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ORIGINAL RESEARCH

Prognostic Value of Reflux of Contrast into the Inferior Vena Cava and Hepatic Veins on CT Pulmonary Angiography in Patients of Pulmonary Embolism

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Abstract

A pulmonary embolism (PE) that obstructs pulmonary arterial blood flow is a medical emergency. Its early detection and appropriate management can be lifesaving. CT pulmonary angiography (CTPA) is currently in use as a standard tool for diagnosis of PE. This study was performed to determine the prognostic accuracy of contrast reflux into the inferior vena cava (IVC) and hepatic veins on CTPA in patients suffering from acute PE.

Materials and Methods

The study was composed of 285 patients between 15 to 85 years of age that had filling defects in pulmonary arteries on CTPA that were consistent with those of a pulmonary embolism. The extent of contrast reflux into the IVC and hepatic veins was determined on the basis of a Groves scale. The patients were followed for a period of 30 days.

Results

Of 285 total patients, 200 (70.17%) survived the post PE period of 30 days and were labeled as survivors. The other 85 (29.83%) patients did not survive the 30-day duration and were called non-survivors. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of IVC contrast reflux grading were 65.8%, 90%, 73.68%, 86.12 % and 82.8 % respectively.

Conclusion

We conclude that IVC contrast reflux grading assessed on helical CT is a beneficial tool for predicting prognosis in cases of acute PE.

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Introduction

The thrombo-embolic phenomena resulting in pulmonary flow obstruction is a medical emergency. Despite recent advances in medicine, the incidence of pulmonary embolism (PE) remains high, up to 40% with increased mortality rate, and reaching up to 65% in patients with massive pulmonary embolism requiring resuscitation (1). Studies based on trends in the incidence of PE have documented increases in all age groups, largely based upon better diagnostic facilities. Multidetector CT (MDCT) has considerably changed the approach for diagnosis of acute PE (2). Currently it is considered a most useful tool for establishing diagnosis of acute PE as it has several advantages including fast acquisition, easy availability, and high sensitivity. It also excludes alternative differentials causing similar symptoms of presentation like shortness of breath and discomfort. MDCT should be performed immediately in patients who have clinically high suspicion of PE as it is more accurate than other diagnostic tools like chest radiograph, electrocardiography (ECG), echocardiography and D-Dimers (3).

Patients suffering from pulmonary embolism have heterogeneous presentation and varying prognosis. The mortality associated with PE is approximately 2 - 6% in normotensive patients with stable hemodynamics. It is significantly high in patients with hemodynamic unstable state, hypotension, or shock (4, 5). The early assessment of mortality risk, therefore, remains an important and crucial approach for optimal treatment of acute PE.

Literature has documented the role of CTPA parameters in assessing the severity and their prognostic value in terms of mortality. Various scoring systems introduced by Qanadli et al., Mastora et al., Miler et al., and Walsh et al. have been investigated for estimating the severity of pulmonary embolism (6,7,8,9). Right ventricular dysfunction is documented as the common factor behind pulmonary embolism related complications (10). Therefore numerous studies in the past have analyzed CTPA parameters for determining the right ventricular function in patients diagnosed with PE. These parameters include ratio of right and left ventricular diameters (RVD/LVD), reflux of contrast in the IVC, coronary sinus (CS) diameter, pulmonary artery (PA) axial diameter, pulmonary artery/Aorta (PA/Ao) ratios and leftward inter-ventricular septum (IVS) bowing (2,10,11). Bach et al. has documented the positive association between degree of contrast reflux in the IVC and adverse outcome of PE (11). These characteristics on CTPA help to categorize patients according to severity and prioritize those who need aggressive thrombolysis to prevent mortality.

The high mortality rate associated with late diagnosis of acute PE clarifies the significance of its early diagnosis and risk assessment (13,14). One of the features of right heart dysfunction is reflux of contrast from right ventricle. More extensive reflux of contrast into the IVC and hepatic veins is linked with increased severity of pulmonary embolism (15). Sensitivity and specificity of IVC reflux grading on CTPA for prediction of mortality is documented to be 71% and 86% respectively, taking mortality, or significant clinical deterioration requiring cardiopulmonary resuscitation or catecholamine infusion, as the gold standard (16).

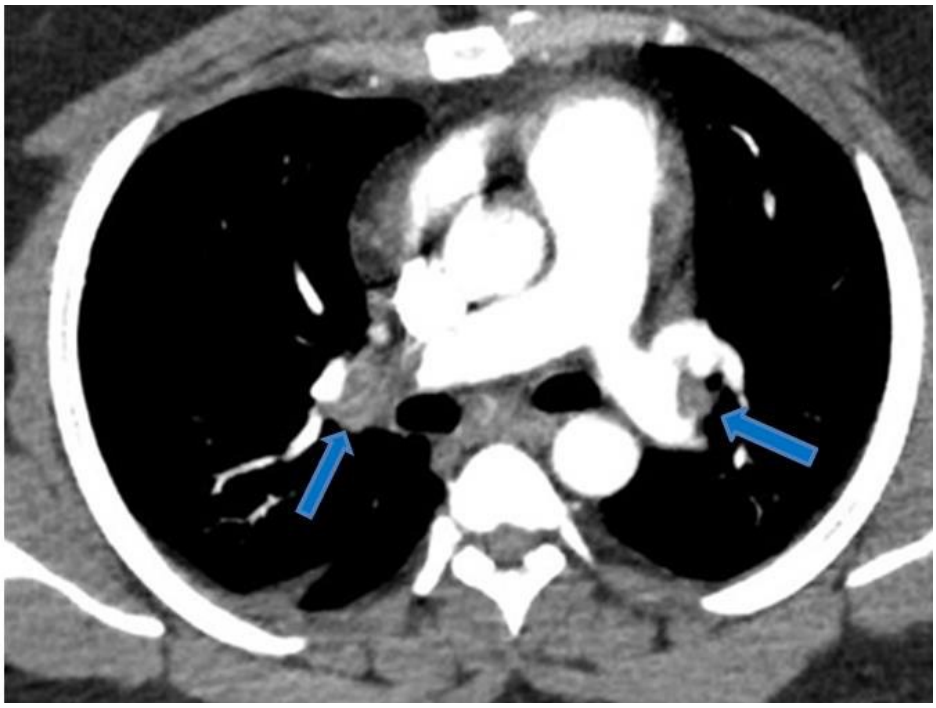
Previous studies in the literature have documented the role of 16 to 64-slice helical CT in diagnosing and assessing PE (10,12). There is, however, a dearth of literature available on the use of 320-slice MDCT for assessing the relationship between vascular distensibility parameters and thromboembolism (17). This research has explored the prognostic accuracy of contrast reflux from the right ventricle on CTPA scans performed on 320-slice MDCT.

Materials and Methods

This descriptive cross-sectional retrospective study was carried out in the Radiology Department of a tertiary care teaching hospital. The study was initiated after acquiring institutional review board approval. A total of 285 patients with pulmonary embolism who underwent CTPA were enrolled in this study. Data was collected from CTPA scans performed between January 2016 to January 2019 in a tertiary state hospital, fulfilling the inclusion and exclusion criteria. The CTPA scans performed during the COVID-19 pandemic were excluded from the study considering the positive association of COVID-19 and thromboembolic phenomena. All CT pulmonary angiographies were performed on 320-MDCT scanner (Aquilion ONE TM 320 Slice CT). Non-ionic contrast medium (320 mg I/mL) was used. The total contrast dose was calculated according to suggested dose of 2 mL/kg (not to exceed 125 mL). The right arm was preferred for injection. Antecubital vein was preferred and cannulated using 18 or 20 gauge IV cannula. The contrast medium was injected via power injector at a uniform rate of four ml/sec. The IVC contrast reflux grade was observed on the 320-slice multi-detector CTPA of each patient. The scan was acquired in caudal-cranial direction. 120 Kilovolt (KV) was used while acquiring CT scans. The milli-amperes were adjusted according to sure exposure standards. The CT datasets were reconstructed using 0.5 mm slice thickness for the review of axial CTPA images. The multiplanar sub-millimeter (0.5 mm) reformats were created in both coronal and sagittal planes. The contrast enhanced CT of bilateral lower limbs in the venous phase was also acquired using the same contrast bolus to look for deep venous thrombosis according to departmental protocols. The images were acquired after three minutes of administration of contrast medium. The images were shifted to picture archive communication systems (PACS).

Both male and female patients ranging between 15 to 85 years of age who presented with symptoms of pulmonary embolism (shortness of breath, tachycardia (pulse rate > 110/min), stabbing chest pain, upper backache, fainting episodes and/or deep venous thrombosis) and underwent CTPA showing filling defects in pulmonary vasculature (Figure 1). were included in the study.

Figure 1. Axial image from CTPA showing filling defects in bilateral main pulmonary arteries representing pulmonary embolism (blue arrows).



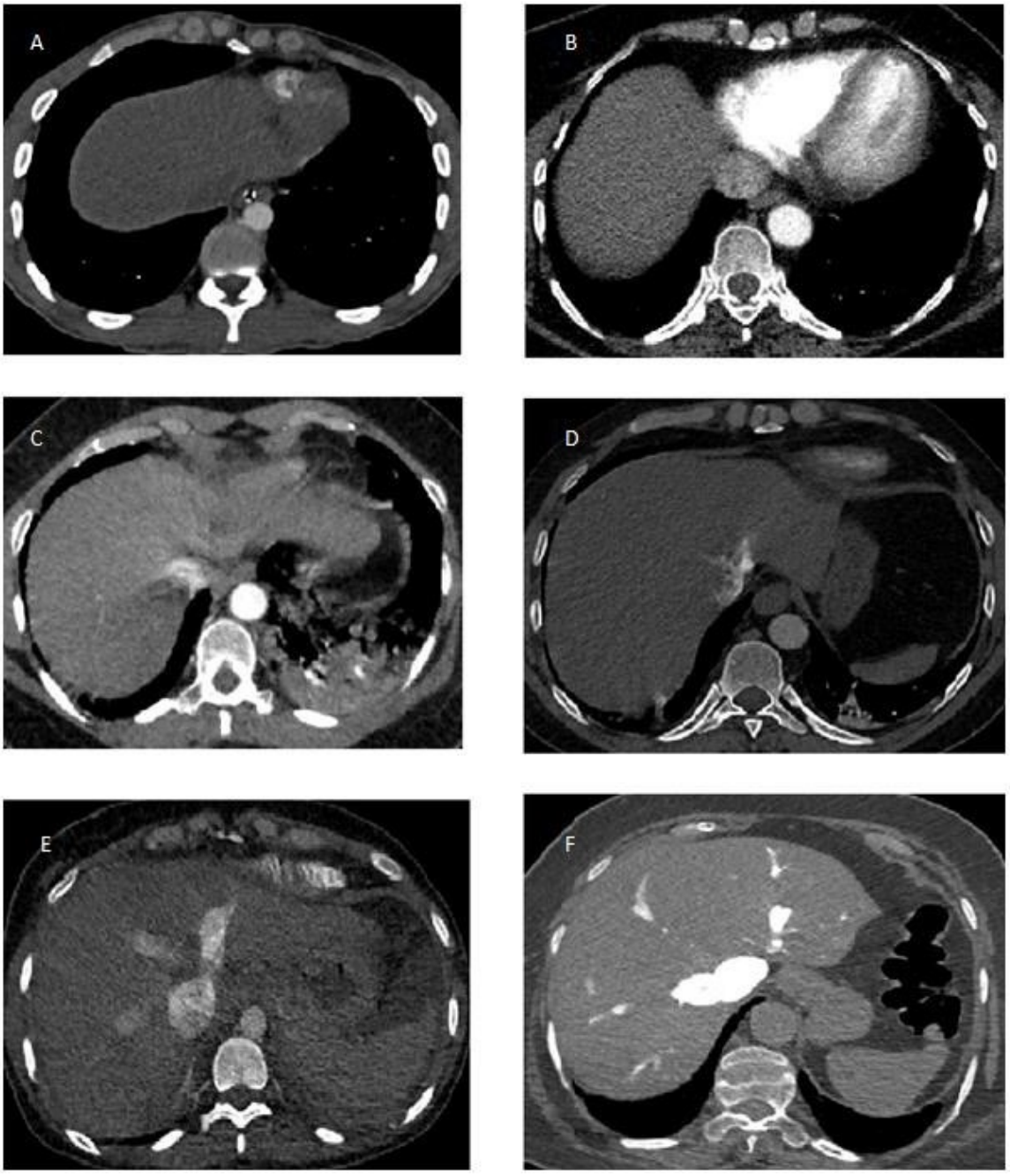
Patients with suboptimal study, such as motion artifacts and poorly opacified pulmonary vessels due to faulty technique, were excluded. Patients whose post-PE 30-day record could not be obtained were also excluded from this study.

The presence of contrast reflux in the IVC was evaluated according to Groves six-point scale elaborated in Table 1 and shown in Figure 2 (18). Grades one to three were grouped as low risk favoring better outcome, whereas grades four to six were taken as high risk group associated with higher mortality (Figures 3,4,5).

Table 1. Groves six-point scale of contrast reflux (18).

Grade of Contrast Reflux	Description
Grade 1	No evidence of contrast opacifiying IVC.
Grade 2	Trace/ minimal contrast reaching into the IVC.
Grade 3	Contrast back flow only limited to the IVC.
Grade 4	Contrast reaching into the IVC and only small part of hepatic veins near IVC confluence.
Grade 5	Contrast opacifying the IVC and reaching up to the mid-part of hepatic veins.
Grade 6	Contrast opacifying the IVC and reaching into the proximal third of hepatic veins in the peripheral hepatic parenchyma.

Figure 2. Grades of contrast reflux. A. Absent contrast reflux in IVC representing grade 1 reflux. B. Trace/minimal contrast reaching into the IVC representing grade 2 reflux. C. Reflux of contrast only limited to IVC representing grade 3 reflux. D. contrast reaching into IVC and only small part of hepatic veins near IVC confluence representing grade four reflux. E. Contrast opacifying IVC and reaching up to the mid part of hepatic veins representing grade five reflux and F. Contrast opacifying IVC and reaching into the proximal third of hepatic veins in the peripheral hepatic parenchyma.



Patients' medical records were studied for their clinical outcomes (mortality) after 30 days from the acute PE episode and were then categorized as survivors and non-survivors. All of the findings were reviewed and confirmed by senior consultant radiologists with more than five years of post-fellowship experience.

Figure 3. Grade four contrast reflux in a 73-year-old male patient diagnosed to have acute PE on CTPA. Mild bilateral pleural effusions are also noted. The patient recovered from acute PE episode.

Figure 4. Grade five contrast reflux in a 35-year-old female patient. She had a massive bilateral pulmonary embolism and did not survive.

Figure 5. Grade six contrast reflux in 74-year-old female patient. Despite early diagnosis the patient did not survive.

Results

A total of 1152 CTPAs were performed between January 1, 2016 and January 31, 2019. Filling defects in pulmonary arteries representing acute pulmonary embolism were detected in 426 scans (36.9% of total CTPA scans). 78 scans demonstrating minor/suspicious filling defects in only one sub-segmental branch with normal opacification of pulmonary trunk, main pulmonary arteries and lobar branches were excluded from the study. Another 27 scans with streak artefacts, venous phase imaging and motion blur were excluded from the study. A total of 35 patients could not be followed for a post one-month outcome and were not included in the study. One patient with a filling defect in the intrahepatic part of the IVC was also deducted from our sample. The remaining 285 subjects of South Asian origin were included in our study (Figure 6).

The age ranged between 15 to 85 years. Mean age was 49.29 years ± 19.409. The study was composed of 178 males (62.5%) and 107 females (37.5%). Among these, 156 were admitted patients and 129 were patients referred to our department from the out-patient department (OPD). The mean score of contrast reflux grade was 2.35 ± 0.81. On the follow-up of 30 days, 85 (29.8 %) patients had died and 200 (70.17 %) survived. These were classified as non-survivors and survivors respectively. The reflux grade was found minimum to be one and the maximum to be six (Table 2).

The contrast reflux was found to be >3 in 76 patients (26.67 %) among whom 56 patients died within 30 days whereas 20 patients survived. The score was ≤3 in 209 patients (73.34 %). 29 patients out of these lost their lives and 180 patients survived.

Among 128 patients with a grade one contrast reflux, 116 (90.6%) patients survived and 12 (9.4%) patients died. Out of a total of 36 patients showing grade two contrast reflux, only six patients died. Out of 45 patients demonstrating grade three contrast reflux, 11 patients (16.67%) died. 23 out of 37 patients (62.2%) with grade 4 contrast reflux died. A total of 21 patients out of 27 (77.8%) showing grade five contrast reflux on CTPA lost their lives in the immediate post PE 30-day span, while all 12 patients (100%) with grade six contrast reflux did not survive.

Among non-survivors (85 patients), 56 patients (65.8 % of non-survivors) had an IVC contrast reflux grade of > 3, whereas the remaining 29 patients (34.2 %) had an IVC contrast reflux grade of ≤3. The results suggested positive association between the higher grade of contrast reflux and an increased risk of mortality. As shown in Figure 7, significant correlation was observed in the predicted and actual outcome of study participants in terms of survival/mortality with a p-value of 0.003 (significant).

The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of IVC contrast reflux grading were 65.8%, 90%, 73.68 %, 86.12 % and 82.8 % respectively. No significant difference in mortality was detected on the basis of age and gender, which had p-values of 0.109 and 0.427 respectively.

Figure 6. Flowchart of study design.

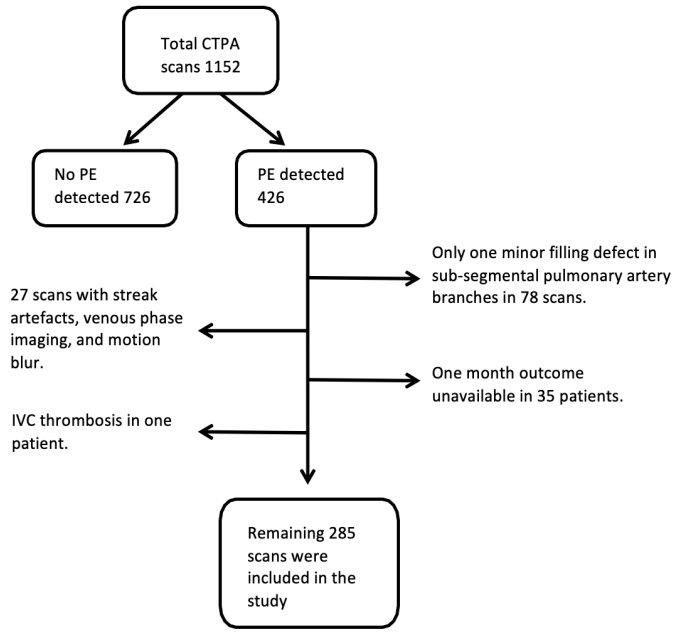
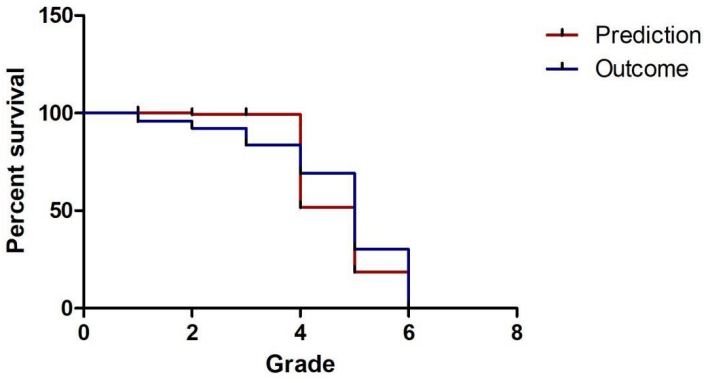


Table 2. Distribution of contrast reflux grade in study population.

Groves grade of contrast reflux	Number of patients	Frequency
Grade 1	128	44.9%
Grade 2	36	12.6%
Grade 3	45	15.8%
Grade 4	37	13%
Grade 5	27	9.5%
Grade 6	12	4.2%

Figure 7. Survival plot showing significant difference (p=0.003) in CTPA prediction vs. disease outcome from grades four to six using the Gehan-Breslow-Wilcoxon Test.



Discussion

The literature has already established CTPA as the first line imaging modality to diagnose PE, replacing nuclear imaging and conventional pulmonary angiography (19,20). It has such a high sensitivity that a negative test can allow a physician to safely discontinue anticoagulation therapy (21).

The contrast reflux after first pass bolus into the IVC is a feature suggesting raised pressure in the right ventricle. Conditions like constrictive pericarditis, restrictive cardiomyopathy and tricuspid regurgitation or raised pulmonary artery pressure also cause an increase in right ventricular pressure (22). Prior studies have reported role of clot burden scores and RV/LV values in determining the prognosis of mortality in patients of pulmonary embolism (23). This assessment, however, is lengthy and time-consuming. The evaluation in multiple planes is also required before concluding these findings. Moreover, the interpretations are controversial. The complex interplay of pulmonary vascular obstruction, vasoconstriction mechanisms, and hypoxia leading to series of events including hemodynamic instability, right heart failure, cardiogenic shock, and cardiac arrest results in patient mortality (24). However, the clot burden scoring only focuses on the extent of pulmonary arterial obstruction. There is no consensus on cut-off values for predicting mortality using these scores (25).

Collins et al. first described backward contrast flow from the right cardiac chambers into the IVC. They reported intense contrast reflux in six patients with opacifying IVC and hepatic veins suffering from tricuspid regurgitation (26). Similar to our study, Ghaye et al. deduced from his study of an 82-patient sample that contrast reflux into the IVC and hepatic veins was more prevalent in patients facing death secondary to pulmonary embolism than survivors (27). Ibrahim et al. also found significant correlation between ICU admissions and IVC contrast reflux suggesting some association between right heart strain and contrast reflux (28). These studies, however, only considered presence or absence of reflux into the IVC and hepatic veins and ignored the differences in degree of reflux. Groves et al. devised a grading scale for contrast reflux on CTPA (18). Based on this scale, Bouvier et al. concluded that contrast reflux of grade four or more was associated with poor outcome and mortality with 86% specificity and 71% sensitivity (AUC 0.88) (16). Hefeda also found a significant association between increased degree of contrast reflux and poor prognosis of pulmonary embolism (p=0.001) with a sensitivity of 66.6% and specificity of 79.2% (10). A few contradictory views have also been reported in literature. Collomb et al., for example, did not find a significant relationship between IVC contrast reflux grading and mortality (29).

Pulmonary embolism is not the only cause of contrast reflux in IVC. The drawback of solely relying on contrast reflux as a prognostic indicator is that it overlooks other causes leading to flow of contrast in backward direction from the right atrium into the IVC. Aviram G et al. in multivariate logistic regression found that acute pulmonary thromboembolic event and pulmonary arterial hypertension were associated with high grade contrast reflux corresponding to grades four to six with odds ratios (95% confidence intervals) of 1.8 (1.2 to 2.9, p = 0.011) and 5.4 (3.0 to 9.9, p <0.001) (19). This suggests that IVC contrast reflux as demonstrated on CTPA may be relied on to indicate right heart dysfunction. It cannot, however, differentiate acute pulmonary embolism from closely linked entities of heart failure, pulmonary arterial hypertension and long-standing atrial fibrillation.

Our study has proved that IVC contrast reflux grading has significant high prognostic accuracy of 82.8 % with a specificity of 90%. Our data demonstrated no significant effect of age or gender on the mortality. Considering these factors, CTPA remains the best accepted modality for assessment of pulmonary embolism (30). Diagnosis of acute or chronic pulmonary thromboembolic disease can be confidently established viewing the direct signs on angiography and CT pulmonary angiography (28). Moreover, contrast reflux via right atrium into the IVC and hepatic veins serves as an indicator of mortality in patients diagnosed with pulmonary embolism, as replicated in our study. The presence of high-grade contrast reflux, therefore, can be taken as a red flag for aggressive management of PE and thereby improve the outcome for patients.

There are a few limitations of this study. First, the study was conducted in a single tertiary care center using a uniform contrast injection rate for all CTPAs. The results, therefore, cannot be extrapolated to institutions using varying contrast injection rates. The diminution of contrast reflux with high contrast injection rate in right ventricular dysfunction as suggested by Yeh et al. needs further exploration (31). This study found that the specificity of contrast reflux into the IVC for the presence of right heart disease is greater (98%) at lower injection rates (less than 3mL/sec). At higher injection rates (greater than 3 mL/sec) the specificity decreases to 69%. In contrast to the specificity rates, the sensitivity of contrast reflux in diagnosing right heart disease rises from 31% at lower injection rates (less than 3mL/sec) to 81% at higher rates (greater than 3mL/sec). Our results, however, are contrary to these results in that they demonstrate higher specificity with greater contrast injection rates (4mL/sec). Similar findings are also documented by Weerakkody (32). To further test this inference, more research in this regard is required. Second, despite maximum efforts, we were unable to get echocardiography results of all patients to confidently exclude underlying cardiac issues that may contribute to right heart strain. Third, we did not evaluate contrast reflux grade in patients having early mortality (within 24 hours). Further research is suggested in this regard to unearth the relation between high grade contrast reflux and 24-hour mortality in patients suffering from acute PE.

Conclusion

We conclude that contrast reflux grading assessed on helical CTPA is a potentially useful and easily comprehendible tool for prediction of poor prognosis in patients with PE in terms of mortality. It enables identification of critical cases which aids in management.

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Conflicts of interest

The authors report no conflicts of interest.

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