







## RESEARCH ARTICLE

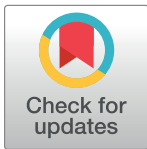
# Clinical and radiological characteristics of acute pulmonary embolus in relation to 28-day and 6-month mortality

Lindsey Norton<sup>1</sup> , Gordon Cooper<sup>2</sup> \*, Owen Sheerins<sup>3</sup>, Killian Mac a' Bháird<sup>1</sup>, Giles Roditi<sup>1,4</sup> , Michael Adamson<sup>5</sup>, David Young<sup>6</sup>, Ross Dolan<sup>7</sup>, Colin Church<sup>8</sup>, Adrian Brady<sup>9</sup> , Campbell Tait<sup>10</sup>, Graham McKenzie<sup>5</sup>, Alasdair McFadyen<sup>5</sup>, Matthew Zelic<sup>5</sup> , Donogh Maguire<sup>5</sup> 

**1** Department of Radiology, NHS Greater Glasgow & Clyde, Glasgow, United Kingdom, **2** Department of Surgery, University Hospital Hairmyres, South Lanarkshire, Scotland, United Kingdom, **3** Department of Orthopaedic Surgery, Glasgow Royal infirmary, Scotland, United Kingdom, **4** Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom, **5** Emergency Medicine Department, Glasgow Royal Infirmary, Scotland, United Kingdom, **6** Department of Mathematics and Statistics, University of Strathclyde, Glasgow, Scotland, United Kingdom, **7** Academic Unit of Surgery, School of Medicine, University of Glasgow, Glasgow, Scotland, United Kingdom, **8** Department of Respiratory Medicine, Queen Elizabeth University Hospital, Scotland, United Kingdom, **9** Department of Cardiology, Glasgow Royal infirmary, Scotland, United Kingdom, **10** Department of Haematology, Glasgow Royal infirmary, Scotland, United Kingdom

 These authors contributed equally to this work.

\* [Gordon.cooper@lanarkshire.scot.nhs.uk](mailto:Gordon.cooper@lanarkshire.scot.nhs.uk)



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**Citation:** Norton L, Cooper G, Sheerins O, Mac a' Bháird K, Roditi G, Adamson M, et al. (2021) Clinical and radiological characteristics of acute pulmonary embolus in relation to 28-day and 6-month mortality. PLoS ONE 16(12): e0258843. <https://doi.org/10.1371/journal.pone.0258843>

**Editor:** Wen-Chi Chou, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, TAIWAN

**Received:** June 11, 2021

**Accepted:** October 7, 2021

**Published:** December 28, 2021

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**Data Availability Statement:** All data files are available from <https://www.ebi.ac.uk/biostudies/studies/S-BSS727?query=S-BSS727> (ebi.ac.uk, accession number S-BSS727).

**Funding:** The author(s) received no specific funding for this work.

**Competing interests:** The authors have declared that no competing interests exist.

## Abstract

### Background

Patients with acute pulmonary embolism (PE) exhibit a wide spectrum of clinical and laboratory features when presenting to hospital and pathophysiologic mechanisms differentiating low-risk and high-risk PE are poorly understood.

### Objectives

To investigate the prognostic value of clinical, laboratory and radiological information that is available within routine tests undertaken for patients with acute PE.

### Methods

Electronic patient records (EPR) of patients who underwent Computed Tomography Pulmonary Angiogram (CTPA) scan for the investigation of acute PE during 6-month period (01.01.2016–30.06.2016) were examined. Data was gathered from EPR for patients that met inclusion criteria and all CTPA scans were re-evaluated. Biochemical thresholds of low-grade and high-grade inflammation, serum CRP >10mg/L and >150mg/L and serum albumin concentrations <35g/L and <25 g/L, were combined in the Glasgow Prognostic Score (GPS) and peri-operative Glasgow Prognostic Score (poGPS) respectively. Neutrophil Lymphocyte ratio (NLR) was also calculated. Pulmonary Embolus Severity Index score was calculated.

## Results

Of the total CTPA reports ( $n = 2129$ ) examined, 245 patients were eligible for inclusion. Of these, 20 (8%) patients had died at 28-days and 43 (18%) at 6-months. Of the 197 non-cancer related presentations, 28-day and 6-month mortality were 3% and 8% respectively. Of the 48 cancer related presentations, 28-day and 6-month mortality were 29% and 58% respectively. On univariate analysis, age  $\geq 65$  years ( $p < 0.01$ ), PESI score  $\geq 100$  ( $p = < 0.001$ ), NLR  $\geq 3$  ( $p < 0.001$ ) and Coronary Artery Calcification (CAC) score  $\geq 6$  ( $p < 0.001$ ) were associated with higher 28-day and 6-month mortality. PESI score  $\geq 100$  (OR 5.2, 95% CI: 1.1, 24.2,  $P < 0.05$ ), poGPS  $\geq 1$  (OR 2.5, 95% CI: 1.2–5.0,  $P = 0.01$ ) and NLR  $\geq 3$  (OR 3.7, 95% CI: 1.0–3.4,  $P < 0.05$ ) remained independently associated with 28-day mortality. On multivariate binary logistic regression analysis of factors associated with 6-month mortality, PESI score  $\geq 100$  (OR 6.2, 95% CI: 2.3–17.0,  $p < 0.001$ ) and coronary artery calcification score  $\geq 6$  (OR 2.3, 95% CI: 1.1–4.8,  $p = 0.030$ ) remained independently associated with death at 6-months. When patients who had an underlying cancer diagnosis were excluded from the analysis only GPS  $\geq 1$  remained independently associated with 6-month mortality (OR 5.0, 95% CI 1.2–22.0,  $p < 0.05$ ).

## Conclusion

PESI score  $> 100$ , poGPS  $\geq 1$ , NLR  $\geq 3$  and CAC score  $\geq 6$  were associated with 28-day and 6-month mortality. PESI score  $\geq 100$ , poGPS  $\geq 1$  and NLR  $\geq 3$  remained independently associated with 28-day mortality. PESI score  $\geq 100$  and CAC score  $\geq 6$  remained independently associated with 6-month mortality. When patients with underlying cancer were excluded from the analysis, GPS  $\geq 1$  remained independently associated with 6-month mortality. The role of the systemic inflammatory response (SIR) in determining treatment and prognosis requires further study. Routine reporting of CAC scores in CTPA scans for acute PE may have a role in aiding clinical decision-making regarding treatment and prognosis.

## Introduction

The spectrum of presentation for patients with acute pulmonary embolism (PE) ranges from incidentally discovered asymptomatic emboli to massive life-threatening embolism [1]. The wide range of baseline physiology, laboratory profiles, radiological findings and clinical outcomes make the management of acute PE difficult to standardise as the pathophysiologic mechanisms differentiating low-risk and high-risk PE are poorly understood. Therefore, currently available risk-stratification scores may be insufficient to guide management for these patients. For example, some acute PE treatment decision pathways promote a reliance on sustained hypotension, whilst others include the finding of right heart strain on Computerised Tomography Pulmonary Angiography (CTPA) [2, 3]. Similarly, currently available treatment guidelines fail to provide a risk/benefit context (e.g. age stratification, underlying cancer diagnosis) to aid clinicians in deciding the most appropriate treatment strategy. Furthermore, information that is easily measured on CTPA, such as coronary artery calcification (CAC), has not routinely been reported or included in decision making algorithms for patients with acute pulmonary embolus. This is despite some existing evidence to suggest this may be associated with mortality independent of PE severity [4].

To the best of our knowledge, no scoring system for prediction of mortality in patients with acute PE has integrated objective measurements of clinical, laboratory and CTPA findings. The aim of the present study was to utilise all information commonly available to a hospital clinician in order to investigate whether significant associations exist between CTPA findings, haemodynamic parameters and laboratory data, and to place this data in the context of 28-day and 6-month mortality in patients diagnosed with an acute PE.

## Patients and methods

Radiological reports of all patients who underwent a CTPA scan for the investigation of PE in Greater Glasgow and Clyde, Scotland, between 1<sup>st</sup> January and 30<sup>th</sup> June 2016 were examined. Caldecott guardian approval was obtained in line with NHS policy.

Following removal of duplicates, a retrospective case-note review of patients who were identified to have had a CTPA confirmed diagnosis of PE was undertaken. Patients were excluded if they received a diagnosis of pneumonia or other intra-thoracic infectious process. Clinical, laboratory and radiological findings were recorded and compared to 28-day and 6-month mortality. Clinical data comprising: presenting complaint, physiological parameters (pulse, blood pressure, temperature, respiratory rate and oxygen saturations), medications and past medical history were recorded from the admission. Laboratory data, which comprised of full blood count (FBC), D-dimer and biochemical assays (including highly sensitive troponin (hsTnI)) were also documented along with biochemical markers of high- and low-grade inflammation (serum C-reactive protein (CRP) and albumin concentrations). Biochemical thresholds that reflect low-grade inflammation, serum CRP >10mg/L and low serum albumin concentrations <35 g/L, were combined in the Glasgow Prognostic Score (GPS) (Table 1) [5]. Biochemical thresholds of high-grade inflammation, serum CRP >150mg/L and low serum albumin concentrations <25 g/L, were combined in the peri-operative Glasgow Prognostic Score (po-GPS) (Table 2) [6]. Neutrophil Lymphocyte Ratio (NLR) was also calculated (Table 3) [7]. NLR is calculated by dividing neutrophil count by lymphocyte count in a full blood count (FBC) sample result [8]. NLR score  $\geq 3$  and NLR  $\geq 5$  are indicative of moderately severe and severe inflammation respectively [9, 10].

Pulmonary Embolism Severity Index (PESI) was also calculated [11] (Table 4). PESI score was not calculated if one or more components of the PESI score were not available e.g. contemporaneous measurement of a physiological parameter.

All positive CTPA scans were re-reported by a specialist-registered radiologist who was blinded to the physiological data and clinical outcome. Scans were re-scored for right heart strain, obstruction index and coronary artery calcification. Radiological parameters measured included right ventricular: left ventricular ratio (transverse diameter  $\geq 1.5$ cm, and 4-chamber desktop reformat), superior vena cava (SVC) area (mm<sup>2</sup>), pulmonary artery (PA) trunk

**Table 1. Glasgow Prognostic Score (GPS)\*.**

| Glasgow Prognostic Score (oGPS) | Score |
|---------------------------------|-------|
| <b>C-reactive protein</b>       |       |
| $\leq 10$ mg/L                  | 0     |
| $> 10$ mg/L                     | 1     |
| <b>Albumin</b>                  |       |
| $\geq 35$ g/L                   | 0     |
| $< 35$ g/L                      | 1     |

\*note measure of SIRS severity from GPS score, 0 = nil, 1 = mild, 2 = moderate.

<https://doi.org/10.1371/journal.pone.0258843.t001>

**Table 2. Combined biochemical markers of high-grade inflammation in the peri-operative Glasgow Prognostic Score (poGPS).**

| peri-operative Glasgow Prognostic Score (poGPS)             | Score | SIRS Severity |
|---|-------|---------------|
| C-reactive protein $\leq$ 150mg/l and Albumin $\geq$ 25 g/l | 0     | Mild          |
| C-reactive protein $>$ 150mg/l and Albumin $\geq$ 25 g/l    | 1     | Moderate      |
| C-reactive protein $\leq$ 150mg/l and Albumin $<$ 25 g/l    | 1     | Moderate      |
| C-reactive protein $>$ 150mg/l and Albumin $<$ 25 g/l       | 2     | Severe        |

<https://doi.org/10.1371/journal.pone.0258843.t002>

diameter (mm), PA trunk area (mm<sup>2</sup>), azygous vein diameter (mm), inferior vena cava (IVC) reflux, and bowing of interventricular septum. Clot burden/obstruction index was assessed using Qanadli score [12]. Coronary artery calcification (CAC) score was assessed using Weston scoring system [13]. Inter-observer variation was controlled by a second re-reporting of a random selection of scans by another specialist registered radiologist who was also blinded to the previous radiological scores, physiological data and clinical outcomes.

CAC scores reported in the present study were performed retrospectively as CAC scoring was not routinely reported contemporaneously at the time of patient inclusion in the present sample. Therefore, CAC scores did not influence subsequent clinical management (coronary artery angiography, stenting or prescription of secondary prevention medication) for patients in the current study sample.

Treatments were categorised into: no treatment administered; low molecular weight heparin (LMWH) alone; thrombolysis; interventional radiology (embolectomy); direct oral anticoagulation (DOAC) (apixaban or rivaroxaban), and warfarin (with LMWH pre-treatment).

### Statistical analysis

Data was analysed in relation to 28-day and 6-month mortality using Chi-squared and Mann-Whitney U test. Binary logistic regression analysis was performed for variables that achieved  $p < 0.1$  on univariate analysis. Calculation of non-parametric bivariate correlations were conducted using Spearman's rank correlation to calculate the correlation coefficient Rho ( $r_s$ ). When taken at  $p < 0.05$ ,  $r_s$  values 0.00–0.100; 0.100–0.39; 0.40–0.69; 0.70–0.89 and 0.90–1.0 indicate negligible, weak, moderately strong, strong and very strong to perfect monotonic relationships respectively between variables [14]. All data was analysed using SPSS version 27.

### Results

A total of 245 positive PE reports were identified from a total of 2,129 CTPA reports. The majority of patients were female (52%) and older than 65 years old (63%). Of note, 20% of patients had a diagnosis of active cancer. Of 245 patients in the sample, 20 (8%) patients had died at 28-days and 43 (18%) had died at 6-months following CTPA. Of the 197 non-cancer related presentations (102 women (52%)), the overall 28-day and 6-month mortality were 3% and 8% respectively.

**Table 3. Calculation of the Neutrophil Lymphocyte Ratio (NLR).**

| Neutrophil Lymphocyte Ratio (NLR): | Ratio | SIRS Severity |
|------------------------------------|-------|---------------|
| Neutrophil count: lymphocyte count | $<$ 3 | Mild          |
| Neutrophil count: lymphocyte count | 3–5   | Moderate      |
| Neutrophil count: lymphocyte count | $>$ 5 | Severe        |

<https://doi.org/10.1371/journal.pone.0258843.t003>

Table 4. PESI scoring system.

| Variable                             |             | Score |
|--------------------------------------|-------------|-------|
| Age (years)*                         | (years = x) | + x   |
| Sex                                  | Male        | +10   |
|                                      | Female      | —     |
| Temperature <36°C/96.8°F             | Yes         | +20   |
|                                      | No          | —     |
| Systolic Blood Pressure <100mmHg     | Yes         | +30   |
|                                      | No          | —     |
| Heart Rate >110bpm                   | Yes         | +20   |
|                                      | No          | —     |
| Respiratory Rate >30bpm              | Yes         | +20   |
|                                      | No          | —     |
| Oxygen Saturation <90%               | Yes         | +20   |
|                                      | No          | —     |
| History of Chronic Pulmonary Disease | Yes         | +10   |
|                                      | No          | —     |
| History of Heart Failure             | Yes         | +10   |
|                                      | No          | —     |
| Altered Mental Status                | Yes         | +60   |
|                                      | No          | —     |
| Malignancy                           | Yes         | +30   |
|                                      | No          | —     |

<https://doi.org/10.1371/journal.pone.0258843.t004>

PESI score was not calculated for 6 patients (2.5%) as contemporaneous measurements of one or more physiological components of the PESI score were not available. In the present study, PESI score  $\geq 100$  ( $n = 239$ ) was associated with CTPA calcium score  $\geq 6$  and IVC reflux (both  $p < 0.001$ ), however PESI score  $\geq 100$  was not associated with bowing of the interventricular septum or right-to-left ventricular ratio  $\geq 1$  (RV: LV  $\geq 1$ ).

Chest pain (40%), shortness of breath (43%) and syncope (5%) were the most common presenting complaints. No association between presenting complaint and final outcome was found, however chest pain and shortness of breath were associated with a PESI score  $\geq 100$  ( $p < 0.001$ ) and a NLR ratio  $\geq 3$  ( $p < 0.05$ ).

There was no evidence of an association between D-dimer categories and mortality (Tables 4–7), however D-dimer concentrations were associated with obstruction index  $\geq 20$  ( $p < 0.001$ ).

Sex specific thresholds of high sensitivity troponin indicating myocardial injury (hsTnI  $> 16$  or  $> 34$  ng/L for female and male respectively) [15, 16] were associated with bowing of the inter-ventricular septum on CTPA ( $p = 0.001$ ). High sensitivity troponin (hsTnI) values  $> 5$  ng/L correlated with PESI score ( $r_s = 0.407$ ;  $p < 0.001$ ;  $n = 138$ ), D-dimer concentrations ( $r_s = 0.452$ ;  $p < 0.001$ ;  $n = 129$ ), higher obstruction index ( $r_s = 0.411$ ;  $p < 0.001$ ;  $n = 140$ ), bowing of the interventricular septum ( $r_s = 0.283$ ;  $p < 0.001$ ;  $n = 140$ ) and coronary artery calcification score ( $r_s = 0.269$ ;  $p < 0.001$ ;  $n = 140$ ).

On non-parametric univariate analysis of continuous data (Mann Whitney U test), initial SaO<sub>2</sub> ( $p < 0.01$ ), PESI score ( $p < 0.001$ ), NLR ( $p < 0.001$ ), CRP ( $p = 0.001$ ) and albumin ( $p < 0.001$ ) were associated with higher 28-day mortality (Table 5). On Chi-squared analysis, PESI score  $\geq 100$  ( $p < 0.001$ ) and NLR  $\geq 3$  ( $p < 0.001$ ) were associated with higher 28-day mortality. Biochemical thresholds of high-grade inflammation, serum CRP  $> 150$  mg/L and low

Table 5. The relationship between baseline characteristics and all cause 28-day mortality in patients with acute pulmonary embolus (n = 245).

|   | Alive (n = 225) | Dead (n = 20)    | P-value <sup>1</sup> | O.R. | Limits   | P-value <sup>2</sup> |
|---|-----------------|------------------|----------------------|------|----------|----------------------|
| Sex (male/female)                             | 108/117         | 9/11             | 0.797                |      |          |                      |
| Age (years)                                   | 69 (55–77)      | 73 (62–81)       | 0.156                |      |          |                      |
| Age (< 65/ ≥ 65 years)                        | 85/140          | 5/15             | 0.257                |      |          |                      |
| <b>Clinical</b>                               |                 |                  |                      |      |          |                      |
| Pulse (bpm)                                   | 95 (80–110)     | 97 (84–126)      | 0.391                |      |          |                      |
| Pulse (</ ≥ 110 bpm)                          | 166/55          | 14/6             | 0.615                |      |          |                      |
| Systolic BP (mmHg)                            | 120 (105–139)   | 115 (92–126)     | 0.069                |      |          |                      |
| Systolic BP (≥/ < 110 mmHg)                   | 151/69          | 12/7             | 0.623                |      |          |                      |
| Diastolic BP (mmHg)                           | 76 (66–88)      | 51 (44–78)       | 0.263                |      |          |                      |
| Diastolic BP (≥/ < 65 mmHg)                   | 169/51          | 12/7             | 0.184                |      |          |                      |
| Mean Arterial pressure (mmHg)                 | 94 (84–107)     | 88 (74–97)       | 0.098                |      |          |                      |
| Mean Arterial pressure (≥/ < 80 mmHg)         | 181/39          | 13/6             | 0.139                |      |          |                      |
| Respiratory rate (min <sup>-1</sup> )         | 18 (16–22)      | 19 (17–22)       | 0.765                |      |          |                      |
| Respiratory rate (</ ≥ 30 min <sup>-1</sup> ) | 209/14          | 18/2             | 0.512                |      |          |                      |
| SaO <sub>2</sub> (%)                          | 96 (93–98)      | 93 (89–96)       | 0.008                |      |          |                      |
| SaO <sub>2</sub> (≥ 94% / < 94%)              | 162/63          | 9/11             | 0.012                |      |          |                      |
| Temperature (°C)                              | 36.5 (36.1–37)  | 36.3 (35.7–36.8) | 0.199                |      |          |                      |
| Temperature (≥/ < 36°C)                       | 185/36          | 13/7             | 0.037                |      |          |                      |
| Consciousness (A/V/P/U)                       | 217/6/1/1       | 18/0/0/2         | 0.005                |      |          |                      |
| Active cancer (yes/no)                        | 34/191          | 14/6             | <0.001               |      |          |                      |
| Heart failure (yes/no)                        | 22/203          | 4/16             | 0.156                |      |          |                      |
| Chronic lung disease (yes/no)                 | 55/168          | 8/12             | 0.135                |      |          |                      |
| PESI  | 98 (78–126)     | 132 (118–153)    | <0.001               |      |          |                      |
| PESI (<100/ ≥ 100)                            | 109/111         | 2/17             | <0.001               | 5.2  | 1.1–24.2 | 0.036                |
| Treatment 0–5                                 | 2/104/4/1/110/4 | 1/16/0/1/2/0     | 0.001                |      |          |                      |
| <b>Laboratory</b>                             |                 |                  |                      |      |          |                      |
| CRP (mg/L)                                    | 34 (15–82)      | 84 (66–237)      | 0.001                |      |          |                      |
| CRP (<10/10–80/ >80 - <150 / ≥150 mg/L)       | 27/132/30/25    | 1/9/4/6          | 0.011                |      |          |                      |
| Albumin (g/L)                                 | 33 (28–37)      | 27 (21–29)       | <0.001               |      |          |                      |
| Albumin (≥35/ 25 - <35/ <25 g/L)              | 90/116/16       | 0/11/9           | <0.001               |      |          |                      |
| GPS (0/1/2)                                   | 18/73/119       | 0/1/19           | 0.002                |      |          |                      |
| poGPS (0/1/2)                                 | 176/30/6        | 9/6/5            | <0.001               | 2.5  | 1.2–5.0  | 0.010                |
| Haemoglobin (g/L)                             | 131 (114–144)   | 116 (105–127)    | 0.027                |      |          |                      |
| Neutrophils (x10 <sup>9</sup> /L)             | 6.4 (5.1–9.0)   | 11.3 (7.6–14.1)  | <0.001               |      |          |                      |
| Neutrophils (</ ≥ 7.5 x 10 <sup>9</sup> /L)   | 136/87          | 5/15             | 0.002                |      |          |                      |
| Lymphocytes (1.1–5.0 x 10 <sup>9</sup> /L)    | 1.5 (1.0–2.1)   | 0.95 (0.7–1.6)   | 0.014                |      |          |                      |
| Lymphocytes (≥/ < 1.1 x 10 <sup>9</sup> /L)   | 168/56          | 8/12             | 0.001                |      |          |                      |
| NLR   | 4.6 (2.8–7.2)   | 9.2 (7.0–19.8)   | <0.001               |      |          |                      |
| NLR (<3 / ≥3 - <5 / ≥5)                       | 68/52/103       | 0/2/18           | <0.001               | 3.7  | 1.0–3.4  | 0.043                |
| NLR (</ ≥4)                                   | 121/103         | 2/18             | <0.001               |      |          |                      |
| D-dimer (ng/dL)                               | 1417 (667–3187) | 1921 (1167–2937) | 0.399                |      |          |                      |
| D-dimer < 230 / ≥ 230 ng/dL                   | 3/190           | 0/8              | 0.723                |      |          |                      |
| High sensitivity Troponin (ng/L)*             | 20.5 (4–115)    | 10.5 (5.0–50)    | 0.561                |      |          |                      |
| hsTnI (≤5/ 5–16 or 34 / >16 or 34 ng/dL)*     | 43/33/58        | 1/4/1            | 0.753                |      |          |                      |
| <b>Radiological</b>                           |                 |                  |                      |      |          |                      |
| Obstruction count                             | 11 (4–19)       | 7.5 (2.0–12.0)   | 0.035                |      |          |                      |
| Obstruction index                             | 28 (10–46)      | 18.7 (5.0–30)    | 0.042                |      |          |                      |

(Continued)

Table 5. (Continued)

|  | Alive (n = 225) | Dead (n = 20) | P-value <sup>1</sup> | O.R. | Limits | P-value <sup>2</sup> |
|--|-----------------|---------------|----------------------|------|--------|----------------------|
| Qanadli Score < / ≥ 20                                     | 95/128          | 10/10         | 0.523                |      |        |                      |
| 4 chamber RV:LV < / ≥ 1.0                                  | 125/100         | 11/9          | 0.962                |      |        |                      |
| Bowing of Inter-ventricular septum (no bowing /flat/bowed) | 150/41/38       | 16/3/1        | 0.509                |      |        |                      |
| SVC area (mm <sup>2</sup> )                                | 276 (205–347)   | 277 (228–295) | 0.456                |      |        |                      |
| PA trunk area (mm <sup>2</sup> )                           | 643 (548–808)   | 620 (512–759) | 0.487                |      |        |                      |
| Azygous vein diameter                                      | 7.0 (6.0–8.0)   | 6.0 (5.0–7.0) | 0.290                |      |        |                      |
| IVC reflux (0–3)   | 135/42/23/25    | 12/4/2/2      | 0.919                |      |        |                      |
| Emphysema score (0–4)                                      | 155/34/20/15/1  | 11/2/1/6/0    | 0.017                |      |        |                      |
| Coronary calcification                                     | 3.0 (0–7.0)     | 7.5 (1.3–9.0) | 0.092                |      |        |                      |
| Coronary calcification (< / ≥ 6)                           | 147/77          | 8/12          | 0.023                | -    | -      | 0.475                |

\*MAP: mean arterial pressure

\*\* 0 = no treatment, 1 = Low molecular weight heparin, 2 = thrombolysis, 3 embolectomy, 4 apixaban/rivaroxaban 5. warfarin.

<https://doi.org/10.1371/journal.pone.0258843.t005>

serum albumin concentrations <25 g/L, combined in the poGPS (p<0.001) were associated with higher 28-day mortality (Table 5). Of the radiological measurements, emphysema score (p = 0.017) and coronary artery calcification score ≥6 (p = 0.023) were associated with higher 28-day mortality on Mann Whitney U test and Chi-squared test respectively (Table 5). On multivariate binary logistic regression analysis, PESI score ≥100 (OR 5.2, 95% CI: 1.1, 24.2, P <0.05), poGPS ≥1 (OR 2.5, 95% CI: 1.2–5.0, P = 0.01) and NLR ≥3 (OR 3.7, 95% CI: 1.0–3.4, P <0.05) remained independently associated with 28-day mortality (Table 5).

On univariate analysis, age ≥65 years (p = 0.007), diastolic BP <65 mmHg (p = 0.005), mean arterial pressure (MAP) <80 mmHg (p = 0.021), PESI score ≥100 (<0.001), albumin <35 g/L (p<0.001), poGPS>1 (p = 0.006), NLR ≥3 (p = 0.04) and CTPA coronary artery calcification score ≥6 (p<0.001) were associated with higher 6-month mortality (Table 6). On multivariate binary logistic regression analysis of factors associated with 6-month mortality, PESI score ≥100 (OR 6.2, 95% CI: 2.3–17.0, p<0.001) and coronary artery calcification score ≥6 (OR 2.3, 95% CI: 1.1–4.8, p = 0.030) remained independently associated with death at 6-months (Table 6); however, when multivariate analysis was conducted with active cancer status (and eligible components of PESI score) replacing PESI score, a stronger independent association was found between active cancer and 6-month mortality (OR 14.5, 95% CI 6.3–33.0, p<0.001).

### Cancer and mortality

48 (20%) of the total patient sample (n = 245) had a concurrent diagnosis of cancer; 14 (29%) and 28 (58%) of these patients had died at 28-days and 6-months respectively post PE-diagnosis. The Glasgow Prognostic Score (GPS) (CRP ≤10 = 0, >10 = 1; albumin ≥35 = 0, <35 = 1) is a validated mortality prediction score used in cancer patients (Table 1) [17]. When GPS was applied to the cancer group, 6-month mortality rates increased with increasing GPS (0 = 0%, 1 = 2%, 2 = 57%).

### Non-cancer mortality

When patients who had an underlying cancer diagnosis were excluded from the analysis, 6 (3%) and 15 (8%) patients died at 28-days and 6-months respectively. MAP<80mmHg

**Table 6. The relationship between baseline characteristics and all-cause 6-month mortality for patients with acute pulmonary embolus (n = 245).**

|  | Alive (n = 202)  | Dead (n = 43)   | P-value <sup>1</sup> | O.R. | Limits   | P-value <sup>2</sup> |
|--|------------------|-----------------|----------------------|------|----------|----------------------|
| Age (< 65/ ≥ 65 years)                                     | 82/120           | 8/35            | 0.007                |      |          |                      |
| Sex (male/female)  | 95/107           | 22/21           | 0.623                |      |          |                      |
| <b>Clinical</b>  |                  |                 |                      |      |          |                      |
| Pulse (< 100 / ≥ 100 bpm)                                  | 150/49           | 30/12           | 0.594                |      |          |                      |
| Systolic BP (≥/ < 110 mmHg)                                | 136/62           | 27/14           | 0.723                |      |          |                      |
| Diastolic BP (≥/ < 65 mmHg)                                | 157/41           | 24/17           | 0.005                |      |          |                      |
| MAP* (≥/ < 80mmHg)   | 166/32           | 28/13           | 0.021                |      |          |                      |
| Respiratory rate (</ ≥ 30 min <sup>-1</sup> )              | 188/13           | 39/3            | 0.873                |      |          |                      |
| SaO <sub>2</sub> (≥ 94% / < 94%)                           | 146/56           | 25/18           | 0.067                |      |          |                      |
| Temperature (≥/ < 36°C)                                    | 168/31           | 30/12           | 0.046                |      |          |                      |
| Consciousness (A/V/P/U)                                    | 196/4/1/1        | 39/2/0/2        | 0.028                |      |          |                      |
| Active cancer (yes/no)                                     | 20/182           | 28/15           | <0.001               |      |          |                      |
| Heart failure (yes/no)                                     | 18/184           | 8/35            | 0.061                |      |          |                      |
| Chronic lung disease (yes/no)                              | 44/156           | 19/24           | 0.003                |      |          |                      |
| PESI (<100/ ≥ 100)   | 105/93           | 6/35            | <0.001               | 6.2  | 2.3–17.0 | <0.001               |
| Treatment** 0–5  | 2/89/4/1/102/4   | 1/31/0/1/10/0   | <0.001               |      |          |                      |
| <b>Laboratory</b>  |                  |                 |                      |      |          |                      |
| CRP (ng/L)   | 42 (17–89)       | 67 (20–122)     | 0.023                |      |          |                      |
| CRP (<10/10–80/ >80 - <150 / ≥150 mg/L)                    | 25/116/27/24     | 3/25/7/7        | 0.243                |      |          |                      |
| Albumin (g/L)  | 33 (28–36)       | 27 (23–30)      | <0.001               |      |          |                      |
| Albumin (≥35 / 25 - <35/ <25 g/L)                          | 89/96/14         | 1/31/11         | <0.001               |      |          |                      |
| GPS (0/1/2)  | 18/71/99         | 0/3/39          | <0.001               |      |          |                      |
| poGPS (0/1/2)  | 157/27/6         | 28/9/5          | 0.006                | -    | -        | 0.141                |
| NLR (<3 / ≥3 - <5 / ≥5)                                    | 62/47/91         | 6/7/30          | 0.004                | -    | -        | 0.185                |
| Hb (g/L)   | 129 (113–144)    | 115 (106–133)   | 0.003                |      |          |                      |
| D-dimer (ng/dL)  | 1418 (660–3178)  | 1421 (932–3159) | 0.450                |      |          |                      |
| D-dimer < 230 / ≥ 230 ng/dL                                | 3/169            | 0/29            | 0.475                |      |          |                      |
| hsTnI (≤5/ 5–16 or 34 / >16 or 34 ng/dL)*                  | 40/26/55         | 4/11/4          | 0.556                |      |          |                      |
| <b>Radiological</b>  |                  |                 |                      |      |          |                      |
| Obstruction count  | 12 (4–19)        | 7 (2–14)        | 0.004                |      |          |                      |
| Obstruction index  | 30.0 (10.0–48.0) | 17.5 (5.0–35.0) | 0.006                |      |          |                      |
| Qanadli Score < / ≥ 20                                     | 82/119           | 23/19           | 0.097                |      |          |                      |
| 4 chamber RV:LV </ ≥1.0                                    | 110/92           | 26/17           | 0.472                |      |          |                      |
| Bowing of Inter-ventricular septum (no bowing /flat/bowed) | 134/35/33        | 32/6/5          | 0.427                |      |          |                      |
| SVC area (mm <sup>2</sup> )                                | 277 (208–351)    | 273 (213–319)   | 0.420                |      |          |                      |
| PA trunk area (mm <sup>2</sup> )                           | 636 (540–806)    | 667 (576–806)   | 0.731                |      |          |                      |
| Azygous vein diameter                                      | 7.0 (6.0–8.0)    | 6.0 (5.0–7.0)   | 0.247                |      |          |                      |
| IVC reflux (0–3)   | 125/35/21/21     | 22/11/4/6       | 0.335                |      |          |                      |
| Emphysema score (0–4)                                      | 144/27/16/14/1   | 22/9/5/7/0      | 0.014                |      |          |                      |
| Coronary calcification                                     | 2 (0–7)          | 6 (2–9)         | 0.001                |      |          |                      |
| Coronary calcification (</ ≥6) (all cases)                 | 94/32            | 16/18           | <0.001               | 2.3  | 1.1–4.8  | 0.030                |

\*MAP: mean arterial pressure

\*\* 0 = no treatment, 1 = Low molecular weight heparin, 2 = thrombolysis, 3 embolectomy, 4 apixaban/rivaroxaban, 5. warfarin.

<https://doi.org/10.1371/journal.pone.0258843.t006>

( $p < 0.01$ ), past medical history of heart failure ( $p < 0.05$ ), PESI score ( $p < 0.05$ ), poGPS  $\geq 1$  ( $p < 0.05$ ), NLR  $\geq 3$  ( $p < 0.05$ ) remained significantly associated with increased 28-day mortality ( $p < 0.05$ ) (Table 7).



**Table 7. The relationship between baseline characteristics and all cause 28-day mortality in non-cancer patients with acute pulmonary embolus (n = 197).**

|   | Alive (n = 191) | Dead (n = 6)            | P-value <sup>1</sup> |
|---|-----------------|-------------------------|----------------------|
| Sex (male/female)                             | 92/99           | 3/3                     | 0.930                |
| Age (years)                                   | 68 (54–77)      | 71 (58–85)              | 0.485                |
| Age (< 65/ ≥ 65 years)                        | 75/116          | 2/4                     | 0.770                |
| <b>Clinical</b>                               |                 |                         |                      |
| Pulse (bpm)                                   | 94 (80–108)     | 85 (76–102)             | 0.402                |
| Pulse (</ ≥ 110 bpm)                          | 145/44          | 6/0                     | 0.180                |
| Systolic BP (mmHg)                            | 120 (105–139)   | 91 (84–121)             | 0.020                |
| Systolic BP (≥/ < 110 mmHg)                   | 129/59          | 2/4                     | 0.070                |
| Diastolic BP (mmHg)                           | 67 (55–75)      | 51 (44–60)              | 0.032                |
| Diastolic BP (≥/ < 65 mmHg)                   | 104/85          | 1/5                     | 0.064                |
| Mean Arterial pressure (mmHg)                 | 84 (74–96)      | 54 (68–80)              | 0.015                |
| Mean Arterial pressure (≥/ < 80 mmHg)         | 113/75          | 1/5                     | 0.034                |
| Respiratory rate (min <sup>-1</sup> )         | 18 (16–22)      | 17 (15–23)              | 0.396                |
| Respiratory rate (</ ≥ 30 min <sup>-1</sup> ) | 179/12          | 5/1                     | 0.314                |
| SaO <sub>2</sub> (%)                          | 96 (93–98)      | 91 (85–97)              | 0.138                |
| SaO <sub>2</sub> (≥ 94% / < 94%)              | 140/51          | 3/3                     | 0.209                |
| Temperature (°C)                              | 36.5 (36.1–37)  | 36.2 (35.4–36.9)        | 0.227                |
| Temperature (≥/ < 36°C)                       | 161/28          | 4/2                     | 0.217                |
| Consciousness (A/V/P/U)                       | 186/3/1/1       | 5/0/0/1                 | 0.002                |
| Heart failure (yes/no)                        | 16/175          | 3/3                     | 0.001                |
| Chronic lung disease (yes/no)                 | 146/43          | 3/3                     | 0.123                |
| PESI  | 96 (75–116)     | 127 (99–171)            | 0.027                |
| PESI (<100/ ≥ 100)                            | 107/81          | 1/5                     | 0.051                |
| Treatment 0–5                                 | 2/76/3/1/105/4  | 1/4/0/0/1/0             | 0.025                |
| <b>Laboratory</b>                             |                 |                         |                      |
| CRP (mg/L)                                    | 29 (14–83)      | 133 (51–278)            | 0.050                |
| CRP (<10/10–80/ >80 - <150 / ≥150 mg/L)       | 25/109/24/22    | 1/1/1/3                 | 0.040                |
| Albumin (g/L)                                 | 34 (29–37)      | 28 (26–29)              | 0.007                |
| Albumin (≥35/ 25 - <35/ <25 g/L)              | 86/88/14        | 0/5/1                   | 0.034                |
| GPS (0/1/2)                                   | 17/69/91        | 0/1/5                   | 0.129                |
| poGPS (0/1/2)                                 | 147/25/6        | 3/2/1                   | 0.027                |
| Haemoglobin (g/L)                             | 132 (116–145)   | 118 (105–152)           | 0.504                |
| Neutrophils (x10 <sup>9</sup> /L)             | 6.4 (5.0–8.9)   | 8.9 (8.0–11.6)          | 0.024                |
| Neutrophils (</ ≥ 7.5 x 10 <sup>9</sup> /L)   | 117/72          | 1/5                     | 0.026                |
| Lymphocytes (1.1–5.0 x 10 <sup>9</sup> /L)    | 1.5 (1.1–2.1)   | 0.9 (0.8–2.0)           | 0.166                |
| Lymphocytes (≥/ < 1.1 x 10 <sup>9</sup> /L)   | 150/40          | 2/4                     | 0.009                |
| NLR   | 4.3 (2.5–6.9)   | 8.9 (5.2–13.0)          | 0.027                |
| NLR (<3 / ≥3 - <5 / ≥5)                       | 61/47/81        | 0/1/5                   | 0.042                |
| D-dimer (ng/dL)                               | 1418 (667–3187) | 1108 (918) <sup>^</sup> | 0.745                |
| D-dimer < 230 / ≥ 230 ng/dL                   | 2/165           | 0/3                     | 0.849                |
| High sensitivity Troponin (ng/L)*             | 23 (4–126)      | 6 (2) <sup>^</sup>      | 0.237                |

\*MAP: mean arterial pressure

\*\* 0 = no treatment, 1 = Low molecular weight heparin, 2 = thrombolysis, 3 embolectomy, 4 apixaban/rivaroxaban, 5. warfarin.

<https://doi.org/10.1371/journal.pone.0258843.t007>

When patients who had an underlying cancer diagnosis were excluded from the analysis, diastolic BP <65mmHg, MAP<80mmHg (both  $p<0.01$ ), past medical history of heart failure ( $p<0.05$ ), past medical history of chronic lung disease ( $p<0.05$ ), PESI score ( $p<0.05$ ), GPS $\geq 1$  ( $p<0.05$ ) and NLR $\geq 3$  ( $p<0.05$ ) remained significantly associated with 6-month mortality. On binary logistic regression analysis, only GPS $\geq 1$  remained independently associated with 6-month mortality (OR 5.0, 95% CI 1.2–22.0,  $p<0.05$ ) (Table 8).

## Treatment

Overall, only 4 patients (1.6%) received thrombolysis and 2 (0.8%) underwent interventional radiology treatment (embolectomy). Almost half of the patients (49%) in the present sample received treatment with low molecular weight heparin (LMWH) (dalteparin) and 46% received Direct Oral Anticoagulation (DOAC) medication (apixaban/rivaroxaban). When treatment with LMWH alone was compared against all other treatments using Chi-squared analysis, treatment with LMWH alone was associated with increased 28-day ( $p = 0.004$ ) and 6-month mortality ( $p = 0.001$ ). However, when patients with an underlying diagnosis of cancer were removed from the analysis, no association was found between treatment category and 28-day ( $p = 0.188$ ) or 6-month mortality ( $p = 0.298$ ).

Only 9 (10%) of the 89 patients who had CAC score  $\geq 6$  in the present study underwent Coronary Artery Angiography during the 6 months following diagnosis of acute PE.

## Discussion

The percentage of positive scans (11.5%) in this study sample is consistent with that reported in other studies [18] and mortality figures are consistent with the prospective validation of the PESI score reported by Donzé *et al.* [11].

In the present study, patients with a PESI score  $\geq 100$  were more than 5 times more likely to die before 28-days. PESI score was also associated with CTPA coronary artery calcium score  $\geq 6$  and 6-month mortality.

Right ventricular ischemia has been proposed as a mechanism for RV dysfunction in acute pulmonary embolism [19, 20]. It is therefore of interest that coronary artery calcification score  $\geq 6$  was associated with increased mortality at 6-months in patients with acute PE in the present study. These results may reflect a reduced capacity of under-perfused myocardium to respond to increased right ventricular afterload following PE.

Coronary artery calcification is a frequent incidental finding on CTPA, however radiologists infrequently report CTPA coronary artery calcification score when reporting scans performed for the investigation of suspected PE [4, 21]. Williams *et al.* have recently reported that the presence of coronary artery calcification identified on CTPA is a more important predictor of all-cause 3-year mortality than the severity of PE [21]. In their cohort, patients with severe calcification were reported to be almost five-times more likely to die at 3-years when compared to patients without coronary artery calcification [21]. To the best of our knowledge, the results of the present study are the first to report an association between coronary artery calcification and 28-day and 6-month mortality in patients with acute PE. Moreover, coronary artery calcification remained independently associated with 6-month mortality in patients with acute PE. Patients with CAC $\geq 6$  were more than two times more likely to die at six months than patients with CAC<6. Therefore, the results of the present study may suggest that routine reporting of coronary artery calcification (CAC) score should be considered for patients undergoing CTPA investigation of suspected PE (Figs 1–3).

The correlation of high sensitivity troponin (hsTnI) concentrations >5ng/L with PESI score  $\geq 100$ , D-dimer concentrations >230 ng/L, higher obstruction index and bowing of the

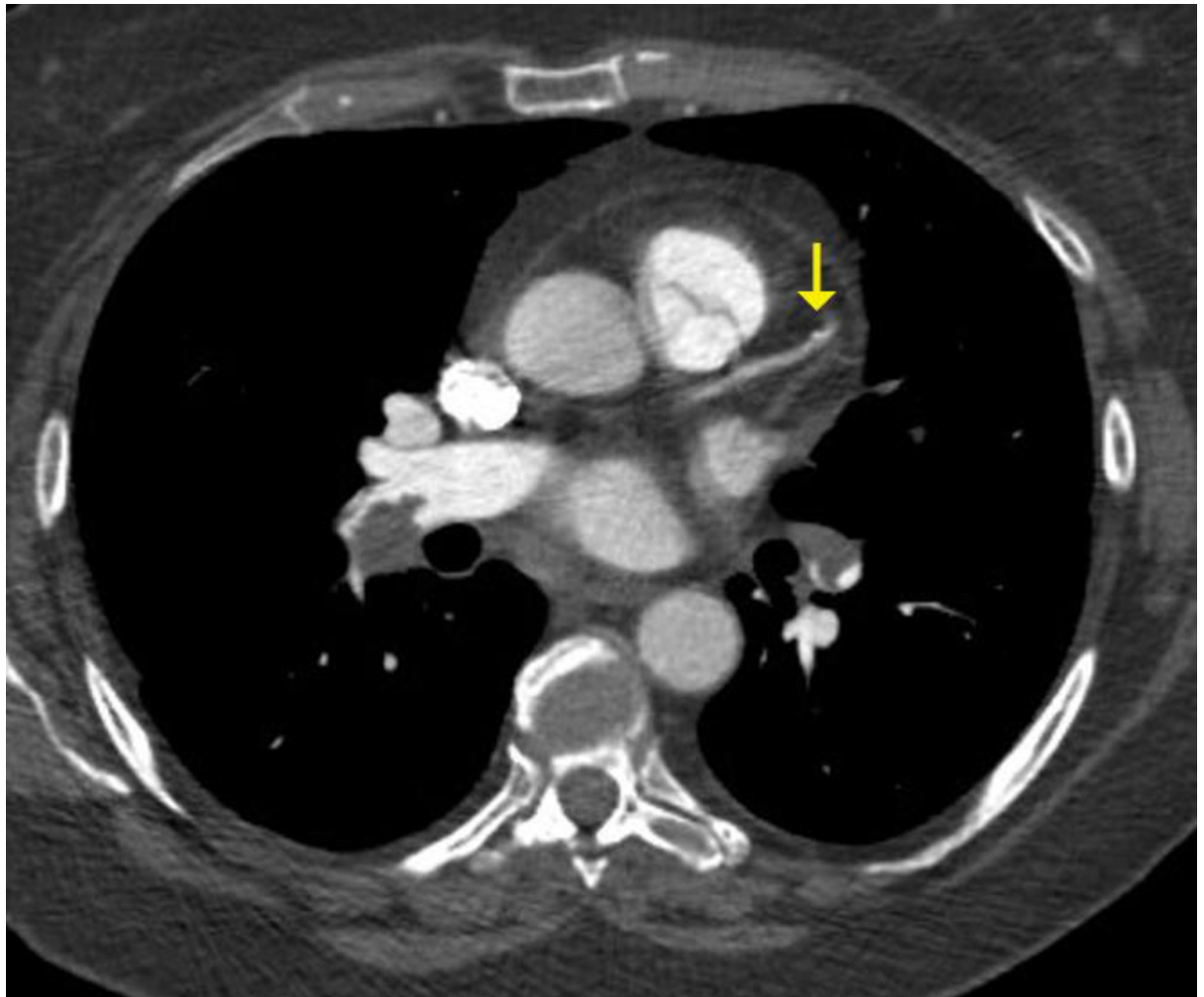
**Table 8. The relationship between baseline characteristics and all cause 6-month mortality in non-cancer patients with acute pulmonary embolus (n = 197).**

|  | Alive (n = 182)  | Dead (n = 15)   | P-value <sup>1</sup> | O.R. | Limits   | P-value <sup>2</sup> |
|--|------------------|-----------------|----------------------|------|----------|----------------------|
| Age (years)  | 68 (54–76)       | 75 (67–85)      | 0.034                |      |          |                      |
| Age (< 65/ ≥ 65 years)                                     | 74/108           | 3/12            | 0.116                |      |          |                      |
| Sex (male/female)  | 89/93            | 6/9             | 0.508                |      |          |                      |
| <b>Clinical</b>  |                  |                 |                      |      |          |                      |
| Pulse (< 100 / ≥ 100 bpm)                                  | 139/41           | 12/3            | 0.805                |      |          |                      |
| Systolic BP (≥/ < 110 mmHg)                                | 124/55           | 7/8             | 0.073                |      |          |                      |
| Diastolic BP (≥/ < 65 mmHg)                                | 102/78           | 3/12            | 0.006                |      |          |                      |
| MAP* (≥/ < 80mmHg)   | 110/69           | 4/11            | 0.009                |      |          |                      |
| Respiratory rate (</ ≥ 30 min <sup>-1</sup> )              | 171/11           | 13/2            | 0.276                |      |          |                      |
| SaO <sub>2</sub> (≥ 94% / < 94%)                           | 133/49           | 10/5            | 0.594                |      |          |                      |
| Temperature (≥/ < 36°C)                                    | 152/28           | 13/2            | 0.819                |      |          |                      |
| Consciousness (A/V/P/U)                                    | 177/3/1/1        | 14/0/0/1        | 0.100                |      |          |                      |
| Heart failure (yes/no)                                     | 15/167           | 4/11            | 0.020                |      |          |                      |
| Chronic lung disease (yes/no)                              | 39/141           | 7/8             | 0.029                |      |          |                      |
| PESI   | 92 (73–116)      | 115 (96–138)    | 0.021                |      |          |                      |
| PESI (<100/ ≥ 100)   | 103/76           | 5/10            | 0.071                | -    | -        | 0.224                |
| Treatment** 0–5  | 2/72/3/1/100/4   | 1/8/0/0/6/0     | 0.130                |      |          |                      |
| <b>Laboratory</b>  |                  |                 |                      |      |          |                      |
| CRP (<10/10–80/ >80 - <150 / ≥150 mg/L)                    | 24/104/20/24     | 2/6/3/3         | 0.318                |      |          |                      |
| Albumin (≥35 / 25 - <35/ <25 g/L)                          | 85/81/13         | 1/2/2           | 0.005                |      |          |                      |
| GPS (0/1/2)  | 17/68/84         | 0/2/12          | 0.012                | 5.0  | 1.2–22.0 | 0.030                |
| poGPS (0/1/2)  | 140/24/6         | 10/3/1          | 0.296                |      |          |                      |
| Neutrophils (x10 <sup>9</sup> /L)                          | 6.5 (5.0–8.9)    | 8.3 (5.7–10.1)  | 0.225                |      |          |                      |
| Neutrophils (</ ≥ 7.5 x 10 <sup>9</sup> /L)                | 111/69           | 7/8             | 0.255                |      |          |                      |
| Lymphocytes (1.1–5.0 x 10 <sup>9</sup> /L)                 | 1.5 (1.1–2.1)    | 1.1 (0.9–1.9)   | 0.046                |      |          |                      |
| Lymphocytes (≥/ <1.1 x 10 <sup>9</sup> /L)                 | 144/37           | 8/7             | 0.020                |      |          |                      |
| NLR  | 4.2 (2.6–6.9)    | 7.3 (3.6–10.0)  | 0.039                |      |          |                      |
| NLR (<3 / ≥3 - <5 / ≥5)                                    | 59/44/77         | 2/4/9           | 0.113                | -    | -        |                      |
| D-dimer (ng/dL)  | 1418 (665–3164)  | 1421 (932–3159) | 0.507                |      |          |                      |
| D-dimer < 230 / ≥ 230 ng/dL                                | 2/156            | 0/12            | 0.696                |      |          |                      |
| hsTnI (≤5/ 5–16 or 34 / >16 or 34 ng/dL)*                  | 34/26/48         | 3/4/3           | 0.648                |      |          |                      |
| <b>Radiological</b>  |                  |                 |                      |      |          |                      |
| Obstruction count  | 13 (5–19)        | 6 (4–14)        | 0.058                |      |          |                      |
| Obstruction index  | 33.5 (12.0–48.0) | 15 (10.0–35.0)  | 0.069                |      |          |                      |
| Qanadli Score < / ≥ 20                                     | 68/113           | 8/6             | 0.149                |      |          |                      |
| 4 chamber RV:LV</ ≥1.0                                     | 98/84            | 9/6             | 0.646                |      |          |                      |
| Bowing of Inter-ventricular septum (no bowing /flat/bowed) | 121/32/29        | 10/1/4          | 0.460                |      |          |                      |
| SVC area (mm <sup>2</sup> )                                | 277 (206–352)    | 282 (228–312)   | 0.865                |      |          |                      |
| PA trunk area (mm <sup>2</sup> )                           | 631 (535–802)    | 692 (584–828)   | 0.318                |      |          |                      |
| Azygous vein diameter                                      | 7.0 (6.0–8.0)    | 7.0 (5.0–7.0)   | 0.472                |      |          |                      |
| IVC reflux (0–3)   | 113/31/20/18     | 9/3/1/2         | 0.865                |      |          |                      |
| Emphysema score (0–4)                                      | 128/27/15/11/1   | 8/5/1/1/0       | 0.542                |      |          |                      |
| Coronary calcification                                     | 2 (0–7)          | 6 (2–11)        | 0.031                |      |          |                      |
| Coronary calcification (< / ≥ 6)                           | 126/55           | 7/8             | 0.068                | -    | -        | 0.059                |

\*MAP: mean arterial pressure

\*\* 0 = no treatment, 1 = Low molecular weight heparin, 2 = thrombolysis, 3 embolectomy, 4 apixaban/rivaroxaban, 5. warfarin.

<https://doi.org/10.1371/journal.pone.0258843.t008>

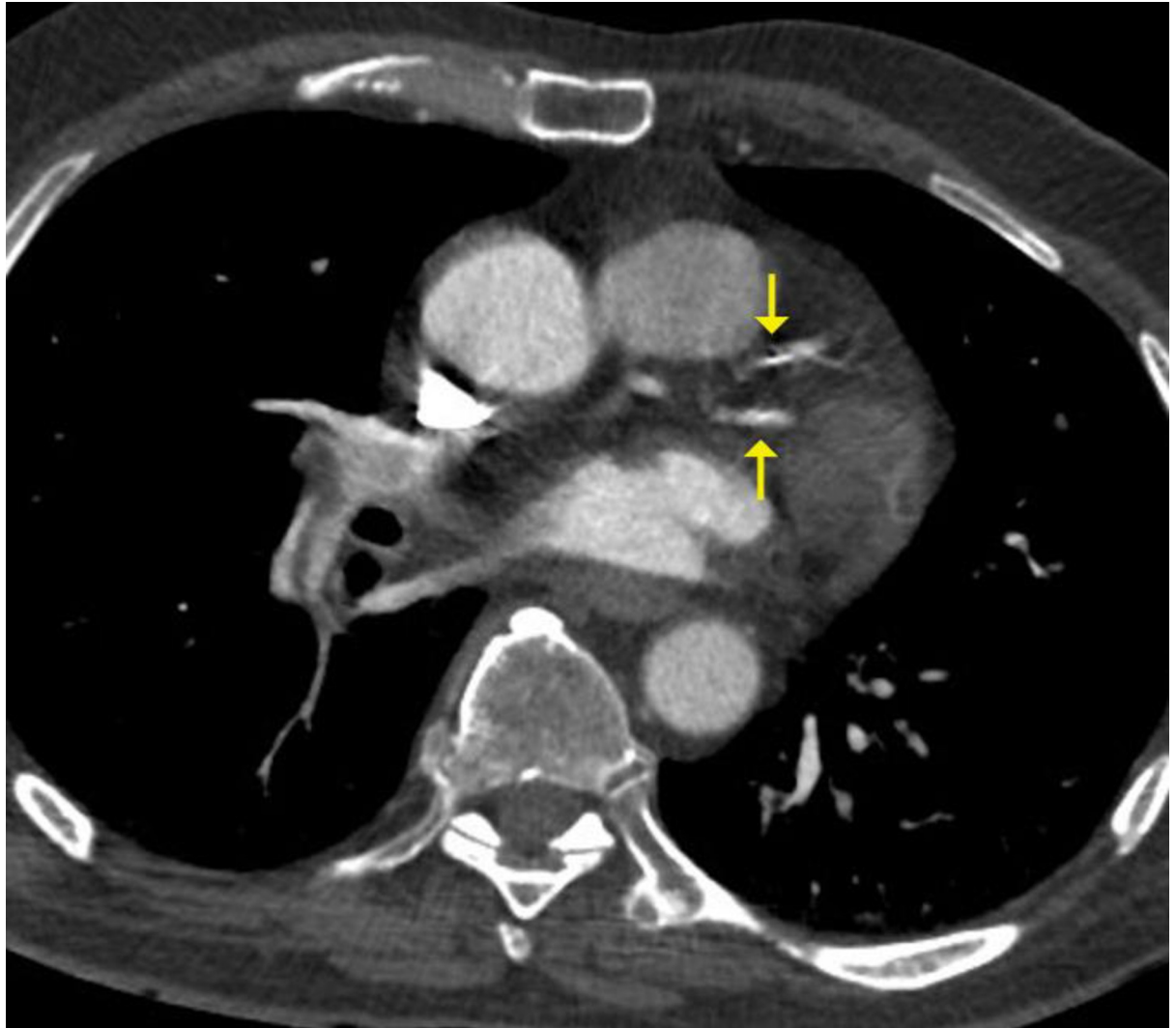


**Fig 1.** Low coronary artery calcium score—single tiny calcified plaque distal left anterior descending coronary artery (arrow).

<https://doi.org/10.1371/journal.pone.0258843.g001>

inter-ventricular septum, indicate that even relatively modest elevation of hsTnI concentrations (into the gender specific intermediate risk intervals [16]) may be of clinical significance in the context of PE.

The results of the present study also suggest that evaluation of the severity of the systemic inflammatory response (SIR) involved in acute pulmonary embolus may have a role in assessing prognosis and guiding clinical decision making [7]. There are a variety of methods that may be used to calculate systemic inflammation; however there is no robust evidence to suggest which score is superior in the context of acute PE. To the best of our knowledge, the results of the present study are the first to highlight the role of biochemical markers of low- and high-grade inflammation (serum C-reactive protein (CRP) and albumin concentrations). Biochemical thresholds that reflect low-grade inflammation, serum CRP >10mg/L and low serum albumin concentrations <35 g/L, combined in the Glasgow Prognostic Score (GPS) remained independently prognostic for patients without an underlying diagnosis of cancer at 6-months post diagnosis of acute PE. In this group, patients with  $\text{GPS} \geq 1$  were five times more likely to die at 6-months than patients with  $\text{GPS} = 0$  at time of diagnosis of acute PE. Similarly, biochemical thresholds of high-grade inflammation, serum CRP >150mg/L and low serum albumin concentrations <25 g/L, combined in the poGPS, remained independently associated



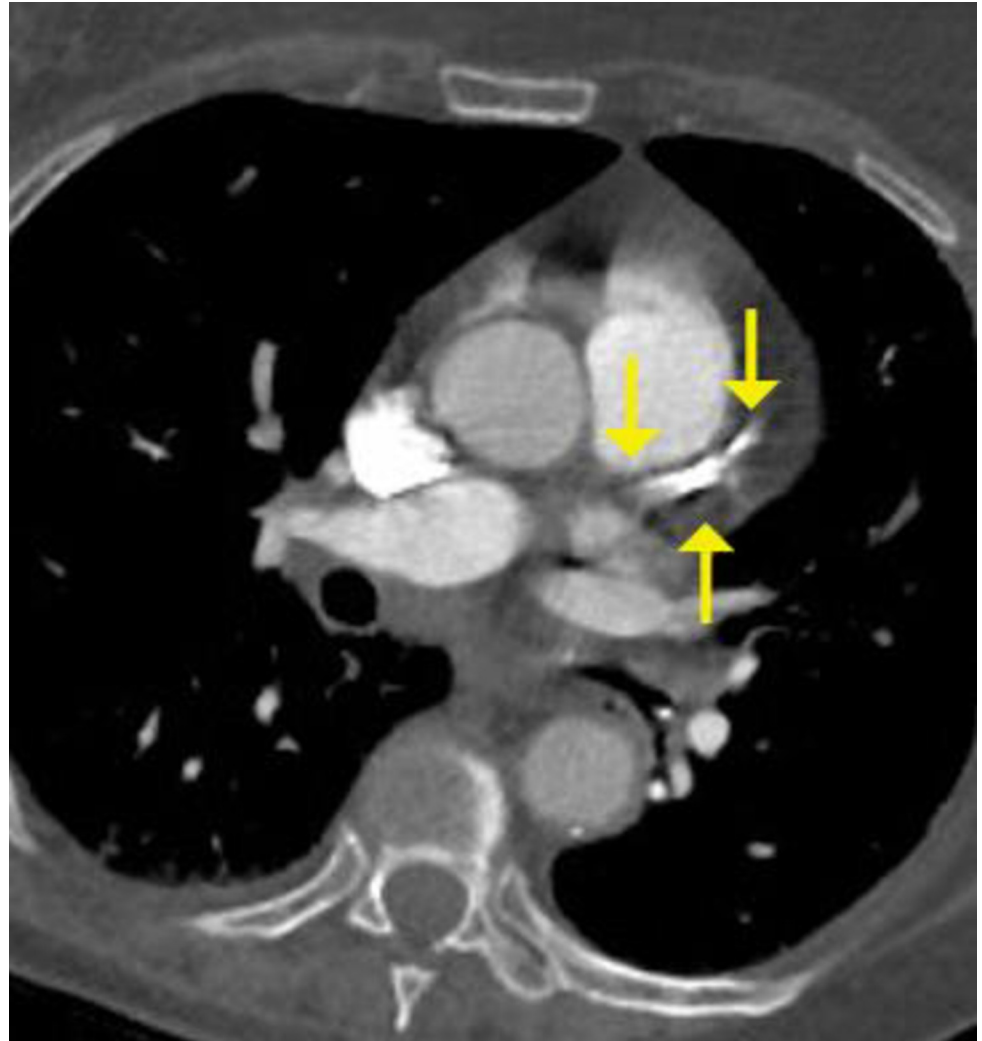
**Fig 2. Moderate coronary artery calcium score—calcified plaques in both left anterior descending and intermediate left coronary artery branches (arrows).**

<https://doi.org/10.1371/journal.pone.0258843.g002>

with higher 28-day mortality. In this group, patients with poGPS = 1 and poGPS = 2 were 2.5 and 5 times respectively more likely to die at 28-days than patients with poGPS = 0 at time of diagnosis of acute PE.

Neutrophil to Lymphocyte Ratio (NLR) is also a widely accepted measure of systemic inflammation that has been reported to have prognostic value in several clinical situations including pulmonary embolus [7]. NLR has been reported to be independently associated with short and medium term mortality in patients with PE [7, 8], and the results of the present study indicate that patients with a NLR  $\geq 3$  and  $\geq 5$  were almost 4 and 7.5 times respectively more likely to die before 28-days.

However, NLR is also a prognostic marker for numerous cancers [10, 22] and this raises the possibility of confounding within scoring systems that include active cancer diagnosis. For example, active cancer is heavily weighted in the PESI score. It is therefore of interest in the present study that NLR remained significantly associated with both 28-day and 6-month mortality when patients who had an underlying cancer were excluded from the analysis.



**Fig 3. High coronary artery calcium score—extensive and dense calcified plaque in left anterior descending coronary artery (arrows).**

<https://doi.org/10.1371/journal.pone.0258843.g003>

Similarly, high serum CRP and low serum albumin concentrations are prognostic markers for numerous cancers [23]. However, when patients who had an underlying cancer were excluded from the analysis and CRP and albumin were combined in the measure of high-grade inflammation, poGPS remained significantly associated with higher 28-day mortality. Moreover, when patients who had an underlying cancer were excluded from the analysis, and CRP and albumin were combined in the measure of low-grade inflammation, GPS remained independently associated with higher 6-month mortality.

Overall, these results may indicate that the systemic inflammatory response has a role in pathophysiological mechanisms that contribute to 28-day and 6-month mortality in patients with acute pulmonary embolus. Furthermore, the role of SIR in the context of acute PE is of greater interest when it is considered that clinical indicators that currently influence treatment decisions, such as systolic hypotension, RV:LV ratio  $\geq 1.0$ , or bowing of the inter-ventricular septum, have not been shown to have a significant association with 28-day or 6-month mortality in the present sample.

Right ventricular myocardial inflammatory response has been described in acute PE, however the role of inflammation in the transition from RV adaptation to RV failure remains incompletely understood [24]. Nonetheless, it is understood that multiple pro-inflammatory changes occur in the RV at a cellular level following acute PE (oxidative stress, apoptosis, infiltration of inflammatory cells, fibrosis, and metabolic reprogramming) [24, 25]. The resulting alteration in RV architecture is reported to result in a spectrum of change that ranges from loss of RV contractility to subsequent RV failure that may result in dysregulated coupling between the RV and the pulmonary circulation [24].

The association between biochemical (GPS and poGPS) and haematological (NLR) inflammatory scores and 28-day and 6-month mortality in the present study is consistent with this evidence base and raises the question of the role of potential anti-inflammatory treatment strategies to mitigate against short- and medium-term mortality following acute PE. Further work may be directed towards the integration of scores that quantify the haemopoietic and metabolic responses to the SIR in acute PE.

In the present study, treatment with LMWH alone was also associated with higher mortality, indicating that clinicians may be undertreating PE with thrombolysis and/or embolectomy. However, this association may be confounded by the fact that the recommended treatment for cancer patients with PE is primarily with LMWH (not DOAC or warfarin), hence explaining the higher mortality in the LMWH alone group. Nonetheless, the association between treatment with LMWH alone and higher 28-day and 6-month mortality may also be reflected in the clinical paradox that higher pulmonary artery obstruction index was associated with better survival at 28-days and 6-months in the present sample.

Given the high 28-day and 6-month mortality of patients who had PE in the context of underlying cancer, PE in these circumstances may represent a pre-terminal event. However, this group warrants further investigation regarding treatment strategies, as treatment of selected patients with PE within the more severe cancer group (GPS = 2) may confer a survival benefit and compliment oncological treatments. Prevention of acute PE in patients with an underlying cancer diagnosis by administration of novel oral anticoagulant (NOAC) or LMWH prophylaxis is gaining traction in the literature [26], and the findings of the present study support this rationale.

Following the results of the PIETHO study [27], clinicians may be reluctant to administer thrombolytic therapy to older patients (>65 years old) with or without an underlying diagnosis of active cancer. The PESI score is heavily weighted for both age and active cancer diagnosis. Therefore, while the PESI score is a useful tool for prediction of mortality, its use in guiding clinicians regarding treatment options for acute PE may be limited. In the future, a score to guide clinicians and patients regarding treatment options may therefore include markers of metabolic distress (e.g. plasma lactate concentrations), inflammation (e.g. poGPS, NLR), measures of physiological compromise (e.g. MAP < 80 mmHg; SaO<sub>2</sub> stratified for FiO<sub>2</sub>), biomarkers of myocardial injury (high sensitivity troponin and BNP), radiological evidence of right heart strain (bowing of the septum or RV: LV ratio  $\geq 1.0$ ) combined with measures of clot burden (e.g. Qanadli score) and coronary artery calcification score. Further, larger studies are required to establish the independent short- and medium-term prognostic value of these variables.

## Limitations

Plasma lactate concentrations are reported to be of prognostic significance in acute PE [28]. It is a limitation of the present study that plasma lactate concentrations were infrequently measured in this patient group. Similarly, serum brain natriuretic peptide (pro-BNP) has an

established role in diagnosis and prognostication for patients with acute PE [29]. Nonetheless, Pro-BNP measurements were unavailable to clinicians at the time of this study. Also of note, ECG (Electrocardiogram) and ECHO (Echocardiogram) information was not included in this data set.

## Conclusion

Combined biochemical markers of high-grade inflammation (poGPS), serum CRP >150mg/L and low serum albumin concentrations <25 g/L, were associated with 28-day and 6-month mortality in patients with acute PE. PESI score  $\geq 100$ , NLR  $\geq 3$  and coronary artery calcification score  $\geq 6$  were also associated with 28-day and 6-month mortality in patients with acute PE. poGPS  $\geq 1$ , PESI score  $\geq 100$  and NLR  $\geq 3$  remained independently prognostic with 28-day mortality in patients with acute PE. PESI score  $\geq 100$  and coronary artery calcification score  $\geq 6$  remained independently prognostic with 6-month mortality in patients with acute PE. When patients with an underlying diagnosis of cancer were excluded from the analysis, combined biochemical markers of low-grade inflammation (GPS), serum CRP >10mg/L and low serum albumin concentrations <35 g/L remained independently associated with higher 6-month mortality. At present, no risk stratifying score for acute PE prognosis or treatment includes markers of inflammation or coronary artery calcification scores.

PE in the context of underlying cancer may represent a pre-terminal event as patients were almost 15 times more likely to die at 6-months, however this group warrants further exploration regarding the cause of death, as PE treatment of selected patients within the GPS = 2 group may confer a survival benefit. Thromboprophylaxis in this patient group requires further investigation.

## Author Contributions

**Conceptualization:** Ross Dolan, Colin Church, Donogh Maguire.

**Data curation:** Lindsey Norton, Gordon Cooper, Owen Sheerins, Killian Mac a' Bháird, Graham McKenzie, Alasdair McFadyen, Matthew Zelic.

**Formal analysis:** David Young, Ross Dolan, Donogh Maguire.

**Methodology:** Donogh Maguire.

**Project administration:** Gordon Cooper.

**Resources:** Donogh Maguire.

**Software:** David Young.

**Supervision:** Gordon Cooper, Donogh Maguire.

**Validation:** Donogh Maguire.

**Visualization:** Donogh Maguire.

**Writing – original draft:** Gordon Cooper, Giles Roditi.

**Writing – review & editing:** Gordon Cooper, Owen Sheerins, Killian Mac a' Bháird, Michael Adamson, Ross Dolan, Colin Church, Adrian Brady, Campbell Tait, Graham McKenzie, Alasdair McFadyen, Matthew Zelic.

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