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Diagnostic approach and use of CTPA in patients with suspected pulmonary embolism in an emergency department in Saudi Arabia

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Background
In patients with suspected pulmonary embolism (PE), the literature suggests the overuse of computerized tomography pulmonary angiography (CTPA) and underuse of clinical decision rules before imaging request. This study determined the potential for avoidable CTPA using the modified Wells score (mWS) and D-dimer assay in patients with suspected PE.

Methods
This hospital-based retrospective study analyzed the clinical data of 661 consecutive patients with suspected PE who underwent CTPA in the emergency department of a tertiary hospital for the use of a clinical prediction rule (mWS) and D-dimer assay. The score was calculated retrospectively from the available data in the files of patients who did not have a documented clinical prediction rule. Overuse (avoidable) CTPA was defined as D-dimer negativity and PE unlikely for this study.

Results
Of 661 patients' data examined, clinical prediction rules were documented in 15 (2.3%). In total, 422 patients (63.8%) had required information on modified Wells criteria and D-dimer assays and were included for further analysis. PE on CTPA was present in 22 (5.21%) of PE unlikely (mWS $\leq$4) and 1 (0.24%) of D-dimer negative patients. Thirty patients (7.11%) met the avoidable CTPA (DD negative+PE unlikely) criteria, and it was significantly associated with dyspnea. The value of sensitivity of avoidable CTPA was 100%, whereas the positive predictive value was 90.3%.

Conclusion
Underutilization of clinical prediction rules before prescribing CTPA is common in emergency departments. Therefore, a mandatory policy should be implemented regarding the evaluation of avoidable CTPA imaging to reduce CTPA overuse.

Key Words Computed tomography, Pulmonary embolism, Wells criteria, D-dimer, Clinical prediction rule, Saudi Arabia

INTRODUCTION

Pulmonary embolism (PE) is estimated to occur in approximately 70 cases per 100,000 [1, 2]. However, the nationwide prevalence of PE in Saudi Arabia remains unknown. A single tertiary care center study suggested that the annual incidence rate of the first venous thromboembolism was 1.7 per 1,000 patients [3]. Other hospital-based studies reported a range of 5–33.8 [4-7]. Computed tomography pulmonary angiog-

raphy (CTPA) has been the most frequently used method for diagnosing PE, with a sensitivity and specificity of 83% and 96%, respectively [8]; however, it may be accompanied by the risk of side effects associated with using contrast media [9].

The use of CTPA has increased significantly over the last decade, with several recent studies highlighting its overuse in emergency departments [10-12], and it does not appear to contribute to population-level mortality reduction [8]. CTPA may have a low yield of PE, and even those with positive results have small subsegmental emboli that may be clinically insignificant [13, 14].

A large study that examined the appropriateness of CTPA use in patients in the emergency department revealed that a substantial proportion of CTPA use could have been avoided [15, 16]. The overuse of such investigations may burden patients and the healthcare system [17-19].

Important issues arise for clinicians in this situation, including selecting a patient for CTPA if a patient is suspected of having PE to avoid unnecessary investigation. To address this issue, Wells *et al.* [20, 21] proposed a clinical prediction rule and D-dimer testing as an algorithm for evaluating patients with suspected PE. An algorithm incorporating the Wells score and D-dimer testing in large-sample studies demonstrated a high negative predictive value [21, 22]. Later modifications to the Wells score defined individuals with a Wells score of ≤4 as PE unlikely and recommended D-dimer testing. A normal D-dimer level does not necessitate imaging, whereas a higher D-dimer level does [15]. The European Society of Cardiology recommends that this algorithm be used in the clinical setting [23].

There are reports of decreased imaging requests when a clinical prediction rule is used in conjunction with the D-dimer assay [24-26]. Pasha *et al.* [25] found that using a pre-test clinical prediction rule in conjunction with the D-dimer assay had a negative predictive value of 99.7%, and the risk of mortality associated with PE was reduced to <1%.

The extent to which pre-test clinical prediction rules and D-dimer assays are used in routine hospital practice, as well as their utility in determining the prescription for CTPA, is unknown, although indirect evidence suggests underutilization [25]. Thus, it is likely that low-risk patients would be subjected to avoidable CTPA and its associated adverse effects, such as radiation, increased expenditure, contrast-induced complications, and increased length of stay in the emergency department [26, 27].

Few studies have evaluated the diagnostic efficacy of pretest clinical prediction rules and D-dimer assay before prescribing CTPA in Saudi Arabian tertiary care settings. Additionally, Owaidah *et al.* [28] reported that the prediction rule might help predict PE, and a significant portion of the requested imaging could have been [16, 29]. Thus, this study was conducted to determine whether a clinical prediction rule combined with D-dimer assay can accurately predict the proportion of avoidable CTPA in unselected patients with suspected PE who underwent CTPA in a tertiary care center.

MATERIALS AND METHODS

Design and setting

This descriptive study (cohort, retrospective electronic chart review) was conducted after receiving approval from the institutional ethics committee. From the beginning of 2010 to the end of 2018, all patients aged ≥18 years who underwent CTPA for suspected PE at the Emergency Department of King Abdulaziz Medical City in Riyadh, Saudi Arabia. Of the 661 patients screened, 422 who met the selection criteria were included in this study (Fig. 1). The patients were identified by reviewing all CTPA requests in the electronic case and radiology databases. This study excluded participants under 18 years of age, pregnant women, and those with known antiphospholipid syndrome.

The CTPA was performed throughout the study period on GE healthcare scanners (Helical scan with 100 Kv, 7 noise index, 0.4 s rotation time, and 1.375:1 pitch and speed) and Siemens scanners (Helical scan with 100 Kv, 1.3 pitch, and 0.33 s rotation time) with Xenetix 350 contrast media. The D-dimer assay was performed using INNOVANCE (Siemens Healthcare Diagnostics, Erlangen, Germany), with a normal value defined as <0.5 mg/L. There were no hospital policies or guidelines requiring modified Wells scores (mWS) and/or D-dimer assays during the study period before requesting CTPA.

Data on demographic characteristics, comorbidities, presenting symptoms, and physical examination results were obtained from the electronic health records. Additionally, we obtained the pretest probability for venous thrombosis at presentation prior to CTPA, as well as the initial laboratory report of the thrombophilia test, CTPA result, and any post-CTPA complications.

Pretest risk scores for PE were calculated retrospectively for each patient using the mWS and D-dimer level with

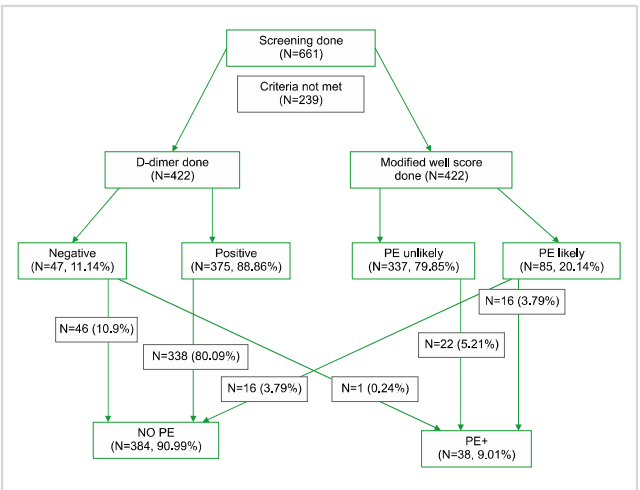

Fig. 1. STROB flow chart.

the investigators blinded to the CTPA results. The mWS was classified as PE unlikely (mWS ≤4) or PE likely (mWS ≥4). To determine the criteria for an "alternative diagnosis less likely than PE" in the Wells score retrospectively, we considered whether the prescriber had the sole diagnosis of PE or the first differential diagnosis in the document prior to requesting CTPA. Avoidable CTPA was defined in this study as unlikely PE (mWS ≤4) with a negative D-dimer.

IBM SPSS version 25 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Demographic and clinical characteristics were analyzed using descriptive statistics, while categorical variables were analyzed using contingency table analysis and t-tests.

Table 1. Relationships of PE in CTPA and clinical variables in patients meeting selection criteria.

Variables		CTPA result				
		No PE	PE present	χ^2	df	*P*
Sex	Male	102	9	0.148	1	0.701
	Female	282	29			
DM	No	238	30	4.296	1	0.038
	Yes	146	8			
HTN	No	228	23	0.019	1	0.890
	Yes	156	15			
HF	No	345	35	0.197	1	0.657
	Yes	39	3			
CVD	No	334	36	1.926	1	0.165
	Yes	50	2			
COPD	No	363	36	0.003	1	0.958
	Yes	21	2			
Smoking	No	375	38	0.910	1	0.340
	Yes	9	0			
OSA	No	364	35	0.484	1	0.487
	Yes	20	3			
Cancer	No	381	38	0.299	1	0.585
	Yes	3	0			
Postpartum	No	378	37	0.242	1	0.623
	Yes	6	1			
Past VTE	No	372	38	1.222	1	0.269
	Yes	12	0			
Chest pain	No	152	17	4.095	2	0.129
	Pleuritic	102	14			
	Non-pleuritic	130	7			
Syncope	No	353	36	0.379	1	0.538
	Yes	31	2			
Dyspnea	No	187	18	0.024	1	0.876
	Yes	197	20			
Cough	No	316	33	0.500	1	0.479
	Yes	68	5			
Hemoptysis	No	374	37	0.000	1	0.992
	Yes	10	1			
Limb pain	No	364	36	0.000	1	0.988
	Yes	20	2			
Limb swelling	No	355	36	0.266	1	0.606
	Yes	29	2			
4-week immobilization	No	366	36	0.025	1	0.873
	Yes	18	2			
Limb cast	No	381	38	0.299	1	0.585
	Yes	3	0			
Surgery in 4 wk	No	362	36	0.014	1	0.906
	Yes	22	2			
Pulse >100/min	No	282	25	1.020	1	0.312
	Yes	102	13			
BP <90/60 mmHg	No	376	37	0.050	1	0.823
	Yes	8	1			

RESULTS

Demographic and clinical characteristics

Of the 661 patients screened, 422 who met the selection criteria and were suspected of having PE underwent CTPA. The mean age was 59.21 (±19.48) years, D-dimer was 2.79 (±4.58) g/L, and the majority of the participants were female (N=311, 73.70%). Diabetes mellitus (36.5%) and hypertension (40.52%) were all common comorbidities. Other common comorbidities included heart failure (9.95%) and cardiovascular diseases (12.3%). Chest pain (59.9%), dyspnea (51.4%), and cough (17.3%) were the frequently reported presenting symptoms. Of 661 patients, 79 (11.9%) had PE on CTPA [64 (9.7%) had segmental PE and 15 (2.3%) had segmental lobar PE] (Supplementary Table 1). The relationships of PE in CTPA and clinical characteristics of patients meeting the selection criteria are given in Table 1.

Clinical prediction rules, D-dimer assays, and diagnostic yield of CTPA

Five hundred twenty-six (79.6%) of all screened patients had an mWS of ≤4 (PE unlikely) and 422 had a D-dimer assay done (63.8%). In routine practice, the pretest probability for PE was documented in only 15 cases (2.3%). A total of 422 (63.8% of screened) patients met the selection criteria of the study, and 337 (79.86%) of them had an mWS of ≤4 (PE unlikely). A total of 22 (5.21%) patients with PE scored PE unlikely (mWS ≤4), while 16 (3.79%) scored PE likely (mWS ≥4). Similarly, 1 (0.24%) patient with PE had D-dimer negative score, while 37 (8.77%) had D-dimer positive scores (Table 2).

Performance of clinical prediction rules

The mWS performance was calculated as a clinical prediction rule. Clinical prediction rules had a high specificity (82%) and low sensitivity (42.22%). Moreover, it had a high negative predictive value (93.47%) but a low positive predictive value (18.82%) (Table 2).

Avoidable CTPA

In this study, among those who met the selection criteria for this study, 30 (7.11%) patients had PE unlikely with negative D-dimer, which can qualify for potentially avoidable CTPA. Avoidable CTPA had 100% sensitivity, 90.3% positive predictive value, and 1.08 value in positive likelihood ratio (Table 2). In the contingency table analysis, patients with avoidable imaging had significantly more dyspnea symptoms (Table 3).

DISCUSSION

CTPA has rapidly become the first-line modality for imaging in emergency departments with suspected PE and undermines the use of clinical predictors of risk. However, an increased CTPA did not result in improved patient outcomes. Thus, there is a need to examine this issue in the clinical setting.

In this study, a significant proportion of CTPA could have been avoided if clinical predictors, such as mWS and D-dimer assay, were adequately used before imaging. However, the

Table 2. Performance characteristics of modified Wells score and estimated avoidable CTPA with actual CTPA results.

		No PE (%)	PE present (%)	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive LR	Negative LR
Modified Wells score	PE unlikely (mWS ≤4)	315 (74.64)	22 (5.21)	42.11%	82%	18.82%	93.47%	2.34	2.34
	PE likely (mWS ≥4)	69 (16.35)	16 (3.79)						
Avoidable	D-dimer negative +PE unlikely (mWS ≤4)	30 (7.1%)	17	100%	7.8%	90.3%	0%	1.08	0

Table 3. Relationships of avoidable/unavoidable CTPA with clinical variables.

		Unavoidable	Avoidable	χ^2	df	*P*
Smoking	No	385	28	3.181	1	0.075
	Yes	7	2			
Cancer	No	390	29	3.147	1	0.076
	Yes	2	1			
Dyspnea	No	198	7	8.240	1	0.004
	Yes	194	23			

findings also highlight that the performance of the clinical predictors is satisfactory, and they are not used judiciously in the emergency department (for various reasons).

Demographic and clinical characteristics were comparable to those observed in previous studies [30, 31]. Although comorbid diabetes was a significant risk factor in this study, other reports from Saudi Arabia reported obesity [16] and age as risk factors [32]. This may be due to differences in the sample size and clinical characteristics of the population studied.

In the study population, 9% had PE. This is in contrast to the higher rates reported in Saudi Arabia [16, 28, 32]. However, this is consistent with other reports [31, 33], although a review and meta-analysis revealed a wide variation in prevalence [34, 35]. The estimate appears to vary according to the hospital setting [36, 37].

In contrast to another study, the results showed a low rate of prediction of PE by mWS PE likely (mWS $\geq$4), probably due to the retrospective study design [38]. The performance characteristics of the clinical prediction of the mWS were also low, which is consistent with a previous report [39]. The D-dimer positive value also had a lower prediction of PE, similar to an earlier account, particularly regarding non-lobar involvement [40]. In contrast to previous reports, we did not observe central artery involvement in CTPA [41-43]. Although the frequency of segmental PE observed in this study was consistent with previous reports [44-46], it frequently presented with complaints of chest pain and dyspnea [47, 48].

The results reveal avoidable (overuse) of CTPA in 7.11% when defined criteria of DD negative+PE unlikely in mWS were considered in the estimation. It had a high sensitivity (100%) and positive predictive value (90.03%), but very low specificity (7.8%) and negative predictive value (0%). This finding is partially supported by a recent study conducted during a pandemic [49]. Thus, if pretest probability estimation had been performed, a large proportion of patients could have been spared CTPA. There is no reason to believe that the pretest probability estimated in this study would have been significantly different if the same estimation was performed prior to the CTPA in a real-world scenario; thus, it is improbable that we are overestimating the frequency of avoidable CTPA. However, our estimation of avoidable CTPA was lower than those in other reports. For example, Venkatesh *et al.* [15] reported 38% imaging in low-risk patients in a large study, whereas Perelas *et al.* [10] observed a minimum of 49% avoidable imaging. One recent study with a design similar to ours observed that one-third of patients underwent CTPA clinically inappropriately [16]. There are several possible explanations for the excessive use of CTPA. Among them are concerns regarding missing potentially life-threatening PE; underestimation of adverse consequences associated with the use of CT, the ease with which this mode of investigation can be used; and an insufficient policy for utilizing prediction rules [17, 18, 50].

In this study, dyspnea symptoms appeared in significantly more patients in the avoidable CTPA group. This finding is partially supported by other reports that dyspnea symptoms are associated with a high rate of CTPA use despite a low positive rate, and a substantial proportion may have other explanations for dyspnea [51-54].

One should be clear that CTPA in suspected PE as it provides rapid and accurate diagnosis, allowing for timely initiation of appropriate treatment, hence preventing significant morbidity and mortality and complications, such as right heart failure, pulmonary hypertension, or even death. Physician anxiety regarding PE, barriers to using the evidence, divergent views on evidence-based PE testing, inherent Wells score problems, the drive to obtain CT rather than diagnose PE, subjective reasoning and cognitive biases supporting deviation from evidence-based tests, and the use of evidence-based testing to rule out PE in very unlikely patients all influenced CT test choices for PE [55].

This study should be interpreted in light of the fact that it was retrospective, and the pretest risk score for PE was estimated accordingly, which may not be exact in all cases due to the nature of clinical symptoms and signs. It likely did not capture the legitimate reason for prescribing CTPA by the concerned clinician, and other associated characteristics may have conferred a high risk of PE.

Underutilization of clinical prediction rules is prevalent, and its use may decrease CTPA overuse. A mandatory policy requiring emergency departments to evaluate avoidable CTPA imaging may reduce CTPA overuse and the associated burden on patients and the healthcare system.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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Supplementary Table 1A. Screened patient: comorbidities characteristics.

Variables		CTPA result				
		No PE	PE present	χ^2	df	*P*
Diabetes mellitus	No	343	58	6.11	1	0.008
	Yes	239	21			
Hypertension	No	329	46	0.08	1	0.775
	Yes	253	33			
Heart failure	No	505	70	0.20	1	0.649
	Yes	77	9			
CVD	No	506	73	1.91	1	0.167
	Yes	76	6			
COPD	No	532	72	0.01	1	0.936
	Yes	50	7			
Smoking	No	562	75	0.52	1	0.468
	Yes	20	4			
OSA	No	548	73	0.37	1	0.540
	Yes	34	6			
Cancer	No	576	76	3.96	1	0.046
	Yes	6	3			
Pregnant	No	508	58	10.86	1	0.001
	Yes	74	21			
Postpartum	No	572	77	0.24	1	0.611
	Yes	10	2			
History of VTE	No	565	79	2.36	1	0.124
	Yes	17	0			

Supplementary Table 1B. Screened patient: presenting symptoms.

Variables		CTPA result				
		No PE	PE present	χ^2	df	*P*
Chest pain	No	267	45	9.46	2	0.009
	Pleuritic	146	24			
	Non-pleuritic	169	10			
Syncope	No	534	72	0.03	1	0.853
	Yes	48	7			
Dyspnea	No	278	39	0.07	1	0.789
	Yes	304	40			
Cough	No	487	67	0.06	1	0.798
	Yes	95	12			
Hemoptysis	No	563	78	0.94	1	0.330
	Yes	19	1			
Limb pain	No	548	70	3.52	1	0.061
	Yes	34	9			
Limb swelling	No	533	70	0.76	1	0.381
	Yes	49	9			
Immobile in the last 4 wk	No	541	71	0.96	1	0.327
	Yes	41	8			
Limb cast	No	578	79	0.54	1	0.460
	Yes	4	0			
Surgery < 4 wk	No	547	72	0.94	1	0.330
	Yes	35	7			

Supplementary Table 1C. Screened patient: examination findings.

Variables		CTPA result				
		No PE	PE present	χ^2	df	*P*
Pulse >100/min	No	404	45	4.95	1	0.026
	Yes	178	34			
BP <90/60 mmHg	No	561	75	0.405	1	0.525
	Yes	21	4			
D-dimer	Not done	198	41	12.00	2	0.002
	Low	46	1			
	Not low	338	37			
Thrombophilia test	Not done	366	45	20.33	4	0.001
	Protein S	3	4			
	ATIII	1	1			
	FVL	2	1			
	APS	1	1			