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Original Article

Clot Burden As a Predictor of Chronic Thromboembolic Pulmonary Hypertension After Acute Pulmonary Embolism: A Cohort Study

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Abstract

OBJECTIVE: A small percentage of acute pulmonary thromboembolisms (PTE) persist as chronic fibrin clots, potentially leading to chronic thromboembolic pulmonary hypertension (CTEPH). A scoring system for evaluating the burden of acute PTE based on computed tomography pulmonary angiogram (CTPA) findings was tested for its association with CTEPH within one year.

MATERIAL AND METHODS: In this retrospective cohort of 475 patients with a definitive diagnosis of acute PTE, the Qanadli score (QS) was calculated on the initial CTPA. Through regular follow-up over 1 year, symptomatic patients underwent extensive evaluation.

RESULTS: Of the 475 patients enrolled in the study [age 58.3 ± 16.6, 195 (41.1%) female, QS: 13.01 ± 7.37/40], 321 patients completed the study. A total of 22 (6.8%) patients were definitively diagnosed with CTEPH. In univariate analysis, the initial QS was significantly higher in patients with subsequent CTEPH than in patients without (17 ± 5.6 vs. 13 ± 7.6, $P = .009$). QS was directly associated with CTEPH (odds ratio: 1.08, 95% confidence interval: 1.0-1.16, $P = .042$). The evolution of CTEPH in men could be predicted with a sensitivity of 100% and a specificity of 54% when a cut-off point of 14.5 (43.5%) was set for QS. The area under the receiver operating characteristic curve in this setting was 0.74 with a *P*-value of .032. Qanadli score failed to predict CTEPH in women.

CONCLUSION: Scoring the clot burden in the pulmonary arteries through the Qanadli method can predict the evolution of CTEPH only in men 1 year after acute PTE. Women comprise most of the CTEPH patients. Thus, strict follow-up adherence seems to be even more important in women.

KEYWORDS: Pulmonary embolism, chronic thromboembolic pulmonary hypertension, computed tomography angiography, Qanadli index

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INTRODUCTION

Around 900 000 people are annually affected by venous thromboembolism in the United States.[1] Although signs and symptoms of acute pulmonary thromboembolism (PTE) depend on the size and location of the clot in the pulmonary arterial tree, it usually presents as acute-onset dyspnea.[2,3] Computed tomography pulmonary angiogram (CTPA) has proven to yield valuable information in the evaluation of acute PTE. Two commonly used indices of pulmonary arterial obstruction severity have been proposed by Qanadli et al[4] for CTPA and Miller et al[5] in angiography. Qanadli score (QS) closely correlates with the Miller index, oxygen saturation, and pulmonary artery pressure and helps distinguish massive PTEs.[6] Around 0.1%-11.8% of survivors of acute PTE eventually develop chronic thromboembolic pulmonary hypertension (CTEPH).[7] It is defined as a mean pulmonary artery pressure ≥25 mmHg and pulmonary artery wedge pressure ≤15 mmHg and a mismatch in perfusion–ventilation despite 3 months of optimal anticoagulation.[8] Although QS can aid in predicting the complications and outcomes of acute PTE, it is not clear if the clot burden is associated with the evolution of CTEPH in the future. It is noteworthy that about 30% of acute PTE patients have persistent perfusion defects after 6 months of anticoagulation, but only 10% of this population will develop CTEPH. Recurrent unprovoked VTEs, delayed onset of anticoagulation, the large size of the initial thrombus, and older age are risk factors for the evolution of chronic perfusion defects.[7,9] Early diagnosis of CTEPH is essential to prevent small vessel vasculopathy and right heart failure.[10] In this retrospective cohort study, the correlation between the initial QS and the evolution of CTEPH was assessed in a 1-year follow-up.

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MATERIAL AND METHODS

Study Material

The present study was conducted from January 2016 to October 2019. All patients received the standard of care based on the latest recommendations by the European Society of Cardiology. In this single-center retrospective cohort, all consecutive adult (≥18 years old) patients with a confirmed diagnosis of acute PTE were included. Patients diagnosed with modalities other than CTPA were excluded. Due to a paucity of evidence regarding the impact of fibrinolytics in the evolution of CTEPH and to avoid the inclusion of patients with additional interventions, those who received fibrinolytic were excluded from the study.

Follow-Up

The patients were followed for 1 year after the acute PTE. Patients who had remained symptomatic after 3 months of optimal anticoagulation underwent transthoracic echocardiography. If pulmonary hypertension was highly probable, based on the last PH guideline, a V/Q scan was performed for screening CTEPH. Patients with at least 1 large segmental perfusion defect were considered to have CTEPH. To rule out other diagnoses such as angiosarcoma or major vessel arteritis and evaluation for operability, CTPA was performed. All patients underwent right heart catheterization (RHC) for a definite diagnosis, hemodynamic examination, and determination of pulmonary vascular resistance (PVR), mean pulmonary artery pressure (mPAP), cardiac output (CO), and right atrial (RA) pressure. A Swan–Ganz catheter (Edwards Lifesciences company, Irvine, California, USA) was employed for all cases.

Computed Tomography Pulmonary Angiography and Qanadli Obstruction Index

Computed tomography pulmonary angiogram imaging was obtained using a 64-slice multi-detector computed tomography device (Somatom Sensation 64, Siemens, Munich, Bavaria, Germany). The procedure was set at 120 kV, 100 mAs, beam collimations of 0.6 mm, and a pitch of 1.22. Images were reconstructed in 1 mm thicknesses and 0.7 mm increments. Using an infusion pump (Ulrich Medical, Ulm, Baden-Württemberg, Germany), 80 mL of contrast media with an iodine concentration of 370 mg/mL was infused at a rate of 5 mL/sec through the antecubital vein. Before and after the infusion, 20 mL of normal saline was infused as an extravasation check and washout bolus. A test bolus in the lumen of the pulmonary trunk calculated the scan delay time, a method described by Wu et al.[11] The obstruction index was calculated according to the method proposed by Qanadli et al.[4] Each lung receives 10 segmental arteries (5 for the lower, 3 for the upper, and 2 for the middle lobe or lingula). The perfusion defect in a given artery is scored 1 if partially occluded and 2 if complete occlusion has occurred. The sum of scores from each involved arterial branch equals the Qanadli obstruction score (QS). Thus, the maximum score is 40. The obstruction index can then be calculated as a percent (Figure 1). Since PTE of the segmental and subsegmental arteries can be over-diagnosed, especially in patients with tachypnea and low pretest probability of acute PTE,[12,13] 2 radiologists evaluated the CTPA images separately. Eventually, patients with scores with higher inter-observer agreement were enrolled in the study.

MAIN POINTS

- Early detection and treatment of chronic thromboembolic pulmonary hypertension (CTEPH) may prevent further pulmonary vasculopathy and right heart remodeling.
- In this cohort, 6.8% of all patients with acute pulmonary embolism (PTE) were complicated with CTEPH after a one-year follow-up.
- Burden of the initial clot, measured through Qanadli score, was aligned with evolution of CTEPH.
- Among male patients, Qanadli score was shown to predict he evolution of CTEPH with an area under the curve of 0.74 when a cut-off point of 14.5 (i.e. 43.5%) was set. However, among female patients, it failed to show statistical significance.

Ventilation–Perfusion Scintigraphy

Patients with a high probability of pulmonary hypertension or low probability without any other reason better explaining the dyspnea underwent a V/Q scan. Scans were performed according to the European Association of Nuclear Medicine guidelines.[14] First, a perfusion scan using ^{99m}Tc-MAA was performed to rule out defects. If there was a suspicious defect(s), at least 24 hours later, a ventilation scan using ^{99m}Tc-DTPA nebulize was performed to check for any mismatches. The probability of persistent thrombus was evaluated according to modified PIOPED criteria. Patients with a high probability of chronic thrombus underwent RHC to investigate the right heart function and mechanics of pulmonary circulation.

Statistical Analysis

The fitness of the numerical variables to normal distribution was assessed via a 1-sample Kolmogorov–Smirnov test. Data was described as mean (SD) for numerical and frequency (percentage) for categorical variables. Comparisons between the 2 groups were performed by independent sample *t*-test for numerical and Pearson's chi-square or Fisher's exact test for categorical variables. Binary logistic regression models were applied for assessing adjusted associations between CTEPH and predictors. $P < .05$ was considered a statistically significant result. The accuracy of QS for diagnosis of CTEPH was assessed via the area under the receiver operating characteristic (ROC) curve (AUC). For interpretation, AUC was considered as no discrimination ability in 0.5-0.6, weak accuracy in 0.6-0.7, acceptable in 0.7-0.8, excellent in 0.8-0.9, and outstanding in 0.9-1. All measurements are presented with a confidence interval (CI) of 95%. The IBM Statistical Package for the Social Sciences Statistics version 22.0 for Windows (IBM Inc., Armonk, NY, USA) was applied for statistical analysis.

Ethics Committee Approval

The study protocol was approved by the ethics committee of the Tabriz University of Medical Sciences, Iran (reference number IR.TBZMED.REC.1396.1058). All patients were thoroughly informed about the study design and were assured that no identifiable data would be shared. All patients or their next of kin signed the informed consent form.

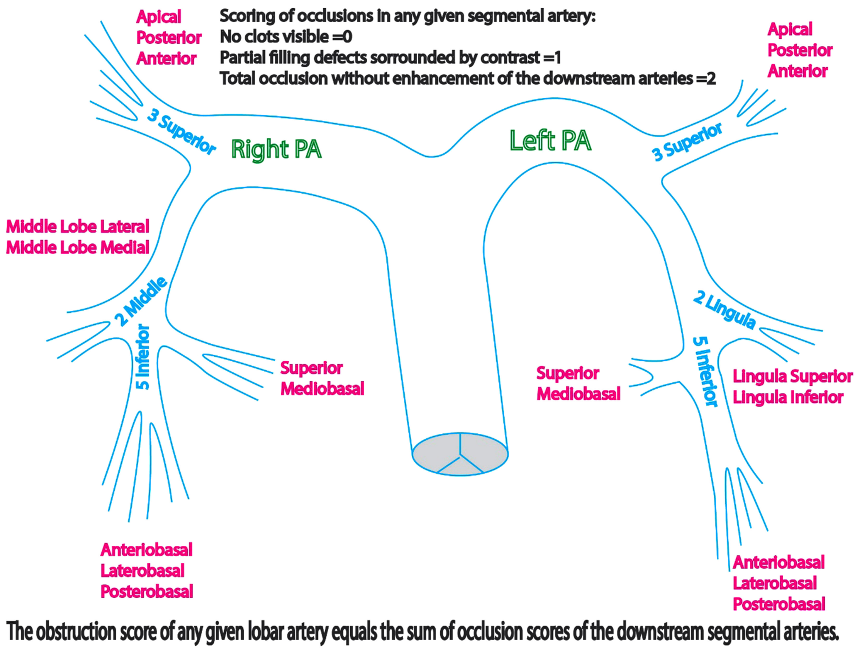

Figure 1. Calculation of the Qanadli obstruction score. The maximum possible score in this scoring system is 40. To report the index in percent, the score should be multiplied by 2.5. In our study, the original score was applied to the analysis. All rights reserved. Copyright for the image: The image in Figure 1 was created using Adobe Illustrator version 2022 by the authors of the present study. All rights for using the image are reserved.

RESULTS

Three hundred twenty-one patients (57% men, age 57 ± 16.3 years) were included in the analysis. Patients' baseline characteristics are described in Table 1.

Twenty-two patients (6.8%) were definitively diagnosed with CTEPH. Associations between the presence of CTEPH and patients' characteristics were assessed, and the results are presented in Table 2. More female patients and patients with higher QS at baseline were observed in the CTEPH group. Considering the potential effects of other relevant factors, including age, provoked versus unprovoked, surgery, and OCP, multivariable analysis was performed using binary logistic regression models.

Table 1. Baseline Demographic, Clinical, and Imaging Characteristics in the Study Population

Characteristics	
Age (years) mean (SD)	57 (16.3)
Sex, n (%)	
Male	184 (57%)
Female	137 (43%)
Surgery, n (%)	58 (18%)
Trauma with fracture, n (%)	31 (10%)
OCP*, n (%)	8 (3%)
Provoked PE, n (%)	192 (40%)
Baseline anatomy of pulmonary vasculature,† n (%)	
Right	56 (18%)
Left	26 (8%)
Bilateral	209 (65%)
Bifurcation	27 (8%)
Symptom, n (%)	107 (33%)
Qanadli score mean (SD), [minimum-maximum]	13 (7.5), [1-30]

Patients characteristics (n = 321).
*OCP, oral contraceptive pills that contain estrogen.
†Based on CT pulmonary angiogram.

Table 2. Baseline Demographic, Clinical, and Imaging Characteristics in the Study Population in Patients With and Without CTEPH During Follow-Up

Variable	CTEPH – (n = 299)	CTEPH + (n = 22)	*P*
Age (years) mean(SD)	57 (16.5)	53 (16.9)	.370
Gender, n (%)			.039
Male	176 (59%)	8 (36%)	
Female	123 (41%)	14 (64%)	
Surgery, n (%)	56 (19%)	2 (9%)	.257
Trauma, n (%)	30 (10%)	1 (5%)	.400
OCP, n (%)	7 (2%)	1 (5%)	.522
Provoke, n (%)	143 (48%)	8 (36%)	.299
Anatomy, n (%)			.124
Right	56 (19%)	0 (0%)	
Left	25 (8%)	1 (5%)	
Bilateral	192 (64%)	17 (90%)	
Bifurcation	26 (9%)	1 (5%)	
Qanadli score mean (SD)	13 (7.6)	17 (5.6)	.009

Univariable analysis, Comparisons between patients with and without CTEPH.
CTEPH, chronic thromboembolic pulmonary hypertension; OCP, oral contraceptive pills that contain estrogen.

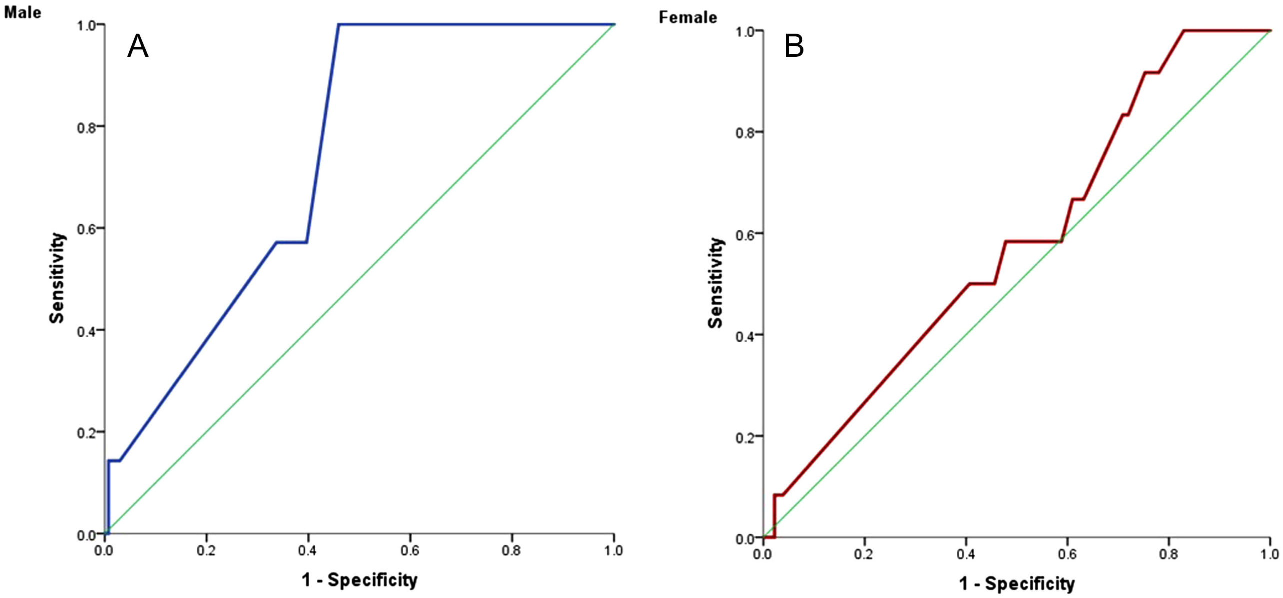

Figure 2. (A) Receiver operating characteristic curve of Qanadli score correlation with the evolution of CTEPH in men. (B) Receiver operating characteristic curve of Qanadli score correlation with the evolution of CTEPH in women. CTEPH, chronic thromboembolic pulmonary hypertension.

The accuracy of QS for diagnosis of CTEPH was assessed via the area under the ROC curve (AUC) (Figure 2). It was observed that only in men, QS had acceptable accuracy [AUC (95% CI): 0.74 (0.61-0.87) and can be used for diagnosis of CTEPH (Table 3).

In multivariable analysis, it was found that in the total population, QS had a statistically meaningful direct association with the presence of CTEPH. However, the correlation was weak [odds ratio (OR) 1.08, 95% CI: [1.00-1.16], *P* = .042] (Table 4, model 3). Besides, separate models were provided for male and female gender (Table 4, models 1 and 2). No significant associations were observed between CTEPH and the factors mentioned earlier in women. On the other hand, in men, CTEPH had a reverse association with unprovoked PTE [OR (95% CI): 0.04 (0.00-0.86), *P* = .040] and strong, direct association with the history of surgery [OR (95% CI): 17 (1.14-265), *P* = .040]. Also, borderline association was observed with QS and CTEPH [OR (95% CI): 1.15 (0.97-1.37), *P* = .102].

Table 3. Area Under the ROC Curve, Qanadli Score for Diagnosis of CTEPH

	AUC (95% CI)	*P*
Male*	0.74 (0.61-0.87)	.032
Female	0.58 (0.42-0.73)	.375

AUC, area under the curve; CTEPH, chronic thromboembolic pulmonary hypertension; ROC, receiver operating characteristic.
*Cut-off point for Qanadli Score: 14.5 (sensitivity = 1, specificity = 0.54).

DISCUSSION

Up to 12% of acute PTEs will eventually be complicated with CTEPH.[7] Before the introduction of pulmonary thromboendarterectomy (PEA), the 5-year survival for CTEPH patients was only 10%.[15] With PEA, the 5-year survival has improved to 72%.[16] Delayed diagnosis of CTEPH can lead to downstream small-vessel vasculopathy and right heart remodeling. Currently, there is 1-year delay in the diagnosis of CTEPH after acute PE.[17] By identification of patients at risk, this delay can be shortened. The incidence of CTEPH in this cohort was 6.8%. Women were found to be significantly predisposed to CTEPH after an acute PTE. Notably, about 25%

Table 4. Binary Logistic Regression Models

	Male (Model 1)		Female (Model 2)		Overall (Model 3)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Score	1.15 (0.97-1.37)	.102	1.05 (0.95-1.14)	.298	1.08 (1.00-1.16)	.042
Provoke	0.04 (0.00-0.86)	.040	2.82 (0.78-10.22)	.115	0.99 (0.36-2.78)	.992
Age	0.99 (0.94-1.04)	.722	0.99 (0.95-1.02)	.577	0.99 (0.96-1.02)	.428
Surgery	17 (1.14-265)	.040	0	.998	.63 (0.12-3.28)	.464
OCP	-	-	0.49 (0.05-5.25)	.558	-	-
Gender*	-	-	-	-	2.45 (0.92-6.50)	.072

**P*-value for score–gender interaction = .157.
OCP, oral contraceptive pills that contain estrogen; OR, odds ratio.

of CTEPH patients do not have a history of diagnosed acute PTE.[18] Virchow's triad of endothelial injury, stasis, and prothrombotic state describes the favorable conditions for the DVT evolution.[19] However, these predisposing factors may not always be identifiable. These unprovoked VTEs carry a 7.4% per patient-year risk of recurrence.[20] Unlike other studies, unprovoked PTE was not significantly associated with CTEPH.

The Qanadli obstruction score is a semi-quantitative estimation of the clot burden which was proposed by Qanadli et al[4] in 2008. In a study of 60 patients with acute PTE, patients with adverse outcomes did not have a significantly different QS than those without. However, a Qanadli index >20% predicted adverse outcomes in ROC analysis.[21] In another study, this scoring model did not correlate well with right ventricular (RV) dysfunction.[22] The largest data available suggested that among CTPA parameters, only right/left ventricular diameter ratio >1.0 could predict death within 30 days, in multivariate analysis, while both Qanadli and Mastora indices failed.[23] The ineffectiveness of QS in predicting mortality was confirmed by the meta-analysis of pooled data from 19 studies.[21] Although QS is not a reliable predictor of short-term outcomes, it correlates closely with the pre-operative PVR and mPAP in CTEPH patients and can predict the response to pulmonary artery thromboendarterectomy.[24] In a previous study, a QS <16 was associated with complete resolution of thrombus.[25] The presence of endothelialized chronic fibrin clots is necessary but not sufficient for the evolution of CTEPH.[9] Our study focused on the evolution of CTEPH rather than unresolved thrombus, and in this regard, higher QSs was correlated with the evolution of CTEPH. In our study, higher obstruction scores were correlated with CTEPH evolution. Moreover, a QS of more than 14.5 (43.5%) had a sensitivity of 100% and specificity of 54% for predicting CTEPH in men. As high as 90% of patients with RV dysfunction (indicated as elevated RV/LV diameter ratio) have a QS >40%-43%.[4,26] Although higher QS was correlated with CTEPH in men, this was not the case in women.

Although we cannot positively explain the inability of QS in predicting CTEPH in the female gender, it might be due to the low statistical power of the study or some other unknown gender-related factor involved in the pathophysiology of CTEPH.

Limitations of this study include the retrospective methodology and a high rate of lost to follow-up. Future studies should use additional indices and more precise reconstruction methods to overcome the disadvantages of the present methods. Especially, QS failed to predict CTEPH in women, who comprise the majority of CTEPH patients.

CONCLUSION

Qanadli obstruction score has a direct association with the evolution of CTEPH in men within 1 year after acute PTE. The results for women were not statistically significant. Recognition of patients at risk would help in the early diagnosis of CTEPH and avoiding downstream vasculopathy and RV remodeling. Since most CTEPH patients are women, it is imperative to encourage them to adhere to follow-up strictly and have a low threshold for further investigation in female patients with persistent symptoms. All patients with V/Q mismatch should be referred to a CTEPH clinic for optimal management.

Ethics Committee Approval: The study protocol was approved by the ethics committee of the Tabriz University of Medical Sciences, Iran (approval number IR.TBZMED.REC.1396.1058).

Informed Consent: All patients were completely informed about the study design and were assured that no identifiable data would be shared. All patients or their next of kin signed the informed consent form.

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