Short-term clinical outcome of normotensive patients with acute PE and high plasma lactate

Simone Vanni,1 David Jiménez,2 Peiman Nazerian,1 Fulvio Morello,3 Michele Parisi,4 Elena Daghini,5 Mauro Pratesi,5 Raquel López,6 Pedro Bedate,7 José Luis Lobo,8 Luis Jara-Palomares,9 Ana K Portillo,2 Stefano Grifoni1

ABSTRACT
Background Strategies for identifying normotensive patients with acute symptomatic PE at high risk of PE-related complications remain to be defined.
Methods This prospective cohort study aimed to determine the role of plasma lactate levels in the risk assessment of normotensive patients with acute PE. Outcomes assessed over the 7 days after the diagnosis of PE included PE-related mortality and haemodynamic collapse, defined as need for cardiopulmonary resuscitation, systolic blood pressure <90 mm Hg for at least 15 min, need for catecholamine administration, or need for mechanical ventilation.
Results Between December 2012 and January 2014, the study enrolled 496 normotensive outpatients with acute symptomatic PE. PE-related complications occurred in 20 (4.0%; 95% CI 2.5% to 6.2%) of the 496 patients. These patients had higher baseline lactate levels (median 2.66 mmol/L; IQR 1.56–5.96 mmol/L) than patients without complications (1.20 mmol/L; IQR 1.20–2.00 mmol/L (p<0.001). Overall, 135 patients (27.2%) had plasma lactate ≥2 mmol/L. Fourteen (10.4%) of them had PE-related complications versus 6 of 361 patients with low lactate (negative predictive value 98.3%; p<0.001). Patients with elevated plasma lactate had an increased rate of PE-related complications (adjusted OR 5.3; 95% CI 1.9 to 14.4; p=0.001) compared with those with low lactate. The combination of elevated plasma lactate with markers of right ventricular dysfunction (by echocardiogram) and myocardial injury (by cardiac troponin) was a particularly useful prognostic indicator (positive predictive value 17.9%; 95% CI 6.1% to 36.9%).
Conclusions Plasma lactate represents a powerful predictor of short-term PE-related complications and may provide guidance for decision-making in PE care.

INTRODUCTION
Haemodynamic status has significant prognostic implications for patients diagnosed with acute PE. Patients with acute symptomatic PE presenting with shock or refractory arterial hypotension (systolic blood pressure <90 mm Hg or a pressure drop of ≥40 mm Hg for ≥15 min), indicating overt right ventricular (RV) failure, are particularly at high risk of early death and should therefore undergo prompt recanalisation treatment.1–3 For haemodynamically stable patients with PE, the categorisation of risk for subgroups may assist with decision-making regarding PE therapy.4

In the subgroup of normotensive patients with PE, rapid and accurate prognostication and risk stratification have focused mainly on RV dysfunction or injury to the myocardium as a result of acute pressure overload.4–7 However, some evidence suggests that a subset of normotensive patients with acute symptomatic PE may have a reasonable risk-to-benefit ratio for thrombolytic therapy, single markers of RV dysfunction and myocardial injury have an insufficient positive predictive value for PE-specific mortality to drive decision-making toward such therapy.8 9 Plasma lactate concentration is a marker of the severity of the tissue oxygen supply-to-demand imbalance. Similar to other scenarios, such as sepsis or trauma, lactate concentration might increase in patients with acute PE before overt haemodynamic impairment.10–13 One small single-centre study found an association between high plasma lactate levels and short-term all-cause mortality in patients with acute PE, independent of the presence of haemodynamic instability or markers of RV dysfunction or injury.14 15 Thus, lactate may be potentially useful for identifying normotensive PE patients at high-risk of PE-related adverse clinical events.

This study was designed to prospectively assess the prognostic significance of elevated lactate in a cohort of haemodynamically stable patients with...
acute symptomatic PE. Furthermore, we aimed to determine the optimal combination of prognostic tools for detecting patients with preserved systemic arterial pressure deemed to be at higher risk of PE-related complications.

METHODS
Study design
This was a prospective, multicentre, observational cohort study (NCT01908231) designed by the authors. The institutional review board of each centre approved the protocol and consent forms.

Setting
Patients were recruited from the emergency department of seven academic and two general urban hospitals in Italy and Spain between 1 December 2012 and 31 January 2014.

Study eligibility and patients
The study required confirmation of the PE diagnosis with a positive contrast-enhanced, PE-protocol, multidetector CT pulmonary angiography. Patients with any of the following conditions were excluded: haemodynamic instability at presentation (defined as systolic blood pressure <90 mm Hg); treatment with thrombolytic agents at the time of PE diagnosis; life expectancy <3 months (ie, terminally ill patients); pregnancy; geographic inaccessibility that precluded follow-up; age younger than 18 years.

Plasma lactate determination
The plasma lactate concentration was determined on arterial blood samples (the type of test used was determined by the department of clinical chemistry at each participating site). Based on previous data, we considered plasma lactate levels ≥2 mmol/L to be abnormal. Transthoracic echocardiography
The study required that patients undergo transthoracic echocardiography within 24 h after diagnosis of PE. Trained and certified local physicians, blinded to the patient’s clinical data and laboratory test results, interpreted each echocardiogram. RV dysfunction was assessed by echocardiography. The study defined RV dysfunction as presence of at least one of the following: (1) RV dilatation (end-diastolic diameter >30 mm or right/ left ventricular end-diastolic diameter ratio ≥1 in apical four-chamber view); (2) pulmonary hypertension (estimated RV-right atrial tricuspidvalve gradient over 30 mm Hg); (3) hypokinesis of the RV free wall (any view).

Cardiac troponin testing
Participant sites used different biomarkers for myocardial injury (troponin I and T) and different cut-off points for abnormal levels. Four of the participating centres used the same assay (cardiac troponin I (cTnI); Abbott, USA) with a cut-off point of 0.05 ng/mL, while three centres used the same assay with a cut-off point of 0.10 ng/mL. The remaining centres used a highly sensitive troponin T immunosassay (Roche, Germany) with a cut-off point of 14 pg/mL. In most of the sites, the cut-off points for troponin assays were defined according to standard criteria, which were values exceeding the 99th percentile of healthy subjects with a coefficient of variation of 10%.

Treatment and follow-up
Clinicians at enrolling sites managed patients according to their local practice (ie, no standardisation of treatment). Most patients received initial anticoagulation with intravenous unfractionated heparin (UFH), subcutaneous low-molecular-weight heparin (LMWH) or fondaparinux, and overlap and long-term therapy with an oral vitamin K antagonist. In patients whose clinical status deteriorated after enrolment, the clinicians administered thrombolytic treatment and/or inotropic support as deemed appropriate. This study analysed outcomes over the 30 days after diagnosis of PE.

Study outcomes
This study used a clinical composite (ie, PE-related complications) of PE-related death or non-fatal haemodynamic collapse within 7 days of diagnosis as the primary outcome. PE was considered the cause of death if there was objective documentation or if the cause was unexplained and PE could not be confidently ruled out. Haemodynamic collapse was defined as at least one of the following: (i) need for cardiopulmonary resuscitation; (ii) systolic blood pressure <90 mm Hg for at least 15 min, with signs of end-organ hypoperfusion (cold extremities, or urinary output <30 mL/h, or mental confusion) or need for catecholamines (except for dopamine at a rate of <5 μg/kg/min) to maintain adequate organ perfusion and a systolic blood pressure of >90 mm Hg; (iii) need for invasive or non-invasive mechanical ventilation. Secondary outcomes included 30-day all-cause and PE-related death. An adjudication committee, composed of three independent experts who were blinded to patients’ clinical characteristics and the results of prognostic testing, adjudicated on all adverse events.

Statistical analysis
The study reported categorical data as proportions, and continuous data as mean±SD or median (first–third IQR). We used unpaired two-tailed t tests or the Mann–Whitney U test (for those variables found not to follow a normal distribution) for comparisons of the distributions of continuous variables between patients with or without elevated plasma lactate, and 2 or Fisher’s exact tests for comparisons of categorical data between the two groups. Sample size was calculated for the primary end point. We calculated a priori a power of 80% (two-sided type 1 error, 5%) to reject the null hypothesis that the presence of elevated plasma lactate will not predict the primary end point in the available sample of 494 patients, using the following assumptions: presence of elevated plasma lactate in 30% of the sample; a difference in mortality rate of 10% between patients with and without elevated plasma lactate; a drop out of 10%.

We used logistic regression to assess independent associations between potential baseline predictors and the outcome in the cohort. For the manual backward stepwise multivariable logistic regression model, we assessed variables that had a significance level of p<0.20 in univariable analyses. The model primarily assessed the prognostic information of lactate and cardiac predictors (ie, echocardiography and troponin testing) and adjusted for clinical confounders deemed statistically significant on univariable analysis. The final model retained variables associated with the outcome at a significance level of p<0.05.

In addition, to evaluate the role of a strategy combining lactate with cardiac biomarkers and echocardiography for identifying normotensive patients with acute symptomatic PE at high risk of PE-related complications, we used multiple logistic regression analysis to compare the complication rate of three patient groups: (1) troponin elevation and RV dysfunction; (2) troponin elevation, RV dysfunction and no lactate elevation; (3) troponin elevation, RV dysfunction and lactate elevation. No

adjustments for other baseline variables were made in the latter model.

To assess the test and performance characteristics of combinations of the simplified PE Severity Index (SPEI), lactate, cardiac troponin and echocardiogram variables, we estimated the positive predictive value and the positive likelihood ratio, as well as the sensitivity, specificity, negative predictive values and negative likelihood ratio for predicting the primary outcome.

Statistical significance was defined as a two-tailed p value of <0.05 for all analyses. We performed our calculations using the SPSS statistical package (V19.0).

RESULTS
Study sample
Study staff screened 539 consecutive outpatients with acute PE for eligibility. Haemodynamic instability ruled out 29 (5.4%) patients from participation. Of the remaining 510 haemodynamically stable patients, the study excluded 14 (2.7%) because they had received initial recanalisation procedures. The remaining eligible 496 patients (242 men and 254 women) were enrolled in the study (figure 1). Of these 496 patients, 319 (64.3%) received initial therapy with LMWH, 156 (31.5%) received UFH, and 21 (4.2%) received an inferior vena cava filter.

Table 1 shows the patients’ clinical symptoms, predisposing conditions, and relevant findings at presentation. On admission, lactate levels ranged from 0 to 18.2 mmol/L and had a median value of 2 mmol/L (IQR 0.93–2 mmol/L). Of the 496 enrolled patients, 135 (27%) had elevated serum lactate levels (lactate-positive group) and the remaining 361 patients had normal serum lactate levels (lactate-negative group). Patients in the lactate-negative group were younger and had fewer signs of clinical severity (eg, tachycardia, RV dysfunction, myocardial injury) than those in the lactate-positive group (table 1).

Outcome
The study had complete outcome information for all patients at the end of follow-up. The primary outcome occurred in 20 of the 496 (4.0%; 95% CI 2.5% to 6.2%) normotensive patients with acute asymptomatic PE who entered the study (table 2).

Table 1 Clinical symptoms and relevant findings at presentation in 496 consecutive normotensive patients diagnosed with acute symptomatic PE in the emergency department

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (N=496)</th>
<th>Lactate-negative group (N =361)</th>
<th>Lactate-positive group (N =135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean±SD)</td>
<td>69±16.5</td>
<td>68±17</td>
<td>73±14.5*</td>
</tr>
<tr>
<td>Age &gt;80 years</td>
<td>124 (25)</td>
<td>83 (23)</td>
<td>41 (30)</td>
</tr>
<tr>
<td>Female gender</td>
<td>254 (51)</td>
<td>185 (51)</td>
<td>69 (51)</td>
</tr>
<tr>
<td>Risk factors for VTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of VTE</td>
<td>64 (13)</td>
<td>49 (14)</td>
<td>15 (11)</td>
</tr>
<tr>
<td>Cancer</td>
<td>122 (25)</td>
<td>81 (22)</td>
<td>41 (30)</td>
</tr>
<tr>
<td>Comorbid diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic cardiopulmonary disease</td>
<td>44 (8.8)</td>
<td>34 (9.4)</td>
<td>10 (7.4)</td>
</tr>
<tr>
<td>Clinical symptoms and signs at presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simplified PESI ≥1</td>
<td>361 (73)</td>
<td>253 (73)</td>
<td>108 (80)*</td>
</tr>
<tr>
<td>Heart rate ≥110/min</td>
<td>83 (17)</td>
<td>48 (13)</td>
<td>35 (26)*</td>
</tr>
<tr>
<td>Arterial oxyhaemoglobin saturation &lt;90%</td>
<td>197 (40)</td>
<td>135 (37)</td>
<td>62 (46)</td>
</tr>
<tr>
<td>SBP 90–100 mm Hg</td>
<td>37 (5.6)</td>
<td>25 (6.9)</td>
<td>12 (8.9)</td>
</tr>
<tr>
<td>Shock index ≥1</td>
<td>41 (8.3)</td>
<td>23 (6.4)</td>
<td>18 (13.3)*</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum lactate, mmol/L (mean±SD)</td>
<td>1.74 ±1.75</td>
<td>1.11±0.39</td>
<td>3.40±2.65*</td>
</tr>
<tr>
<td>Elevated cardiac troponin†</td>
<td>117 (24)</td>
<td>70 (19)</td>
<td>47 (35)*</td>
</tr>
<tr>
<td>RV dysfunction (echocardiogram)</td>
<td>201 (40)</td>
<td>127 (35)</td>
<td>74 (55)*</td>
</tr>
</tbody>
</table>

Values are number (%) unless otherwise indicated. *p<0.05 compared with lactate-negative group. †Active or under treatment in the last year. ‡See definitions, tests and cut-off points in the Methods section. PESI, PE Severity Index; RV, right ventricle; SBP, systolic blood pressure; VTE, venous thromboembolism.
study population) with an sPESI
and lactate, we found that, of 108 patients (21.8% of the entire
By combining the prognostic information provided by sPESI
(p=0.034; table 4;
17.9% for patients also presenting elevated lactate levels
dysfunction and a positive troponin was 8.6%, but increased to
the presence of lactate eleva-
tion. The primary outcome rate of the combination of an RV
dysfunction and a positive troponin was associated with a 2.8-fold (95% CI 1.0 to
lysis revealed that the combination of RV dysfunction and a
≥
RV dysfunction and injury markers, either alone4
–
7 or in
combination with clinical variables.18–20 The PE Thrombolysis
Trial (PEITHO) determined the ef
>80 years 2.1 (0.8 to 5.2) 0.121
SBP 90
Heart rate
≥
110 beats/min 3.6 (1.4 to 9.0) 0.007 2.4 (0.9 to 6.3) 0.075
SBP 90–100 mm Hg 3.4 (1.1 to 10.6) 0.034 – –
Age >80 years 2.1 (0.8 to 5.2) 0.121 – –
Arterial oxyhaemoglobin saturation <90% 1.9 (0.8 to 4.7) 0.160 – –
Elevated cardiac troponin* 1.8 (0.7 to 4.6) 0.198 – –
Table 3 Unadjusted and adjusted ORs for 7-day PE-related complications in normotensive patients with acute symptomatic PE

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Unadjusted OR (95% CI)</th>
<th>p Value</th>
<th>Adjusted OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated lactate</td>
<td>6.9 (2.6 to 18.2)</td>
<td>&lt;0.001</td>
<td>5.3 (1.9 to 14.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>RV dysfunction</td>
<td>3.6 (1.4 to 9.6)</td>
<td>0.010</td>
<td>2.5 (0.9 to 6.8)</td>
<td>0.075</td>
</tr>
<tr>
<td>Heart rate ≥110 beats/min</td>
<td>3.6 (1.4 to 9.0)</td>
<td>0.007</td>
<td>2.4 (0.9 to 6.3)</td>
<td>0.075</td>
</tr>
<tr>
<td>SBP 90–100 mm Hg</td>
<td>3.4 (1.1 to 10.6)</td>
<td>0.034</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age &gt;80 years</td>
<td>2.1 (0.8 to 5.2)</td>
<td>0.121</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Arterial oxyhaemoglobin saturation &lt;90%</td>
<td>1.9 (0.8 to 4.7)</td>
<td>0.160</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Elevated cardiac troponin*</td>
<td>1.8 (0.7 to 4.6)</td>
<td>0.198</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Variables that had a significance level of p<0.20 in univariable analyses are shown.

*See definitions, tests and cut-off points in the Methods section.

RV, right ventricle; SBP, systolic blood pressure.

all-cause (OR 2.5; 95% CI 1.1 to 5.5; p=0.024) and PE-related
(OR 4.6; 95% CI 1.3 to 15.8; p=0.015) death.

Incremental prognostic value of plasma lactate
The above results suggest that lactate levels alone are per se
independent predictors of the primary outcome. Overall, the
positive predictive value of lactate (with the use of the above
cut-off point) was 10.4% for the primary end point (table 4).
By combining the prognostic information provided by sPESI
and lactate, we found that, of 108 patients (21.8% of the entire
study population) with an sPESI ≥1 point and lactate levels
≥2 mmol/L, 12 (11.1%; 95% CI 7.0% to 13.9%) experienced
the primary outcome (table 4). Multiple logistic regression ana-
ysis revealed that the combination of RV dysfunction and a
positive troponin was associated with a 2.8-fold (95% CI 1.0 to
7.4) elevated risk of the primary outcome, which increased to
6.6-fold (95% CI 2.2 to 19.6) in the presence of lactate eleva-
tion. The primary outcome rate of the combination of an RV
dysfunction and a positive troponin was 8.6%, but increased to
17.9% for patients also presenting elevated lactate levels
(p=0.034; table 4; figure 3).

DISCUSSION
This large European multicentre prospective cohort study shows
that raised lactate is an independent predictor of PE-related
mortality or clinical deterioration in normotensive patients with
PE. The combination of RV dysfunction, elevated troponin and
increased lactate predicted a 6.6-fold increase in the risk of
adverse short-term PE-related adverse events.

A validated explicit clinical prediction rule that recognises a
group of normotensive patients at high risk of adverse clinical
events that might benefit from recanalisation procedures is still
lacking. Previous observational studies have suggested a role for
RV dysfunction and injury markers, either alone4–7 or in

Table 2 Clinical events after diagnosis and treatment of 496 normotensive patients with acute symptomatic PE

<table>
<thead>
<tr>
<th>Event</th>
<th>All patients, N (%)</th>
<th>Lactate-negative group, N (%)</th>
<th>Lactate-positive group, N (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>20 (4.0)</td>
<td>6 (1.7)</td>
<td>14 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>7-day PE-related death</td>
<td>7 (1.4)</td>
<td>1 (0.3)</td>
<td>6 (4.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Shock/hypotension</td>
<td>11 (2.2)</td>
<td>3 (0.8)</td>
<td>8 (5.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>5 (1.0)</td>
<td>2 (0.6)</td>
<td>3 (2.2)</td>
<td>0.127</td>
</tr>
<tr>
<td>CPR</td>
<td>8 (1.6)</td>
<td>2 (0.6)</td>
<td>6 (4.4)</td>
<td>0.006</td>
</tr>
<tr>
<td>30-day PE-related death</td>
<td>12 (2.4)</td>
<td>4 (1.1)</td>
<td>8 (5.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>30-day all cause mortality</td>
<td>27 (5.4)</td>
<td>14 (3.8)</td>
<td>13 (9.6)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Table 3 Unadjusted and adjusted ORs for 7-day PE-related complications in normotensive patients with acute symptomatic PE

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Unadjusted OR (95% CI)</th>
<th>p Value</th>
<th>Adjusted OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated lactate</td>
<td>6.9 (2.6 to 18.2)</td>
<td>&lt;0.001</td>
<td>5.3 (1.9 to 14.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>RV dysfunction</td>
<td>3.6 (1.4 to 9.6)</td>
<td>0.010</td>
<td>2.5 (0.9 to 6.8)</td>
<td>0.075</td>
</tr>
<tr>
<td>Heart rate ≥110 beats/min</td>
<td>3.6 (1.4 to 9.0)</td>
<td>0.007</td>
<td>2.4 (0.9 to 6.3)</td>
<td>0.075</td>
</tr>
<tr>
<td>SBP 90–100 mm Hg</td>
<td>3.4 (1.1 to 10.6)</td>
<td>0.034</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age &gt;80 years</td>
<td>2.1 (0.8 to 5.2)</td>
<td>0.121</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Arterial oxyhaemoglobin saturation &lt;90%</td>
<td>1.9 (0.8 to 4.7)</td>
<td>0.160</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Elevated cardiac troponin*</td>
<td>1.8 (0.7 to 4.6)</td>
<td>0.198</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
not significantly differ from that of other single tests (e.g., cTnI, echocardiogram) for prediction of short-term PE-related complications. Hence, lactate per se should not significantly drive the decision to give thrombolytic therapy, and the current evidence does not support the use of lactate levels for such decision-making. Instead, our results show that lactate levels are likely to be most useful when used in combination with echocardiographic evidence of RV strain, and with markers of myocardial injury. Indeed, we found that the association of elevated troponin, RV dysfunction and elevated lactate levels contributed to fine-tuning of risk stratification for normotensive patients with acute symptomatic PE.

Strengths of our analysis that increase the precision and validity of the present findings are that (a) we included data from a large number of participants, (b) baseline variables were recorded at enrolment rather than retrospectively, and (c) participants were followed prospectively. Furthermore, an adjudication committee accurately diagnosed outcomes. Compared with previous studies, our study’s large sample size, the adjustment for potential confounders (e.g., troponin, RV dysfunction), and the robustness of the findings provide strong evidence supporting the concept that measurement of lactate at the time of acute PE diagnosis is a predictor of short-term PE-related complications. Some methodological limitations should be considered. First, the incidence of the primary outcome was lower than expected, partially reducing the statistical power of the sample size. Second, we did not address the prognostic relevance of the sample size, which are reported to have higher accuracy than a single one.

Table 4 Prediction rule test characteristics for 7-day PE-related complications in 496 normotensive patients with acute symptomatic PE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Positive test, N (%)</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive predictive value, %</th>
<th>Negative predictive value, %</th>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>sPESI variable</td>
<td>361 (72.7)</td>
<td>85.0 (61.7 to 96.0)</td>
<td>27.7 (26.0 to 28.2)</td>
<td>4.7 (3.4 to 5.3)</td>
<td>97.8 (94.3 to 99.4)</td>
<td>1.18 (0.84 to 1.33)</td>
<td>0.54 (0.44 to 1.43)</td>
</tr>
<tr>
<td>Lactate variable</td>
<td>135 (27.2)</td>
<td>70.0 (46.2 to 87.0)</td>
<td>74.6 (73.6 to 75.3)</td>
<td>10.4 (5.8 to 16.8)</td>
<td>98.3 (97.0 to 99.3)</td>
<td>2.75 (1.75 to 3.52)</td>
<td>0.40 (0.17 to 0.73)</td>
</tr>
<tr>
<td>Troponin variable</td>
<td>117 (23.6)</td>
<td>35.0 (16.5 to 58.5)</td>
<td>76.9 (76.1 to 77.9)</td>
<td>6.0 (2.8 to 10.8)</td>
<td>96.6 (95.6 to 97.8)</td>
<td>1.51 (0.69 to 2.64)</td>
<td>0.85 (0.53 to 1.10)</td>
</tr>
<tr>
<td>TTE variable</td>
<td>201 (40.5)</td>
<td>70.0 (46.1 to 87.1)</td>
<td>60.7 (59.7 to 61.4)</td>
<td>7.0 (4.6 to 8.7)</td>
<td>98.3 (96.3 to 99.1)</td>
<td>1.78 (1.15 to 2.26)</td>
<td>0.49 (0.21 to 0.90)</td>
</tr>
<tr>
<td>sPESI plus lactate variable</td>
<td>108 (21.7)</td>
<td>60.0 (36.9 to 79.7)</td>
<td>79.8 (78.9 to 80.7)</td>
<td>11.1 (7.9 to 15.3)</td>
<td>96.7 (95.9 to 97.8)</td>
<td>2.98 (1.75 to 4.12)</td>
<td>0.50 (0.25 to 0.80)</td>
</tr>
<tr>
<td>Troponin plus TTE variable</td>
<td>70 (14.1)</td>
<td>86.6 (85.8 to 87.5)</td>
<td>86.6 (85.8 to 87.5)</td>
<td>8.6 (3.7 to 15.3)</td>
<td>96.7 (95.9 to 97.8)</td>
<td>2.23 (0.92 to 4.28)</td>
<td>0.81 (0.53 to 1.01)</td>
</tr>
<tr>
<td>Troponin plus TTE plus lactate variable</td>
<td>28 (5.6)</td>
<td>25.0 (9.9 to 46.8)</td>
<td>95.2 (94.5 to 96.1)</td>
<td>17.9 (6.1 to 36.9)</td>
<td>96.8 (96.1 to 97.7)</td>
<td>5.17 (1.81 to 11.97)</td>
<td>0.79 (0.55 to 0.95)</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, values in parentheses are 95% CI. sPESI, simplified PE Severity Index; TTE, transthoracic echocardiography.
Figure 3  Escalation of PE-related complication rates depending on lactate levels in combination with echocardiography and troponin. cTn, elevated cardiac troponin; Lac (+), lactate ≥2 mmol/L; Lac (--), lactate <2 mmol/L; RVD, right ventricular dysfunction.


