Methods and M mode measurements are used for left ventricular dimension assessment. A dedicated RV views are used to measure the RV diameter. RV systolic function is assessed using Tricuspid Annular Plane Systolic Excursion (TAPSE) and -Derived Tricuspid Lateral Annular Systolic Velocity S. RVSP is estimated from the tricuspid regurgitant (TR) jet velocity using the modified Bernoulli equation (RVSP = 4V2 + RAP) where V is the maximal TRjet velocity and RAP is the estimated right atrial pressure. Pulmonary acceleration time is measured from the pulsed wave across the pulmonic valave in short access view. Data related to socio-demographic factors, clinical presentation, echocardiographic, and CTPA findings were extracted from the electronic records and recorded in a structured data collection sheet. The medications used for the initial treatment of PE and the PE outcomes from the time of diagnosis up to six months post-discharge were also reported.

2.3. Statistical analysis

Qualitative and quantitative data were expressed as the frequency with percentage and mean \pm SD with median and range. Descriptive statistics were used to summarize the demographic and all other clinical characteristics of the participants. Associations between at least 2 qualitative or categorical variables were assessed using the X² test. For small cell frequencies, the X² test with a continuity correction factor or the Fisher exact test was applied. A 2-sided P value less than .05 was considered statistically significant. A binary logistic regression analysis was applied to identify the factors that predict the presence of saddle PE. All statistical analyses were performed using SPSS 22.0 (SPSS, Inc, Chicago, Illinois).

2.4. Ethical approval

The study was approved by the Medical Research Center at Hamad Medical Corporation (approval No: MRC-01-19-059).

3. Results

A total of 436 patients received the diagnosis of acute PE during the study period. PE diagnosis was confirmed by CTPA in 432 patients, VQ scan in three patients, and direct visualization of the clot by echocardiography in one patient. Among the 432 patients diagnosed by CTPA, 73 (16.9%) had saddle PE and 359 had non-saddle PE. Tables 1 and 2 summarize the clinical characteristics and risk factors of the two groups. The mean ages of patients with saddle PE and non-saddle PE were 47 \pm 16 and 49 \pm 17.6 years respectively (P= .759). Males constituted 57.5% in the saddle group and 52.1% in the non-saddle group (P= .395). Compared to those with non-saddle PE, patients with saddle PE presented more frequently with tachycardia (68.5% vs. 46.2%, P= .001), and tachypnea (58.9% vs. 42.1%, P= .009) on admission. Admission to ICU (45.8% vs. 26.6%, P= .001) and the need of thrombolysis/thrombectomy (19.1% vs. 6.7%, P= .001) were also observed more frequently in the saddle PE group. Patients with saddle PE were at more risk of developing decompensation and cardiac arrest after their initial admission (15.3% vs. 5.9%, P= .006). More frequent elevations of troponins were also observed in the saddle than non-saddle PE (68.2% vs. 54.2%, P= .039). On echocardiography, patients with saddle PE were more frequently observed to develop RV enlargement (60% vs. 31.1%, P= .000), RV dysfunction (45.8% vs. 22%, P= .000), and RVSP of greater than 40 mmHg (61.5% vs. 39.2%, P= .003) (Table 3). The two groups did not differ concerning the rates of hypotension (17.8% vs. 18.7%, P=.864) and hypoxemia (41.1% vs. 34.3%, P= .336) on admission. Furthermore, no significant differences were observed in the rates of PE recurrence, PE-related mortality rates, risk factors, and the development of chronic thromboembolic pulmonary hypertension (CTEPH) up to six months post-discharge (Tables 1 and 2). A binary logistic regression was performed to ascertain the effects of various PE risk factors, clinical and echocardiographic parameters on the likelihood of exhibiting a saddle PE. The logistic regression model was statistically significant ($X^2 = 43.024$, and P = .007). The overall correct prediction rate was 85.4%. Use of OCP (OR = 10.134, P = 0.04, CI = 1.027–99.990), development of hypotension and decompensation following admission (OR = 3.180, P = .012, CI = 1.286–7.862), and RVSP reading > 40 mmHg (OR = 1.108, P = .004, CI = 1.033-1.189) were significantly associated with an increased likelihood of exhibiting saddle PE. Non-significant positive prediction was associated with hospitalization for surgical reason (OR = 2.145, P = .508, CI = .224-20.547), prolonged immobilization (OR = 5.031, P = .056, CI .956–26.466), presence of tachypnea (OR = 1.718, P = .410, CI = .473-6.238), ICU admission (OR = 2.049, P = .310, CI = .514-8.176), and development of cardiac arrest (OR = 1.495, P = .829, CI = .039-56.850).

4. Discussion

Recent clinical guidelines classified PE severity based on hemodynamic or cardiovascular effects produced by the clot. Such effects include the presence of cardiac arrest, obstructive shock, persistent hypotension, presence of signs of RV dysfunction on transthoracic echocardiography, or elevated cardiac biomarker levels [14]. A little or no attention has been considered for the importance of the clot's anatomic location in the severity classification. Before the era of CT diagnosis of PE, saddle PE was regarded as a grave form of PE as most of the cases were diagnosed at necropsy [11,15]. By virtue of CT techniques, the anatomical locations of PE are now easily identified and studies addressing the contribution of such locations to the clinical and hemodynamic presentations are permitted. In the current study, CTPA was undertaken in 432 of the 436 patients diagnosed with acute PE during the study period. This allowed the identification of the exact anatomical locations in the vast majority of cases included in this study. Saddle PE accounted for 16.9% of all PE cases diagnosed by CTPA during the study period. This figure far exceeds the previously reported rates by other investigators. Ryu et al and Pruszczyk et al reported 2.6% and 5.2% of their patients with acute PE to have a saddle component respectively [10,11]. In a recent large nationwide perspective from the USA, saddle PE accounted for 1.2% of the total PE cases [16]. Patients with saddle PE in the current study were observed to have more frequent tachycardia and tachypnea than those with non-saddle PE on their initial presentation. These findings were seldom reported in previous studies that involved a comparison between the saddle and nonsaddle PE. Based on the 2019 European Society of Cardiology (ESC) severity classification, 17.8% and 18.7% of saddle and non-saddle PE cases in the current study respectively fulfilled the criteria of high-risk PE [14]. This rate was not statistically significant. In a study from Mayo Clinic, Minnesota, Alkinj et al did not find significant differences in the heart rate and systolic blood pressure on presentation between the saddle and non-saddle groups [17]. Lack of significant difference in the blood pressure between the two groups was also reported by Pruszczyk et al [11]. Some studies that involved only patients with saddle PE also reported a low incidence of hypotension on admission in saddle PE patients [10]. The rates of ICU admission, use of thrombolysis/thrombectomy, and development of cardiac arrest following the initial presentation in the present study were significantly

Table 1. Clinical characteristics of saddle and non-saddle PE

Variable		Non-saddle	Saddle	P value
Age		N: 359	N: 73	
-	Mean \pm SD	49 ± 17.6	47 ± 16	0.759
	Median (IQR)	47(35-62)	43 (36-58)	
Sex		N: 359	N: 73	
	F	172	31	0.395
	M	187	42	0.075
Initial presenting symptom	IMI	N: 334	N: 71	
initial presenting symptom	Dyspnea	124	36	0.068
	Chest pain	102	21	0.008
	•			
	Syncope	14	5	
	Hemoptysis	10	0	
	Cough	9	0	
	Cardiac arrest	5	4	
	Dizziness	9	1	
	Asymptomatic	17	1	
BMI		N:243	N: 48	
	Normal	64	13	0.994
	Overweight	61	12	
	Obese	118	23	
Oxygen saturation at admission		N: 271	N: 56	
, 	96–100%	178	33	0.336
	≤95%	93	23	0.550
Tachycardia (PR >100)	37370	N: 359	N:73	
Tacifycardia (FR >100)	Present	166	50	
Tachymnas (DD > 20)	riesent		N: 73	
Tachypnea (RR > 20)	Durant	N: 359		0.000
	Present	151	43	0.009
Hypotension	_	N: 359	N: 73	
	Present	67	13	0.864
ICU admission		N: 346	N: 72	
	Yes	92	33	0.001
Thrombolysis/Thrombectomy		N: 359	N: 73	
	Thrombolysis	23	13	0.001
	Thrombectomy	1	1	
Initial anticoagulation received	•	N: 315	N: 69	
•	Low molecular weight heparin	238	53	0.607
	Unfractionated heparin	58	11	
	Fondaprinox	1	0	
	Warfarin	5	3	
	Rivaroxaban	13	2	
Maintanance therapy	Nivaloxabali		66	
Maintenance therapy	D:	N: 318		0.653
	Rivaroxaban	126	22	0.652
	Dabigatran	14	3	
	Warfarin	132	33	
	Low molecular weight heparin	44	7	
	Vena cava filter	2	1	
Elevated troponins		N: 275	N: 66	
	Yes	149	45	0.039
Elevated Pro-BNP		N: 169	N: 52	
	Yes	128	41	0.644
СТЕРН		N: 303	N: 64	
	Yes	19	3	0.628
Development of cardiac arrest	163	N: 339	N: 72	0.020
bevelopment of caldiac affest	Voc			0.000
DE valated moutality	Yes	20 N. 350	11 N. 27	0.006
PE-related mortality	V	N: 359	N: 37	2 222
	Yes	11	2	0.882
Recurrence of PE		N: 333	N: 72	
	Yes	31	6	0.794

higher in the saddle PE group. Interestingly, similar rates of late decompensation of saddle PE patients after their initial presentation were also reported by other investigators. In a comparative study between the saddle and non-saddle PE, Alkinj et al reported that the use of vasopressors and the need for cardiopulmonary resuscitation along with mechanical ventilation were not statistically significantly different between the two groups in the acute phase. Nevertheless, during the delayed phase (>6 hours from hospital admission), the rates of decompensation resulting in PE-related shock, mechanical ventilation, and thrombolysis happened more frequently in the saddle PE group [17]. In a nationwide inpatient sample to identify all hospitalizations related to acute PE in the USA from the year 2009 to 2011, Pathak et al also reported higher rates of development of cardiac arrest, cardiogenic shock, respiratory failure, and thrombolysis use among their saddle PE patients [18]. In the present study, we found higher rates of RV enlargement, RV dysfunction, and elevated RVSP on echocardiography. These findings were also reported in previous studies that involve comparisons between the two groups. Alkinj et al reported a higher proportion of mild RV dilatation and mild RV systolic dysfunction among the saddle PE group

Table 2. Risk factors and comorbidities associated with saddle and non-saddle PE.

Variable		Non-saddle	Saddle	P value
Provoked/Non-provoked		N: 328	N: 69	
•	Provoked	233	40	0.033
	Non-provoked	95	29	
Provoking factors	·	N: 359	N: 73	
-	Malignancy	47	7	0.409
	Pregnancy	7	0	0.229
	Use of contraceptive pills	20	3	0.612
	Stroke	14	1	0.282
	Hospitalization for a medical reason	42	6	0.388
	Hospitalization for surgical reason	76	12	0.360
	Femur fracture	12	1	0.368
	Other fractures	25	3	0.367
	Recent flight	40	11	0.343
	Prolonged immobilization	95	16	0.418
	Thrombophilia	27	6	0.838
	Family history of VTE	8	1	0.640
Associated comorbidities	, ,	N: 359	N: 73	
	Diabetes	93	15	0.335
	Hypertension	110	17	0.209
	Heart failure	14	2	0.632
	Chronic respiratory illness	27	7	0.609
	Smoking	31	5	0.615
	Alcohol consumption	14	4	0.538

Table 3. Echocardiographic characteristics of saddle and non-saddle PE.

Variable		Non-saddle	Saddle	P value
Right ventricular enlargement		N: 267	N: 60	
-	Present	83	36	0.000
Right ventricular dysfunction		N: 264	N: 59	
•	Present	58	27	0.000
RVSP		N: 227	N: 52	
	≤40	138	20	0.003
	>40	89	32	
Presence of right atrial thrombus		N: 267	N: 60	
-	Present	4	3	0.090

[17]. Utilizing CTPA parameters, Granada et al also reported higher rates of RV dilatation among patients with saddle PE [13]. Nevertheless, a comparable degree of RV strain on echocardiography was reported in a small study that involved 17 patients with saddle PE [11]. In the current study, the rates of PE recurrence and development of CTEPH at six months after acute PE diagnosis did not differ between the two groups. Granada et al examined that rate of PE recurrent at 30 days after initial acute PE diagnosis and found no statistically significant difference between the saddle and non-saddle groups. OCP use, development of hypotension and decompensation following admission, and RVSP reading > 40 mmHg were significant positive predictors of exhibiting saddle PE in the current study. OCP-induced procoagulant effects are mediated by many hemostatic abnormalities including increases in the levels of prothrombin, factor VII, factor VIII, factor X, fibrinogen, and prothrombin fragment 1 + 2 and decreases in the levels of factor V and fibrinolytic potentials [19]. Despite the plethora of studies linking the use of OCP to the development of VTE, only a few case reports described its association with saddle PE [20]. Our study is among the few studies with a considerably large number of patients that attempted to explore different characteristics of saddle PE. In this study, we

compared the clinical characteristics and echocardiographic findings of saddle PE with non-saddle PE. Furthermore, some important outcomes such as the rate of PE recurrence, PE-related rates, and the development of CTEPH were also investigated in the current study. The very high number of CTPA performed in this study has also permitted proper anatomical identification of the clots in the vast majority of patients. There is a trend in our center to perform echocardiography for the majority of patients admitted with acute PE which permitted the availability of echocardiographic studies for the majority of patients investigated in this study. Nevertheless, the current study has important limitations. The retrospective nature of the study did not allow the exclusion of hidden confounders such as preexisting cardiac or pulmonary diseases or other comorbidities that could affect the findings and the outcomes. A PE response team (PERT) is a multidisciplinary team established to improve the clinical care for patients with PE [21,22]. Although Rapid Response Teams (RRT) are always available in our institution, however, specialized teams that deal with PE such as the PERT are not. Hence, we were unable to determine the effects of the PERT approach on the outcomes of the two groups. The importance of some echocardiographic parameters such as the Tricuspid Annular Plane



Systolic Excursion (TAPSE) for risk stratification and prognostication of patients with PE has not been addressed in this study. Furthermore, the finding of a high rate of saddle PE in the current study is fascinating. A simplistic explanation is the high rate of utilization of CTPA in PE diagnosis in the current study. Nevertheless, a further investigation of this finding is warranted.

5. Conclusions

Saddle PE may account for a higher proportion among all PE cases than previously reported. Patients with saddle PE tend to present more frequently with tachycardia and tachypnea, have more frequent elevations of cardiac troponins, and require more frequent ICU admissions and thrombolysis than those with non-saddle PE. They have also higher rates of RV enlargement and dysfunction. More importantly, patients with saddle PE tend to have higher rates of late decompensation and cardiac arrest after their initial presentation. History of OCP use, development of hypotension and decompensation following admission, and RVSP > 40 mmHg are significant predictors of saddle PE. Physicians should keep these characteristics in consideration when managing patients with saddle PE. Further studies addressing the optimal clinical management, admission triaging, and use of thrombolysis/thrombectomy for patients with this PE entity are desperately needed.

Ethics approval

The study was approved by the Medical Research Center at Hamad Medical Corporation (approval No: MRC-01-19-059).

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon a reasonable request.

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Disclosure statement

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Author contributions

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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