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Incidence and predictors of chronic thromboembolic pulmonary hypertension following first episode of acute pulmonary embolism

Abstract

Introduction: Late obstructive pulmonary artery remodeling presented as CTEPH portends adverse sequelae and therapeutic challenges. Although progressive dyspnea on exertion beyond three-month period of treatment with anticoagulants is a diagnostic cornerstone, uncertainty still surrounds early identification and risk factors.

Material and methods: We have conducted a prospective study among survivors of acute pulmonary embolism (PE) who were treated by anticoagulants for at least 3 months. Patients with preexisting pulmonary hypertension (PH), severe chronic obstructive pulmonary disease (COPD), and low ejection fraction (EF) in baseline echocardiography (EF $<$ 30%) were excluded. Complete follow-up for 290 subjects were performed. According to a predetermined stepwise diagnostic protocol, patients with exertional Dyspnea and PH probable features in echocardiography underwent lung perfusion scan.

Results: Cumulative two-year incidence of CTEPH was 8.6% (n = 25). There was no patient with normal baseline right ventricular (RV) function in CTEPH group. In the same way, none of these patients had only segmental involvement in baseline CT angiography (CTA) in CTEPH group. Greater proportion of CTEPH group received fibrinolytic therapy, however the difference was not significant (2.6% *vs* 8 %, P = 0.16). Multivariate logistic regression demonstrated significant association of RV diameter, and PAP in baseline echocardiography as well as RV strain in CTA with development of CTEPH. Corresponding odds ratios were 1.147 (1.063–1.584) P $<$ 0.0001) , 1.062 (1.019–1.106, P = 0.004), and 2.537 (1.041–6.674), P = 0.027), respectively.

Conclusions: We found that incidence of CTEPH was relatively high in the present investigation. RV diameter, baseline PAP and RV dysfunction were independent predictors of CTEPH.

Key words: pulmonary hypertension, pulmonary embolism, CTEPH, echocardiography, predictor, RV dysfunction

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"The Known" facts regarding CTEPH risk factors are relatively inconsistent. However, history of recurrent PE or VTE, RV dysfunction, elevated PAP, RVD and the (RV/LV) ratio >1 are frequent. Unprovoked pulmonary embolism, older age, and splenectomy have been mentioned, too. Besides the incidence varies widely among different populations.

"The New" findings in our prospective long-term study were high incidence of CTEPH after first index PTE and exploration of some important risk factors. Of those, were RV diameter, baseline PAP and RV dysfunction as determined via CT angiographic measures. Furthermore, relative risks for developing CTEPH were persistent in majority of subgroups.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious chronic form of pulmonary hypertension (PHTN) which is thought to be caused by deposition of fibrotic material and vascular remodeling following the initial pathologic insult of an acute pulmonary embolism (APE). Consequently, a cascade of events pertaining to inflammation and healing process occurs leading to elevation of pulmonary arterial pressure and right ventricular failure [1, 2].

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Incidence of CTEPH in observational studies has been reported in a wide range to be as low as 0.5% or as high as 9.1% [3–6]. Given that CTEPH is one of the few etiologies of PHTN potentially curable by means of pulmonary end artrectomy (PEA) in addition to high levels of morbidity and mortality in untreated patients [5], a timely diagnosis and management is of great value with eminent prognostic implications.

An essential question is when and how to screen APE patients for detection of CTEPH [7]. There has been multiple studies [8, 9] linking several medical and surgical conditions to development of CTEPH following an APE episode . Likewise, there are also clinical risk scores predicting the occurrence of CTEPH after APE [10]. However, limited number of patients and lack of focus on laboratory data, making their results either unrepresentative or incomplete, might have plagued most of them. In the current study, we sought risk factors and potential clinical predictors of CTEPH in APE patients who were followed in Tehran Heart Center. The main purpose was to form a better understanding of risk markers as encountered in clinical practice in a patient with a history of APE to alert the physician regarding possibility — and indeed the peril — of developing CTEPH.

Material and methods

A prospective cohort structure was designed in the present research. The study population consisted of all consecutive patients who were diagnosed with first episode of APE between 2014 and 2017 in our hospital. We enrolled all those patients with first episode of APE who survived and were fully anticoagulated for at least three months after admission. Patients who were already diagnosed with PHTN, those with severe COPD based on GOLD criteria and patients with a Left Ventricular Ejection Fraction (LVEF) of < 30 % were excluded from the study. Then we performed a scheduled follow-up program for eligible patients with unresolved pulmonary hypertension who were at increased risk of CTEPH. Primary endpoint of the study was incidence of CTEPH according to pulmonary perfusion scan. We have also investigated the occurrence of this diagnosis using right heart catheterization among those with positive scan findings.

The diagnosis of CTEPH was made according to the existing guidelines [7, 11]. In summary, we defined the diagnosis of CTEPH based on abnormal lung ventilation/perfusion scans despite at least three months of anticoagulation in patients with a previous history of APE. The diagnosis was confirmed if mean pulmonary artery pressure exceeded ≥ 25 mm Hg at rest with a pulmonary wedge pressure < 15 mm Hg in right heart catheterization or any of the following criteria was met:

— abnormal ventilation/perfusion scan with at least one or more segmental perfusion defect;
— an abnormal computed tomography scan.

Experienced echocardiography physicians to assess right ventricular (RV) size and function did echocardiographic assessment. RV function indices like Tricuspid annular plane systolic excursion (TAPSE), right ventricular systolic motion (RVSM) and subjective parameters like tricuspid regurgitation (TR) severity and inferior vena cava (IVC) plethora were applied. Laboratory data including D-dimer, high-sensitivity cardiac troponin (hs-CTnT) and N-terminal proBNP (NT-ProBNP) levels were gathered, at both baseline and at prespecified certain points during follow up. All laboratory measurements were done using Tehran Heart Center's Central Laboratory equipment. All demographic, clinical and laboratory data of patients were extracted from Tehran Heart Center's Data Bank (THC-DB). Definition of right heart strain (RHS) was performed based on the definition of recent studies which encompasses different RV to LV size ratios in addition to IVC(inferior vena cava) plethora and interventricular septal bowing [12].

Continuous variables were presented as mean ± SD and categorical variables were expressed as a percentage. Continuous variables were compared using the standard t-test. Categorical variables were compared using the chi-square test or Mann-Whitney U test regarding the presence or absence of normal distribution. A P value of less than 0.05 was considered significant. All statistical analysis was done using SPSS Statistics 25.0 (SPSS Inc, Chicago, IL). Multivariable Logistic regression analysis with and without bootstrap was recruited in order to determine potential risk factors of CTEPH. We have also evaluated adjusted effects of two major predictors using subgroup analysis due to decline interactions. Receiver Operating Curves (ROC) graphs were applied to show association of continuous variables predicting CTEPH either via pulmonary scan or right heart catheterization.

Results

Overall, during the study period 359 patients were initially admitted with a diagnosis of APE.

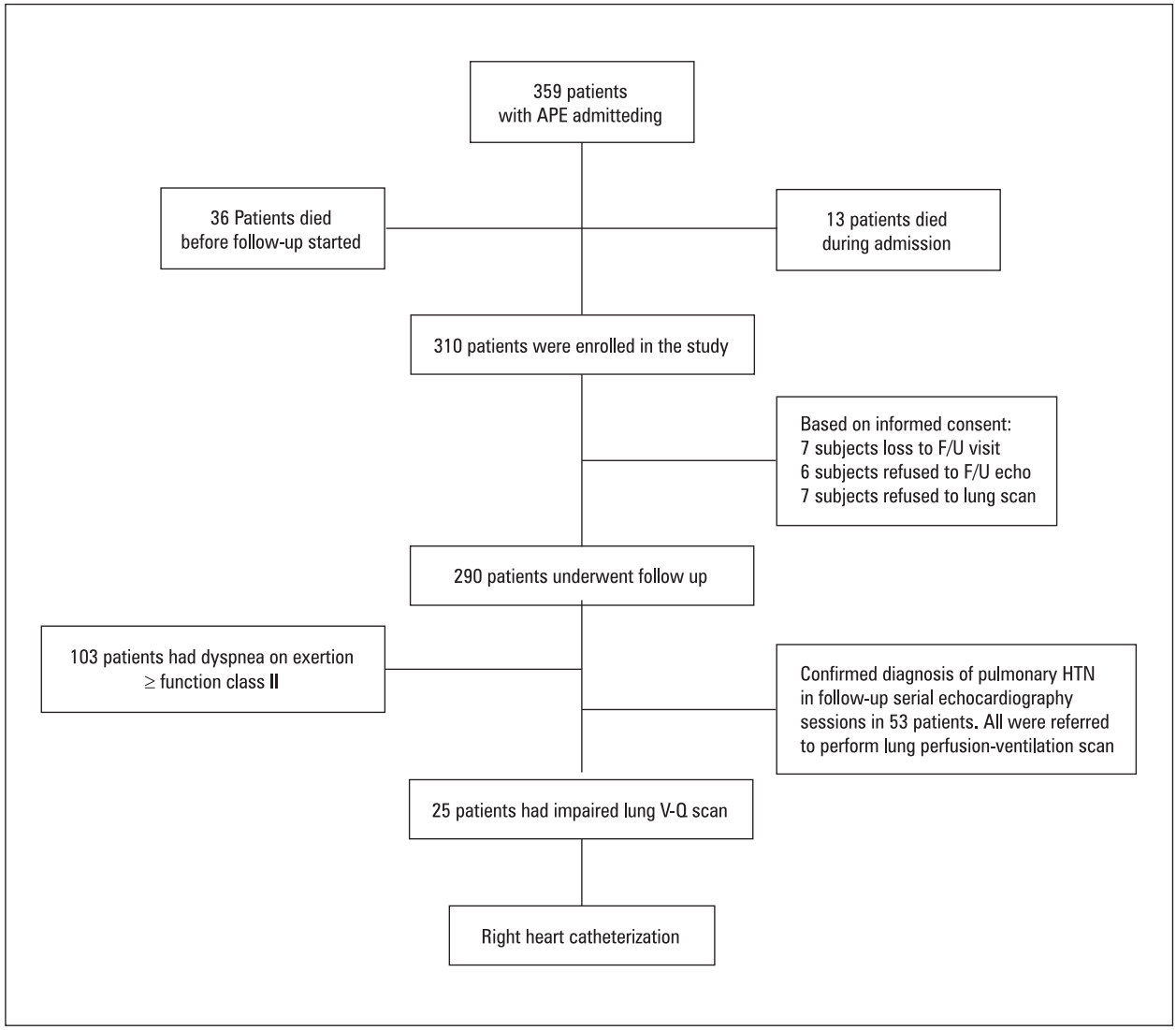


Figure 1. Scheme of study population and reasons for exclusion

Of these patients, 49 were excluded on different grounds (Figure 1), of 310 remaining patients 20 (6.5%) were lost to follow-up for various reasons. To calculate the incidence of CTEPH in study population we evaluated all patients three months after their initial presentation, they were asked about their functional capacity and their functional class according to New York Heart Association (NYHA) were determined. All patients who were in NYHA functional class of 2 and greater were evaluated with trans thoracic echocardiography (TTE), based on their TTE results and their RV function we performed lung perfusion scan to detect possible CTEPH in patients who were symptomatic and had RV dysfunction in their follow up period. Figure 1 shows steps in this diagnostic work up and its results.

Tables 1 and 2 have shown the demographic and baseline clinical characteristics of patients, physical examination findings and initial lab data results, electrocardiography, echocardiography and CT Angiography results upon admission respectively. Mean length of follow-up period was 21 months, which was similar for patients with CTEPH and the others as well.

Overall, of 290 patients who met the inclusion criteria and whose complete data was available to us 25 were diagnosed with CTEPH (8.6%). However, the incidence rate was 3.79% according to diagnosis via mean systolic PAP ≥ 25 mm Hg in right heart catheterization. Of note there was no patient in CTEPH group who had a normal baseline RV function in echocardiography, they all had at least some grades of TR and all of them had more than segmental involvement of pulmonary vasculature based on CT angiography findings.

Among echocardiography parameters, that we examined an increased diameter of RV was

Table 1. Clinical characteristics including lab parameters of patients at baseline of the study

	Non-CTEPH	CTEPH	Total	P value
Gender (female)	46.4% (n = 123)	44% (n = 11)	46.2% (n = 134)	0.81
Age (mean)	56.8	61.4	57.2	0.19
Diabetes mellitus	20.4% (n = 54)	28% (n = 7)	21% (n = 61)	0.30
Hypertension	41.1% (n = 109)	52% (n = 13)	42.1% (n = 122)	0.29
History of smoking	25.3% (n = 67)	24% (n = 6)	25.2% (n = 73)	0.88
Body mass index (Kg/m^2)	29.8	30.3	29.8	0.64
Systolic blood pressure (mm Hg)	129	130	129	0.81
Oxygen saturation	93.1%	90.8%	92.9%	0.053
Neutrophil to lymphocyte ratio	2.78	2.46	2.76	0.39
High sensitivity troponin (ng/ml)	65.9	35.5	63.1	0.12
D-dimer (mg/L)	7	5.4	6.9	0.30
NT-proBNP (pg/mL)	3228	5035	3406	0.38
Episode of unprovoked acute PE	45.5% (n = 120)	52% (n = 13)	46% (n = 133)	0.53
Fibrinolytic therapy	2.6% (n = 7)	8% (n = 2)	3.1% (n = 9)	0.16
Symptom duration (days)	5.3	6.7	5.5	0.29

Table 2. Electrocardiographic, echocardiographic and CT angiographic results of patients enrolled in the study upon admission

			Non-CTEPH	CTEPH	Total	P value
ECG	RBBB	Incomplete	14.3% (n = 38)	24% (n = 6)	15.2% (n = 44)	0.27
		Complete	7.5 % (n = 20)	0% (n = 0)	6.9% (n = 20)	
	T wave inversion in precordial leads		38.9 % (n = 103)	44% (n = 11)	39.3% (n = 114)	0.61
	S1Q3T3		47.9% (n = 127)	52% (n = 13)	48.3% (n = 140)	0.69
ECHO	RV dysfunction	Yes	60 % (n = 156)	100% (n = 25)	63.5% (n = 181)	< 0.001
		No	40% (n = 104)	0% (n = 0)	36.5 % (104)	
	TR	Yes	88.5 % (n = 231)	100% (n = 25)	89.5% (256)	0.014
		No	11.5% (n = 29)	0% (n = 0)	10.5% (n = 29)	
	IVC plethora	Non	51.8% (n = 127)	25 % (n = 5)	49.8% (n = 132)	0.015
		Severe	24.1% (n = 59)	55% (n = 11)	26.4% (n = 70)	0.006
	RVSM (mean)		10.6	9.4	10.3	0.08
	TAPSE (mean)		17.7	15.4	17.7	0.016
	RV (strain)		33.3% (n = 88)	64% (n = 16)	36% (n = 104)	0.004
	RVD		35.4 mm	41.9 mm	35.9 mm	< 0.001
CT angiography	Segmental involvement		16.3% (n = 44)	0% (n = 0)	14.9% (n = 43)	< 0.001
	More than segmental involvement		83.7% (n = 220)	100% (n = 25)	85.1 % (n = 245)	

CT — computed tomography; ECHO — echocardiography; IVC — inferior vena cava; RBBB — right bundle branch block; RV — right ventricle; RVD — RV diameter; RVSM — right ventricular peak systolic velocity; TAPSE — tricuspid annular plane systolic excursion

associated with development of CTEPH in follow-up period. In fact multivariate analysis revealed that with each one millimeter increase in RV diameter the risk of developing CTEPH escalates by 10–14%.While a normal IVC diameter and respiratory collapse were protective for development of CTEPH, these two parameters being abnormal were predictive of CTEPH development in the future. A diagnosis of RV strain by echocardiography also is predictive of CTEPH in the follow-up period, based on results from multivariate analysis it increased risk of CTEPH

Table 3. Multivariate regression models with and without bootstrap method to determine main risk factors of chronic thromboembolic pulmonary hypertension

	Model 1			Model 2		
	OR	**(95% CI)**	**P value**	**OR**	**(95% CI)**	**P value**
WBC	0.97	(0.89–1.210)	0.185	0.95	(0.92–1.340)	0.072
hs-CTnT	0.968	(0.943–0.994)	0.017	0.954	(0.876–1.070)	0.066
NT-proBNP	1.060	(1.010–1.170)	0.033	1.11	(0.96–1.42)	0.169
PAP (per 5 mm Hg increase)	1.079	(1.024–1.138)	0.005	1.062	(1.019–1.106)	0.004
Sex (male vs female)	0.410	(0.091–1.858)	0.248	0.748	(0.515–1.739)	0.146
Syncope	0.874	(0.636–2.088)	0.297	0.76	(0.69– 1.17)	0.178
RVD (per 1 mm increase)	1.104	(1.038–1.175)	0.002	1.147	(1.063–1.584)	0.000
RV strain in CTA	7.577	(1.668–14.418)	0.009	2.537	(1.041–6.674)	0.027
O2 saturation (per 5 % increase)	1.062	(0.951–1.186)	0.162	0.93	(0.731–1.06)	0.063
Systolic BP (per 1 mm Hg)	1.018	(0.976–1.061)	0.408			
Platelet	1.230	(0.920–1.870)	0.223			
Symptom duration	0.933	(0.796–1.094)	0.394			
CAD	6.440	(0.609–68.136)	0.122			

Model 1 represents the multivariate logistic regression while Model 2 refers to the same analysis using bootstrapping method. Both models have been adjusted fora, BMI, heart rate, hemoglobin, baseline creatinine, D-dimer, RVSM, RV dysfunction, diabetes, hypertension, smoking, LVEF, CAD, RBBB and other specific ECG results, TR severity, initial fibrinolysis, beta blocker use, unprovoked PTE , and statin therapy. WBC — white blood cells; PAP— pulmonary alveolar proteinosis; RVD — RV diameter; RV — right ventricular; CTA — CT angiography; CAD — computer aided diagnosis

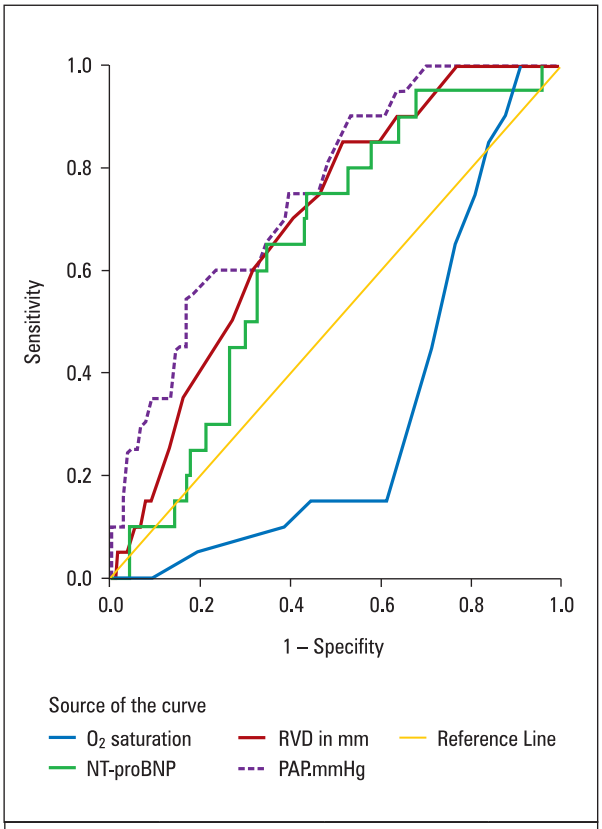
by 2.53 folds. Table 3 have summarized the integrated impacts of different risk factors of CTEPH derived via two adjusted models. Figures 2 and 3 illustrates the relationship between major risk factors and incidence of CTEPH .

Discussion

This prospective cohort study was conducted to: a) establish the incidence of CTEPH in APE patients who are diagnosed and followed in our center; and b) find possible clinical, imaging or laboratory predictors that can help in distinguishing patients who are at high risk of developing CTEPH in the post admission period.

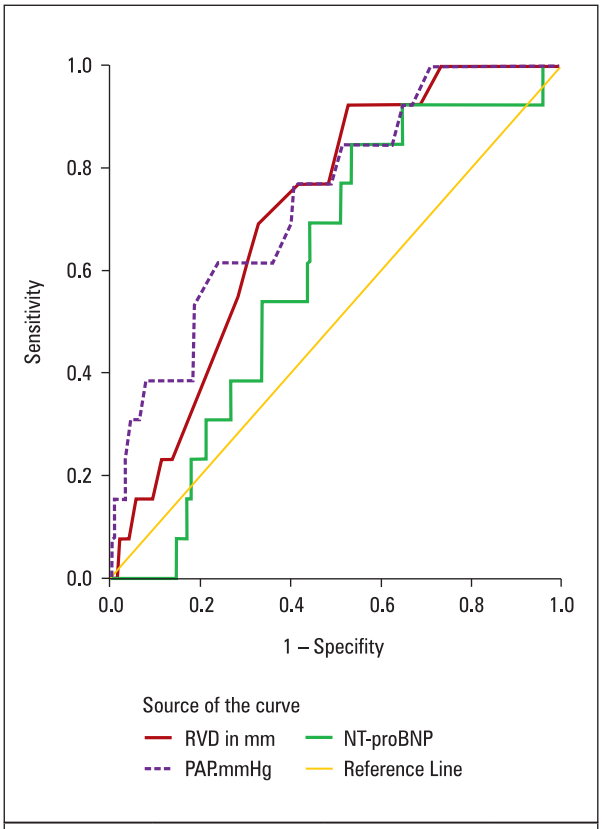
Incidence of CTEPH was 8.6% among patients who participated in the present study. This rate is surprisingly higher than that of outstanding European and US registries [13–20] that reported a weighted average of 4%. Nevertheless, it was lower than values reported in Japanese patients in a systematic literature review. CTEPH incidence from a Chinese registry was 11% which is also higher that what we discovered among our patients [21–23]. The observed discrepancy in results can be due to several factors, including quality of patient care, timing of treatment initiation, follow up protocols (routine *vs* per symptom screening for CTEPH), and modalities used to detect CTEPH and environmental and genetic factors that are not measured or adjusted are all variables which play their own roles.

To date diversity of proposed risk factors for chronic thromboembolic pulmonary hypertension has emerged as a substantial issue. A recent systematic review and meta-analysis have explored multiple relevant factors extracted from eight studies. History of recurrent PE or VTE, initial dysfunction of right ventricle (RV) were the most frequent ones followed by elevated PAP, right ventricular diameter and the (RV/LV) ratio > 1. Unprovoked pulmonary embolism, older age, and size heterogeneity of erythrocytes (RDW) were also indicated in at least two studies. Other uncommon correlates stated were as following :large perfusion defects, higher BNP, having varicose veins, intermediate-risk PE , CT obstruction index over 30%, hypothyroidism, prolonged symptom onset prior to index PE, diabetes mellitus , history of fibrinolysis or surgical embolectomy



Variables	AUC ± SE	95 % CI	P-value
O_2 saturation	0.318 ± 0.048	(0.223–0.413)	0.007
NT pro-BNP	0.643 ± 0.054	(0.537–0.750)	0.033
RVD [mm]	0.716 ± 0.052	(0.595–0.797)	0.004
PAP [mm Hg]	0.782 ± 0.051	(0.653–0.851)	0.000

Figure 2. ROC curve showing the predictors of CTEPH diagnosed via lung scan



Variables	AUC ± SE	95 % CI	P-value
NT pro-BNP	0.602 ± 0.065	(0.474–0.730)	0.215
RVD [mm]	0.785 ± 0.057	(0.604–0.847)	0.009
PAP [mm Hg]	0.811 ± 0.066	(0.612–0.873)	0.003

Figure 3. ROC curve showing the predictors of CTEPH diagnosed via RHC

[19]. In our study, there was no association between Unprovoked PE, symptom duration, DM or thrombolytic therapy with incidence of CTEPH. However consistent with some of previous reports, we have also revealed that RV diameter, baseline PAP, and RV strain comprise a considerable part of its risk factors [10, 24, 25]. A crucial principle in this regard is the combination of tests applied to diagnose CTEPH. Since it is not feasible to conduct catheterization for all suspected individuals, a constellation of perfusion-ventilation scan, follow-up echocardiography, and CTA have been considered in most studies. In our study, RHC was performed in subjects with a positive lung scan. Another caveat in researches in this line appears when asymptomatic patients or those with mild symptoms develop CTEPH [26]. Thus, relatively silent CTEPH might be missed if only patients with persistent dyspnea of function class ≥ 2 enter the screening as we did. There is not an agreement neither about common classifications for RV dysfunction, which we have focused on, nor regarding the severity of PTE. In fact, beside influence of inter-observer errors, potential measurement biases and subjective findings in echocardiography, indices of RV dysfunction such as TAPSE, RVSM, RVD, RV/LV ratio are not yet consistent. Furthermore, interpretation of CT angiography and perfusion scan requires an optimal expertise as well as standard criteria. Yongping Yu *et al.* with a prospective cohort have declared that symptoms- to-treatment over 1 month, intermediate to high risk embolism, segmental and sub segmental involvement were more likely to develop CTEPH [23]. Likewise, the severity of PTE is composed of clinical PESI score, hemodynamic status, biomarkers particularly hs-CTNT, and RV dysfunction according to TTE or CTA. Thus, a stringent comparison in terms of PTE severity is not available. Although high-risk PTE patients had not a greater likelihood of CTEPH in the present study (despite Yongping Yu *et al.*), this stratification was applied in our multivariate

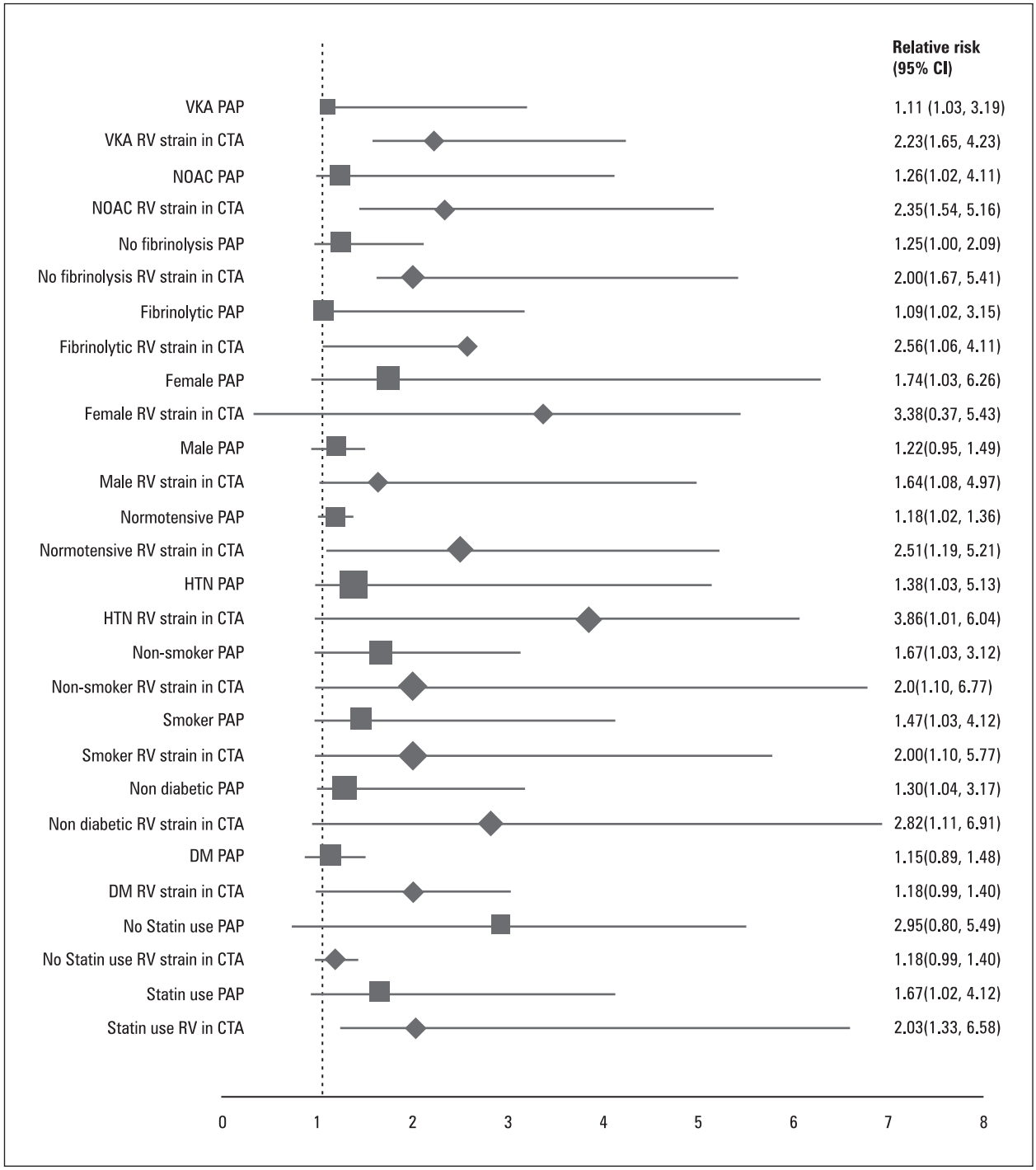


Figure 4. Subgroup analysis of major risk factors of CTEPH including PAP and RV strain in CTA **[missing reference to the table in text]**

analysis. Baseline proportion of patients who had received thrombolytic agents representing a high-risk category in their research was comparable to our results (3.1 *vs* 5%). However, thrombolytics might have also accelerated salvage of the clots but the paradoxical theory describes distal embolization of degraded particles. On the contrary, we had no patient with IVC filter. Besides 4.5% of our participants underwent treatment with Novel oral anticoagulant (NOAC) medications mainly rivaroxaban. The data regarding the use of NOAC agents were not available for evaluation of our findings against that of previous studies. A substantial difference between our study and previous ones pertains to duration of symptoms or symptom onset to treatment interval. It was 5.5 days showing that timely diagnosis was made for the majority of patients and it was also identical for those

with and without CTEPH. In addition, only 4.48% of our subjects were symptomatic for 3 weeks or more while 90.6 % of cases were treated after 1 month in a recent study [23]. Since segmental and sub segmental branches involvement might serve as an independent predictor of pulmonary hypertension, experts have suggested a link between delayed treatment of PTE and CTEPH. This concept is explained through propagation or embolization of the thrombus particles into distal pulmonary vasculature following deferred anticoagulation. Therefore, the aggregated clots become organized in an underlying structure, which is fulfilled with inflammatory cytokines as well as fibrosis triggering factors. Although, all patients identified as CTEPH in this study had sub segmental obstruction, calculated average of symptom duration was the same as non-CTEPH cases.

Although we failed to show the association of oxygen saturation of individuals at presentation with incidence of CTEPH in multivariate models, a borderline statistical significance was achieved. Indeed, there was a trend toward protective effect of higher oxygen supply at the time of index PTE. It was in agreement with few previous reports [6]. In addition, the receiver operating curve (ROC) analysis have confirmed such an association. We have also demonstrated that relative risk of CTEPH incidence was modified via sex. In other words, the association of RV strain and outcome was significant in male subjects. By contrast, greater risk of CTEPH in patients with higher baseline PAP was only significant for female gender. In the same way diabetes mellitus and statin regimen after PTE diagnosis have influenced the association of PAP and incidence of subsequent CTEPH. Thus, these relationships were observed in diabetics as well as those who did not used statins.

Study limitations

There were several limitations and challenges in the present study. We had not collected the data regarding inflammatory conditions such as biomarkers like CRP, blood groups, history of splenectomy, thyroid disorders, anti-phospholipid syndrome, Ventriculo-atrial shunts, infected chronic intravenous lines or pacemakers and objective evidence of malignancy. Furthermore, target population did not subtend patients with recurrent thromboembolism so the results could be generalized only to survivors of first acute PTE. The subgroup of patients for whom fibrinolytic treatment was applied at the time of index PTE diagnosis constituted a small fraction of the total number. However, this feature was similar when compared between patients with and with CTEPH. A wide variety of determinants has not been indicated here since the exact pathophysiology of this long-term complication are unclear, yet. Adherence to anticoagulant therapy, which was mainly based on subjective patient reports, could not be verified neither in the present study nor in prior reports.

Conclusions

Due to uncertainty and controversy surrounding contemporary risk factors of CTEPH along with insidious clinical course of this entity, we still need aggregate body of evidence to identify its major determinants. Moreover, validation of the predictors in prospective investigations as well as targeting the appropriate subset of patients who have survived pulmonary embolism suffering chronic symptoms beyond 3 months is of great value. To best of our knowledge, this is the first prospective study in Iran, which have focused on a structured model of diagnosis, incidence and risk factors of CTEPH.

In a brief look we recruited a stepwise algorithm in prospective diagnosis and follow-up of the patients: First step was screening echocardiography (at baseline and follow up): N = 290. Second step included V-Q scan plus pulmonary CT angiography in all patients with PH (PAP > 40 mm Hg in echocardiography): N = 53. Third step was RHC for positive results of step 2 which comprised 25 patients.

Herein, we have demonstrated that a considerable proportion of PTE survivors (8.6%) were at increased hazard of developing CTEPH over 2 years. This estimate was expected according to previously reported ranges of 0.1–9%. However, it was greater than that observed in Europe but less than the values reported in latest study in China. However, the incidence rate was 6.55 % according to diagnosis via systolic PAP > 25 in right heart catheterization. Furthermore, we found that baseline PAP, RV strain detected via CT angiography, and RV diameter were independent measures predicting CTEPH. Prevailing well-established stepwise approach to execute screening for pulmonary hypertension among PTE survives after 3 months appears to be effective.

Conflict of interest

None declared.

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