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ORIGINAL CONTRIBUTION

The impact of COVID-19 on the sensitivity of D-dimer for pulmonary embolism

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Abstract

Objective: This study seeks to evaluate the test characteristics of D-dimer for pulmonary embolism (PE) in patients with a concurrent diagnosis of COVID-19. We hypothesized that the sensitivity of D-dimer for PE at current institutional cut points would be similar to those without COVID-19.

Methods: This is a multicenter retrospective observational cohort study across five urban and suburban EDs in the same health care system. The electronic health record was queried for all computed tomography pulmonary angiography (CTPA) studies from December 1, 2019, to October 22, 2020. All ED patients who underwent CTPA had D-dimer and COVID-19 testing completed in a single encounter were included in the study. Baseline demographics were obtained. Test characteristics of D-dimer for PE were calculated for patients with and without COVID-19. Additionally, receiver operator characteristics (ROC) curves were constructed for two different D-dimer assays.

Results: There were 1158 patient encounters that met criteria for analysis. Performance of D-dimer testing for PE was similar between COVID-19–positive and –negative patients. In COVID-19–positive patients, the sensitivity was 100% (95% confidence interval [CI] = 87.6%–100%), specificity was 11.9% (95% CI = 7.9%–17.1%), and negative predictive value (NPV) was 100%. In COVID-19–negative patients the sensitivity was 97.6% (95% CI = 91.5%–99.7%), specificity was 14.4% (95% CI = 12.1%–17%), and NPV was 98.3% (95% CI = 93.8%–99.6%). For assay 1 the area under the curve (AUC) for COVID-19–positive patients was 0.76 (95% CI = 0.68–0.83), and for COVID-19–negative patients, 0.73 (95% CI = 0.69–0.77). For assay 2, AUC for COVID-19–positive patients was 0.85 (95% CI = 0.77–0.92), and for COVID-19–negative patients, 0.80 (95% CI = 0.77–0.84). Inspection of the ROC curve for assay 1 revealed that 100% sensitivity was maintained up to a threshold of 0.67 FEU (fibrinogen equivalent units; from 0.50 FEU) with an increase in specificity to 29% (from 18.7%), and for assay 2, 100% sensitivity was maintained up to a threshold of 662 D-dimer units (DDU; from 230 DDU) with an increased specificity to 59% (from 6.1%).

Conclusion: Results from this multicenter retrospective study did not find a significant difference in sensitivity of D-dimer for PE due to concomitant COVID-19 infection.

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Further study is required to determine if PE can safely be excluded based on D-dimer results alone in patients with suspected or proven COVID-19 or if adjusted D-dimer levels could have a role in management.

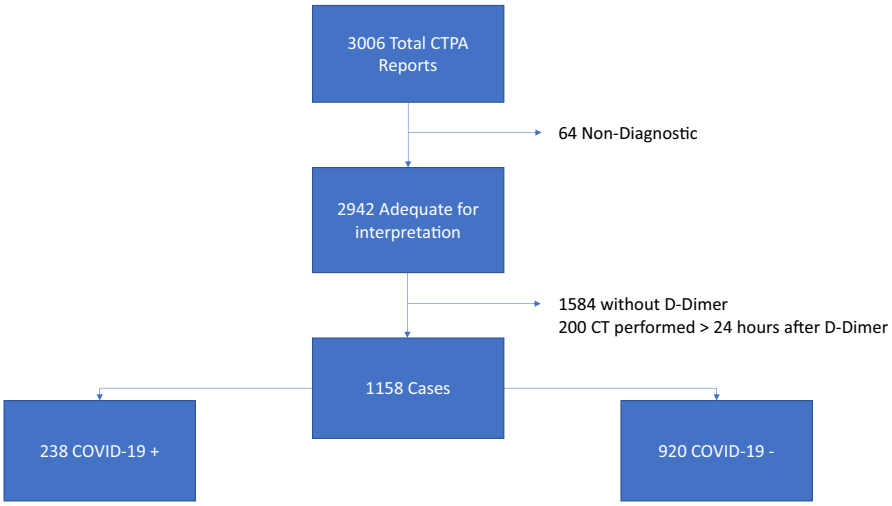

FIGURE 1 Flow chart of patients in each cohort after applying exclusion and inclusion criteria

INTRODUCTION

Pulmonary embolism (PE) is an important cause of emergency department (ED) visits, accounting for approximately 0.08% of annual ED visits.[1] The current criterion standard diagnostic imaging modality for PE is the multidetector computed tomography pulmonary angiography (CTPA). Clinical decision rules and D-dimer assays help risk stratify patients with presentations concerning for PE and have helped reduce the number of unnecessary CT scans in this population.[2]

COVID-19 has added new uncertainty to the role of D-dimer testing in the evaluation of PE. COVID-19 creates a hypercoagulable state, leading to the increased incidence of venothromboembolism (VTE) within this population.[3–6] Research has demonstrated D-dimer levels have clinical utility as surrogate markers for disease severity in COVID-19 patients, with higher levels associated with poor prognosis.[7–10] This has led to widespread adoption of screening COVID-19 patients with D-dimer levels in an attempt to characterize disease severity. Numerous cohort studies have shown an increased burden of thromboembolic disease in hospitalized patients with COVID-19, despite prophylactic anticoagulation, ranging from 2.6% to 8.9% of all hospitalized patients.[6] The D-dimer's role in workup for PE in the setting of COVID-19 has not been fully elucidated. Among patients with COVID-19, the additional presence of VTE is associated with higher D-dimer values than in COVID-19 patients without VTE, and higher cutoff values have been suggested when ruling out VTE.[11]

The purpose of this study was to determine the test characteristics of D-dimer for diagnosing PE in ED patients with COVID-19. We hypothesized that the sensitivity of D-dimer for PE in ED patients with COVID-19 will be similar to those without COVID-19.

METHODS

Study design

This is a multicenter retrospective observational cohort study. The study was approved by the hospital institutional review board. Study design follows the standards for reporting diagnostic accuracy (STARD).[12]

Study setting and population

Records from two urban and three suburban EDs within the same hospital system were included in this study. One of the urban sites is a large tertiary hospital with an annual volume of 70,000 ED visits annually. The other urban site is a community teaching hospital with 35,000 annual visits. The three suburban sites are community teaching hospitals with annual volumes ranging from 32,000 to 43,000. Within the health care system, two different immunoturbidimetric D-dimer assays are used. Assay 1 is the STA Liatest D-dimer performed on a Stago platform with a recommended threshold value of 0.50 mg/L fibrinogen equivalent units (FEU). Assay 2 is the HemosIL D-dimer HS, performed on ACL TOP 550 by Instrumentation Laboratory with a recommend threshold value of 230 ng/mL D-dimer units (DDU). The three suburban sites use assay 1 and the two urban sites use assay 2. All hospitals used the same electronic medical record (EPIC). The population studied was a consecutive series of patients that presented to any of the five EDs from December 1, 2019, and October 22, 2020.

Study protocol

EPIC, the electronic health record (EHR) for all five sites, was queried for all CTPA studies between December 1, 2019, and October 22, 2020. All ED patients who underwent CTPA and had D-dimer and COVID-19 testing ordered in a single encounter were included in the study (Figure 1). Patients were excluded if they did not have a CTPA scan with adequate interpretation, did not undergo D-dimer testing, or did not have a D-dimer test performed within 24 h of the CTPA scan.

Patients were classified as COVID-19 positive if they had a positive COVID test at any point during the encounter. This method was chosen because of the frequent false-negative rate in early disease or due to inadequate specimen collection. Of note, universal testing for COVID-19 testing was instituted on June 4, 2020, which was mid-way through the study period. Prior to this only patients who were symptomatic or those who were undergoing procedures would have received testing. At our enterprise, D-dimer was a part of the admission labs for patients with COVID-19 and empiric anticoagulation was not an institutionally recommended practice.

All final CTPA reports were reviewed by one of the three study personnel (two resident emergency medicine physicians and one third-year medical student) for presence or absence of acute PE, as reported by the attending radiologist, using a predetermined data abstraction method. Reviewers were blinded to the patient's clinical data except as contained in the radiology report. All emboli noted to be definitively chronic per the radiologist's report were considered negative studies. Studies were diagnostic if the report characterized the quality of the study to be sufficient to be read to the segmental arteries, otherwise they were considered non-diagnostic and removed from the cohort. We chose to include sub-segmental PEs to err on the side of inclusion of any level of PE. Additionally, equivocal studies as to chronicity of emboli or studies with a filling defect in which the radiologist felt PE remained a diagnostic possibility were considered positive. A subset of 215 cases (approximately 20%) underwent a second review by one of the other two reviewers. There was perfect agreement among the three reviewers for the decision of studies being positive or negative for acute PE with a Cohen's kappa of 1.0.

Measures

The EHR was additionally queried for demographics including age, sex, race, and body mass index, as well as history of prior VTE, presence of hypercoagulable disorder, and presence of active malignancy, D-dimer values, and COVID-19 status. Additionally, in-hospital mortality is reported as a surrogate for severity of illness in each cohort.

Data analysis

To calculate the primary outcome 2 × 2 tables were constructed for D-dimer and CTPA results for both cohorts (COVID positive and negative). D-dimer values were categorized as positive or negative based on institutional laboratory designated cutoff values to reflect actual practice and interpretation of D-dimer values. Subgroup analysis was performed to compare the performance of the two different assay types through creation of receiver operator characteristics (ROC) curves. D-dimer results outside the testing range were changed to the next closest value for ease of analysis (e.g., <150 DDU becomes 149, >14 FEU becomes 14.1). A priori sample size calculations were not performed due to the lack of historical data for COVID-19 and D-dimer values. All calculations were done in IBM SPSS Statistics 27.

RESULTS

Out of 3006 radiologist reports, 64 were nondiagnostic leaving 2954 cases (Figure 1). Of these, 1584 did not have a D-dimer result and were thus excluded from the study. Another 212 were removed because the CT scan occurred greater than 24 h apart from D-dimer. The remaining 1158 comprised our study cohort. D-dimer testing occurred before the CTPA in 903 patients (78%) and after CTPA in the remaining 255 patients (22%). Of the study cohort, 231 patients (28%) had a positive test for COVID-19. Baseline demographics and history of hypercoagulable disorders, malignancy, or previous VTE were similar in the two cohorts (Table 1). An acute PE was present in 110 (9%) patients, 28 (12%) in the COVID-19–positive group and 82 (9%) in the COVID-19–negative group. In-hospital mortality (from any cause) was 12% in patients with COVID-19 compared to 2% for COVID-19–negative patients.

Primary outcome

Test characteristics of D-dimer to predict PE for all patients regardless of assay used was similar between patients with and without COVID-19 (Table 2). In COVID-19–positive patients, the sensitivity was 100% (95% CI = 87.6% to 100%), specificity was 11.9% (95% CI = 7.9% to 17.1%), and negative predictive value (NPV) was 100%. In COVID-19–negative patients the sensitivity was 97.6% (95% CI = 91.5%–99.7%), specificity was 14.4% (95% CI = 12.1%–17%), and NPV was 98.3% (95% CI = 93.8%–99.6%). There were no false-negatives in the COVID-19–positive patients; however, there were two false-negatives (missed embolism) in the COVID-19–negative group, both subsegmental.

ROC curve analysis by assay type

ROC curves for each assay type are shown in Figure 2. Overall areas under the curve (AUCs) for both assays were similar between COVID-positive and -negative patients. For COVID-19–positive patients, the AUC for assay 1 was 0.76 (95% CI = 0.68–0.83) and for assay 2 was 0.85 (95% CI = 0.77–0.92). For COVID-19–negative patients, the AUC

TABLE 1 Baseline demographics and history of hypercoagulable disorders, malignancy, or previous VTE

	All	COVID +	COVID –
Total	1158 (100)	238 (21)	920 (79)
Gender			
Female	660 (57)	117 (49)	543 (59)
Race			
White	631 (54)	110 (46)	521 (57)
Black	385 (33)	92 (39)	293 (32)
Asian	64 (6)	18 (8)	46 (5)
Hispanic	58 (5)	14 (6)	44 (5)
Native American	5 (0)	0 (0)	5 (1)
Unknown	15 (1)	4 (2)	11 (1)
BMI	31.0 (±9.5)	30.8 (±8.7)	31.1 (±9.6)
Age (y)	57 (±17)	60 (±16)	56 (±17)
Hypercoaguable disorder	3 (0)	1 (0)	2 (0)
Hx of active malignancy	73 (6)	14 (6%)	59 (6)
Hx of VTE	65 (6)	24 (10)	41 (4)
D-dimer			
Assay 1—FEU	2.22 (±3.11)	2.49 (±3.43)	2.14 (±2.99)
Assay 2—DDU	1541 (±4521)	2908 (±8173)	1259 (±3219)
PE present	110 (9)	28 (12)	82 (9)
In-hospital mortality	49 (4)	29 (12)	20 (2)

Note: Data are reported as *n* (%) or mean (±SD).

Abbreviations: BMI, body mass index; DDU, D-dimer units; FEU, fibrinogen equivalent units; Hx, history; PE, pulmonary embolism; VTE, venous thromboembolism.

TABLE 2 Test characteristics of D-dimer for PE in patients with a positive versus a negative COVID1- result

	COVID-negative		COVID-positive	
	PE present	PE absent	PE present	PE absent
D-dimer +	80	717	28	185
D-dimer –	2	121	0	25
Test characteristic	D-dimer	95% CI	D-dimer	95% CI
Sensitivity	97.56%	91.47%–99.70%	100.00%	87.66%–100.00%
Specificity	14.44%	12.13%–17.00%	11.90%	7.85%–17.07%
Positive likelihood ratio	1.14	1.09–1.19	1.14	1.08–1.19
Negative likelihood ratio	0.17	0.04–0.67	0	
Disease prevalence	8.91%	7.15%–10.94%	11.76%	7.96%–16.55%
PPV	10.04%	9.65%–10.44%	13.15%	12.59%–13.72%
NPV	98.37%	93.84%–99.59%	100.00%	
Accuracy	21.85%	19.22%–24.66%	22.27%	17.15%–28.09%

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

for assay 1 was 0.73 (95% CI = 0.69–0.77) and for assay 2 was 0.80 (95% CI = 0.77–0.84). Inspection of the ROC curve for assay 1 reveals that a threshold value of 0.67 FEU would still yield a sensitivity of 100% and achieve a higher specificity of 28.9% (95% CI = 21.2%–37.6%) (from 18.7%). Similarly, for assay 2, a threshold value of 662 DDU would increase specificity to 58.5% (95% CI = 47.1%–69.3%) (from 8.5%) while maintaining a sensitivity of 100%.

DISCUSSION

This study demonstrates that D-dimer is a valid tool for the assessment of PE in COVID-19 with very similar overall performance using recommended cutoffs to non-COVID patients. There were no missed PEs in patients with COVID-19. Results from this study suggest that the current D-dimer cutoffs effectively rule out PE in COVID-19

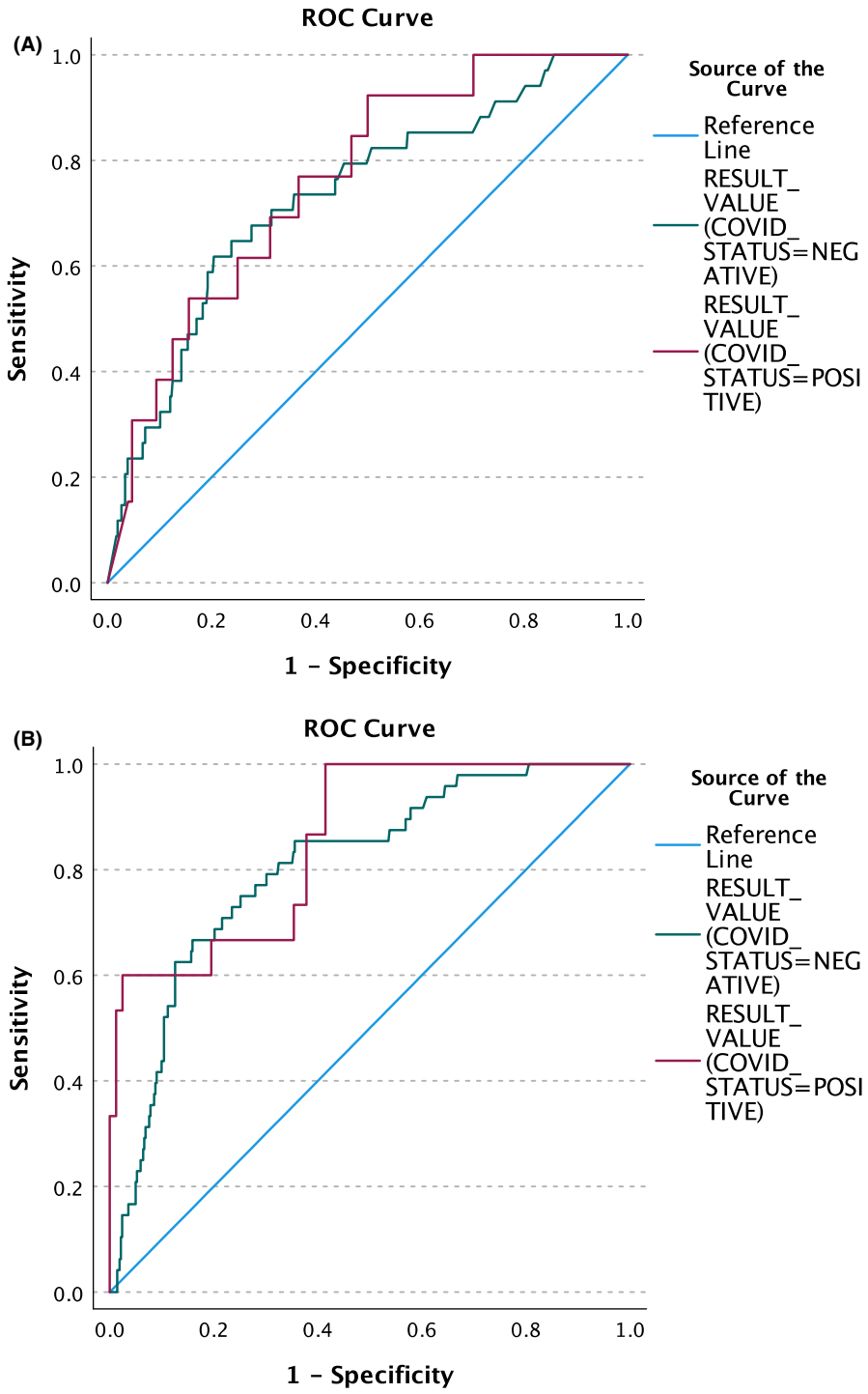

FIGURE 2 ROC curves. (A) Assay 1 = STA Liatest D-dimer, (B) Assay 2 = HemosIL D-dimer HS. ROC, receiver operating characteristics

patients presenting to the ED. For our cohort in COVID-19 patients, the specificity overall was very low at 11.9%, which is supported in clinical practice. Interestingly, the ROC curve revealed a higher AUC in both COVID-19–positive cohorts than their respective counterparts. The findings suggests that a negative D-dimer in a patient with suspected or proven COVID-19 should be given the same weight as that in a COVID-19–negative patient.

Standard ED practice in the evaluation of PE is to utilize D-dimer testing in combination with pretest probability scores or clinical gestalt. Studies have shown that a negative D-dimer in low- to moderate-risk patients eliminates the need for further imaging.[2,13-15] The focus of the current study was D-dimer's performance for PE in COVID-19, but we chose to include the COVID-19–negative cohort as a comparator. Interestingly, there were no missed PEs in the former, but two in the latter. Review of these two cases from the COVID-negative group both occurred with assay 1 and were both isolated subsegmental PEs, one of which was read as equivocal by the radiologist. Despite these cases the results are consistent with false-negative rates of D-dimers for PE in other studies.[16]

Findings from the current study are consistent with those in other studies in the literature evaluating D-dimer and COVID-19. Both increased D-dimer values and higher mortality rates are described in patients with COVID-19, which was seen in the current study.[17] One recent study by Choi et al.[18] performed an ROC analysis of the Hemosil D-dimer for VTE in patients with COVID-19, one of the assays evaluated in the current study (assay 2). Despite a longer threshold from D-dimer to imaging (48 h) and study period primarily in the inpatient setting, they found a similar AUC of 0.79 (the current study found AUC of 0.85). A study by Leonard-Lorant et al[19] evaluated COVID patients with acute PEs on CTPA and found significantly higher D-dimer values in this population compared to patients with negative CTPAs. Similar findings for D-dimer values were reported by Artifoni et al.[20] in a study evaluating for asymptomatic DVTs in patients with COVID-19. The propensity of data suggests that in the setting of COVID, the increased risk of VTE is associated with elevated D-dimer levels preserving the ability to rule out disease with a normal D-dimer value.

Recently, studies have shown that use of an adjusted D-dimer in certain subgroups improves specificity with minimal sacrifice of sensitivity.[21] We constructed an ROC curve to examine overall test performance. International data suggest that D-dimer levels are indeed elevated in the setting of both COVID-19 and PE compared to patients with COVID-19 without PE.[20,22-25] Analysis of the coordinates of the ROC may support these conclusions suggesting that in COVID-19 patients, a higher cutoff for D-dimer positivity (and triggering subsequent advanced imaging workups) may be appropriate because both assays in the current study maintained 100% sensitivity to higher threshold levels. If validated, a COVID adjusted D-dimer approach has the potential to improve diagnostic accuracy and reduce the need for advanced imaging such as CTPA or ventilation perfusion scans, patient exposure to ionizing radiation and hospital expenditure of resources. Given the routine practice of ordering a D-dimer as part of the COVID-19 blood work, this could have a meaningful effect on radiation, cost, and length of stay. What is not clear from the current study is the level of adjustment that would be reasonable for individual D-dimer assays, because there was significant variation between the two assays. The variation is possibly due to differences in the assays themselves or differences within the cohort due to variation in patient pretest probability, setting (urban vs. suburban), or COVID severity, which are possible sources of bias in this retrospective study. Still, other studies have suggested higher thresholds for effectively diagnosing VTE in inpatient settings.[11,18-20] The findings from this study further support the idea that D-dimer has increased sensitivity in the setting of COVID for PE in the ED setting and an adjusted D-dimer value for PE in patients with COVID-19 is worthy of future study.

LIMITATIONS

There are several limitations to the current study. The study is retrospective and therefore subject to biases typical of its study design. The study may introduce selection bias by only including patients who underwent CTPA studies and by excluding patients who had a CTPA but no D-dimer. There may be some patients who were diagnosed or treated for PE based on alternative imaging or clinical suspicion. Additionally, given the overlap of symptoms in COVID-19 and PE, some PEs are likely to have been missed in patients that did not undergo a CTPA.

Universal testing for COVID began midway throught the study period. Patients who were not ordered a COVID test prior to June 4 may have been not captured in the study. We believe that this selection bias would be minimal because most patients undergoing CTPA are likely to have respiratory or thoracic symptoms that would also warrant a COVID swab. Misclassification bias may have occurred if a patient had a false-negative or false-positive COVID-19 test; however, our sites utilized PCR testing for COVID-19 swabs, which demonstrates high sensitivity and specificity. The study design was unable to distinguish whether a patient whose COVID test became positive later in the hospitalization may have been due to an initial false-negative swab versus contracting COVID in the hospital. As a result, some misclassification bias may have occurred in the latter scenario.

The current study fails to distinguish the severity of illness or level of symptoms in the COVID-19 cohort. It is possible that some patients had only minimal disease. However, the inclusion criterion of undergoing CTPA implies some degree of respiratory symptoms or signs of cardiopulmonary concern. Additionally, the COVID-19 cohort had higher in-hospital mortality as shown in Table 1.

Due to resource limitations, most chart reviews to code CTPA results for acute PE were performed by a single reviewer, which could have led to misclassification bias of patients being PE positive or negative. Inter-rater reliability testing did demonstrate perfect agreement on a substantial subset of charts. Additionally, we decided a priori to err on the side of inclusion for any PE as our goal was to demonstrate the sensitivity of D-dimer in PE and to reflect what is typical of clinical practice. In doing so some equivocal CTPA results (e.g., filling defects or questionable chronic PEs) were classified as positive PEs in the study, which may have overestimated the disease prevalence. The fact that we were very conservative in including any possible PE helps to further demonstrate the primary outcome of D-dimer sensitivity in COVID-19.

Another limitation is the retrospective design of the study prevented the analysis of risk stratification for PE or generation of a Wells score. Standard practice is to utilize D-dimer testing in a Bayesian fashion in patients with a low to moderate suspicion for PE. In the setting of COVID-19 many D-dimers are ordered for COVID severity prognosis and we could not be sure if the D-dimer was also being used to rule out PE. In 22% of patients the D-dimer was after the CTPA and therefore definitely could not have been part of prospective decision making. A post hoc analysis was performed and found that the sensitivity of D-dimer for PE remained 100% regardless of whether the D-dimer occurred before or after the CTPA. Additionally, our goal is to describe the relationship between D-dimer values and the presence of PE in COVID-positive patients, which should not significantly

be altered by the order of tests so long as the tests occur within a reasonable time frame of one another. Another limitation is that our data only included the results of single D-dimer assays, whereas many admitted patients with COVID-19 receive serial testing, the utility of which is not addressed in this study.

The current study did not evaluate for all causes of VTE. It is possible that patients may have had DVT or other types of VTE that would be not be diagnosed by CTPA and so the results of the current study are not applicable to all VTE. Other studies have evaluated the relationship between D-dimer and LE/UE DVTs and found similar test performance.[11,20]

Finally, as with all studies, the reader should take note of the lower bounds of the 95% confidence intervals of the primary outcome. For example, the sensitivity of D-dimer for PE in COVID-positive patients was 100% but, due to sample size limitations, the lower bound of the 95% CI is 88%. Future studies or meta-analysis of similar studies are needed to further clarify the bounds of D-dimer performance.

CONCLUSION

Results from this study support that D-dimer at baseline cutoffs can reliably exclude PE in the setting of COVID-19 in a large cohort of patients using two different assays and five different EDs. Furthermore, our results suggest that in this subpopulation, the threshold for a positive may be able to be raised for an increase in specificity without sacrificing sensitivity. Future prospective studies should focus on improving the specificity of D-dimer assays via prospective testing of cutoff thresholds in patients with COVID-19.

CONFLICT OF INTEREST

The authors have no potential conflicts to disclose.

AUTHOR CONTRIBUTIONS

Samuel J. Elberts and J. Matthew Fields conceived the study. Samuel J. Elberts, J. Matthew Fields, Kory S. London, and Jennifer L. White designed the trial. Samuel J. Elberts and J. Matthew Fields supervised the data collection. Samuel J. Elberts, Alexandra Koutsoubis, and Ryan Bateman reviewed the data and prepared it for statistical analysis. Samuel J. Elberts performed and J. Matthew Fields supervised the statistical analysis. Samuel J. Elberts, Alexandra Koutsoubis, and Ryan Bateman drafted the manuscript. All authors contributed substantially to its revision. J. Matthew Fields takes responsibility for the paper as a whole.

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