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Pleural fluid lactate: a diagnostic tool in pleural effusion management?

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TO THE EDITOR:

Malignant pleural effusion (MPE) is a common condition, defined as the accumulation of exudate in pleural space in the presence of cytological or histological evidence of tumor cells, representing an advanced stage. The incidence of MPE is rising, alongside the increase of global cancer incidence and the improvement in overall survival.[1,2]

Infectious pleural effusion (IPE) is also a common clinical problem, as up to 57% of patients with pneumonia develop pleural effusion (PE). It represents a progressive process translating from simple parapneumonic pleural effusion (PPE) into fibrinopurulent collection (complicated PPE), culminating in purulent PE (empyema).[3] The incidence of tuberculosis in Portugal remains high, as tuberculous pleural effusion (TBPE) and lymphadenitis are the most common extrapulmonary manifestations, leading to exudative PE.[4,5]

In the presence of new PE, diagnostic thoracentesis should be performed initially. Currently, available bedside tests using a blood gas analyzer include pH, glucose, and hematocrit. Lactate level is also automatically obtained through this method in most settings. Lactate is a product from the metabolic pathway of anaerobic glycolysis, via lactate dehydrogenase.[6] Bacterial metabolism enhances in IPE, leading to elevation of pleural lactate. In MPE cases, we typically observe chronic progression, potentiating lower levels of lactate.[4] Due to these differences in PE lactate, we hypothesized that MPE lactate would be lower than that in IPE cases, the two most common etiologies observed in our setting.

We aimed to (1) describe the levels of lactate in different etiologies of PE, (2) compare the levels of lactate in IPE and MPE, and (3) determine a cut-off level of lactate in PE to distinguish IPE from MPE.

This study prospectively included all of the patients who underwent diagnostic thoracentesis in our Pulmonology Department in a hospital centre in the city of Viseu, Portugal, between November of 2019 and November of 2020. Patients with PE of known etiology, already under treatment or undergoing evacuating thoracentesis were excluded. Our standard routine protocol for PE analysis includes assessment of glucose, pH, lactate dehydrogenase, protein, cytology and microbiology cultures. Glucose, pH, and hematocrit were measured using a blood gas analyzer (GEM Premier 3500; Werfen, Bedford, MA, USA), which also automatically provides lactate levels (range, 0-15 mmol/L). The study protocol was approved by the research ethics committee of our institution (Protocol no. 03/21/10/2019).

The Light criteria were used to differentiate between transudative and exudative PE.[7] IPE includes all cases of PPE, empyema and TBPE. Patients with PE and pneumonia were classified as having PPE (including complicated PPE), or as having empyema (when purulent pleural fluid or positive cultures were present). TBPE was defined as a positive culture for *Mycobacterium tuberculosis* or positive *M. tuberculosis* DNA (GeneXpert) in PE and pleural biopsy with caseous granuloma, or confirmed pulmonary tuberculosis, with no other alternative cause. MPE was defined as a positive cytological or histological result for malignant cells in PE or an exudative PE in a patient with known advanced tumor with no obvious alternative cause (para-malignant PE). Statistical analysis was performed with the IBM SPSS Statistics software package, version 28.0.0.0 (IBM Corporation, Armonk, NY, USA). All data were expressed as means ± SDs or medians [IQRs].

Of the 129 patients evaluated due to PE, 17 were excluded according to the exclusion criteria. Therefore, 112 patients were included. Most were male (65.2%), with a median age of 73 years [64-81 years]. Exudative PE accounted for 82.1% of cases (n = 92): MPE, in 41 cases; PPE, in 15; empyema, in 7; TBPE, in 7; and other causes, in 22 (cardiac failure, chronic liver disease, chronic kidney disease and pulmonary thromboembolism). Characteristics of the patients, characteristics of pleural fluid according to the distinct types of PE and lactate levels are shown in Table 1.

Pleural fluid lactate levels were significantly higher in the exudate group than in the transudate group ($p < 0.001$) . Regarding the exudate group, patients with MPE had significantly lower levels of lactate than did those with IPE: PPE ($p = 0.030$), TBPE ($p = 0.032$) and empyema ($p < 0.001$). Of the 41 patients with MPE, 56.1% had positive cytological results. No statistical differences in lactate levels were found between para-malignant and malignant PE ($p = 0.121$). Conversely, the patients with exudative PE due to other causes showed significantly lower median levels of lactate than did those with MPE ($p = 0.007$).

A ROC curve analysis was used in order to determine the optimal cut-off point of pleural fluid lactate to differentiate between IPE and MPE. A lactate level ≥ 6.4 mmol/L showed a specificity of 83% and a sensitivity of 55% to predict IPE. The AUC was 0.753 (95% CI: 0.636-0.870; $p < 0.001$).

This study demonstrated the lactate levels in diverse types of PE in a cohort of patients with PE of unknown etiology. To obtain lactate levels, we used a bedside test that has been in use in our department to measure

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Table 1. Patient characteristics and biochemistry results of pleural fluid samples classified in accordance with the Light[7] criteria and subgroups.[a]

Characteristic	Total	Group		Subgroup				
		Transudate	Exudate	MPE	PPE	Empyema	TBPE	Other causes[b]
Patient	(n = 112)	(n = 20)	(n = 92)	(n = 41)	(n = 15)	(n = 7)	(n = 7)	(n = 22)
Gender								
Male	73 (62.5)	13 (65.0)	60 (65.2)	23 (56.1)	11 (73.3)	4 (57.1)	6 (85.7)	16 (72.7)
Female	39 (34.5)	7 (35.0)	32 (34.8)	18 (43.9)	4 (26.7)	3 (42.9)	1 (14.3)	6 (27.3)
Age, years	73 [64-81]	75.6 ± 11.1	73 [64-80]	72.2 ± 12.6	67.3 ± 14.0	66 ± 22.7	58.1 ± 18.8	78.5 [70-83]
Pleural fluid biochemistry								
pH	7.40 [7.27-7.47]	7.44 ± 0.14	7.39 [7.25-7.46]	7.41 [7.29-7.46]	7.22 ± 0.24	6.86 ± 0.46	7.25 ± 0.13	7.43 ± 0.06
Glucose, mg/dL	99.3 ± 52.3	127.1 ± 29.8	93.3 ± 54.2	101 [76-119]	85.1 ± 64.0	5 [5-37]	46.3 ± 25.4	108 [93-150]
LDH, U/L	293 [158-642]	122.6 ± 57.8	336 [196-727]	337 [216-443]	758 [285-1058]	2819 [2118-32110]	792 ± 358	230.7 ± 153.6
Protein, g/dL	3.8 ± 1.2	2.6 ± 1.1	4.0 ± 1.1	3.9 ± 1.0	4.2 ± 0.9	3.7 ± 1.4	4.8 ± 0.6	3.9 ± 1.2
Lactate, mmol/L	3.0 [1.6-5.8]	1.6 [1.1-2.0]	3.5 [2.0-6.5]	3.4 [2.0-5.8]	6.3 ± 4.5	12.5 ± 2.8	6.6 ± 2.7	2.2 ± 1.1
p[c]					0.030	< 0.001	0.032	0.007

MPE: malignant pleural effusion; PPE: parapneumonic pleural effusion; and TBPE: tuberculous pleural effusion. [a]Values expressed as n (%), mean ± SD, or median [IQR]. [b]Cardiac failure, chronic liver disease, chronic kidney disease and pulmonary thromboembolism. [c]p values calculated by comparing the lactate levels in the MPE subgroup with those in the other subgroups.

glucose, pH and hematocrit. In our study, the most common forms of PE had infectious or malignant origins. We demonstrated significantly higher median levels of lactate in IPE than in MPE, which might be explained by high metabolic cell activity during pleural infection, accompanied by bacterial metabolism producing lactic acid. Otherwise, MPE represents chronic inflammation with lower cell production of lactate. As demonstrated in other studies, cases of transudative PE showed the lowest levels of lactate, supported by the underlying pathophysiology, with no pleural disease or minimal inflammation.[4]

We demonstrated that a lactate cut-off level ≥ 6.4 mmol/L can help clinicians differentiate between IPE and MPE, eventually guiding the decision of whether antibiotic treatment should be initiated even if there is no obvious indication, or whether chest pleural drainage should be carried out in cases of complicated PPE and empyema. If lactate levels are < 6.4 mmol/L, other etiologies (such as malignancy) should be suspected, and other tests (such as cytology, pleural biopsy and thoracoscopy) should be performed.

This study has several limitations. Firstly, despite being a prospective study, it had a limited sample size. Secondly, other less common exudative causes were not investigated, which could have introduced biases.

In conclusion, rapid bedside evaluation of lactate levels in patients with PE can be a diagnostic tool in differentiating infection from other causes, particularly malignancy. Therefore, this fact may impact the subsequent management in the event of a new PE, especially following an initial thoracentesis.

AUTHOR CONTRIBUTIONS

SSG: study conception, data collection, statistical analysis, and drafting of the manuscript. RF: data collection, statistical analysis, and drafting of the manuscript. TA and CA: revision of the manuscript. All of the authors read and approved the final version.

CONFLICTS OF INTEREST

None declared.

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