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The Diagnostic Accuracy and Impact of Computer-Aided Diagnosis of Pulmonary Emboli Using CT Pulmonary Angiography

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The diagnosis of pulmonary embolism (PE) remains a challenge to treating physicians as PE can occur unpredictably and fast and the symptoms are often unspecific in some patients. This ultimately means that adequate and accurate diagnosis of PE is crucial and necessary. CT pulmonary angiography (CTPA) is the imaging of choice for patients with suspected PE. However, small PE could potentially be missed resulting in morbidity and mortality if left untreated. The primary objective of this literature review is to summarise and analyse the diagnostic accuracy and impact of computer-aided diagnosis (CAD) software within the current literature to diagnose a PE on a CTPA examination. The current findings suggest that CAD technology as a "first reader" has a comparable sensitivity but substantially decreased specificity compared to radiologist read studies. CAD technology as a "second reader" or "concurrent reader" has a higher sensitivity and comparable specificity. The increase in sensitivity is small at this stage and reading time has been reported as increasing with CAD technology as a second reader. CAD as "concurrent reader" is unlikely to achieve FDA approval due to the theoretical possibility of missing a lesion.

Key words CT Scan · CTPA · Pulmonary embolism · Computer-assisted diagnosis · Pulmonary embolism.

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BACKGROUND

Pulmonary embolism

Pulmonary embolism (PE) is a potentially fatal condition associated with the highest incidence of mortality, morbidity and hospitalization [1-4]. It is the third most common cause of cardiovascular death, preceded by stroke and myocardial infarction [5]. This condition occurs when a blood clot or a thrombus/embolus, usually from large veins of the lower extremity, enters the pulmonary arteries and causes blockages [5,6].

As a result, this contributes to a rise in resistance to the bloodstream, chest pain, shortness of breath and breathing difficulties, causing increased arterial pressure, decreased cardiac output, consequently hemodynamic disturbances, heart failure or even death [5].

CT pulmonary angiography

CT pulmonary angiography (CTPA) has been one of the primary diagnostic tests for PE since its introduction in 1992 [7]. CTPA has advantages over conventional angiography and ventilation/perfusion scans because it is capable of directly imaging the emboli, resulting in greater accuracy and interobserver agreement [8]. A past limitation of CTPA was in the detection of a small peripheral PE [8]. Single-detector spiral CT was limited by cardiac and pulmonary motion, as well as partial volume effects [8]. The advent of multi-detector CT (MDCT) allows single-breath-hold high-resolution acquisition of cross-sectional thoracic images of submillimeter section thickness [7]. Radiologists can now detect emboli in the 6th order branches of subsegmental arteries [8]. MDCT may not be a standalone test even with the higher detection rate as some studies report only a moderate sensitivity at 83% (with specificity 96%) [9]. Another disadvantage is that the typical MDCT scan produces 500−600 transverse images to read, increasing reading time [8].

Computer-aided diagnosis

Computer-aided diagnosis (CAD) has been an important area for research in the last two decades. Due to a high prevalence of breast cancer and challenges in mammographic interpretation, the development of CAD was originally devoted to the detection and characterization of masses and micro-calcifications on mammograms. In the last decade, however, several studies have been published to pursue further development and utilization of CAD techniques for other diseases and imaging modalities. CAD in the detection of PE in CTPA has been a topic of interest recently. Radiologists may benefit from CAD because of the complexity of the pulmonary vascular structures and the large number of vessels to be interpreted for PE in each individual case. The evaluated PE CAD algorithm is a multi-step algorithm with the purpose of detecting filling detects. The algorithm concentrates on filling defects in the segmental and submental regions of the pulmonary artery tree. This is because these regions are most likely to be missed by radiologists [8,10]. Generally, the first two stages include lung segmentation and candidate generation. These stages are solely based on image processing functionalities whereas the third stage, feature extraction, consists of both image processing and machine learning. The fourth stage, classification, is exclusively a machine learning method [8,10]. The application of CAD technology is thought to be viable option in increasing CTPA sensitivity and specificity, as well as in reducing reading time [10]. Current innovations in computer visualisation techniques include the ability for CAD software to distinguish arteries from veins, track pulmonary vessels, and alert radiologists to the appearance of pulmonary emboli [8,11]. If CAD can improve detection of subtle peripheral emboli, this may reduce the need for further diagnostic procedures as well as provide more accurate information for the selection of a treatment plan [8].

This literature review will compare the current process of PE diagnosis with CTPA in a clinical setting, with and without the aid of CAD software and synthesise findings on the diagnostic impact. The review, in particular, will summarise studies investigating diagnostic accuracy, discuss these findings and provide a conclusion. In effect, the review aims to investigate reading times and sensitivity and specificity of CTPA either:

1) Without CAD (radiologist only),
2) With CAD as a stand-alone performance, and/or
3) With CAD as a second or concurrent reader

RESULTS AND DISCUSSION

Diagnostic accuracy of CTPA with radiologist interpretation only

The largest clinical trial on the diagnostic accuracy of CTPA, as reported in the literature, is the Prospective Investigation of Pulmonary Embolism Diagnosis second study (PIOPED II) [9]. Between 2001−2003, the study included a dataset from 824 patients using MDCT scanners. The study reported a sensitivity of 83% (correct diagnosis of patients with PE) and a specificity of 96% (correct diagnosis of patients without PE).

This literature review has synthesised data from three studies which used MDCT PA to detect PEs, at all vessel levels, not just the segmental and subsegmental level. This was done initially with radiologist reading only, then also CAD software only, and then with the use of CAD software as a second reader to the radiologist [12-14].

Table 1 displays the sensitivity and specificity of radiologist interpretation only. Only studies which used MDCT scanners of similar diagnostic value were included. The patient data size ranged from 79 to 196 patients. The sensitivity and specificity of radiologist diagnosis of PE in these studies corresponds with the PIOPED II large clinical trial of 83% sensitivity and 96% specificity, with the exception of 68−100% sensitivity reported by Wittenberg et al. [13].

These findings within Table 1 correlate to the review by Doğan et al. [15] where the variation in sensitivity and specificity for radiologist diagnosis of PE was reviewed and respectively re-

Table 1. CT pulmonary angiography sensitivity and specificity of pulmonary embolism diagnosis by radiologist only

Author	Without computer-aided diagnosis (radiologist only)			
	Slice thickness (mm) MDCT device	Data size (patients)	Sensitivity (%)	Specificity (%)
Blackmon et al. [12]	1.0 16, 64 rows MDCT	79	84.4	92.6
Wittenberg et al. [13]	1.5 64 rows MDCT	196	68–100	90–98
Zimmermann et al. [14]	1.0 64 rows MDCT	100	84	100

MDCT: multi-detector CT

ported as ranging from 83−100%, and from 89−96%, again with the exception of 68−100% sensitivity reported by Wittenberg et al. [13].

The study by Wittenberg et al. [13] also further reported on individual reporting radiologist's sensitivity and specificity for diagnosis of patients with PE, and can account for the greater range in sensitivity (68−100%) reported in their study, where one particular radiologist had a lower diagnostic sensitivity of 68%.

This variation in performance was attributed to the "study effect" in the article by Wittenberg et al. [13]. The three residents performed higher than the three radiologists (sensitivity 95%, 92%, and 100% compared to 89%, 92%, and 68%). The study effect considers that residents would be more attentive and comprehensive in order to attain a higher baseline performance, as compared to radiologists who would read faster due to time constraints and possibly with less alertness due to lack of clinical consequences [13]. The radiologists spent 75% less time on average reading the CTPA scans [13].

Worldwide acceptance of CTPA as a gold standard diagnostic tool for PE has been achieved following the PIOPED II study and reviews like that published by Doğan et al. [15]. Although a high sensitivity for PE diagnosis has been established, there is still a false negative proportion of 13% as per the PIOPED II results, and this could lead to significant negative health outcomes. The radiological difficulties in diagnosing PE on CTPA have been reported in the literature as due to too much data per routine scan, complexity of the small subsegmental branches of pulmonary arteries in comparison to voxel size, and time constraints [13,14,16-18]. These reported difficulties in diagnosing a PE on CTPA have gained the interest of CAD technology experts who aim to increase the sensitivity of CTPA to 100%.

Diagnostic accuracy of CTPA with CAD only

In 2002, the first study using CAD software for PE detection on CTPA examinations was published by Masutani et al. [16]. They reported on detection of PE "per clot" as opposed to diagnosis of PE positivity "per patient" as is now studied in the literature. The results of this study were a 100% sensitivity of detected clots within a patient's pulmonary vessels, although the technology had an average of 7.7 false-positive clots per patient [16].

It has been reported in current literature that initial CTPA-CAD image reading will produce a high sensitivity, in-line with expert radiologist reading, but a substantially lower specificity (ranging from 13−21%) [12-14,19]. This low specificity is due to the false positives which occur [14].

Table 2 displays the sensitivity and specificity of CTPA with CAD as the stand-alone reader, also known as "first reader" within the literature. The sensitivity (93.8%, 95%, and 81%) is comparable or higher than the sensitivity of radiologist read CTPA recorded in Table 1 (84.4%, 68−100%, and 84%). But the specificity was significantly less by CAD technology as a first reader (14.9%, 17%, and 16%) compared to the specificity of radiologist read CTPA (92.6%, 90−98%, and 100%, per Table 1).

Diagnostic accuracy of CTPA with CAD as a second or concurrent reader

Due to the low specificity of CAD algorithms as a "first reader," they are designed to be a "second reader" to the radiologist [13]. The radiologist completes an unassisted interpretation of the full scan before applying a second look at candidates alerted to them by the CAD algorithm, leading to an increased sensitivity [13]. This method increases reading time and slightly reduces specificity [12]. Another method is concurrent reading where the CAD algorithm works simultaneously with the radiologist and leads to a reduction in reading time [13].

As seen in Table 3, Blackmon et al. [12] reported sensitivity of CAD as a second reader was 92.2% compared to 84.4% with radiologist only (Table 1). This is less than CAD technology sensitivity as a first reader (93.8%). Wittenberg et al. [13] also described this increased sensitivity with the use of CAD technol-

Table 2. CT pulmonary angiography sensitivity and specificity of pulmonary embolism diagnosis by CAD stand-alone or "first reader" technology

Author	CAD stand-alone			
	Slice thickness (mm) MDCT device	Data size (patients)	Sensitivity (%)	Specificity (%)
Blackmon et al. [12]	1.0 16, 64 rows MDCT	79	93.8	14.9
Wittenberg et al. [13]	1.5 64 rows MDCT	196	95	17
Zimmermann et al. [14]	1.0 64 rows MDCT	100	81	16

CAD: computer-aided diagnosis, MDCT: multi-detector CT

Table 3. CT pulmonary angiography sensitivity and specificity of pulmonary embolism diagnosis by CAD as "second reader" or concurrent reader technology

Author	With CAD as a second or concurrent reader			
	Slice thickness (mm) MDCT device	Data size (patients)	Sensitivity (%)	Specificity (%)
Blackmon et al. [12]	1.0 16, 64 rows MDCT	79	92.2	88.3
Wittenberg et al. [13]	1.5 64 rows MDCT	196	76–100	90–99
Zimmermann et al. [14]	1.0 64 rows MDCT	100	NR	NR

CAD: computer-aided diagnosis, MDCT: multi-detector CT

Table 4. Comparison of the sensitivity and specificity of three different MDCT market vendors (Philips, GE, and Siemens)

MDCT vendor	Slice thickness (mm) MDCT scanner	Data size (patients)	Sensitivity (%)	Specificity (%)
Philips	0.6 64 rows MDCT	78	100	18
GE	0.9 64 rows MDCT	79	97	15
Siemens	1.5 64 rows MDCT	75	92	13

MDCT: multi-detector CT

ogy as a concurrent reader. Specificity decreased slightly with CAD technology as a second reader from 92.6% ot 88.3% [12]. It remained comparable with CAD technology as a concurrent reader at 90−99% [13].

Reading time

Blackmon et al. [12] stated that an increased reading time occurred with the use of CAD technology as a second reader, as radiologists would then have to interpret the false positives detected by the software. Wittenberg et al. [13] found a reduction in reading time with the use of CAD technology as a concurrent reader. The reduction in reading time was higher for less experienced readers. Residents had a 17% reduction in reading time and the more experienced radiologists had a reduction of 12%.

Diagnostic differences in MDCT scanners and scanning protocols

Different MDCT scanners and scanning protocols were used within the literature. Wittenberg et al. [13] state that the diagnostic results of PE were independent of the MDCT market vendor (Philips, GE, and Siemens), but highly impacted by the image thickness set by the CTPA scanning protocol.

The study by Wittenberg et al. [17] compared the sensitivity and specificity of CTPA-CAD applied to three different MDCT market vendors (Philips, GE, and Siemens). This is summarised in Table 4. The conclusion of this study is that although the MDCT device brand (Philips, GE, or Siemens) had no impact on diagnostic outcome, the scanning protocol had a significant impact. Slice thickness of 0.6 mm resulted in a sensitivity of 100% and specificity of 18% [19]. As slice thickness increased between different scanning protocols, this sensitivity and specificity reduced.

The study by Jung et al. [18] also supports the importance of thin slice thickness for accurate PE diagnosis on CTPA when read by a radiologist. They utilised a 64 row MDCT device and acquired scans at 0.625, 1.3, and 2.5 mm. As slice thickness increased, diagnosis of clots particularly in subsegmental branches significantly decreased [20]. A slice thickness of 1 mm or less was recommended for a high sensitivity to be achieved [20].

Implications

The integration of CAD as a second reader into the clinical workflow has shown an increase in sensitivity with only one study showing a negative impact on reading time [12,19,21]. The specificity as a second reader was comparable or worse within current studies [12,19]. CAD as concurrent reader is unlikely to achieve FDA approval as it has not been achieved in other areas of study due to the risk of missing a true lesion or scrutinising CAD candidates which are false positives [13]. The diagnostic gain of CAD for PE detection is clinically small and relates mainly to a subgroup of patients with subtle subsegmental emboli

[13]. The strengths of CAD technology could lie in increasing readers' confidence, particularly inexperienced readers, and this is an area of further research.

CONCLUSION

The diagnosis of PE remains challenging to physicians as PE can occur rapidly and unpredictably and the symptoms are unspecific in some patients. This ultimately means that sufficient and accurate diagnosis of PE is crucial and necessary. CTPA is the modality of choice for patients with suspected PE. However, small PE could potentially be missed resulting in morbidity and mortality if left untreated. The utilisation of CAD software as a second reader has proven effective in improving the sensitivity for detection of PE. This review has thoroughly depicted the current research and clinical statuses of PE CAD prototypes. The cruciality of CAD software in PE diagnosis as both "first reader" and "second reader" has also been described. For instance, as a "first reader," CAD provides comparable or worse sensitivity and significantly reduces specificity. On the other hand, CAD as a "second reader" or concurrent reader can outweigh the radiologist performance by increasing the sensitivity to up to 100%. Research has effectively shown that this is the best operating scenario, i.e. the "second reader" basis, as the software improves sensitivity (meaning, less false negative results) and simultaneously promises no effect on specificity of radiologist performance. CAD should not be used as a stand-alone method for diagnosis and recommendations should be followed, particularly the CTPA acquisition parameters and patient preparation, which the CAD software relies on.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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