



Right ventricle dysfunction measured by echocardiogram and lactate levels in pulmonary embolism

Disfunción del ventrículo derecho medida por ecocardiograma y niveles de lactato en la embolia pulmonar

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ABSTRACT. Introduction: In patients with pulmonary embolism, multiple risk stratification tools have developed in order to decrease short-term complications and mortality. Nonetheless, current instruments can underestimate the actual risk as prognosis largely depends on hemodynamic instability, which does not exclude the presence of right ventricular dysfunction, an independent predictor of mortality. **Objective:** This study aimed to determine the association between hyperlactatemia and right ventricular dysfunction by echocardiography in patients with pulmonary embolism. **Material and methods:** A single-center retrospective cohort study was conducted, including all patients older than 18 admitted to the coronary unit with objective pulmonary embolism diagnosis by imaging at the Emergency Department. All medical records from August 1st, 2013, to January 31st, 2020 were individually reviewed to identify eligible patients. Patients were stratified based on serum lactate levels and classified into < 2.0 and > 2.0 mmol/L. Baseline patient characteristics were collected, including all simplified pulmonary embolism severity index (sPESI) scale variables. The primary endpoint was right ventricular dysfunction by echocardiography. Secondary outcomes included death by any cause, mechanical ventilation, thrombolysis, and vasopressor agent use. Data collected included all Emergency Department discharge serum biomarkers values (lactate, NT-proBNP, and troponin I) and right ventricular function evaluation reports by imaging. Plasma lactate levels cut-point was used to determine the primary objective indicated by receiver operator characteristic (ROC) curve analysis. The odds ratio (OR) and 95% confidence intervals (CI) were estimated to define an association between hyperlactatemia and each sPESI scoring system variable and RV dysfunction occurrence. Significance was determined if the p-value was < 0.05 . All data were analyzed with the SPSS program. **Results:** Overall, in-hospital mortality was 6.66% ($n = 2$). The primary outcome was observed in 70% ($n = 21$), while the secondary outcome was observed in 43% ($n = 13$). Elevated serum lactate levels (> 2 mmol/L) were associated with the presence of markers by echocardiography of right ventricular dysfunction in patients with PE (OR 8.7; 95% CI 1.3 to 54; p-value 0.02). Among its comparison with sPESI parameters, a significant association was found with hypotension (OR 13.2; 95% CI 2.1 to 82.5, p-value of 0.003) and age over 80 years (OR 4.76; 95% CI 0.9 to 23.8, p-value of 0.05). An area below the curve of 0.85 (95% CI from 0.71 to 0.99, $p < 0.05$) and a false-positive rate of 11% were found when considering a lactate value greater than 2.0 mmol/L as a marker of RV dysfunction. **Conclusion:** Hyperlactatemia could be used as an easy-to-perform and inexpensive marker of right ventricular dysfunction in patients with pulmonary embolism for early risk stratification, particularly when RV assessment by imaging is not available.

Keywords: Hyperlactatemia, right ventricular dysfunction, pulmonary embolism.

RESUMEN. Introducción: En pacientes con tromboembolia pulmonar (TEP) se han desarrollado múltiples herramientas de estratificación de riesgo para disminuir las complicaciones y la mortalidad a corto plazo. Sin embargo, los instrumentos actuales pueden subestimar el riesgo real, ya que el pronóstico depende en gran medida de la inestabilidad hemodinámica, la cual no excluye la presencia de disfunción ventricular derecha, un predictor independiente de mortalidad. **Objetivo:** Determinar la asociación entre hiperlactatemia y disfunción ventricular derecha mediante ecocardiografía en pacientes con tromboembolia pulmonar. **Material y métodos:** Se realizó un estudio de cohorte retrospectivo, que incluyó a todos los pacientes mayores de 18 años ingresados en la Unidad Coronaria con diagnóstico comprobable de tromboembolia pulmonar por imagen en el Servicio de Urgencias. Todos los registros médicos desde el 1° de agosto de 2013 hasta el 31 de enero de 2020 fueron revisados individualmente para identificar a los pacientes elegibles. Los pacientes fueron clasificados en función de los niveles séricos de lactato y clasificados en < 2.0 y > 2.0 mmol/L. Se recogieron las características basales de los pacientes, incluyendo todas las variables de escala del índice de severidad de la embolia pulmonar simplificada (sPESI). El criterio de valoración primario fue la disfunción ventricular derecha por ecocardiografía. Los resultados secundarios incluyeron la muerte por cualquier causa, ventilación mecánica, trombólisis y uso de agentes vasopresores. Los datos recopilados incluyeron todos los valores de biomarcadores séricos al momento de alta de urgencias (lactato, NT-proBNP y troponina I) y reporte ecocardiográfico de la función ventricular derecha. Se utilizaron niveles plasmáticos de lactato para determinar el objetivo primario indicado por el análisis de curva ROC. Los odds ratio (OR) y los intervalos de confianza (IC) del 95% se estimaron para definir una asociación entre la hiperlactatemia y cada variable del sistema de puntuación sPESI y la ocurrencia de disfunción del VD. La significación se determinó si el valor p era < 0.05 . Todos los datos se analizaron con el programa SPSS. **Resultados:** La mortalidad intrahospitalaria total fue de 6.66% ($n = 2$). El resultado primario se observó en 70% ($n = 21$), mientras que el resultado secundario se observó en 43% ($n = 13$). Los niveles elevados de lactato sérico (> 2 mmol/L) se asociaron a la presencia de marcadores por ecocardiografía de disfunción ventricular derecha en pacientes con TEP (OR 8.7; IC del 95%: 1.3 a 54; $p = 0.02$). En el análisis de hiperlactatemia con los parámetros de sPESI, se encontró una asociación significativa con la hipotensión (OR 13.2; IC del 95%: 2.1 a 82.5; p de 0.003) y la edad mayor de 80 años (OR 4.76; IC del 95%: 0.9 a 23.8; p de 0.05). Se encontró un área por debajo de la curva de 0.85 (IC del 95% de 0.71 a 0.99, $p < 0.05$) y una tasa de falsos positivos de 11% al considerar un valor de lactato superior a 2.0 mmol/L como marcador de disfunción del ventrículo derecho (VD). **Conclusión:** La hiperlactatemia podría ser utilizada como un marcador fácil de realizar y económico de la disfunción ventricular derecha en pacientes con embolia pulmonar para estratificación temprana de riesgo, particularmente cuando no se dispone de evaluación del VD por imágenes.

Palabras clave: Hiperlactatemia, disfunción ventricular derecha, embolia pulmonar.

INTRODUCTION

Pulmonary embolism (PE) represents the third leading cardiovascular death cause worldwide, only behind acute myocardial infarction and stroke.¹ PE is associated with a significant mortality rate, primarily if adequate treatment is not initiated, affecting up to 30% as opposed to the 8% observed when properly managed.² Still, death is not unusual, with over 70% of deaths occurring within the first hour of disease onset due to hemodynamic instability,³ reflecting the severe yet life-threatening character of the disease. Its prompt recognition and risk stratification allow decision-making and tailoring adequate management tools in order to decrease the burden of the disease.

In this regard, multiple risk stratification instruments, such as the pulmonary embolism severity index (PESI)⁴ score and simplified pulmonary embolism severity index (sPESI),⁵ have been developed to predict short-term mortality in PE. Still, these tools can underestimate the actual risk as prognosis largely depends on hemodynamic instability and right ventricular (RV) dysfunction, related to up to 24.5% 30-day mortality risk.⁴ Furthermore, instability absence does not exclude the presence of RV dysfunction, an independent predictor of mortality.⁶

Plasma lactate concentration, a marker of severity and prognosis in sepsis, may provide valuable information for risk stratification of PE patients, reflecting tissue oxygen supply-to-demand mismatch secondary to right heart hypoperfusion and subsequent impairment.^{3,7}

Therefore, a more significant risk assessment and stratification tool based on clinical and imaging evidence of hemodynamic instability and right ventricular dysfunction are required to decrease morbidity and mortality. Thus, the objective of this study was to determine the association between hyperlactatemia and right ventricular dysfunction by echocardiography and to explore its potential usefulness as a clinical tool in patients with PE.

MATERIAL AND METHODS

Study design and population. A single-center retrospective cohort study was conducted, including all patients older than 18 admitted to the coronary unit with PE diagnosis at Emergency Department discharge demonstrated by tomography or with high probability reported by ventilation/perfusion scintigraphy identified between August 1st, 2013, and January 31th, 2020. Patients with arterial blood gas at the emergency evaluation prior to treatment initiation and transthoracic echocardiography performed during hospital stay were included. Those with a history of previous PE or chronic venous thromboembolism (VTE) were excluded. All medical records from this period were individually reviewed to identify eligible patients.

Data collection and outcomes. The primary endpoint was right ventricular dysfunction by echocardiography. Secondary outcomes included death by any cause, mechanical ventilation, thrombolysis, and vasopressor agent use. Based on previous studies,⁷ patients were stratified based on serum lactate levels and classified into < 2.0 and > 2.0 mmol/L. Baseline patient characteristics were collected, including all sPESI scale variables (age > 80 years, cancer, chronic cardiopulmonary disease, heart rate > 110 bpm, systolic pressure < 100 mmHg, and arterial oxygen saturation $< 90\%$) and the presence or absence of right ventricular dysfunction.

Right ventricular dysfunction by transthoracic echocardiography was determined based on 2019 European Society of Cardiology guidelines demonstrated by the presence of any of the following: 1) RV dilation in the parasternal axis; 2) RV basal dilation with an RV/LV ratio > 1.0 in the 4-chamber view

and McConnell's sign; 3) septal flattening in the parasternal short-axis; 4) dilatation of the inferior vena cava with decreased inspiratory collapse; 5) 60/60 sign (coexistence of a pulmonary systolic acceleration time > 60 ms and a midsystolic notch with a systolic peak gradient < 60 mmHg in the tricuspid valve); 6) presence of mobile thrombus in the right cavities, 7) tricuspid annular plane systolic excursion (TAPSE) < 16 mm; 8) decreased peak systolic velocity of tricuspid annulus < 9.5 cm/min.⁶ All echocardiograms were performed by certified echocardiographers and following local protocols.

Statistical analysis. Data collected included all Emergency Department discharge serum biomarkers values (lactate, NT-proBNP, and troponin I) and RV function evaluation reports by imaging. Plasma lactate levels were used to determine the receiver operator characteristic (ROC) curve analysis, using the area under the curve, sensitivity, and specificity based on objective documentation of RV dysfunction.

Frequencies and percentages were used for categorical variables. According to their distribution, numerical variables are presented as mean and standard deviation or median and quartile 1 and 3. The odds ratio (OR) and 95% confidence intervals (CI) were estimated to define an association between hyperlactatemia and each sPESI scoring system variable and RV dysfunction occurrence. Significance was determined if the p-value was < 0.05 . All data were analyzed with the SPSS program.

RESULTS

One hundred and fifty four medical records with PE diagnosis were reviewed, 82 of which were admitted to the Coronary Unit. After eliminating those with inconclusive criteria, 30 patients were included in the final registry. The median age was 67 ± 17 years. Approximately half of the patients presented with hemodynamic instability at admission, defined as systolic blood pressure < 100 mg.

Thrombolytic therapy was administered in 13% ($n = 4$) of the subjects. Overall, in-hospital mortality was 6.66% ($n = 2$). The primary outcome (right ventricular systolic dysfunction by echocardiography) was observed in 70%

(n = 21), while the secondary outcome (death by any cause, mechanical ventilation, thrombolysis, and vasopressor agent use) was observed in 43% (n = 13). Patient characteristics at coronary unit admission are compiled in [Table 1](#).

Elevated serum lactate levels (> 2 mmol/L) were associated with the presence of at least one of the markers by echocardiography of right ventricular dysfunction in patients with acute pulmonary thromboembolism (OR 8.7; 95% CI 1.3 to 54; p-value 0.02).

The analysis between lactate values > 2.0 mmol/L and each sPESI scoring system variable and RV dysfunction occurrence are shown in [Table 2](#). Among these parameters, a significant association was found between lactate values > 2.0 mmol/L and systolic blood pressure < 100 mmHg (OR 13.2; 95% CI 2.1 to 82.5) and age over 80 years (OR 4.76; 95% CI 0.9 to 23.8) with a p-value of 0.003 and 0.05 respectively.

A sensitivity and specificity analysis was performed using the ROC curve to evaluate hyperlactatemia > 2.0 mmol/L as a cutoff point for diagnosing RV systolic dysfunction, finding an area below the curve of 0.85 (95% CI from 0.71 to 0.99, p < 0.05). A false-positive rate of 11% was found when considering a lactate value greater than 2.0 mmol/L as a marker of RV dysfunction ([Figure 1](#)).

DISCUSSION

This study showed an association between elevated serum lactate levels and echocardiographic documentation of RV dysfunction in patients with acute PE. These results are not dissimilar to those previously observed by Vanni et al., where the presence of RV dysfunction was more frequent in lactate levels greater than two mmol/L.⁷ However, to our knowledge, this is the first study to observe a statistical association between lactate levels and RV dysfunction.

RV dysfunction is an independent predictor of mortality found in ≥ 25% of unselected patients with acute PE.⁶ Likewise, it has been correlated with an elevated risk of short-term mortality in hemodynamically stable patients.⁸ However, these findings are not limited to intermediate and high-risk patients.

A metaanalysis found that RV dysfunction on admission was associated with early mortality in low-risk patients.⁹ Thus its sole presence sustains PE risk stratification. In the context of our findings, it seems reasonable to investigate RV dysfunction in those patients with elevated lactate concentrations, regardless of other clinical criteria and hemodynamic stability, to adequately stratify their risk in order to tailor the most appropriate management.

Although our study did not find an association between lactate levels and in-hospital short-term complications and mortality, hyperlactatemia has been associated with PE short-term complications as well, even in initially normotensive patients.¹⁰ Galic et al. demonstrated that the lactate value could be used as an independent prognostic indicator of shock and right heart failure in patients diagnosed with intermediate to high-risk PE.¹¹

Table 1: Patient baseline characteristics (N = 30).

Characteristics	n (%)
Male	11 (36)
Age (years)	67 ± 17
Hypertension	14 (46)
Diabetes mellitus	11 (36)
Coronary artery disease	2 (6)
sPESI	2.76 ± 1.13
Age > 80 years old	13 (43)
History of cancer	5 (16)
History of chronic cardiopulmonary disease	20 (66)
Heart rate > 100 bpm	20 (66)
Systolic blood pressure < 100 mmHg	14 (46)
Oxygen saturation < 90%	24 (80)
Vasopressor use	10 (33)
IMV	4 (13)
RVD	21 (70)
BNP (pg/mL)	18 (60)
TnI (ng/mL)	19 (63)

sPESI = simplified pulmonary embolism severity index; IMV = intermittent mandatory ventilation; RVD = right ventricular dysfunction; BNP = B-type natriuretic peptide; TnI = troponin I.

Table 2: Association between hyperlactatemia and clinical, biochemical and outcome variables in patients with acute pulmonary thromboembolism.

Variable	Lactate, n (%)		p	OR (CI 95%)
	< 2.0 mmol/L (N = 13)	> 2.0 mmol/L (N = 17)		
sPESI parameters				
Male	4 (30)	7 (41)	0.70	1.57 (0.3-7.2)
Age > 80 years	3 (23)	10 (58)	0.05	4.76 (0.9-23.8)
History of cancer	2 (15)	3 (17)	1.00	1.17 (0.1-8.3)
History of chronic cardiopulmonary disease	8 (61)	12 (70)	0.70	1.5 (0.3-6.9)
Heart rate > 100 bpm	9 (69)	11 (64)	1.00	0.81 (0.1-3.8)
Systolic blood pressure < 100 mmHg	2 (15)	12 (70)	0.003	13.2 (2.1-82.5)
Oxygen saturation < 90%	10 (76)	14 (82)	1.00	1.4 (0.2-8.4)
Other variables				
Hypertension	4 (30)	10 (58)	0.12	3.2 (0.7-14)
Diabetes mellitus	4 (30)	7 (41)	0.70	1.5 (0.3-7.2)
Coronary artery disease	1 (7)	1 (5)	1.00	0.7 (0-13)
Outcomes				
Vasopressor use	3 (23)	7 (41)	0.44	2.3 (0.4-11.6)
IMV	2 (15)	2 (11)	1.00	0.7 (0-6)
Thrombolysis	1 (7)	3 (17)	0.61	2.5 (0.2-28)
Death	0	2 (11)	0.49	—
RVD	6 (46)	15 (88)	0.02	8.7 (1.3-54)
BNP	6 (46)	12 (70)	0.17	2.8 (0.6-12.6)
TnI	9 (69)	10 (58)	0.70	0.6 (0.1-2.9)
Secondary outcome	11 (84)	16 (94)	0.56	2.9 (0.2-36)

sPESI = simplified pulmonary embolism severity index; IMV = intermittent mandatory ventilation; RVD = right ventricular dysfunction; BNP = B-type natriuretic peptide; TnI = troponin I; OR = odds ratio.

According to recent European Society of Cardiology guidelines, risk stratification tools such as PESI or sPESI score scale along with RV dysfunction imaging evaluation should be performed to identify patients with an intermediate-high risk of PE-related short-term complications or death.⁶ Hemodynamic instability features such as low systolic blood, tachycardia, and respiratory insufficiency have also been associated with poor prognosis.⁴⁻⁶ Our analysis seems to support this premise, as hypotension and age older than 80 were also associated with high lactate levels. Nonetheless, these parameters could underestimate the actual risk, as previous studies have reported.⁸

Hence, the presence of hyperlactatemia could support PE risk stratification. Accordingly, previous studies observed an association between elevated lactate levels and 28-day mortality in ICU patients admitted for PE, independent of systolic blood pressure.¹²

Elevated serum lactate levels have been described as a prognostic survival factor in patients with PE, independent of acid-base status and RV dilation or positive biomarkers.^{7,11,12}

In this study, we evaluated hypoperfusion manifested as hyperlactatemia and found this parameter could be a helpful, easy-to-perform, and inexpensive marker to identify high-risk patients in acute PE. Accordingly,

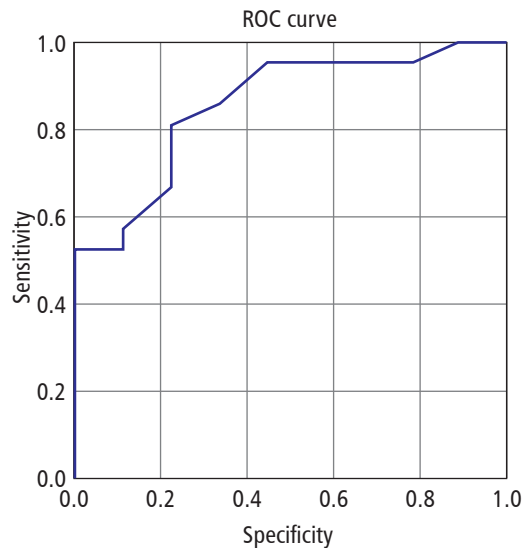


Figure 1: ROC curve analysis for hyperlactatemia and right ventricular dysfunction by echocardiography showing an AUC of 0.85%.

lactate association with RV dysfunction may be explained by the subsequent oxygen supply-demand imbalance secondary to thrombotic obstruction-related hypoxemia.⁷ Lactate concentration might increase in acute PE before overt hemodynamic impairment as in other clinical settings like sepsis or trauma.¹⁰ Hence, serum lactate could be used as a marker of hemodynamic severity in PE, particularly in the absence of RV assessment by imaging.

These results reflect the potential lactate application in PE early risk stratification to identify patients at high risk of complications and death who may benefit from more aggressive monitoring and management instruments. Nonetheless, to confirm our findings, a properly designed prospective study must be conducted to complement the results with a new registry with a larger number of patients.

We recognize several limitations in our study, in particular, its retrospective nature, as well as the small sample evaluated. In this regard, due to its convenience sample, no statistical significance sample size was reached. Although this study demonstrated association, no conclusions can be made based on its results as it is a hypothesis generator.

In summary, an association between elevated serum lactate levels and the objective documentation of RV dysfunction in patients with acute pulmonary thromboembolism was observed. Hyperlactatemia could be used as an easy-to-perform and inexpensive marker of RV dysfunction in patients with PE for early risk stratification, particularly when RV assessment by imaging is not available.

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