ORIGINAL SCIENTIFIC PAPER

Outcome of patients with different clinical presentations of high-risk pulmonary embolism

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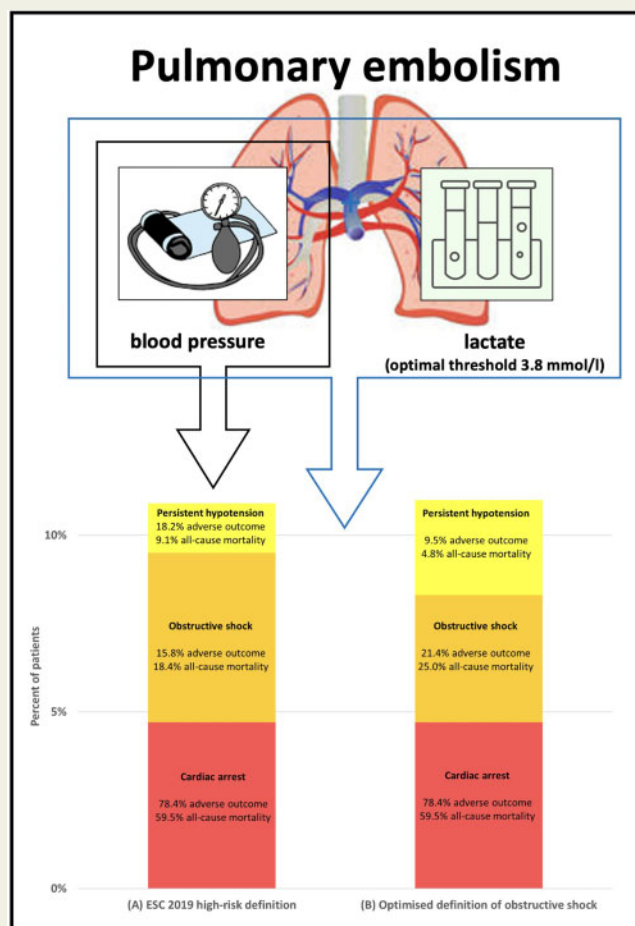|	
Aims	The 2019 European Society of Cardiology (ESC) guidelines provide a revised definition of high-risk pulmonary embolism (PE) encompassing three clinical presentations: Cardiac arrest, obstructive shock, and persistent hypotension. This study investigated the prognostic implications of this new definition.
Methods and results	Data from 784 consecutive PE patients prospectively enrolled in a single-centre registry were analysed. Study outcomes include an in-hospital adverse outcome (PE-related death or cardiopulmonary resuscitation) and in-hospital all-cause mortality. Overall, 86 patients (11.0%) presented with high-risk PE and more often had an adverse outcome (43.0%) compared to intermediate-high-risk patients (6.1%; $P < 0.001$). Patients with cardiac arrest had the highest rate of an in-hospital adverse outcome (78.4%) and mortality (59.5%; both $P < 0.001$ compared to intermediate-high-risk patients). Obstructive shock and persistent hypotension had similar rates of adverse outcomes (15.8% and 18.2%, respectively; $P = 0.46$), but the only obstructive shock was associated with an increased all-cause mortality risk. Use of an optimised venous lactate cut-off value (3.8 mmol/L) to diagnose obstructive shock allowed differentiation of adverse outcome risk between patients with shock (21.4%) and persistent hypotension (9.5%), resulting in a net reclassification improvement (0.24 ± 0.08; $P = 0.002$).
Conclusion	The revised ESC 2019 guidelines definition of high-risk PE stratifies subgroups at different risk of in-hospital adverse outcomes and all-cause mortality. Risk prediction can be improved by using an optimised venous lactate cut-off value to diagnose obstructive shock, which might help to better assess the risk-to-benefit ratio of systemic thrombolysis in different subgroups of high-risk patients.

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Graphical Abstract

Introduction

Pulmonary embolism (PE) is associated with high mortality and remains a major contributor to global disease burden.[1,2] Thus, current guidelines emphasize the importance of rapid identification of high-risk patients, who require reperfusion therapy as life-saving treatment. Despite these recommendations, data from health care registries indicate an underuse of systemic thrombolysis and other forms of reperfusion therapy in haemodynamically unstable patients.[3,4]

The recently published 2019 European Society of Cardiology (ESC) guidelines provide a revised definition of high-risk PE encompassing the following clinical presentations: (i) cardiac arrest; (ii) obstructive shock (defined as systolic blood pressure <90 mmHg or vasopressors required to achieve a blood pressure ≥90 mmHg despite adequate filling status, in combination with end-organ hypoperfusion); or (iii) persistent hypotension (defined as systolic blood pressure <90 mmHg or a systolic pressure drop by ≥40 mmHg for longer than 15 min, if not caused by new-onset arrhythmia, hypovolemia or sepsis).[2] This definition is based on the established role of systemic hypotension in predicting PE-related adverse outcome and mortality,[5,6] and on the exceptionally high mortality rates observed in PE patients presenting with cardiac arrest.[7,8] In addition, the inclusion of frank obstructive shock based on signs of end-organ hypoperfusion such as lactate elevation (in addition to arterial hypotension) in the updated ESC 2019 definition of high-risk PE relies on

pathophysiological considerations and analogies to other acute cardiovascular syndromes. However, the prognostic implications of this extended definition of high-risk PE have not yet been investigated.

In the present study, we investigated in-hospital outcomes of patients with different clinical presentations of high-risk PE as proposed by the ESC 2019 guidelines. In addition, we examined the performance of lactate as a marker of tissue hypoperfusion to diagnose obstructive shock and determined an optimal lactate cut-off value for this purpose.

Methods

Study design and definition of outcomes

The Pulmonary Embolism Registry of Göttingen (PERGO) prospectively includes consecutive patients with objectively confirmed PE ≥18 years of age admitted to the University Medical Centre Göttingen, Germany. The study protocol has been described in detail previously.[8,9] The present analysis included patients enrolled in PERGO between September 2008 and March 2018. We excluded patients (i) with subsegmental PE as an incidental and asymptomatic finding during diagnostic work-up for another suspected disease and (ii) with significant concomitant acute cardio-respiratory illness, such as acute myocardial infarction, left heart failure, or respiratory failure responsible for the clinical presentation and/or symptoms. All patients were followed for the hospital stay. One-year survival status was assessed by contacting the responsible registration offices.

Diagnostic and therapeutic management was in accordance with the ESC 2008 (September 2008 to August 2014) and 2014 (September 2014 to March 2018) guidelines[10,11] and local standard operating procedures. All related decisions were left to the discretion of the treating physicians and were not influenced by the study protocol. The study was conducted in accordance with the amended Declaration of Helsinki and was approved by the local independent Ethical Committee of the Medical University Göttingen, Germany (protocol number 14/6/10); all patients gave informed written consent for participation in the study. Patients were stratified to risk classes according to the simplified Pulmonary Embolism Severity Index (sPESI) and the algorithm proposed by the ESC 2019 guidelines.[2] Of note, patients were classified as high-risk with cardiac arrest if cardiac arrest was the initial symptom of PE and initial cardiopulmonary resuscitation resulted in documented return of spontaneous circulation prior to PE diagnosis. For calculation of all algorithms and scores, missing values were considered to be normal.[12] Altered mental status was defined as disorientation, somnolence, stupor or coma; respiratory insufficiency as need for non-invasive or invasive ventilation; hypotension as systolic blood pressure <90 mmHg or vasopressors required to achieve a blood pressure ≥90 mmHg. Obstructive shock was defined based on the presence of hypotension in combination with altered mental status or venous lactate concentrations above the upper limit of normal (≥2.3 mmol/L). Major bleeding was defined as fatal and/or symptomatic bleeding in a critical area organ and/or bleeding causing a fall in haemoglobin level of ≥2 g/dL or transfusion of ≥2 units of erythrocyte concentrate according to the definition of the International Society of Thrombosis and Haemostasis (ISTH).[13] Further definitions are provided in the Supplementary material online.

The main study outcomes were the occurrence of an adverse outcome during hospitalization (defined as PE-related death or need for cardiopulmonary resuscitation after diagnosis of PE) and in-hospital all-cause mortality. In addition, we evaluated one-year all-cause mortality. Death was determined to be PE-related if either confirmed by autopsy or following a clinically severe episode of acute PE in absence of an alternative diagnosis. All events and causes of death were independently adjudicated by two of the authors (M.E. and C.S.) and disagreements were resolved by a third author (M.L.).

Biomarker measurements

Venous blood sampling was performed on admission or at the time of PE diagnosis as part of routine clinical management. Routine venous blood gas analyses were performed using a standard point-of-care full blood gas analyses assay (GEM Premier 4000 analyser; Instrumentation Laboratory, Kirchheim, Germany). Plasma concentrations of high sensitivity troponin T (hsTnT; Roche Diagnostics, Mannheim, Germany) and copeptin (BRAHMS GmbH, Thermo Fisher Scientific, Hennigsdorf/Berlin, Germany) were measured by the *amedes MVZ wagnerstibbe* laboratory in Göttingen, Germany. Elevated biomarker concentrations were prospectively defined as hsTnT ≥14 pg/mL[12] and copeptin ≥24 pmol/L.[14]

Statistical analysis

Categorical variables are presented as total numbers and percentages; continuous variables are presented as medians with interquartile ranges. Associations between binary and categorical variables were analysed using Fisher's exact test or χ^2 test, as appropriate. For comparison of continuous variables, the Mann–Whitney U test was employed.

To investigate the diagnostic performance of different venous lactate cut-off values in patients without cardiac arrest, receiver operating characteristic (ROC) curve analysis was performed, and the lowest value providing >90% specificity was selected as an optimised cut-off value. In addition, to test the potential benefit of (i) using an optimised lactate cut-off value to diagnose obstructive shock and (ii) an expanded definition of high-risk PE (classifying all patients with altered mental status and/or respiratory insufficiency to the high-risk category; shown in the Supplementary material online), we calculated the net reclassification improvement (NRI) with the corresponding standard error.[15,16]

The prognostic relevance of patient characteristics and results of risk stratification with regard to study outcomes was tested using univariable logistic regression analyses and results expressed as odds ratios (OR) with corresponding 95% confidence intervals (CIs). Further, the following variables were entered simultaneously in two multivariable logistic regression models: (i) variables defining high-risk PE (cardiac arrest at presentation, signs of hypoperfusion [defined as altered mental status or lactate above the newly identified optimised cut-off value] and systolic blood pressure persistently below 90 mmHg) and (i) altered mental status, respiratory insufficiency, and hypotension.

Kaplan–Meier analysis was used to compare the probability of one-year survival in subgroups stratified according to the ESC 2019 high-risk definition; the log-rank test was used for comparison between groups (shown in the Supplementary material online).

A two-sided significance level of α < 0.05 was defined as appropriate to indicate statistical significance. *P*-values were provided for descriptive reasons only and should be interpreted with caution. Statistical analysis was performed through Statistics Package for Social Sciences (IBM SPSS Statistics, Version 25, IBM Corp. Armonk, NY, USA).

Results

Between September 2008 and March 2018, 851 patients were enrolled in PERGO. After the exclusion of 42 asymptomatic patients with subsegmental PE as an incidental finding during diagnostic work-up for another suspected disease and 25 patients with another acute cardio-respiratory illness responsible for clinical presentation and

symptoms, 784 (92.1%) patients were included in the present analysis.

Overall, 85 (10.8%) patients were classified as low-risk, 367 (46.8%) as intermediate-low-risk, 246 (31.4%) as intermediate-high-risk and 86 (11.0%) as high-risk according to the risk stratification algorithm proposed by the ESC 2019 guidelines. During hospitalization, an adverse outcome was observed in 59 (7.5%) patients. Overall, 59 (7.5%) patients died during hospitalization; of those, 44 (74.6%) deaths were due to PE. Seventy-six (9.7%) patients received reperfusion treatment (*Table 1*); of those, 46 with high-risk PE including 29 with cardiac arrest at presentation. Information on comorbidities, initial presentation, and outcomes is shown in *Table 1*.

Outcomes in patients classified as high-risk according to the ESC 2019 guidelines

Of 86 patients classified as high-risk PE, 37 (43.0%) presented with cardiac arrest, 38 (44.2%) with obstructive shock, and 11 (12.8%) with persistent hypotension only. One patient, who initially presented with obstructive shock, was treated with veno-arterial extracorporeal membrane oxygenation. High-risk patients who received systemic thrombolysis had a high rate of major bleeding [14 of 44 (31.8%)]. Of those, 2 (14.3%) patients suffered intracranial bleeding; no fatal bleeds occurred. Of note, compared to not-high-risk patients, high-risk patients more frequently had renal insufficiency (in more detail: 70.3% of patients with cardiac arrest, 62.3% with obstructive shock, and 50.0% with persistent hypotension) (*P* < 0.001) which was due to acute kidney injury in 83.6% of patients (Supplementary material online, *Table S1*).

In patients who presented with cardiac arrest as the initial symptom of PE and in whom initial cardiopulmonary resuscitation was successful, an adverse outcome during hospitalization occurred in 29 (78.4%) patients (*Figure 1A*), and 22 (59.5%) patients died in hospital. Patients with either obstructive shock or persistent hypotension had similar rates of adverse outcomes [6 of 38 (15.8%) and 2 of 11 (18.2%) patients, respectively; *P* = 0.46]. The prognostic performance of different clinical presentations of high-risk PE according to the ESC 2019 high-risk definition is shown in Supplementary material online, *Table S2*; however, odds ratios should be interpreted with caution given the small number of events. Of note, obstructive shock, but not persistent hypotension, was associated with an increased risk of in-hospital all-cause mortality (Supplementary material online, *Table S2*).

The outcomes of high-risk patients with available lactate measurements are provided in Supplementary material online, *Table S3*.

Prognostic value of lactate levels for the classification of obstructive shock patients

Venous lactate levels above the upper limit of normal (≥2.3 mmol/L) predicted an adverse outcome in the overall cohort [OR 6.0 (95% CI 2.6–13.8)] but not in patients without cardiac arrest [OR 2.2 (95% CI 0.8–5.9); *Table 2*]. Using ROC curve analysis, we identified a venous lactate concentration of 3.8 mmol/L as the optimal cut-off value to predict an adverse outcome in both, the overall cohort [OR 13.0 (95% CI 6.0–28.5); *Table 2*, left column] and patients without cardiac arrest at presentation [OR 4.2 (95% CI 1.4–12.6); *Table 2*, right column].

Of 38 patients with obstructive shock, 18 (47.4%) were diagnosed based on venous lactate levels ≥2.3 mmol/L. These patients had a numerically lower rate of adverse outcomes compared to patients diagnosed with obstructive shock based on either altered mental status or a combination of altered mental status *and* venous lactate levels ≥2.3 mmol/L [1 of 18 (5.6%) vs. 5 of 20 (25.0%) patients, *P* = 0.18]. If the optimised venous lactate cut-off value of 3.8 mmol/L was used to diagnose obstructive shock, 10 of 38 (26.3%) patients with obstructive shock were reclassified as having 'isolated' persistent hypotension. None of these patients suffered an adverse outcome, resulting in a net reclassification improvement (NRI 0.24 ± 0.08, *P* = 0.002) compared to the lower cut-off value of 2.3 mmol/L. In accordance, if obstructive shock was diagnosed using the 3.8 mmol/L venous lactate cut-off value, the diagnosis was associated with a higher OR for the prediction of an adverse outcome compared to obstructive shock diagnosed based on the conventional 2.3 mmol/L cut-off value (Supplementary material online, *Table S2*).

Importantly, 'isolated' persistent hypotension failed to reach statistical significance for predicting an adverse outcome if the optimised venous lactate cut-off value was used [OR 3.2 (95% CI 0.7–14.8)]. For comparison, the OR for an adverse outcome of patients in the intermediate-high risk category was 4.1 (95% CI 1.7–10.3), compared to other initially normotensive patients. Moreover, the rates of an adverse outcome were similar in high-risk patients defined by 'isolated' persistent arterial hypotension and in intermediate-high-risk patients [9.5% (2 of 21) vs. 6.1% (15 of 246), *P* = 0.54], and substantially lower compared to those in patients with obstructive shock [21.4% (6 of 28)]. In a multivariable model including a cardiac arrest at presentation, signs of hypoperfusion and persistent hypotension, only cardiac arrest at presentation [OR 11.5 (95% CI 3.7–35.0)] and hypoperfusion [OR 5.0 (95% CI 2.0–11.8)] were independently associated with an adverse outcome, while persistent hypotension alone failed to reach statistical significance [OR 2.6 (95% CI 0.95–7.2), *P* = 0.06].

To identify further parameters characterising patients at the highest risk for adverse outcomes, univariate logistic regression analyses were performed (*Table 2*). Although hypotension was a strong predictor of life-threatening adverse outcomes (*Table 2A*) and all-cause mortality (*Table 2B*), altered mental status and respiratory insufficiency were of higher prognostic value in the entire study cohort and in patients not presenting with cardiac arrest. In a multivariable model including the three variables, only altered mental status [OR 9.1 (95% CI 3.8–22.0)] and respiratory insufficiency [OR 4.3 (95% CI 1.1–6.2)] remained independent predictors of a life-threatening adverse outcome in patients without cardiac arrest at presentation. Further results are shown in the Supplementary material online.

One-year mortality
Results are shown in the Supplementary material online.

Discussion

In acute PE, rapid identification of high-risk patients is a critical component of risk stratification, as these patients require immediate reperfusion therapy as potentially life-saving treatment. The recently

Table 1 Comorbidities, initial presentation, and outcome of study patients

	All patients n/N (%)	ESC 2019 high-risk patients n/N (%)	ESC 2019 not-high-risk patients n/N (%)	P-value
Age (years)	70 (57–78)	71 (59–79)	70 (56–78)	0.21
Sex (female)	406/784 (51.8)	43/86 (50.0)	363/698 (52.0)	0.73
Comorbidities				
Chronic heart failure	118/784 (15.1)	20/86 (23.3)	98/698 (14.0)	**0.024**
Coronary artery disease	143/784 (18.2)	23/86 (26.7)	120/698 (17.2)	**0.030**
Chronic pulmonary disease	118/784 (15.1)	16/86 (18.6)	102/698 (14.6)	0.33
Renal insufficiency	264/773 (34.2)	55/85 (64.7)	209/688 (30.4)	**<0.001**
Active cancer	142/783 (18.1)	15/86 (17.4)	127/697 (18.2)	0.86
Symptoms at presentation				
Syncope	121/781 (15.5)	32/85 (37.6)	89/696 (12.8)	**<0.001**
Altered mental status	87/784 (11.1)	57/86 (66.3)	30/698 (4.3)	**<0.001**
Clinical findings at presentation				
Tachycardia	273/770 (35.5)	41/85 (48.2)	232/685 (33.9)	**0.009**
Hypotension	86/755 (11.4)	86/86 (100.0)	0/669 (0.0)	**<0.001**
Hypoxaemia	203/672 (30.2)	66/80 (82.5)	137/592 (23.1)	**<0.001**
Respiratory insufficiency	53/736 (7.2)	44/81 (54.3)	9/655 (1.4)	**<0.001**
Laboratory and imaging markers				
hsTnT ≥14 pg/mL	487/729 (66.8)	68/78 (87.2)	419/651 (64.4)	**<0.001**
Copeptin ≥24 pmoL	285/639 (44.6)	68/72 (94.4)	217/567 (38.3)	**<0.001**
Venous lactate ≥3.8 mmol/L	55/474 (11.6)	33/55 (60.0)	34/419 (8.1)	**<0.001**
Venous lactate ≥2.3 mmol/L	166/474 (35.0)	47/55 (85.5)	119/419 (28.4)	**<0.001**
RV/LV diameter ratio ≥1.0 on CTPA	434/594 (73.1)	53/62 (85.5)	381/532 (71.6)	**0.020**
Outcome				
In-hospital adverse outcome	59/784 (7.5)	37/86 (43.0)	22/698 (3.2)	**<0.001**
Cardiopulmonary resuscitation	43 (5.5)	30 (34.9)	13 (1.9)	**<0.001**
PE-related death	44 (5.6)	28 (32.6)	16 (2.3)	**<0.001**
Catecholamine administration	80/784 (10.2)	53/86 (61.6)	27/698 (3.9)	**<0.001**
In-hospital all-cause mortality	59/784 (7.5)	30/86 (34.9)	29/698 (4.2)	**<0.001**
Reperfusion treatment	76/784 (9.7)	46/86 (53.5)	30/698 (4.3)	**<0.001**
Systemic thrombolysis	71 (9.1)	44 (51.2)	27 (3.9)	**<0.001**
Surgical thrombectomy	7 (0.9)	4 (4.7)	3 (0.4)	**0.004**
One-year all-cause mortality				
All patients	153/784 (19.5)	44/86 (51.2)	112/698 (15.6)	**<0.001**
Patients discharged alive	94/775 (13.0)	14/56 (25.0)	80/669 (12.0)	**0.005**

CTPA, computed tomography pulmonary angiography; ESC, European Society of Cardiology; hsTnT, high sensitivity troponin T; LV, left ventricular; PE, pulmonary embolism; RV, right ventricular. Bold p-values indicate significant findings.
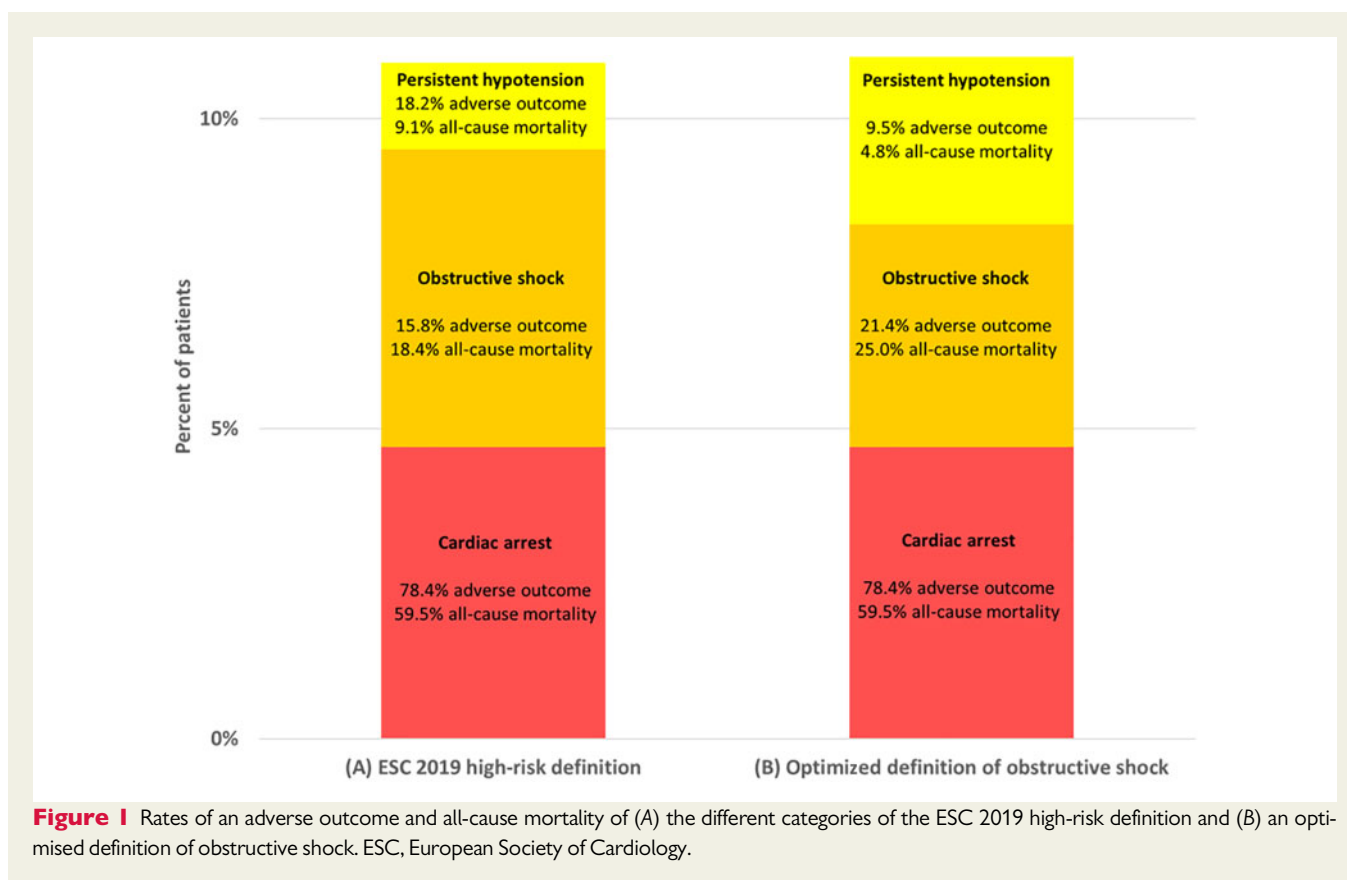
published ESC 2019 guidelines provide an extended definition of haemodynamic instability (and thus high-risk PE) encompassing three distinct clinical presentations: cardiac arrest, obstructive shock, and persistent hypotension.[2] In the present analysis of 784 PE patients consecutively included in a real-world single-centre cohort over a 10-year period, we demonstrate that these three clinical presentations identify subgroups at different risk for adverse outcomes. Importantly, if an optimised definition of obstructive shock is used, the adverse outcome risk of persistent hypotension without signs of tissue hypoperfusion seems comparably low and may not justify immediate systemic thrombolysis in all of these patients.

Clinical presentations of high-risk *pulmonary embolism* and risk of an adverse outcome

In our study cohort, we observed a large proportion of patients with high-risk PE according to the ESC 2019 guidelines. While the

Figure 1 Rates of an adverse outcome and all-cause mortality of (*A*) the different categories of the ESC 2019 high-risk definition and (*B*) an optimised definition of obstructive shock. ESC, European Society of Cardiology.

prevalence of 11.0% was higher than those reported from the U.S. multicentre *Emergency Medicine Pulmonary Embolism in the Real World Registry* (EMPEROR)[17] and the *Registro Informatizado de la Enfermedad TromboEmbólica* (RIETE)[18] (3.0% and 3.3%, respectively), it concurs with those reported in a more recent analysis of three pooled prospective European cohorts (11.6%)[19] and an analysis of the German nationwide inpatient sample (8.9%).[3] The latter study further observed an in-hospital mortality rate of 84.2% in PE patients with cardiac arrest while haemodynamically unstable patients not requiring cardiopulmonary resuscitation had a lower mortality rate of 46.9%.[3] In accordance, presentation with cardiac arrest as the initial symptom of PE was associated with a worse prognosis than other types of high-risk PE in the present study. Reperfusion treatment was administered to 78.4% of patients with cardiac arrest at presentation in our cohort, a much higher rate than the rate of 25.9% in the German nationwide inpatient sample.[3] Despite this high adherence to guideline-recommended treatment, the occurrence of either another episode of cardiac arrest or death from PE-related complications during the in-hospital stay could not be avoided in more than 75% of cardiac arrest patients.

In the absence of a cardiac arrest, persistent hypotension (defined as systolic blood pressure <90 mmHg or vasopressors required to achieve a blood pressure ≥90 mmHg despite adequate filling status) has been recognized for a long time as a critical determinant of mortality in acute PE[5,6] and thus serves as the main defining feature of high-risk PE.[2] The newly introduced criterion of obstructive shock (i.e. end-organ hypoperfusion in addition to persistent hypotension

'alone') is meant to align the diagnosis of PE-related shock with other definitions of cardiogenic shock (due to left- or right-sided heart failure) that are all based on a combination of hypotension and inadequate tissue perfusion (Supplementary material online, *Table S6*). If risk stratification was based on the 'standard' ESC 2019 definition (using a venous lactate cut-off value of 2.3 mmol/L), persistent hypotension was present in only 1.4% of the entire cohort (12.7% of high-risk patients), while obstructive shock was more than three times as frequent. The two clinical presentations did not differ in rates of adverse outcomes, but the only obstructive shock was associated with an increased risk of in-hospital all-cause mortality compared to intermediate-high-risk patients.

An optimized lactate concentration threshold for diagnosis of obstructive shock

Elevated venous lactate levels, predefined as concentrations exceeding the upper limit of normal, were the most frequent sign of end-organ hypoperfusion in patients with obstructive shock in our cohort. While this definition of elevated lactate is in accordance with the ESC 2019 guidelines,[2] it should be noted that a specific cut-off value for the diagnosis of obstructive shock has not been investigated so far.

Until now, the prognostic value of lactate in acute PE (using a cut-off value of 2 mmol/L) has mostly been investigated in normotensive patients[20,21] and only two studies also included a low number of high-risk patients.[22,23] In our cohort, lactate concentrations above

Table 2 Prognostic relevance of comorbidities and results from risk stratification in patients with regard to different in-hospital outcomes

A: Adverse outcome

	All patients				Excluding patients with cardiac arrest			
	Adverse outcome n/N (%)	No adverse outcome n/N (%)	Outcome rate if positive (%)	OR (95% CI)	Adverse outcome n/N (%)	No adverse outcome n/N (%)	Outcome rate if positive (%)	OR (95% CI)
Age ≥75 years	27/59 (45.8)	250/725 (34.5)	9.7	1.60 (0.94–2.74)	13/30 (43.3)	248/717 (34.6)	5.0	1.45 (0.69–3.03)
Sex (female)	29/59 (49.2)	377/725 (52.0)	7.1	0.89 (0.52–1.52)	15/30 (50.0)	375/717 (52.3)	3.8	0.91 (0.44–1.89)
Comorbidities								
Chronic heart failure	14/59 (23.7)	104/725 (14.3)	11.9	1.86 (0.98–3.50)	8/30 (26.7)	101/717 (14.1)	7.3	2.22 (0.96–5.12)
Coronary artery disease	15/59 (25.4)	128/725 (17.7)	10.5	1.59 (0.86–2.94)	7/30 (23.3)	126/717 (17.6)	5.3	1.43 (0.60–3.4)
Chronic pulmonary disease	9/59 (15.3)	109/725 (15.0)	7.6	1.02 (0.49–2.13)	5/30 (16.7)	108/717 (15.1)	4.4	1.13 (0.42–3.01)
Renal insufficiency	39/59 (66.1)	225/714 (31.5)	14.8	4.24 (2.42–7.43)	16/30 (53.3)	222/706 (31.4)	6.7	2.49 (1.20–5.19)
Active cancer	12/59 (20.3)	130/724 (18.0)	8.5	1.17 (0.60–2.26)	7/30 (23.3)	129/716 (18.0)	5.1	1.38 (0.58—3.30)
Symptoms at presentation								
Syncope	20/57 (35.1)	101/724 (14.0)	16.5	3.33 (1.86–5.97)	8/29 (27.6)	99/716 (13.8)	7.5	2.37 (1.02–5.51)
Altered mental status	39/59 (66.1)	48/725 (6.6)	44.8	27.50 (14.89–50.79)	10/30 (33.3)	40/717 (5.6)	20.0	8.46 (3.71–19.28)
Clinical findings at presentation								
Tachycardia	30/58 (51.7)	243/712 (34.1)	10.9	2.07 (1.21–3.54)	16/29 (55.2)	239/704 (33.9)	6.3	2.40 (1.13–5.06)
Hypotension	37/58 (63.8)	49/697 (7.0)	43.0	23.30 (12.67–42.85)	8/29 (27.6)	41/689 (6.0)	16.3	6.02 (2.51–14.42)
Hypoxaemia	41/55 (74.5)	162/617 (26.3)	20.2	8.23 (4.37–15.48)	12/26 (46.2)	154/609 (25.3)	7.2	2.53 (1.15–5.59)
Respiratory insufficiency	32/53 (60.4)	21/683 (3.1)	60.4	48.04 (23.83–96.85)	5/26 (19.2)	14/675 (2.1)	26.3	11.24 (3.71–34.10)
Laboratory and imaging markers								
hsTnT ≥14 pg/mL	51/56 (91.1)	436/673 (64.8)	10.5	5.54 (2.18–14.08)	24/28 (85.7)	430/667 (64.5)	5.3	3.31 (1.13–9.64)
Venous lactate ≥2.3 mmol/L	23/31 (74.2)	143/443 (32.3)	13.9	6.03 (2.63–13.82)	8/16 (50.0)	138/437 (31.6)	5.5	2.17 (0.80–5.89)
Venous lactate ≥3.8 mmol/L	19/31 (61.3)	48/443 (10.8)	28.4	13.03 (5.96–28.49)	5/16 (31.3)	43/437 (9.8)	10.4	4.16 (1.38–12.55)
RV/LV diameter ratio ≥1.0 on CTPA	32/39 (82.1)	402/555 (72.4)	7.4	1.74 (0.75–4.03)	12/19 (63.2)	396/548 (72.3)	2.9	0.66 (0.25–1.7)

B: All–cause mortality

	All patients				Excluding patients with cardiac arrest			
	All-cause mortality n/N (%)	Survivors n/N (%)	Outcome rate if positive (%)	OR (95% CI)	All-cause mortality n/N (%)	Survivors n/N (%)	Outcome rate if positive (%)	OR (95% CI)
Age ≥75 years	27/59 (45.8)	250/725 (34.5)	9.7	1.60 (0.94–2.74)	15/37 (40.5)	246/710 (34.6)	5.7	1.29 (0.66–2.52)
Sex (female)	31/59 (52.5)	375/725 (51.7)	7.6	1.03 (0.61–1.76)	20/37 (54.1)	370/710 (52.1)	5.1	1.08 (0.56–2.1)
Comorbidities								
Chronic heart failure	12/59 (20.3)	106/725 (14.6)	10.2	1.49 (0.77–2.90)	7/37 (18.9)	102/710 (14.4)	6.4	1.39 (0.60–3.25)
Coronary artery disease	12/59 (20.3)	131/725 (18.1)	8.4	1.16 (0.60–2.24)	6/37 (16.2)	127/710 (17.9)	4.5	0.89 (0.36–2.17)
Chronic pulmonary disease	11/59 (18.6)	107/725 (14.8)	9.3	1.32 (0.67–2.63)	8/37 (21.6)	105/710 (14.8)	7.1	1.59 (0.71–3.57)
Renal insufficiency	36/58 (62.1)	228/715 (31.9)	13.6	3.50 (2.01–6.08)	18/36 (50)	220/700 (31.4)	7.6	2.18 (1.11–4.27)
Active cancer	20/59 (33.9)	122/724 (16.9)	14.1	2.53 (1.43–4.49)	16/37 (43.2)	120/709 (16.9)	11.8	3.74 (1.90–7.38)
Symptoms at presentation								
Syncope	16/57 (28.1)	105/724 (14.5)	13.2	2.30 (1.25–4.25)	8/36 (22.2)	99/709 (14.0)	7.5	1.76 (0.78–3.97)
Altered mental status	33/59 (55.9)	54/725 (7.4)	37.9	15.77 (8.80–28.28)	11/37 (29.7)	39/710 (5.5)	22.0	7.28 (3.35–15.81)
Clinical findings at presentation								
Tachycardia	27/58 (46.6)	246/712 (34.6)	9.9	1.65 (0.96–2.83)	18/36 (50.0)	237/697 (34.0)	7.1	1.94 (0.99–3.80)
Hypotension	30/56 (53.6)	56/699 (8.0)	34.9	13.25 (7.33–23.95)	8/34 (23.5)	41/684 (6.0)	16.3	4.83 (2.06–11.32)
Hypoxaemia	35/55 (63.6)	168/617 (27.2)	17.2	4.68 (2.63–8.33)	13/33 (39.4)	153/602 (25.4)	7.8	1.91 (0.93–3.93)
Respiratory insufficiency	26/52 (50.0)	27/684 (3.9)	49.1	24.33 (12.50–47.37)	6/32 (18.8)	13/669 (1.9)	31.6	11.64 (4.10–33.07)
Laboratory and imaging markers								
hsTnT ≥14 pg/mL	50/56 (89.3)	437/673 (64.9)	10.3	4.50 (1.90–10.65)	29/35 (82.9)	425/660 (64.4)	6.4	2.67 (1.09–6.53)
Venous lactate ≥2.3 mmol/L	20/32 (62.5)	146/442 (33.0)	12.0	3.38 (1.61–7.10.)	9/21 (42.9)	137/432 (31.7)	6.2	1.61 (0.66–3.92)
Venous lactate ≥3.8 mmol/L	16/32 (50.0)	51/442 (11.5)	23.9	7.67 (3.61–16.26)	5/21 (23.8)	43/432 (10.0)	10.4	2.83 (0.99–8.1)
RV/LV diameter ratio ≥1.0 on CTPA	32/37 (86.5)	402/557 (72.2)	7.4	2.47 (0.94–6.45)	17/22 (77.3)	391/545 (71.7)	4.2	1.34 (0.49–3.69)

CI, confidence interval; CTPA, computed tomography pulmonary angiography; hsTnT, high sensitivity troponin T; LV, left ventricular; OR, odds ratio; RV, right ventricular.

the upper limit of normal ($\geq$2.3 mmol/L) were not predictive of adverse outcomes in patients without cardiac arrest. In accordance, obstructive shock patients with lactate levels $\geq$2.3 mmol/L as the only sign of hypoperfusion had an adverse outcome rate of 'only' 5.6%.

Thus, we identified an optimized lactate cut-off value of 3.8 mmol/L that adequately predicted adverse outcomes in both the entire cohort and in patients without cardiac arrest at presentation. Importantly, the use of the optimised lactate cut-off value for the diagnosis of obstructive shock allowed differentiation of risk in patients with obstructive shock and patients with isolated persistent hypotension.

Further, when this more specific definition of obstructive shock was used, patients with persistent hypotension had similar outcome rates compared to those classified into the intermediate-high-risk category. Our findings thus suggest that isolated persistent hypotension may not independently predict a high risk of adverse outcomes. At the same time, a substantial rate of major bleeding of 31.8% was observed in high-risk patients treated with systemic thrombolysis, and the rates did not differ across the clinical presentations within the high-risk category. Hence, the risk-to-benefit ratio of full-dose systemic thrombolysis in a patient presenting with isolated persistent hypotension but no signs of organ hypoperfusion may be less favourable than that of a patient at a similar bleeding risk but presenting with obstructive shock. This should be taken into account in clinical decision making, i.e., for setting the indication and then choosing the optimal reperfusion option for a patient with acute PE.

Limitations

There are limitations of the present study that deserve consideration: First, the single centre design and the limited number of patients and events, especially when the high-risk group was further stratified according to the three clinical presentations, are major limitations of our study. However, information on clinical signs of hypoperfusion (namely, criteria to define obstructive shock according to the definition of the ESC 2019 guidelines) are not available in most registries making a pooled analysis of a larger patient cohort difficult. Second, in the present patient cohort, information on clammy skin and oliguria was not available and thus not used for defining obstructive shock. However, the diagnosis of oliguria requires the determination of urine output over the course of 6 h,[24] making this parameter less suitable for decision making in the emergency setting. Third, venous lactate concentrations on admission were available for 474 patients (60.5%) only; however, the proportion was lower in high-risk patients without cardiac arrest [15 of 49 patients (30.6%) with missing lactate measurements]. Given these limitations, the number of patients with obstructive shock might be underestimated.

Conclusion

Our study confirms that the three clinical presentations of high-risk PE defined in the ESC 2019 guidelines identify subgroups at different risk for adverse outcomes and in-hospital all-cause mortality. In addition, we provide an optimised cut-off value defining increased venous lactate for diagnosing obstructive shock. If this optimised cut-off value is applied, the risk for adverse outcomes and mortality of hypotensive patients without obstructive shock is comparably low and may not justify accepting the risk of bleeding associated with systemic thrombolysis in all of these patients. Further research is warranted to validate these findings in a larger cohort of patients.

Supplementary material

Supplementary material is available at *European Heart Journal: Acute Cardiovascular Care*.

UMG Biobank as a core facility of the University Medical Center Göttingen, Germany by provision of quality assured biomaterial.

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