Clinical Radiology 74 (2019) 973.e7–973.e14

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Coronary artery calcification is associated with mortality independent of pulmonary embolism severity: a retrospective cohort study

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ARTICLE INFORMATION

Article history:
Received 15 May 2019
Accepted 23 August 2019

AIM: To assess coronary artery calcification (CAC) and vascular calcification in patients with pulmonary embolism (PE) and correlate this with mortality.

MATERIALS AND METHODS: PE severity was quantified using computed tomography pulmonary angiography (CTPA) in 400 consecutive cases using the modified Miller score (1–5, mild; 6–11, moderate; 12–16, severe). Right ventricle strain was assessed using the right/left ventricle diameter (RV/LV) ratio. CAC score (CACS) was assessed using a four-point scale (CACS mild 1–3, moderate 4–8, severe 9–12) for each vessel and summed to give the total CACS. Follow-up for mortality was obtained at 3 years.

RESULTS: PE severity was classified as mild in 48%, moderate in 21%, and severe in 32% of cases. The median modified Miller score was 6 (Interquartile range [IQR] 2, 14) and median total CACS was 2 (IQR 0, 7). All-cause mortality occurred in 128 (32%) patients. Patients with CAC were three times more likely to die than patients without CAC (Hazard ratio [HR] 2.96; 95% CI 1.84, 4.77; $p<0.001$), and patients with severe CAC were at the highest risk (HR 4.62; 95% CI 2.73, 7.83, $p<0.001$). Gender, modified Miller score and RV/LV ratio were not predictive of mortality. In multivariate analysis both CACS and age were independent predictors of 3-year all-cause mortality. Of the patients with CAC who died, the presence of coronary artery disease was only documented in 34 (32%).

CONCLUSION: CACS is an independent predictor of all-cause mortality in patients with PE, and has important implications for subsequent patient management.

Introduction

Acute pulmonary embolism (PE) is a common emergency with a wide spectrum of disease severity and high mortality.[1] Identification of patients who are at risk of

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https://doi.org/10.1016/j.crad.2019.08.023
0009-9260/

short- and long-term mortality is important in order to stratify appropriate treatment. A variety of clinical parameters have been identified that are associated with increased mortality in patients presenting with PE.[2,3] These reflect the physiological and haemodynamic sequelae of PE. In addition, imaging parameters such as the identification of right ventricular (RV) dysfunction can identify patients who are at an increased risk of mortality.[4–7] The relationship between cardiovascular disease and PE is incompletely understood. There is overlap between these two conditions, as patients with PE are at risk of future cardiovascular events and patients with cardiovascular risk factors are at risk of venous thromboembolism in some studies,[8,9] but not in others.[10] This study assesses the impact of co-existing cardiovascular disease on long-term outcomes in patients with PE.

Coronary artery calcification (CAC) is a component of atherosclerotic plaque and is a surrogate marker for presence of coronary heart disease. CAC scoring (CACS) is usually performed on non-contrast electrocardiogram-gated computed tomography (CT) images of the heart and extensive evidence shows that it is associated with mortality.[11–13] CAC can also be identified and quantified on non-gated CT of the chest performed for non-cardiac indications.[14–16] Ordinal assessment of CAC is a useful method to assess calcification on CT pulmonary angiogram (CTPA) images where motion artefact and contrast medium preclude traditional quantitative CACS methods. The presence of incidental CAC on non-gated CT is associated with mortality in a variety of patient cohorts, including patients with chronic obstructive pulmonary disease (COPD),[17,18] lung cancer screening[19,20] and other respiratory conditions.[21] International guidelines now recommend the reporting of incidental CAC on all thoracic CT.[22]

This study assesses the presence of CAC and right heart strain in patients with PE, and their association with subsequent mortality. It was hypothesised that CAC will be a marker of long-term mortality over and above PE severity.

Materials and methods

Study design

A retrospective assessment of the presence of CAC in patients with PE identified on CTPA was performed. The study population consisted of 400 consecutive patients with PE identified on CTPA at a single institution (April 2011 to March 2012). The local ethics committee waived the requirement for informed consent for this retrospective audit. PE severity in the patients included in this study was reported in a previous study.[23]

CTPA

Patients underwent clinically indicated CTPA for suspected PE. CTPA was performed during inspiration using a 64 multidetector scanner (Toshiba Medical Systems, The Netherlands). Iodinated contrast medium was injected through a peripheral venous catheter (Iomeron 400, Bracco, UK; 50–75 ml; 4.5–5.5 ml/s). Tube voltage was 120 kV and tube current was adjusted based on body habitus. Images were reconstructed with a section thickness of 1 mm using filtered back projection and a soft-tissue kernel. Images were transferred to the picture archiving and communication system, which was used for image visualisation (Vue PACS, Version 11, Carestream Health, Rochester, NY, USA). A history of malignancy was identified from the CTPA request.

PE severity

PE severity was assessed using the modified Miller score[24] by three trained observers, with disagreements resolved by consensus. The modified Miller score was then categorised as mild (1–5), moderate (6–11) or severe (12–16).

CT assessment of right heart strain

Right heart strain was assessed on axial CT images by calculating the ratio of the maximum diameter of the RV to the maximum diameter of the left ventricle (RV/LV ratio).[4] An RV/LV ratio >1.2 was previously defined as a "tipping point" to identify patients with RV strain secondary to PE.[7]

Ordinal assessment of CAC

Semi-quantitative assessment of CAC was performed using an ordinal scale on axial images of the thorax.[25] Each vessel was assigned a score (Fig 1) of 0 (none), 1 (mild), 2 (moderate) or 3 (severe) CAC. CAC was assessed in the left main, left anterior descending, left circumflex, and right coronary artery. Arterial branches were included in the assessment of the feeding artery. Ramus intermedius vessels were included in the assessment of the left anterior descending artery. Individual vessel results were summed to give a total CACS, which was then classified as mild (1–3), moderate (4–8) or severe (9–12).

Mortality

Information on mortality was obtained from the electronic Data Research and Innovation Service (eDRIS) of the National Health Service (NHS) Scotland 3 years after the index events. Categorisation of outcomes was performed independently and without knowledge of other clinical or imaging data. PE-related mortality was defined as the presence of PE as a primary or secondary cause of death, as recorded on the death certificate.

Statistical analysis

Statistical analysis was performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria). Normally distributed quantitative variables are presented with mean and 95% confidence interval (CI). Non-normally distributed data are presented with median and interquartile range. Statistical significance was assessed using analysis of variance, chi-squared test, Kruskal–Wallis test,

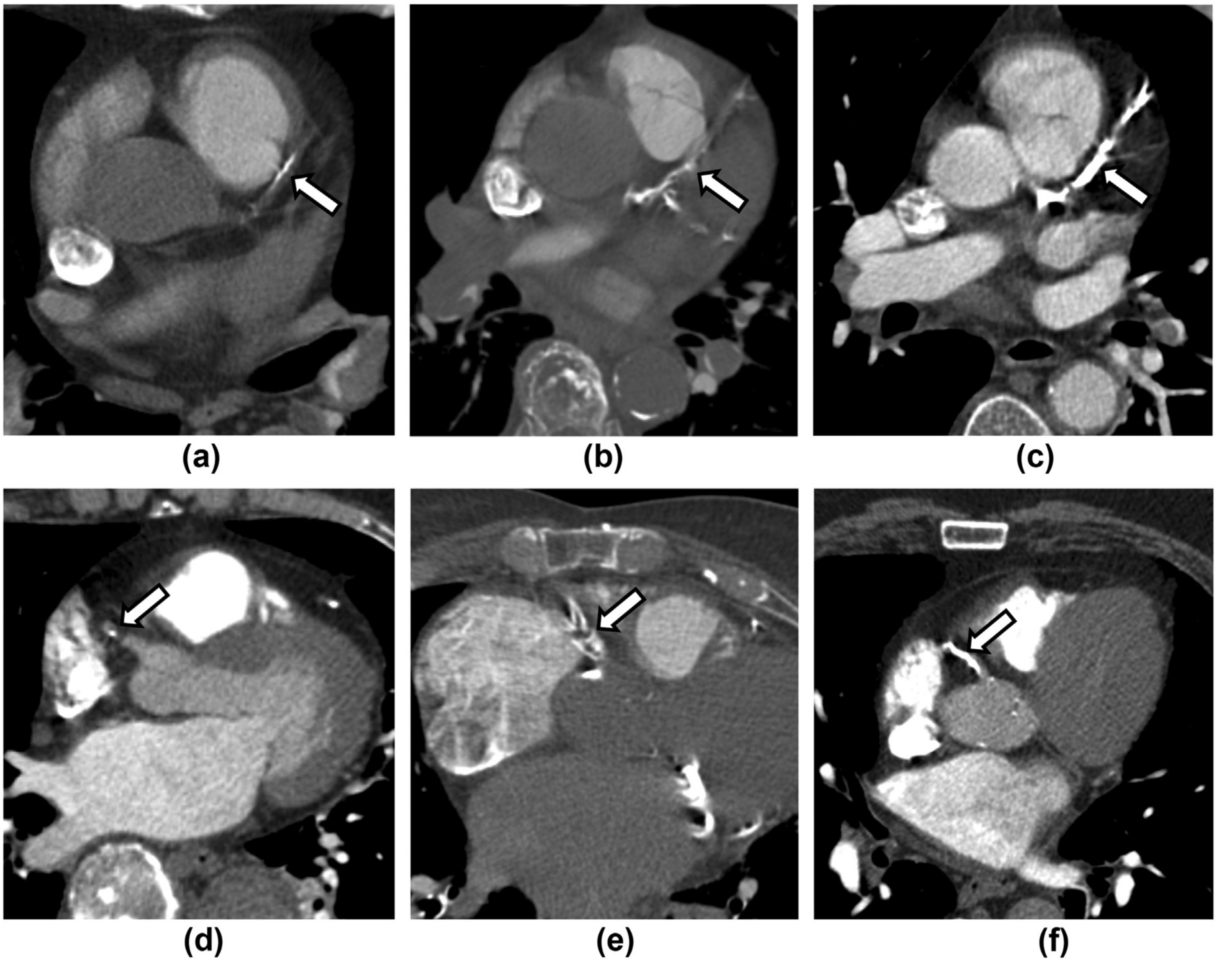

Figure 1 Ordinal scoring of CAC on non-gated CT, showing in the left anterior descending coronary artery (a) mild, (b) moderate, and (c) severe CAC, and in the right coronary artery (d) mild, (e) moderate, and (f) severe calcification.

Student *t*-test or Fisher's exact test, as appropriate. Correlations were assessed using Spearman's correlation. Logistic regression analysis was performed to assess the impact of variables on the RV/LV ratio. Cox proportional hazards regression and Kaplan–Meier curves were constructed. CACS, RV/LV ratio and modified Miller score were log transformed for regression analysis. Parameters were included in multivariate analysis if they were statistically significant in univariate analysis. Hazard ratios (HR) and 95% CI are presented. A statistically significant difference was defined as a two-sided p-value <0.05.

Results

The images of 400 consecutive patients were assessed. The mean age was 66±17 years and 200 (50%) were male (Table 1). The median modified Miller score was 6 (interquartile range [IQR] 2 to 14). Using the modified Miller score to classify PE severity there were 191 (48%) mild, 84 (21%) moderate and 125 (31%) severe PE. There was no association between age or gender and PE severity (Table 1). A history of malignancy was provided in 51 patients (13%).

CT assessment of right heart strain

The median RV/LV ratio was 1 (IQR 0.89 to 1.05) and an RV/LV ratio >1.2 was present in 84 (21%) patients. Patients with severe PE had a higher RV/LV ratio compared to patients with mild or moderate PE ($p<0.001$; Fig 2, Table 1). In logistic regression analysis age and gender were not independent predictors of the presence of an RV/LV ratio >1.2 ($p<0.05$ for both), but the presence of severe PE was (HR 21.79; 95% CI 10.92, 47.83; $p<0.001$, compared to patients with mild PE).

CAC

CAC was present in 271 (68%) patients and the median total CACS was 2 (IQR 0 to 7). Patients with CAC were older (73±13 vs 52±17 years, $p<0.001$) and with no difference in gender ($n=143$, 53% versus $n=128$, 47%, $p=0.109$). CAC was more frequent and severe in the left anterior descending

Table 1
Pulmonary embolism severity and computed tomography markers of right heart strain.

	All patients	Pulmonary embolism severity			*p*-Value
		Mild	Moderate	Severe	
N	400	191 (48%)	84 (21%)	125 (31%)	
Age	66±17	65±18	68±16	67±16	0.426
Male	200 (50%)	102 (53%)	41 (49%)	57 (46%)	0.387
Modified Miller score	6 [2, 14]	2 [1, 4]	8 [7, 10]	16 [14, 16]	<0.001
RV/LV ratio > 1.2	83 (21%)	10 (5%)	5 (6%)	68 (54%)	<0.001
RV/LV ratio	1 [0.89, 1.05]	0.97 [0.98, 1.05]	0.97 [0.91, 1.06]	1.25 [1.03, 1.53]	<0.001
CAC present	271 (68%)	129 (68%)	59 (70%)	83 (66%)	0.841
Total CACS	2 [0 to 7]	3 [0 to 8]	2 [0, 7]	1 [0, 6]	0.453

Mean±standard deviation; Median [interquartile range]; Number (percentage).
RV/LV ratio, right ventricle to left ventricle ratio; IVC, inferior vena cava; CAC, coronary artery calcification; CACS, coronary artery calcification score.

coronary artery (Table 2). When the total ordinal CACS was categorised, 124 (31%) had mild, 68 (17%) moderate and 79 (20%) had severe CAC.

Patients with severe PE and patients with right heart strain (RV/LV ratio >1.2) had a lower total CACS, but this difference was not statistically significant (Table 1, Fig 3). There was no correlation between CACS and modified Miller score ($r=-0.049$, $p=0.333$) or RV/LV ratio (r 0.052, $p=0.302$).

Mortality

After a median follow-up of 3 years (IQR 1.9 to 3.4) there were 128 deaths (32%, Table 3). CACS and age were predictors of 3-year all-cause mortality on univariable analysis, but gender, modified Miller score, and RV/LV ratio were not (Table 4). Patients with any CAC were three times more likely to die than patients without CAC (HR 2.96; 95% CI 1.84, 4.77; $p<0.001$, Fig 4). Patients with mild (HR 1.91; 95% CI 1.10, 3.32; $p=0.022$), moderate (HR 3.26; 95% CI 1.85, 5.77; $p<0.001$), and severe (HR 4.62; 95% CI 2.73, 7.83; $p<0.001$) total CACS were all at increased risk compared to patients without CAC (Fig 5). In multivariate analysis both CACS and age remained independent predictors of 3-year mortality (Table 4).

PE-related mortality occurred in 50 patients (13%). Age, gender, and CAC were predictors of PE-related mortality on univariable analysis (Table 5). Patients with severe CAC were three times more likely to have PE-related mortality than patients without CAC (HR 2.98; 95% CI 1.35, 6.57; $p=0.007$); however, age was the only independent

Table 2
Coronary artery calcification.

	Coronary artery calcium severity			
	None	Mild	Moderate	Severe
Left main	239 (60%)	65 (16%)	32 (8%)	64 (16%)
Left anterior descending	146 (37%)	87 (22%)	58 (15%)	109 (27%)
Left circumflex artery	235 (59%)	50 (13%)	40 (10%)	75 (19%)
Right coronary artery	206 (52%)	80 (20%)	43 (11%)	71 (18%)

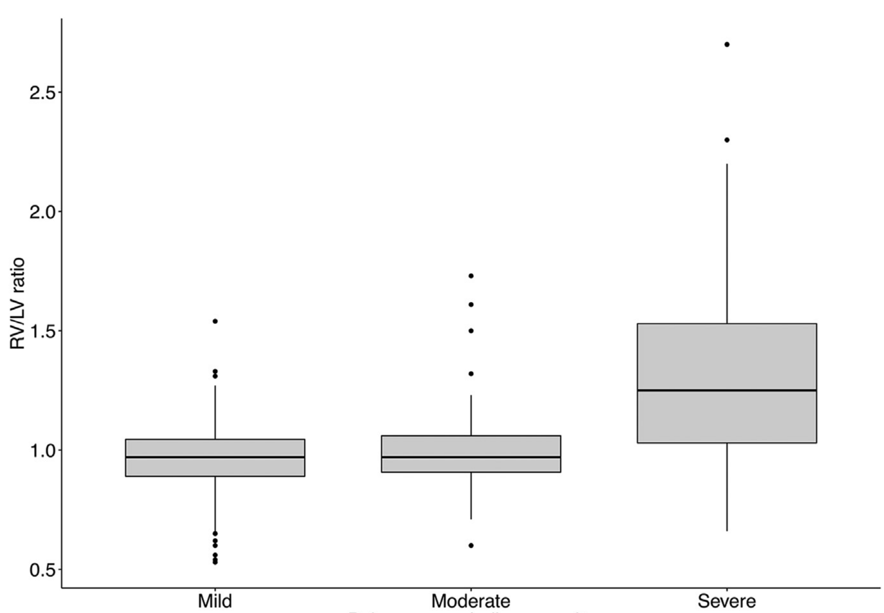

Figure 2 Box plot of RV/LV ratio in patients with different PE severity.

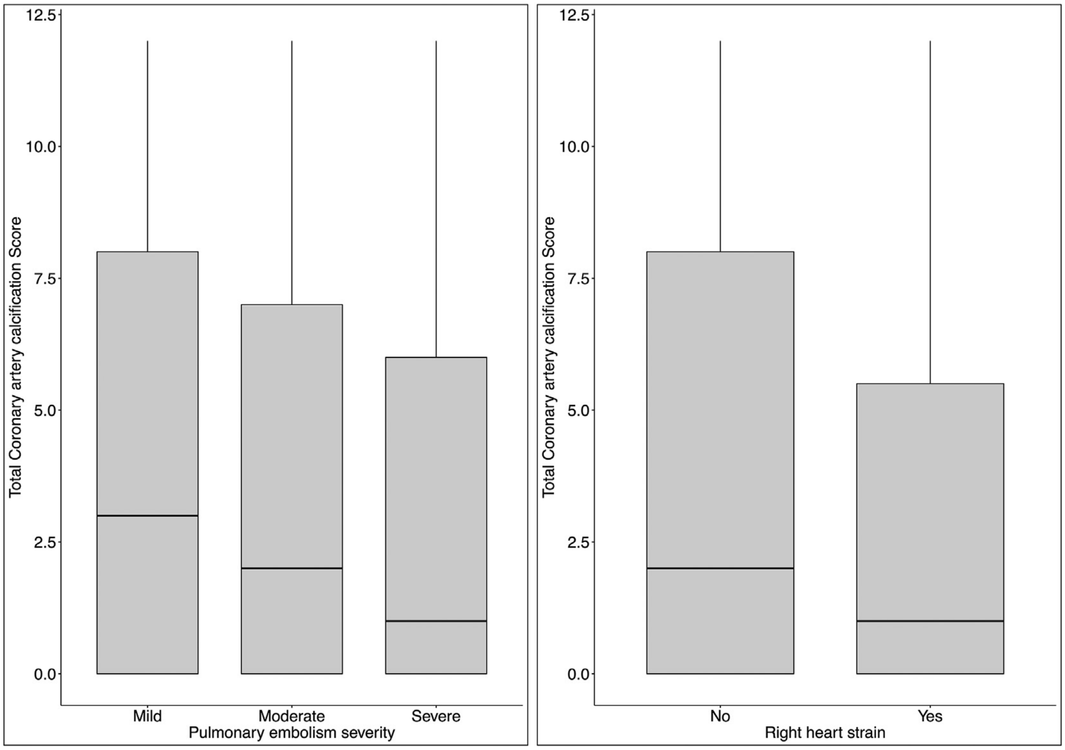

Figure 3 Total CACS for patients with different PE severity and those with and without RV strain.

Table 3
Mortality in patients with different severity of coronary artery disease.

	All patients	Coronary artery calcification				*p*-Value
		None	Mild	Moderate	Severe	
N	400	129 (32%)	124 (31%)	68 (17%)	79 (20%)	
All-cause mortality	128 (32%)	20 (16%)	34 (27%)	29 (43%)	45 (57%)	$<$0.001
Pulmonary embolism as primary or secondary cause of death	50 (12%)	10 (8%)	16 (13%)	8 (12%)	16 (20%)	0.074
Coronary artery disease on death certificate	36 (28%)	2 (10%)	8 (24%)	10 (34%)	16 (36%)	0.153

predictor of PE-related mortality on multivariate analysis (Table 5).

Coronary artery disease was documented on the death certificate for 36 patients (28%). Of the 107 patients with CAC who died, the presence of coronary artery disease was only documented on the death certificate in 34 (32%, $p=0.047$). Patients with coronary artery disease documented on the death certificate were more likely to have severe CAC ($n=16$, 36%), compared to those with moderate ($n=10$, 34%), mild ($n=8$. 24%), or no CAC ($n=2$, 10%), although this difference was not statistically significant ($p=0.153$).

Discussion

For patients with PE after 3 years of follow-up the presence of CAC is a more important predictor of mortality than the severity of PE. CAC is a frequent incidental finding on CTPA and patients with severe calcification are nearly five-times more likely to die compared to patients without CAC. This is in keeping with the hypothesis that for patients who survive the initial haemodynamic insult of PE, the long-term mortality is related to the presence of co-existent coronary artery disease; however, despite the presence of CAC, a diagnosis of coronary artery disease is infrequently documented on death certificates.

Table 4
Univariate and multivariate analysis of predictors of all-cause mortality.

	Univariate analysis	Multivariate analysis
Male gender	1.27 (0.90, 1.80) $p=0.179$	-
Age	1.06 (1.04, 1.07) $p<0.001$	1.05 (1.03, 1.06) $P<0.001$
Modified Miller score[a]	0.77 (0.46, 1.28) $p=0.316$	-
RV/LV ratio[a]	0.43 (0.02, 9.49) $p=0.593$	-
Total CACS[a]	4.03 (2.58, 6.31) $p<0.001$	1.75 (1.06, 2.90) $p=0.029$

Hazard ratios and (95% confidence interval).
RV/LV ratio, right ventricle to left ventricle ratio; IVC, inferior vena cava; CACS, coronary artery calcification score.
[a] Log transformed for analysis; per unit increment change.

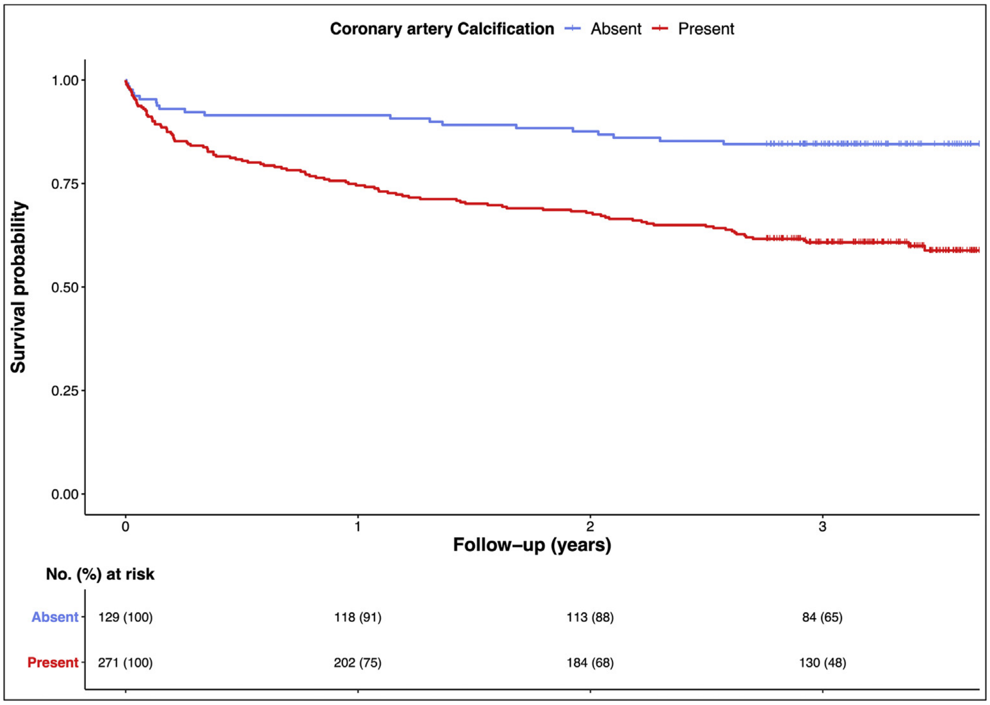

Figure 4 Kaplan–Meier survival curve for all-cause mortality for patients with and without CAC.

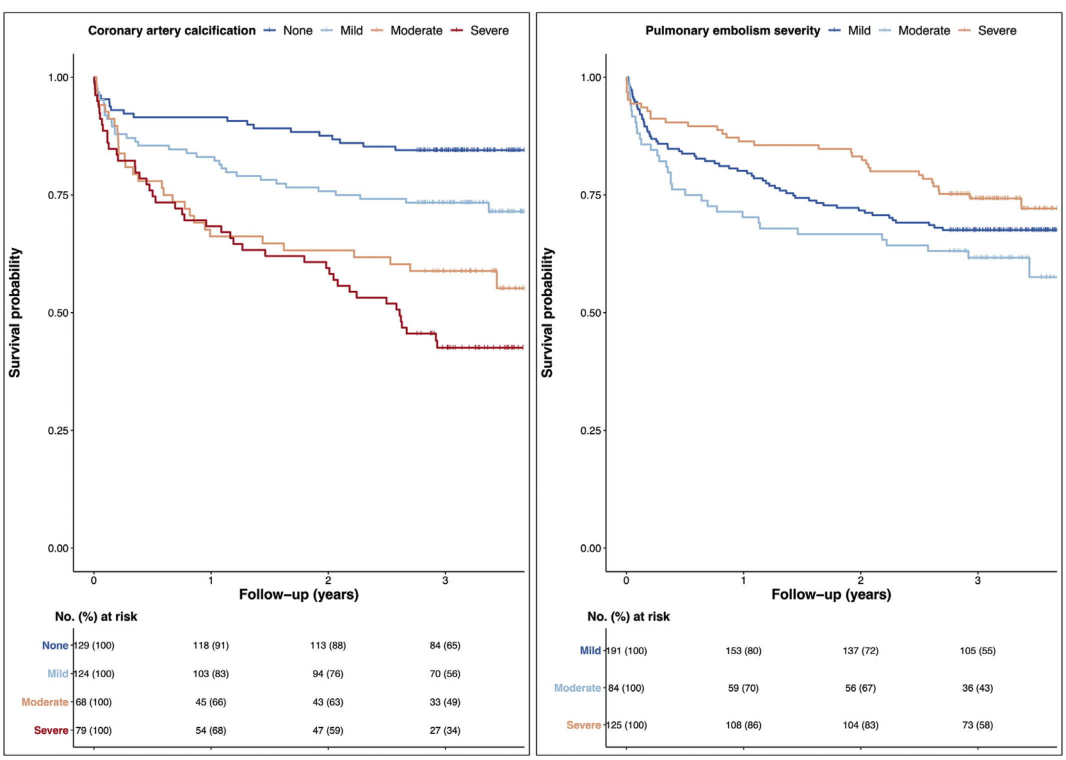

Figure 5 Kaplan–Meier survival curve for all-cause mortality, stratified by CACS and PE severity.

CAC is prevalent in patients with PE, occurring in over 60% of patients in the present study. This is similar to the frequency identified in previous cohorts.[26,27] After 3 years of follow-up, CAC and age were the only independent predictors of mortality. This suggests that if patients survive the early haemodynamic effects of PE and receive appropriate treatment, the subsequent prognosis depends more on comorbidities than the severity of the initial PE. Comorbidities, such as malignancy, chronic lung disease, hypertension, diabetes, dementia, and peripheral vascular

Table 5
Univariate and multivariate analysis of predictors of mortality attributed to pulmonary embolism.

	Univariate analysis	Multivariate analysis
Gender	1.83 (1.03, 3.26) p=0.040	1.21 (0.66, 2.23) p=0.543
Age	1.06 (1.04, 1.08) p<0.001	1.06 (1.03, 1.09) p<0.001
Modified Miller score[a]	1.15 (0.50, 2.65) p=0.736	-
RV/LV ratio [a]	2.81 (0.23. 33.76) p=0.415	-
Total CACS [a]	2.26 (1.05, 4.43) p=0.018	0.84 (0.39, 1.82) p=0.665

Hazard ratios and (95% confidence interval).
RV/LV ratio, right ventricle to left ventricle ratio; IVC, inferior vena cava; CACS, coronary artery calcification score.
[a] Log transformed for analysis; per unit increment change.

disease, are predictors of mortality in patients with PE.[28] Scores incorporating comorbidities such as the Pulmonary Embolism Severity Index, Cumulative Illness Rating Scale, and Charleston comorbidity index are associated with mortality in patients with PE.[3,29,30] Furthermore, in a cohort of patients investigated for suspected PE, those in whom PE was excluded had a 6-month mortality, which was higher than those with proven PE[31]; however, in the Multi-Ethnic Study of Atherosclerosis a high CACS was not associated with an increased risk of PE.[10] A prior history of cardiovascular disease[32] and a higher CHA2DS2-VASc score[33] have been shown to be associated with increased mortality in patients with acute PE. The presence of known coronary artery disease was associated with a 2.2-fold increase in all-cause mortality at nearly 4 years of follow-up in a cohort study of 1,023 patients admitted with confirmed PE.[34] In the present study, the presence of severe CAC was associated with a nearly fivefold increase in all-cause mortality at 3 years. Thus, the presence of CAC is a more important predictor of long-term all-cause mortality than PE severity.

Previous studies have also shown that CAC is prevalent in patients with PE, but that it is underreported.[16] Patients referred for CT for suspected PE are more likely to have CAC than those referred for CT for other indications.[36] Thus, reporting the presence of CAC on CTPA is important, and may help to guide the downstream management of these patients. Although it is known that changing management for patients with symptoms of coronary artery disease based on CT findings can improve subsequent outcomes,[38] there are to-date no randomised studies of treatment changes based on the identification of incidental CAC on thoracic CT.

Patients with a combination of severe PE and severe CAC may be more likely to develop early right heart strain and die before undergoing CTPA. This may be the cause of the increased frequency of PE as a cause of death in patients with more severe CAC, although this did not reach statistical significance in this study. This concept of a “tipping point” after which the RV can no longer compensate has previously been established.[7] If this is the case, then it is likely such pre-hospital deaths are going unrecognised. In a registry study of sudden cardiac arrest, PE was the cause in only 3%.[39] With the increasing use of CTPA higher numbers of PE are being diagnosed, including both large and small PE.[23] The number of unsuspected PE being diagnosed on contrast CT of the chest performed for other reasons also supports this hypothesis.[40] There may be out-of-hospital cardiac deaths occurring that are precipitated by the haemodynamic consequences of PE in patients with undiagnosed severe coronary artery disease; however, further studies are required to investigate this.

The primary limitation of the present study is that CAC was assessed on standard CTPA images rather than non-contrast, electrocardiogram-gated images. This meant that quantitative CACS could not be performed; however, previous studies have shown good correlation between quantitative and ordinal CACS, and gated and non-gated CT.[14,41] The study size and number of patients who died was also small. Selection bias is an important factor in this study as patients with the most severe PE or CAC may die before reaching hospital or the imaging department. This is an unavoidable bias, which might confound attempts to study this population using clinical imaging techniques. In addition, patients presenting with PE represent a heterogeneous population in terms of age, gender, and other comorbidities that may also account for changes in CACS or PE severity.

In conclusion, CAC is prevalent in patients with PE and is a more important predictor of long-term mortality than the severity of the initial PE. It is therefore important to report the presence of CAC on CTPA as it may guide future management.

Conflicts of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. van Beek reports other from QCTIS Ltd, personal fees from Mentholatum, personal fees from Aidence, other from Siemens, personal fees from InHealth, outside the submitted work.

Acknowledgements

M.C.W. is supported by The Chief Scientist Office of the Scottish Government Health (PCL/17/04). E.v.B. is supported by the Scottish Imaging Network: A Platform of Scientific Excellence (SINAPSE).

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